This book is intended for all persons in pharmaceutical technology and quality control of drugs.

A comprehensive alphabetical index at the end of the book leads the reader straight to the product properties, applications, formulations with a large number of active ingredients, processing technologies for a wide range of dosage forms, and analytical methods.

This completely revised edition was actualized by the inclusion of three new grades of Kollidon®, new formulations, new publications etc.

Volker Bühler **Kollidon®** –
Polyvinylpyrrolidone excipients for the pharmaceutical industry

MEP070802e-00

Kollidon® Polyvinylpyrrolidone excipients for the pharmaceutical industry

Volker Bühler

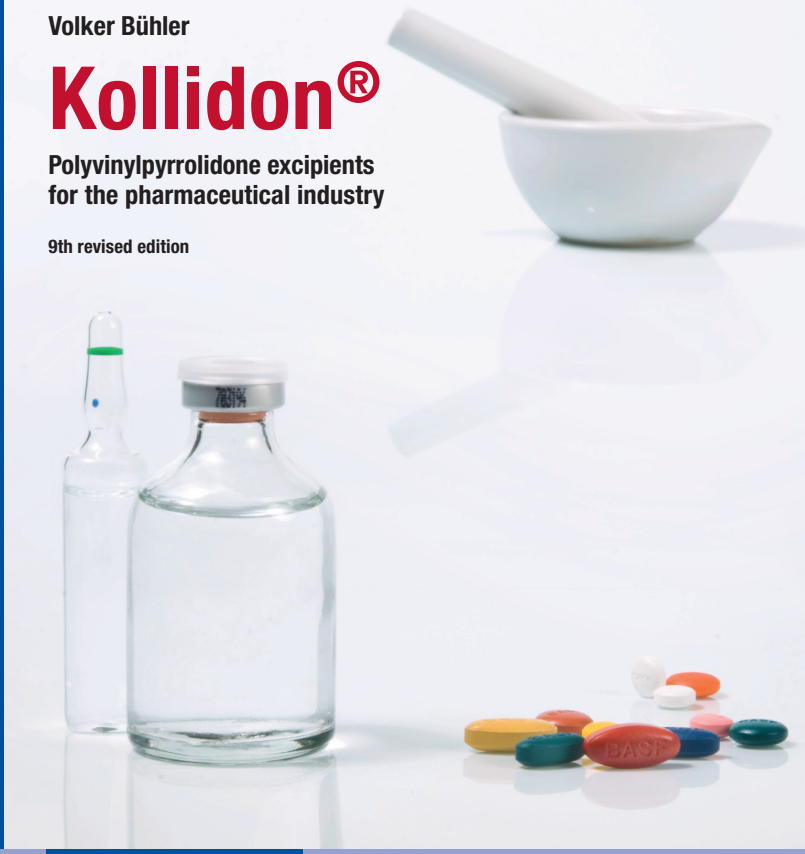
BASF
The Chemical Company

Volker Bühler

Kollidon®

Polyvinylpyrrolidone excipients for the pharmaceutical industry

9th revised edition



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Kollidon®

Polyvinylpyrrolidone excipients for the pharmaceutical industry

BASF SE
Pharma Ingredients & Services
67056 Ludwigshafen, Germany

BASF

The Chemical Company

March 2008
(9th revised edition)

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Preface

Among synthetic excipients, polyvinylpyrrolidone (povidone), marketed under the brand name Kollidon®, is one of the most important substances in the pharmaceutical and cosmetic industries. Starting from the soluble Kollidon® grades which were synthesized by W. Reppe in 1939, a number of products followed, including insoluble grades, copolymerisates and sustained release preparations for numerous applications. The insoluble grades (Kollidon® CL) are prepared using a physical cross-linking process as popcorn polymers of vinylpyrrolidone. Kollidon® VA 64 (copovidone) is a water-soluble copolymerisate of vinylpyrrolidone and vinyl acetate and is mainly used as a binder in tablets, granules, capsules and in coating processes. For sustained release purposes, a mixture of polyvinyl acetate and povidone in a ratio of 8 : 2 is available under the name Kollidon® SR. "The Kollidon® family" is thus nowadays a set of modern excipients based on polyvinylpyrrolidone for use in the pharmaceutical industry.

Although the products are included in all relevant pharmacopoeias, there is a need for a detailed description with special emphasis on their technological properties and applications. This 9th edition of the "Kollidon®-Book" provides answers to all questions relevant to product properties, stability, analytical methods and applications of Kollidon®. It includes three new products: **Kollidon® CL-F** and **Kollidon® CL-SF**, both insoluble and differing in their mean particle diameter and particle size distribution, and **Kollidon® VA 64 Fine**, a water-soluble fine powder, developed as a dry binder for direct compression formulations in tableting and for dry granulation purposes.

The book is divided into 7 main chapters:
1. General notes on synthesis and applications, 2. Soluble Kollidon® grades (povidone), 3. Insoluble Kollidon® grades (crospovidone), 4. Kollidon® VA 64 grades (copovidone), 5. Kollidon® SR, 6. Registration in pharmaceuticals and food, and 7. Toxicological data. It is completed by a current list of references and an alphabetic index. Chapters 2 to 5 are constructed in an identical way, starting with the structure of the product, going on to its physical, physicochemical and chemical properties, methods of analysis, including pharmacopoeial and non-pharmacopoeial methods, and applications. Data are presented in a clear and informative way, often with the help of tables and figures. More than 600 literature citations, including the latest relevant publications, present a complete overview of povidone and related compounds.
The alphabetic index is of high quality and serves as a quick reference guide. I do not know of any other book about excipients that presents such highly concentrated scientific information with valuable practical help.

Any book going to a 9th edition must be a good one. This reflects on the author, Dr. Volker Bühler. He is a pharmacist and spent nearly 30 years with BASF in the application department. Although officially retired, he is still consulting for BASF and writing books. His "Kollidon® Book" started off as a German version in 1992 and was immediately translated into English. The first Japanese edition was published in 1996. Besides this, he has written books on vitamins, on generic drug formulations, on BASF excipients for pharmaceutical technology, on polyvinylpyrrolidone and on the Kollicoat® grades, the coating excipients of BASF. I am convinced that this 9th edition of the "Kollidon® Book" will be equally successful and I wish him many more editions.

Tübingen and Nürnberg, September 2007

Dr. Peter C. Schmidt
Prof. em. of Pharmaceutical Technology
Institute for Pharmacy
University of Tuebingen/Germany

1 General notes on synthesis and applications

1.1 Soluble polyvinylpyrrolidone (soluble Kollidon® grades)

Modern acetylene chemistry is based on the work of Reppe at BASF. One of the many products of this work is N-vinylpyrrolidone (Fig. 1.1).

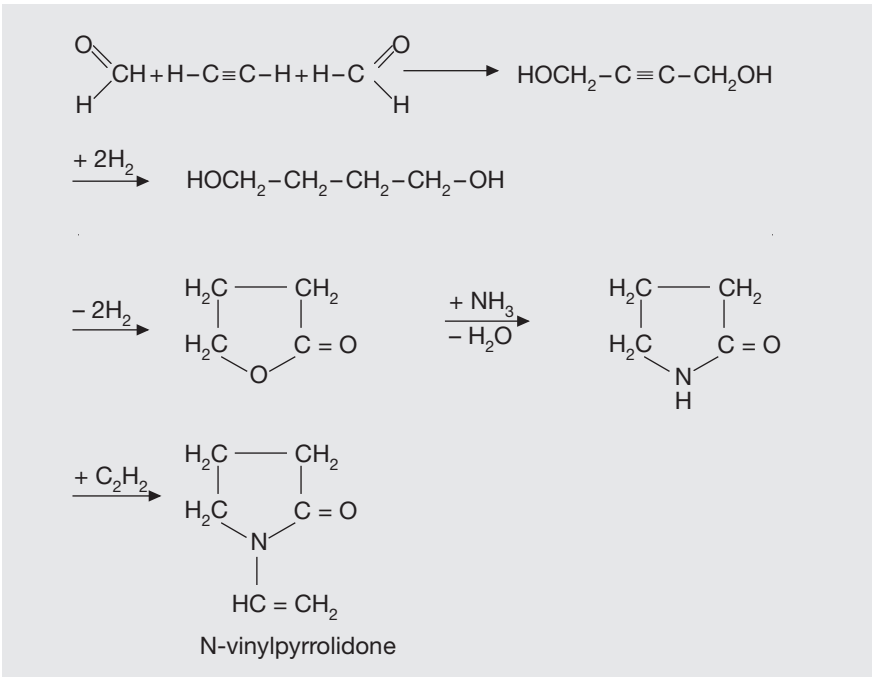


Fig. 1.1: Reppe's synthesis of N-vinylpyrrolidone (C_6H_9NO; Mr 111.1) [669]

The first polymerization product of N-vinylpyrrolidone was soluble polyvinylpyrrolidone, which was patented in 1939. Fig. 1.2 shows one of the mechanisms of polymerization: free-radical polymerization in water using hydrogen peroxide as initiator [1, 141].

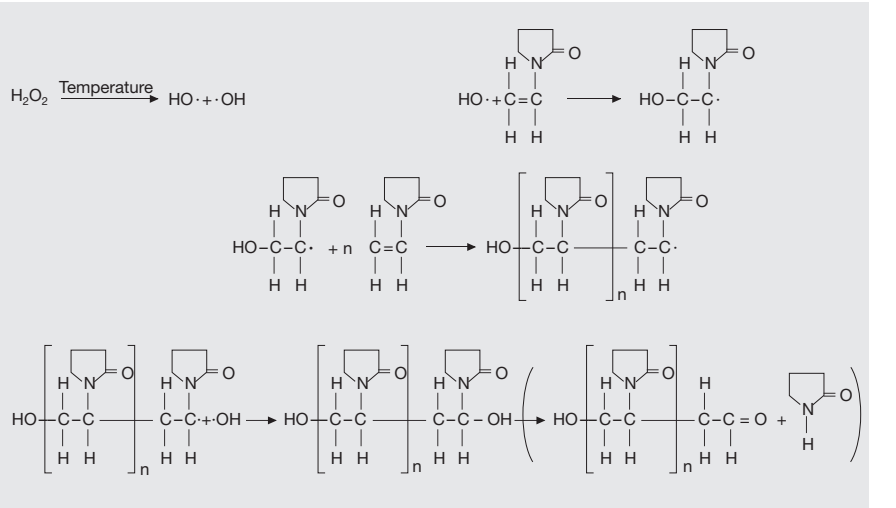


Fig. 1.2: The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in water [669]

The mechanism for terminating the polymerization reaction makes it possible to produce soluble polyvinylpyrrolidone of almost any molecular weight.

Apart from the method of production in water shown in Fig. 1.2, it is also possible to conduct the polymerization in an organic solvent, e. g. 2-propanol. This technology is used today in the production of low-molecular polyvinylpyrrolidone for injectables.

The low and medium-molecular weight grades of soluble polyvinylpyrrolidone are spray-dried to produce the pharmaceutical-grade Kollidon® powders, while the high-molecular weight grade is roller-dried.

Soluble polyvinylpyrrolidone was first used during World War II as a blood-plasma substitute. Although it has excellent properties for this purpose, it has no longer been used for a number of decades. The organism does not metabolize the polymer, with the result that after parenteral administration, small quantities of high-molecular components may remain within the body. This problem does not exist with oral administration.

Today, soluble polyvinylpyrrolidone (e. g. Kollidon®) is one of the most versatile and widely used pharmaceutical auxiliaries.

It is also used in the production of one of the most important topical disinfectants, PVP-Iodine.

1.2 Insoluble polyvinylpyrrolidone (crospovidone, Kollidon® CL grades)

Insoluble polyvinylpyrrolidone (crospovidone) is obtained by popcorn polymerization of N-vinylpyrrolidone [2], which yields a crosslinked polymer [4–6]. The process is illustrated in Fig. 1.3 and uses either an alkali hydroxide at temperatures over 100 °C, which yields some bifunctional monomer, or a small percentage of bifunctional monomer in water to initiate crosslinking of the polymer.

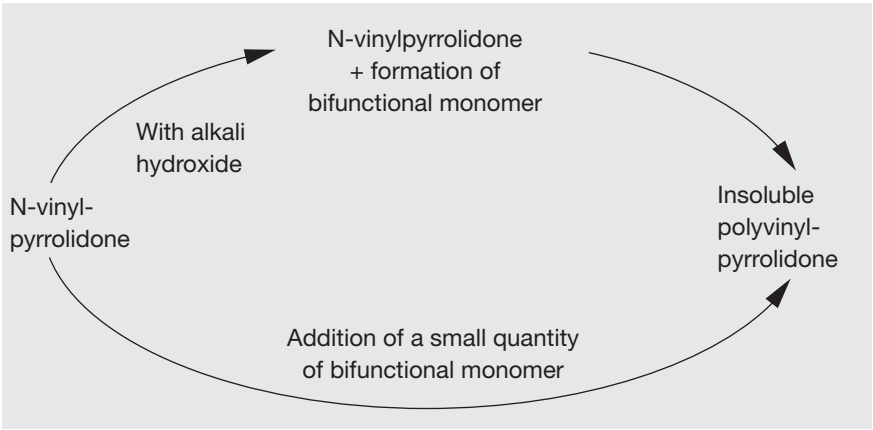


Fig. 1.3: Production processes for insoluble N-vinylpyrrolidone popcorn polymers

A comparison of the infrared spectra of the insoluble popcorn polymer obtained as shown in Fig. 1.3 and that of soluble polyvinylpyrrolidone shows practically no difference, while the infrared spectrum of chemically crosslinked insoluble polyvinylpyrrolidone polymer prepared in the laboratory is quite different, which indicates that the crosslinking in the popcorn polymer is essentially of a physical nature.

Insoluble polyvinylpyrrolidone finds extensive applications in the pharmaceutical and beverage industries as a swelling popcorn polymer with selective adsorptive properties. Its disintegration effect in tablets, its ability to hydrophylize insoluble active ingredients and to adsorb and form complexes are the main properties that make it useful as a pharmaceutical auxiliary. Today, Kollidon® CL is regarded as one of the “superdisintegrants” for tablets.

Further, micronized insoluble polyvinylpyrrolidone is of considerable significance as an active substance against diarrhoea in certain parts of the world. The high bulk density product could be obtained by micronization of normal crospovidone (e. g. Kollidon® CL) and a micronized low bulk density product is available as Kollidon® CL-M.

1.3 Vinylpyrrolidone-vinyl acetate copolymer (copovidone, Kollidon® VA 64 grades)

Water-soluble vinylpyrrolidone-vinyl acetate copolymer contains the two components in a ratio of 6 : 4. It is produced in the same way as soluble polyvinylpyrrolidone, by free-radical polymerization reaction (Fig. 1.4). As vinyl acetate is not soluble in water, the synthesis is conducted in an organic solvent such as ethanol or 2-propanol.

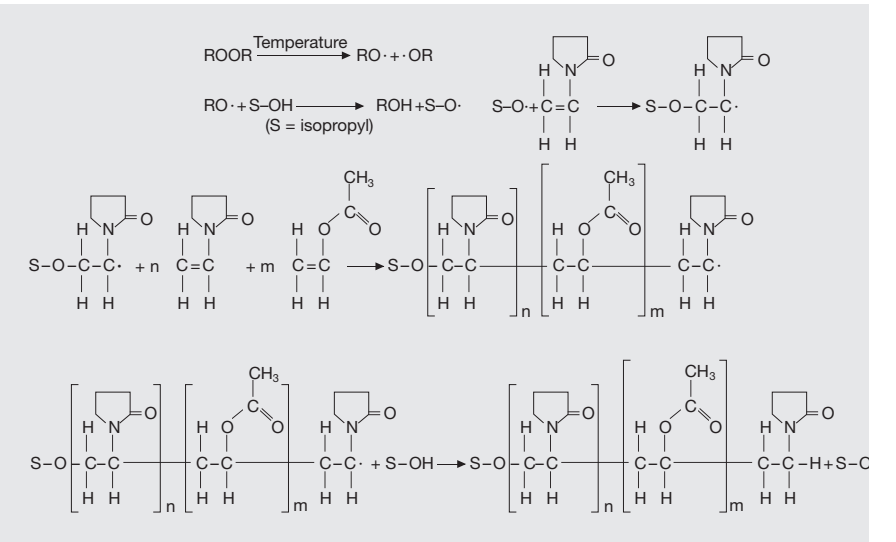
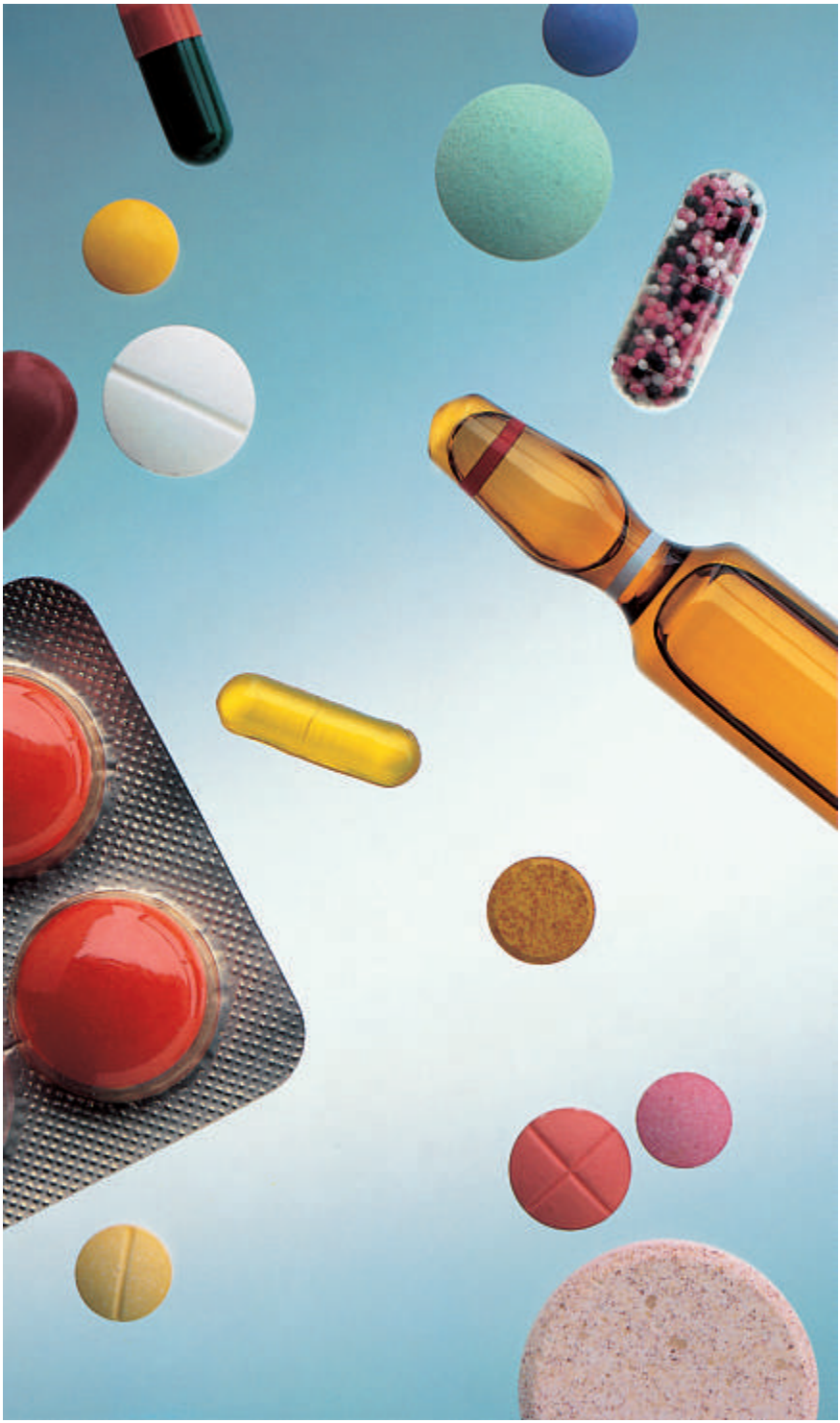


Fig. 1.4: Free-radical polymerization of vinylpyrrolidone-vinyl acetate copolymer (n + 1) : m = 6 : 4 [669]

Because of its vinyl acetate component, Kollidon® VA 64 grades are somewhat more hydrophobic and gives less brittle films. This gives the products their favourable properties as soluble binders or dry binders and film-forming agent, particularly for solid dosage forms.

1.4 Spray dried polyvinyl acetate containing povidone (Kollidon® SR)

Polyvinyl acetate having a average molecular weight of about 450 000 is produced by radical polymerization as aqueous dispersion in water (Kollicoat® SR 30D), addition of about 19 % of povidone (Kollidon® 30) and spray drying.
The addition of about 0.8 % sodium lauryl sulfate and about 0.6 % of silica are further auxiliaries needed as stabilizer and flowability agent to obtain the free flowing spray dried powder Kollidon® SR.



2 Soluble Kollidon® grades (povidone)

2.1 Structure, product range and synonyms

The soluble grades of Kollidon® are obtained by free-radical polymerization of vinylpyrrolidone in water or 2-propanol according to the cGMP regulations, yielding the chain structure of polyvinylpyrrolidone [1, 141].

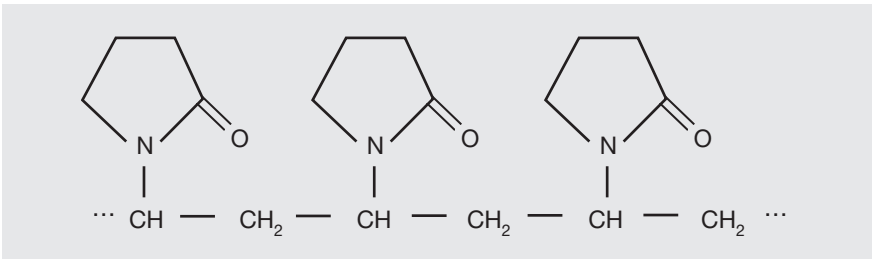


Fig. 2.1: The chemical structure of polyvinylpyrrolidone (povidone) Mr $(111.1)_x$

The current range of soluble Kollidon® grades consists of pharmaceutical grade products with different nominal K-values given in Table 2.1.
All Kollidon® grades are produced in Ludwigshafen, Germany, according to the cGMP regulations. Only Kollidon® 30 also is produced in an identical process in the USA.

Table 2.1: Soluble Kollidon® grades

Product name with nominal (stated) K-value	BASF Article number (Standard packaging size)	PBG number
Kollidon® 12PF*	50444166 (50 kg)	10011265
Kollidon® 17PF*	50029276 (50 kg)	10010750
Kollidon® 25	57254799 (25 kg)	10000996
Kollidon® 30	57254693 (25 kg)	10066831
Kollidon® 30	50017669 (50 kg) USA	10066831
Kollidon® 90F	51031936 (25 kg)	10096088

** PF = free of bacterial entotoxins ("pyrogen free")*

Spray drying technology is used in the production of all the soluble Kollidon® grades with the exception of Kollidon® 90 F. Because of its very high average molecular weight, it has to be dried on a roller.

Soluble polyvinylpyrrolidone is known under the names and abbreviations given in Table 2.2, most of which are specific to the pharmaceutical industry.

The CAS number of polyvinylpyrrolidone is 9003-39-8.

Table 2.2: Official names and abbreviations for soluble polyvinylpyrrolidone

Name/abbreviation	Origin/area of application
Povidone	Current valid Pharmacopoeias (e. g. USP, Ph.Eur., JP)
Polyvidon(e)	Former editions of Pharmacopoeias (e. g. Ph.Fr.)
Povidonum	Pharmacopoeias (e. g. Ph.Eur.)
Polyvidonum solubile	Former edition of the DAC (1986)
Poly(1-vinyl-2-pyrrolidon)	Deutsches Arzneimittelgesetz 1984 § 10 (6)
PVP	General abbreviation, commercial name for cosmetics/technical grade

This book subsequently uses the name “Povidone”.

2.2 Product properties

2.2.1 Description, specifications, pharmacopoeias

2.2.1.1 Description

All the Kollidon® grades are of pharmaceutical purity. They are free-flowing white or yellowish-white powders with different particle sizes (see Section 2.2.4).

The typical odour of the individual products depends on their method of synthesis and is therefore not the same for all the grades of Kollidon®. Kollidon® 25 and Kollidon® 30, for instance, always have a typical amine or ammonia odour, as ammonia is used for neutralisation.

All the soluble grades of Kollidon® give aqueous solutions with very little taste.

2.2.1.2 Specifications, test methods

The soluble Kollidon® grades are tested according to the corresponding monographs for "Povidone" in the actual editions of the pharmacopoeias Ph.Eur. and USP. Their release for sale depends on fulfilment of the requirements of these monographs.

The specifications of 2007 are listed in Table 2.3. Most of the parameters listed are included among the Ph.Eur. requirements. The actual specifications are available on request.The testing and guarantee of a particular microbial status and absence of pyrogens or endotoxins are not required by the pharmacopoeias for povidone.

Kollidon® 12 PF and Kollidon® 17 PF are tested for absence of bacterial endotoxins according to Ph.Eur. method 2.6.14. A 6 % solution of Kollidon® in 0.9 % sodium chloride solution is used. The validation of the endotoxin test (Ph.Eur., method 2.6.14) was done with Kollidon® 17 PF [609].

All soluble Kollidon® grades meet the ICH requirements on residual solvents according to Ph.Eur., chapter 5.4: only Class 3 solvents (2-propanol or formic acid) are likely to be present (< 0.5 %).

Low molecular weight povidone is polymerized in 2-propanol and therefore it contains the radical 2-propanol-vinylpyrrolidone adduct (hydroxy-methyl)-butylpyrrolidone as impurity (structure and determination see Section 2.3.3.7). The level of this impurity depends on the average molecular weight.

Table 2.3: Specifications of the soluble Kollidon® grades

	Kollidon® 12 PF	Kollidon® 17 PF	Kollidon® 25	Kollidon® 30 (Germany, USA)	Kollidon® 90 F
Clarity and colour (10 % in water)	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6	Clear and lighter than B6/BY6/R6
K-value (see 2.3.2.1)	10.2 – 13.8	15.3 – 18.0	22.5 – 27.0	27.0 – 32.4	81.0 – 96.3
Nitrogen content (%, see 2.3.3.7)	11.5 – 12.8	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8
Water (K. Fischer, %)	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0	≤ 5.0
pH (5 % in water)	3.0 – 5.0	3.0 – 5.0	3.0 – 5.0	3.0 – 5.0	4.0 – 7.0
Vinylpyrrolidone (ppm, see 2.3.3.2)	≤ 5	≤ 5	≤ 10	≤ 10	≤ 10
Sulfated ash (%)	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Aldehyde (%, see 2.3.3.3)	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
Heavy metals (ppm)	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10
Hydrazine (ppm)	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
Peroxides (ppm H_2O_2)	≤ 400	≤ 400	≤ 400	≤ 400	≤ 400
2-Pyrrolidone (%, see 2.3.3.2)	≤ 1.0	≤ 1.0	≤ 3.0	≤ 3.0	≤ 1.0
Formic acid (%, see 2.3.3.4)	–	–	≤ 0.5	≤ 0.5	≤ 0.5
2-Propanol (%, see 2.3.3.5)	≤ 0.5	≤ 0.5	–	–	–
Microbial status (see Table 4)	Passes test	Passes test	Passes test	Passes test	Passes test
Bacterial endotoxins (Ph.Eur.) 6 % Solution	≤ 6 I.U./ml (= ≤ 0.1 I.U./mg)	≤ 6 I.U./ml (= ≤ 0.1 I.U./mg)	Not tested	Not tested	Not tested

The microbial status is determined according to Ph.Eur. methods 2.6.12 and 2.6.13. The limits (see Table 2.4) given in the European Pharmacopoeia apply to all the soluble Kollidon® grades.

Table 2.4: Microbial purity requirements (Ph.Eur.,Chapter 5.1.4, Categories 2 + 3A)

– Max. 10^2 aerobic bacteria and fungi/g
– No Escherichia coli/g
– Max. 10^1 enterobacteria and other gramnegative bacteria/g
– No Pseudomonas aeruginosa/g
– No Staphylococcus aureus/g

2.2.1.3 Pharmacopoeias

The soluble grades of Kollidon® comply with the harmonized monographs in the pharmacopoeias of the countries listed in Table 2.5. The list is not comprehensive. The povidone monographs in all national pharmacopoeias of european countries mentioned in Table 2.5 are identical with the povidone monograph in the European Pharmacopoeia Ph.Eur.

Table 2.5: Examples of countries in which the soluble Kollidon® grades fulfil the requirements of the pharmacopoeias

Country	Pharmacopoeia
More than 30 european countries:	Ph.Eur.
Austria	ÖAB
Belgium	Ph.Belg.
France	Ph.Fr.
Germany	DAB
Great Britain	BP
Italy	F.U.
Netherlands	Ph.Ned.
Scandinavia	Ph.Nord.
Spain	F.E.
USA	USP
Japan (only Kollidon® 25, 30 and 90 F)	J.P.
Japan (only Kollidon® 17 PF)	JPE

2.2.2 Solubility, dissolution

One of salient features of the soluble Kollidon® grades is their universal solubility, which extends from extremely hydrophilic solvents, such as water, to hydrophobic liquids, such as butanol.

Today, the use of organic solvents, such as methylene chloride or chloroform is severely restricted, but nevertheless, small quantities of organic solvents are still used by most pharmaceutical companies. The most commonly used are ethanol, 1,2-propylene glycol, 2-propanol or low-molecular macrogol, e.g. Lutrol® E 400. Soluble Kollidon® is miscible in practically all proportions

in these solvents and in water, though, above a certain concentration, the solution obtained has a high viscosity (see Section 2.2.3).
Table 2.6 lists a number of solvents that are capable of forming solutions containing either more than 10 % or not more than 1 % of the soluble Kollidon® grades. The solubility in acetone is 1 – 2 %.

Table 2.6: Solubility of soluble Kollidon® grades (povidone)

More than 10 % in:	Less than 1 % in:
Water	
Diethylene glycol	Ethyl acetate
Methanol	Dioxane
Ethanol	Diethyl ether
n-Propanol	Pentane
2-Propanol	Cyclohexane
n-Butanol	Carbon tetrachloride
Chloroform	Toluene
Methylene chloride	Xylene
2-Pyrrolidone (Soluphor® P)	Liquid paraffin
Macrogol 400 (Lutrol® E 400)	Cyclohexanol
1,2 Propylene glycol	
1,4-Butanediol	
Glycerol	
Triethanolamine	
Propionic acid	
Acetic acid	

The dissolution behaviour and dissolution rate are typical for a polymer. It is recommended to add the powder slowly and in small portions to the solvent with vigorous stirring to ensure that it disperses and dissolves rapidly without forming lumps. Larger lumps dissolve rather slowly. This applies particularly to Kollidon® 90 F, as this high-molecular grade of Kollidon® dissolves more slowly than the low-molecular grades.

The surface tension and the conductivity of solutions with surfactants is not affected by the addition of Kollidon® [492, 616].

2.2.3 Viscosity, K-value

2.2.3.1 Viscosity in water

The viscosity of aqueous solutions of the soluble Kollidon® grades depends on their average molecular weight. This can therefore be calculated from the viscosity, giving the viscosity-average molecular weight (see Section 2.2.6). Fig. 2.2 shows the very considerable differences in dynamic viscosity between solutions of the different Kollidon® grades in water, as a function of their concentration. A 20 % aqueous solution of Kollidon® 12 PF shows hardly any visible difference to pure water, while a 20 % solution of Kollidon® 90 F in water gives high viscosities between 6 and 25 Pa · s.

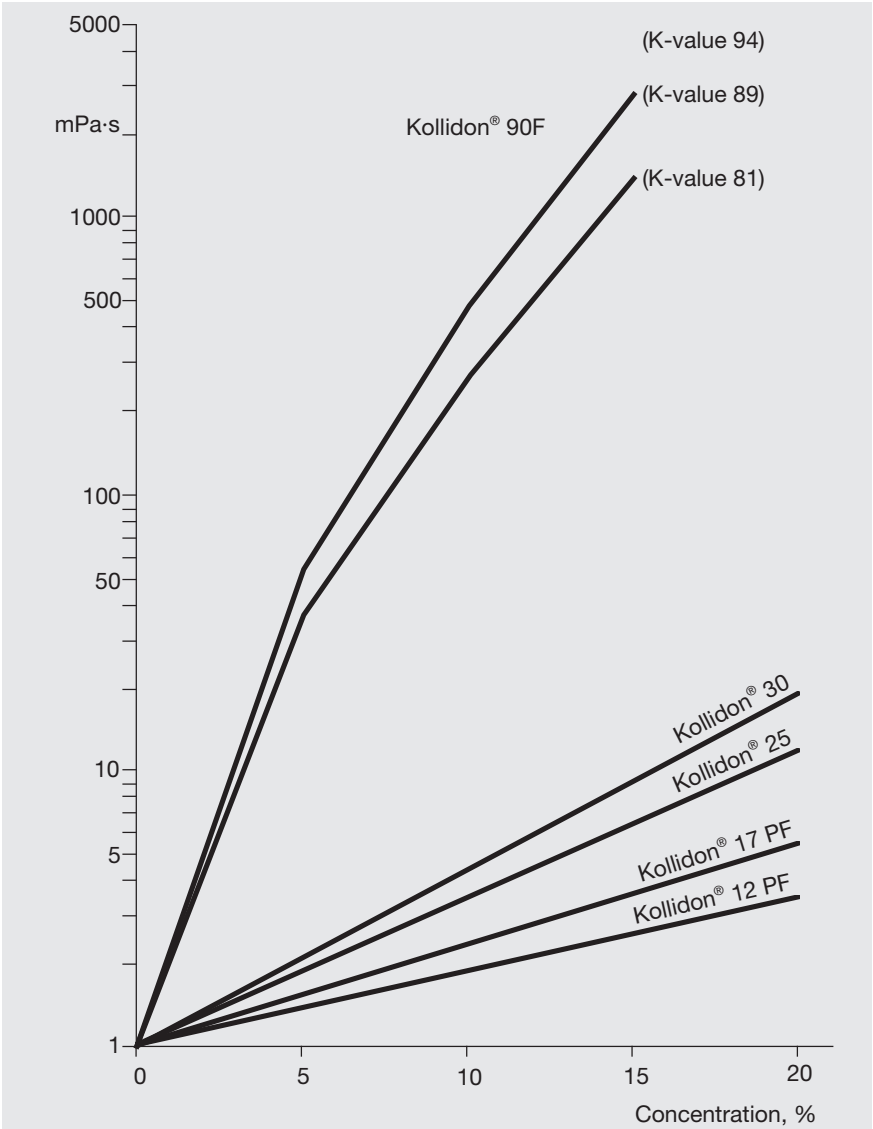


Fig. 2.2: Typical dynamic viscosity curves for the soluble Kollidon® grades in water (capillary viscometer, 25 °C)

Differentiations between the individual Kollidon® types of different molecular weight are made on the basis of their relative viscosity in water and their K-value, which can be calculated from the former according to the Ph.Eur. and USP monographs, “Povidone”. The tolerance limits for the K-value given in Table 2.9 can similarly be calculated from the viscosity limits given in Table 2.7 using the methods given in these monographs.

Table 2.7: Relative viscosity values for povidone in water for calculating the K-value according to Ph.Eur. and USP (capillary viscometer, 25 °C)

Nominal K-value	Concentration	Relative viscosity USP and Ph.Eur. limits
12	5 %	1.222 – 1.361
17	5 %	1.430 – 1.596
25	1 %	1.146 – 1.201
30	1 %	1.201 – 1.281
90	1 %	3.310 – 5.195

If the concentrations of the solutions are increased, the viscosity ranges become even greater, as can be seen from the values given in Table 2.8 for 10 % (g/ml) solutions in water. These typical values have been taken from the former monograph “Lösliches Polyvidon” in Deutscher Arzneimittel-Codex 1986.

Table 2.8: Typical dynamic viscosity values for 10 % (g/ml) solutions of the Kollidon® grades in water at 20 °C

Product	K-value range	Typical viscosity range
Kollidon® 12 PF	11 – 14	1.3 – 2.3 mPa·s
Kollidon® 17 PF	16 – 18	1.5 – 3.5 mPa·s
Kollidon® 25	24 – 27	3.5 – 5.5 mPa·s
Kollidon® 30	28 – 32	5.5 – 8.5 mPa·s
Kollidon® 90 F	85 – 95	300 – 700 mPa·s

The viscosity, e. g. of Kollidon® 30 in water at concentrations up to 10 %, is hardly affected by temperature (Fig. 2.3). At higher concentrations, however, the viscosity decreases rapidly with increasing temperature.

It was reported that most cations increase the viscosity and most of anions decrease the viscosity of povidone K 90 solutions [530]. Some polymers such as carragheenan show a synergistic viscosity increasing effect with Kollidon® 90 F.

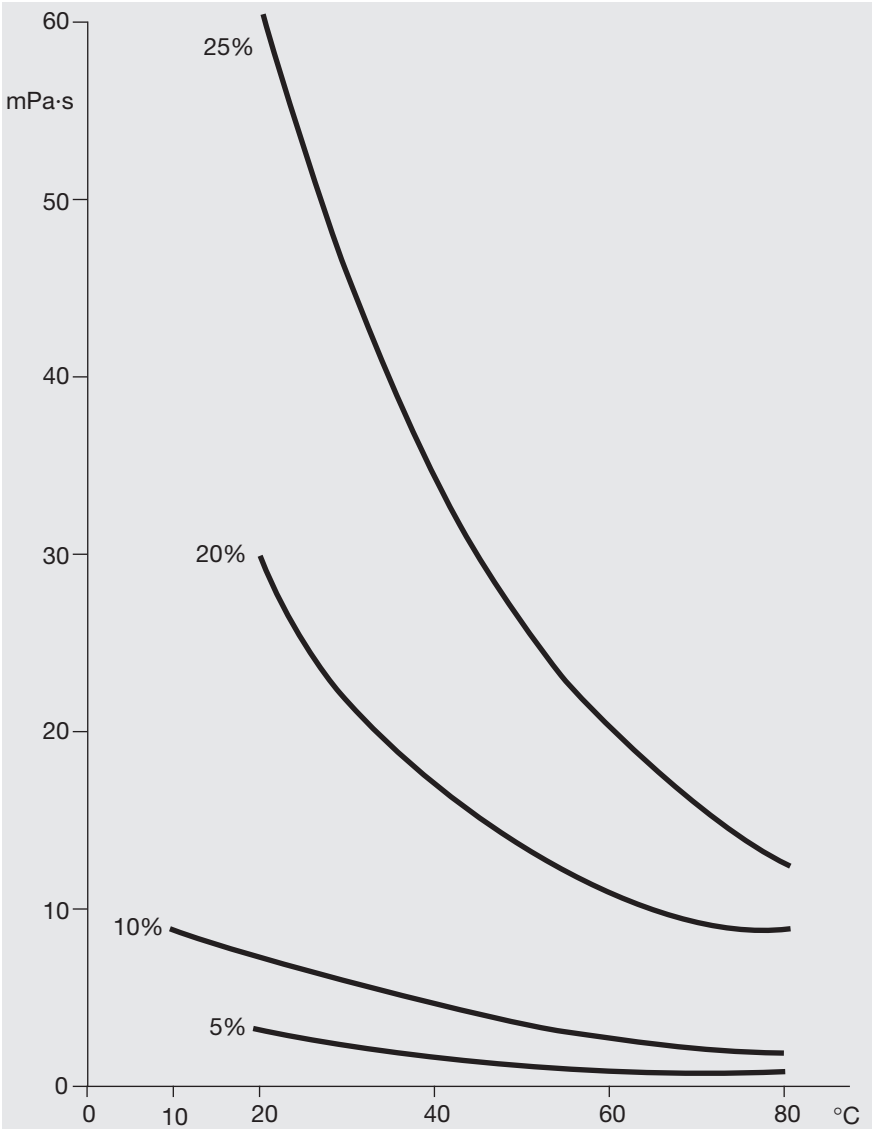


Fig. 2.3: Typical dynamic viscosity of different Kollidon® 30 solutions in water as a function of temperature

It must be emphasized that the viscosity of Kollidon® solutions is independent of their pH over a wide range. Only in extreme cases does this rule not apply: concentrated hydrochloric acid increases their viscosity; strong alkali precipitates povidone. However, it usually redissolves on addition of water.

Highly concentrated solutions of Kollidon® 90 F demonstrate a certain degree of associative thickening and their viscosity is reduced by strong shear forces.

2.2.3.2 K-value

The average molecular weight of the soluble Kollidon® grades is expressed in terms of the K-value in the pharmacopoeias valid in Europe, Japan and the USA [13]. It is calculated from the relative viscosity in water and always forms a part of the commercial name. The K-values specified in Section 2.2.1.2, which are almost identical with the ranges specified in the European Pharmacopoeia (Ph.Eur.), apply to the soluble Kollidon® grades. As can be seen from Table 2.9, the K-value ranges specified in the USP are identical. The USP and Ph.Eur. specify harmonized limits of 85 – 115% for nominal (= stated) K-values up to 15, while for nominal K-values above 15, they allow limits of 90 – 108% of the nominal K-value. The values in Table 2.9 were calculated from the data in Table 2.7 (formula: see Section 2.3.2.1).

Table 2.9: Pharmacopoeia specifications for the K-values of povidone (calculated from Table 2.7)

Nominal K-value	USP and Ph.Eur. specification
12	10.2 – 13.8
17	15.3 – 18.4
25	22.5 – 27.0
30	27.0 – 32.4
90	81.0 – 97.2

Figures 2.4 and 2.5 show the relative viscosity of low to medium- and high-molecular weight povidone as a function of the K-value for 1 % and 5 % solutions in water.

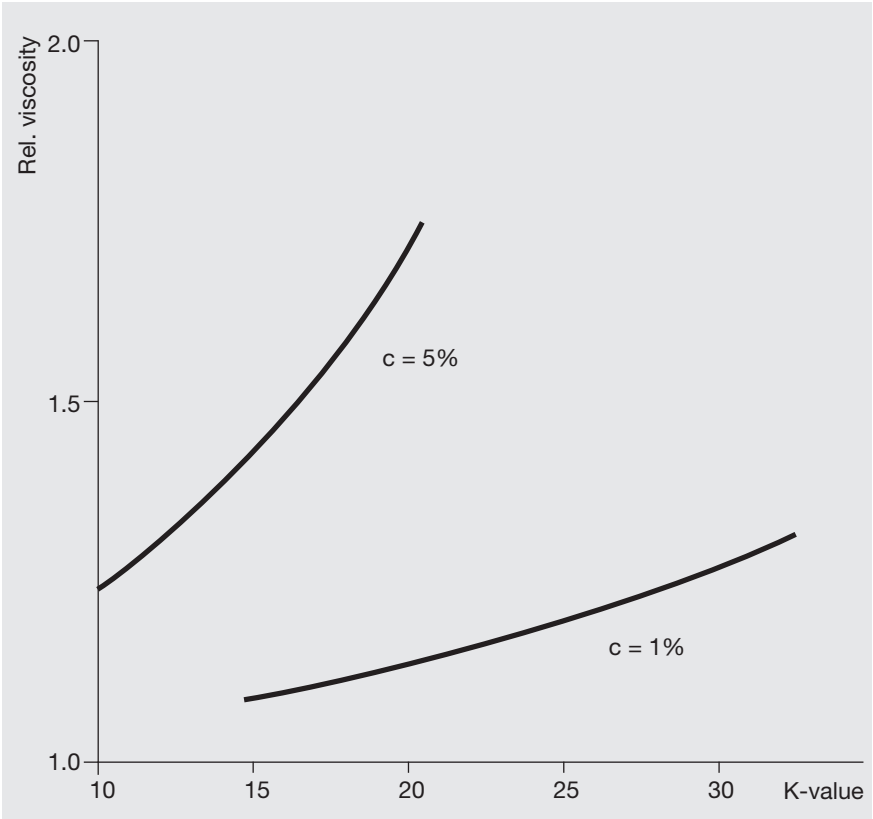


Fig. 2.4: Relative viscosity of povidone in water between K-values 10 and 33 at 25 °C [13]

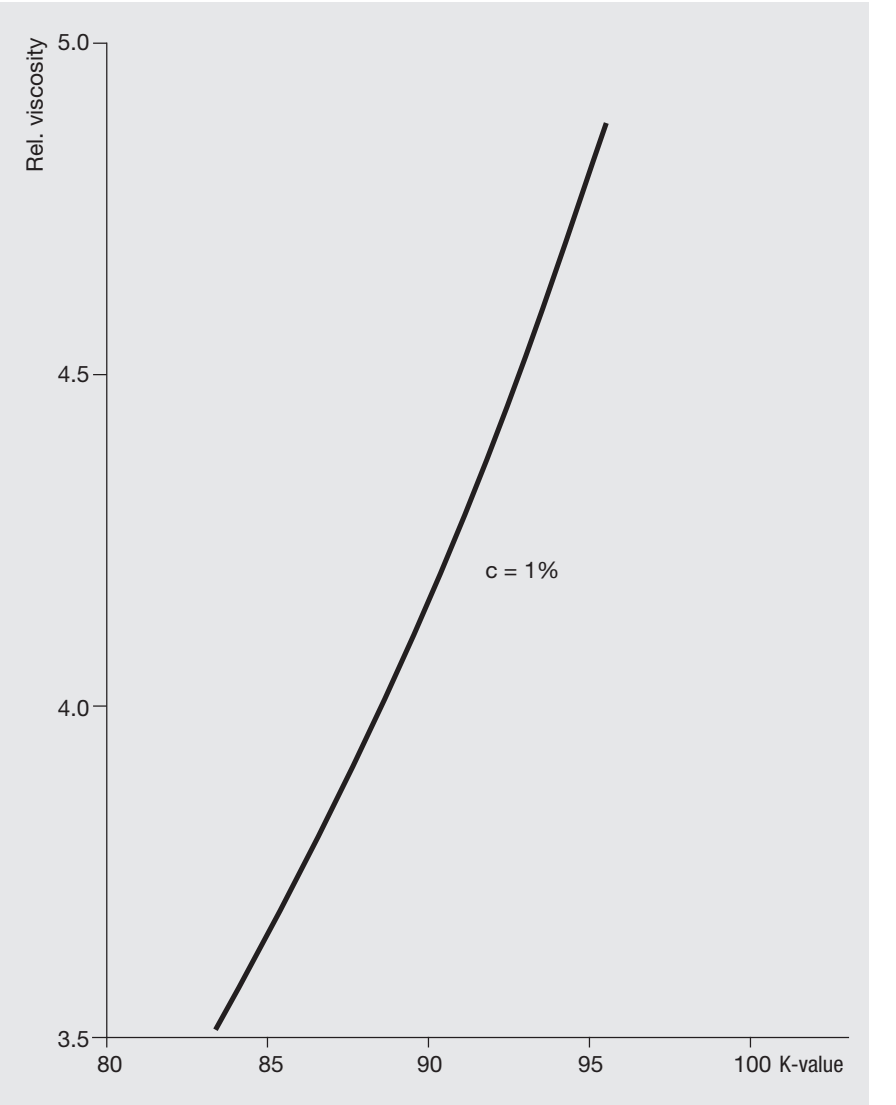


Fig. 2.5: Relative viscosity of povidone in water between K-values 83 – 95 at 25 °C [13]

2.2.3.3 Viscosity in alcohols

The viscosity of alcoholic solutions of soluble Kollidon® grades is significantly higher than that of aqueous solutions, as can be seen from the values in Table 2.10. The solvents most commonly used in tablet granulation, ethanol and 2-propanol, have been selected as examples.

Table 2.10: Dynamic viscosity of 5 % organic solutions of Kollidon® at 25 °C (typical values)

	Ethanol	2-Propanol
Kollidon® 12 PF	1.4 mPa·s	2.7 mPa·s
Kollidon® 17 PF	1.9 mPa·s	3.1 mPa·s
Kollidon® 25	2.7 mPa·s	4.7 mPa·s
Kollidon® 30	3.4 mPa·s	5.8 mPa·s
Kollidon® 90 F	55.0 mPa·s	90.0 mPa·s

The values given in Table 2.10 vary, of course, according to the K-value range of the individual product. Major deviations are found particularly with the high-molecular Kollidon® 90 F.

2.2.3.4 Intrinsic viscosity

The intrinsic viscosity of unfractionated soluble Kollidon® grades can be determined by various methods [212]. In Fig. 2.6, the intrinsic viscosity of Kollidon® 30 is determined by extrapolation to zero concentration of measurements at different concentrations, giving a value of 0.207 dl/g.

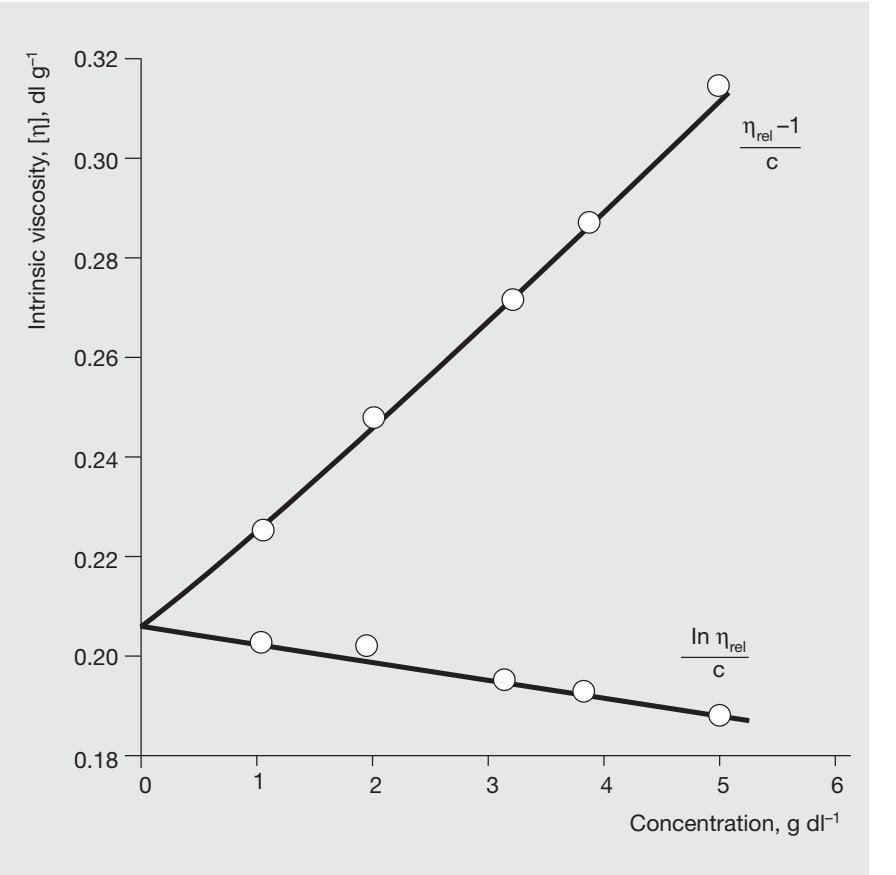


Fig. 2.6: Determination of the intrinsic viscosity [η] of Kollidon® 30 in water by extrapolation [212]

A simpler method for determining the intrinsic viscosity is to calculate it from the relative viscosity at a single concentration [16]:

$$[\eta] = \frac{\eta_{rel} - 1}{c + 0.28\ c\ (\eta_{rel} - 1)} \quad (dl/g)$$

Fig. 2.7 shows the intrinsic viscosity values obtained with this equation for Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30 at different concentrations in water [212]. Kollidon® 17 PF is the only grade in which there is any significant variation in the viscosity between concentrations of 2 % and 5 %.

The values obtained in Fig. 2.6 by extrapolation agree with the results in Fig 2.7.

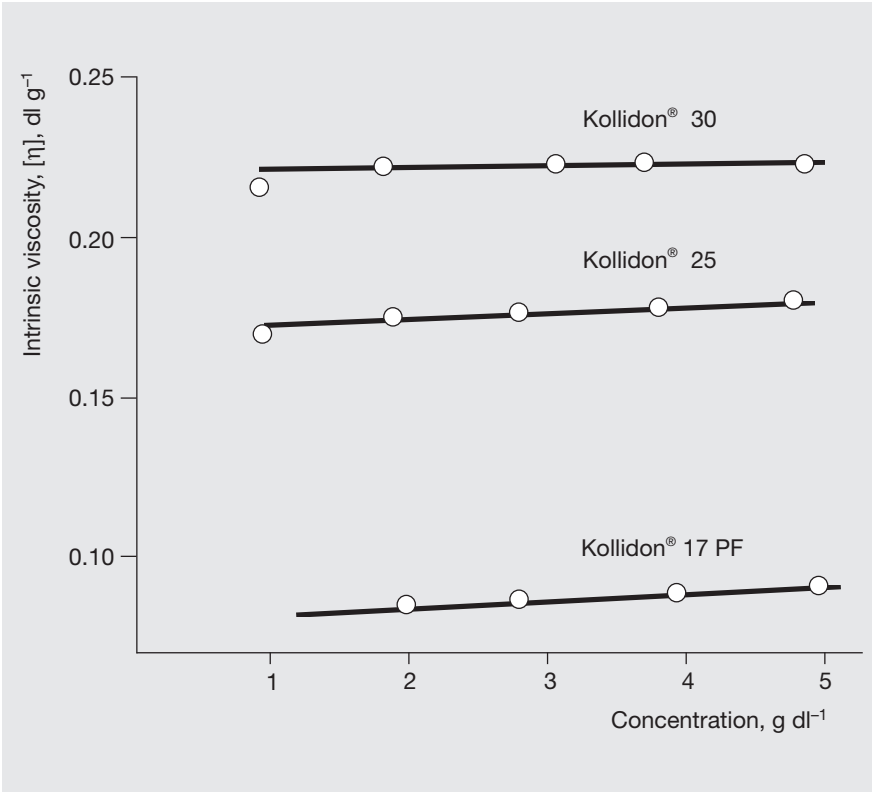


Fig. 2.7: Influence of the concentration of Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30 on their intrinsic viscosities, calculated according to [16]

A further method of determining the intrinsic viscosity from a single measurement is to calculate it from the K-value [223]:

$[\eta] = 2.303\ (0.001\ K + 0.000075\ K^2)$

The values obtained with this equation at different concentrations of Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30 largely agree with those in Fig. 2.7 [212].

A further method for determining the intrinsic viscosity from a measurement at a single concentration has been adopted in the former monographs of Japanese Pharmacopoeia (e. g. J.P. XII). It is based on the relative viscosity of a 1 % solution of povidone in water and is calculated with the following equation:

$$\text{Intrinsic viscosity} = \frac{\ln \eta_{rel}}{\text{Sample concentration (g/dl)}}$$

Table 2.11 shows the ranges prescribed for the intrinsic viscosity in the monographs of former editions of J.P., e. g. J.P. XII.

Table 2.11: Intrinsic viscosity of soluble Kollidon® grades from former editions of J.P.

Kollidon® 25	0.15 – 0.19
Kollidon® 30	0.19 – 0.25
Kollidon® 90 F	1.30 – 1.60

2.2.4 Particle size, particle structure, bulk density

2.2.4.1 Particle size

In the manufacture of solid dosage forms, the particle size distribution of auxiliaries such as Kollidon® can play a major role. This applies particularly to direct compression of tablets. However, the particle size of medium or high-molecular polymers also plays a role when they are used in liquid dosage forms. Table 2.12 lists a number of important factors related to the particle size, that must be considered in the manufacture of pharmaceuticals.

Table 2.12: Important effects of particle size on the manufacture of pharmaceuticals

- A high proportion of fines spoils the flow properties.
- Fines produce dust.
- A high proportion of coarse particles leads to demixing.
- The coarse fraction is unevenly distributed in tablets.
- With high-molecular polymers, a large coarse fraction seriously delays dissolution.
- In direct compression of tablets, the coarse particles of a binder demonstrate a weaker binding effect.

For these reasons, the fine fraction below 50 µm and the coarse fraction above 500 µm have been kept as small as possible in the soluble Kollidon® grades including Kollidon® 90 F. Table 2.13 shows typical values for the individual soluble Kollidon® grades based on measurements with an air-jet screen.

Table 2.13: Typical particle size distribution values for the soluble Kollidon® grades (air-jet screen, 5 min, 20 mbar)

Kollidon® type	Fine fraction smaller than 50 µm	Coarse fraction larger than 250 µm
Kollidon® 25	Approx. 10 %	Less than 5 %
Kollidon® 30	Approx. 10 %	Less than 5 %
Kollidon® 90 F	Less than 10 %	Less than 20 %

2.2.4.2 Particle structure

All soluble Kollidon® grades with exception of roller dried Kollidon® 90 F are spray dried powders and have therefore the typical particle structure of this technology.
The scanning electron micrograph (SEM) of Fig. 2.8 shows as an example of spray dried Kollidon® grades the structure of Kollidon® 30 which are holow and mainly spherical particles. The SEM of Fig. 2.9 shows the completely different particle structure of the roller dried Kollidon® 90 F.

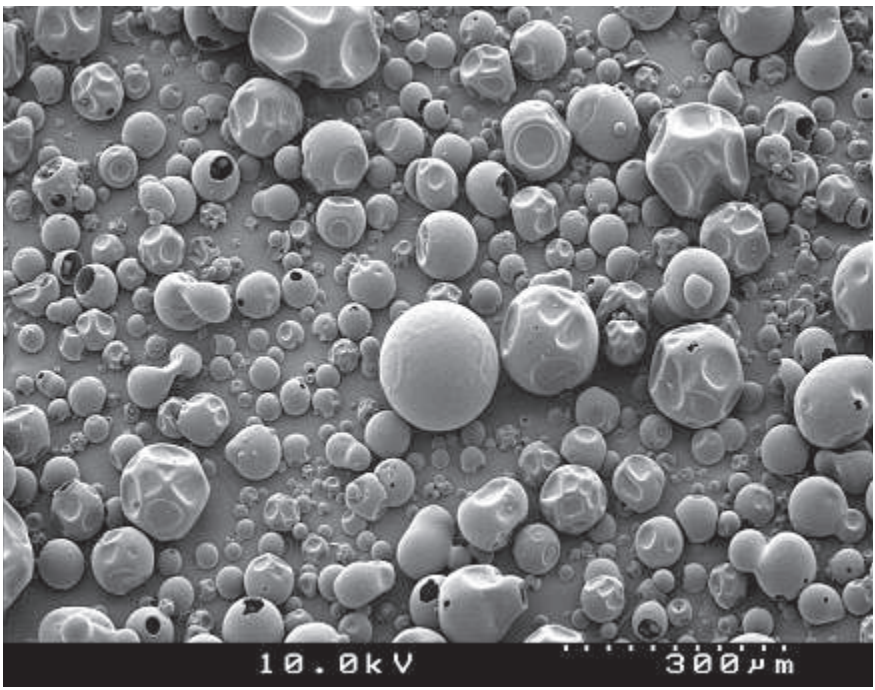


Fig. 2.8: Typical particle structure of Kollidon® 30 (batch 49-0064)

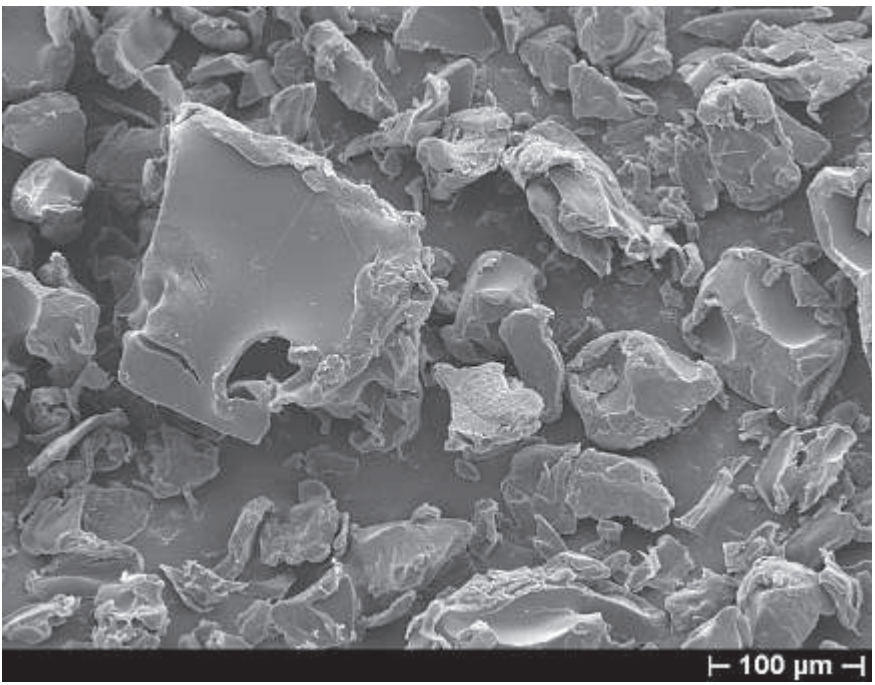


Fig. 2.9: Typical particle structure of Kollidon® 90 F (batch 24-3318)

2.2.4.3 Bulk density, tapped density

The bulk densities of the soluble Kollidon® grades are very similar. Only that of the low-molecular weight Kollidon® 12 PF is somewhat higher. Table 2.14 gives typical values for the bulk and tapped densities of the soluble Kollidon® grades. The Hausner ratio calculated from these densities is in the case of Kollidon® 25 and Kollidon® 30 approximately 1.2.

Table 2.14: Typical values for the bulk and tapped densities of the soluble Kollidon® grades (Ph.Eur., method 2.9.15)

Kollidon® grade	Bulk density	Tapped density (500 taps)
Kollidon® 12 PF	0.55 – 0.65 g/ml	0.65 – 0.75 g/ml
Kollidon® 17 PF	0.40 – 0.50 g/ml	0.50 – 0.60 g/ml
Kollidon® 25	0.40 – 0.50 g/ml	0.50 – 0.60 g/ml
Kollidon® 30	0.40 – 0.50 g/ml	0.50 – 0.60 g/ml
Kollidon® 90 F	0.40 – 0.50 g/ml	0.55 – 0.65 g/ml

2.2.5 Hygroscopicity

Povidone is a hygroscopic substance [140, 197], which can be an advantage or a disadvantage, depending on the application. When it is used as a binder or adhesive, it is an advantage, while for film-coating tablets it is a disadvan-

tage. It has no effect on other applications, e. g. in solutions or suspensions. Fig. 2.10 shows the moisture absorption curve as a function of relative humidity. It applies to all the soluble grades of Kollidon® and is one of the few parameters that is largely independent of the molecular weight. The increase in weight was determined after 7 days' storage at 25 °C over the solutions given in Table 2.15.

Table 2.15: Saturated solutions of salts for establishing constant relative humidity for the determination of moisture absorption

Salt	Relative humidity in the enclosed space above the solutions, %			
	20 °C	25 °C	30 °C	37 °C
Lithium chloride	12	11	11	11
Potassium acetate	24	23	23	23
Magnesium chloride	33	33	32	31
Potassium carbonate	44	43	42	41
Magnesium nitrate	53	52	52	51
Sodium nitrite	66	64	63	62
Sodium chloride	76	75	75	75
Potassium bromide	84	83	82	81
Potassium nitrate	94	93	92	91

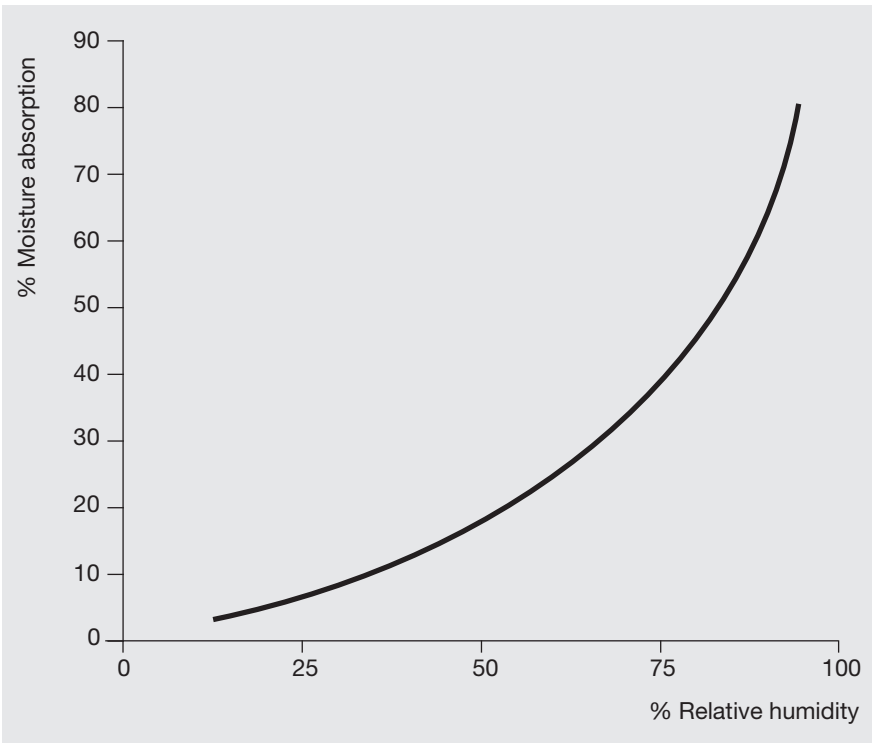


Fig. 2.10: Moisture absorption of the soluble Kollidon® grades at 25 °C after 7 days

The adsorption and desorption curves for the soluble powder grades of soluble Kollidon® at room temperature are not the same. The two curves are shown for comparison in Fig. 2.11 [140].

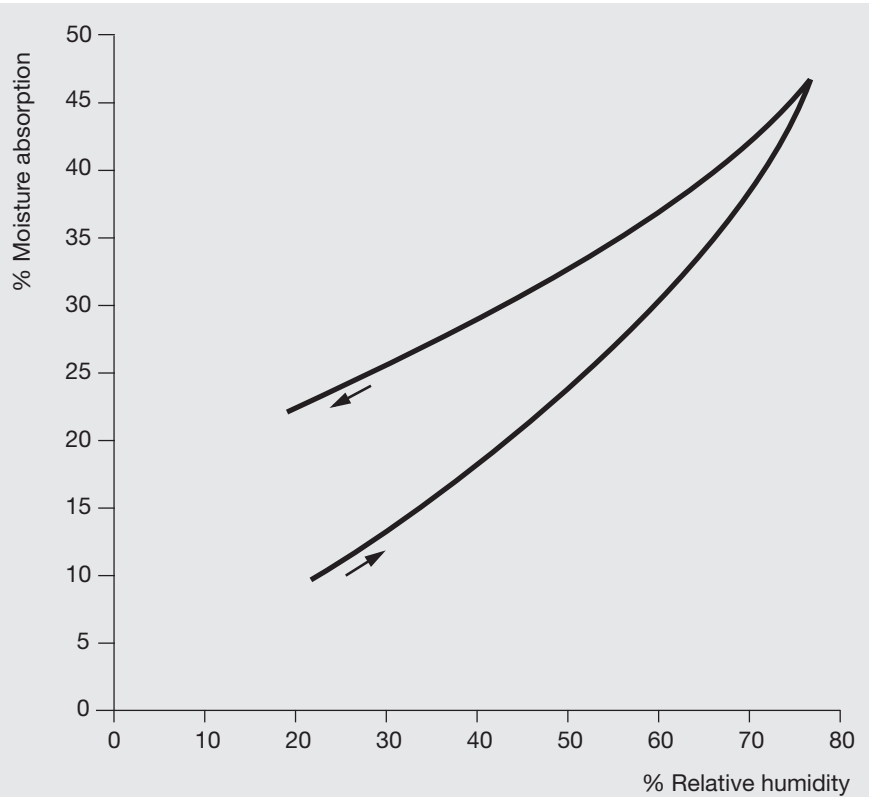


Fig. 2.11: Adsorption and desorption of atmospheric humidity by the soluble Kollidon® grades at room temperature [140]

As the adsorption of water from the air is particularly critical in the film-coating of tablets, it was tested with cast films of Kollidon® 30 that contained 2.5 % glycerol as a plasticizer. Fig. 2.12 shows that a film of this type adsorbs significantly less water within 72 hours at 85 % relative humidity than the powder in Fig. 2.10. The adsorption of moisture from the air is not completed within this period of time.

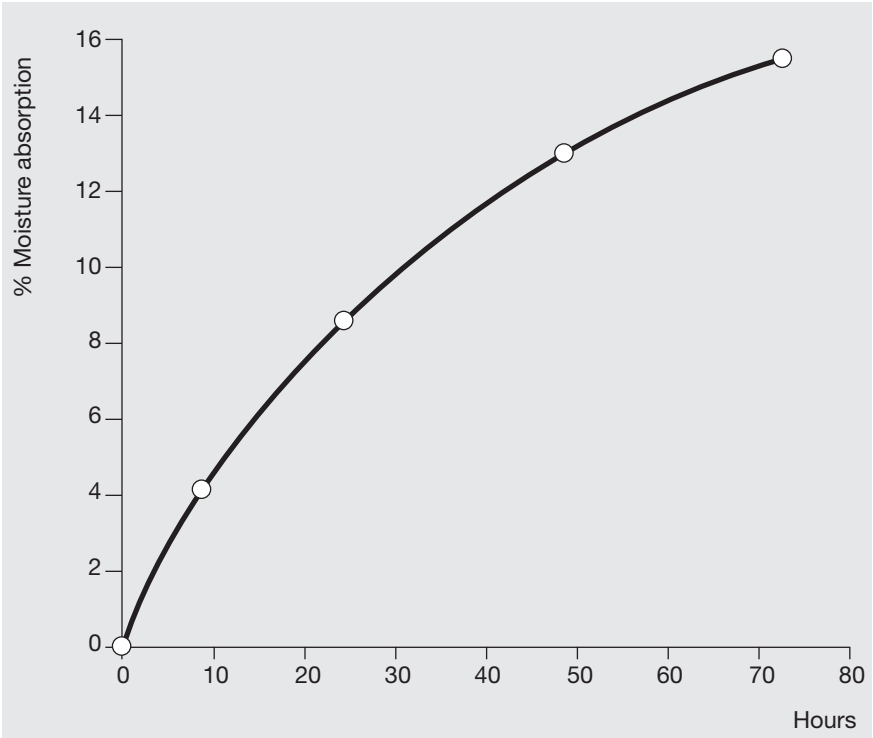


Fig. 2.12: Moisture absorbed by Kollidon® 30 films with 2.5 % glycerol over 72 hours at 25 °C and 85 % relative humidity

2.2.6 Molecular weight

2.2.6.1 Average molecular weight

The average molecular weight of a polymer can be viewed and measured in three different ways [14, 212] as indicated in Table 2.16 below.

Table 2.16: Average molecular weights of polymers and their methods of determination

Type of average molecular weight	Symbol	Method of determination
Weight-average	$\overline{M}w$	Light scattering, ultracentrifuge
Number-average	$\overline{M}n$	Osmometry, membrane filtration
Viscosity-average	$\overline{M}v$	Viscosity

As these methods of determining the average molecular weight are relatively complicated, it is now expressed in terms of the K-value, in accordance with the European and U.S. Pharmacopoeias (see also Section 2.2.3.2).

Fig. 2.13 shows the relationship between the K-value and the weight-average molecular weight $\overline{M}w$, determined by light scattering. A similar graph with the viscosity-average molecular weight $\overline{M}v$ is given in the Section 2.3.2.2.

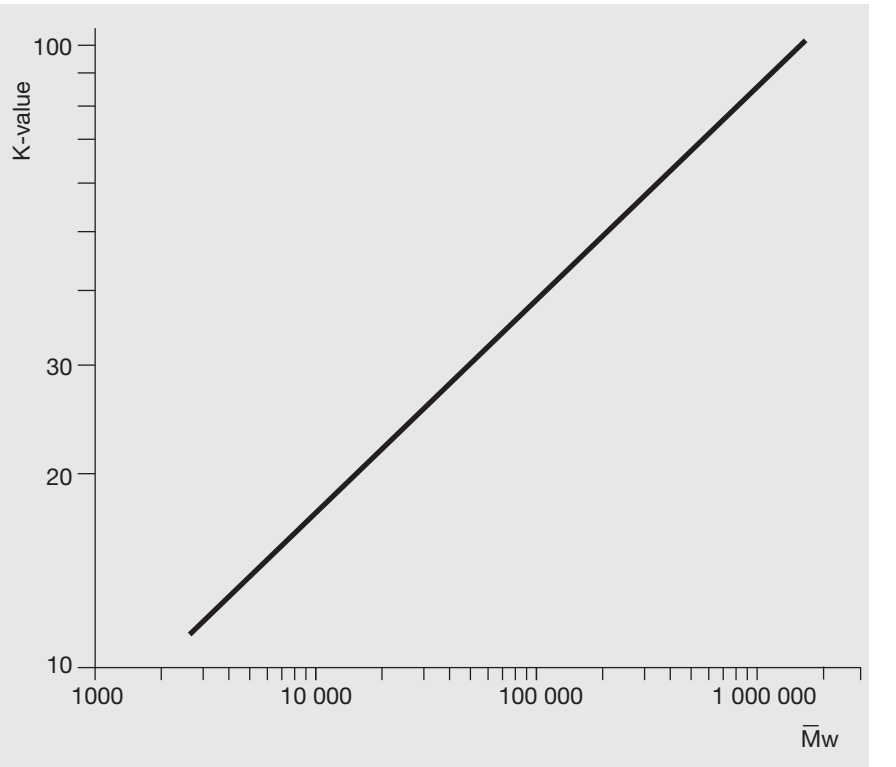


Fig. 2.13: K-value versus weight-average molecular weight, $\overline{M}w$ determined by light scattering

The *weight-average* of the molecular weight, $\overline{M}w$ is determined by methods that measure the weights of the individual molecules. The measurement of light scattering has been found to be the most suitable method for the Kollidon® grades [212]. Values determined by this method are given in Table 2.17. Recent results do not always agree well with older results, as the apparatus used has been improved significantly over the years. The products themselves have not changed, however.

The *number-average* of the molecular weight, $\overline{M}n$ is determined by methods that measure the number of molecules. This value is very seldom determined or published for the Kollidon® grades or for povidone generally. Table 2.17 shows some older values.

Table 2.17: Weight and number-averages of the molecular weights of the soluble Kollidon® grades

Kollidon® grade	Weight-average		Number-average (older determinations)
	Actual values	Measured before 1980	
Kollidon® 12 PF	2 000 – 3 000	2 500	1 300
Kollidon® 17 PF	7 000 – 11 000	9 000	2 500
Kollidon® 25	28 000 – 34 000	25 000	6 000
Kollidon® 30	44 000 – 54 000	40 000	12 000
Kollidon® 90 F	1 000 000 – 1 500 000	700 000	360 000

The *viscosity-average* of the molecular weight, $\overline{M}v$ has attracted some interest recently, as it can be calculated direct from the relative viscosity, the intrinsic viscosity or the K-value (see Section 2.3.2.2). Table 2.18 shows typical viscosity-average values for the different Kollidon® grades.

Table 2.18: Viscosity-average values of the molecular weight, $\overline{M}v$ for the soluble Kollidon® grades, calculated from the K-value [212]

Kollidon® grade	$\overline{M}v$ calculated from the nominal K-value	$\overline{M}v$ calculated from the K-value range given in Ph.Eur.
Kollidon® 12 PF	3 900	2 600 – 5 500
Kollidon® 17 PF	9 300	7 100 – 11 000
Kollidon® 25	25 700	19 300 – 31 100
Kollidon® 30	42 500	31 700 – 51 400
Kollidon® 90 F	1 100 000	790 000 – 1 350 000

2.2.6.2 Molecular weight distribution

Polymers do not consist only of molecules of the same molecular weight, they consist of molecules with a range of molecular weights with, in the ideal case, a Gaussian distribution.

Gel permeation chromatography:

The molecular weight distribution of the soluble grades of Kollidon® can best be determined with the aid of high-performance gel permeation chromatography (GPC). Fig. 2.14 gives a qualitative comparison between Kollidon®17 PF and Kollidon® 30 in a gel permeation chromatogram marked at a mole-cular weight of 35 000.

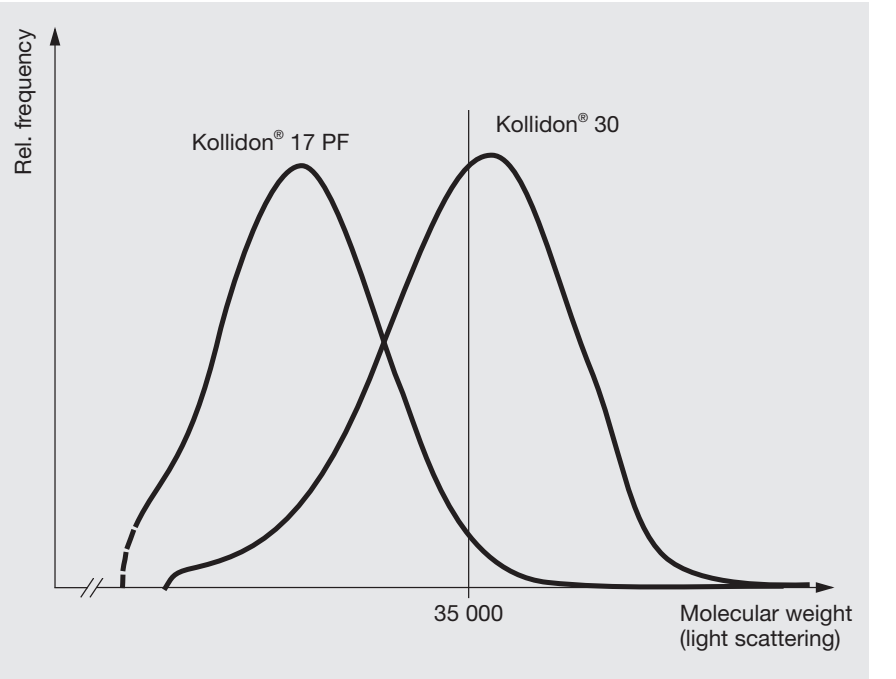


Fig. 2.14: Qualitative comparison of the molecular weight distributions of a batch of Kollidon® 17 PF and Kollidon® 30 (gel permeation chromatogram marked at a molecular weight of 35 000)

Fig. 2.15 shows the integral curve for a gel permeation chromatogram of Kollidon® 17 PF, which gives a quantitative evaluation. The chromatograph was calibrated with povidone calibration fractions with sharply defined molecular weight ranges between 20 000 and 44 000. The curve shows that the cumulative percentage with a molecular weight greater than 35 000 is less than 5 % for Kollidon® 17 PF.

Dynamic light scattering:

A method suitable for the determination of the molecular weight distribution is the dynamic light scattering. The results are completely identical with the results obtained by the gel permeation chromatography because the method is not so sensitive for the low molecular weight part. But the reproducibility is better.

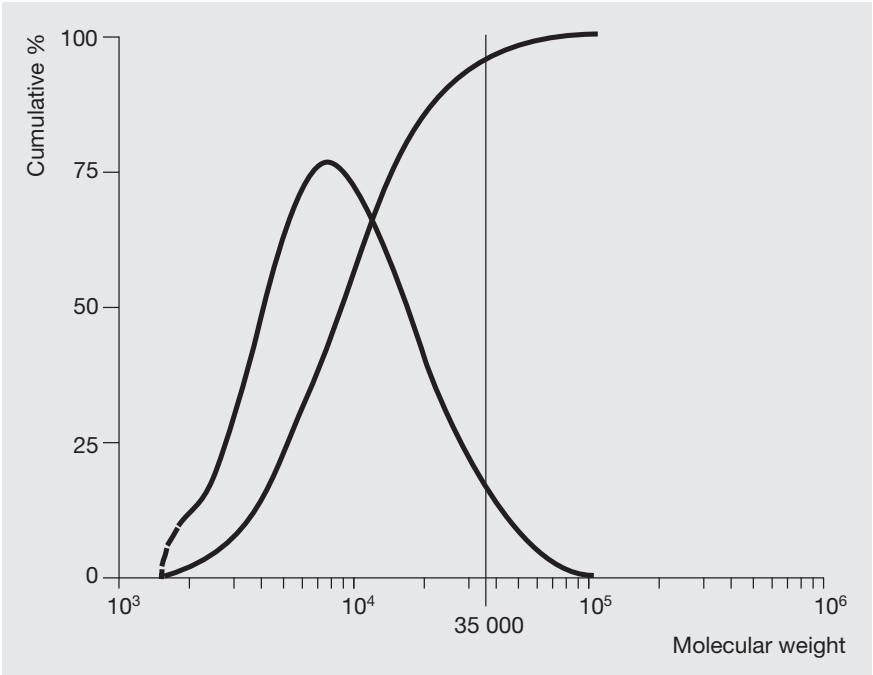


Fig. 2.15: Typical molecular weight distribution curve of Kollidon® 17 PF with integral curve, determined by GPC

Fractionation:

A further means of obtaining information on the distribution of molecular weights in povidone could be fractionation. This technique is very imprecise and gives only the proportions above and below a particular molecular weight. It is based on the difference in solubility of molecules of different sizes in certain solvents and their mixtures, e. g. water and 2-propanol or ether.

This fractionation method has been adopted by the former Japanese Pharmacopoeia (e. g. J.P. XII) as a means of characterizing the high and low-molecular components of povidone. Certain combinations of water, 2-propanol and acetone have been selected for this purpose and limits that have been established empirically are shown in Table 2.19.

Table 2.19: Limits for the low and high-molecular components of povidone according to the former monograph of J.P. XII

Kollidon® grade	Low-molecular fraction	High-molecular fraction
Kollidon® 25	max. 15 %	max. 20 %
Kollidon® 30	max. 15 %	max. 20 %
Kollidon® 90 F	max. 20 %	–

Diafiltration:

In special cases, diafiltration with calibrated membranes can also be used to determine the proportions above and below a particular molecular weight. However, extensive testing has shown that the variations in the results are too great for the method to be readily reproducible, because of differences in pore size from one membrane to another and because of changes in the properties of the membranes after repeated use.

Electrophoresis:

Electrophoresis has also been described in the literature as a technique for determining the molecular weight distribution of soluble Kollidon® grades [377].

2.2.7 Complexation, chemical interactions

2.2.7.1 Complexation

Because of their chemical structure, the Kollidon® grades form chemical complexes with a number of substances, including pharmacologically active ingredients [7, 8, 44c, 99, 103, 106, 179, 220]. Both the solubility and the stability of these complexes vary greatly. They almost always dissolve more readily or more quickly in water than the pure drug substance. Detailed information on the increase in solubility for individual active ingredients is given in Sections 2.4.3 and 2.4.5.

The only known exceptions, i. e. substances that become less soluble or even precipitate, are polyphenols, e. g. tannin, and hexylresorcinol [10, 108]. In general, all complexes with povidone are formed only under acidic conditions and are unstable and can decompose in the alkaline pH range. Typical examples are cobalt [388] and the well known disinfectant, PVP-iodine [9] in which all the iodine, with the exception of a few ppm of free iodine, is complexed.

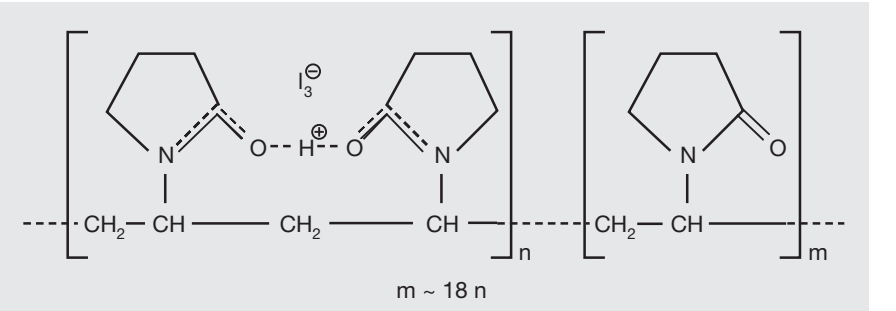


Fig. 2.16: Chemical structure of the PVP-iodine complex [9]

In systematic investigations into the dependence of complex formation on structure, no difference was found between soluble polyvinylpyrrolidone (povidone) and insoluble polyvinylpyrrolidone (crospovidone) for complexes with organic compounds [192].

The complex formation constant can be determined by a number of methods. The most important physical methods are based on adsorption tests, chromatography and dialysis. Table 2.20 lists the constants for a series of substances, mainly pharmaceutically active ingredients, in 0.1 N hydrochloric acid.

Table 2.20: Complex formation constants (l/mol) of a number of pharmaceutical ingredients with soluble Kollidon® grades [192]

Substance	Complex formation constant (l/mol)		
	Sorption	Chromato-graphy	Dialysis
Acetaminophen (= paracetamol)	< 1	< 1	1.5
Acetylsalicylic acid	< 1	< 1	0.7
Benzocaine	< 1	–	–
Benzoic acid	< 1	< 1	0.9
Chloramphenicol	*	*	0.4
Methotrimeprazine	4.6	5.2	3.2
Methylparaben	2.6	< 1	1.8
Riboflavin	< 1	–	–
Salicylamide	1.6	1.5	1.3
Salicylic acid	1.7	1.1	1.5
Sorbic acid	< 1	< 1	0.5
Sulfamoxole	*	*	0.3
Sulfathiazole	< 1	< 1	0.4
Tannic acid	> 1000	> 1000	–
Trimethoprim	*	*	0.2

** Not measurable*

Many further investigations into the formation of complexes by povidone with active ingredients have been described [e. g. 158, 179]. One of the methods used is differential scanning calorimetry [406a – 406c], though this gives little information on the properties of the complex relevant to pharmaceutical technology. Sections 2.4.3 and 2.4.5 list a large number of publications of interest to the pharmaceutical technologist. In normal concentrations, the bonds that active ingredients form with povidone are comparable with those it forms with other auxiliaries in solid dosage forms, e. g. corn starch, cellulose and carboxymethyl cellulose [160]. However, the efficacy of certain preservatives, e. g. thiomersal, is affected, if there is a great excess of povidone [7, 11].

The influence that complexation can have on the absorption of an active ingredient by the body can be estimated with the aid of Fig. 2.17, if the concentration of Kollidon® and the complexation constant are known [192].

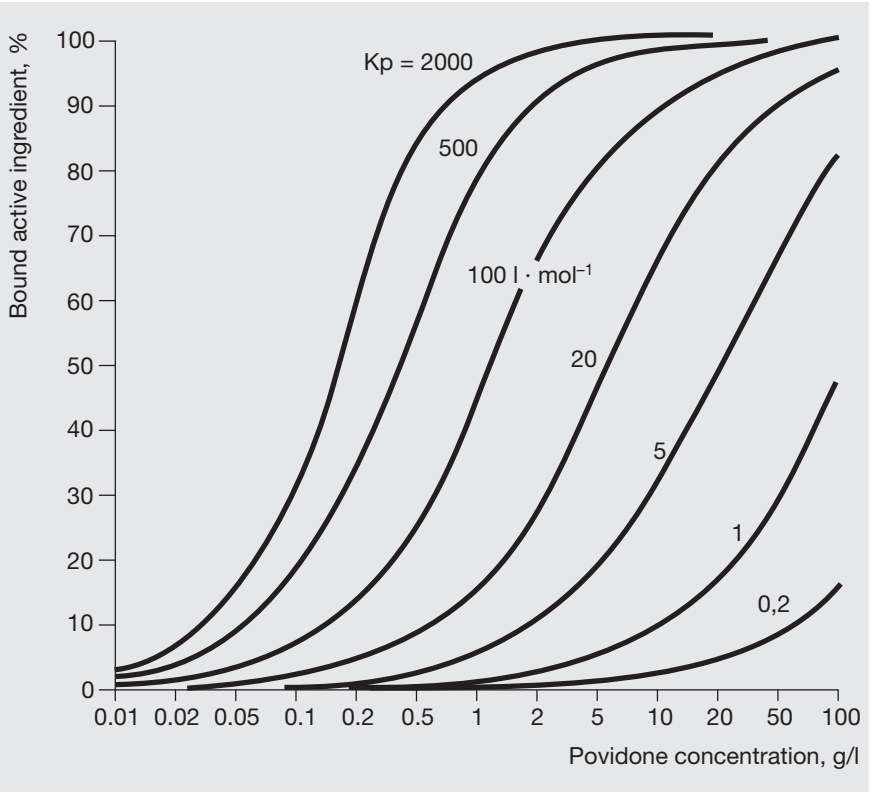


Fig. 2.17: Curves of complexation of active ingredients by povidone against povidone concentration for different complexation constants, Kp

The use of Fig. 2.17 in practice is illustrated in the following example: in a 4 % aqueous solution of povidone (= 40 g/l), it was found by ultrafiltration that 48.1 % of the salicylic acid was complexed [179]. If these values are applied to Fig. 2.17, a complexation constant of about 2.9 l/mol is obtained. Even if high values for gastro-intestinal povidone concentration, e. g. 0.5 g/l are taken, the complexed proportion of salicylic acid is less than 1 % and can therefore be ignored.

As all the pharmaceutically active substances, apart from tannin, that have been checked to date have shown complexation constants of less than 10 l/mol, the above example for salicylic acid can be applied to almost all active ingredients. Complexation is widely used in pharmaceutical technology (Table 2.21).

Table 2.21: Use of the complexation of active ingredients with soluble Kollidon® grades in pharmaceutical technology

1. Improvement of the solubility of the active ingredient in liquid dosage forms (Section 2.4.5)		
Examples:	antibiotics	melphalan
	iodine	metronidazol
	acetaminophen	taurolidine
	sulfonamides	trimethoprium
2. Acceleration of the dissolution rate of the drug from solid dosage forms (Section 2.4.3)		
Examples:	dihydroergotamine	
	nabilone	
	nifedipine	
3. Reduction of the toxicity of active ingredients (Section 2.4.8.4)		
Examples:	iodine	
	oxytetracycline	
	endotoxins (of microbiological origin)	

2.2.7.2 Further chemical interactions

Povidone can become insoluble as a result of crosslinking, particularly at higher temperatures, if it is combined with strongly alkaline substances such as lithium carbonate or sodium hydroxide [141]. In extreme cases, this could result in an increase in viscosity in liquid dosage forms or delayed bioavailability in tablets and capsules [217].

The soluble Kollidon® grades contain peroxides within the limits of the specification, though the content can increase in the course of storage. This can interfere with certain active substances such as ergot alkaloids and diagnostics.

2.2.8 Osmotic pressure, sterilization by filtration (Kollidon® 12 PF, Kollidon® 17 PF)

2.2.8.1 Osmotic pressure

The osmotic pressure of solutions is of particular importance with parenteral administration. In the case of the human blood serum it is about 7.5 bar at 37 °C. It is not very affected by the molecular weight and the concentration of Kollidon® 12 PF and Kollidon® 17 PF. The simplest method for determining the osmotic pressure uses the Van't Hoff equation.

Table 2.22: Van't Hoff equation for calculating osmotic pressure, P

$$P = \frac{c \cdot R \cdot T}{\overline{M}n} \quad \text{(bar)}$$

c = concentration in g/l
R = gas constant 0.0821 l bar/degree
T = absolute temperature, °K
$\overline{M}n$ = number average of the molecular weight

The calculated osmotic pressure values given in Table 2.23 were obtained for solutions of Kollidon® 12 PF and Kollidon® 17 PF in water, using the equation given in Table 2.22. These values apply to pure povidone. As Kollidon® contains only traces of impurities the osmotic pressure is hardly affected. This is confirmed by comparing the values measured for Kollidon® 17 PF with those calculated, in Table 2.23.

Table 2.23: Osmotic pressure of Kollidon® 12 PF and Kollidon® 17 PF solutions, calculated according to Table 2.22, and measured

Product	Concentration in water	Osmotic pressure (calculated)	Osmotic pressure (measured)
Kollidon® 12 PF	5 %	approx. 1 bar	–
Kollidon® 12 PF	10 %	approx. 2 bar	–
Kollidon® 17 PF	5 %	approx. 0.5 bar	0.53 bar
Kollidon® 17 PF	10 %	approx. 1 bar	1.06 bar

2.2.8.2 Sterilization by filtration

It is important that injection solutions that contain Kollidon® 12 PF or Kollidon® 17 PF can be sterilized by filtration. The feasibility of filtering these solutions is mainly determined by the concentration of these two Kollidon® grades. The viscosity evidently plays a subordinate role, as this is always less than 5 mPa·s for Kollidon® 17 PF up to a concentration of 15 % in water. With Kollidon® 12 PF it is even lower (see Section 2.2.3.1). Taking a batch of Kollidon® 17 PF as an example, it can be seen from Fig. 2.18 that the filtration time depends very much on the concentration. The results are based on laboratory measurements on 500 ml of solution under a vacuum of 90 mbar.

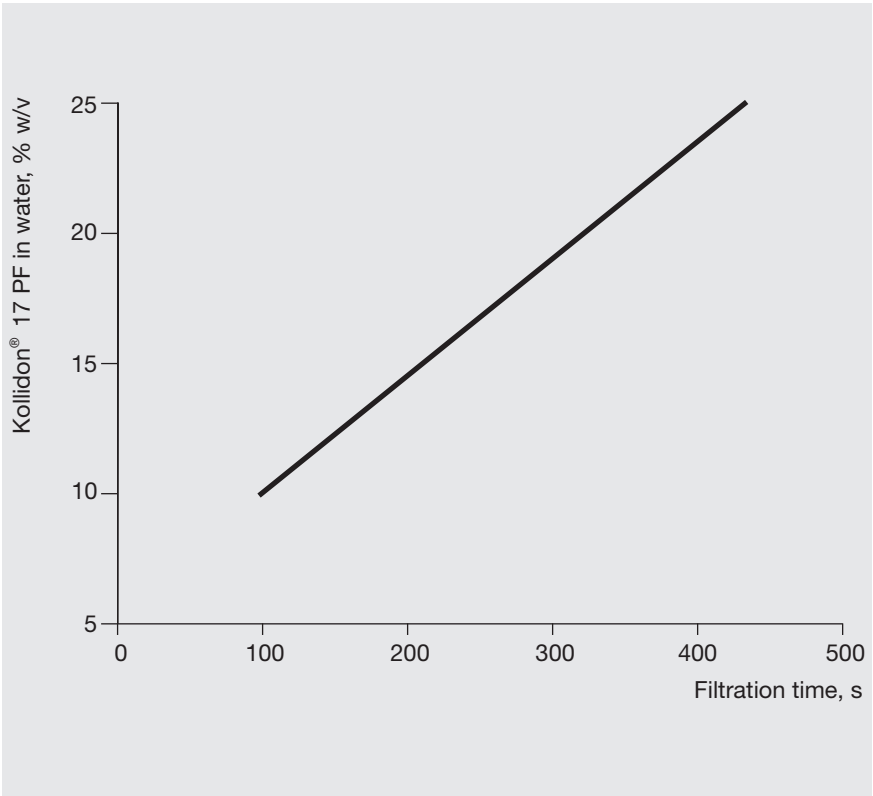


Fig. 2.18: Influence of the concentration of Kollidon® 17 PF in water on the filtration time through a 0.45 µm filter of 47 mm diameter (500 ml solution, vacuum 90 mbar, room temperature)

2.2.9 Stability, storage, packaging

2.2.9.1 Stability of the pure products, packaging

The soluble Kollidon® grades, with exception of Kollidon® 90 F, have very good storage stability in the pure form. Table 2.24 lists the standard packaging and the minimum stabilities in the original sealed container at room temperature when these are stored and tested according to the requirements of the pharmacopoeias (see Section 2.2.1.2). The PE-aluminium inliners are hermetically sealed under nitrogen and vacuum.

Table 2.24: Packaging and guaranted minimum stability ("retest date") of the soluble Kollidon® grades in the original containers (max. 25 °C, Ph.Eur. and USP requirements

Product	Standard packaging	Minimum shelf life
Kollidon® 12 PF	50 kg PE drum + PE inliner	More than 3 years
Kollidon® 17 PF	50 kg PE drum + PE inliner	More than 3 years
Kollidon® 25	25 kg cardboard box + PE-Alu inliner	More than 3 years
Kollidon® 30 (Germany)	25 kg cardboard box + PE-Alu inliner	More than 3 years
Kollidon® 30 (USA)	50 kg PE drum + PE inliner	More than 3 years
Kollidon® 90 F	25 kg cardboard box + PE-Alu inliner	More than 2 years

The lower stability of Kollidon® 90 F, compared with the other grades, is due to a slow decrease in the K-value. All the other parameters change just as little over a period of years, as those of other grades. If Kollidon® 90 F is stored under cool conditions or if the original packaging never was opened the K-value decreases much less and the peroxides level remains much lower.

In the presence of atmospheric oxygen, the peroxide content of all the Kollidon® grades slowly increases, but remains below the value of 400 ppm, calculated as H_2O_2, specified in Ph.Eur., within the storage periods given in Table 2.24.

The influence on the Kollidon® powders of sterilization with gamma radiation was determined on a batch of Kollidon® 17 PF. Table 2.25 shows that this form of sterilization does not change either the molecular weight or the molecular weight distribution.

Table 2.25: Influence of gamma radiation on the stability of the molecular weight of Kollidon® 17 PF powder

	Molecular weight	
Radiation	Number average	Weight average
None	4700	9500
10 kGy	4700	9500
25 kGy	4700	9600
50 kGy	4700	9600

2.2.9.2 Stability in solid dosage forms

Because of the good stability of Kollidon® on its own, its stability in solid dosage forms is usually also good.

Up to now, only isolated cases have become known, in which the stability of povidone has deteriorated in solid dosage forms. One of these is the combination with strongly alkaline substances, which can cause the polymer to crosslink, particularly at elevated temperatures [141]. As the example of lithium carbonate has shown many years ago, this can lead to a reduction in bioavailability [217].

The peroxides formation was studied in tablets based on microcrystalline cellulose, magnesium stearate and 5 % Kollidon® 30 at room temperature. The low level of peroxides decreased continuously during 2 years to less than 25 % of the initial value in all tablets obtained by direct compression or by wet granulation.

2.2.9.3 Stability in liquid dosage forms

A change in colour is sometimes observed in aqueous solutions of the soluble Kollidon® grades after storage or heating, e. g. during sterilization. The yellow or brown-yellow colour is formed as a result of oxidation and can therefore be prevented by the addition of a suitable antioxidant.

The change in colour of a 20 % solution of Kollidon® 17 PF in water was from a slight yellow tint (colour reference solution Yellow 7 according to Ph.Eur.) to stronger yellow (colour reference solution Yellow 4) after thermal sterilization at 120 – 121 °C for 20 min. The addition of 0.2 % of sodium bisulfite provided excellent colour stabilization. Ascorbic acid cannot be used as an antioxidant as it undergoes hydrolysis itself, giving rise to an even darker yellow-brown colour.

A 10 % solution of Kollidon® 30 in water could be stabilized by the addition of 0.5 % of cysteine or 0.02 % of sodium sulfite against discolouration by heat sterilization.
Table 2.26 shows in a storage test of aqueous solutions of Kollidon® 30 and Kollidon® 90 F at 40 °C that the application of nitrogen is not effective because it contains always some residues of oxygen. The formation of peroxides, free vinylpyrrolidone or turbity is no problem and the influence of the pH is negligible. Similar results were found with respective solutions of Kollidon® 17 PF.

If sodium bisulfite is to be used as an antioxidant in parenteral preparations, the legal situation in the respective country must be considered.

Table 2.26: Storage of solutions of 10 % of Kollidon® 30 and Kollidon® 90 F in water at different pH's in the dark during 3 months at 40 °C (Ph.Eur. methods)

Parameter	pH	Initial values	After storage under air	After storage under nitrogen	After storage with addition of 0.5 % cysteine
Kollidon® 30					
Colour* (B = brown, Y = yellow)	2.0 6.4 9.0	B 6–7 B 6–7 B 6–7	Y 4–5 Y 3–4 BY 4–5	Y 3–4 Y 3–4 Y 4–5	BY 5–6 Y 5–6 B 6–7
Clarity**	2.0–6.4 9.0	1.3 FTU 1.5 FTU	< 1 FTU 1.3 FTU	< 1 FTU 1.3 FTU	< 1 FTU 1.1 FTU
Peroxides	2.0 6.4 – 9.0	70 ppm 30 ppm	20 ppm 20 ppm	< 20 ppm < 20 ppm	< 20 ppm < 20 ppm
Vinylpyrrolidone	2.0–9.0	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm
Kollidon® 90 F					
Colour* (B = brown, Y = yellow)	2.0 6.4	B 6–7 B 6–7	BY 6–7 BY 5–6	BY 5–6 BY 4–5	BY 6–7 B 7
Clarity**	2.0 6.4	1.0 FTU 1.3 FTU	1.1 FTU 1.4 FTU	1.6 FTU 1.3 FTU	1.2 FTU 2.7 FTU
Peroxides	2.0	180 ppm	180 ppm	140 ppm	< 20 ppm
Vinylpyrrolidone	≤ 2.0–6.4	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm

* *In the Ph.Eur. colour reference solutions (e.g. yellow and brown) the number indicates the colour intensity: the higher the number the less intensive the colour of the solution.*

** *The definition of the clarity like water according to Ph.Eur. corresponds to ≤ 2.0 FTU (= Formazine Turbity Unit)*

2.2.9.4 Stability of the molecular weight in liquid dosage forms after thermal sterilization and storage

As the molecular weight determines many of the properties of the soluble Kollidon® grades that affect their use, it is worth knowing that it is not changed by storage or heating. In solutions, a change in the relative viscosity most readily reveals an increase or decrease in the average molecular weight. Extensive tests have been conducted with Kollidon® 12 PF and Kollidon® 17 PF solutions (Table 2.27), in which the viscosity was measured to determine the influence of sterilization on the average molecular weight (Table 2.28). No change was found even at pH as high as almost 10.

Table 2.27: Aqueous solutions used to test for changes in the average molecular weight after sterilization or storage

Solution No.	Kollidon® 12 PF	Kollidon® 17 PF	pH (adjusted)	Sodium bisulfite addition
1	–	10 %	4.0	–
2	–	10 %	9.0	–
3	–	10 %	9.9	0.17 %
4	10 %	–	6.1	–
5	20 %	–	6.1	–
6	20 %	–	7.0	0.4 %

The influence of storage on the average molecular weight was tested under stress conditions by keeping the solutions in Table 2.27 for four weeks at 60 °C and 70 °C. Even after this accelerated storage test, no increase or decrease in the mean molecular weight of Kollidon® 12 PF and Kollidon® 17 PF could be measured.

Table 2.28: Effect of sterilization (20 min at 120–121 °C) on the relative viscosity and the average molecular weight of aqueous solutions of Table 2.27 ($\bar{M}v$ calculated according to Section 2.3.2.2)

Solution No.	Rel. viscosity (25 °C)		Average molecular weight ($\bar{M}v$)	
	Before sterilization	*After* sterilization	*Before* sterilization	*After* sterilization
1	2.10	2.09	8870	8770
2	2.08	2.08	8650	8650
3	2.11	2.07	8990	8540
4	1.65	1.67	4100	4290
5	2.67	2.70	4360	4440
6	2.65	2.62	4290	4200

To determine the influence of storage on the molecular weight distribution, gel permeation chromatography separations were conducted on new and up to 5-year-old, commercially available pharmaceutical specialities that contained Kollidon® 17 PF or Kollidon® 25, with samples from the original Kollidon® batches for reference. No change in the molecular weight distribution of both Kollidon® grades could be found.

2.2.9.5 Stability of the molecular weight in liquid dosage forms after sterilization with gamma radiation

Unlike the Kollidon® powders, aqueous solutions of Kollidon® are sensitive to gamma radiation. This was checked with Kollidon® 17 PF and Kollidon® 30. Table 2.29 presents the results of molecular weight measurements on Kollidon® 17 PF that was exposed, as the 10 % aqueous solution, to radiation of different intensities. A clear increase in the average molecular weight and a broadening of the molecular weight distribution were found.

Table 2.29: Influence of gamma radiation on the molecular weight of 10 % solutions of Kollidon® 17 PF

Radiation dose	Molecular weight	
	Number average	Weight average
None	4 800	9 600
10 kGy	4 900	11 100
25 kGy	5 300	13 200
50 kGy	5 900	19 500

There are cases in which the molecular weight of the Kollidon® grade used does not change, as it has been found that certain substances such as iodine or iodides can prevent this undesirable effect. Further, no increase in the molecular weight of a solution of Kollidon® 30 in a mixture of 90 % macrogol 400 (Lutrol® E 400) and 10 % water was observed after gamma radiation.

2.3 Analytical methods for the soluble Kollidon® grades

2.3.1 Qualitative and quantitative methods of determination

2.3.1.1 Identification

A series of identification reactions are described in the literature for the qualitative analysis of the soluble Kollidon® grades.

The most important and clearest means of identification is provided by the infrared spectrum. It is the same for all the soluble Kollidon® grades. Fig. 2.19 shows the infrared spectrum of Kollidon® 90 F, and in Section 4.3.1.1 the infrared spectra of Kollidon® 30 is shown. The only disadvantage of this method of identification lies in the fact that insoluble polyvinylpyrrolidone (crospovidone), e. g. Kollidon® CL gives the same spectrum (see Section 3.3.1). However, the difference can readily be determined from the solubility of the products.

The following section contains the chemical identification reactions of the pharmacopoeias for the soluble Kollidon® grades. Their molecular weight determines the sensitivity of the tests.

1. An aqueous solution of Kollidon® is mixed with a saturated solution of potassium iodide followed by 0.1 N iodine solution. A thick brown-red flocculent precipitate immediately forms.

2. 10 ml of 1 N hydrochloric acid and 2 ml of 10 % potassium dichromate solution are added to 5 ml of 2 % Kollidon® solution in water. A yellow-orange precipitate forms.

3. 0.2 ml of dimethylaminobenzaldehyde reagent (0.2 g reagent + 20 ml ethanol absolute + 0.5 ml conc. hydrochloric acid decoloured with activated charcoal) and 2 ml of conc. sulfuric acid are added to 1 ml of a 2 % aqueous solution of Kollidon®. After 30 seconds, the solution is cooled. A persistent orange-pink coloration is obtained.

4. 2 ml of an aqueous solution of 75 mg cobalt nitrate and 300 mg ammonium thiocyanate is added to 5 ml of a 2 % aqueous solution of Kollidon® and the mixture acidified with 3 N hydrochloric acid. A light blue precipitate forms.

The pharmacopoeias in european countries specify identification reactions 1 – 3 in addition to the infrared spectrum for the identification of povidone. The U.S. Pharmacopoeia specifies reactions Nos. 1, 2, and 4 for this purpose. Further identification reactions are mentioned in Section 2.3.4.1.

The near-infrared spectrometry (NIR) can also be used for the identification of different Kollidon® grades [619].

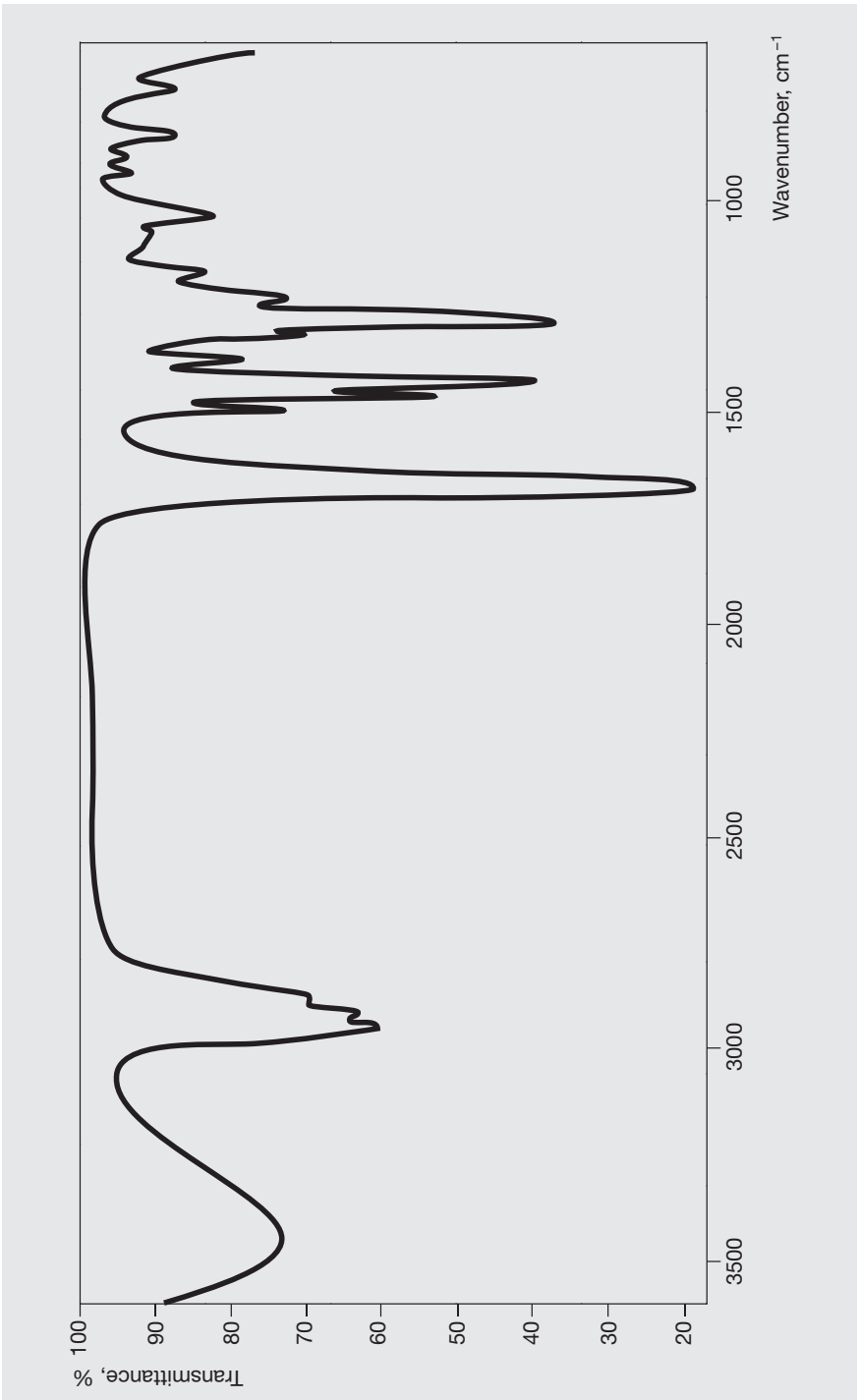


Fig. 2.19: Infrared spectrum of Kollidon® 90 F recorded in potassium bromide

2.3.1.2 Quantitative methods of determination

A simple and rapid method for the quantitative determination of the soluble Kollidon® grades is by photometry of the povidone-iodine complex [18, 19]:

50 ml of sample solution, which may contain up to 50 µg of povidone/ml, is mixed with 25 ml of 0.2 M citric acid solution. This is mixed with 10 ml of 0.006 N iodine solution (0.81 g of freshly sublimed iodine and 1.44 g of potassium iodide dissolved in 1000 ml of water), and after exactly 10 minutes, the absorbance of the solution is measured against a blank solution (50 ml of water + 25 ml of 0.2 M citric acid solution + 10 ml 0.006 N iodine solution) at 420 nm.

The povidone content is determined from a calibration curve, which must be plotted for each Kollidon® grade, as their absorptivities are not the same. Fig. 2.20 shows the calibration curves for Kollidon® 17 PF, Kollidon® 30 and Kollidon® 90 F.

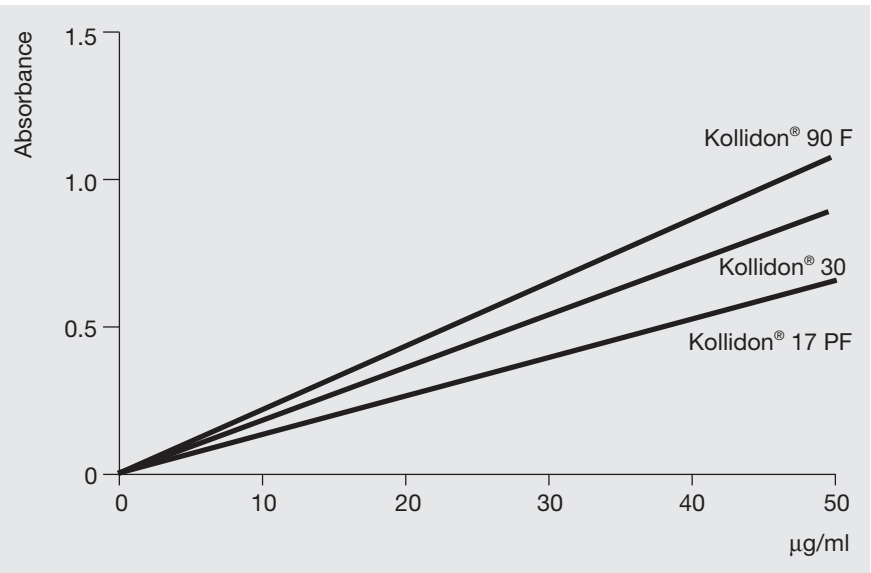


Fig. 2.20: Calibration curves for the photometric determination of Kollidon® 17 PF, Kollidon® 30 and Kollidon® 90 F with iodine

A further method of determination described in the literature uses Vital Red [20, 202]. Determinations using Congo Red and by measuring the turbidity after addition of perchloric acid have also been reported.

A selective method for quantitatively determining povidone, even in traces, uses pyrolytic gas chromatography [130].

2.3.2 Methods for the determination of K-value and molecular weight

2.3.2.1 Determination of the K-value

The significance and the official limits of the K-value for the soluble Kollidon® grades have been described in Section 2.2.3.2. The value for aqueous solutions is determined according to the povidone monographs of Ph.Eur. and USP by methods similar to the original method [13] from the relative viscosity in water as follows.

1. Measurement of the relative (kinematic) viscosity:

A 5 % solution is prepared, if the K-value is expected to be lower than 20, and a 1 % solution, if it is expected to be over 20. The sample weights take into account the solids content of the respective Kollidon® grade, which must first be determined from the loss on drying at 105 °C.

To prepare the sample solution, a quantity of sample that has not been heated and that is exactly equivalent to 1.00 or 5.00 g of the dry product is weighed into a 100-ml volumetric flask and dissolved in a little distilled water by shaking at room temperature. The volumetric flask is then made up to the mark with water and the solution transferred to an Ubbelohde capillary viscometer (Schott & Gen, No. 1).

It is suspended in a thermostatic bath for 30 minutes at 25 + 0.1 °C, then the time taken for the solution to flow between the calibrated marks is measured several times and the average taken. To determine the relative viscosity, it is necessary to measure the flow time of water between the two marks by the same method. The Hagenbach-Couette corrections, which are enclosed with the viscometer by the manufacturer, must be subtracted from the flow times.

The relative kinematic viscosity, (z) is calculated as follows:

$$z = \frac{\text{Flow time of the solution}}{\text{Flow time of water}}$$

Five measurements are done and the average value is calculated.

2. Calculation of the K-value:

The K-value is calculated from the relative viscosity with the aid of the equation given in Table 2.30.

Table 2.30: Calculation of the K-value from the relative viscosity

$$\log z = \frac{75 \cdot k^2}{1 + 1.5 \cdot k \cdot c} + k \cdot c$$

or, according to the harmonized monograph in Ph. Eur. and USP.

$$\text{K-Value} = \frac{\sqrt{300\ c \cdot \log z + (c + 1.5\ c \cdot \log z)^2} + 1.5\ c \cdot \log z - c}{0.15\ c + 0.003\ c^2}$$

where

z = relative viscosity of the solution at concentration c
k = K-value · 10^{-3}
c = concentration in % (w/v)

Section 2.2.3.2 contains two graphs showing the relationship between the relative viscosity and the K-value according to the above equation. However, it is preferable to use the mathematical formula as it is more accurate.

2.3.2.2 Methods for the determination of the viscosity-average of the molecular weight, $\bar{M}v$

In addition to the weight-average of the molecular weight, which is determined by light scattering, the viscosity-average, $\bar{M}v$ is becoming more and more widely used, as it is easy to determine. It can be calculated either from the K-value or from the relative viscosity via the intrinsic viscosity.
Table 2.31 gives two equations for this purpose from the literature.

Table 2.31: Equations for the calculation of the viscosity-average of the molecular weight, $\bar{M}v$ of soluble Kollidon® grades

1. *Calculation of $\bar{M}v$ from the K-value [212]*

   $\bar{M}v = 22.22\ (K + 0.075\ K^2)^{1.65}$

2. *Calculation of $\bar{M}v$ from the relative viscosity via the intrinsic viscosity [η]*

   A. Intrinsic viscosity [16]:

   $$[\eta] = \frac{\eta_{rel} - 1}{c + 0.28\ c\ (\eta_{rel} - 1)}$$

   B. Viscosity-average molecular weight [15]:

   $\bar{M}v = 8.04 \cdot 10^5\ [\eta]^{1.82}$

Fig. 2.21 illustrates the relationship between the viscosity-average of the molecular weight and the K-value as given by Equation 1 in Table 2.31.

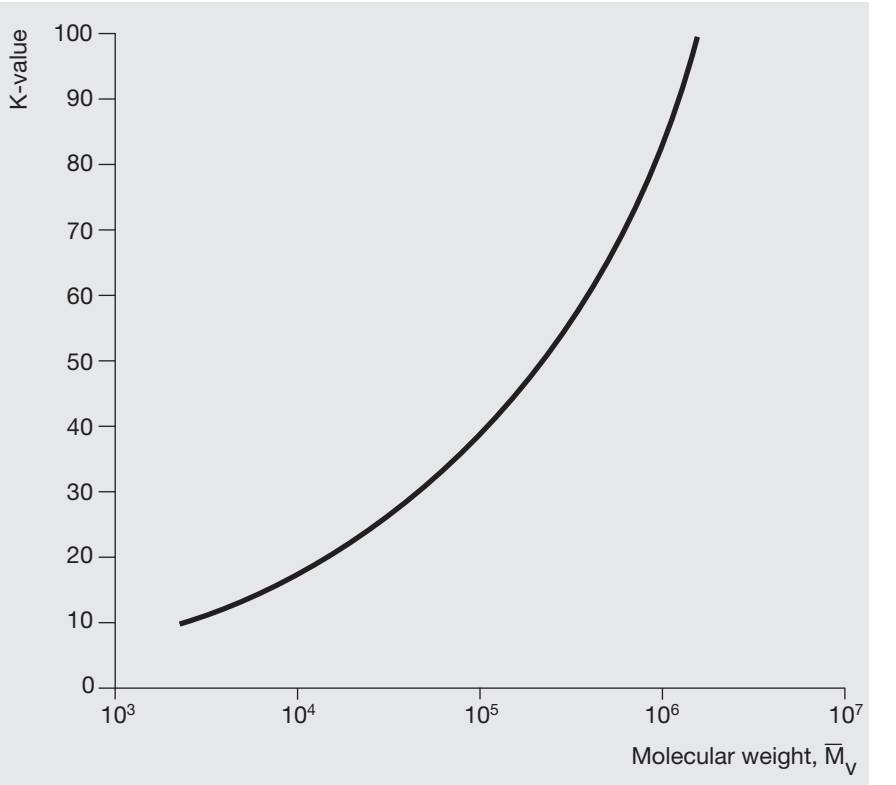


Fig. 2.21: Relationship between the K-value and the viscosity-average of the molecular weight, $\overline{M}v$, calculated with equation 1 in Table 2.31

Calculations by the two different methods in Table 2.31 do not always give the same results. As can be seen from Fig. 2.22, this is particularly evident at higher K-values. The viscosity-average of the molecular weight calculated from the K-value with Equation 1 is lower than that calculated with the other equation. The same relative viscosities were taken for the calculation of both the K-value and the intrinsic viscosity.

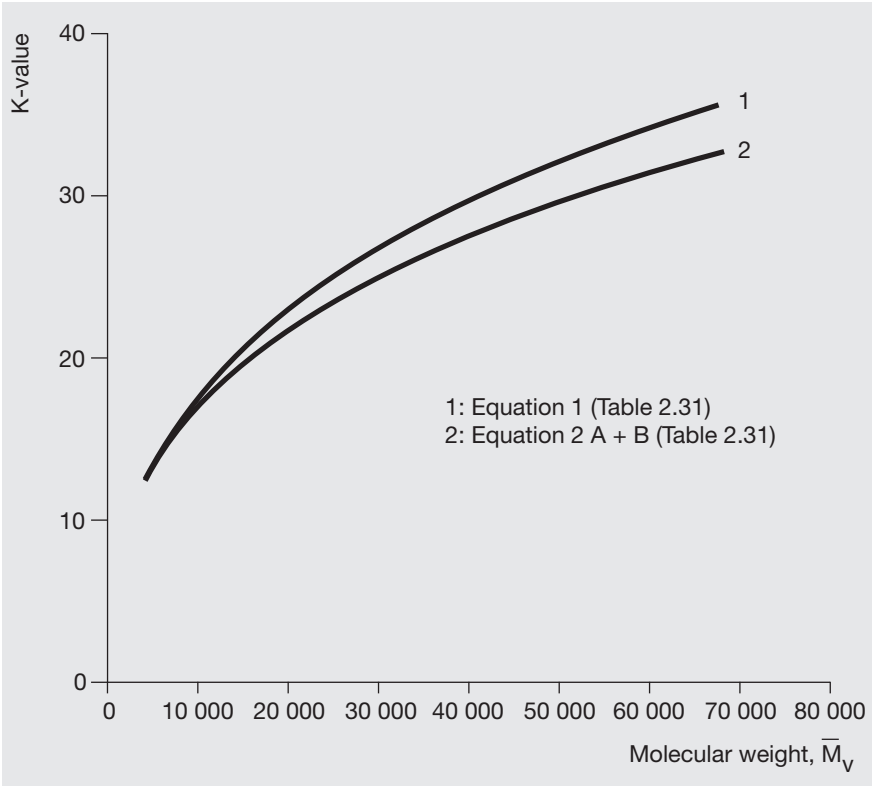


Fig. 2.22: Relationship between K-values from 12 to 33 and the viscosity average of the molecular weight, calculated by different methods

2.3.3 Methods for the determination of purity

2.3.3.1 Pharmacopoeia methods

Methods for determining the purity of the soluble Kollidon® grades are described in detail in the European, U.S. and Japanese pharmacopoeias. They cover all the parameters listed in Table 2.32.

Table 2.32: Purity test methods for soluble Kollidon® grades given in pharmacopoeias

Colour and clarity of solution
Acetaldehyde
pH
N-vinylpyrrolidone (= Impurity A of the Ph.Eur. monograph)
2-Pyrrolidone (= Impurity B of the Ph.Eur. monograph)
Hydrazine
Peroxides
Water
Sulphated ash = residue on ignition
Heavy metals
Residual solvents (Formic acid or 2-propanol)
Nitrogen as assay
Microbial status
Endotoxins (only Kollidon® 12 PF and Kollidon® 17 PF)

Some of the former pharmacopoeial methods are not always entirely relevant. This applies particularly to the titration tests of N-vinylpyrrolidone or aldehydes, as the methods are not specific and inaccurate, and therefore no longer do justice to the purity of the Kollidon® grades availabe today. For this reason, the harmonized monograph “Povidone” introduced an HPLC method for N-vinylpyrrolidone and an enzymatic test for acetaldehyde.

2.3.3.2 HPLC method for the determination of free N-vinylpyrrolidone, 2-pyrrolidone and vinyl acetate in povidone and copovidone

Principle:

A sample of povidone (soluble Kollidon® grades) or copovidone (Kollidon® VA 64 grades) is analyzed after dissolution in a water/methanol mixture using HPLC reverse phase chromatography (gradient run). The polymeric material is kept away from the chromatographic system using a precolumn and switching technique.
The determination limits are 2 mg/kg N-vinylpyrrolidone, 200 mg/kg 2-pyrrolidone and 10 mg/kg vinyl acetate.

Sample preparation:

Weight about 250 mg of povidone or copovidone in a 10 ml volumetric flask, add 1 ml of methanol and apply ultrasonic action until complete dissolution is achieved. Fill up to volume with water. If the sample of povidone K 90 is not dissolved completely in methanol stirr after filling up to volume with water until the complete dissolution. Aliquotes of this sample solution are used for injection after filtration.

For samples of povidone containing more than 1.5 g/100 g 2-pyrrolidone (e. g. povidone K 25 and K 30), the sample weight has to be reduced if the linear range of calibration is exceeded.

Calibration solutions:

Dissolve reference substances (50 mg of N-vinylpyrrolidone, about 300 mg of 2-pyrrolidone and 50 mg of vinyl acetate in the case of copovidone) in methanol and dilute with the same solvent. Further dilutions are done with eluent A (see Table 2.33). At least two sample weights of each reference substance and at least four concentrations derived thereof are used for the calibration curve.
The concentrations have to be selected in such a way that the concentration of the individual analyte in the sample is included.
Concerning the determination of 2-pyrrolidone, calibration up to about 1.5 g per 100 g of sample usually is linear.

Table 2.33: Chromatographic conditions

Column:	250 x 4 mm packed with Aquasil® C18, 5 µm (ThermoHypersil)		
Precolumn:	30 x 4 mm packed with Nucleosil® 120-5 C18 (Macherey & Nagel)		
Mobile phases:	Eluent A: water + acetonitrile + methanol (90+5+5, v/v/v) Eluent B: water + acetonitrile + methanol (50+45+5, v/v/v)		
Gradient run:	t (min)	% Eluent A	% Eluent B
	0	100	0
	26	80	20
	27	0	100
	38	100	0
Flow rate:	1.0 ml/min		
Injection volume:	10 µl		
Detection:	UV (205 nm and 233 nm)		
Column temperature:	30 °C		
Rf value of 2-pyrrolidone:	about 6 min		
Rf value of vinyl acetate:	about 17 min		
Rf value of N-vinylpyrrolidone:	about 21 min		

When starting the analysis, precolumn and separation column are in series. After 2.5 min (depending on the separation characteristics of the precolumn) column switching is applied in such way that the eluent is guided directly onto the separation column avoiding the precolumn. The precolumn is simultaneously flushed backwards in order to eliminate the polymer components. After 40 min the system is set back for the next injection (see Fig. 2.23 and Table 2.34).

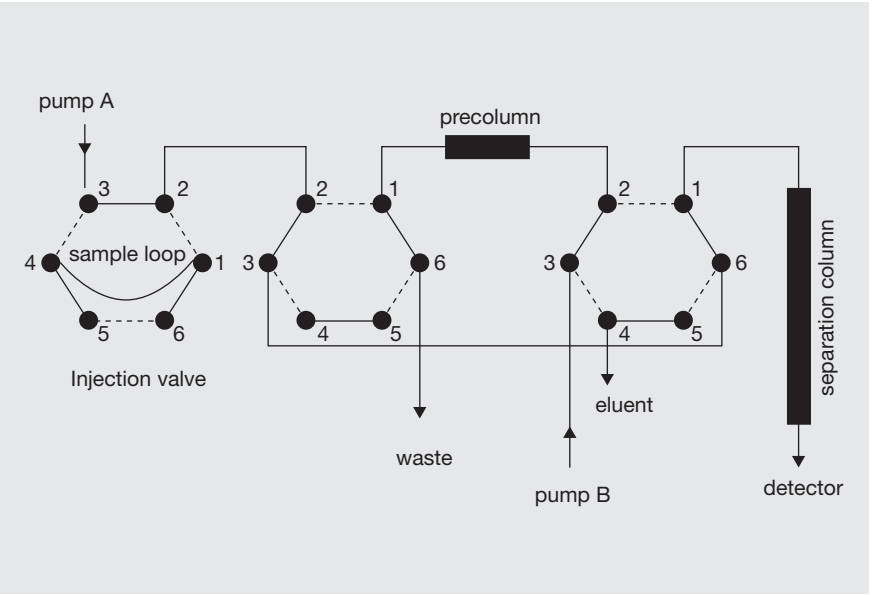


Fig. 2.23: Column flow and back flashing scheme

Table 2.34: Chromatographic run scheme

T (min)	Action/State of system
0	Eluent A
0.1	Detector wave length 205 nm
0.2	Base line reset
2.5	Column switching
19.6	Detector wave length 233 nm
19.7	Base line reset
26.0	Eluent B 20 %
27.0	Eluent B 100 %
38.0	Eluent A
40.0	Column switching
53.0	Next injection

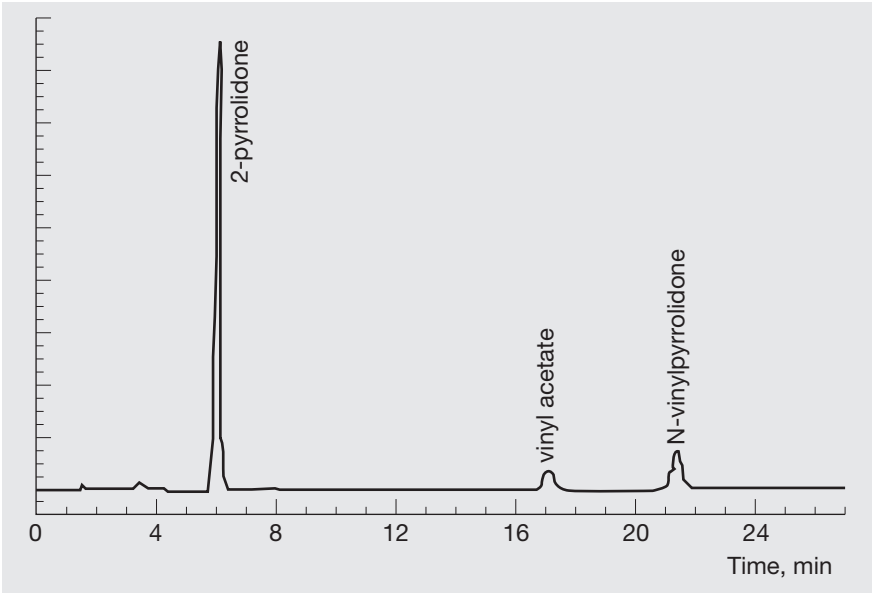


Fig. 2.24: Typical chromatogram of the three reference substances

Calculation of the calibration factor:

$$KF = \frac{FK}{ß\,(K)} \quad [\,\frac{mV\ s\ 10\ ml}{mg}\,]$$

KF = Calibration factor
FK = Peak area of the reference substance 2-pyrrolidone resp. N-vinyl-pyrrolidone resp. vinyl acetate
ß(K) = Calculated concentration of the reference substance

Calculation of 2-pyrrolidone resp. N-vinylpyrrolidone resp. vinyl acetate in the sample:

$$w(P) = \frac{FP}{KF \cdot ß\,[P]} \times 100 \quad [g/100\ g]$$

w(P) = Mass fraction of 2-pyrrolidone resp. N-vinylpyrrolidone resp. vinyl acetate in the sample [g/100 g]
KF = Calibration factor
FP = Peak area of 2-pyrrolidone resp. N-vinylpyrrolidone resp. vinyl-acetate in the sample chromatogram [mV s]
ß(P) = calculated concentration of the sample solution [mg/10 ml]

Validation

Linearity:

The calibration curves given in Fig. 2.25, 2.26 and 2.27 were obtained with the reference substances 2-pyrrolidone, N-vinylpyrrolidone and vinyl acetate.

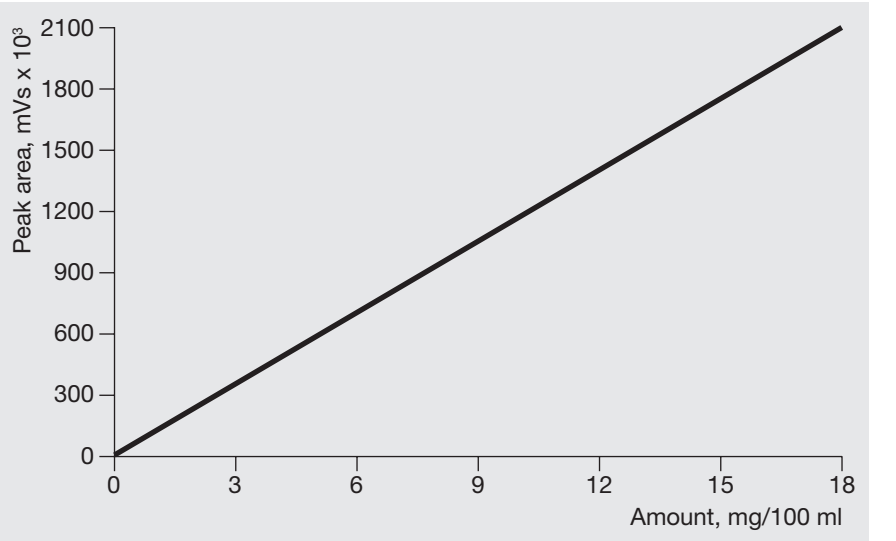


Fig. 2.25: Calibration curve of 2-pyrrolidone

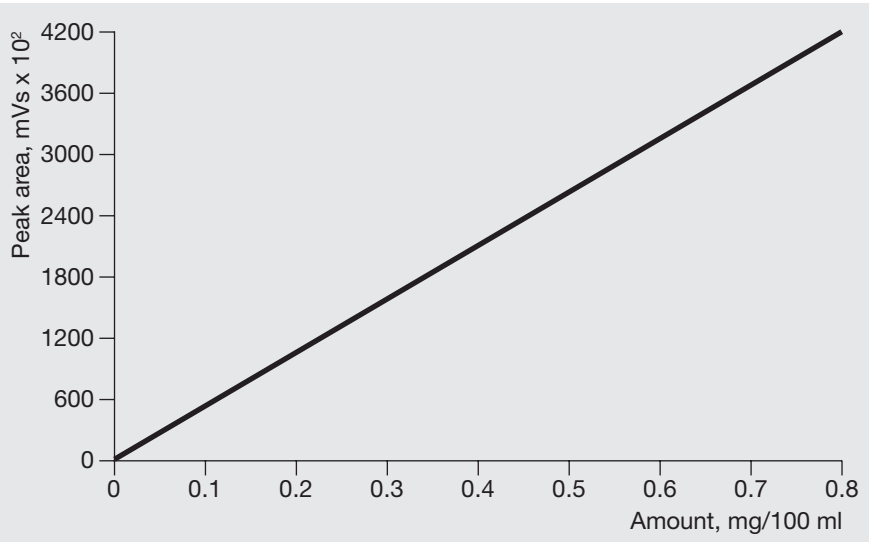


Fig. 2.26: Calibration curve of N-vinylpyrrolidone

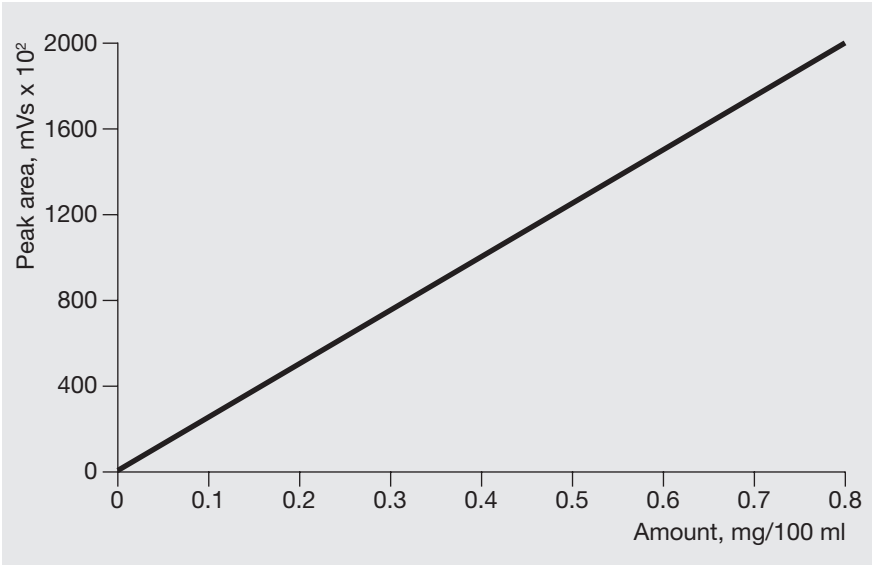


Fig. 2.27: Calibration curve of vinyl acetate

Reproducibility:

The content of the 2-pyrrolidone and N-vinylpyrrolidone was determined six times on Kollidon® 30, batch 13128775L0.

Table 2.35: Reproducibility on Kollidon® 30

	2-pyrrolidone [g/100 g]	N-vinylpyrrolidone [mg/kg]
1. Measurement	1.174	< 2
2. Measurement	1.191	< 2
3. Measurement	1.178	< 2
4. Measurement	1.170	< 2
5. Measurement	1.160	< 2
6. Measurement	1.149	< 2
Average	1.17	< 2
Rel. standard deviation	1 %	

The content of the 2-pyrrolidone and N-vinylpyrrolidone was determined six times on Kollidon® 17 PF, batch 80472716K0.

Table 2.36: Reproducibility on Kollidon® 17 PF

	2-pyrrolidone [g/100 g]	N-vinylpyrrolidone [mg/kg]
1. Measurement	537	< 2
2. Measurement	533	< 2
3. Measurement	536	< 2
4. Measurement	535	< 2
5. Measurement	539	< 2
6. Measurement	533	< 2
Average	536	< 2
Rel. standard deviation	< 1 %	

The content of the 2-pyrrolidone, N-vinylpyrrolidone and vinyl acetate was determined six times on Kollidon® VA 64, batch 19265124U0.

Table 2.37: Reproducibility on Kollidon® VA 64

	2-pyrrolidone [mg/kg]	N-vinylpyrrolidone [mg/kg]	Vinyl acetate [mg/kg]
1. Measurement	441	8.9	< 10
2. Measurement	439	8.6	< 10
3. Measurement	440	8.7	< 10
4. Measurement	440	8.8	< 10
5. Measurement	442	8.7	< 10
6. Measurement	442	8.8	< 10
Average	441	8.7	<10
Rel. standard deviation	< 1 %	1 %	

Recovery:

The content of 2-pyrrolidone and N-vinylpyrrolidone was determined in povidone before and after addition of two different amounts of the reference substances.

Table 2.38: Recovery in Kollidon® 30

	Initial value [mg/kg]	Added amount [mg/kg]	Theoretical content [mg/kg]	Found content [mg/kg]	Recovery rate [mg/kg]
2-pyrrolidone	11 700	223	11 923	11 860	71 %
	11 700	412	12 112	12 120	101 %
N-vinylpyrro-	1.5	10.9	12.4	9.0	69 %
lidone	1.5	20.2	21.7	23.6	109 %

The content of 2-pyrrolidone, N-vinylpyrrolidone and vinyl acetate was determined in Kollidon® VA 64 before and after addition of two different amounts of the reference substances.

Table 2.39: Recovery in Kollidon® VA 64

	Initial value [mg/kg]	Added amount [mg/kg]	Theoretical content [mg/kg]	Found content [mg/kg]	Recovery rate [mg/kg]
2-pyrrolidone	441	79	520	520	100 %
	441	325	766	777	103 %
N-vinylpyrro-	8.7	3.9	12.6	12.4	94 %
lidone	8.7	15.9	24.6	24.5	99 %
Vinyl acetate	< 10	16.0	16.0	16.1	100 %
		26.9	26.9	26.0	97 %
		60.1	60.1	57.0	95 %

Comparison with the methods of the povidone monograph in Ph.Eur., 5th edition:

The batches of soluble Kollidon® grades and Kollidon® VA 64 mentioned above in Tables 2.35 to 2.37 were tested in parallel with this HPLC method and the Ph.Eur. methods for 2-pyrrolidone and N-vinylpyrrolidone. Tables 2.40 to 2.42 illustrates the results obtained with the Ph.Eur. methods. These results are comparable with the results mentioned in the Tables 2.35 to 2.37.

Table 2.40: Results of the Ph.Eur. methods on Kollidon® 30

	2-pyrrolidone [g/100 g]	N-vinylpyrrolidone [mg/kg]
1. Measurement	1.27	1.4
2. Measurement	1.27	1.4
3. Measurement	1.28	1.3
4. Measurement	1.27	1.4
5. Measurement	1.28	1.3
6. Measurement	1.26	1.3
Average	1.27	1.3
Rel. standard deviation	< 1 %	2 %

Table 2.41: Results of the Ph.Eur. methods on Kollidon® 17 PF

	2-pyrrolidone [mg/kg]	N-vinylpyrrolidone [mg/kg]
1. Measurement	520	< 1
2. Measurement	505	< 1
3. Measurement	480	< 1
4. Measurement	446	< 1
5. Measurement	437	< 1
6. Measurement	463	< 1
Average	475	< 1
Rel. standard deviation	6 %	

Table 2.42: Results of the Ph.Eur. methods on Kollidon® VA 64

	2-pyrrolidone [mg/kg]	N-vinylpyrrolidone [mg/kg]
1. Measurement	368	9.2
2. Measurement	353	9.1
3. Measurement	359	9.1
4. Measurement	344	8.9
5. Measurement	365	9.0
6. Measurement	368	9.0
Average	360	9.1
Rel. standard deviation	2.4 %	1 %

2.3.3.3 Enzymatic determination of acetaldehyde

As the titration method for the determination of acetaldehyde is very unspecific and measures more than just aldehydes or acetaldehyde, the following specific enzymatic method is recommended. It was introduced in the harmonized monograph of povidone in Ph.Eur., USP and JP.

Principle:

Acetaldehyde is stoichiometrically oxidized to acetic acid by nicotinamide-adenine dinucleotide (NAD) in the presence of aldehyde dehydrogenase. This method measures the sum of free and bound acetaldehyde.

$$\text{Acetaldehyde} + NAD^+ + H_2O \xrightarrow{\text{Al-DH}} \text{Acetic acid} + NADH + H^+$$

Reagent solutions:

I. Buffer (potassium dihydrogen phosphate, 0.05 mol/l, pH 9.0):
Dissolve 1.74 g of KH_2PO_4 in about 80 ml water, adjust to pH 9.0 with 1 mol/l potassium hydroxyde and make up to 100 ml with water.
The solution is stable for two months at 4 °C.

II. Nicotinamide-adenine dinucleotide solution, NAD:
Dissolve 40 mg of NAD (e. g. Boehringer Mannheim Order No. 127329) in 10 ml of water. The solution is stable for four weeks at 4 °C.

III. Aldehyde dehydrogenase, Al-DH (7 U/ml):
Dissolve 7 units of aldehyde dehydrogenase lyophilisate (e. g. Boehringer Mannheim Order No. 171832) in 1.0 ml of water.
The solution is stable for eight hours at 4 °C or for two days when frozen.

Sample solution:

Weigh 200 – 500 mg of the Kollidon® sample (W, mg), accurate to 0.2 mg, into a 10-ml volumetric flask, dissolve in buffer (I) and make up to the mark with buffer (I). Heat the closed flask for 60 minutes at 60 °C, then cool to room temperature.

Procedure:

Mix 0.2 ml of NAD solution (II) with 3 ml of the sample solution in a 1-cm photometric cell and measure the absorbance at 340 nm against water (A_{0S}). Add 0.05 ml of Al-DH solution (III), mix and, after 5 min measure the absorbance at 340 mm against water again (A_{1S}).
Conduct a blank determination using 3 ml of buffer (I) instead of the sample solution (A_{0B} and A_{1B}).

Calculation:

$$\text{ppm acetaldehyde in Kollidon®} = \frac{75\,750}{W} \cdot [(A_{1S} - A_{0S}) - (A_{1B} - A_{0B})]$$

Validation

Linearity:

Measurements with pure acetaldehyde with a concentration of 5 – 55 µg/10 ml demonstrate the linearity of the method with a correlation coefficient of 0.99998.

Reproducibility:

The acetaldehyde content of a sample of Kollidon® 30 was determined 6 times. The values found, the average and the relative standard deviation are given in Table 2.43.

Table 2.43: Acetaldehyde content of a Kollidon® 30 sample

Determination No.	Acetaldehyde [mg/kg]
1	102.0
2	103.3
3	102.6
4	103.6
5	100.4
Average	102.4
Standard deviation, s_{rel}	1.1 %

Recovery rate:

To a sample of Kollidon® 30 (batch 822) different amounts of acetaldehyde-ammonia trimer (= Hexahydro 2.4.6-trimethyl 1.3.5-triazine, $C_6H_{15}N_3 \cdot 3H_2O$, CAS number 76231-37-3, available at Fluka/Sigma Aldrich) were added and determined enzymatically. The acetaldehyde in this Kollidon® batch was 45 mg/kg before the addition.

Table 2.44: Recovery of acetaldehyde in Kollidon® 30

Added acetaldehyde – ammonia trimer (calculated as acetaldehyde) [mg/kg]	Theoretical content of acetaldehyde [mg/kg]	Found acetaldehyde [mg/kg]	Recovery rate [%]
46	91	91	100
58	103	102	98
77	122	120	97
92	137	134	97
111	161	158	97

Notes:

Because of the volatility of acetaldehyde, all flasks and cells must be well sealed during the determination.

Acetaldehyde for calibration purposes must be distilled before use.

If the sample solution is not heated to 60 °C, only the free acetaldehyde is determined and proper validation is not possible.

2.3.3.4 Enzymatic determination of formic acid in Kollidon® 25, 30 and 90 F

Principle:

Formic acid is oxidized in the presence of formate dehydrogenase (FDH) by nicotinamide-adenine dinucleotide (NAD) quantitatively to bicarbonate. The amount of NADH formed during this reaction is stoichiometric with the amount of formic acid. The increase in NADH is measured by means of its absorbance at 340 nm.

Reagents:

Test combination of Boehringer/Mannheim
(Germany, Catalogue No. 979 732):
Bottle 1: 22 ml of potassium phosphate buffer pH 7.5, stabilizer.
Bottle 2: 420 mg NAD lithium salt, lyophilisate.
Bottle 3: 200 mg formate dehydrogenase (FDH), lyophilisate, 80 U.

Preparation of the reagent solutions:

1. Dissolve the content of bottle 2 with the content of bottle 1
   (= NAD solution 2, stable for 2 weeks at 4 °C, to use at 20–25 °C)
2. Dissolve the content of bottle 3 with 1.2 ml of water
   (= FDH enzyme solution 3, stable for 20 days at 4 °C).

Sample solution:

Weight accurately approx. 3 g of Kollidon® into a volumetric flask. Fill up with 60–70 ml of water and dissolve the sample completely. Fill up to the mark with water and shake.

Measurement:

In two glass cuvettes with stopper pipette the following amounts:

	blank	sample
NAD solution 2	1.00 ml	1.00 ml
Water	2.00 ml	1.90 ml
Sample solution	–	0.10 ml

Shake the cuvettes and after 5 min measure against air the absorbances at 340 nm of the sample cuvette ($E0_s$) and of the blank ($E0_b$). Now start the enzyme reaction by adding 0.05 ml of the FDH enzyme solution 3 into both cuvettes. Wait for 20 min at 20–25 °C and measure the absorbances again of the blank ($E1_b$) and the sample ($E1_s$) against air.

Calculation:

$$E = (E1_s - E0_s) - (E1_b - E0_b)$$

$$C\ [\%] = \frac{E \cdot 2.229}{\text{Sample [g]}}$$

Validation

Linearity:

The calibration curve of formic acid was plotted from 6 points covering a concentration range of 10–220 µg/ml to check their linearity (Table 2.45).

Table 2.45: Linearity of formic acid determination

Concentration of formic acid [µg/ml]	Absorbance 340 nm
10.9	0.049
20.3	0.091
42.1	0.189
107.7	0.483
172.3	0.773
219.8	0.960

Reproducibility:

The formic acid content of batch 719 of Kollidon® 30 was determined 5 times. The values found, the average and the relative standard deviation are given in Table 2.46.

Table 2.46: Reproducibility of the formic acid determination in Kollidon® 30

Measurement	Formic acid (%)
1.	0.2697
2.	0.2683
3.	0.2674
4.	0.2647
5.	0.2666
Average	0.2673
Standard deviation, S_{rel}	17

Recovery rate:

To batch 719 of Kollidon® 30 different known amounts of formic acid were added and determined (Table 2.47).

Table 2.47: Recovery rate of formic acid in Kollidon® 30

Formic acid added [mg]	Formic acid found [mg]	Recovery rate [%]
4.38	4.06	93
6.03	5.68	94
8.04	7.66	95
10.95	10.74	98

2.3.3.5 GC Determination of 2-propanol in low molecular weight povidone and in copovidone

Principle:

The determination of 2-propanol can be done by the following modified gaschromatographic method given in ISO 13741-1.

Internal standard solution:

Weight about 250 mg of propionitrile, dissolve it in water and dilute to 1000 ml with the same solvent.

Test solution:

Weight about 10 g of the povidone (copovidone) sample and dissolve in 30 g of the internal standard solution.

Table 2.48: Modified chromatographic conditions

Parameter	Material/adjustment
Column:	DB-Wax® 30 m x 0.25 mm, film 1 µm
Carrier gas:	Nitrogen
Flow rate of carrier gas:	1 ml/min
Split:	1 : 30
Detector:	FID
Injection volume:	1 µl
Temperature injection block:	200 °C
Temperature detector:	200 °C
Temperature program, column:	a. 3 min at 50 °C b. Heating from 50 °C to 200 °C with 20 °C/min c. 200 °C during 37.5 min
Rf value of propionitrile	about 6.6 min
Rf value of 2-propanol	about 4.4 min

2.3.3.6 Determination of nitrogen in povidone and crospovidone

As the description of the nitrogen determination in the povidone and crospovidone monographs included in the supplements of Ph.Eur. and in USP is not exact enough to obtain always a complete degradation of the polyvinylpyrrolidone polymer a modified Ph.Eur. method is given here:

Place 450.0 mg of the substance to be examined (*m*, mg) in a combustion flask, add 10 g of a mixture of 48.9 g of dipotassium sulphate R, 48.8 g disodium sulphate R and 0.3 g of copper sulphate R, and 3 glass beads. Wash any adhering particles from the neck into the flask with a small quantity of sulphuric acid R. Add in total 20 ml of sulphuric acid R, allowing it to run down the sides of the flask, and mix the contents by rotation.
Close the mouth of the flask loosely, for example by means of a glass bulb with a short stem, to avoid excessive loss of sulphuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulphuric acid in the neck of the flask; precautions are to be taken to prevent the upper part of the flask from becoming overheated. Continue the heating for 60 minutes until a completely clear greenish solution is obtained.
Cool, cautiously add to the mixture 35 ml of water R, and after 10 seconds add 65 ml of strong sodium hydroxide solution R, cool again and place in a steamdistillation apparatus. Distill immediately by passing steam through the mixture. Collect about 150 ml of distillate in a mixture of 100 ml of a 40 g/l solution of boric acid R and 3 drops of bromcresol greenmethyl red solution R and 100 ml of water R to cover the tip of the condenser. Towards the end of the distillation lower the receiver so that the tip of the condenser is above the surface of the acid solution and rinse the end part of the condenser with a small quantity of water R.
Titrate the distillate with 0.25 M sulphuric acid until the colour of the solution changes from green through pale greyishblue to pale greyishredpurple (n_1, ml of 0.25 M sulphuric acid).

Repeat the test using about 450.0 mg of glucose R in place of the substance to be examined (n_2, ml of 0.25 M sulphuric acid).

Calculation:

$$\text{Nitrogen [\%]} = \frac{700.4\ (n_1 - n_2)}{m\ (100 - d)} \times 100$$

d = loss on drying, %.

2.3.3.7 GC Determination of (hydroxy-methyl)-butylpyrrolidone ("2-propanol-vinylpyrrolidone adduct") in low molecular weight povidone

As the low-molecular weight povidone types are polymerized in 2-propanol instead of water small amounts of the radical adduct of 2-propanol to the monomer N-vinylpyrrolidone can be formed. Its chemical structure is shown in Fig. 2.28.

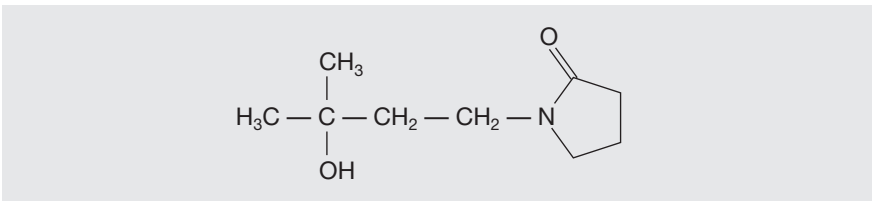


Fig. 2.28: (3'-Hydroxy, 3'-methyl)-N-butylpyrrolidin-2-one (HMBP)

The detection limit of this gaschromatographic method is about 100 mg/kg.

Internal standard solution:

Weight about 0.125 g of benzonitrile and dissolve it in anhydrous ethanol (Ph.Eur.) and dilute to 100 ml with the same solvent. Dilute 10 ml of this solution to 250 ml with anhydrous ethanol (= 0.05 mg/ml).

Reference solution:

Weight about 0.1 g of (3'-Hydroxy,3'-methyl)-N-butyl-pyrrolidin-2-one (HMBP), dissolve in anhydrous ethanol and dilute to 100 ml with the same solvent (= 1 mg/ml).

Calibration solutions:

For the determination of the calibration factor prepare at least three calibration solutions by mixing 20 ml of the internal standard solution with different amounts between 1 and 10 ml of the reference solution and by diluting to 50 ml with anhydrous ethanol.

Test solution:

Weight about 0.2 g of the povidone sample, dissolve in 5 ml of the internal standard solution and dilute to 25 ml with anhydrous ethanol.

Table 2.49: Chromatographic conditions

Parameter	Material/adjustment
Column:	DB-wax® 30 m x 0.25 mm, film 0.5 µm (J&W Scientific)
Carrier gas:	Helium, 1 bar
Flow rate of carrier gas:	1 ml/min
Split:	1 : 60
Detector:	Nitrogen detector
Injection volume:	1 µl
Temperature injection block:	240 °C
Temperature detector:	260 °C
Temperature program, column:	a. Heating from 180 to 240 °C with 4 °C/min b. 240 °C during 7.5 min c. Cooling from 240 to 180 °C with 8–9°C/min

Calibration:

The following calibration curve of Fig. 2.29 was plotted from five different points covering a concentration range of 9 to 200 µg HMBP/ml.

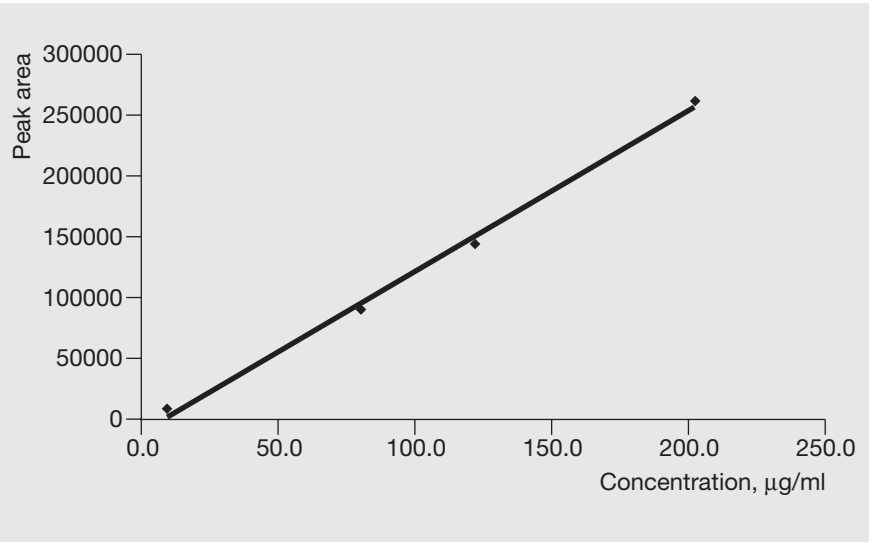


Fig. 2.29: Calibration curve of HMBP

Calculation of the calibration factor:

Calculate the calibration factor F of each calibration solution and the average of the obtained factors (= F_{av}).

$$F = \frac{A_s \times C_r}{A_r \times C_s}$$

A_s = peak aerea of the internal standard benzonitrile (mV · s)
A_r = peak aerea of the reference substance (mV · s)
C_s = concentration of the internal standard in the calibration solution (µg/ml)
C_r = concentration of the reference substance in the calibration solution (µg/ml)

Calculation of the content of HMBP in the sample:

$$\text{HMBP (ppm)} = \frac{C_{st} \times 5}{W} \times \frac{F_{av} \times A_a \times 1000}{A_{st}}$$

A_{st} = peak aerea of the internal standard benzonitrile (mV · s)
A_a = peak aerea of the 2-propanol-vinylpyrrolidone adduct HMBP (mV · s)
C_{st} = concentration of benzonitril in the internal standard solution (mg/ml)
F_{av} = average calibration factor
W = Weight of the sample of Kollidon® (g)

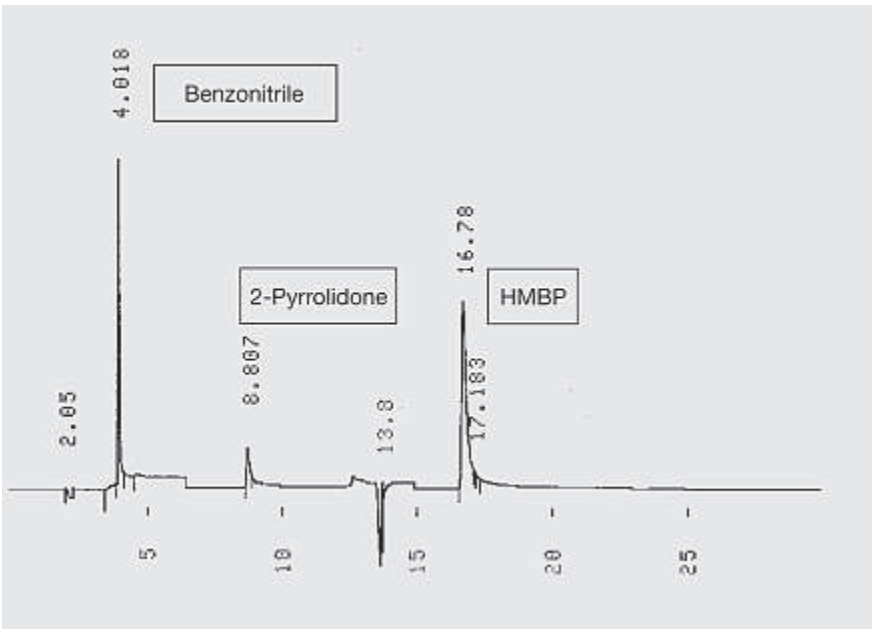


Fig. 2.30: Typical GC chromatogram of Kollidon® 17 PF

A *validation* of this GC method of the determination of HMBP also was done. The linearity, reproducibility and recovery were validated. The results are available on request.

2.3.4 Determination of soluble Kollidon® grades in preparations

2.3.4.1 Qualitative determination

The various means of detecting the soluble Kollidon® grades in preparations have been described in detail in the literature [17, 18]. Not all the detection reactions listed in Table 2.50 (see also Section 2.3.1.1) are suitable for every pharmaceutical preparation. The best method can only be determined by trial with the preparation involved.

Table 2.50: Detection reactions for soluble Kollidon® grades [18]

Reagent	Reaction
10 % aqueous barium chloride solution + 1 N hydrochloric acid + 5 % aqueous silicotungstic acid solution	White precipitate
10 % aqueous barium chloride solution + 1 N hydrochloric acid + 5 % aqueous phosphotungstic acid solution	Yellow precipitate
10 % potassium dichromate solution + 1 N hydrochloric acid	Orange-yellow precipitate
Saturated aqueous potassium bromide solution + bromine water	Orange-yellow precipitate
Saturated aqueous potassium iodide solution + 0.1 N iodine solution	Brown-red precipitate
Dragendorff's reagent + 1 N hydrochloric acid	Brown-red precipitate
Nessler's Reagent	Yellow-white precipitate
Saturated aqueous potassium ferrocyanide solution + 6 N hydrochloric acid	White precipitate
Saturated aqueous potassium ferricyanide solution + 6 N hydrochloric acid	Yellow precipitate
Aqueous ammonium cobalt rhodanide solution + 6 N hydrochloric acid	Blue precipitate
Concentrated aqueous phenol solution	White precipitate

The separation scheme shown in Fig. 2.31 can be used for the detection of povidone, e. g. Kollidon® 30, in solid dosage forms, e. g. tablets, granules, capsules and coated tablets.

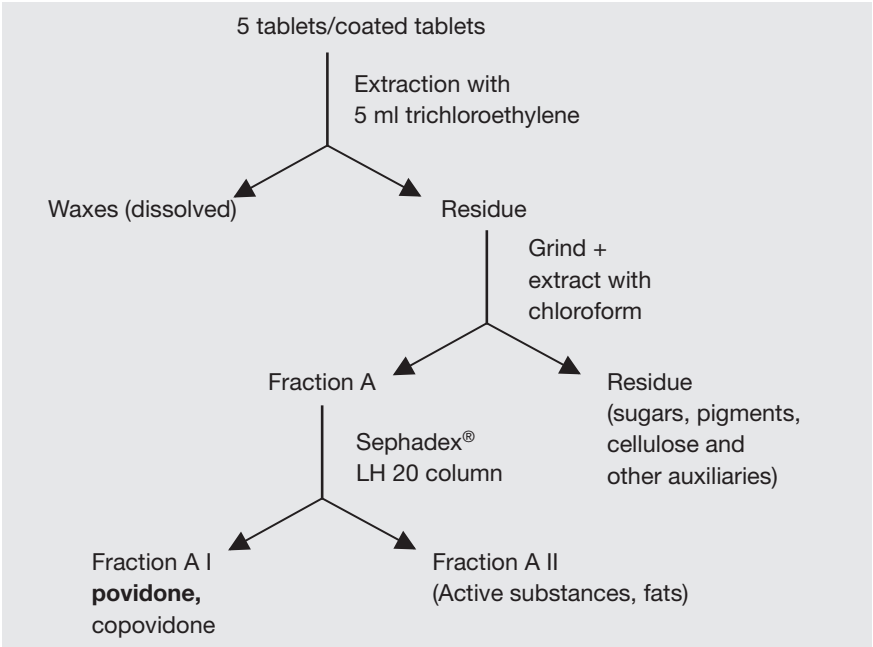


Fig. 2.31: Separation scheme for the isolation of povidone in solid dosage forms [17]

The detection and differentiation of povidone and copovidone obtained in Fraction A I in Fig. 2.31 is best carried out by thin layer chromatography on silica gel or paper. A suitable eluent is a mixture of 6 parts n-propanol and 4 parts 2 N ammonia solution by volume, which gives the Rf values shown in Table 2.51. The chromatogram is then sprayed with Lugol's solution.

Table 2.51: Rf values for povidone and copovidone separated by thin layer and paper chromatography using propanol + ammonia solution (6 + 4) as eluent [17]

Substance	Rf values Silica gel plate	FP 3 paper
Povidone	0.59 – 0.64	0.33 – 0.66
Copovidone	0.64 – 0.75	0.72 – 1.00

Electrophoresis can also be used to detect povidone in the presence of copovidone [17].

Povidone can be detected in tissue with the aid of chlorazol or Congo Red [143, 144].

2.3.4.2 Quantitative determination in preparations

The most versatile method for quantitatively determining the soluble Kollidon® grades is probably the photometric measurement of the PVP-iodine complex described in Section 2.3.1.2. It has been successfully tested on samples that also contained a series of auxiliaries and active ingredients [18].

In these tests, aqueous solutions containing 50, 100 and 200 µg of Kollidon® 25 and 20 times the quantity of the active ingredients and excipients listed in Table 2.52 were prepared, and their povidone content determined.

Table 2.52: Active ingredients and excipients combined with povidone for its quantitative determination [18]

Acetylsalicylic acid	Meprobamate
Ascorbic acid	Phenylbutazone
Bromoisovalerylurea	Acetphenetidine
Caffeine	Phenobarbital
Diphenhydramine hydrochloride	Salicylamide
Ephedrine hydrochloride	Sodium salicylate
Ethylpapaverine	Starch
Glucose	Tartaric acid
Lactose	Thiamine hydrochloride
Lidocaine	

Table 2.53 shows that Kollidon® 25 can be determined with sufficient accuracy in the presence of 12 of the compounds listed in Table 2.52.

Diphenhydramine, ethylpapaverine, phenylbutazone, ascorbic acid and starch react with iodine. The general method, in which iodine is used as a reagent, must be modified because it cannot be used directly if these substances are present. However, it is possible to pretreat the samples to enable povidone to be determined in solutions that contain these substances. Diphenhydramine hydrochloride, ethyl papaverine and phenylbutazone can be extracted by shaking the aqueous solution with a suitable organic solvent in a separating funnel.

The povidone remains in the aqueous phase and can then be determined by the general method. Ethyl papaverine and diphenhydramine hydrochloride can be extracted with cyclohexanol from the alkaline aqueous solution; phenylbutazone can be extracted from neutral aqueous solutions with the same solvent. Unlike povidone, starch is insoluble in methanol. The evaporation residue of a solution containing starch and povidone is therefore treated with methanol and povidone can then be determined by the general method in the methanolic solution after filtration.

Table 2.53: Photometric determination of Kollidon® 25 in the presence of different compounds [18]

	µg of povidone, recovered in the presence of 20 times the quantity of:										
Kollidon® 25 added, µg	Lactose	Glucose	Tartaric acid	Acetyl-salicylic acid	Thiamine hydro-chloride	Caffeine	Ephedrine hydro-chloride	Lidocaine	Meproba-mate	Pheno-barbital	Salicyl-amide
50	48	49	47	48	47	50	50	46	48	46	50
100	100	99	99	99	99	102	99	97	99	97	100
200	199	200	201	198	203	203	202	195	200	200	204

If ascorbic acid is present, this is stoichiometrically oxidized to dehydroascorbic acid, which does not interfere with the determination, by titration with iodine solution.

Table 2.54 shows the results of analyses of solutions containing the interfering substances by the general method with the modifications described above.

Table 2.54: Photometric determination of Kollidon® 25 by the modified general method [18].

	µg of povidone recovered in the presence of 20 times the quantity of:				
Kollidon® 25 added, µg	Diphenhydramine hydrochloride	Ethylpapaverine	Phenylbutazone	Ascorbic acid	Starch
50	52	51	52	49	48
100	100	100	101	97	96
200	200	198	200	196	196

Methods for the determination of povidone in contact lens fluids with the aid of Congo Red [142] as well as a fluorimetric method that uses aniline-naphthaline sulfonate [111, 181] are described in the literature.

A UV-spectrophotometric determination of more than 20 % of Kollidon® 30 in mixtures with active ingredients was developed by multicomponent analysis [618].

2.4 Applications of the soluble Kollidon® grades

2.4.1 General properties

The soluble grades of Kollidon® possess a number of very useful properties for which they are widely used in pharmaceuticals.

Because of these properties, the products can perform different functions in different dosage forms.

Table 2.55: General properties of the soluble Kollidon® grades in pharmaceuticals

– Solubility in all conventional solvents
– Adhesive and binding power
– Film formation
– Affinity to hydrophilic and hydrophobic surfaces
– Ability to form water-soluble complexes
– Availability in different average molecular weights
– Thickening properties

Their excellent *solubility* in water and in other solvents used in pharmaceutical production (Section 2.2.2) is an advantage in almost all dosage forms, e. g. in wet granulation in tablet production, in oral solutions, syrups and drops, in injectables and topical solutions and in film-coatings on tablets.

Their *adhesive and binding power* is particularly important in tabletting (wet granulation, dry granulation, direct compression). This property is also useful in film-coatings and adhesive gels.

Their *film-forming properties* are used in the coating of tablets, in transdermal systems and in medicinal sprays. The film formation, moistening and lubrication effect of povidone are used in ophthalmic solutions having the medical indication of the dry eye sydrom.

Their *affinity to hydrophilic and hydrophobic surfaces* is particularly useful in the hydrophilization of a wide range of substances, ranging from hydrophobic tablet cores – to permit sugar or film-coating, to medical plastics.

Their ability to *form complexes* with such a large number of substances is a special feature of the Kollidon® grades (Section 2.2.7). The complexes formed are almost always soluble and are stable only in an acid medium. This property can be used to increase the solubility of active ingredients in liquid dosage forms, as in the case of PVP-iodine. In solid dosage forms, the ability to form soluble complexes is used to increase bioavailability. A reduction in the local toxicity of certain drugs can also be achieved by complexation with Kollidon®.
A special use for the complexation properties of Kollidon® lies in the stabilization of proteins and enzymes in diagnostics.

Their *thickening properties* (Section 2.2.3) are used in oral and topical liquid dosage forms, e. g. syrups and suspensions.

Table 2.56 gives a overview of the main applications of povidone in many different dosage forms of drugs.

Table 2.56: Main applications of povidone in the pharmaceuticals industry

Function	Dosage form
Binder	Tablets, capsules, granules
Bioavailability enhancer	Tablets, capsules, granules, pellets, suppositories, transdermal systems
Film former	Ophthalmic solutions, tablet cores, medical plastics
Solubilizer	Oral, parenteral and topical solutions
Taste masking	Oral solutions, chewing tablets
Lyophilisation agent	Injectables, oral lyophilisates
Suspension stabilizer	Oral and parenteral suspensions, instant granules, dry syrups, coating suspensions
Hydrophilizer	Medical plastics, sustained release forms, suspensions
Adhesive	Transdermal systems, adhesive gels
Stabilizer	Enzymes in diagnostics, different forms
Intermediate	Povidone-Iodine as active ingredient
Toxicity reduction	Injectables, oral preparations etc.

The soluble Kollidon® grades are available in different average molecular weights (Section 2.2.6), as the above properties almost all depend on the molecular weight, to a greater or lesser extent: With increasing molecular weight, the dissolution rate of the soluble Kollidon® grades decreases, while the adhesive power, the viscosity and often also the ability to form complexes increase. The rate of elimination from the organism after parenteral administration decreases with increasing molecular weight.

This dependence of the properties on the molecular weight makes it possible to provide the optimum grade for each dosage form or formulation and to achieve the optimum effect.

2.4.2 Binders for tablets, granules and hard gelatin capsules

2.4.2.1 General notes on tabletting and on soluble Kollidon® as binder

The main area of application of Kollidon® 25, 30 and 90 F is as a binder for tablets, pellets and granules, as well as hard gelatin capsules. Its use is independent of whether wet or dry granulation or direct compression is used (Fig. 2.32), as Kollidon® acts as a binder in all these processes.

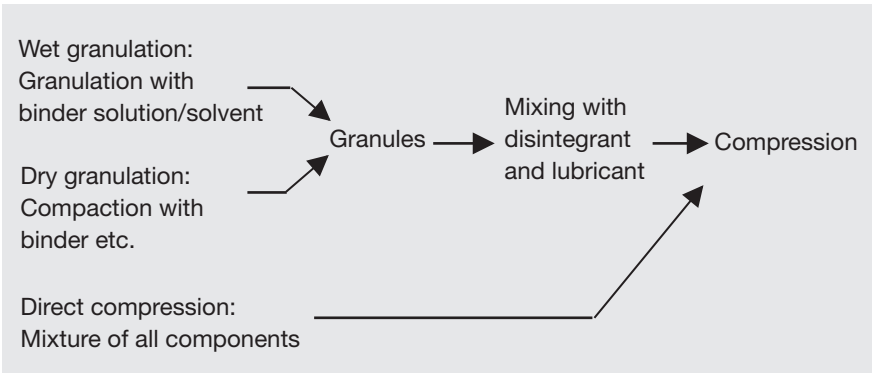


Fig. 2.32: Most important methods of tabletting

The usual concentrations in which soluble Kollidon® is used as a binder in tablets and granules are given in Table 2.57.

Table 2.57: Usual concentrations for soluble Kollidon® grades as binders

Kollidon® grade	Concentration in tablet/pellets/granules
Kollidon® 25	2–5 %
Kollidon® 30	2–5 %
Kollidon® 90 F	1–3 %

As Kollidon® 90 F is a stronger binder than Kollidon® 25 or Kollidon® 30, the concentration given in Table 2.57 is about half that of the other two grades. This is confirmed in Table 2.58, which shows that the coarse fraction of a granulate increases and the fine fraction is reduced to a greater extent with Kollidon® 90 F than with the other two types of lower average molecular weight, for the same concentration.

Table 2.58: Influence of different grades of Kollidon® in a concentration of 5 % on the particle size distribution of corn-starch granules obtained by wet granulation

	Without	Kollidon® 25	Kollidon® 30	Kollidon® 90 F
Fraction < 50 µm	> 99 %	28 %	27 %	23 %
50 µm – 100 µm	< 1 %	23 %	22 %	10 %
Fraction > 250 µm	–	44 %	44 %	61 %

It can also be seen from Table 2.58 that there is hardly any difference in the particle sizes of the granules produced with Kollidon® 25 and Kollidon® 30. A similar relationship is found when the hardness of placebo tablets is compared. It can be seen from Figs. 2.33 and 2.34 that there is no major difference between Kollidon® 25 and Kollidon® 30, even over a range of compression forces, while Kollidon® 90 F gives significantly harder tablets.

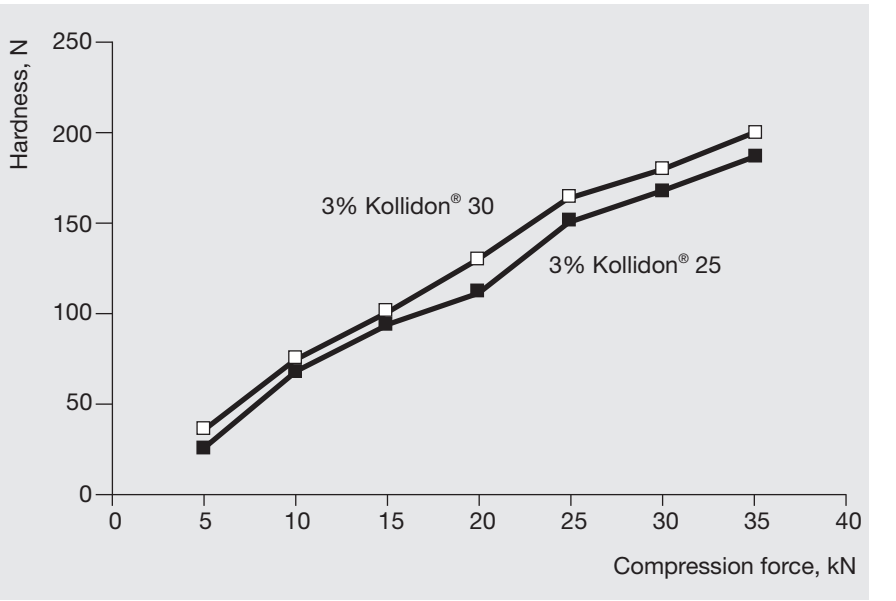


Fig. 2.33: Influence of the compression force on the hardness of calcium hydrogen phosphate placebo tablets containing 3 % Kollidon® (wet granulation)

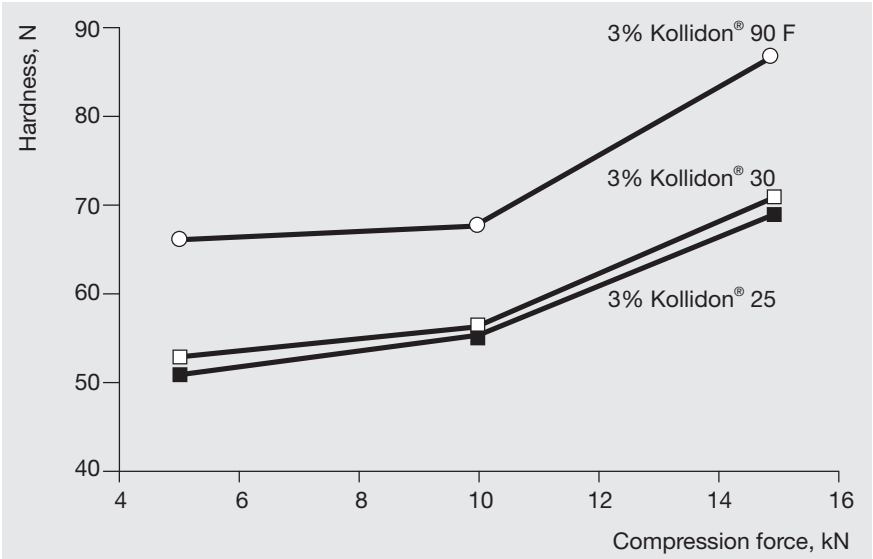


Fig. 2.34: Influence of the compression force on the hardness of lactose monohydrate placebo tablets containing 3 % Kollidon® (wet granulation)

Because of their good solubility in water, Kollidon® 25, Kollidon® 30 and Kollidon® 90 F have hardly any adverse effect on the disintegration time of tablets in which they are used. Fig. 2.35 shows how the disintegration time of calcium hydrogen phosphate placebo tablets with 3 % Kollidon® 25 as binder remains more or less the same up to a very high compression force of 30 kN. With 3 % Kollidon® 90 F, it remains equally fast up to a compression force of 25 kN.

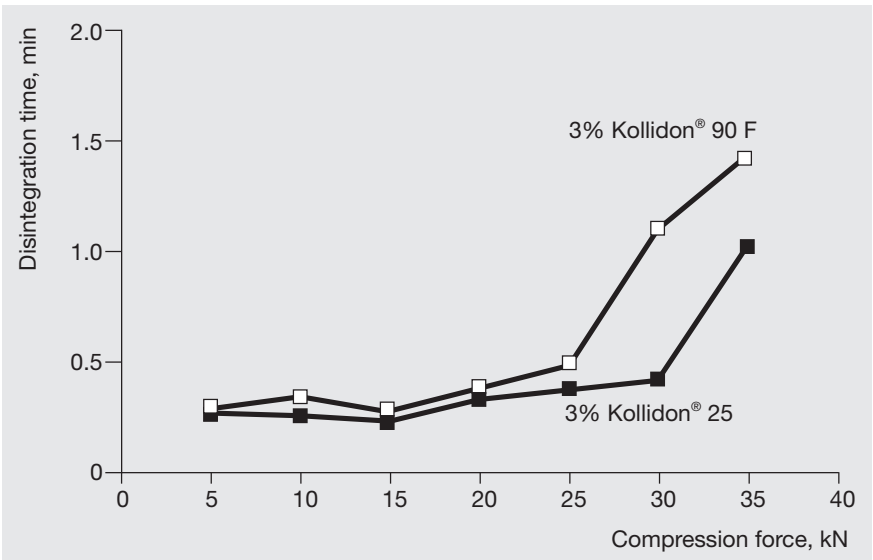


Fig. 2.35: Influence of the compression force on the disintegration time of calcium hydrogen phosphate placebo tablets with 3 % Kollidon® CL as disintegrant (wet granulation)

2.4.2.2 Production of tablets by wet granulation

Wet granulation is still the most widely used technique for preparing a tabletting mixture. There are at least four different variations of the procedure (Table 2.59).

Table 2.59: Methods of wet granulation with a binder

1. Granulation of the active substance (+ filler) with a binder solution.
2. Granulation of the active substance (+ filler)-binder mixture with the pure solvent.
3. Granulation of a mixture of the active substance (+ filler) and a portion of the binder with a solution of the remaining binder.
4. Granulation of the active substance (+ filler) with the solution of a portion of the binder followed by dry addition of the remaining binder to the finished granules.

Water is nowadays the most commonly used solvent. Sometimes, if water cannot be used, as with effervescent tablets, active ingredients that are prone to hydrolysis etc., ethanol or 2-propanol are used as solvents, though fluidized bed granulation technology is preferred.

There are a number of factors that dictate which of the methods in Table 2.59 must be used. With many formulations, Method 1 gives tablets with a shorter disintegration time and quicker release of the active substance than Method 2 [314]. In many cases, Method 1 gives somewhat harder tablets than Method 2. Method 3 in Table 2.59 is useful if Method 1 cannot be used, as when the tabletting mixture lacks the capacity for the quantity of liquid required. If the disintegration time of a tablet presents a problem, it is worth trying Method 4, mixing in about a third of the binder together with lubricant and, last of all, the disintegrant.
Methods 2 and 3 have proved best for drugs of high solubility, as the quantity of liquid can be kept small to avoid clogging the granulating screens.

Wet granulation with Kollidon® 25, Kollidon® 30 or Kollidon® 90 F generally gives harder granules with better flow properties than with other binders [64–77, 107, 234, 241, 243, 275, 503] with lower friability and higher binding strength. Fig. 2.36 shows a comparison with cellulose derivatives in placebo tablets, and it can be seen in Fig. 2.37 that Kollidon® 30 gives more than the double hardness of hydrochlorothiazide tablets in comparison to maltodextrin [527]. However, not only the hardness or friability can be better, Kollidon® also promotes the dissolution of the active ingredient. As can be seen in Fig. 2.38, acetaminophen (paracetamol) tablets with 4 % povidone K 90 as binder release the drug more quickly than tablets with gelatin or hydroxypropylcellulose (hypromellose) as binder, even though the povidone tablets are harder. Similar results were obtained with 0.6 or 1.0 % of povidone K 90 or hypromellose [544].

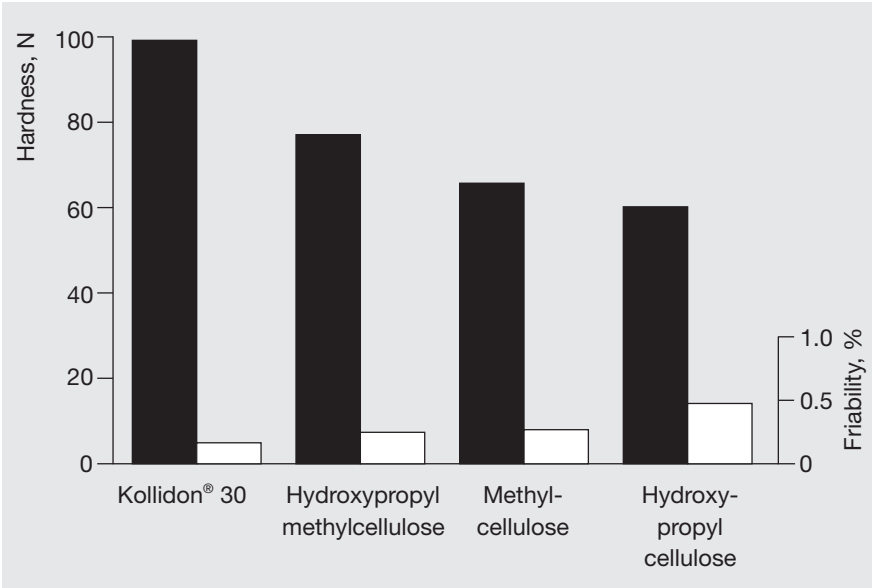


Fig. 2.36: Hardness and friability of calcium phosphate placebo tablets with 3% binder (wet granulation)

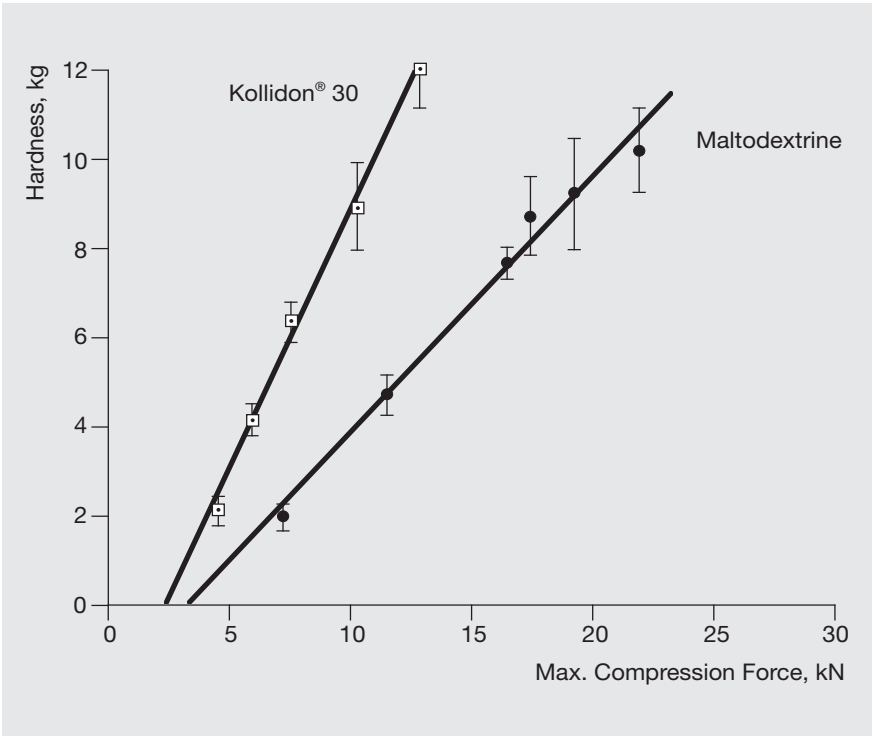


Fig. 2.37: Influence of 5% maltodextrine (Lycatab® DSH, Roquette) or Kollidon® 30 on the hardness of hydrochlorothiazide tablets [527]

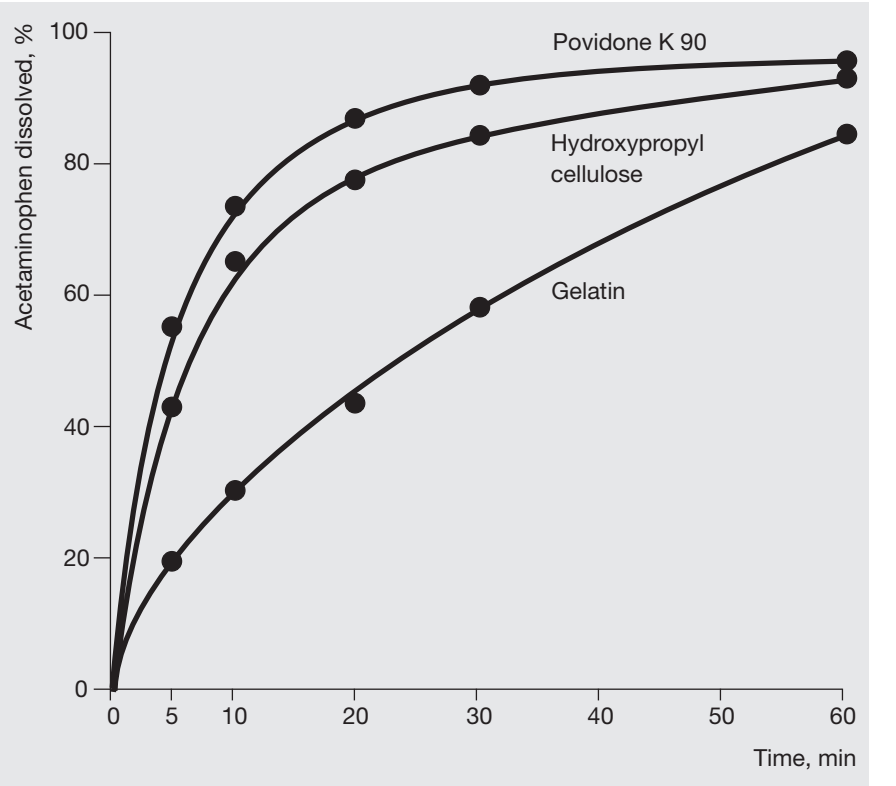


Fig. 2.38: Dissolution characteristics of acetaminophen tablets containing 4 % binder [425]

The Kollidon® grades can be used in all the current wet granulation techniques, including fluidized bed granulation [82, 156, 425] and extrusion spheronisation [157, 591, 602] or drying by microwave radiation [561], though with Kollidon® 90 F, the viscosity of the granulating solution can be critical if the technique used does not permit the use of an adequate quantity of solvent. In difficult cases, it is actually possible to improve the properties of the granules by using granulating solutions containing a mixture of different Kollidon® grades instead of a single grade [218] or a mixture with hypromellose (HPMC) [581]. The addition of low-molecular macrogol, e. g. Lutrol® E 400, to the granulating solution can improve the plasticity of the granules [78 – 81].

As already shown in Table 2.58, particle size is increased by granulation with Kollidon® 30, for instance. This increase also depends on the quantity of Kollidon® used. If microcrystalline cellulose is granulated in a range of concentrations of 0 – 4 % of the binder by Methods 1 and 2 in Table 2.59, the increase in particle size of the cellulose granulate is much the same in both methods (Fig. 2.39).
However, it has been possible to demonstrate in the production of caffeine tablets, that Kollidon® 25 increases the particle size and bulk density of the granules, giving it better flow properties and reducing the friability of the tablets [400].

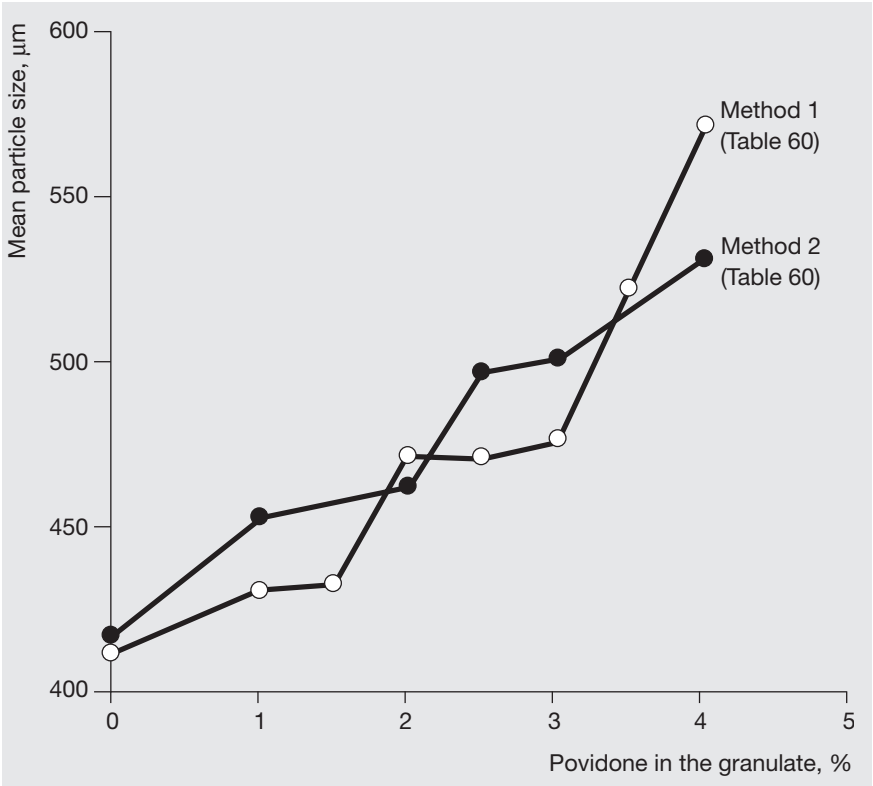


Fig. 2.39: Increase in the mean particle size of a cellulose granulate as a function of the binder concentration [362]

In wet granulation, the quantity of solvent, usually water, has a definite influence on the tablet properties. Increasing the amount of water as granulation liquid gave naproxen tablets with a significantly higher dissolution rate [534], acetaminophen granules that were coarser and had better flowability [549], and calcium hydrogen phosphate tablets with shorter disintegration times (Table 2.60). The amount of granulation liquid showed a stronger effect on to the particle size and drug release than the percentage of povidone in phenylbutazone pellets manufactured by extrusion-spheronisation [157] and had an influence on the yield [591].

The optimum quantity of solvent can best be determined from the power consumption of the granulator, though it must be noted that this can vary considerably, even with the same active ingredient, depending on its origin [484]. For the comparison with Kollidon® VA 64 see Section 4.4.2.2.

Table 2.60: Influence of the quantity of granulation liquid (water) on the properties of calcium hydrogen phosphate tablets

Kollidon® 90 F (% per tablet)	Hardness 31 ml H_2O*	52 ml H_2O*	Disintegration time 31 ml H_2O*	52 ml H_2O*
1.5 %	94 N	99 N	105 min	34 min
3.0 %	114 N	110 N	118 min	28 min

** In each case, the quantity of water relates to 515 g of $CaHPO_4$ granules*

The function and use of Kollidon® 30 and Kollidon® 90 F as binders for wet granulation is shown in Tables 2.61 to 2.63 for several tablet formulations with rifampicin, pyrazinamide and alpha-methydopa, developed on a laboratory scale. They were prepared by Method 1 in Table 2.59.

Table 2.61: Rifampicin tablets (450 mg) [615]

Formulation:

I	Rifampicin	450 g
	Corn starch	58 g
II	Kollidon® 90 F	9 g
	2-Propanol	50 ml
III	Kollidon® CL	15 g
	Stearic acid	10 g
	Magnesium stearate	2 g
	Aerosil® 200 (Degussa)	2 g

Granulate Mixture I with Solution II, dry, sieve and mix in the components of III, then press into tablets on a rotary tablet press using a low compression force.

Properties of tablets obtained in the laboratory:

Weight:	550 mg
Diameter:	12 mm
Hardness:	95 N
Disintegration time (gastric juice):	1 – 2 min
Friability:	0.6 %
Dissolution in 0.1 N hydrochloric acid according to USP:	15 min: 86 %
	30 min: 90 %

Table 2.62: Pyrazinamide tablets (500 mg) [615]

Formulation:

I	Pyrazinamide	500 g
	Corn starch	50 g
II	Kollidon® 30	20 g
	Water	approx. 200 ml
III	Kollidon® CL	10 – 11 g
	Magnesium stearate	6 g

Granulate Mixture I with Solution II, sieve, dry and mix in the components of III, then press into tablets on a rotary tablet press with a low compression force.

Properties of tablets obtained in the laboratory:

Weight:	610 mg
Diameter:	12 mm
Hardness:	131 N
Disintegration time (gastric juice):	3 min
Friability:	0.25 %
Dissolution in water (USP method):	15 min: 78 % 30 min: 96 %

Table 2.63: Alpha-methyldopa tablet cores (275 mg) [615]

Formulation:

I	Alpha-methyldopa	275 g
	Lactose monohydrate	55 g
II	Kollidon® 30	15 g
	2-Propanol (or water)	80 ml
III	Kollidon® CL	8 g
	Magnesium stearate	2 g

Granulate Mixture I with Solution II, dry, sieve and mix in the components of III, then press into tablets on a rotary press with a medium compression force (approx. 15 kN).

Properties of tablets obtained in the laboratory:

Weight:	361 mg
Hardness:	118 N
Disintegration time (gastric juice):	5 min
Friability:	0 %
Dissolution in 0.1 N hydrochloric acid (USP method):	15 min: 77 % 30 min: 98 %

Kollidon® 25 and Kollidon® 30 are very good binders for effervescent tablets, as they dissolve rapidly in water to form a clear solution. This particularly applies to effervescent vitamin tablets, e. g. ascorbic acid tablets [368]. Tables 2.64 and 2.65 give formulations for ranitidine effervescent tablets and multivitamin effervescent tablets as typical examples that were developed on a laboratory scale. For the granulation of multivitamin preparations, it is always preferable to use a fluidized bed to reduce the contact time between vitamins and water. In Table 2.65, the vitamin A palmitate should be replaced by a more modern water-dispersible vitamin A acetate dry powder, for better stability.

Table 2.64: Ranitidine effervescent tablets [360]

I	Ranitidine hydrochloride	168 g
	Anhydrous monosodium citrate	840 g
	Sodium bicarbonate	836 g
	Saccharin sodium	11 g
II	Povidone K 30 (e. g. Kollidon® 30)	40 g
	Ethanol 96 %	q. s.
III	Lemon flavour (powder)	25 g
	Sodium benzoate, siliconized (10 %)	80 g

Granulate Mixture I with Solution II, dry, sieve and mix in III, then press into 2-g tablets.

Table 2.65: Multivitamin effervescent tablets [615]

Formulation:

I	Thiamine mononitrate	13 g
	Riboflavin	4 g
	Pyridoxine hydrochloride	11 g
	Nicotinamide	66 g
	Calcium pantothenate	17 g
	Tartaric acid	360 g
	Sodium bicarbonate	550 g
	Sucrose, crystalline	300 g
	Sucrose, powder	300 g
	Kollidon® 30	35 g
II	Kollidon® 30	5 g
	2-Propanol	approx. 80 g

Table 2.65: Multivitamin effervescent tablets (continued)

III	Riboflavin	6 g
	Ascorbic acid, powder	550 g
	Cyanocobalamin 0.1 % gelatin dry powder	20 g
	Vitamin A palmitate 250 000 I.U./g dry powder CWD	12 g
	Vitamin E acetate dry powder SDG 50	60 g
	PEG 6000, powder	80 g
	Kollidon® CL	100 g

Granulate Mixture I with Solution II, in a fluidized bed granulator, if possible; dry, then mix with the components of III and press into tablets on a rotary tablet press with a relatively high compression force.

Properties of the tablets obtained in the laboratory:

Weight:	2500 mg
Diameter:	20 mm
Hardness:	140 N
Disintegration time (gastric juice):	1 – 2 min
Friability:	1 %

Stability (vitamin loss after 12 months at 23 °C, HPLC methods):

Ascorbic acid:	8 %
Cyanocobalamin:	8 %
Vitamin A:	29 %
All other vitamins:	Not more than 6 %

An interesting application for Kollidon® 25, Kollidon® 30 or Kollidon® 90 F as a binder lies in the wet granulation of auxiliaries in the manufacture of direct compression auxiliaries (e. g. Ludipress® [376], Table 2.66) and in the granulation of active ingredients for direct compression.

Table 2.66: Composition of the direct compression auxiliary Ludipress®

Lactose monohydrate	93.0 %
Kollidon® 30	3.5 %
Kollidon® CL	3.5 %

Active ingredients that are marketed in the pre-granulated form for direct compression are almost always substances that are difficult to press into tablets and/or are prone to hydrolysis. Typical examples are the vitamins and acetaminophen (paracetamol) [540]. Table 2.67 contains details on the production of ascorbic acid for direct compression, which is granulated with Kollidon® 30 as binder in a fluidized bed granulator.

Table 2.67: Ascorbic acid granules for direct compression [369]

I	Ascorbic acid powder	1920 g
II	Kollidon® 30	80 g
	Water	600 ml

Granulate the ascorbic acid (I) with an aqueous solution of Kollidon® 30 (II) in a fluidized bed granulator under the following conditions:

Inlet air temperature:	60 °C
Inlet air rate:	Maximum setting
Spray pressure:	2 – 3 bar
Spraying time:	8 – 10 min
Drying time:	5 min
Final water content:	< 0.5 %

Stability:
After storage for 3 months at 40 °C, the white colour of the product had not changed.

It is essential to carry out the aqueous wet granulation of active ingredients that are prone to hydrolysis on a fluidized bed granulator, to preserve their stability. If ascorbic acid granules with 2.5 % Kollidon® 30 and 2.5 % Kollidon® CL are produced as described in Table 2.67, and compared with granules of the same composition produced in a traditional wet granulation mixer (Diosna Mixer), only the granules produced on the fluidized bed granulator prove stable. Fig. 2.40 shows the change in colour of these two granules after 6 months' storage at room temperature. The results demonstrate clearly that reports of incompatibility of povidone with ascorbic acid in a number of publications are based on misinterpretations or the use of inappropriate methods.

Fig. 2.40: Influence of different methods of wet granulation on the colour stability of ascorbic acid granulate with Kollidon® 30 (after 6 months at room temperature)
Left: Fluidized bed granulate
Right: Diosna Mixer granulate

2.4.2.3 Production of tabletting mixtures by dry granulation

Dry granulation is less frequently used than wet granulation or direct compression in the preparation of tablets. The most widely known dry granulation technology is the roller compaction technique. A new technology is the ultrasonic compaction [607]. Similar to the roller compaction it offers advantages when wet granulation would affect the stability, and when the physical properties of the drug do not allow direct compression.

Kollidon® 25, Kollidon® 30 and Kollidon® 90 F are very good binders for this type of granulation, too [324]. Ascorbic acid provides a typical example (Table 2.68).

Table 2.68: Roller compacted ascorbic acid-Kollidon® 30 powder mixture [367]

Ascorbic acid powder	96 %
Kollidon® 30	3 %
Kollidon® CL, micronized	1 %

Compact a homogeneous mixture of the three components and break up by forcing through a screen. Sieve off the coarse fraction.

The compacted powder described in Table 2.68 was pressed into tablets and provided a preparation that hardly changed its colour during storage at room temperature over a period of 3 years (Table 2.69).

Table 2.69: Ascorbic acid tablets from roller compacted powder with Kollidon® 30 [367]

Formulation:

Ascorbic acid compacted powder 96 % (Table 2.68)	300.0 g
Microcrystalline cellulose	200.0 g
Polyethylene glycol 6000, powder	20.0 g
Talc	4.0 g
Aerosil® 200 (Degussa)	0.5 g
Calcium arachinate	0.5 g

Mix all the components and press into tablets on a rotary tablet press with a relatively low compression force.

Properties of the tablets obtained in the laboratory:

Weight:	525 mg
Diameter:	12 mm
Hardness:	115 N
Disintegration (gastric juice):	90 s
Friability:	< 0.1 %
Colour stability (23 °C):	Hardly any change over 3 years

2.4.2.4 Direct compression

Although most active ingredients are not in themselves suitable for direct compression in the concentrations required, this technique has recently grown in importance.

Not only substances with good compressibility can be used in direct compression (Table 2.70). DC-preparations of active ingredients – usually granules with a binder – that can be tabletted directly, as well as direct compression auxiliaries are available on the market for problem substances.

Table 2.70: Different forms of direct compression

Properties of the active ingredient	Type of direct compression
Directly compressible in adequate concentrations	The active substance is tabletted with the usual auxiliaries
Not directly compressible in the desired concentration with the usual auxiliaries	A direct compression agent, is used (e. g. Ludipress®)
	Direct compression granules of the active ingredient are used.

Kollidon® 25 and Kollidon® 30 can be used for all three types of direct compression of Table 2.70 but the more plastic and less hygroscopic Kollidon® VA 64 grades would be better for this technique (see Section 4.4.2.4). Many direct compression auxiliaries, e. g. Ludipress® or grades of active ingredients suitable for direct compression already contain a binder such as Kollidon® 30. In such cases, little or no further Kollidon® 25 or Kollidon® 30 need be added.

In direct compression, the moisture content of the tabletting mixture is important, though under normal conditions, the usual residual quantity of water in Kollidon® already provides an adequate binding effect between the particles.

To demonstrate the application of Kollidon® 30 in the direct compression technique, metronidazole tablets (Table 2.71) and vitamin B complex tablets (Table 2.72) were tested in the laboratory.

Table 2.71: Direct compression of metronidazole tablets with Kollidon® 30 [615]

Formulation:	
Metronidazole	200 g
Microcrystalline cellulose	200 g
Kollidon® 30	6 g
Kollidon® CL	10 g
Aerosil® 200 (Degussa)	5 g
Magnesium stearate	5 g

Properties of the tablets (compression force 25 kN):

Weight	426 mg
Diameter	12 mm
Hardness	133 N
Disintegration time (gastric juice)	1 – 2 min
Friability	< 0.1 %

Table 2.72: Direct compression of vitamin B complex tablets with and without Kollidon® 30

Formulation	No. 1	No. 2
Thiamine mononitrate	25 g	25 g
Riboflavin	25 g	25 g
Nicotinamide	50 g	50 g
Calcium-D-pantothenate	40 g	40 g
Pyridoxine hydrochloride	16 g	16 g
Cyanocobalamin 0.1 % in gelatin	16 g	16 g
Microcrystalline cellulose	175 g	175 g
Kollidon® 30	16 g	–
Aerosil® 200 (Degussa)	6 g	6 g
Properties of the tablets obtained in the laboratory:		
Weight	365 mg	358 mg
Diameter	12 mm	12 mm
Hardness	171 N	135 N
Disintegration (gastric juice)	10 min	8 min
Friability	0 %	0.1 %

2.4.2.5 Granules, pellets, hard gelatin capsules

The granulation and binding properties of Kollidon® 25, Kollidon® 30 and Kollidon® 90 F used in tabletting obviously also make these products suitable for the production of granules or pellets as a final dosage form.
There are various types of granules and pellets (Table 2.73), for which different granulation techniques can be used.

Table 2.73: Different types of granules and pellets

– Instant granules
– Effervescent granules
– Chewable granules
– Dry syrup granules
– Granules for filling hard gelatin capsules
– Drug pellets for filling hard gelatin capsules
– Drug pellets for sustained release coating

The active ingredients most frequently incorporated in instant granules are antacids and vitamins. Table 2.74 gives details of a magaldrate instant granule formulation developed in the laboratory with Kollidon® 90 F, as an example of this dosage form. In this formulation Kollidon® 90 F also enhances the redispersibility of the suspension obtained by shaking the instant granules with water (see Section 2.4.6.2).

Table 2.74: Magaldrate instant granules with Kollidon® 90 F [615]

I	Magaldrate	100 g
	Kollidon® CL-M	80 g
	Sorbitol, crystalline	50 g
	Orange flavouring	10 g
II	Kollidon® 90 F	10 g
	Coconut flavouring	1 g
	Banana flavouring	1 g
	Saccharin sodium	0.2 g
	Water	approx. 70 ml

Granulate Mixture I with Solution II, sieve and dry.

Vitamins are very often incorporated in effervescent granules. Table 2.75 illustrates details of a multivitamin effervescent granule formulation developed in the laboratory. The chemical stability of this guide formulation has not been tested.

Table 2.75: Multivitamin effervescent granules with Kollidon® 30 (3–4 g = 1 RDA) [615]

I	Thiamine mononitrate	2.6 g
	Riboflavin	3.0 g
	Nicotinamide	11.0 g
	Pyridoxine hydrochloride	2.5 g
	Calcium-D-pantothenate	15.0 g
	Ascorbic acid	200.0 g
	Citric acid	500.0 g
	Sucrose	1300.0 g
	Fructose	800.0 g
	Kollidon® CL-M	200.0 g
	Cyclamate sodium	20.0 g

	Saccharin sodium	1.0 g
	Flavouring	250.0 g
II	Kollidon® 30	150.0 g
	2-Propanol or ethanol	350.0 g
III	Vitamin A acetate dry powder 325 000 CWD	15.0 g
	Vitamin D3 dry powder 100 000 CWD	8.0 g
	Vitamin E acetate dry powder SD 50	21.0 g
	Cyanocobalamin 0.1 % in gelatin	6.6 g
	Sodium bicarbonate	400.0 g

Granulate Mixture I with Solution II in a fluidized bed granulator, dry, sieve and mix with III. Thoroughly dry before packaging.

The most important reasons for using granules or pellets to fill hard gelatin capsules are to improve the flow properties and to reduce dust formation in the filling machine. If the filling is free-flowing, it can be metered with greater conformity into the individual capsules. To a certain extent, these arguments also apply to granules in other dosage forms, particularly when they are packaged as individual portions in sachets.

Further examples of formulations for instant granules are described in Chapter 3, "Insoluble Kollidon® grades" under Section 3.4.4.3.

The active ingredients also can be incorporated in drug pellets by wet granulation with soluble Kollidon® grades for the sustained release coating with Kollicoat® SR 30 D or Kollicoat® EMM 30 D [662] or other sustained release polymers suitable for pellet coating.

2.4.3 Improvement of the dissolution rate and bioavailability of active ingredients

2.4.3.1 Physical mixtures with soluble Kollidon® grades

One problem with many of the active ingredients used today is their poor solubility in water and their limited bioavailability. One of the simplest means of improving the bioavailability of a drug is to improve its dissolution by adding solubilizing agents, such as the soluble Kollidon® grades. These form water-soluble complexes with many active ingredients (see Sections 2.2.7.1 and 2.4.5). With some of such substances, it may be sufficient to produce a physical mixture. Fig. 2.41 shows the improvement in the dissolution rate of reserpine achieved by simply mixing it with an excess of Kollidon® 30. For the mixture with indomethacin see Section 3.4.3.1. Similar results can be expected with the active ingredients listed in Section 2.4.5. That this effect also applies to finished preparations can be seen for phenytoin tablets in Section 2.4.3.6 [326]. The bioavailability of peroral gidazepam is increased by the addition of povidone too [536].

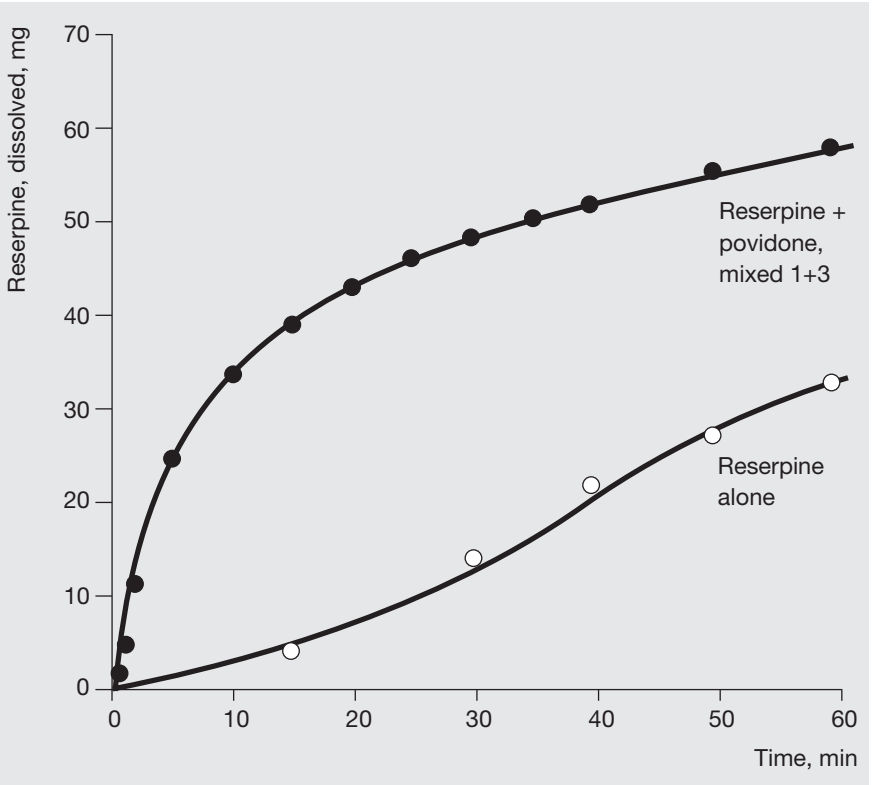


Fig. 2.41: Influence of povidone on the dissolution of reserpine [27]

2.4.3.2 Solid solutions/solid dispersions

If it is not possible to improve the bioavailability of a substance as desired by the addition of a solubilizing agent, this is frequently because the surface area of the crystals of active ingredient exposed to the solvent is too small. It is therefore necessary to increase the surface area, to accelerate dissolution. The first "solid dispersions" with antibiotics in povidone were described in the literature in about 1960 [49, 60]. In solid solutions and dispersions the active ingredient is embedded in a hydrophilic carrier to improve its bioavailability. The difference between a solid solution and a solid dispersion can be defined in terms of the state of the active substance. In a solid solution, it is present in an amorphous molecular form, while in a solid dispersion it is in the form of crystals that must be as fine as possible.

The soluble Kollidon® grades are excellent auxiliaries for the manufacture of effective solid solutions and dispersions as they
– possess excellent hydrophilization properties,
– are available in different molecular weights for different viscosities,
– form water-soluble complexes with many active ingredients, in contrast to most other carrier materials,
and
– are almost universally soluble.

This is why more than 150 active ingredients in solid solutions and dispersions with povidone have been described in the literature.

Manufacture of solid solutions:

Various techniques can be used to produce solid solutions and dispersions. The nomenclature for these is varied and not uniform, as can be seen from Table 2.76.

Table 2.76: Techniques of manufacture and nomenclature for solid solutions and solid dispersions with soluble Kollidon® grades

Technique	Designation of the solid solution/solid dispersion
Solvent method:	
– Spray-drying	Spray-embedded preparation
– Normal drying, vacuum-drying	Coprecipitate, coevaporate
– Freeze-drying, lyophilization	Lyophilisate
– Spray-drying of suspension	Spray-dried suspension [538]
Cogrinding, roll-mixing	Trituration
Melt extrusion (see also Section 2.4.3.7)	Extrudate

Unlike other polymers such as macrogol, melted povidone is almost not used as an embedding matrix for active ingredients, except in melt extrusion [663, 664, 666], because of its high melting point (over 180 °C).

Coprecipitates:

The most frequently described method of manufacturing solid solutions and dispersions with soluble Kollidon® grades has up to now been the solvent method. In this, the active ingredient and Kollidon® are dissolved together in a solvent and this is subsequently evaporated in an oven, under vacuum or sometimes by spray-drying.

If possible, ethanol is used as the solvent. Unfortunately, its solvent power is inadequate for a number of active substances. However, as the active ingredient should be completely dissolved to distribute it in the carrier in a very fine crystalline to amorphous form, it is then necessary to resort to the use of another organic solvent such as methylene chloride.

Triturations:

As it is nowadays often no longer practical to use organic solvents, it is recommended to select a different technique such as roll-mixing or comilling with povidone. That this method is also capable of producing an amorphous distribution of phenytoin and many other active ingredients is shown in Fig. 2.42 and in Table 2.77. In Fig. 2.42 two roll-mixed preparations are compared with the crystalline active substance and a solvent-coprecipitate by X-ray diffraction.

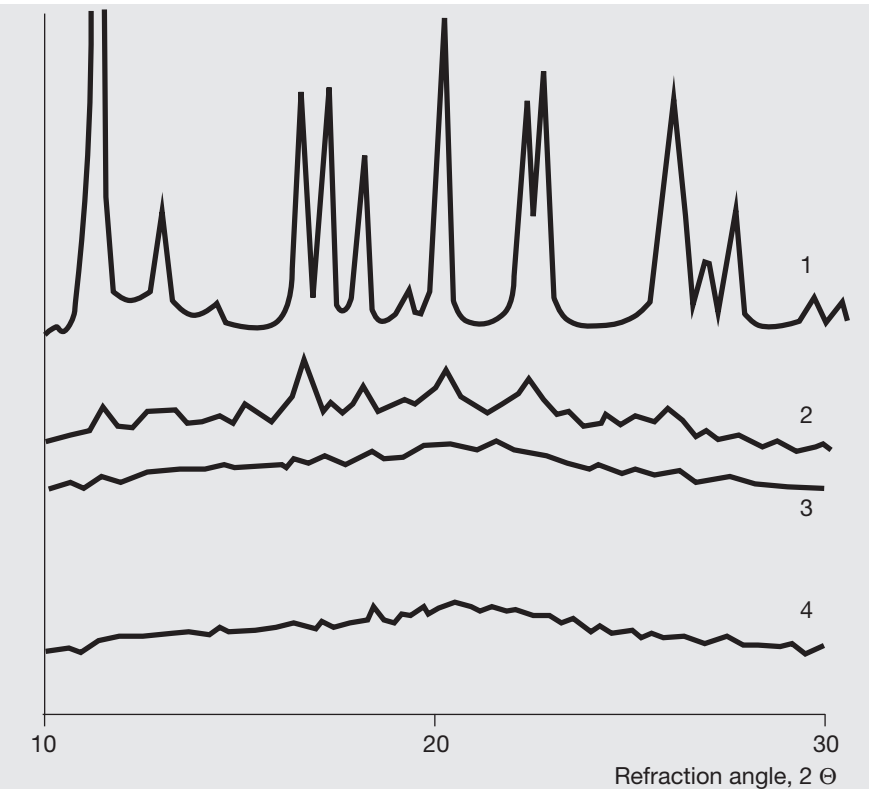


Fig. 2.42: Effect of the roll-mixing process on the crystallinity of phenytoin [226]:
1: Phenytoin without povidone
2: Phenytoin + povidone K 30 1 + 1
3: Phenytoin + povidone K 30 1 + 3
4: Phenytoin + povidone K 30 coprecipitate 1 + 3 (for comparison)

Table 2.77 shows that this milling or intimate mixing technique improves the dissolution and the bioavailability [378, 438] of many active ingredients. All the active substances were found to have an amorphous or at least partly amorphous structure in the mixtures, which indicates that they form complexes with povidone even in the absence of a solvent.

Table 2.77: Literature on the effect of comilling or physically mixing active ingredients with povidone on their crystallinity and dissolution rate (selection)

Active substance	Crystallinity	Improvement in dissolution	Literature reference
Amorbarbital	Amorphous	+	[430]
Atenolol	Partly amorphous	+	[613]
Chlordiazepoxide	Partly amorphous	+	[254]
Chlormadinone	n. d.	+	[378]
Clonazepam	Partly amorphous	+	[254]
Diacetylmidecamycin	Amorphous	n. d.	[432]
Diazepam	Partly amorphous	+	[254, 433]
Estradiol	Amorphous	+	[592]
Furosemide	Partly amorphous	+	[636]
Glibenclamide	(Partly) Amorphous	+	[572]
Griseofulvin	Amorphous	+	[351, 428, 436]
Hydrochlorothiazide	Partly amorphous	+	[550]
Ibuprofen	Amorphous	–	[557]
Indobufen derivative	Amorphous	+	[438]
Indomethacin	Amorphous	+	[351]
Medazepam	Partly amorphous	+	[254]
Menadione	Amorphous	+	[429]
Mydecamycin	Amorphous	n. d.	[381]
Nifedipine	Amorphous	+	[251, 352]
Nitrazepam	Partly amorphous	+	[254]
Oxytetracycline	Partly amorphous	+	[431]
Phenothiazine	Amorphous	+	[429]
Phenytoin	Amorphous	+	[226]
Praziquantel	Amorphous	+	[610, 638]
Prednisolone	n. d.	+	[437]
Sulfathiazol	Amorphous	+	[551]
Theophylline	Partly amorphous	+	[569]

n. d. = not determined

The physical stability of the mixtures tested [326, 352, 381, 432, 569] was found to be good, and no decrease in the dissolution rate was found after storage.

Kollidon® 25 and Kollidon® 30 are suitable for comilling, while the average molecular weight of Kollidon® 90 F could decrease under prolonged mechanical stress. As a rule, the mixtures are milled for one hour, though the best time must be determined individually for each active ingredient.

Ratio of active ingredient to povidone:

As can already be seen from Fig. 2.42, the ratio of the quantities of active ingredient and povidone is a further factor that influences the way in which the active substance is distributed in the matrix and therefore also the dissolution and bioavailability of the active ingredient. Although a 1 + 1 ratio already achieves a certain effect, it is only when the auxiliary is used in larger proportions, typically 1 + 3 to 1 + 10, that a molecular dispersion of the active ingredient in the carrier is obtained. Fig. 2.43 shows as an example the dissolution rate of sulfathiazole triturations with different quantities of povidone. Similar results were obtained with furosemide coprecipitates [259] and sulindac coprecipitates [604].

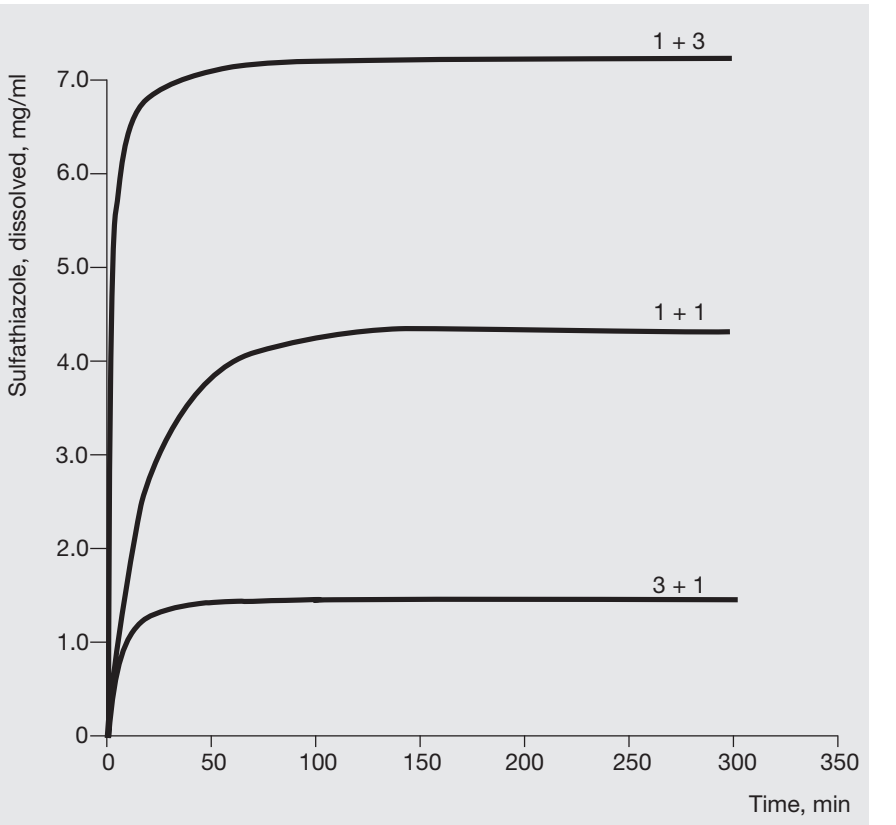


Fig. 2.43: Influence of the drug – povidone ratio on the dissolution of sulfathiazole triturations [551]

2.4.3.3 Influence of the molecular weight of the soluble Kollidon® grade

The influence of the molecular weight of the soluble Kollidon® grade on the dissolution and bioavailability of the embedded substance varies. It can generally be said only that the high-molecular Kollidon® 90 F grade is less suitable, as it has a high viscosity in water and therefore dissolves too slowly, delaying dissolution of the active ingredient. Frequently, no major differences

could be observed between the lower molecular weight grades, e. g. Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30, though with certain active substances, the dissolution rate was found to depend directly on the molecular weight of the povidone grade used [e. g. 44 b, 52 a, 306]. Naproxene [542] and sulfathiazole are such substances. Fig. 2.44 shows the dissolution of tablets made with 1 + 2 sulfathiazole coprecipitates with povidone of different molecular weights.

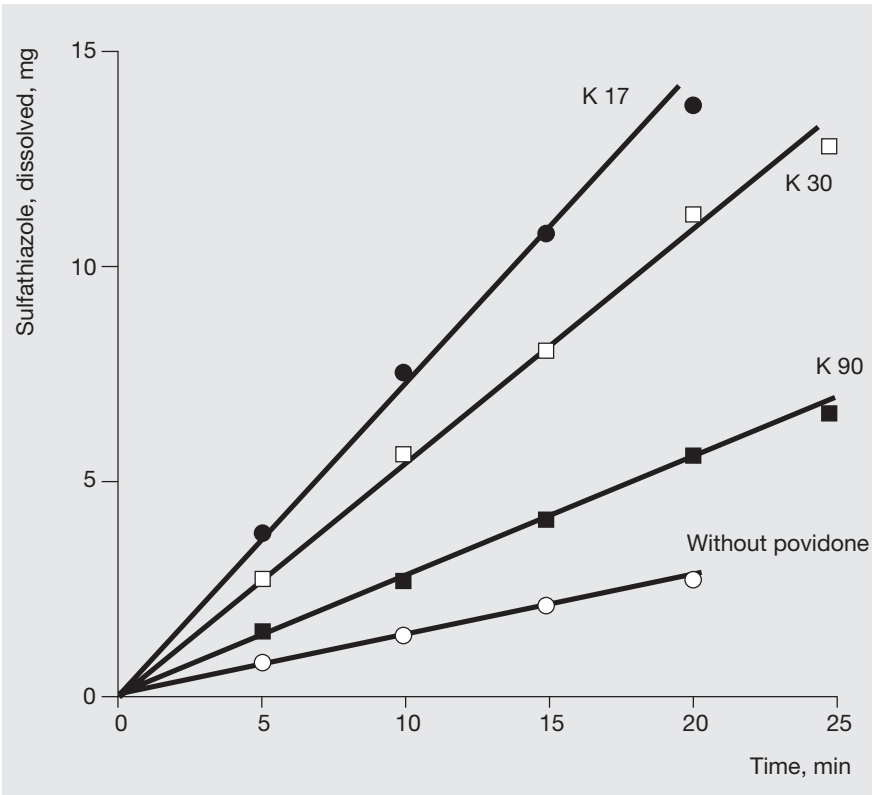


Fig. 2.44: Effect of the K-value of povidone on the dissolution of tablets made with sulfathiazole coprecipitates [30 a]

2.4.3.4 Bioavailability (in vivo)

Unfortunately, only a part of the many papers published on povidone deal with its influence on bioavailability in vivo. However, where results are available, they almost always show an improvement in bioavailability. Figs. 2.45 – 2.47 illustrate the effect of coprecipitation with povidone on the bioavailability of different active ingredients administered by different routes. Fig. 2.45 shows, as a typical example, the oral bioavailability of a nifedipine coprecipitate in the rat, Fig. 2.46 shows the rectal bioavailability of suppositories of a phenobarbital coprecipitate in rabbits, while Fig. 2.47 shows the effect of a hydrocortisone coprecipitate on the human skin after percutaneous administration. In all three cases, the same dose of the pure active ingredient without povidone was applied for reference.

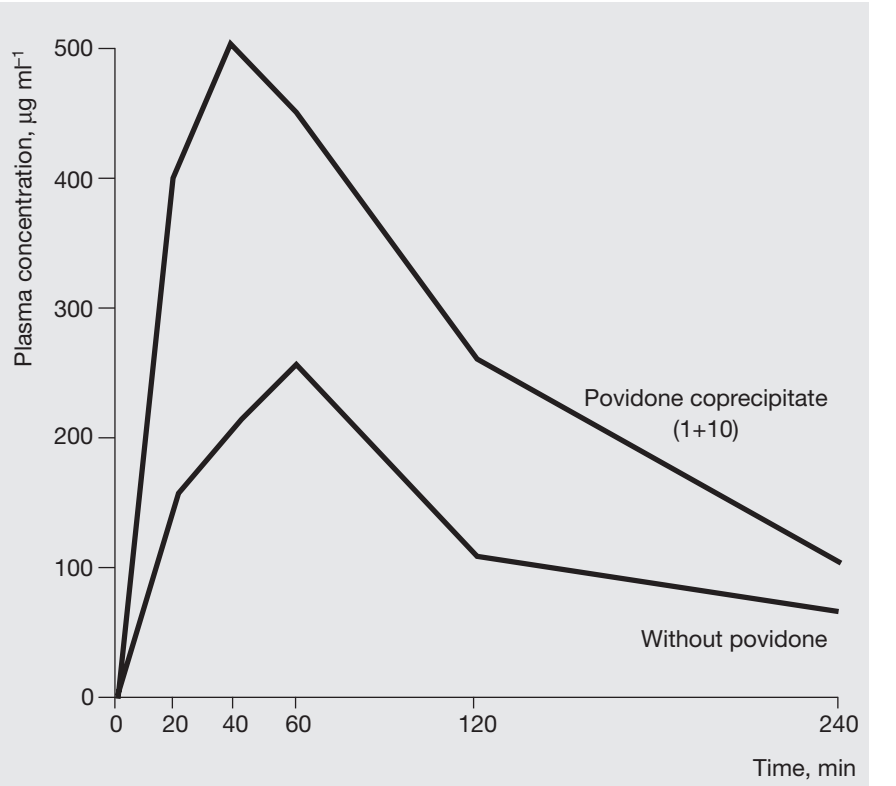


Fig. 2.45: Oral bioavailability of nifedipine in rats [253]

With nifedipine, the plasma level of the coprecipitate reaches twice that of the pure substance after two hours and in the case of the phenobarbital suppositories, it even reaches three times the level of the pure active substance. Also in the case of Lonetil suppositories the use of a povidone coprecipitate could increase the resorption [146].

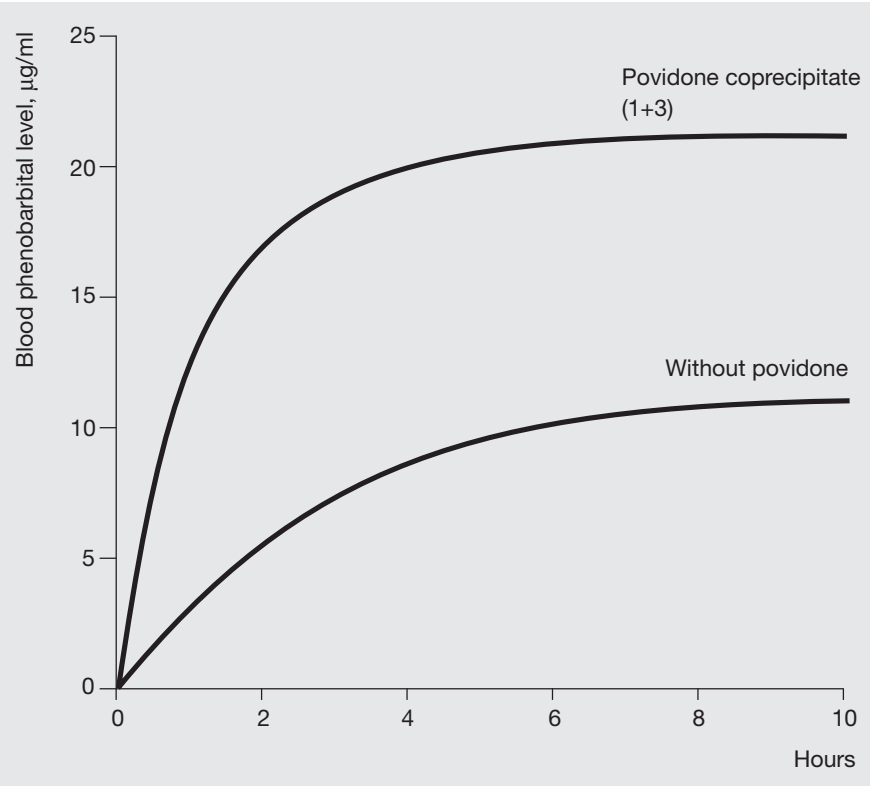


Fig. 2.46: Absorption of phenobarbital from suppositories in rabbits [224]

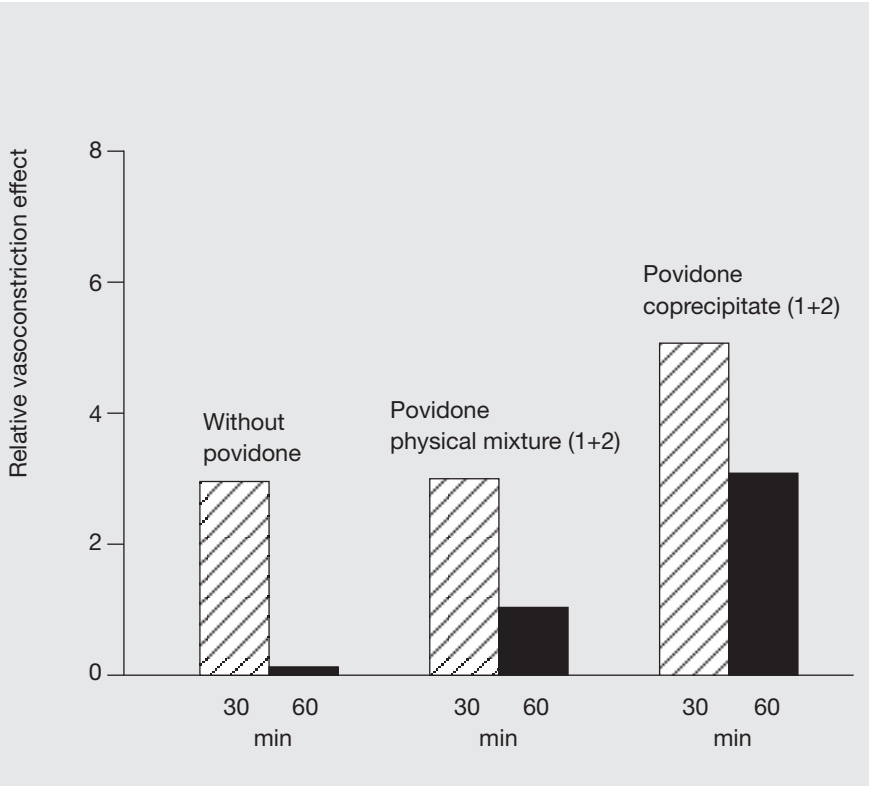


Fig. 2.47: Percutaneous effect of hydrocortisone acetate on the human skin [291]

With hydrocortisone acetate, coprecipitation with povidone not only results in a doubling of the percutaneous effect after 30 minutes, the effect also lasts much longer. Without povidone, no further effect could be observed after 60 minutes, while with the coprecipitate, the effect was as strong after one hour as it was after 30 minutes for the pure active ingredient. Similar effects of povidone are observed with progesterone in rats [645] and in transdermal systems (see Section 2.4.8.2), in combination of hydrocortisone with beta-cyclodextrin [556] and combined with 1,2-propylene glycol and estradiol [567].

Also the ocular bioavailability of disulfiram could be strongly increased after the instillation of a 1 % suspension of a solid dispersion with povidone K 30 in the eye of rabbits [634].

The bioavailability of solid solutions and dispersions of active ingredients in povidone has mainly been tested in rabbits, dogs, rats and in man. Table 2.78 lists a selection of the active substances for which results are available in the literature.

Table 2.78: Literature on improvement in bioavailability in vivo through the use of solid solutions and dispersions in povidone (selection)

Active ingredient	Man	Rabbit	Rat	Dog	Other
Azapropazone		[283], [284]			
Betamethasone	[291]				
Chloramphenicol				[45]	[230]
Chlormadinone			[378]		
Chlorothiazide			[285]		
Cyclosporine			[575]		
Digitoxin			[47b]		
Dihydroergotamine			[379]		
Dihydroergotoxine	[280]				
Furosemide	[287]				
Gentamycin			[336]		
Glibenclamide			[288]		
Gliquidone	[279]				
Griseofulvin				[290]	
Hexobarbital				[37]	
Hydrochlorothiazide	[53], [361]				
Hydrocortisone	[291]				
Indobufen derivative				[438]	
Kanamycin			[336]		
Lonetil			[146]		
Lorazepam			[292]		
Mefenamic acid	[366]	[283], [284], [293]			
Nabilone	[294]			[294]	
Nifedipine		[295], [299], [358]	[253]	[205], [297]	[298]
Nitrofurantoin	[300]				
Nystatin					[301]
Phenobarbital		[224]			
Phenytoin	[25], [150], [303]	[184], [304]			
Reserpine		[224]	[47a], [305]		
Rifampicin	[270]		[270]		
Sulfamethoxazole	[194]				
Sulfisoxazole	[145], [306]	[261]			
Tetracycline	[274]				
Tinidazole			[292]		
Tolbutamide		[111]	[63]		
Tyrothricin					[49]

2.4.3.5 Stability of solid solutions

As the active ingredient in a solid solution is in an amorphous state and therefore in a more energetic form, and as its surface area is much greater both in solid solutions and in solid dispersions, the question of its physical and chemical stability arises. The main criterion for physical stability is the extent of recrystallization, which can reduce the bioavailability of the active ingredient. Surprisingly, a survey of publications in which recrystallization and chemical stability have been investigated reveals only relatively few cases of instability. Table 2.79 contains a list of publications with stability data for solid solutions of active ingredients in povidone with a brief assessment of the results for both the chemical and the physical stability. A negative influence of the storage on the release was reported for ibuprofen.

One of the substances that have been subjected to a very long stability test, in a coprecipitate with Kollidon® 30 (1 + 9), is phenytoin. Its dissolution rate was practically the same after two years (Section 2.4.3.6).

Table 2.79: Literature on the stability of solid solutions/dispersions of active ingredients in povidone compared with the pure active ingredients (selection)

Active ingredient	Chemical stability		Physical stability	
	Good	Inferior	Good	Inferior
Amoxicillin		[292], [355]		
Chlordiazepoxide		[104]		
Chlorthalidone			[308]	
Clonazepam			[149a]	
Colecalciferol	[309]			
Diacetylmidecamycin			[432]	
Diazepam	[481]		[481]	
Dihydroergotamine			[310]	
Flunitrazepam			[149a]	
Furosemide	[259], [265]		[178], [259], [265]	
Gliquidone			[614]	
Griseofulvin			[588]	[312]
Hydrocortisone	[313]		[295], [313]	
Hydroflumethiazide			[315], [316]	
Indomethazin		[513]		
Ketoconazol			[643]	
Lonetil	[318]		[318]	
Lorazepam	[292]			
Lynestrenol		[311]		
Medazepam	[104]			
Mefruside			[319]	
Mydecamycin			[381]	
Nabilone			[294]	
Nifedipine	[135], [205], [297], [321]		[321], [352] [576]	[135], [205], [297], [322]
Nitrazepam			[149a], [323]	
Nitrofurantoin	[300]			
Oxodipine			[508]	
Phenobarbital			[314]	
Phenytoin	[326]		[31], [326]	
Prostaglandin	[327]			
Reserpine	[387]			
Salbutamol	[292], [328]		[328]	
Sulfamethizole			[61]	
Sulfisoxazole				[61]
Sulindac			[604]	
Testosterone			[52a]	
Tinidazole		[292]		

2.4.3.6 Practical application in formulations

In spite of the many papers published on them and the often major improvements in bioavailability and the stability they provide, solid solutions and dispersions in povidone have up to now only found use in a few commercial products. Tables 2.80 and 2.81 show how phenytoin and nifedipine, for example, can be processed relatively straightforwardly in the form of a physical mixture or coprecipitate with soluble Kollidon®. Cyclosporine, oxodipine and spironolactone tablets or norethindrone suppositories are further examples [508, 533, 566, 575]. It is interesting to compare the dissolution data for phenytoin after manufacture and after two years' storage at room temperature. In Figs. 2.48 and 2.49 no major difference can be seen.

Table 2.80: Tablet formulation with phenytoin and Kollidon® 30 [326]

Formulation:

I	Phenytoin	10 mg
	Kollidon® 30	90 mg
II	Corn starch	7 mg
	Lactose	3 mg

Production:

Method I (physical mixture):
Prepare Mixtures I and II, mix and press into tablets.

Method II (coprecipitate):
Dissolve phenytoin and Kollidon® 30 together in an organic solvent, evaporate this to dryness and mix the resulting coprecipitate with II, then press into tablets.

Properties of the tablets:

	Method I	Method II
Weight:	110 mg	110 mg
Diameter:	6 mm	6 mm
Disintegration time (after manufacture):	7 min	8 min
Disintegration time (after 2 years):	7–8 min	10 min
Dissolution:	see Figs. 2.48 and 2.49	

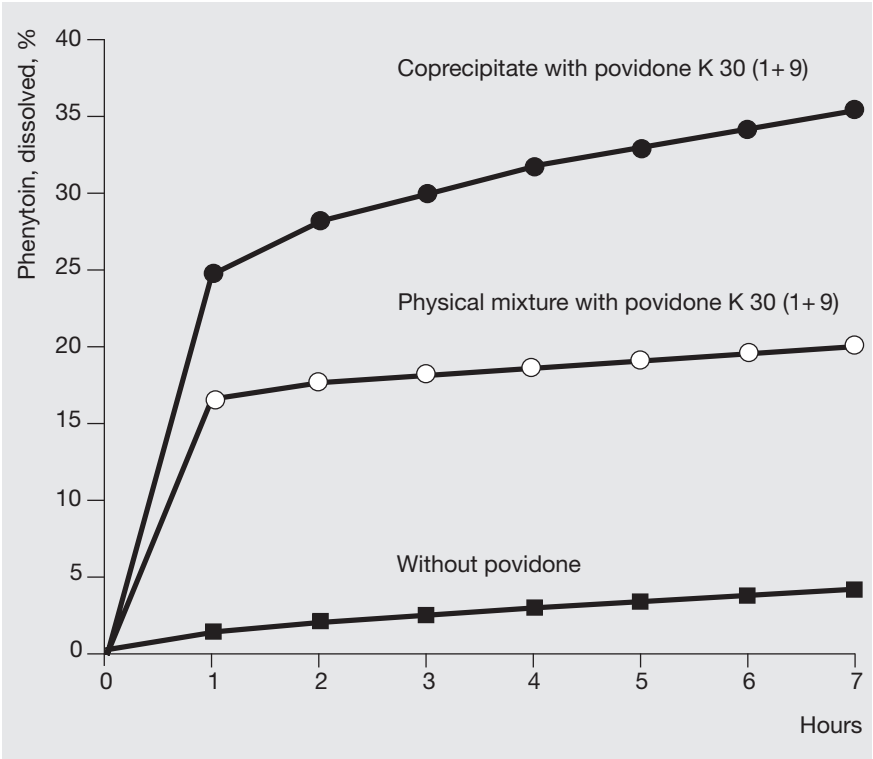


Fig. 2.48: Dissolution of phenytoin from tablets after manufacture (formulation see Table 2.80) [326]

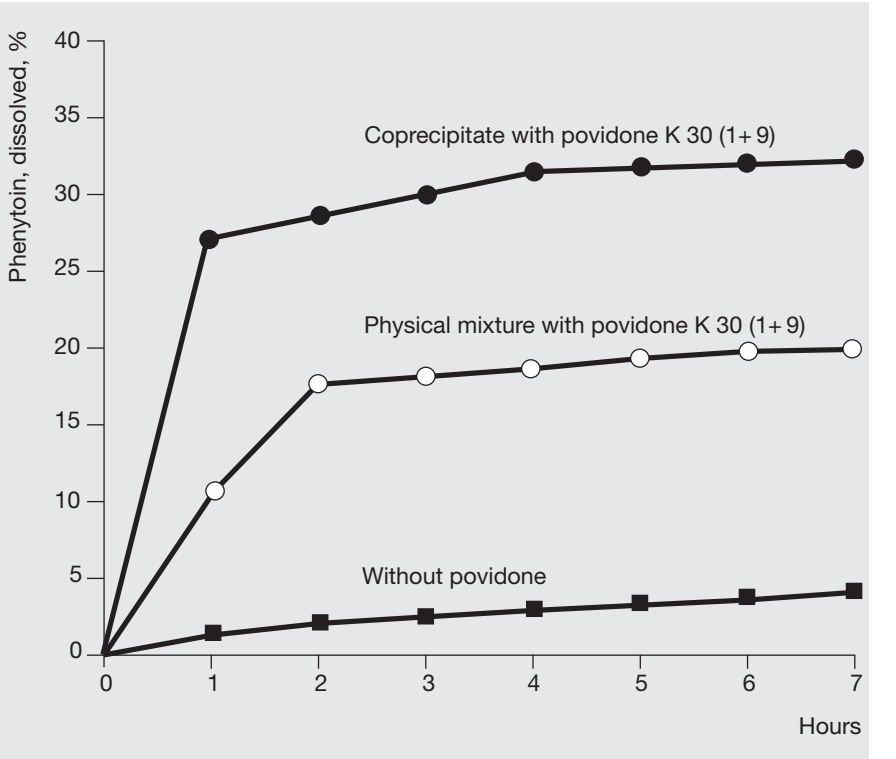


Fig. 2.49: Dissolution of phenytoin from tablets after storage for 2 years at 20 °C (formulation see Table 2.80) [326]

The difference found between the two nifedipine tablet formulations in Table 2.81 stems from the way in which the coprecipitate is produced. In Formulation No. 1 it is produced separately and subsequently pressed together with a further granulate. In Formulation No. 2, the coprecipitate is formed on the surface of the cellulose during granulation, an interesting variation. If all Kollidon® CL was used intragranulary the dissolution was even faster.

Table 2.81: Nifedipine tablets made from coprecipitates with Kollidon® 25 [240b]

Formulations:	No. 1	No. 2
I Nifedipine	100 g	100 g
Kollidon® 25	400 g	400 g
II Methylene chloride	1500 g	1800 g
III Microcrystalline cellulose	1050 g	1050 g
Corn starch	350 g	200 g
Kollidon® CL	–	100 g
IV Corn starch paste	50 g	–
V Kollidon® CL	246 g	146 g
Magnesium stearate	4 g	4 g

Production of Formulation No. 1:
Dissolve I in II, dry, sieve. Granulate III with IV, dry and sieve. Mix I/II, III/IV and V and press into tablets.

Production of Formulation No. 2:
Dissolve I in II and granulate mixture III with solution I/II. Dry, sieve, mix with V and press into tablets.

Properties of the tablets:

	No. 1	No. 2
Nifedipine content	10 mg (± 4.1 %)	10 mg (± 1.0 %)
Weight	220 mg	220 mg
Dissolution rate (USP)	50 % in 10 min	50 % in 5 min

There are two reasons why there are relatively few preparations based on coprecipitates. One is that it is necessary to use an organic solvent and the other is that an excess of the matrix is required to achieve the desired improvement in bioavailability.

With drugs that must be given in high doses, the large quantity of matrix limits the applications of solid solutions considerably, as it is difficult to produce tablets, capsules etc. of normal size. In addition, a large quantity of active ingredient and polymers requires the use of a large quantity of organic solvent.

There are at least theoretical solutions to these two problems. The large volume is less of a problem in dosage forms such as instant or effervescent granules of ibuprofen [505], while the use of large quantities of solvents can sometimes be avoided by using a solvent-free production process such as the roll-mixing process or triturations.

2.4.3.7 Further publications on solid solutions/solid dispersions including melt extrusion

In addition to the publications listed in Tables 2.77 – 2.79, there is a series of further literature sources in which only the dissolution or the crystallinity of the solid solutions is investigated, without any determination of their stability, bioavailability or solubilization effect (i. e. increase in absolute solubility, see Section 2.4.5). Table 2.82 gives a limited selection of such publications including melt extrusions.

Table 2.82: Literature on solid solutions/dispersions or melt extrusion of active ingredients and povidone, without stability, bioavailability or solubilization results (selection)

Active ingredient	Literature reference
Albendazole	[537]
Carbamazepine	[252, 664 melt extrusion]
Dexamethasone	[59]
Diazepam	[183]
Digoxin, acetyldigoxin	[105, 112, 204]
Dihydroergotamine	[109, 263]
Dipyridamole	[268]
Estradiol	[57, 629 melt extrusion, 667 melt extrusion]
Felodipine	[531]
Furosemide	[258]
Glibenclamide	[237]
Gramicidin	[49]
Hydrocortisone	[139, 148]
Indomethacin	[668 melt extrusion]
Itraconazole	[665 melt extrusion]
Lacidipine	[668 melt extrusion]
Mefruside	[219]
Methylprednisolone	[52b]
Naproxen	[264]
Nifedipine	[668 melt extrusion]
Nimodipine	[577]
Nystatin	[56]
Piroxicam	[585]
Prednisone	[52b, 148]
Propylthiouracil	[348]
Spironolactone	[206]
Streptomycin	[60]
Temazepan	[597]
Terfenadine	[470]
Tolbutamide	[668 melt extrusion]
Trimethoprim	[153, 496, 664 melt extrusion]

2.4.4 Tablet coatings

2.4.4.1 Sugar coating

Mainly Kollidon® 25 and Kollidon® 30 are used in traditional sugar coating. The use of Kollidon® 90 F often leads to an excessive increase in viscosity. Kollidon® 25 and Kollidon® 30 have a number of physical properties (Table 2.83) that benefit the coating process and improve the quality of the coatings.

Table 2.83: Important properties and functions of Kollidon® 25 and Kollidon® 30 for tablet coatings

Property	Function
Film formation	Avoidance of hairline cracks/crazing
Adhesion	Adhesion of the sugar layer to the tablet core
Affinity to hydrophobic surfaces	Adhesion of the tablet coating to cores with hydrophobic substances
Dispersive effect	Homogeneous distribution of the pigment or colour lake in the tablet coating
	Stabilization of the coating suspension containing a pigment or colour lake
Retardation of crystallization	Slower and more homogeneous crystallization of the sugar

Sugar coatings are particularly susceptible to cracking when they are applied to large batches of tablet cores that are dried rapidly. As most active ingredients are hydrophobic, Kollidon® 25 and Kollidon® 30 are useful as additives to prevent the tablet coating peeling during manufacture. Particularly when soluble dyes are used, Kollidon® 25 and Kollidon® 30 are useful in achieving an even distribution of the dye and preventing its migration, as well as increasing the capacity of the coating suspension for the dye.

Povidone also stabilizes suspensions of iron oxide pigment particles particulary when it is combined with small amounts of sodium dodecyl sulfate [421].

The formulation for a sugar-coating solution in Table 2.84 was taken from one of the many publications on the use of povidone in sugar coating [168–173].

Table 2.84: Coating suspension with Kollidon® 30 for manual sugar coating

Sucrose	2130 g
Titanium dioxide	45 g
Kollidon® 30	15 g
Colour lake	12 g
Lutrol® F 68 (= Poloxamer 188)	3 g
Water	870 g

Apart from its use in traditional manual sugar coating, Kollidon® 30 makes it possible to automate the sugar coating process. Table 2.85 gives a suitable formulation.

Table 2.85: Spray suspension for automatic sugar coating [231]

Sucrose	76 g
Kollidon® 30	8 g
Titanium dioxide	9 g
Calcium carbonate	9 g
Talc	29 g
Colorant/pigment (e. g. Sicovit® iron oxide)	q. s.
Glycerol	4 g
Water	63 g

40 kg of tablet cores with a weight of 420 mg were sprayed with 25 kg of the above suspension in a conventional coating pan under the following conditions:

Spray phase:	5 s
Interval:	10 min
Drying phase (warm air):	10 min
Total coating time:	16 h

2.4.4.2 Film-coatings

The properties given in Table 2.83 for Kollidon® 25 and Kollidon® 30 are also useful in the film-coating of tablets, pellets and hard gelatin capsules [281].

The glass transition temperatures (Tg) of the soluble Kollidon® grades lie between 90 °C and 189 °C, depending on their molecular weight and on the moisture content [524]. Tg values of 130 °C, 155 °C, 168 °C and 178 °C have been measured for dried Kollidon® 17 PF, Kollidon® 25, Kollidon® 30 and Kollidon® 90 [485].

Kollidon® 90 F is only seldom used for film-coating (see Table 2.86). Its most important properties here are film formation, adhesion promotion [276], pigment suspension stabilization and the improvement of the solubility of other film-forming agents and of the final coating in water [100].

A disadvantage of the Kollidon® grades in film-coating is their hygroscopicity (see Section 2.2.5) and tackiness. This is why they are normally never used as the sole film-forming agent for tablets. Table 2.86 gives formulations for coating solutions containing ethylcellulose and shellac, which give non-stick tablet coatings [176]. The incorporation of Kollidon® in these soluble film-coatings brings about an increase in the dissolution rate of the other film-forming agent, thus accelerating the disintegration of the tablet and the release of the active substance [100].

Table 2.86: Film-coating solutions with ethylcellulose or shellac and Kollidon® [176]

	Shellac	Ethylcellulose
Kollidon® 30	125 g	125 g
Kollidon® 90 F	125 g	125 g
Shellac	250 g	–
Ethylcellulose 10 mPa · s	–	250 g
Diethyl phthalate	200 g	200 g
Colorant	q. s.	q. s.
Ethanol 75 %	ad 10 kg	ad 10 kg

In formulations with shellac, Kollidon® 25 and Kollidon® 30 can be used to compensate for variations in quality of this natural product, which can affect the flexibility and dissolution rate of the coating [174, 175]. In other formulations, it may be possible to reduce the quantity of povidone (10–20%, in terms of the shellac) [174].

Kollidon® 25 and Kollidon® 30 have also proved useful in acrylate copolymer (e. g. Kollicoat® MAE grades) or polyvinyl acetate (e. g. Kollicoat® SR 30D) film-coatings. In this application the film-forming and pigment suspension stabilizing properties of soluble Kollidon® are used [662]. Table 2.87 gives typical formulations for a spray suspension for enteric coatings with Kollicoat® MAE 30DP or Kollicoat® MAE 100P.

Table 2.87: Formulation of an enteric coating with methacrylic acid copolymer Kollicoat® MAE and Kollidon® 30 [662]

	Weight (g) for 5 kg pellets	Per cent
Polymer suspension:		
Alternative I:		
Kollicoat® MAE 30DP	2250,0	50,0
1,2-Propylene glycol	67,5	1,5
Water	1435,0	31,9
Alternative II:		
Kollicoat® MAE 100P	675,0	15,0
1,2-Propylene glycol	67,5	1,5
Water	3010,5	66,9
Pigment suspension:		
Talc	180,0	4,0
Titanium dioxide	45,0	1,0
Kollidon® 30	22,5	0,5
Water	500,0	11,1
Total	4500,0	100,0

2.4.4.3 Subcoatings for tablet cores

As mostly aqueous solutions and dispersions are used for coating these days, it has become increasingly necessary to provide the tablet cores with a subcoating before sugar or film-coating. This is mainly to provide a barrier to protect active ingredients in the tablet core that are sensitive to water, i. e. substances that are prone to hydrolysis or react with each other in the presence of water, e. g. vitamins, or to avoid swelling of high-performance tablet disintegrants, which start to swell even with small quantities of water. From Table 2.88 it can be seen that Kollidon® 25 and Kollidon® 30 are also able to hydrophilize the surface of the tablet core and reduce dust formation.

Table 2.88: Reasons for subcoating tablet cores and the functions of Kollidon® 25/ Kollidon® 30 in these applications

Reasons for subcoating tablet cores	Function of Kollidon® 25/Kollidon® 30
Instability of the active substance towards water (hydrolysis)	Formation of a barrier layer on the surface and in the pores
Chemical reactions between the active ingredients (e. g. vitamins)	Formation of a barrier layer on the surface and in the pores
The presence of high-performance disintegrants	Formation of a barrier layer on the surface and in the pores
Hydrophobic surface of the tablet core	Improvement in adhesion of subsequent coatings by hydrophilization of the surface
Dust formation (friability of the tablet cores)	Loose particles are bound to the surface of the tablet core

Subcoating with Kollidon® 25 or Kollidon® 30 is best carried out in the same machine as the subsequent sugar or film-coating. Using a 10 % solution in 2-propanol or ethanol, adequate protection can be obtained with a coating of less than 1 mg of Kollidon®/cm^2 tablet surface.

2.4.5 Improvement of the solubility of active ingredients by soluble Kollidon® grades (solubilization)

2.4.5.1 General

As the majority of the active ingredients used today have relatively poor solubility in water, and organic solvents are very seldom used in liquid dosage forms, the use of auxiliaries for solubilization is playing an increasingly important role.

The excellent solubility in water of the soluble Kollidon® grades as well as their ability to form water-soluble complexes with active ingredients can be taken advantage of to increase the absolute solubility of an active substance. As explained in Section 2.2.7.1, whether an active ingredient forms a complex with Kollidon® depends on its chemical structure.

This property can be taken advantage of in almost all liquid dosage forms (Table 2.89), though in particular applications, some grades of Kollidon® are more suitable than others.

Table 2.89: Kollidon® grades used as solubilizers in liquid dosage forms

Dosage form	Soluble Kollidon® grade				
	12 PF	17 PF	25	30	90 F
Injectables (solutions or suspensions)	+	+	–	–	–
Lyophilisates for injection	+	+	–	–	–
Lyophilisates for oral administration	–	–	+	+	+
Oral drops	–	–	+	+	+
Syrups, oral solutions	–	–	+	+	+
Ophthalmic products	–	+	+	+	+
Nose drops, ear drops	–	+	+	+	+
Topical solutions	–	–	+	+	+

There is a direct connection between the use of soluble Kollidon® as a solubilizer and its function in delaying crystallization. This is particularly important in suspensions as recrystallization of the dissolved active ingredients brings about significant changes in the physical properties of the suspension (volume of sediment, redispersibility by shaking).

2.4.5.2 Injectables for human and veterinary administration

When drugs are to be administered by the parenteral route, solubilization plays a more important role than in oral administration, as with the latter, a solid dosage form is equally acceptable. Therefore the endotoxin-free types, Kollidon® 12 PF and Kollidon® 17 PF are recommended for parenterals. The molecular weight of both products is low enough (see Section 2.2.6) to allow rapid renal elimination without storage. In many countries in Europe, e. g. Germany and Austria, only such low-molecular povidone types with a K-value of up to 18 are allowed for injection (see Section 6.1.3).

Kollidon® 12 PF and Kollidon® 17 PF are nowadays widely used in different injectables e. g. in antibiotic, sulfonamide, melphalan, meclofenoxat, metronidazol, mistellectine, taurolidine and trimethoprim formulations. Fig. 2.50 shows, as an example, how the solubilization of rifampicin depends directly on the povidone concentration. A similar linear relationship between the concentrations of povidone and solubilized active ingredient was found for sulindac [604].

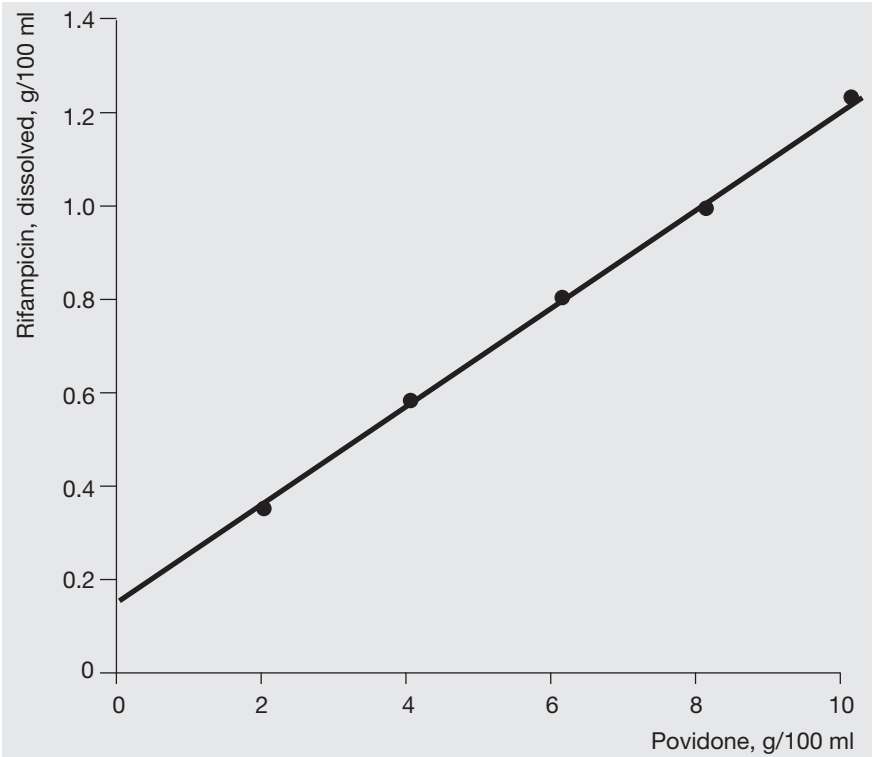


Fig. 2.50: Solubilization of rifampicin with low-molecular povidone [270]

In some veterinary injectables low molecular weight povidone is combined with 2-pyrrolidone (Soluphor® P). Typical examples are oxytetracycline [163], ivermectin [628] and sulfonamides [164].

Table 2.90 shows the composition of a commercially available oxytetracycline preparation for injection in animals, that contains Kollidon® 17 PF as a solubilizing agent. A positive side-effect of the use of Kollidon® 17 PF is a reduction in the local toxicity of oxytetracycline.

Table 2.90: Composition of a commercially available oxytetracycline ampoule [113]

Oxytetracycline hydrochloride	5.70 g
Magnesium oxide	0.46 g
Reducing agent	0.50 g
Kollidon® 17 PF	10.00 g
Ethanolamine	q. s. (pH 8.8)
Water	ad 100 ml

There are a large number of publications and papers in which the increase in absolute solubility of active ingredients by povidone has been tested and described. However, if the selection is restricted to the low-molecular types,

Kollidon® 12 PF and Kollidon® 17 PF, this number becomes significantly smaller (Table 2.92). Naturally, a solubilization effect can also be expected of Kollidon® 12 PF and Kollidon® 17 PF, even if such an effect is reported in the literature only for the higher molecular weight Kollidon® 30 (see Table 2.96), though the amounts of active substance complexed may differ according to the molecular weight of the Kollidon® (see Table 2.91). However, the influence of the molecular weight depends very much on the active ingredient: with trimethoprim and chloramphenicol it is very large, while with phenobarbital it is small.

Table 2.91: Influence of the molecular weight of the Kollidon® grade on solubilization

Kollidon® grade	Active ingredient dissolved in 25 % aqueous Kollidon® solution	
	Trimethoprim	Phenobarbital
Without	0.4 mg/ml	approx. 1 mg/ml
Kollidon® 12 PF	2.5 mg/ml	10.5 mg/ml
Kollidon® 17 PF	5.0 mg/ml	12.5 mg/ml
Kollidon® 25	10.0 mg/ml	> 13 mg/ml

Table 2.92: Selection of literature on increase in the solubility of active ingredients by low-molecular povidone, e.g. Kollidon® 12 PF and Kollidon® 17 PF (see also Table 2.96)

Active ingredient	Solubility increase factor	Ratio of active ingredient to povidone	Literature reference
Acetaminophen	approx. 2	1 + 9	[154, 659]
Ajmaline	approx. 10	1 + 5	[33]
Allopurinol	–	–	[32]
Amoxicillin	–	2 + 1 to 1 + 3	[185]
Carbamazepine	–	–	[529]
Clonazepam	16	–	[149b]
Danofloxacin	–	1 + 1	[626]
Doxycycline	–	–	[110]
Flunitrazepam	9	–	[149b]
Furaltadone	approx. 7	1 + 5	–
Hydrochlorothiazide	7–9	1 + 4	[53, 550]
Hydroflumethiazide	4	3 + 1	[34, 316]
Hydroxystaurosprine	500	–	[552]
Metronidazole	5	1 + 5	–
Nitrazepam	13	–	[149b]
Oxytetracycline	>13	1 + 1	[22, 23, 163, 193, 562]
Piroxicam	–	1 + 2	[512]
Prednisolone	2	1 + 10	[345]
Rafoxanide	–	1 + 3	[182]
Rifampicin	>6	1 + 6	[270]
Sulfadimethoxine	–	–	[164]
Sulfamethazine	–	–	[164]
Tenidap	>30	3 + 1	[526]
Trimethoprim	>12	1 + 50	[496]

2.4.5.3 Lyophilisates

Lyophilisates are produced for parenteral and for oral preparations, e. g. drink ampoules. Soluble Kollidon® grades are used to bind the lyophilisate together during freeze-drying and to improve the solubility, stability and even the absorption of the active ingredient by virtue of its hydrophilic and complexing properties [185, 186, 244 – 249, 264, 278, 424, 482, 622, 656]. A typical example is melphalan [608, 611]. Table 2.93 shows a simple example of an antibiotic lyophilisate. An important reason for incorporating antibiotics in lyophilisates is that they are more stable in this form than in solutions.

Table 2.93: Amoxicillin lyophilisate for injection [185]

Amoxicillin sodium	6.25 g
Kollidon® 12 PF	7.50 g
Water for injections	ad 100 ml

After freeze-drying, fill 550-mg portions of the lyophilisate into ampoules.

Prior to administration, the contents of an ampoule are mixed with 1.9 ml of water to give a clear injection solution.

2.4.5.4 Oral and topical solutions

The different grades of soluble Kollidon® can be used in oral drops, oral solutions, syrups and in topical solutions to improve the solubility of active ingredients in the same way as in parenteral dosage forms. The medium and higher molecular weight grades, Kollidon® 25, Kollidon® 30 and Kollidon® 90 F are usually used for this purpose, as they increase the viscosity of the solutions, which can be an advantage in providing a constant drop rate or improving the appearance or the adhesion to the skin.

Tabs. 2.94 and 2.95 give formulations for acetaminophen and diclofenac oral solutions that were developed on a laboratory scale, as typical examples. In the case of acetaminophen, Kollidon® 25 not only solubilizes the active substance, it also reduces its bitter taste [625]. Similar effects are described in the case of sulfamethoxazol and trimethoprim [21, 625].

Table 2.94: Acetaminophen oral solution (500 mg/10 ml)

Acetaminophen (paracetamol)	50 g
Sorbitol, cryst.	50 g
Kollidon® 25	200 g
Sodium cyclamate	30 g
1,2-Propylene glycol	200 g
Flavouring	2 g
Glycerol	150 g
Water	318 g

Dissolve all the solid substances in a mixture of the liquid components at room temperature.

Table 2.95: Diclofenac oral solution (1.5 %)

Diclofenac sodium	1.5 g
Kollidon® 30	2.5 g
Sucrose	40.0 g
Water	56.0 g

Dissolve Kollidon® 30 and then diclofenac sodium in the sucrose syrup.

Further to the active ingredients listed in Table 2.92, that can be solubilized with the low-molecular grades of Kollidon®, Table 2.96 gives a series of further active ingredients whose solubility can be increased with medium and high-molecular Kollidon®. Naturally, the solubility of the active substances listed in Table 2.92 can also be improved with Kollidon® 25, Kollidon® 30 or Kollidon® 90 F, though not always to the same extent as shown in Table 2.91.

Table 2.96: Examples of further active ingredients whose solubility can be increased with povidone, e.g. Kollidon® 30 (= Supplement to Table 2.92)

Active ingredient	Solubility increase factor (where given)	Ratio of drug to povidone (where given)	Literature reference
Aminobenzoic acid		1 + 1	[269]
Chloramphenicol	15	1 + 5	–
Chlordiazepoxide	1.7–3.5	1 + 25	[104, 228, 254]
Chlorhexidine			[356]
Cinnarizine	2	1 + 3	[165, 333]
Clonazepam	2	1 + 25	[254]
Cloxacillin			[334]
Coumarin		2 + 3	[25]
Dapsone			[356]
Diazepam	2	1 + 25	[254]
Diclofenac		1 + 3	[630]
Digoxin	2.5	1 + 100	[159]
Ergot alkaloids			[337]
Erythromycin		1 + 5	[242, 338]
Furosemide			[356]
Glibenclamide			[339]
Gramicidin		1 + 3	[49]
Griseofulvin	2	1 + 1	[24, 337, 340]
Ibuprofen	8	1 + 1	[277, 342]
Indomethacin			[333, 356]
Iodine	>100	1 + 10	–
Ketoprofen		1 + 2	[196]
Lonetil	2	1 + 10	[136, 333]
Lorazepam			[330]
Medazepam		1 + 25	[104, 254]
Nifedipine	3.5	1 + 3	[205]
Nitrofural	4		[162]
Nitrofurantoin	3–5		[162]

Active ingredient	Solubility increase factor (where given)	Ratio of drug to povidone (where given)	Literature reference
Nystatin	6–10	1 + 5	[52b, 301, 343, 347]
Oxazepam			[228]
Pentazocine	> 8	1 + 3	[344]
Phenobarbital	2	1 + 10	[159]
Phenytoin	1.5	1 + 10	[187, 256, 326]
Progesterone	2.8		[151]
Reserpine	3.5	1 + 10	[27, 305]
Rutin			[334]
Spironolactone			[346]
Sulfathiazole	10	1 + 2	[138]
Sulindac	4		[604]
Testosterone	2		[151]
Tetramisole		2 + 1	[579]
Tranilast		1 + 3	[354, 596]
Tyrothricin		1 + 2	[29, 49]

2.4.5.5 Ophthalmic solutions

The ability of the soluble Kollidon® grades to increase the solubility of active ingredients is just as useful in eye drops as in parenterals (Table 2.97).

Table 2.97: Examples of active ingredients for ophthalmic preparations, that can be solubilized with Kollidon®

Chloramphenicol
Prednisolone
Rifampicin
Tyrothricin

Table 2.98 below gives an example of a formulation for a 3 % chloramphenicol solution developed on a laboratory scale for application to the eye.

Table 2.98: Chloramphenicol solution for eye drops [615]

Chloramphenicol	3.0 g
Kollidon® 25	15.0 g
Preservative	q. s.
Water	ad 100.0 g

The film-forming and viscosity-increasing effects of the Kollidon® products have been recognized as positive side-effects in ophthalmic solutions (see Section 2.4.7).

2.4.5.6 Soft gelatin capsules

To obtain clear soft gelatin capsules of insoluble active ingredients povidone and e. g. triesters of citric acid can be combined [560].

Also for the solubilization and enhancement of bioavailability of active ingredients incorporated in soft gelatin capsules povidone is used.

2.4.6 Soluble Kollidon® grades in suspensions, dry syrups and instant granules

2.4.6.1 General

Various auxiliaries with different functions are used in suspensions or dry syrups and instant granules for the preparation of suspensions. These include thickeners, hydrophilic polymers as dispersing agents, sugars, surfactants, electrolytes, colorants, etc. [296].

All the Kollidon® grades can be used as hydrophilic polymers to physically stabilize suspensions [39, 119]. Their most important and primary function in all suspensions is as protective colloids, which hydrophilize the individual solid particles and sterically separate them. This increases the volume of any sediment and makes it easier to redisperse by shaking. Soluble Kollidon® grades also prevent the dissolved portion of the active ingredient from crystallizing out by forming soluble complexes with it [389] (see also Sections 2.2.7.1 and 2.4.5). The Zeta potential of many substances, e. g. iron oxide pigments, can also be reduced with povidone [421].

2.4.6.2 Oral suspensions, dry syrups and instant granules

In addition to the functions given above, the thickening effect of medium and high-molecular povidone is also used in oral suspensions. This particularly applies to Kollidon® 90 F, which gives solutions of significantly higher viscosity than, for example, Kollidon® 25 (Section 2.2.3) and enhances the redispersibility. The effect of the viscosity on the sedimentation rate of a suspension is given by Stokes' Law for Newtonian fluids (Table 2.99).

Table 2.99: Stokes law for the calculation of the sedimentation rate of a suspension

$$\text{Sedimentation rate} = \frac{2\, r^2\, (d_1 - d_2) \cdot g}{9\, \eta} \text{ (cm/s)}$$

η = Viscosity of the suspension
r = Radius of the particles
d_1 = Density of the suspended phase
d_2 = Density of the liquid phase
g = Gravity

If the suspension has pseudoplastic properties, the sedimentation rate is greater according to the difference between the gravitational force on the suspended particles and the yield point of the system. Thus the sedimentation rate of such systems can also be reduced by a thickening agent such as Kollidon® 90 F.

With some suspensions it was actually found that the sediment volume was directly proportional to the viscosity over a certain range, which confirms that Stokes' Law can be applied here [370].

Fig. 2.51 shows the influence of an addition of Kollidon® 90 F on the sedimentation behaviour of micronized crospovidone (Kollidon® CL-M) in water at different concentrations. A 7.5 % suspension of Kollidon® CL-M to which 5 % Kollidon® 90 F had been added showed no sedimentation within 24 hours, and its redispersibility was very good. Without Kollidon® 90 F, significant amounts of Kollidon® CL-M settled out.

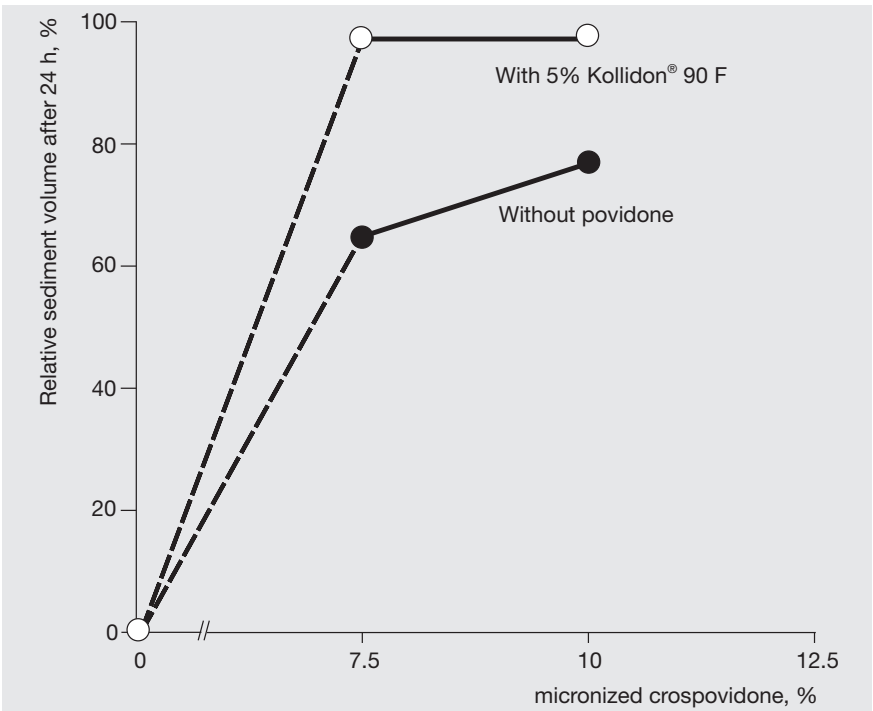


Fig. 2.51: Reduction in sedimentation of Kollidon® CL-M with Kollidon® 90 F

The active ingredients that are most frequently marketed in form of suspensions or dry syrups and instant granules for the preparation of suspensions are antibiotics, chemotherapeutics and antiacids. Table 2.100 gives a formulation that was developed in the laboratory for an antiacid suspension of magaldrate. In this formulation Kollidon® 90 F also enhances strongly the redispersibility of the suspension. This formulation can also be modified to obtain instant granules instead of a suspension ready for use as described in Section 2.4.2.5.

Table 2.100: Antiacid suspension of magaldrate with Kollidon® 90 F

Formulation:

Magaldrate (USP)	100.0 g
Kollidon® CL-M	80.0 g
Kollidon® 90 F	30.0 g
Sucrose	150.0 g
Orange flavouring	9.0 g
Coconut flavouring	0.5 g
Banana flavouring	0.8 g
Saccharin sodium	0.2 g
Preservative	q. s.
Water	ad 1000 ml

Dissolve or suspend all the solids in water under aseptic conditions.

Properties of the suspension:

– Remains homogeneous without sedimentation for more the 24 hours.
– Very readily redispersible after 2 weeks by shaking.

Further examples of laboratory formulations for dry syrups, instant granules and suspensions containing soluble Kollidon® grades are given in Section 3.4.4.3.

In granules for the preparation of suspensions, soluble Kollidon® grades can also act as binder (see Section 2.4.2.5).

The use of the soluble Kollidon® grades in coating suspensions is described in Section 2.4.4 and their use in ophthalmic suspensions in Section 2.4.7.

2.4.6.3 Parenteral suspensions

Kollidon® 12 PF and Kollidon® 17 PF can be used as dispersing agents for parenteral suspensions (crystalline suspensions, lyophilisates, nanoparticles) [115, 116, 120–122, 633]. These low-molecular endotoxin-free Kollidon® grades have been developed specially for parenterals and produce suspensions with about the same physical properties as, for example, Kollidon® 25 or Kollidon® 30, except that their viscosity is somewhat lower.

Some typical active ingredients combined with low-molecular weight povidone in commercialized parenteral suspensions are benzylpenicillin, fluspirilen, methylprednisolone and streptomycin.

2.4.7 Applications of soluble Kollidon® grades in ophthalmic preparations

All the soluble Kollidon® grades have applications in ophthalmic preparations [83–86, 102, 267, 354]. Kollidon® 17 PF, Kollidon® 25 and Kollidon® 30 are usually used in eye drops while the higher-molecular type, Kollidon® 90 F, is prefered for contact lens solutions [87, 88, 203, 382]. Povidone is usually added to these dosage forms in concentrations beween 2 % and 10 % and performs the functions shown in Table 2.101.

Table 2.101: Main functions of soluble Kollidon® grades in ophthalmic products

– Film formation
– Thickening (see Sections 2.2.3 and 2.4.8.1)
– Prolonged retention of the active ingredient in the eye
– Increase of bioavailability (see Section 2.4.3)
– Lubrication and moistening (Dry eye syndrom) [623, 624]
– Solubilization of active ingredients (see Section 2.4.5)
– Reduction of eye irritation caused by some active ingredients

The *film formation* and *thickening* actions of soluble Kollidon® grades, and sometimes also its ability to form complexes with active ingredients, keep the solution in the eye for longer time, increasing its therapeutic effect. Pilocarpine [86], timolol [166] and tropicamide [422] are typical active ingredients whose efficacy can be improved by these functions of povidone.

The general *improvement in bioavailability* of active ingredients that is brought about by the soluble Kollidon® grades is described in Section 2.4.3. However, there are also a number of publications that investigate this parameter specifically in ophthalmic preparations [230, 235, 267, 427, 442, 480] or in ocular delivery systems of fluorometholone [558].

The increase of the *lubricant effect* by povidone is used, e. g. in tear fluid substitutes [558] and solutions for the treatment of the dry eye syndrom.

The *solubilization* of active ingredients, such as chloramphenicol, in eye drops is described in Section 2.4.5.5.

Oxymetazoline is a typical example of a substance, whose *irritation effect on the eye can be reduced* by soluble Kollidon® grades.

Soluble Kollidon® grades can also be used as a sedimentation inhibitor in ophthalmic suspensions. Mefenamic acid suspension is a typical example [492].

The use of Kollidon® 30 in effervecent cleaning tablets for contact lenses would be an indirect ophthalmic application. Table 2.102 shows the composition of a perborate cleaning tablet taken from the literature [382].

Table 2.102: Composition of sodium perborate effervecent tablets for cleaning contact lenses [382]

Sodium perborate	69.2
Sodium hydrogen carbonate	260.0
EDTA sodium	27.4
Citric acid	121.6
Povidone K 30	4.6
Macrogol 6000, powder	9.2
EDTA manganese	8.0

2.4.8 Miscellaneous applications of solube Kollidon® grades

2.4.8.1 Thickener for solutions

Above all the high-molecular grade, Kollidon® 90 F, is used as thickener in oral and topical solutions and suspensions (viscosity curves see Section 2.2.3). The thickening effect also can be used to adjust the viscosity of solutions – oral drops, eye drops, syrups – to give a particular drip or flow rate. The thickening effect reduces diffusion processes in the solution, improving the stability of some active ingredients.

The good solubility of povidone in different solvents enables it to be used also as thickener in solutions which contain also other solvents like ethanol or 1,2-propylene glycol.

2.4.8.2 Adhesive gels, transdermal and mucosal systems

Because of their excellent adhesion and physiological safety, Kollidon® 30 and Kollidon® 90 F are used as adhesives on the skin or mucous membranes. Examples include transdermal systems, oral adhesive gels, buccal adhesive patches or tablets [511, 546, 547, 559, 573, 574], contact gels for electrocardiograph or electroencephalograph electrodes and adhesives for colostomy bags. Table 2.103 shows a formulation for a contact gel developed on a laboratory scale for ultrasonic scanning.

Table 2.103: Formulation for an ultrasonic contact gel

I	Kollidon® 30	1.5 g
	Water	20.0 g
II	Preservative	0.5 g
	Polyacrylic acid (Carbopol® 940, Goodrich)	0.6 g
	Water	75.4 g
III	Sodium hydroxide solution 10 % in water	2.0 g

Prepare suspension II then add III and mix with solution I.

A relatively concentrated, e.g. 20 – 30 %, clear solution of Kollidon® 90 F is adequate as the basis for adhesive gel formulations for application in the mouth or for colostomy bags [375].

In transdermal or mucosal systems, povidone, particularly Kollidon® 30 and Kollidon® 90 F, can be used as an bioadhesive, to improve or to control transdermal absorption [535, 571, 658], or to stabilize active ingredients or to inhibit the crystallization of the active substance [58]. The most important active ingredients used in transdermal or mucosal systems, with which soluble Kollidon® grades can be used, include bromhexine [455], captopril [582], chlorhexidine [594], diclofenac [491], dilthiazem [599], ephedrine [417], flurbiprofen [627], hormone [559], hydrocortisone [412], indomethacin [599], isosorbide dinitrate [418, 518, 535, 570, 578], nabulphine [658], nitroglycerin [384 – 386, 578], pentazocine [539], promethazine [456], propranolol [578], salicylic acid [413, 415, 416], terbutalin [657], testosteron [514], tetracycline [632] and verapamil [563, 571].

2.4.8.3 Plastics for medical use

Many plastics materials are too hydrophobic for use in direct contact with body fluids such as blood, plasma, etc. Plastics are nowadays hydrophilized by different methods with povidone, e. g. Kollidon® 30 or Kollidon® 90 F as shown in Table 2.104 [494, 621].

By adding povidone during the polymerization of plastics, it is possible to adjust the size of the pores in the plastics material, used for filtration and dialysis purposes.

Table 2.104: Applications of soluble Kollidon® grades in plastics

– Addition of soluble Kollidon® during polymerization of plastics (formation of pores)
– Coating of plastics with povidone followed by crosslinking by means of: 1. Alkaline treatment [1, 141, 217] 2. Radiation curing [371] 3. Reaction with isocyanates and curing [621]

With the methods given in Table 2.104, great care must be taken that no high-molecular povidone can be leached out of or peeled away from the plastics material in the body or in contact with body fluids. Kollidon® 90 F and Kollidon® 30 become insoluble hydrophilic substances after crosslinking. Alkaline treatment, e. g. with sodium hydroxide is an established and effective method.

2.4.8.4 Reduction of the toxicity of active ingredients and other substances

Because of their ability to form complexes with a large number of substances (see Sections 2.2.7, 2.4.3 and 2.4.5) soluble Kollidon® grades can be used to reduce the toxicity of certain active ingredients (Table 2.105). This effect is mainly used with active substances such as oxytetracycline, that are given parenterally as well as those that are applied topically to the skin or mucousa (e. g. iodine).

Table 2.105: Examples of reduction in toxicity of active ingredients by complexation with soluble Kollidon® grades

Active ingredient	Administration				Literature reference
	Oral	Topical	Ocular	Parenteral	
Acetylsalicylic acid	+				[189]
Azapropazone	+				[284, 319]
Closantel				+	
Floctafenine	+				[284, 319]
Florifenine		+			[545]
Glafenine	+				[284, 319]
Indomethacin	+				[123]
Iodine		+	(+)		[124]
Mefenamic acid	+				[284, 319]
Oxymetazoline			+		
Oxytetracycline				+	[22, 373, 374]
Polymyxin B	+			+	[489]
Temafloxacin				+	[517]

Not only can the toxicity of active ingredients be reduced by povidone. The irritant or toxic effects of other substances such as cyanides, nicotine, formaldehyde, formamide, and other toxins, with which povidone forms complexes of adequate stability, can also be reduced [126].

2.4.8.5 Cryoprotection

The inhibition of the crystallization of water and active ingredients by povidone has been investigated in a number of publications with respect to the freeze-drying of histological specimens. This cryoprotective effect of the soluble Kollidon® grades therefore plays a greater role in biotechnology than in the manufacture of drugs (see also Section 2.4.5.3).

2.4.8.6 Stabilization of enzymes

The soluble Kollidon® grades, particularly Kollidon® 30, can be used to stabilize many enzymes, as is extensively described in the literature. Complexation also plays a role here in binding deactivating substances such as phenols and tannins. This and other properties are used to advantage both in diagnostic reagents, including those in the rapid test kits, and in microbiological

processes. Table 2.106 contains a list of enzymes that, according to the literature, can be stabilized directly or indirectly by complexation with povidone.

Table 2.106: Stabilization of enzymes with povidone (selection)

Asparaginase
beta-Interferon
Catalase
Dehydrogenase
Ferrochelatase
Galactosidase
Glucose oxidase
Hyaluronidase
Peroxidase
Phenolase
Prostaglandin E
Pyruvate carboxilase
Transaminase
Urease

2.4.8.7 Chemical stabilization of active ingredients

The soluble Kollidon® grades are capable of chemically stabilizing certain active ingredients. This effect does not depend on the dosage form, as soluble Kollidon® is used to stabilize nitroglycerin and isosorbide dinitrate, particularly in transdermal systems [384, 386], iodine in topical solutions and vitamins in oral and parenteral solutions and in solid forms. Table 2.107 shows a formulation for a vitamin B complex solution for parenterals, developed in the laboratory, in which cyanocobalamin was found to be very unstable without the addition of Kollidon® 17 PF. The use of Kollidon® 17 PF reduced the loss of cyanocobalamin to only 13 % during 9 months' storage.

Table 2.107: Vitamin B complex parenteral solution [368]

Formulation

I	Thiamine hydrochloride	11.0 mg
	Riboflavin monophosphate sodium	6.6 mg
	Nicotinamide	44.0 mg
	Pyridoxine hydrochloride	4.4 mg
	Cyanocobalamin	8.8 µg
	EDTA sodium	0.2 mg
	Propyl gallate	0.5 mg
	Kollidon® 17 PF	99.0 mg
II	Parabens	1.6 mg
	Citric acid	22.7 mg
	Sodium hydroxide solution, 1 mol/l	0.216 ml
	Hydrochloric acid, 0.1 mol/l	0.720 ml
	1,2-Propylene glycol	0.200 ml
	Water	0.864 ml

Dissolve mixture I in solution II, purge with nitrogen for 5 min, sterilize by filtration and fill into ampoules under nitrogen. The pH is about 4.

Stability (9 months, room temperature)

Vitamin	Loss
B_1	8 %
B_2	6 %
B_6	9 %
Nicotinamide	0 %
B_{12}	13 %

Further active ingredients, in addition to cyanocobalamin, that can be stabilized with soluble Kollidon® grades are mentioned in Table 2.108.

Table 2.108: Chemical stabilization of active ingredients by povidone

Active ingredient	Literature reference
Ascorbic acid	[420]
Colecalciferol	[309]
Dehydroandrosterone (prasterone)	[424]
Erythrocytes	[507]
Hydrogen peroxide	[516]
Hydroxystaurosprine	[552]
Immunoglobulin	[515]
Interferon	[482]
Iodine	
Isosorbide dinitrate	
Methylprednisolone	[12]
Nitroglycerol	[422, 423]
Prostaglandin	[327]
Taurolidine	[568]
Theophylline	[569]
Thiamine hydrochloride	[419]
L-Tyroxin	[532]

2.4.8.8 Controlled-release preparations

Because of their excellent solubility, the soluble grades of Kollidon® normally have no delaying effect on the dissolution of active ingredients. Though a substance embedded in Kollidon® 90 F dissolves slightly more slowly than it would in Kollidon® 30, this minor difference cannot be described as a controlled-release effect. On the contrary, the dissolution rate is frequently higher than that of the pure active ingredient (see Sections 2.4.3 and 2.4.5).

A number of publications appeared since 1981, in which it was reported that povidone forms insoluble flocculates with polyacrylic acid and that these can be used to control release by enveloping crystals or tablet cores in the flocculate [407, 410, 520, 583].

Soluble Kollidon® can also be used as a hydrophilic component or pore former in preparations that contain sustained release auxiliaries like polyvinyl acetate (e. g. Kollicoat® SR 30D) [662], cellulose derivatives like HPMC [490, 509, 660], alginate [461], cetylacohol [600], polylactic acid [506], Gelucire® (Gattefossé) [510], polyvinyl alcohol [522], ceresine wax [523], stearic acid [606] or acrylate copolymers (e. g. Kollicoat® EMM 30D) [491, 662] to control or regulate the release of active ingredients, as binders and/or sometimes as plasticizers. They can also be extruded together with the active ingredient in melted stearyl alcohol and filled into hard gelatin capsules to achieve the same effect [471]. Ocular delivery systems are also described [598].

2.4.8.9 Buccal preparations

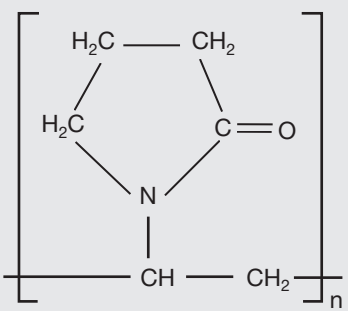
Povidone reduces the adherence of oral bacteria to tooth enamel and therefore it could be used in buccal preparations e. g. mouthwash solution as microbial antiadherent agent [589]. It also can be used as mucoadhesive for buccal coats of verapamil [612] or for bioadhesive buccal tablets of nicotine [639, 641]

3 Insoluble Kollidon® grades (crospovidone)

3.1 Structure, product range, synonyms

The Kollidon® CL grades are manufactured by a polymerization process in water without any organic solvents. This polymerization produces a mainly physically crosslinked insoluble polyvinylpyrrolidone in the form of a popcorn polymer [2].

The physical crosslinking is supported by comparison of the infrared spectra of povidone (e. g. Kollidon® 30) and the popcorn polymer crospovidone (e. g. Kollidon® CL) which do not reveal any differences. In contrast, the infrared spectrum of a chemically crosslinked insoluble vinylpyrrolidone polymer prepared in the laboratory is quite different.



$Mr = (111.1)_x$

With the Kollidon® CL grades, it is not possible to use the molecular weight or the K-value as a means of identifying the different types, as is done with the soluble Kollidon® grades, since the Kollidon® CL grades are completely insoluble in all of the usual solvents and their molecular weight cannot be determined. Table 3.1 gives the product range with product numbers.

Table 3.1: Range of Kollidon® CL grades

Product name	Type	BASF Article number (Standard packaging)	PBG number
Kollidon® CL	Standard	50000695 (40 kg)	10010115
Kollidon® CL-F	Fine	53216545 (30 kg)	10702795
Kollidon® CL-SF	Super fine	52595650 (30 kg)	10702794
Kollidon® CL-M	Micronized	50000697 (30 kg)	10061458

The products differ in their physical properties, particulary in their particle sizes, particle structures, bulk densities and swelling characterisitcs. These differences are caused by polymerization modifications. Only in the case of Kollidon® CL-M the fine particle size is obtained by micronization. The other three Kollidon® CL grades are neither milled nor micronized.

Insoluble polyvinylpyrrolidone (crospovidone) has got the same CAS-number as soluble polyvinylpyrrolidone (povidone): 9003-39-8.

Since the products are insoluble, they can be thoroughly washed with water to achieve a very high degree of purity.

The names and abbreviations in Table 3.2 are generally used for insoluble polyvinylpyrrolidone in pharmaceuticals.

Table 3.2: General names and abbreviations for insoluble polyvinylpyrrolidone

Name/abbreviation	Origin/area of application
Crospovidone, Crospovidonum	Current pharmacopoeias (e. g. Ph.Eur., USP-NF)
Crospolyvidone	First Ph.Eur. draft 1991
Insoluble polyvidone	DAC until 1986
Insoluble PVP	General abbreviation
Crosslinked PVP	General abbreviation
Polyvinylpolypyrrolidone	Chemically incorrect designation often encountered in the food literature
PVPP	Abbreviation used in the beverages industry

The chemically incorrect designation polyvinylpolypyrrolidone (PVPP) has been still used in the literature, although it is certainly not correct because the infrared spectra of povidone and crospovidone reveal no recognizable difference (see Section 3.3.1.1).

In the following sections of this chapter, the pharmaceutical term “crospovidone” is allways used for insoluble polyvinylpyrrolidone.

3.2 Properties of the Kollidon® CL grades

3.2.1 Description, specifications, pharmacopoeias

3.2.1.1 Description

All Kollidon® CL grades are products of pharmaceutical purity obtained according to the cGMP regulations. They are white or almost white powders of different particle sizes with a porous structure (see Section 3.2.2). Kollidon® CL, and, to a lesser extent, the other Kollidon® CL grades have good flow properties.

The products have a slight characteristic odour and are practically tasteless.

One of the main properties of crospovidone is its complete insolubility in all the usual solvents.

3.2.1.2 Specifications, pharmacopoeias

The specifications of 2007 are listed in Table 3.3. Most of the parameters listed are included among the Ph.Eur. requirements. The actual specifications are available on request.
The products are tested and released in accordance with the methods and limits given in the monographs "Crospovidone" of the current editions of Ph.Eur. and USP-NF. Kollidon® CL is classified as Type A and the other Kollidon® CL grades asType B of the current Ph.Eur. monograph.
The Kollidon® CL grades also meet the requirements of the monograph "Crospovidone" of the current edition of the Japanese Pharmaceutical Excipients (JPE).

Table 3.3: Current specifications of the Kollidon® CL grades

Parameter	Kollidon® CL	Kollidon® CL-F Kollidon® CL-SF	Kollidon® CL-M
Identity	Passes test	Passes test	Passes test
Ph.Eur. classification	Type A	Type B	Type B
Nitrogen, %	12.0–12.8	12.0–12.8	12.0–12.8
Water (Karl Fischer), %	≤ 5.0	≤ 5.0	≤ 5.0
pH (1 % in water)	5.0–7.5	5.0–7.5	5.0–7.5
Vinylpyrrolidone (iodometric), %	≤ 0.1	≤ 0.1	≤ 0.1
Vinylpyrrolidone (HPLC* or GC**), ppm	≤ 10	≤ 10	≤ 10
Sulphated ash, %	≤ 0.1	≤ 0.1	≤ 0.1
Heavy metals, ppm	≤ 10	≤ 10	≤ 10
Water-soluble substances, %	≤ 1.0	≤ 1.0	≤ 1.0
Peroxides, ppm H_2O_2	≤ 400	≤ 400	≤ 1000
Microbial status (Table 3.4)	Passes test	Passes test	Passes test
Residual solvents	Not present	Not present	Not present

* *Method see Section 3.3.2.2*
** *Method see Section 3.3.2.3*

The water-soluble substances are determined after centrifugation and filtration through a 0.4 µm membrane.

All Kollidon® CL grades meet the ICH requirements on residual solvents according to Ph.Eur., chapter 5.4. It can be stated: No residual solvents (class 1–3) are likely to be present.

The microbial status is determined according to Ph.Eur. methods 2.6.12 and 2.6.13. The limits given in chapter 5.1.4 of Ph.Eur. apply (Table 3.4).

Table 3.4: Microbial purity requirements (Ph.Eur., chapter 5.1.4, Category 2 + 3A)

– Max. 10^2 aerobic bacteria and fungi/g
– No Escherichia coli/g
– Max. 10^1 enterobacteria and other gramnegative bacteria/g
– No Pseudomonas aeruginosa/g
– No Staphylococcus aureus/g

3.2.2 Particle size, particle structure, flowability

3.2.2.1 Particle size distribution

The particle size is the prominent product property to differentiate the Kollidon® CL grades. Table 3.5 shows the typical sieving results of particle size measurements of the four products, determined in a air jet screen after 5 min at 20 mbar using sieves of 15, 50 and 250 µm.

The current crospovidone monograph of Ph.Eur. requires a functional classification into Type A (coarse product) and Type B (fine product) by means of a particle size measurement in identification test D. Kollidon® CL corresponds clearly to the definition of Type A since in the air jet screening usually 60–80 % of the particles are coarser than 50 µm without any swelling. The other three Kollidon® CL grades are Type B.

Table 3.5: Particle sizes of the Kollidon® CL grades determined in a air jet screen (typical values)

	Kollidon® CL	Kollidon® CL-F	Kollidon® CL-SF	Kollidon® CL-M*
< 15 µm	–	–	≥ 25 %	≥ 90 %
< 50 µm	≤ 40 %	> 50 %	–	–
< 250 µm	≥ 95 %	≥ 95 %	≥ 99 %	–

* = *micronized*

The particle size distribution and its effect on the flow and swelling properties of crospovidone are important factors in its use in solid pharmaceutical dosage forms. In comparison with the corresponding competition product a relatively fine particle size was selected for Kollidon® CL to minimize changes in the tablet surface as a result of atmospheric humidity and swelling, although large particles, with their greater swelling volume, would have given a somewhat more rapid disintegration. All other Kollidon® CL grades have even finer particle sizes.

One of the usual methods for the determination of the particle size distribution of the finer Kollidon® CL grades is the laser light diffraction measurement (e. g. in a Malvern Mastersizer, Malvern Instruments). Figs. 3.1 to 3.4 show the typical results of all Kollidon® CL grades with this method measured in powder form without any solvent at 2 bar. By this method the following typical values of the volume average diameter D [4.3] were found:

– Kollidon® CL:	90–130 µm
– Kollidon® CL-F:	20– 40 µm
– Kollidon® CL-SF:	10– 30 µm
– Kollidon® CL-M:	3– 10 µm

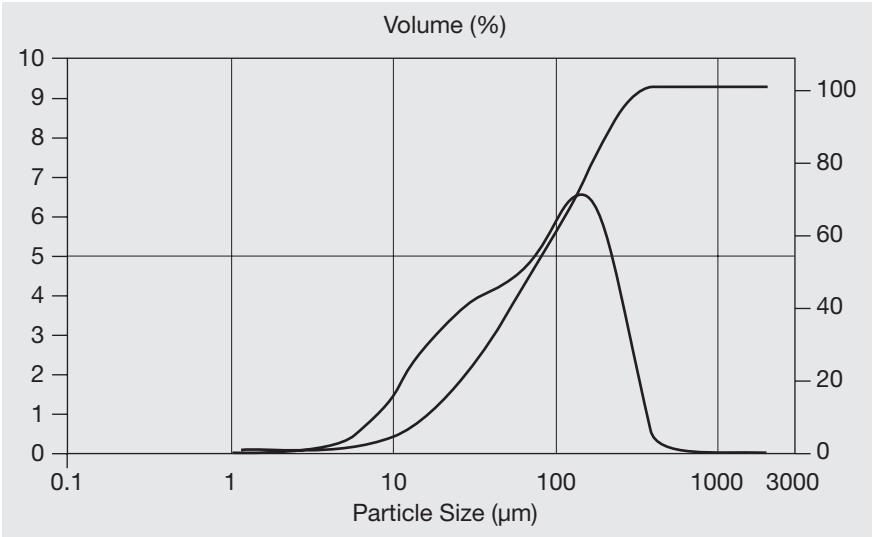


Fig. 3.1: Typical particle size distribution of Kollidon® CL determined by laser diffraction

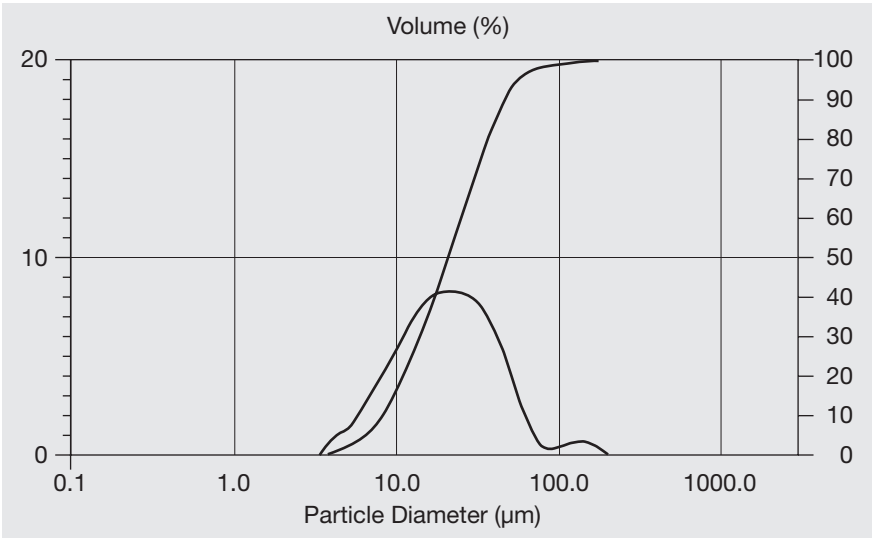


Fig. 3.2: Typical particle size distribution of Kollidon® CL-F determined by laser diffraction

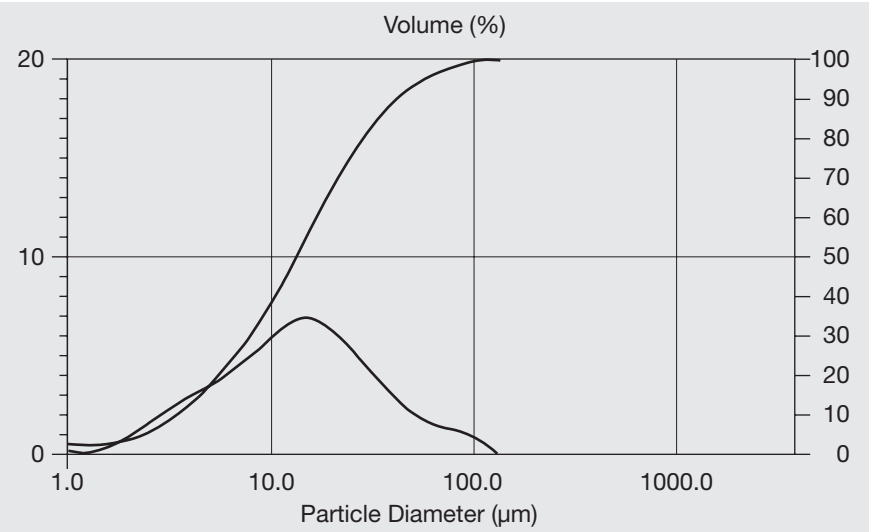


Fig. 3.3: Typical particle size distribution of Kollidon® CL-SF determined by laser diffraction

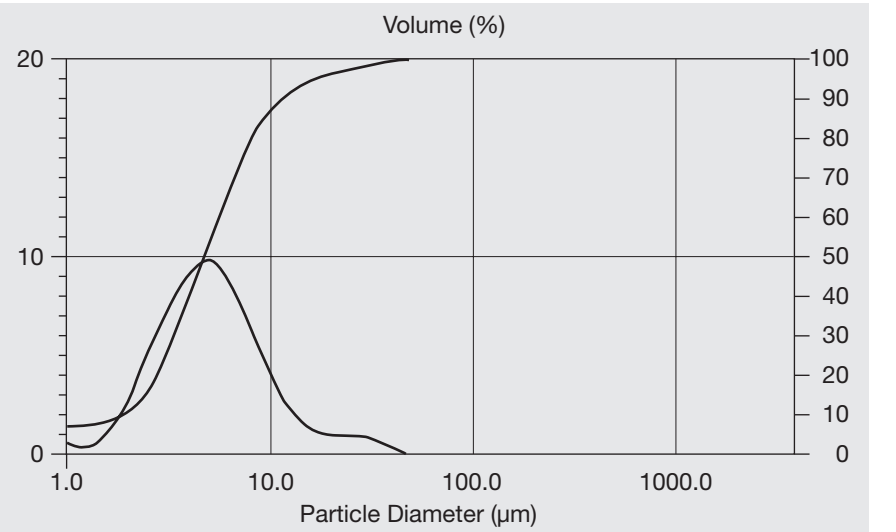


Fig. 3.4: Typical particle size distribution of Kollidon® CL-M determined by laser diffraction

3.2.2.1 Particle structure

The Kollidon® CL grades have a porous so-called popcorn structure which explains the high swelling and hydration capacity. Fig. 3.5 shows the scanning electron micrograph (SEM) of the structure of the particles of Kollidon® CL and Fig. 3.6 shows the SEM of the very fine particle structure of Kollidon® CL-M. These graphs also show the strong difference of particle size between the standard type and the micronized form of crospovidone because both figures have the identical magnification.

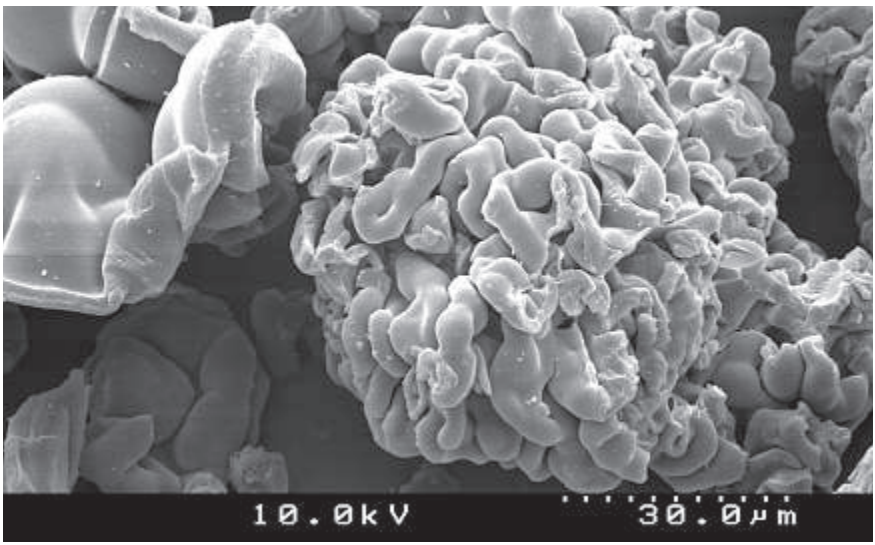


Fig. 3.5: Typical scanning electron micrograph (SEM) of Kollidon® CL

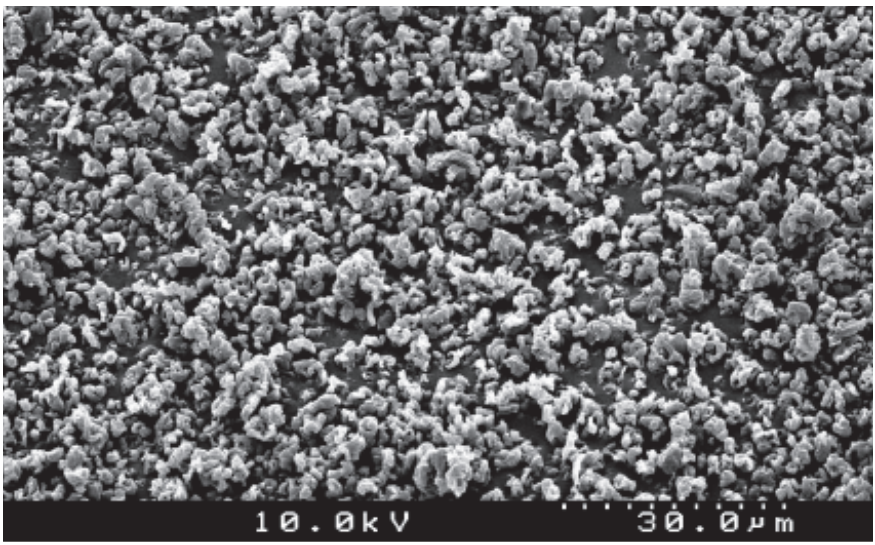


Fig. 3.6: Typical scanning electron micrograph (SEM) of Kollidon® CL-M

3.2.2.3 Flowability

Kollidon® CL has good flow properties. The flowability of all Kollidon® CL grades was tested in the usual concentrations as disintegrant of 3 and 6 % in granulated lactose monohydrate (Ludipress® LCE) mixed with 0.5 % magnesium stearate. No significant influence of the Kollidon® CL grades on the flowability was observed in comparison with pure Ludipress® LCE. The angle of repose was always 30 to 32 degree in all mixtures with exception of 6 % Kollidon® CL-M (Table 3.6).

Table 3.6: Influence of 3 and 6 % Kollidon® CL grades on the flowability of a mixture with Ludipress® LCE

	Ludipress® LCE alone	+ Kollidon® CL 3 %	+ Kollidon® CL 6 %	+ Kollidon® CL-F 3 %	+ Kollidon® CL-F 6 %	+ Kollidon® CL-SF 3 %	+ Kollidon® CL-SF 6 %	+ Kollidon® CL-M 3 %	+ Kollidon® CL-M 6 %
Angle of repose [degree]	30	31	31	30	32	30	32	30	34

3.2.3 Bulk density, tapped density

Table 3.7 gives typical values for the bulk and tapped densities after 500 taps of all of the Kollidon® CL grades. One of the major differences of Kollidon® CL and the finer grades lies in their bulk densities. Particullary in the case of the micronized product Kollidon® CL-M the low bulk density is an important factor which affects in its application in suspensions.

Table 3.7: Bulk and tapped densities of the Kollidon® CL grades (typical values)

Product	Bulk density	Tapped density (500 taps)
Kollidon® CL	0.30 – 0.40 g/ml	0.40 – 0.50 g/ml
Kollidon® CL-F	0.18 – 0.28 g/ml	0.25 – 0.35 g/ml
Kollidon® CL-SF	0.10 – 0.16 g/ml	0.18 – 0.25 g/ml
Kollidon® CL-M	0.15 – 0.25 g/ml	0.25 – 0.35 g/ml

3.2.4 Specific surface area

The specific surface area can be determined with the N_2-BET method according to DIN 66131-132 or Ph.Eur., chapter 2.9.14. Typical results are given in Table 3.8 which shows a strong difference between the standard grade Kollidon® CL and the very fine grade Kollidon® CL-SF or the micronized product Kollidon® CL-M.

Table 3.8: Specific surface area of the Kollidon® CL grades (typical values)

Product	Specific surface area (N_2-BET)
Kollidon® CL	< 1 m^2/g
Kollidon® CL-F	approx. 1.5 m^2/g
Kollidon® CL-SF	approx. 3 m^2/g
Kollidon® CL-M	> 6 m^2/g

3.2.5 Hygroscopicity

The hygroscopic properties of the Kollidon® CL grades are important in many applications. There is hardly any difference between the individual grades so that they can all be represented by a single curve (Fig. 3.7). The curve shows the amount of water adsorbed after seven days exposure to different conditions of relative humidity. Furthermore crospovidone is almost as hygroscopic as the soluble grades of Kollidon® (povidone).

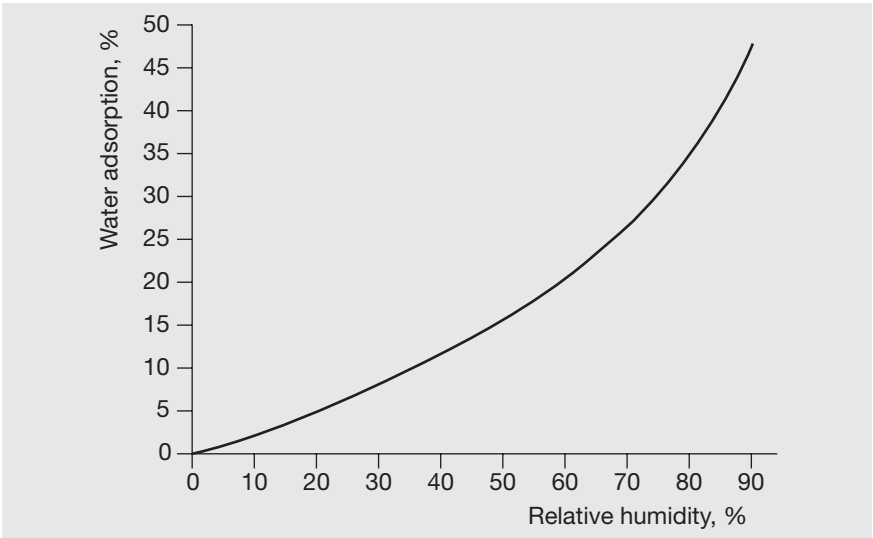


Fig. 3.7: Water uptake by Kollidon® CL grades at 25 °C after 7 days

3.2.6 Hydration capacity

If water is added to crospovidone instead of merely exposing it to atmospheric humidity, it binds significantly more. Its hydration capacity is best determined by the following method [3]:

Weigh and add 2.0 g of crospovidone (e. g. Kollidon® CL) to 40 ml of water in a 100-ml centrifuge tube and shake vigorously until a suspension is obtained. Shake up again after 5 and after 10 minutes. Then centrifuge for 15 minutes at 2000 rpm with a relative centrifugal acceleration of 750. Decant off the supernatant liquid. Then reweigh.

The hydration capacity is calculated as the quotient of the weight after hydration and the initial weight. The Kollidon® CL grades have different hydration capacities determined with this method. Table 3.9 shows typical results.

Table 3.9: Hydration capacity of Kollidon® CL grades (typical values)

Product	Hydration capacity (g water/g polymer)
Kollidon® CL	3.5–5.5
Kollidon® CL-F	5.0–6.6
Kollidon® CL-SF	7.0–8.5
Kollidon® CL-M	3.0–4.5

3.2.7 Swelling properties

One of the most important properties of crospovidone in its application as tablet disintegrant is its ability to swell in a predictable manner without forming a gel. A number of methods are described in the literature for measuring swelling, the most important being listed in Table 3.10.

Table 3.10: Some methods for determining the swelling of crospovidone

Method	Literature source
– Swelling volume of compacted powder	[392]
– Swelling pressure of lightly compacted powder	see Table 3.11
– Swelling volume of the particles in the Coulter Counter® (Beckman Coulter)	[221]
– Swelling volume of the particles under the microscope	–
– Water adsorption with and without magnesium stearate	[392, 394]
– Water binding capacity	[3]
– Water adsorption in placebo tablets	[262]
– Swelling volume in placebo tablets	[392]
– Swelling pressure of placebo tablets	[395]
– Disintegration force with placebo tablets	[391, 398, 399]

The swelling pressure of poured and slightly compacted Kollidon® CL powder in water is much higher than that of other Kollidon® CL grades. The pressure increase per time depends on the particle size distribution of the non-micronized products and is highest for Kollidon® CL, followed by Kollidon® CL-F and Kollidon® CL-SF. The relative high swelling pressure of Kollidon® CL-M is achieved after a comparable long swelling time (Table 3.11). The ideal particle size with the highest swelling pressure is the Kollidon® CL fraction of 100–125 µm [391].

Table 3.11: Swelling pressure (kpa) and time to reach 90 % of the maximum swelling pressure of the Kollidon® CL grades (typical values)

Product	Swelling pressure, kpa	Time to reach 90 % of the maximum swelling, s
Kollidon® CL	approx. 170	< 10
Kollidon® CL-F	approx. 30	< 15
Kollidon® CL-SF	approx. 25	< 35
Kollidon® CL-M	approx. 70	> 100

Comparing the swelling pressures of Kollidon® CL and Kollidon® CL-M in different solvents no difference was found between water and ethanol. In nonpolar solvents such as cyclohexane, hexane, dioxane and ethyl acetate, crospovidone hardly swells at all. Even in acetone it swells much less than in water.
In 0.1 N hydrochloric acid too, it swells significantly less than in isotonic salt solution [221].

Fig. 3.8 shows how the volume of Kollidon® CL increases with time when it swells. These results were also obtained with tablets of pure Kollidon® CL produced with a compression force of only 1.5 kN, and their increase in volume was measured against time when they were exposed to water on one side only. If the tablets were exposed to water on all sides, swelling would set in somewhat earlier. It is interesting to note that a similar swelling volume was measured for Kollidon® CL-M, even though the swelling pressure it develops is much lower.

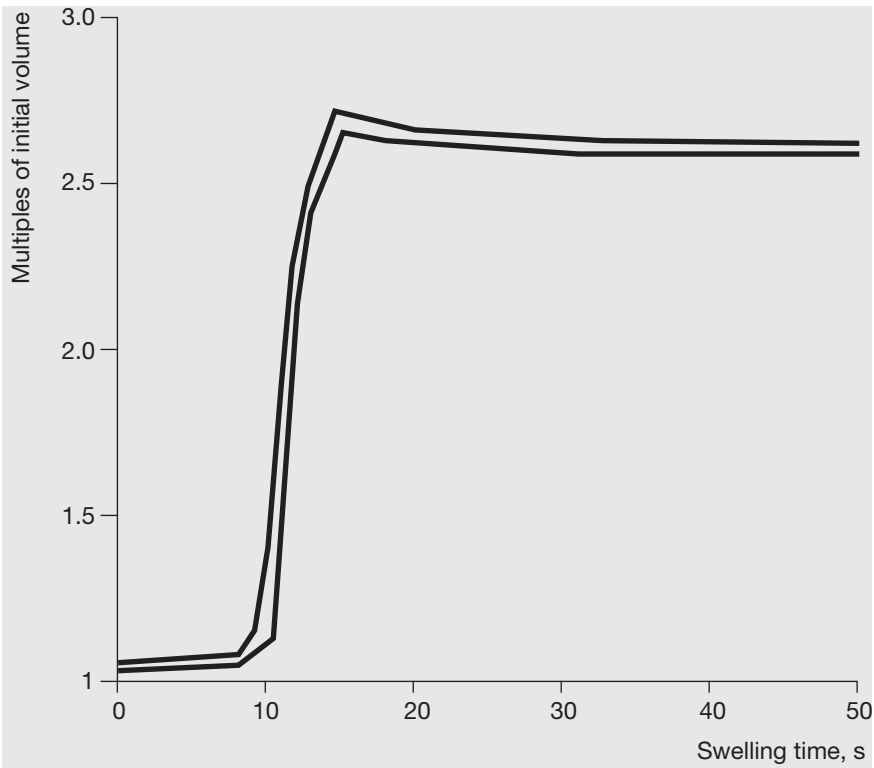


Fig. 3.8: Swelling volume of lightly compacted Kollidon® CL tablets as a function of time (two determinations)

3.2.8 Complexation, chemical interactions

3.2.8.1 Complex formation

As with the soluble Kollidon® grades, the insoluble Kollidon® CL grades also form chemical complexes or associates with a large number of active ingredients and other substances. For a typical example of comparison see Section 3.4.3.1. Here, too, the formation of the complexes is reversible and they do not form in alkaline medium. Whether crospovidone forms a complex with an active ingredient depends on its chemical structure.

Systematic investigations of aromatic compounds have shown that phenol and carboxyl groups have a strong influence on complexation. This is shown in Fig. 3.9.

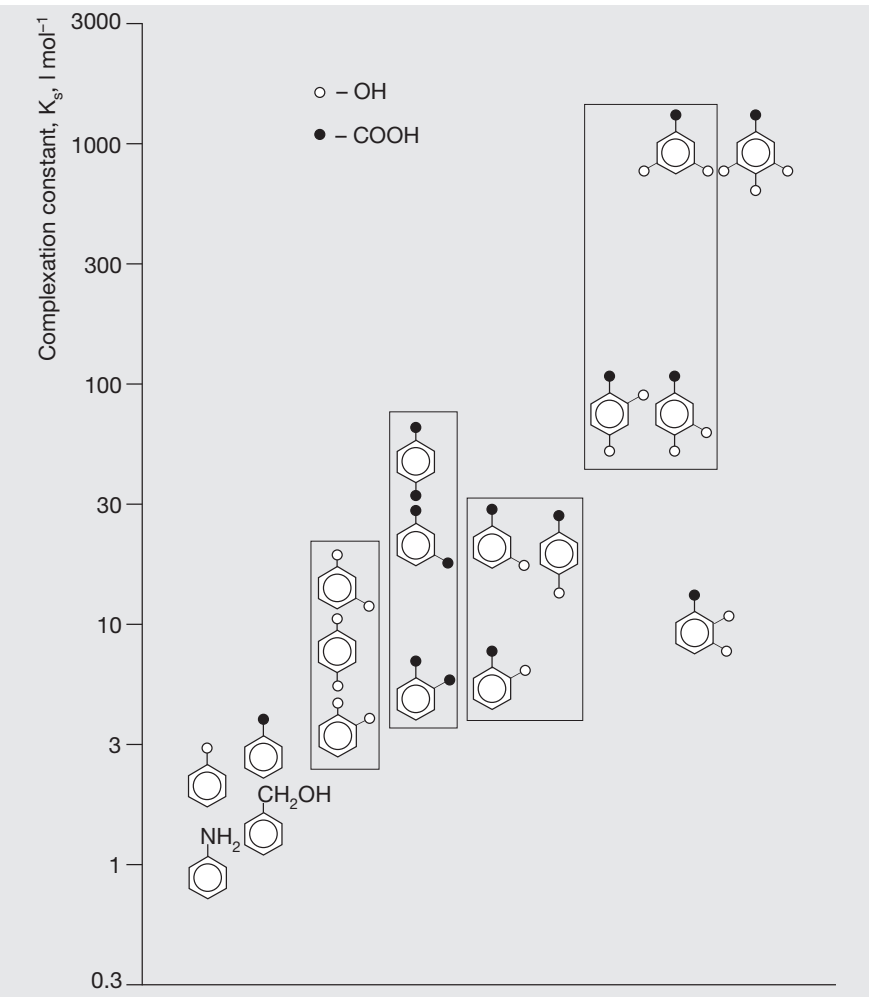


Fig. 3.9: Influence of the structure of aromatic compounds on their formation of complexes with Kollidon® CL [192]

For almost all pharmaceutically active ingredients, the degree of complexation is so low that, at best, an acceleration in the dissolution rate of the active ingredient can be observed (see Section 3.4.3). The complexation constants of a number of active ingredients in 0.1 N hydrochloric acid can be seen in Table 3.12. They were also determined by adsorption on Kollidon® CL in 0.01 N hydrochloric acid and, in some cases, in synthetic gastric juice according to USP [158]. The only high complexation constant is shown for tannic acid (tannin).

Table 3.12: Complexation constants for some pharmaceutical ingredients with Kollidon® CL in 0.1 N hydrochloric acid [192]

Substance	Complexation constant, K_s, $l \cdot mol^{-1}$
Acetaminophen (paracetamol)	2.0
Acetylsalicylic acid	1.5
Benzocaine	1.9
Benzoic acid	2.9
Chloramphenicol	≈ 0
Caffeine	≈ 0
Methyldopa	0.2
Methylparaben	4.2
Promethazine HCl	0.4
Riboflavin	≈ 0
Salicylamide	3.7
Salicylic acid	6.2
Sorbic acid	0.5
Sulfamethazine	≈ 0
Sulfamoxole	≈ 0
Sulfathiazole	1.0
Tannin	> 1000
Tetracaine HCl	≈ 0
Trimethoprim	≈ 0

The complexation constants given in Table 3.12 can be used in Fig. 3.10 to estimate any adverse effects of the adsorption of an active ingredient on its release and absorption by the body. Fig. 3.10 covers the range of active ingredient concentrations encountered in practice.

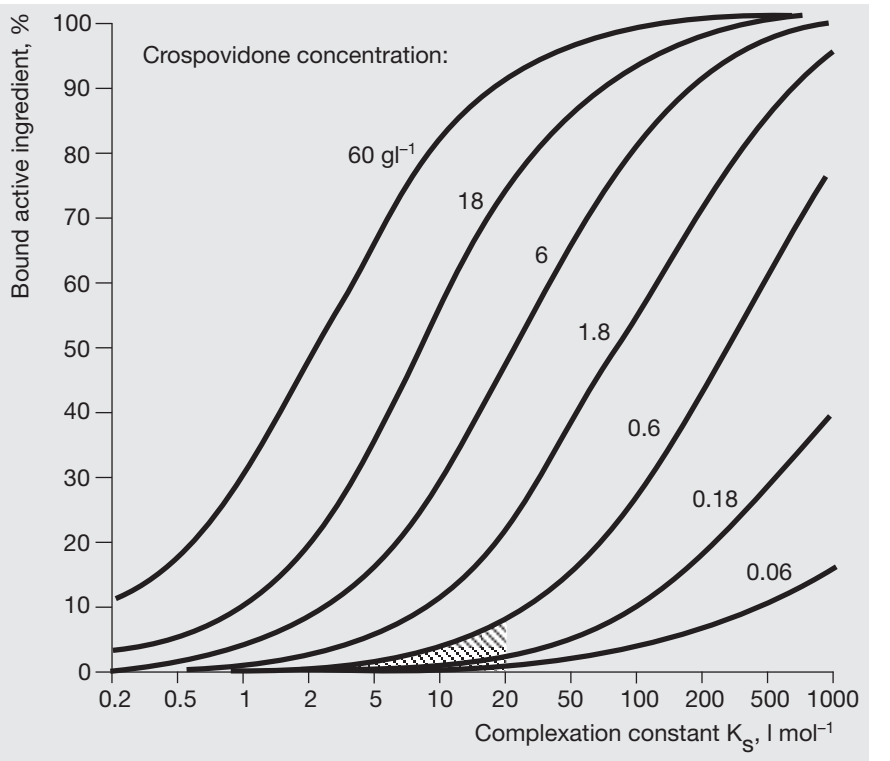


Fig. 3.10: Curves for the proportion of bound active ingredient as a function of the complexation constant, K_s at different crospovidone concentrations [192]

The shaded area in Fig. 3.10 shows the usual systemic concentration range of crospovidone after medication. Thus for a complexation constant of less than 20 l · mol-1, the bound portion of the active ingredient is always considerably less than 10 %. Tannin and hexylresorcinol are exceptions with higher complexation constants [158]. Certain halogen compounds may have complexation constants in excess of 20 l · mol^{-1}.

That complexes are formed only in the acidic range is shown for resorcinol in Fig. 3.11.

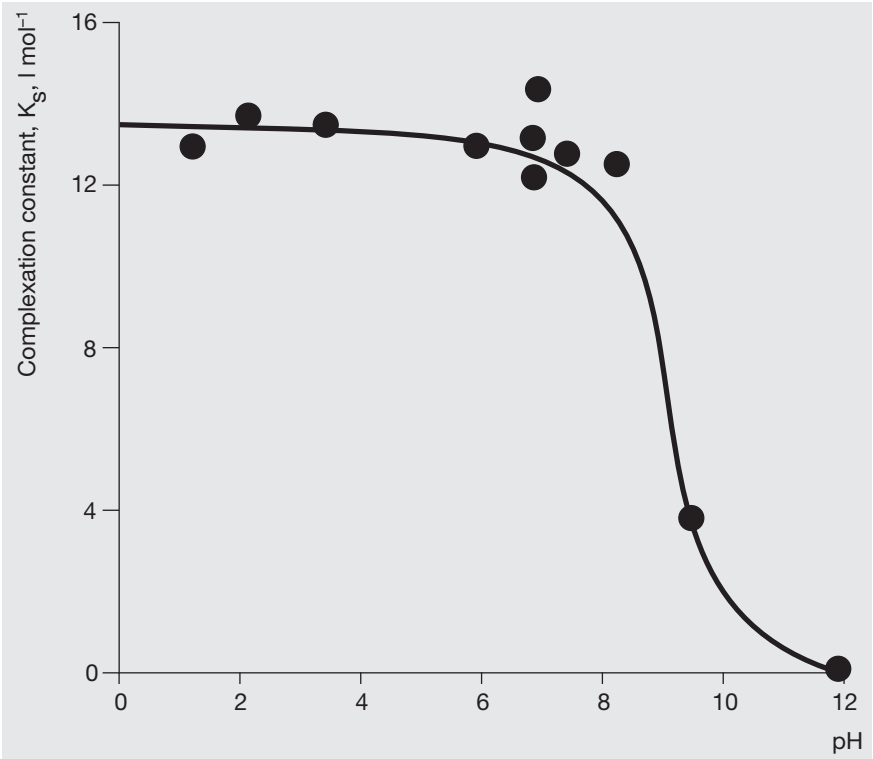


Fig. 3.11: Effect of pH value on the complex between resorcinol and Kollidon® CL [192]

As with soluble Kollidon®, the ability of the Kollidon® CL grades to form complexes, as an auxiliary or as an active ingredient in its own right, is widely used in pharmaceuticals (Table 3.13).

Table 3.13: Applications of normal and micronized crospovidone as complexing agent in drugs

1. Improvement of the dissolution and bioavailability of active ingredients (Sections 3.4.2 and 3.4.3)
2. Active ingredient against diarrhoea, gastritis, ulcers and hiatus hernia (Section 3.4.5)
3. Adsorption and removal of the polyphenols and tannins from tinctures and plant extracts (Section 3.4.6)
4. Improvement of the taste of acetaminophen, azithromycin and some other active ingredients

The complex formation capacity of individual batches of the Kollidon® CL grades can be measured in terms of their adsorption of salicylic acid (see Section 3.3.3).

3.2.8.2 Chemical interactions

The Kollidon® CL grades can contain small quantities of peroxides, within the limits of the specifications, which could theoretically react with sensitive active ingredients in exceptional cases. However, no evidence of this has been found in practice. On the contrary, it has been observed that the vitamins in multivitamin drink granulates were stabilized by Kollidon® CL-M (see Section 3.4.6.2).

3.2.9 Stability, storage, packaging

3.2.9.1 Stability of the pure products, packaging

The Kollidon® CL grades have a shelf life of more than three years, after which they still meet the specifications given in Section 3.2.1.2, when they are stored in the original, sealed containers at room temperature (20–25 °C).

As Kollidon® CL (40 kg), Kollidon® CL-F (30 kg) and Kollidon® CL-SF (30 kg) are packaged in gas-tight, welded PE-Aluminium laminated bags in PE drums, only a low increase in the water or peroxide levels is to be expected. There
is no change in any of the other parameters over periods in excess of three years. Kollidon® CL-M is packaged in PE drums with PE inliners (30 kg).

3.2.9.2 Stability in finished pharmaceuticals

The Kollidon® CL grades also demonstrate excellent stability after processing into tablets, granules, capsules or suspensions, so that no changes are to be expected over many years. However, it should be borne in mind that the products are hygroscopic, so that if there are any leaks in the packaging, through which atmospheric humidity can enter, the crospovidone particles may swell. Tablets made from such product may have a rough surface.

3.3 Analytical methods for the Kollidon® CL grades

3.3.1 Qualitative and quantitative methods of determination

3.3.1.1 Identification

The pharmacopoeias and the literature describe only three detection reactions for the identification of crospovidone.

The most important and clearest method of identification is by infrared spectroscopy. The same method can be used for all the Kollidon® CL grades. Fig. 3.12 shows the infrared spectrum of Kollidon® CL. The only disadvantage of this method of identification is that soluble Kollidon® grades (povidone) give the same infrared spectrum (see Section 2.3.1.1 for Kollidon® 90 F and Section 4.3.1.1 for Kollidon® 30). However, the difference can readily be determined from the solubility.

In an alternative method, 0.1 ml of 0.1 N iodine solution is added to a suspension of 1 g of crospovidone in 10 ml of water. After vigorous shaking, 1 ml of starch solution is added. The iodine is complexed by the crospovidone, so that no blue coloration develops within 30 seconds.

The fact that the Kollidon® CL grades do not dissolve in any of the usual solvents provides a further indication of identity.

The current crospovidone monograph of Ph.Eur. requires as identification D a functional classification of crospovidone into Type A (= coarse product) and Type B (= fine product) by means of a particle size measurement. This classification was developed originally by the laboratory of Ph.Eur. measuring samples of Kollidon® CL and Kollidon® CL-M as aqueous suspensions in water and observing the swollen particles under the microscope. It was found that in the case of the micronized product Kollidon® CL-M almost all particles were finer than 50 µm (= definition of Type B) and that in the case of the standard product Kollidon® CL more than 50 % (= the majority) were coarser than
50 µm (= definiton of Type A) [631]. Kollidon® CL-F and Kollidon® CL-SF correspond also to Type B.

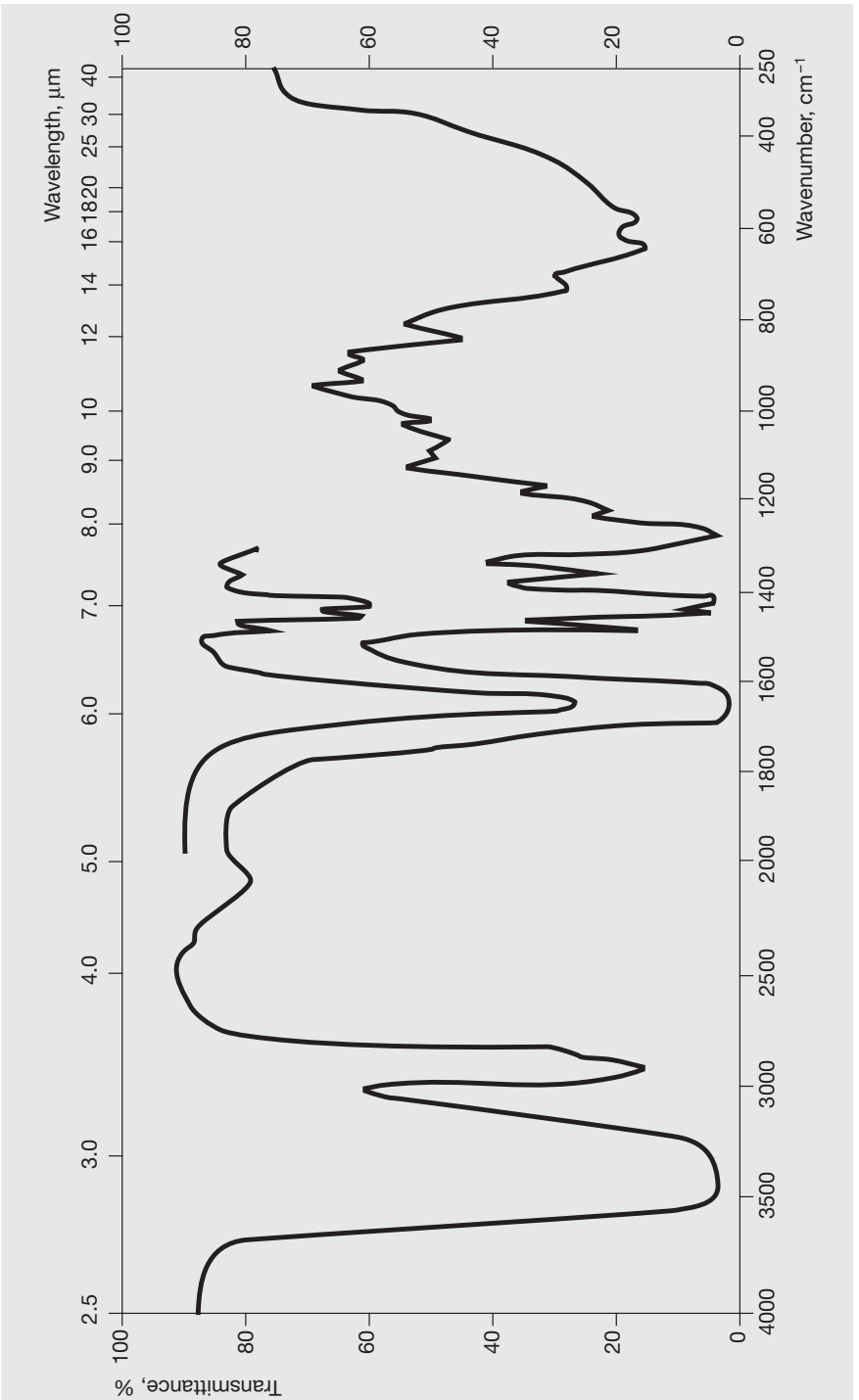


Fig. 3.12: Infrared spectrum of Kollidon® CL recorded in potassium bromide

3.3.1.2 Quantitative determination of Kollidon® CL grades

The Kollidon® CL grades can be quantitatively determined by one or both of following methods.

1. Nitrogen determination

The nitrogen content is determined by the method of the monograph "Crospovidone" of USP-NF or Ph. Eur. The theoretical value is 12.6 %.

As the description of the pharmacopoeial method is not exact enough to obtain always a complete degradation of the polymer a modified method is given in Section 2.3.3.6.

2. Gravimetric determination

Accurately weigh a sample of Kollidon® CL, thoroughly wash with water and dry for 3 hours at 105 °C. The final weight must be more than 98 % of the initial weight, calculated for the dried substance.

3.3.2 Methods for the determination of purity

3.3.2.1 Pharmacopoeia methods

The methods for the determination of the purity of the Kollidon® CL grades are described in detail in the crospovidone monographs of the current editions of the United States Pharmacopoeia (USP-NF) and the European Pharmacopoeia (Ph.Eur.). They cover all the parameters listed in Table 3.14.

Table 3.14: Purity test methods for the Kollidon® CL grades decribed in the pharmacopoeias

Classification as Type A or Type B by the particle size
Monomer (N-vinylpyrrolidone = impurity A of the Ph.Eur. monograph)
Water-soluble compounds
Peroxides (different limits for Type A and Type B)
Water/loss on drying
Sulphated ash
Heavy metals
Nitrogen (= Assay)
Residual solvents/Organic volatile impurities
Microbial status

The tests for hydrazine and 2-pyrrolidone, which are specified by the pharmacopoeias for povidone, are not required for crospovidone, as these impurities are almost not present. Also residual solvents are not present but this is a general requirement for all Ph.Eur. monographs.

3.3.2.2 HPLC method for the determination of free N-vinylpyrrolidone in Kollidon® CL grades

As the Kollidon® CL grades contain levels of N-vinylpyrrolidone that lie well below the detection limit of the iodometric titration method given in the crospovidone monograph of USP-NF, it is recommended to employ a more sentitive method such as gas chromatography or high performance liquid chromatography as now included in the crospovidone monograph of the current edition of Ph.Eur. These chromatographic methods have proved both accurate and precise.

The following HPLC method mentioned in the crospovidone monograph of Ph.Eur. gives a detection limit of less than 1 ppm of N-vinylpyrrolidone.

Principle:

An extract of the sample is separated by reversed phase chromatography. The interfering polymeric matrix is removed by switching columns.
A UV detector operating at 235 nm, calibrated with an external standard, is used to determine the level of monomer.

Sample preparation:

Weigh about 800 mg of crospovidone, accurate to 0.1 mg, into a conical flask, add 25 ml of the mobile phase and shake for 60 minutes. After the particles have settled filtrate through a 0.2 µm filter. Aliquots of this solution are used for the HPLC analysis.

If the N-vinylpyrrolidone content would exceed 10 ppm, the sample weight should be reduced or the solution diluted accordingly.

Preparation of the calibration solution:

Weigh 40 – 50 mg of N-vinylpyrrolidone, accurate to 0.01 mg, into a 50-ml volumetric flask and dissolve in about 20 ml of eluent. Then make up to the mark with eluent.

Prepare a dilution series from this stock solution to cover the range in which the N-vinylpyrrolidone content of the Kollidon® sample is expected.

Table 3.15: Chromatographic conditions

Guard column:	25 x 4 mm cartridge packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Separation column:	250 x 4 mm steel column packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Eluent (mobile phase):	Water/acetonitrile (92 + 8 % wt.)
Flow rate:	1 ml/min
Sample volume:	20 µl
Detection wavelength:	235 nm
Column temperature:	Room temperature
Retention time:	Approx. 11 min

Column switching:

The analysis is started with the guard column and separation column in series. After about 3 min, the valves, controlled by the detector programme, switch over such that the eluent flows past the guard column, direct to the separation column. The columns are switched at a point when the components to be determined, but not the interfering matrix, have reached the separation column. After about 35 min the columns are washed out in the reverse direction by a second pump, to remove the unwanted matrix components (0–10 min: eluent + acetonitrile 3 + 7; after 10 min: only acetonitrile). An illustration of this column switching system is given in a Figure in Section 2.3.3.2.

If a detector without a programming option is used, switching can be carried out manually or by another programmable component, e. g. the pump.

Calculation:

1. Calibration factor:

$$F = \frac{A_C}{W_{St}}$$

A_C = calibration substance peak area [mV · s]
W_{St} = weight of calibration substance per 100 ml [mg/100 ml]

2. N-Vinylpyrrolidone in the sample

The content of the sample is calculated with the aid of an external standard:

$$\text{N-vinylpyrrolidone [ppm]} = \frac{A \cdot 10^6}{F \cdot W_{Sa}}$$

A = peak area [mV · s]
W_{Sa} = sample weight [mg/100 ml]

Validation

Linearity:

The calibration curve was plotted from 7 points covering a concentration range of 0.01 to 11.0 µg/ml to check the linearity. Fig. 3.13 shows the calibration curve obtained.

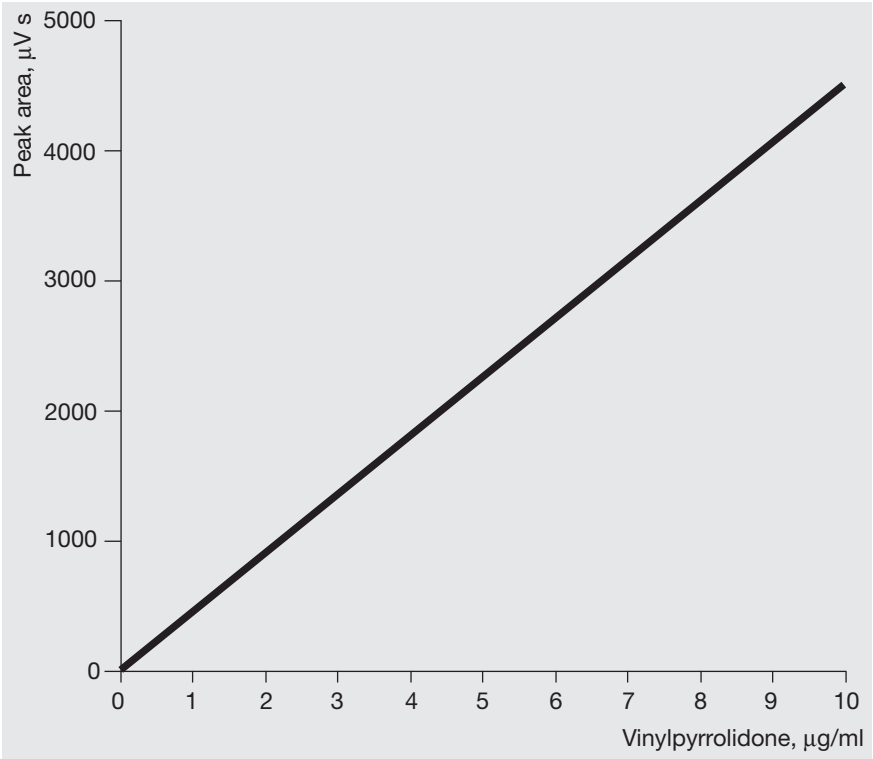


Fig. 3.13: Calibration curve for the HPLC determination of N-vinylpyrrolidone in Kollidon® CL grades

Reproducibility:

The N-vinylpyrrolidone content of a sample was determined six times. The values found and the average are given in Table 3.16.

Table 3.16: Vinylpyrrolidone content of a sample of Kollidon® CL

Determination No.	N-vinylpyrrolidone [mg/kg]
1	15.0
2	15.5
3	15.0
4	15.4
5	15.4
6	15.4
Average	15.3

3.3.2.3 Gas chromatography determination of free N-vinylpyrrolidone and 2-pyrrolidone in Kollidon® CL grades

As an alternative to the HPLC method given in Section 3.3.2.2, it is also possible to use gas chromatography to determine free N-vinylpyrrolidone and 2-pyrrolidone. The following routine method has a detection limit of 2 ppm for each impurity.

Principle:

The acetone extract of the polymer is analyzed by capillary gas chromatography, using benzonitrile as an internal standard. A nitrogen-specific detector (NSD) is used.

Internal standard solution:

Dissolve 25 mg of benzonitrile, weighed accurate to 0.2 mg, in 100 ml of acetone.

Apparatus and column:

Capillary gas chromatograph with automatic sample feeder and nitrogen-specific detector (NSD).
A fused silica capillary column with a film of polyethylene glycol, e. g. DB-Wax® (available from J & W Scientific), having a length of 30 m, an internal diameter of 0.25 mm and a film thickness of 0.5 µm.

Sample preparation:

Weigh 2 g, accurate to 0.1 mg, of the Kollidon® CL grade and mix with 1 ml of the internal standard solution and 24 ml of acetone. Subsequently roll the sample on a roller mixer for 4 hours or leave it to stand for 24 hours analyse the supernatant solution (the solid settles).
For routine determinations each sample is analysed in duplicate.

Table 3.17: Chromatographic conditions

Parameter	Value
Temperatur of injector:	220 °C
Temperatur of column oven	160 – 240 °C, 5 °C/min 240 °C, 4 min isothermal
Temperatur of detector (NSD)	250 °C
Carrier gas:	Helium
Inlet pressure:	1.4 bar
Split:	10 ml/min
Septum purging:	3 ml/min
Injection volume:	0.5 µl

System suitability:

To test the resolution a solution of benzonitrile and vinylimidazole (10 and 2 µg/ml in ethanol) is injected. The gas chromatography system is suitable if the two signals are at least baseline-separated (R > 1.5):

Calibration:

At least two calibration solutions of different concentrations shall be prepared, in acetone. The solutions shall contain a suitable amount of internal standard plus, in each case, the reference materials N-vinylpyrrolidone and 2-pyrrolidone as analyte in concentrations such that the calibration points surround the respective measurement value.

Example:
In each case 25 – 200 µl of different concentrations of N-vinylpyrrolidone and 2-pyrrolidone stock solutions in acetone + 24 ml acetone + 1 ml internal standard solution.

Calculations

1. Gas-chromatographic calibration factor F:

$$F = \frac{A(a)_o \cdot M(is)_o}{M(a)_o \cdot A(is)_o}$$

where,

$A(a)_o$ = peak area of analyte in the chromatogramm of the calibration solution [mV · s]
$M(a)_o$ = initial mass of reference material of the analyte in the calibration solution [mg]
$A(is)_o$ = peak area of the internal standard in the chromatogramm of the calibration solution [mV · s]
$M(is)_o$ = initial mass of internal standard in the calibration solution [mg]

2. Mass fraction M(a) of the analyte:

$$M(a) = \frac{A(a) \cdot M(is)}{M(s) \cdot A(is) \cdot F} \; [\mu g/g]$$

where,

$A(a)$ = peak area of the analyte in the chromatogramm of the sample solution [mV · s]
$M(s)$ = initial mass of sample [g]
$A(is)$ = peak area of the internal standard in the chromatogramm of the sample solution [mV · s]
$M(is)$ = initial mass of internal standard added to the sample [µg]
F = gas-chromatographic calibration factor

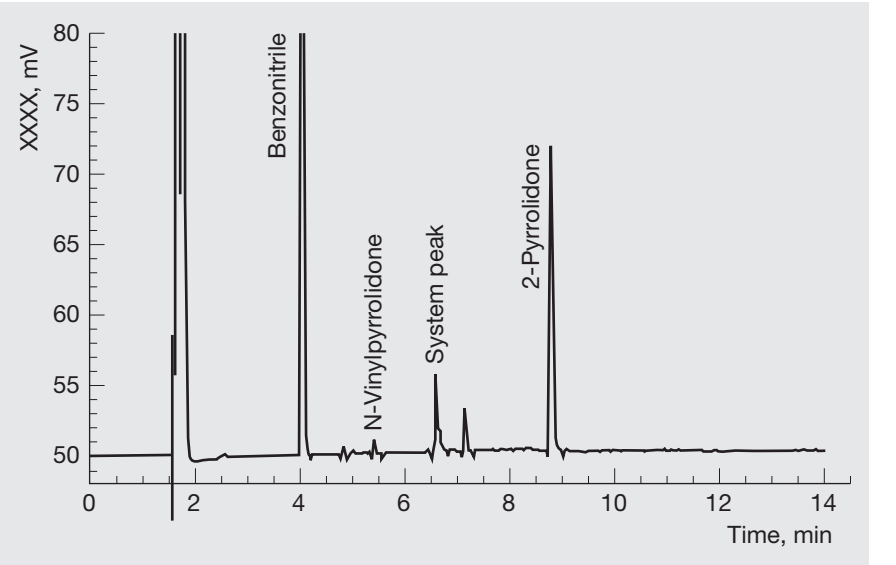


Fig. 3.14: Typical gas chromatogram of Kollidon® CL with internal standard

Validation

Linearity:

For the purpose of calibration the GC factors for N-vinylpyrrolidone and 2-pyrrolidone were determined at 6 concentration levels in each case. Linear calibration curves were obtained with the follwing certainities:
– N-Vinylpyrrolidone: $R^2 = 0.9987$
– 2-Pyrrolidone: $R^2 = 0.9990$.

Reproducibility and precision:

To determine the precision under repeatability conditions a batch of Kollidon® CL was analyzed 6 times. The results are given in Table 3.18.

Table 3.18: Reproducibility of N-vinylpyrrolidone and 2-pyrrolidone determinations on a sample of Kollidon® CL (batch 020053P050)

Determination No.	N-vinylpyrrolidone [mg/kg]	2-pyrrolidone [mg/kg]
1	< 2	33
2	< 2	32
3	< 2	32
4	< 2	32
5	< 2	33
6	< 2	32
Average	< 2	32.5
Standard deviation, S_{rel}	–	0.3

Additionally on 6 samples of the same batch of Kollidon® CL standard addition experiments were carried out in the following concentration ranges: N-vinylpyrrolidone: 2.1 – 20.1 µg/g and 2-pyrrolidone: 4.9 – 200.0 µg/g. Table 3.19 shows the accuracy obtained in these trials. The results confirm the precision of the method over the tested concentration ranges.

Table 3.19: Precision of the determinations of added N-vinylpyrrolidone and 2-pyrrolidone on a sample of Kollidon® CL (batch 020053P050)

Determination No.	N-vinylpyrrolidone [%]	2-pyrrolidone [%]
1. Addition	102.9	99.7
2. Addition	107.5	100.5
3. Addition	102.8	96.1
4. Addition	102.2	95.2
5. Addition	99.5	93.0
6. Addition	102.8	95.7

Recovery:

For the purpose of determining the recovery, to a sample of the same batch of Kollidon® CL has both analytes added to it as standard additions. The precision under repeatability conditions can be read off from the recovery of the standard additions in 6 determinations (Table 3.20).

Table 3.20: Recovery rates in per cent of added N-vinylpyrrolidone and 2-pyrrolidone on a sample of Kollidon® CL (batch 020053P050)

Determination No.	N-vinylpyrrolidone [%]	2-pyrrolidone [%]
1	103.0	101.6
2	97.2	95.7
3	99.3	97.6
4	110.9	143.2
5	108.5	115.8
6	111.3	138.0
Average	105.0	115.3
Standard deviation, S_{rel}	6.1	20.9

Conformity with the HPLC method of Ph.Eur. for the determination of N-vinyl-pyrrolidone

Using the HPLC method of the Ph.Eur. monograph “Crospovidone” the content of N-vinylpyrrolidone in batch 020053P050 of Kollidon® CL was < 2 ppm. Since the GC method also gives the same concentration and the validation of this method is confirmed the results of both method can be considered as equivalent.

3.3.3 Determination of the complexation capacity with salicylic acid

Salicylic acid has been selected as a model substance to provide a standard method for measuring the complexation capacity of crospovidone. Measurement of the complex formation constant for this substance in water gave a value of 4.1 $l \cdot mol^{-1}$ [158].

The following method measures the percentage of salicylic acid that is complexed by a given quantity of Kollidon® CL grade. The value normally lies between 30 % and 50 % at 20 °C.

Preparation of the 0.1 N salicylic acid solution:

Dissolve 13.81 g of salicylic acid in 500 ml of methanol in a 1000-ml volumetric flask and make up almost to the mark with water. After 24 hours at 23 – 25 °C, make up exactly to the mark.

Procedure:

Accurately weigh about 2 g of crospovidone into a conical flask (sample weight = W [g]).

Calculate the volume of 0.1 N salicylic acid solution required, taking into account the water content, w [%] of the sample to be tested, with the following formula:

$$\text{Volume (ml)} = \frac{W \cdot 43 \cdot (100 - w)}{100} \quad (= \text{approx. } 80)$$

Transfer the calculated volume of 0.1 N salicylic acid solution to the conical flask with crospovidone, close and shake vigorously for 5 min at 23 – 25 °C. Fill the resulting suspension non-quantitatively into centrifuge tubes, and centrifuge for 10 min at 4000 rpm.

Filter the supernatant solution through a No. 4 glass frit covered by a paper filter. Titrate exactly 20 ml of the clear or opalescent filtrate against 0.1 N sodium hydroxide solution, using phenolphthalein as indicator (titre in ml = t).

To obtain the 100-% value, titrate exactly 20 ml of 0.1 N salicylic acid solution against 0.1 N sodium hydroxide solution in the same manner (titre in ml = T).

Calculation:

Calculate the complexed salicylic acid with the following formula:

$$\text{Salicylic acid complexed (\%)} = \frac{(T - t) \cdot 100}{T}$$

3.3.4 Quantitative determination of Kollidon® CL grades in preparations

Gravimetric analysis provides the best method for the quantitative determination of crospovidone in preparations.

Principle:

Suspend the sample material in water and/or a suitable solvent that dissolves all the other components of the preparation. Crospovidone is determined gravimetrically after filtration and drying.

Procedure:

Accurately weigh about 5 g of sample, that contains 2–5 % of crospovidone, into a glass beaker and mix with about 250 ml of water or other solvent. Insert a magnetic stirrer bar and cover the beaker with a clock glass. Stir for 2 hours.

Then leave to settle and draw off the supernatant solution through a dried and preweighed G 4 Gooch crucible. Wash and leave to stand again, decant the supernatant solution through the Gooch crucible, then quantitatively transfer the residue to the Gooch crucible with small portions of water.

Dry at 105 °C for 3 hours.

Calculation:

The crospovidone content is given as a percentage by the following formula:

$$\% \text{ crospovidone} = \frac{\text{Weight after filtration [g]} \times 100}{\text{Original sample weight [g]}}$$

3.4 Applications of the Kollidon® CL grades

3.4.1 General application properties

The Kollidon® CL grades possess a series of properties that are used in the manufacture of different pharmaceutical products and dosage forms.

Table 3.21: Functions and properties of Kollidon® CL grades as pharmaceutical excipients

– Acceleration of tablet disintegration and therefore also of dissolution and bioavailability of the active ingredients as a result of predictable swelling in normal tablets
– Strong acceleration of tablet disintegration as a result of predictable swelling in fast disintegrating or buccal tablets
– Improvement of dissolution and bioavailability of insoluble active ingredients by complex formation
– Stabilization of suspensions by Kollidon® CL-M as a hydrophilic polymer
– Stabilization of vitamins and other active ingredients sensitive against hydrolisis by adsorption of water (desiccant effect)
– Selective adsorption of polyphenols by complex formation
– Adsorption of endotoxins by complexation
– Taste masking of acetaminophen, azithromycin etc.

The most important property of the Kollidon® CL grades as auxiliaries is their disintegration and dissolution enhancing effect, which can be used in different tablets, granules and hard gelatin capsules including fast disintegrating tablets and tablets with low concentrations of active ingredient (see Section 3.4.2).

The improvement brought about by Kollidon® CL grades in the dissolution of insoluble active ingredients by complex formation is particularly useful for tablets and granules (see Section 3.4.3).

The ability of Kollidon® CL-M to stabilize suspensions without viscosity finds its most important application in oral antibiotics, antacids and vitamin preparations (see Section 3.4.4).

The hygroscopicity of Kollidon® CL grades can be used to adsorb water in preparations that contain moisture-sensitive active ingredients, to improve their stability (see Section 3.4.6).

The use of micronized crospovidone (e. g. Kollidon® CL-M) as an active ingredient against diarrhoea (see Section 3.4.5) depends on its ability to form complexes, as does the use of crospovidone (“PVPP”) in removing polyphenols from wine, beer and plant extracts.

3.4.2 Kollidon® CL grades as disintegrants and dissolution agents for tablets, granules and hard gelatine capsules

3.4.2.1 General

The active ingredient of a tablet or capsule must be bioavailable. To achieve or improve this, one must be aware of the following sequence of events after the tablet or capsule is taken (Table 3.22).

Table 3.22: Steps to the bioavailability of the active ingredient in a tablet or capsule

Normal tablets and capsules	Fast disintegrating buccal tablets
Ingestion	Mouth
↓	↓
Disintegration of the tablet or capsule in the gastric or intestinal juice	Disintegration of the tablet in the mouth
↓	↓
Distribution of the particles in the gastrointestinal tract	Distribution of the particles in the mouth
↓	↓
Dissolution of the active ingredient in the gastric or intestinal juice	Dissolution of the active ingredient in the saliva
↓	↓
Absorption of the active ingredient by the mucous membrane of the stomach or intestine	Absorption of the active ingredient by the mucousa

The disintegration of the normal and fast disintegrating tablet or capsule can be regarded as the first step on the path to bioavailability and to the pharmacological action of the drug taking effect. To achieve this, it is usually necessary to add a disintegrant to the tablet.

Different disintegrants work in different ways, which can involve swelling, wicking and deformation effects, and the repulsion of charged particles. The effect of the Kollidon® CL grades as disintegrant is based mainly on its predictable swelling properties (see Section 3.2.7).

3.4.2.2 Quantities of Kollidon® CL grades and processing

The optimum quantity of Kollidon® CL grades in a tablet or in granules is specific to each particular formulation and cannot be predicted accurately. It also depends very much on the desired disintegration time, which is different for an analgesic than for a coated multivitamin tablet or a fast dispersable tablet. In practice it has been found that the usual concentration of Kollidon® CL grades lies in the 1–8 % range. If the proportion of Kollidon® CL is increased beyond 5 or 6 % in normal tablets, the disintegration time is sometimes no longer improved by a worthwhile amount. With the placebo tablets consisting of calcium hydrogen phosphate and lactose (3 + 1), which were used to measure the values in Fig. 3.15, as little as 1 % of disintegrant was sufficient to reduce the disintegration time to less than 5 minutes.

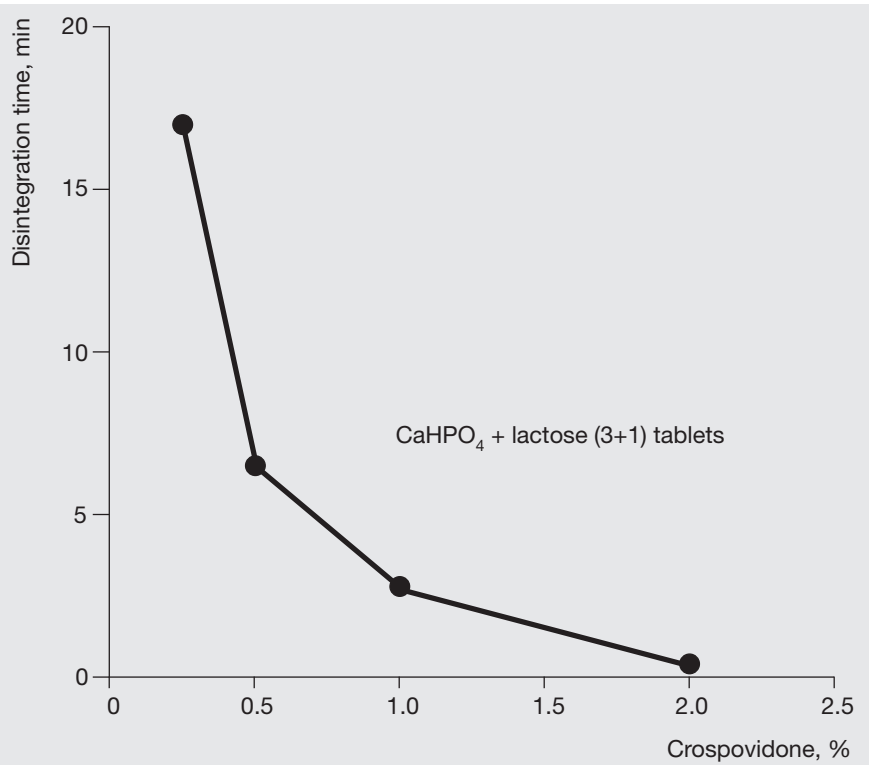


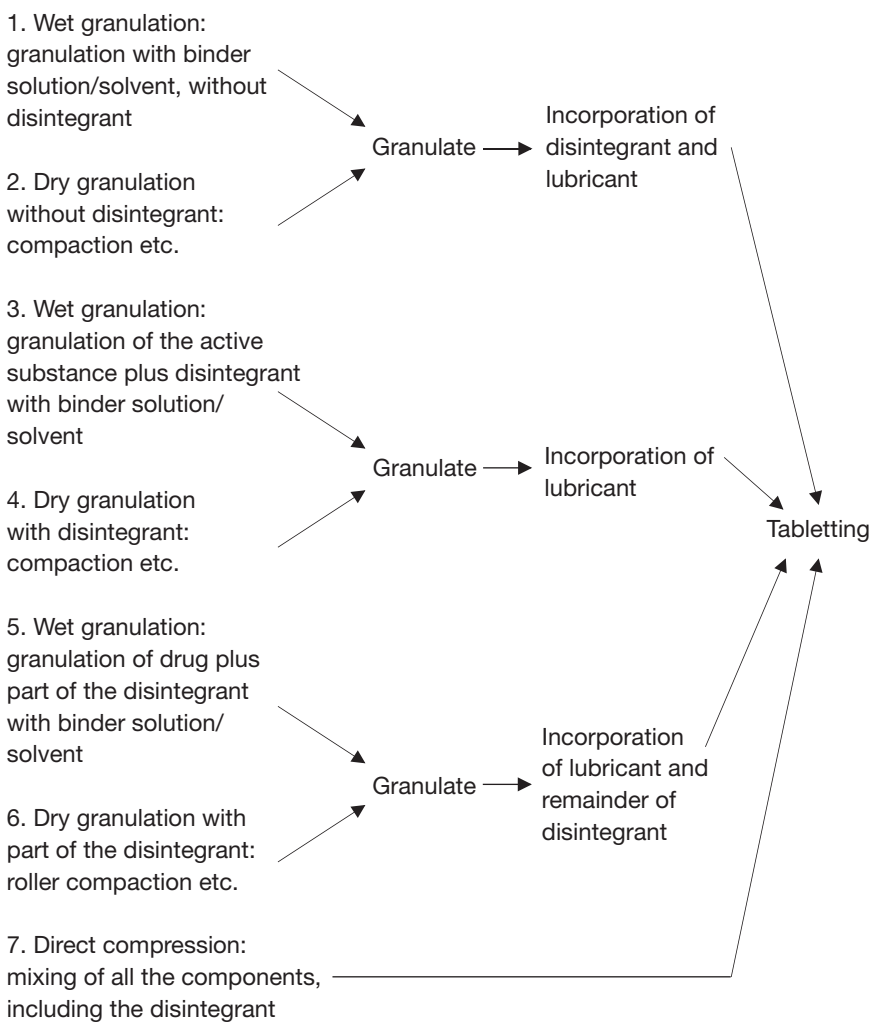
Fig. 3.15: Effect of the concentration of crospovidone on the disintegration time of calcium hydrogen phosphate-lactose placebo tablets [396]

In difficult cases, such as griseofulvin tablets, however, a higher proportion of Kollidon® CL can provide a significant improvement [93].

Apart from the proportion of Kollidon® CL grade, the method by which it is incorporated and the point at which it is added to the tabletting mixture also play a certain role.

Methods Nos. 1 and 2 in Table 3.23, in which the disintegrant is added after granulation (= extragranular addition), are used most frequently. In Methods Nos. 3 and 4, the disintegrant is added prior to granulation (= intragranular addition), while in Nos. 5 and 6 part of the disintegrant is added before, and the rest after granulation. Direct compression, Method No. 7, can also be used. The application of Kollidon® CL grades in the roller compaction technology (Method No. 6) is described in the literature [650, 651].

Table 3.23: General tabletting methods with particular regard to the point of addition of the disintegrant



Incorporating crospovidone prior to granulation has no adverse effect with regard to swelling, as this is reversible and – in contrast to carboxymethyl starch – the swelling effect and the disintegration time remain unchanged by wetting and drying [405].

Nevertheless, adding the disintegrant after granulation makes it easier to reprocess a batch of tablets, should this become necessary [243].

It is always worth investigating the relative merits of adding the Kollidon® CL grade before or after granulation (Methods 3–6 in Table 3.23) whenever problems occur in tabletting. As shown in Table 3.24 for magnesium trisilicate tablets, the addition of 4 % crospovidone prior to granulation reduces the friability of the tablets without noticeably changing their disintegration or hardness, compared to when it is added after granulation.

Table 3.24: Effect of adding 4 % crospovidone before or after granulation on the properties of magnesium trisilicate tablets [397]

Parameter	Intragranular addition	Extragranular addition
Hardness	108 N	110 N
Disintegration	30 s	36 s
Friability	2.3 %	1.6 %

In a few cases, the intragranular inclusion of the disintegrant in the granulation mixture can provide tablets with shorter disintegration times [216].
This particularly applies when the tablet disintegrates quickly enough, but the granules do not, as when they are very hard. In such cases, it is recommended to add some of the Kollidon® CL grade before granulation and some after. Such combination of the extragranular and intragranular addition of Kollidon® CL was the best method to obtain the optimal release of atenolol or an other water-soluble drug from tablets [635, 640]. Also Kollidon® CL-SF is applied in this manner in the loperamide formulation of fast dispersible tablets given in Table 3.27.

The solubility of the tabletting mixture (active ingredient and/or filler) in water also has a definite influence on the effectiveness of disintegrants. These are generally more effective in insoluble mixtures. Thus, for instance, calcium phosphate placebo tablets with 4 % crospovidone disintegrate significantly more quickly than corresponding tablets with lactose [441].

3.4.2.3 Comparison of the Kollidon® CL grades used as disintegrants in tablets

Kollidon® CL is used as the standard disintegrant for all kind of different tablet formulations. Since many years the pharmaceutical industries know quite well the performance of the material. Main reasons for taking this disintegrant is the strongest disintegration power with benefits especially in large tablets. It has advantages compared to other disintegrants which are based on a different chemistry due to disintegration and dissolution speed.
The particle size of Kollidon® CL must be regarded as a compromise: although even coarser particles provide a slightly better disintegration effect than Kollidon® CL, the latter probably gives tablets whose surface finish is less affected by humidity than tablets made with a coarser crospovidone which does not contain the fine fraction that makes up the major portion of Kollidon® CL. But it must be stated that the differences of few minutes of the disintegration time of a tablet normally have no significant influence on the dissolution of the active ingredient.
Table 3.25 gives a overview of the general properties and functions of the Kollidon® CL grades normally used as disintegrants in tablets. Table 3.26 and also Fig. 3.16 in the next Section show the comparison of disintegration and dissolution of analgesic tablets caused by these Kollidon® CL grades and other disintegrants.

Table 3.25: Comparison of general properties of Kollidon® CL grades used as disintegrants

Product	Disintegration power	Drug dissolution	Mouthfeel (for buccal tablets)	Smooth tablet surface	Tablet hardness
Kollidon® CL	++	++	–	–	+/–
Kollidon® CL-F	+	+	+	+/–	+
Kollidon® CL-SF	+	+/–	++	+	++

Kollidon® CL-F has a strong disintegration power although the particles are finer compared with Kollidon® CL. Tablets containing Kollidon® CL-F do not tend to form rough surfaces after storage under humid conditions. Therefore it is a perfect alternative to Kollidon® CL when formulators are looking for a disintegrant with short disintegration time and fast dissolution in combination with a smooth tablet surface (see Tables 3.25 and 3.26 and also Fig. 3.16). With Kollidon® CL rough surfaced tablets might occur with very hygroscopic formulations packed in a multidose packaging. This sensitivity increases with a decreased size of the tablet. As a consequence Kollidon® CL-F should be taken for the development of small tablets or micro tablets.

Furthermore the material is able to adsorb large amounts of solvent. This behavior can be beneficial when the disintegrant is used in the intragranular form and large amounts of granulation liquid have to be used for wet granulation (e. g. for dissolving the active ingredient in the granulation liquid).

Table 3.26: Comparison of disintegrants in analgesic tablets

1. Composition:		
I	Acetaminophen cryst.	250 mg
	Acetylsalicylic acid cryst.	250 mg
	Caffeine cryst.	50 mg
II	Kollidon® 90 F (dissolved in 2-propanol)	17 mg
III	Magnesium stearate	5 mg
	Disintegrant	27 mg

Granulate Mixture I with Solution II, sieve through a 1000 µm sieve, dry and mix 10 min with III and press on a rotary tablet press with a high compression force of 18 kN.

2. Disintegration times of the tablets in synthetic gastric juice:

Disintegrant	Min
None	> 60
Kollidon® CL	9
Kollidon® CL-F	11
Kollidon® CL-SF	9
Croscarmellose	23
Carboxymethylstarch	34

Kollidon® CL-SF is the finest crospovidone grade for disintegration purposes and it has a good disintegration power and less surface defects of the tablets after humid storage. This grade is perfect for fast disintegrating buccal tablets (e.g. Flash tabs®) since it gives a very smooth cream-like mouth feel superior to the other Kollidon® CL types. For this kind of tablets – first of all of analgesics – a "superdisintegrant" like crospovidone is used to obtain a disintegration within less than one minute. A typical example is ibuprofen [654, 655]. Table 3.27 illustrates the practical use of Kollidon® CL-SF in a formulation of fast disintegrating buccal loperamide tablets.

Table 3.27: Kollidon® CL-SF in a formulation of fast disintegrating buccal loperamide tablets

Formulation (wet granulation):		
I	Loperamide-HCl (Select Chemie)	2.0 mg
	Mannitol powder (Roquette)	85.5 mg
	Kollidon® CL-SF	4.0 mg
II	Kollicoat® IR	3.0 mg
	Water	27.0 mg
III	Kollidon® CL-SF	3.0 mg
	Chocolate flavour (Symrise)	1.5 mg
	Sodium stearyl fumarate (JRS Pharma)	1.0 mg

Granulate mixture I with binder solution II in a fluidized bed granulator (inlet air temperature 40 – 45 °C, outlet air temperature 30 °C, atomizing pressure 0.5 bar), mix with the components III, pass through a 0.8 mm sieve, blend and press with low compression force (about 4 kN).

Tablet properties:

Tablets pressed on a rotary tabletting press had the following properties:

Weight	100 mg
Diameter and form	7 mm, concave
Hardness	27 N
Disintegration time in water	27 s
Friability	less than 0.2 %
Dissolution (0.01 N HCl/100 rpm)	84 % after 5 min, 94 % after 10 min
Content uniformity	corresponds to Ph.Eur.

Due to its interesting properties Kollidon® CL-SF also forms a part of a new direct compression agent (Ludiflash®) developed for the production of fast disintegrating buccal tablets. It is a preparation of mannitol, Kollidon® CL-SF and Kollicoat® SR 30D.

Furthermore Kollidon® CL-SF shows the strongest ability of all Kollidon® CL grades to adsorb water or ethanol.

Table 3.25 gives a overview of the general properties of the three Kollidon® CL grades normally used as disintegrants. Table 3.26 and also Fig. 3.16 show the comparison of disintegration and dissolution of analgesic tablets caused by these Kollidon® CL grades and other disintegrants.

Kollidon® CL-M is seldom used as disintegrant. The reason was demonstrated by the comparison of the disintegration times of analgesic tablets containing Kollidon® CL or Kollidon® CL-M. In all tablets no difference in the hardness was found but a strong difference in the disintegration properties. In the case of the tablets made with 3 % or 5 % Kollidon® CL the disintegration time was 1 or 2 min. The tablets made with the same concentrations of Kollidon® CL-M instead of Kollidon® CL showed disintegrations times of 6 to 15 min.

3.4.2.4 Comparison of Kollidon® CL grades with other disintegrants

Today crospovidone is described in the literature as one of the three "superdisintegrants" [216, 403, 441, 654]. This is also demonstrated by the examples in Tables 3.26 and Tables 3.29–3.30 below. A large number of papers have been published that substantiate this in comparisons of various disintegrants in tablets. They come to the conclusion that there is no universal ideal disintegrant and that the best disintegrant must be determined individually for each formulation.

As not all disintegrants function in the same manner, and as their action is not only based on swelling, they can behave somewhat differently. This is why the physical methods given in Section 3.2.7 do not allow reliable comparison of the disintegrants used today. The same applies also to a large number of investigations using placebo tablets [89–91, 95, 167, 191, 216, 392, 393, 396, 404, 441]. A combination of several of these methods is more likely to provide information that is relevant to practical requirements

[391]. In view of the fact that the dissolution is the final quality criteria of the effect of a disintegrant in a tablet these published physical characterizations of disintegration are more of theoretical interest.
A further result of these publications and references is that a difference of the disintegration time of few minutes normally has not any significant influence on the dissolution of the active ingredient.

Thus, it is necessary to compare different disintegrants in the same drug formulation. Table 3.28 lists a series of publications in which disintegrant trials are described on tablets or capsules containing active ingredients. Unfortunately, not all the papers contain investigations into the dissolution of the drug.

Table 3.28: Literature on comparisons between different disintegrants

Drug	Disintegration test	Dissolution test	Literature source
Acetaminophen (paracetamol)	+	+	[402]
Acetylsalicylic acid	+	+	[239]
Acetylsalicylic acid	+	–	[398, 404]
p-Aminobenzoic acid	+	+	[403]
Amoxicillin	+	–	[519]
Ampicillin	+	–	[519]
Ascorbic acid	+	+	[239]
Cefalexin	+	–	[519]
Cefadroxil	+	–	[519]
Diazepam	+	–	[96]
Diethylenediamine sultosylate	+	+	[210]
Harpagophytum plant extract	+	–	[250]
Hydrochlorothiazide	+	+	[390, 543]
Ibuprofen	–	+	[555, 584]
Ketoconazol	+	+	[525]
Magnesium trisilicate	+	–	[397]
Prednisone	+	+	[216]
Terfenadin	+	+	[553]
Tiaramide HCl	+	–	[405]

Apart from the enhancement of the tablet disintegration it is even more important that the dissolution of the active ingredient is increased as well to achieve a fast resorption of the drug. Figures 3.16 and 3.17 and Tables 3.29 and 3.30 show examples of dissolution data of various formulations with different disintegrants including also Kollidon® CL-F and Kollidon® CL-SF in the case of an acetaminophen tablet. In some formulations there is no significant difference of the dissolution between the disintegrants, in other formulations the difference is strong. But allways the increase of the dissolution in comparison with the tablets without disintegrant is enormous.

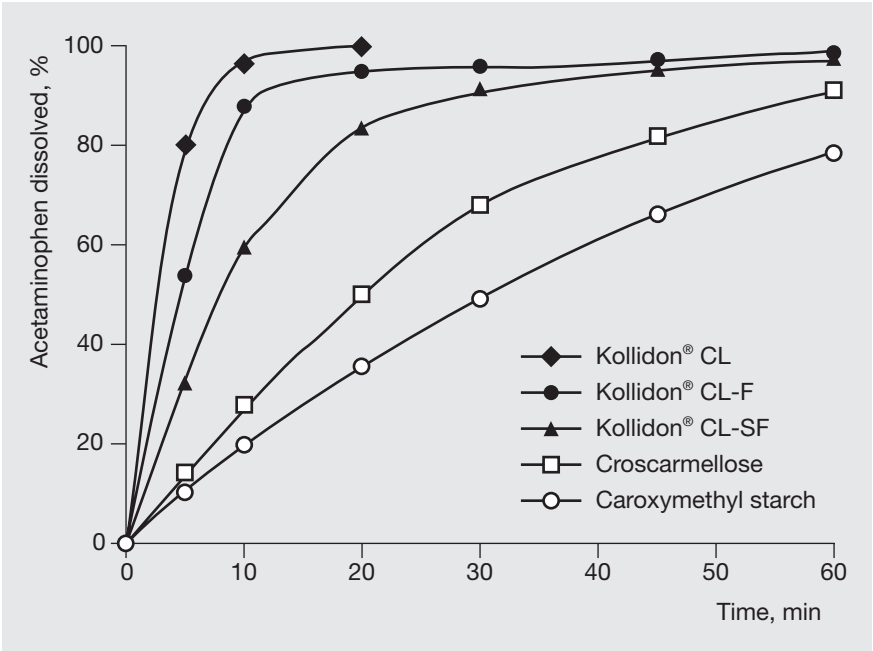


Fig. 3.16: Dissolution of an acetaminophen tablet (2.7 % disintegrant)

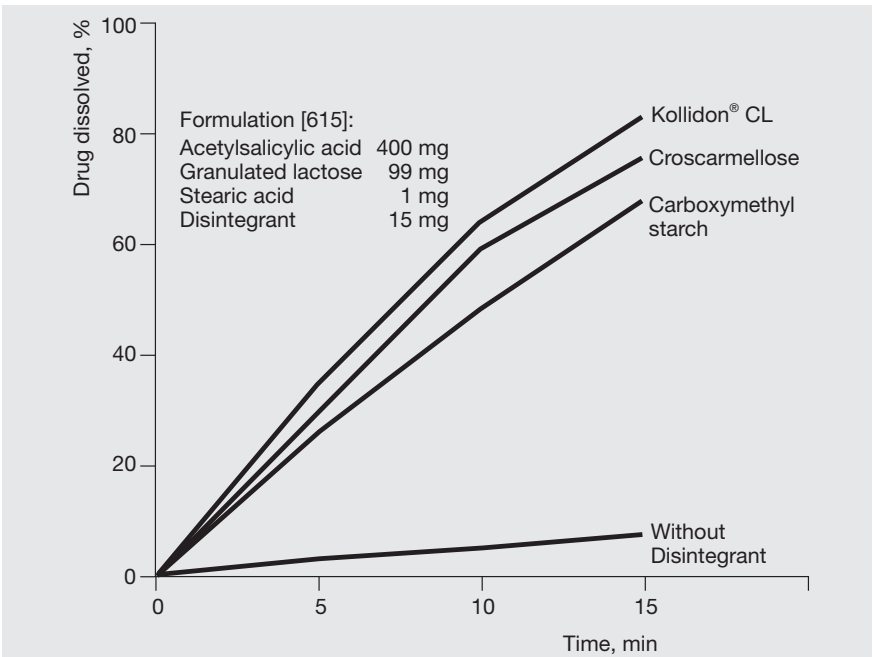


Fig. 3.17: Dissolution of acetylsalicylic acid tablets according to USP prepared with different disintegrants (3 %)

Table 3.29: Comparison of the influence of disintegrants on the dissolution in a p-aminobenzoic acid tablet before and after storage [403]

1. Composition:

p-Aminobenzoic acid	1.0 %
Sorbitol	48.3 %
Dicalcium phosphate	48.3 %
Magnesium stearate	0.5 %
Disintegrant	2.0 %

2. Dissolution of the drug after 15 min:

Disintegrant	After manufacture	After 14 months storage at 30 °C (packaged)
None	27 %	34 %
Kollidon® CL	78 %	81 %
Polyplasdone® XL (ISP)	79 %	82 %
Croscarmellose	80 %	74 %
Carboxymethyl starch	68 %	74 %

Table 3.30: Comparison of the influence of disintegrants on the dissolution of prednisone tablets [216]

1. Composition:

I	Prednisone	1.0 %
	Disintegrant	4.0 %
	Lactose	94.5 %
II	Gelatin (dissolved in water)	0.5 %

Granulate Mixture I with Solution II, dry, sieve and press into tablets.

2. Properties of the tablets:

Disintegrant	Disintegration time	Dissolution (10 min)
Potato starch (20 %)	215 s	65 %
Crospovidone	26 s	99 %
Croscarmellose	149 s	93 %
Carmellose	424 s	45 %
Carboxymethyl starch	49 s	100 %

Apart from the disintegration and dissolution the influence of the compression force on the other tablet properties in the presence of disintegrants always must be considered. The addition of crospovidone has no adverse effect on tablet hardness. The hardness often remains proportional to the compression force over a wide range [390, 404], so that tablets of high hardness and rapid disintegration or dissolution can be obtained [393, 404]. The performance of crospovidone, starch and carboxymethyl starch in hydrochlorothiazide is compared in Fig. 3.18.

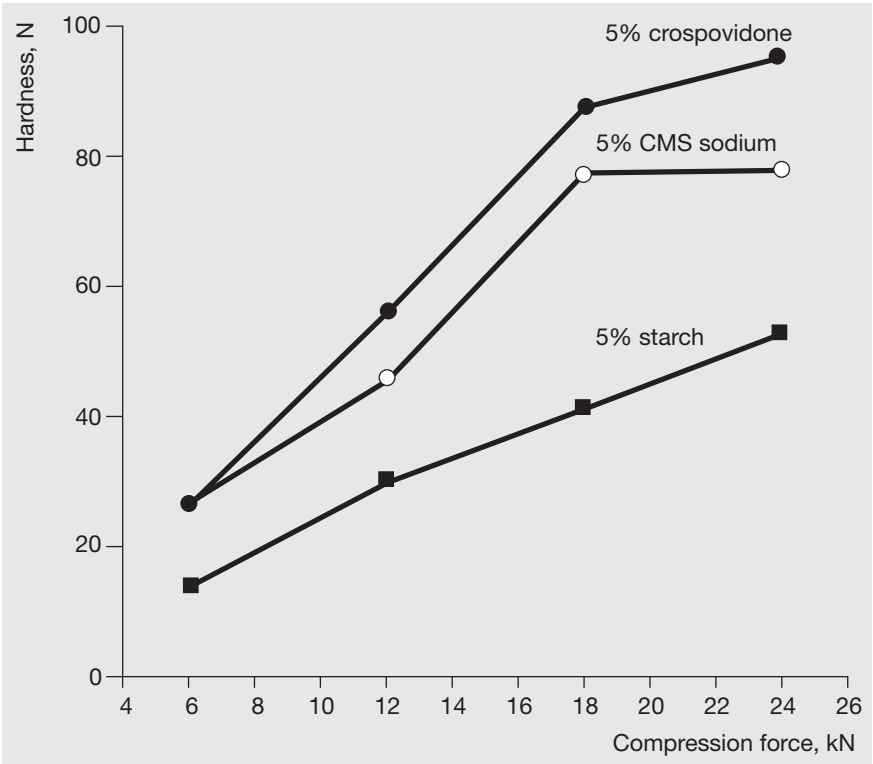


Fig. 3.18: Influence of compression force on the hardness of hydrochlorothiazide tablets containing 5 % of disintegrant [390]

The compression force and the tablet hardness usually have little effect on the disintegration time of tablets that contain Kollidon® CL. This relationship between compression force and disintegration time of drug-containing tablets made with crospovidone is also described in the literature [243, 390]. In Fig. 3.19, the curve for crospovidone is the lowest, indicating that the compression force has little effect on disintegration in comparison with the other tested disintegrants.

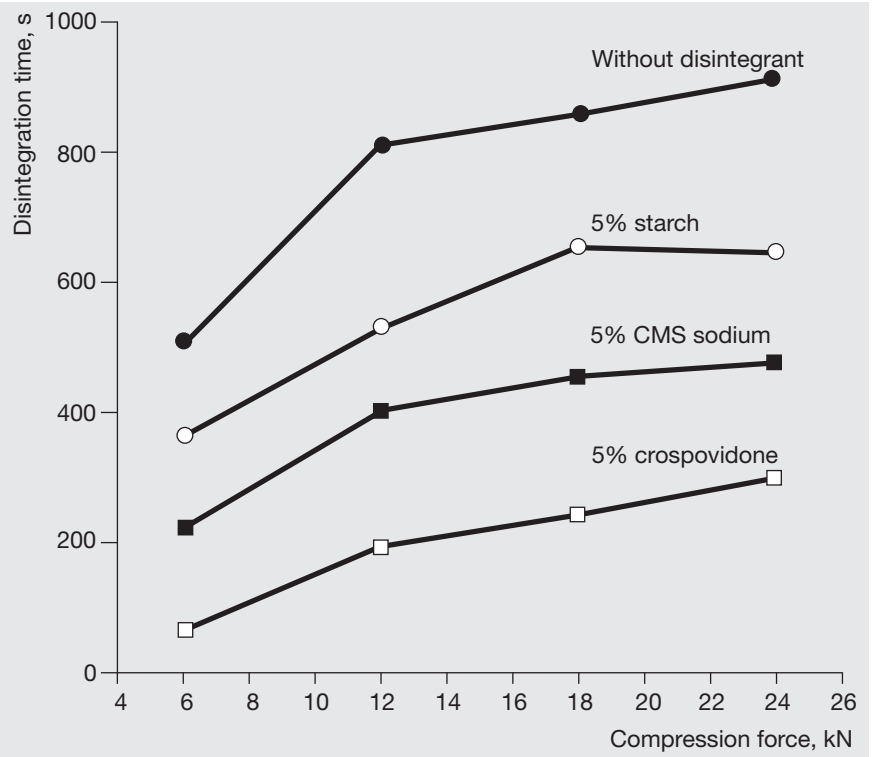


Fig. 3.19: Effect of compression force on the disintegration time of drug-containing tablets with different disintegrants [390]

It has also been found with acetaminophen tablets that, compared with other disintegrants, the addition of 2 % Kollidon® CL gives harder tablets with a comparable, short disintegration time at a lower compression force [402].

As with the disintegration time, the dissolution of the active ingredient is usually not adversely affected over a certain compression force range. This was reported in the case of amaranth placebo tablets with 5 % crospovidone. The dissolution rate of the dye was not reduced at higher compression forces [91].

3.4.2.5 Influence of storage on the physical properties of tablets containing Kollidon® CL grades

Changes in the physical properties, e. g. hardness, disintegration and dissolution of tablets during storage are a common problem. An important feature of Kollidon® CL grades is that the disintegration times of tablets made with crospovidone remain largely unchanged over long periods, if they are correctly packaged. To demonstrate this, analgesic tablets (250 mg acetylsalicylic acid + 250 mg phenacetin + 50 mg caffeine) with 5 % disintegrant were stored for 12 months at room temperature. Kollidon® CL was the only one of the 5 disintegrants tested that gave tablets whose short disintegration time of 1 min did not change during storage (Table 3.31). The disintegration

times of tablets made with the other disintegrants were longer from the start and increased markedly during storage. The hardness and friability of the tablets remained largely unchanged, regardless of the formulation. Similar results are described for the dissolution time of hydrochlorothiazide tablets [543].

Table 3.31: Influence of storage at room temperature on the disintegration of analgesic tablets

Disintegrant (5 %)	Disintegration in synthetic gastric juice	
	After preparation	After 12 months
Kollidon® CL	1 min	1 min
Croscarmellose	7 min	12 min
Carmellose	22 min	46 min
Carboxymethyl starch	16 min	48 min
L-Hydroxypropyl cellulose	15 min	20 min

Table 3.29 in Section 3.4.2.4 shows the results of storing para-aminobenzoic acid tablets containing 2 % Kollidon® CL for 14 months at 30 °C [403]. Here, too, no reduction in the release of the drug was found after storage.

Even when calcium hydrogen phosphate tablets with 2.5 % crospovidone were stored for 3 months at 75 % relative humidity, the rate of dissolution of the amaranth dye was increased rather than reduced [95]. Similar results were obtained with tiaramide tablets [405].

The packaging always has a major effect on the properties of tablets that contain a Kollidon® CL grade, when they are stored under humid conditions. Crospovidone is highly hygroscopic and the individual particles begin to swell when they adsorb water. This can have two detrimental effects in the case of coarse types of crospovidone. Firstly, the surface of the tablets becomes rough and unsightly, and secondly, the tablets become softer [95].
It is therefore important to always provide the tablets with moisture-proof packaging.

On the other hand, Kollidon® CL grades can indirectly stabilize drugs in tablets by adsorbing water (see also Section 3.4.6.2). Water promotes degradation by hydrolysis and other reactions, particularly in multivitamin tablets [368].

3.4.2.6 Coating tablets that contain Kollidon® CL grades

As tablet cores that contain crospovidone or croscarmellose swell readily in the presence of water, care must be taken when coating such tablets with aqueous solutions in the coating pan [493]. In many cases it is advisable to subcoat the cores before applying the actual sugar or film coating.

A 10 % solution of Kollidon® VA 64 in acetone, ethyl acetate or 2-propanol has been found to give good results in subcoating. The solution is sprayed onto the prewarmed tablet cores for a short time in the same coating machine in which the final aqueous coating is to be applied (see Section 4.4.3.2).

3.4.2.7 The use of Kollidon® CL grades as disintegrant in suppositories

Kollidon® CL grades can be used as disintegrants to increase the bioavailability not only of tablets, but also of suppositories. The dissolution rate of drugs in polyethylene glycol-based suppositories can be improved by adding 1 – 10 % Kollidon® CL [211].

3.4.3 Improvement of the dissolution and bioavailability of drugs with Kollidon® CL grades by complex formation

3.4.3.1 General

As described in Section 3.4.2, Kollidon® CL grades can contribute to improving the dissolution of an active ingredient, as a result of its disintegrating properties. However, these properties are inadequate for a number of active ingredients, as their solubility in gastric juice is poor. In such cases it is worth considering complexing them with Kollidon® CL grades in the same manner as with the soluble Kollidon® grades (see Section 3.2.8.1).

It is interesting to note that, although the Kollidon® grades are insoluble, they can be used in solid pharmaceutical preparations to improve the dissolution rate of an insoluble active ingredient. That this is not merely the result of a short-term increase in the surface area of the active substance but of the formation of a complex, can be seen in Fig. 3.20. Simply mixing indomethacin with Kollidon® CL-M (or Kollidon® 30) multiplies the dissolution rate of this active ingredient during more than two hours. Similar results were obtained with indoprofen [439], propyphenazone [426] and prostaglandin ester [359].

Furthermore Fig. 3.20 shows that povidone and crospovidone increase in a comparable way the dissolution of indomethacin forming the same complex between active ingredient and polymer. As the particle size and the swelling of these two polymers is quite different, this could explain the slight difference of dissolution.

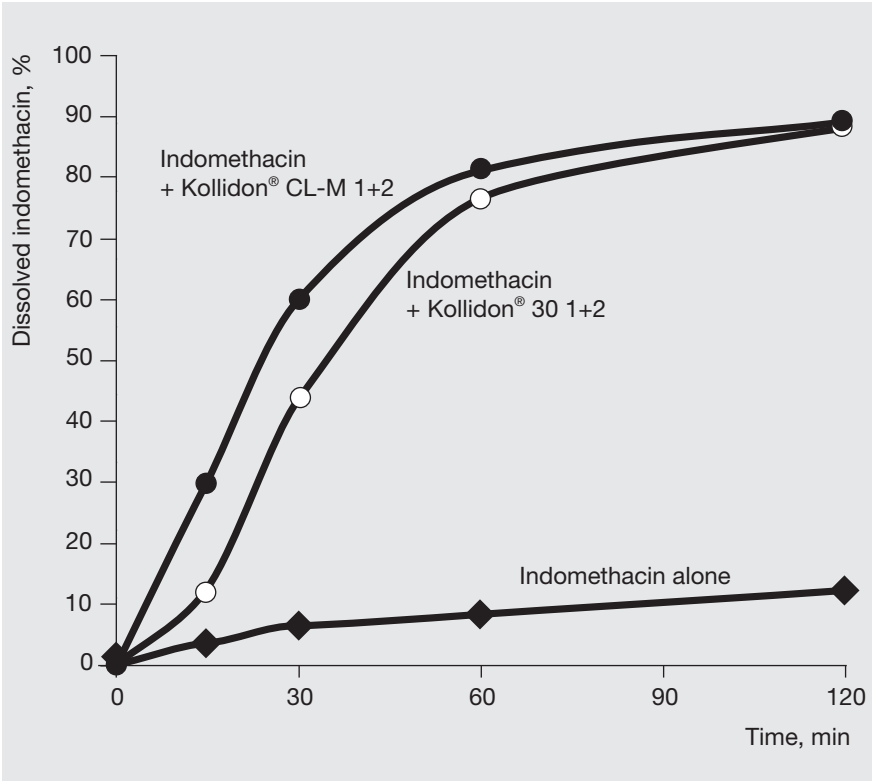


Fig. 3.20: Improvement of the dissolution fo indomethacin in water at 25 °C mixed with Kollidon® CL-M or Kollidon® 30

There are a number of techniques to take advantage of this property of the Kollidon® CL grades:
– Physical mixture of the active ingredient with the Kollidon® CL grade
– Trituration of the active ingredient with the Kollidon® CL grade (co-milling or co-grinding)
– Coevaporation after mixing a solution of the active ingredient with the Kollidon® CL grade

If one of the first two techniques gives the desired result, it is always preferable to the coevaporation technique, as this requires the use of a solvent.

The influence of the active ingredient/auxiliary ratio was investigated for cavain [38]. The results in Fig. 3.21 show clearly that more than three parts of crospovidone are required for one part of this active ingredient to accelerate its dissolution by a worthwhile amount. The best results with other active ingredients are also obtained with an excess of Kollidon® CL or a finer Kollidon® CL grade. In the case of cavain, the best compromise would be a ratio between 1 + 3 and 1 + 6.

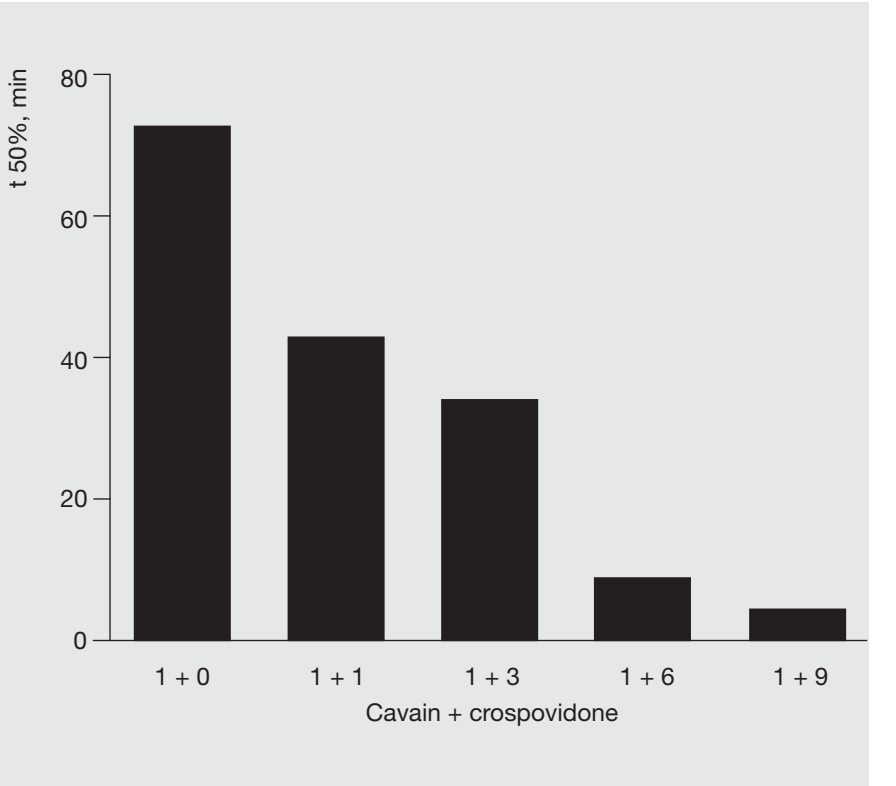


Fig. 3.21: Influence of the proportion of crospovidone on the dissolution time (t 50%) of cavain [38]

3.4.3.2 Triturations (Co-milling)

The factor by which the dissolution of an active ingredient is increased by triturating it with one of the Kollidon® CL grades usually lies between 2 and 10. This is shown in Fig. 3.22 for medroxyprogesterone acetate tablets, in which a six-fold excess of Kollidon® CL improves the dissolution rate by a factor of 5, compared with that of tablets without crospovidone.
Also Fig. 3.23 illustrates similar results for furosemide.

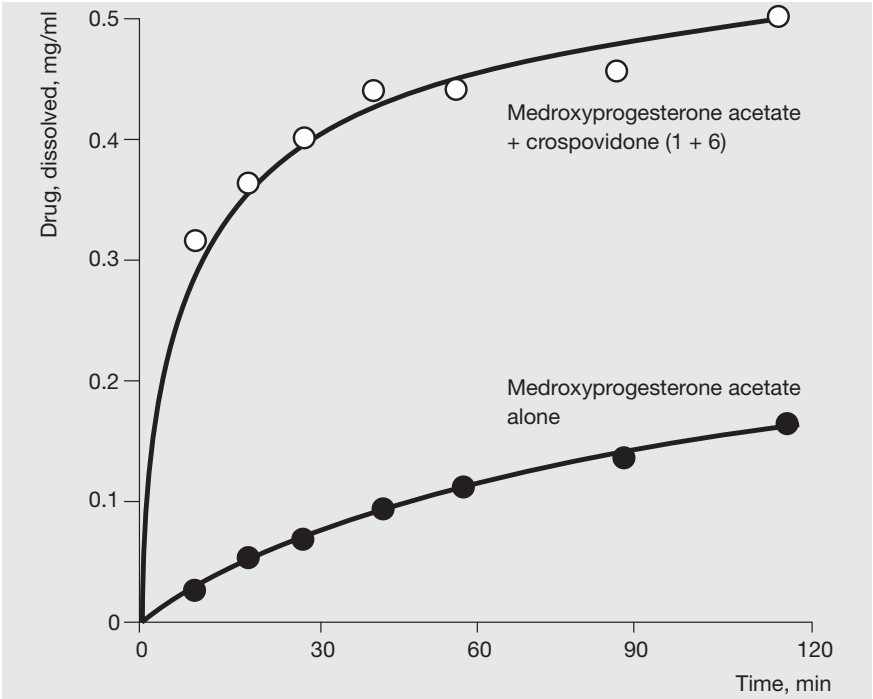


Fig. 3.22: Dissolution of medroxyprogesterone acetate from tablets made from a trituration with Kollidon® CL, compared with tablets without crospovidone [272]

The optimum time of trituration must be determined individually for each active ingredient. Factors that must be taken into consideration include the dissolution rate, bioavailability, chemical and physical stability of the drug, and the costs. Usually one hour is adequate.

Further trials have shown that in triturations with certain active ingredients, reducing the size of the crospovidone particles improves the dissolution rate and bioavailability. One possible reason is the doubling of the specific surface area achieved, for example, by micronization (see Section 3.2.4). However, the absolute value of the specific surface area appears to play only a subordinate role, as milled Kollidon® CL is more effective than Kollidon® CL-M in individual cases, although the latter has twice the surface area. On the other hand, it only develops half the swelling force. In each individual case comparison trials with the different Kollidon® CL grades should be done to find the optimal effect of dissolution enhancement.

All the active ingredients investigated so far were converted to the amorphous form by trituration with crospovidone, and this always remained stable in the few trials that have been conducted so far. Stability results are available for a much larger number of active ingredients in coevaporates with crospovidone (Table 3.32). As all the active ingredients tested in coevaporates were found to have very good physical stability of their amorphous state, the same can be assumed for triturations. This correlates with similar results obtained with the soluble Kollidon® grades.

Table 3.32 contains a selection of literature references of active ingredients with which triturations with crospovidone have been prepared.

Table 3.32: Active ingredients whose dissolution rate is increased by trituration or physical mixing with crospovidone (e. g. Kollidon® CL)

Active ingredient	Increased dissolution	Physical state	Stability of the state	Literature source
Ansamycin	+	amorphous	stable	[272]
Atenolol	+	partly amorphous	n. d.	[613]
Carbamazepin	+	cryst.	n. d.	[565]
Diacerein	+	n. d.	n. d.	[364, 365]
Diacetylmidecamycin	n. d.	amorphous	stable	[432]
Diltiazem	+	n. d.	n. d.	[365]
Etoposide	+	n. d.	n. d.	[139]
Furosemide	+	amorphous	stable	[617]
Griseofulvin	+	n. d.	n. d.	[364, 365, 440b]
Indomethacin	+	n. d.	n. d.	[365]
Indoprofen	+	n. d.	n. d	[439, 440b]
Medroxyprogesterone	+	amorphous	stable	[272, 440]
Megestrol acetate	+	n. d.	n. d.	[364, 365]
Nicergoline	+	n. d.	n. d.	[365]
Piroxicam	+	n. d.	n. d.	[365]
Uracil	+	amorphous	n. d.	[380]

n. d. = not determined

3.4.3.3 Coevaporates

The technique of coevaporation has been adopted for crospovidone. The earliest papers were published in 1978 [36]. The drug is dissolved in a suitable solvent, the Kollidon® CL grade is wetted with this solution, and the solvent is then evaporated. A disadvantage of this technique, compared with trituration, is that it requires an organic solvent.

The effect on dissolution of coevaporating furosemide with Kollidon® CL is shown in Fig. 3.23. The dissolution rate increases by a factor of 5 – 10 for a active ingredient/Kollidon® CL ratio of 1 : 2 compared with that for furosemide alone and the ground mixture 1 : 2.

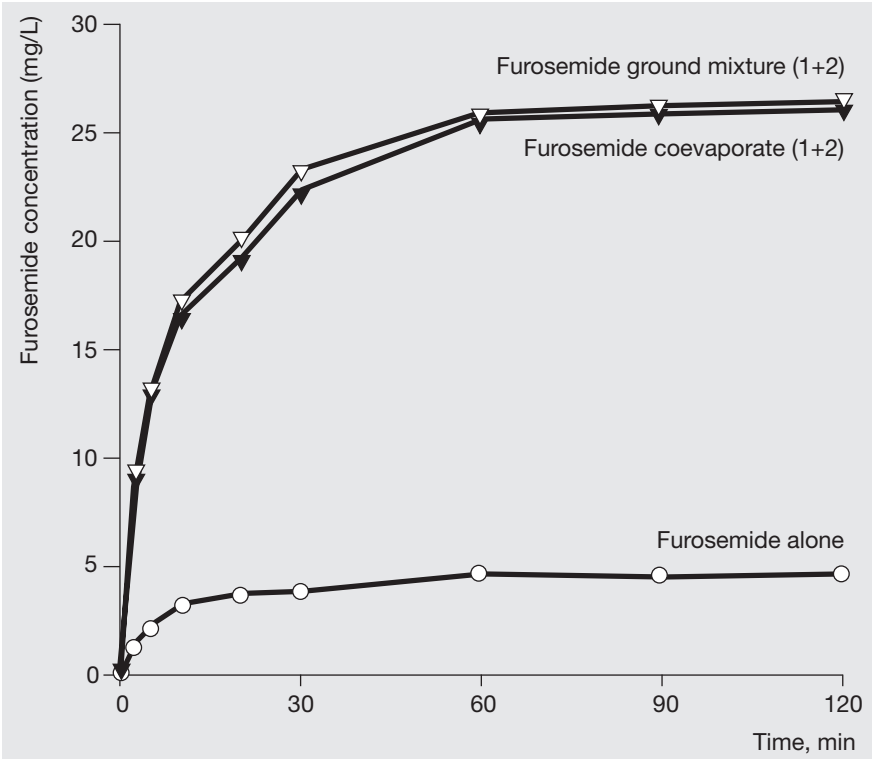


Fig. 3.23: Dissolution of furosemide from a coevaporate and a trituration with Kollidon® CL [617]

More papers have been published on coevaporates of active ingredients with crospovidone, e. g. Kollidon® CL, than on triturations. In particular, the crystalline or amorphous state of the active ingredient and its stability have been investigated much more frequently (Table 3.33). In no case was a return to the crystalline form reported. The chemical stability of indomethacin in a coevaporate with Kollidon® CL was found to be good in an accelerated test [401]. As it has also been found to be good in a large number of coprecipitates with soluble Kollidon® grades, the same can be assumed with a high degree of certainty for coevaporates with Kollidon® CL grades.

Table 3.33: Active ingredients whose dissolution rate is improved by coevaporation with crospovidone (e.g. Kollidon® CL)

Active ingredient	Increased dissolution	Physical state	Stability of the state	Literature source
Cavain	+	amorphous	stable	[36, 38]
Dexamethasone	+	amorphous	n. d.	[457]
Ethyl biscoumacetate	+	amorphous	stable	[36]
Flufenamic acid	+	amorphous	n. d.	[207]
Furosemide	+	amorphous	stable	[486, 617]
Griseofulvin	+	amorphous	stable	[36, 232]
Hexobarbital	+	amorphous	n. d.	[36, 37]
Indomethacin	+	amorphous	stable	[222, 273]
Itraconazole	+	amorphous	n. d.	[642]
Medroxyprogesterone acetate	+	amorphous	n. d.	[272, 440]
Megestrol acetate	+	n. d.	n. d.	[271]
Nifedipine	+	n. d.	n. d.	[240c, 364]
Nimodipine	+	n. d.	n. d.	[240c, 364]
Nitrendipin	+	n. d.	n. d.	[240c]
Phenprocoumon	+	amorphous	stable	[36]
Phenytoin	+	amorphous	stable	[36]
Propyphenazone	+	n. d.	n. d.	[426]
Prostaglandin ester	+	n. d.	n. d.	[359]
Tolbutamide	+	amorphous	stable	[36]

n. d. = not determined

3.4.3.4 Bioavailability

Unfortunately, the many publications listed in Tables 3.32 and 3.33 contain only a few active ingredients whose bioavailability has been tested in animals or in man. It has been significantly higher for all the active ingredients tested (ansamycin [272], hexobarbital [37], medroxyprogesterone acetate [272, 440b], megestrol acetate [271]). This is shown more clearly in Fig. 3.24 for megestrol acetate tablets, which were formulated with a 1+ 3 active ingredient-Kollidon® CL coevaporate. The bioavailability from coevaporate tablets after a single administration in dogs was about twice as high as from tablets with micronized megestrol acetate without Kollidon® CL.

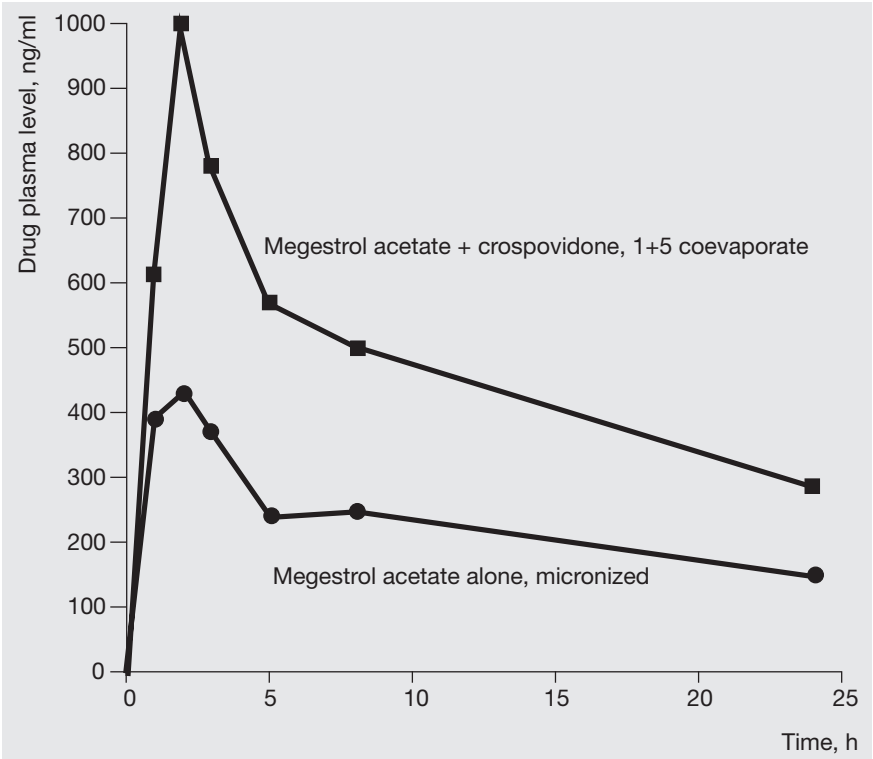


Fig. 3.24: Bioavailability in dogs of megestrol acetate from tablets [271]

In principle, an improvement in the dissolution rate and bioavailability of all the drugs, whose dissolution and bioavailability can be accelerated with soluble Kollidon® (Section 2.4.3) can also be expected if they are coevaporated or triturated with Kollidon® CL grades. This may be expected, as the effect of increasing the surface area by reducing the size of the crystals, or even converting the active ingredient to a stable amorphous form [38, 207], and the effect of complexation are comparable [192].

3.4.4 Kollidon® CL-M as a stabilizer for oral and topical suspensions

3.4.4.1 General

From a physical point of view, suspensions of pharmaceutically active ingredients are usually unstable systems, as the solid phase always tends to form a sediment. One of the most important aims with this type of dosage form must therefore be to prevent sedimentation. As this ideal condition can usually not be achieved, it is at least attempted to reduce the sedimentation rate and, above all, to make any sediment easy to redisperse. A number of auxiliaries are used in pharmaceutical technology to achieve this. They include thickeners, hydrophilic polymers, sugars and sugar alcohols, surfactants and electrolytes [296]. In spite of its insolubility, Kollidon® CL-M can be classed as a hydrophilic polymer.

The function of these polymers is governed mainly by Stokes' law (see Section 2.4.6.2), which states that the rate of sedimentation is proportional to the square of the radius of the suspended particles and the difference in density between them and the continuous phase, and inversely proportional to the viscosity.

The effect of Kollidon® CL-M in stabilizing suspensions can be partly explained in terms of Stokes' law. Its particle size is very fine (see Section 3.2.2), its bulk density low and its density in water also low as a result of swelling. These properties make it useful as an auxiliary for oral and topical suspensions for reducing sedimentation and by its low viscosity improving redispersibility [98]. The same applies, whether the commercial product is a suspension or a dry syrup, or instant granules from which the patient prepares an oral suspension.

When Kollidon® CL-M is used in such suspensions, it is found beneficial in practice to combine it with other auxiliaries such as sodium citrate as an electrolyte, sugar, Lutrol® F 127 or soluble grades of Kollidon®, to increase the sediment volume or to enhance the redispersibility. In the example given in Section 2.4.6.2, this is done by adding Kollidon® 90 F. A suspension of 7.5 % Kollidon® CL-M with 5 % Kollidon® 90 F showed no further sedimentation after a 24-hour test.

Even better results were obtained with drug formulations, the redispersibility being at least as important as the sediment volume.

3.4.4.2 Concentrations, viscosity

In induvidual cases, the concentration of Kollidon® CL-M may be lower or higher but usually it lies in the range of 5 – 10 % in suspensions. At these concentrations, the viscosity evidently does not play a role in preventing sedimentation, as it is relatively low.

To determine the importance of viscosity in suspensions containing Kollidon® CL-M, the viscosity of an amoxicillin dry syrup (Table 3.34) was measured at different concentrations. Fig. 3.25 shows that the viscosity hardly changes over a range of 0 – 6 % Kollidon® CL-M. However, the relative sediment volume increased greatly, as can be seen from Fig. 3.26.

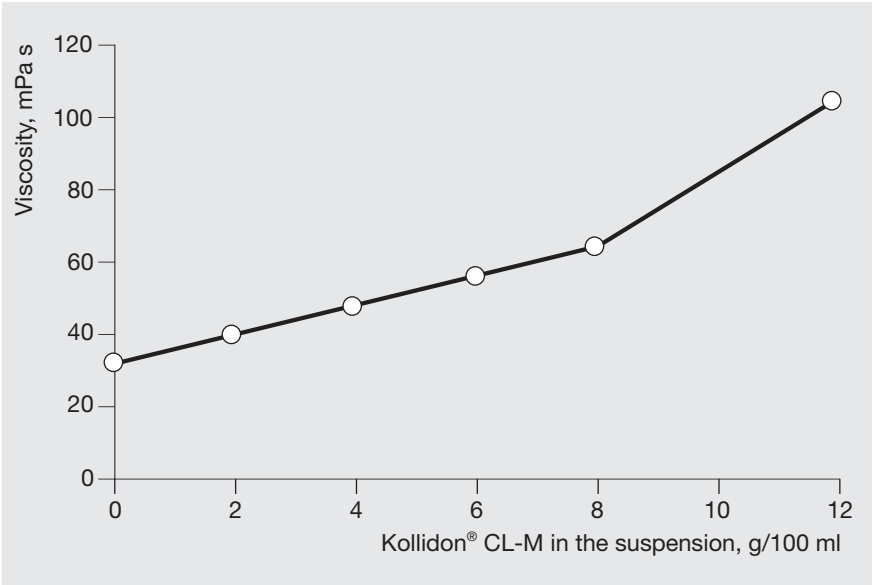


Fig. 3.25: Influence of the concentration of Kollidon® CL-M on the viscosity of an amoxicillin suspension (formulation see Table 3.34)

3.4.4.3 Examples of applications of Kollidon® CL-M in suspensions

Dry syrups and instant granules are more important these days than finished suspensions, as the active ingredient is more stable in these dry forms, and the physical stability requirements of the suspension, as the actual administration form, are not so critical. Because of their stability, dry syrups are often used as the dosage form for antibiotics. Instant granules are widely used for antiacids, because of the possibility of microbial contamination with finished suspensions, for vitamins (plus minerals) for stability reasons, and for analgesics.

An antibiotic dry syrup formulation is shown in Table 3.34 as an application of Kollidon® CL-M. The formulation has been developed in the laboratory for two different active ingredients, so that it can be regarded as a typical guide formulation. It contains citric acid, to adjust the pH to 4.9, to optimize the chemical stability of the active ingredient, ampicillin trihydrate or amoxicillin trihydrate.

The optimum quantity of 6 % Kollidon® CL-M in the formulation in Table 3.34 was determined from the relative sediment volume. Fig. 3.26 shows that, at this concentration of Kollidon® CL-M, no further sedimentation takes place after 24 hours. With lower quantities of Kollidon® CL-M, a sediment was clearly visible.

Table 3.34: Antibiotic dry syrup with Kollidon® CL-M for children [615]

Formulation (sales product):

Amoxicillin trihydrate or ampicillin trihydrate	5.0 g
Sodium citrate	5.0 g
Citric acid	2.1 g
Sodium gluconate	5.0 g
Sorbitol	40.0 g
Kollidon® CL-M	6.0 g
Orange flavour	1.5 g
Lemon flavour	0.5 g
Saccharin sodium	0.4 g

Administration form (suspension):

Preparation of the suspension (administration form with 250 mg active ingredient/5 ml):
shake 66 g of the powder mixture with water (total volume 100 ml).

Sedimentation is very slow and the sediment is very easy to redisperse by shaking, even after several weeks.

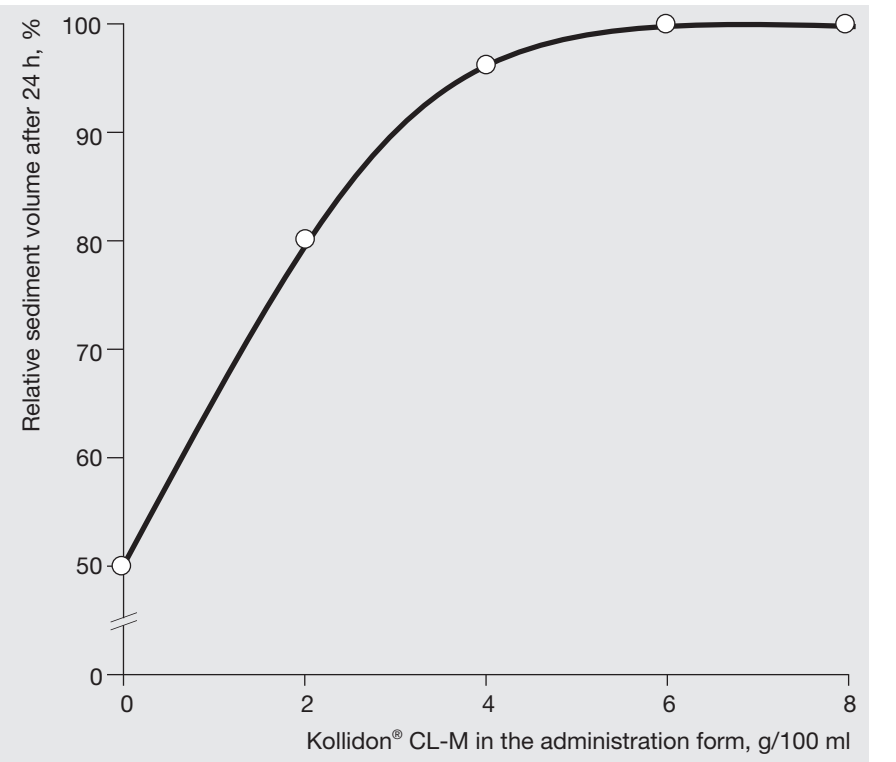


Fig. 3.26: Effect of the concentration of Kollidon® CL-M on the relative sediment volume of an amoxicillin suspension (Table 3.34)

The laboratory formulation in Table 3.35 provides an example of the use of Kollidon® CL-M in acetaminophen instant granules, e. g. for children [296]. In this formulation, Kollidon® CL-M has two additional functions: it masks the bitter taste of acetaminophen almost completely, and it guarantees the release of the active substance, possibly by forming a complex with it, as does povidone [154]. The concentration of Kollidon® CL-M in the administration suspension of these acetaminophen instant granules is well below 1 % and therefore significantly lower than in dry syrups, as, in this case, the suspension only needs to be stabilized for a very short time. The chemical stability of the sales-product, which can be packaged in individual sachets, was very good in an accelerated test.

Table 3.35: Acetaminophen instant granules with Kollidon® CL-M [615]

1. Formulation (sales form):

I	Acetaminophen powder (< 100 µm)	50 g
	Sugar (< 100 µm)	128 g
	Kollidon® CL-M	50 g
	Aspartame	7 g
	Orange flavour	5 g
	Strawberry flavour	5 g
II	Kollidon® 30	12 g
	Ethanol 96 %	75 g

Granulate Mixture I with Solution II and sieve.

2. Manufacture and properties of the suspension (administration form):

Stir 1.3 or 2.6 g of granules (= 250 or 500 mg of acetaminophen) into a glass of water. The milky suspension tastes sweet and fruity instead of bitter. No sedimentation is observed within two hours.

3. Dissolution of the active substance:

In the USP test, 94 % of the active ingredient is dissolved within 5 minutes at pH 5.8.

4. Chemical stability:

In an accelerated test (2 months at 40 °C), no loss of acetaminophen was observed in the sales product.

In an azithromycin dry syrup Kollidon® CL-M not only stabilizes the suspension physically but also maskes the bitter taste of the active ingredient [615].

The formulation given in Table 3.36 was also developed on a laboratory scale and demonstrates the use of Kollidon® CL-M in an antiacid dry syrup from which a suspension is prepared as the administration form.

Again, the quantity of Kollidon® CL-M was determined from the relative sediment volume. As is evident from Fig. 3.27, no sedimentation was observed above a Kollidon® CL-M concentration of 9 % in the final suspension (= 29 g Kollidon® CL-M in the sales product). After several weeks, it was still very easy to redisperse the suspension with a few rocking movements.

Table 3.36: Antiacid dry syrup with Kollidon® CL-M [615]

1. Formulation (granules as sales form):

I	Aluminium hydroxide dried gel (Giulini)	25.0 g
	Magnesium carbonate basic	25.0 g
	Kollidon® CL-M	29.0 g
	Sorbitol	25.6 g
	Orange flavour	5.0 g
II	Kollidon® 30	10.0 g
	Coconut flavour	0.4 g
	Banana flavour	0.5 g
	Saccharin sodium	0.1 g
	Water	approx. 36 ml

Granulate Mixture I with Solution II, sieve and dry.

2. Administration form (suspension):

Shake 120 g of the granules with 200 ml of water.

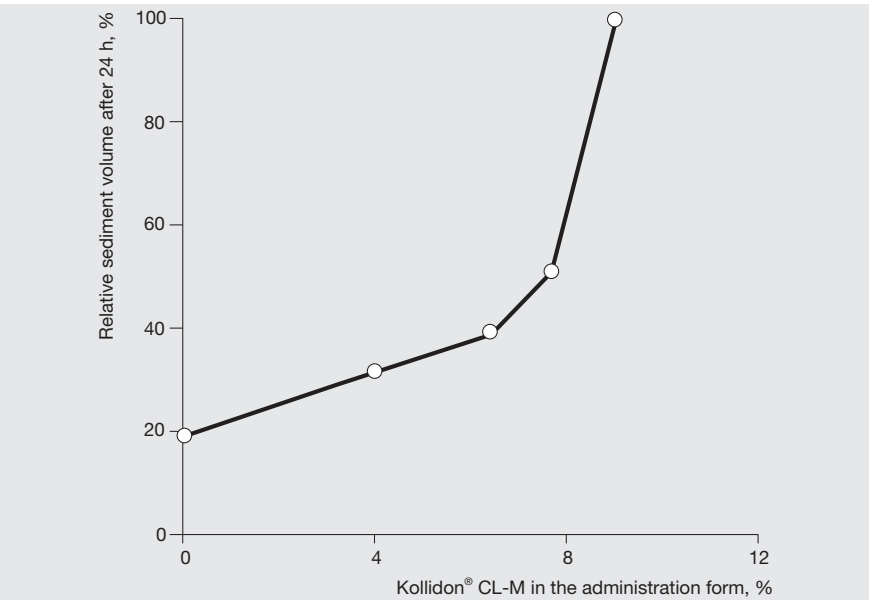


Fig. 3.27: Influence of the concentration of Kollidon® CL-M on the relative sediment volume of the administration form of the antiacid dry syrup described in Table 3.36 [296]

3.4.5 Crospovidone as an active ingredient

As early as 1968, a patent was granted for the use of insoluble polyvinylpyrrolidone as an active substance for treating certain stomach and intestinal disorders [125]. Pharmaceutical products containing micronized crospovidone as an active ingredient have been sold in France since the 70s on the basis of the results in a series of publications [443–454]. They contain 2 g of crospovidone per dose, which, in one case, is combined with karaya gum as a further active substance. The functions and medical indications listed in Table 3.37 are to be found in the clinical literature and with the pharmaceutical products. This application of micronized crospovidone is based on the local effect on the mucous membrane, as opposed to a systemic effect, as it is insoluble and therefore not absorbed. This is why practically no side-effects are listed.

Table 3.37: Properties, functions and indications of crospovidone as an active ingredient against gastrointestinal complaints

1. Functions and properties [444, 447, 449, 452]:

– Formation of a protective layer on the mucous membranes
– Adsorption of gas
– Adsorption of water
– Swellability
– Complexation of toxins of microbial origin
– X-ray transparency

2. Medical indications (papers on clinical trials):

– Diarrhoea, dyspepsia, meteorism and other functional colopathy [125, 443, 444, 446, 447, 450–452, 605]
– Colitis from antibiotics [125, 443–446, 448, 453, 454]
– Gastritis [125, 451]
– Gastroduodenal ulcers [125]
– Hiatus hernia with reflux oesophagitis [125, 451]

The preferred commercialized dosage forms are “instant drink tablets” for suspension in a glass of water, instant granules, and ready suspensions. These dosage forms make it possible both for adults and children to take the large quantity of active ingredient without problems.

Table 3.38 gives a guide formulation developed in the laboratory for effervescent tablets for children, containing 1 g of micronized crospovidone as the active ingredient. No problems are to be expected with the chemical stability of this formulation. However, moisture-proof packaging is recommended, to stabilize the physical properties of the tablets for the duration of their intended shelf-life.

Table 3.38: Formulation of micronized crospovidone effervescent tablets (lab scale) [615]

1. Formulation:

I	Kollidon® CL-M	1000 g
	Citric acid	150 g
	Aerosil® 200 (Degussa)	25 g
II	Sucrose, crystalline	100 g
	Saccharin sodium	1 g
	Water	q. s.
III	Sodium bicarbonate	125 g
	Flavour	65 g
	Magnesium stearate	5 g

Granulate mixture I with solution II, pass through a 0.8-mm sieve, dry, mix with III and press into tablets on a rotary tablet press with a medium compression force.

2. Tablet properties:

Diameter	20 mm
Weight	1590 mg
Hardness	111 N
Disintegration in water	1 min
Friability	0.4 %

In another formulation for a water-dispersible tablet based on 74 % of micronized crospovidone, containing as auxiliaries, microcrystalline cellulose, corn starch, silicon dioxide, talc etc. [615], it was possible to confirm that the compression force and the hardness of the tablets are directly proportional (compression curve for Kollidon® CL-M see Fig. 3.28).

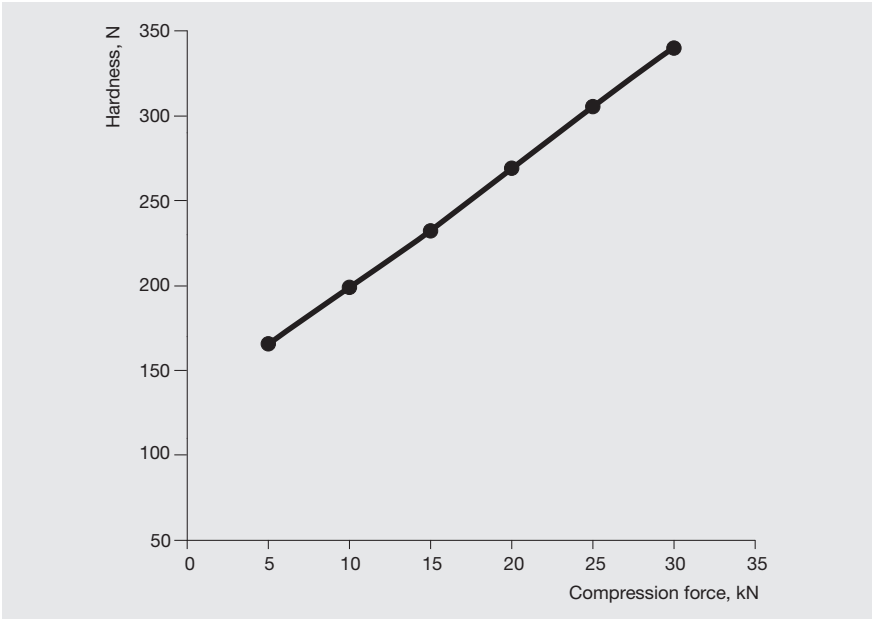


Fig. 3.28: Compression force/hardness curve for a water-dispersible tablet with 74 % of Kollidon® CL-M [615]

For the production of an antidiarrhoeal suspension the use of Kollidon® CL-M is recommendable as active ingredient because its sedimentation and redispersibility properties are optimal (see chapter 3.4.4). In the typical example given in Table 3.39 almost no sedimentation was observed after 4 weeks and the redispersibility is very easy.

Table 3.39: Formulation of an antidiarrhoeal suspension of micronized crospovidone [615]

Kollidon® CL-M	20 g
Sorbitol, crystalline	10 g
Kollidon® 90 F	2 g
Preservatives and flavours	q. s.
Water	ad 100 ml

Dissolve sorbitol, Kollidon® 90 F, the preservatives and flavours in water, add Kollidon® CL-M and homogenize by shaking.

3.4.6 Miscellaneous applications of Kollidon® CL grades

3.4.6.1 Filtration aid (Kollidon® CL)

Because of its ability to form complexes (see Section 3.2.8) and its large surface area in the swollen state, Kollidon® CL is a good filtration auxiliary. It is particularly useful for selectively binding polyphenols, e. g. tannins in the form of an insoluble complex. As in the clarification of beer and wine, this feature can be used in the preparation of galenical products, particularly tinctures, aqueous and alcoholic extracts and medical wines, to extend their long-term stability by preventing precipitation.

In practice, it is best to add the Kollidon® CL to the preparation to be purified as an aqueous slurry or as a powder. This is stirred into the preparation and then filtered off again. As an alternative, Kollidon® CL can be used in a filtration bed, though it must be checked whether the duration of contact with the polyphenols to be bound is adequate.

3.4.6.2 Stabilization of active ingredients by Kollidon® CL grades

As with the soluble Kollidon® grades, the Kollidon® CL grades can also be used to stabilize active ingredients in pharmaceutical products. A typical example is the formulation for multivitamin drink granules [368]. This formulation was prepared in the laboratory, and the stability of the vitamins was found to be excellent (Tables 3.40 and 3.41).

Should a fluidized bed granulator not be available for the manufacture of this formulation, it is recommended not to granulate the vitamin A, B_{12}, D and E dry powders with the other ingredients but to add them to the finished granules.

Table 3.40: Multivitamin drink granules with Kollidon® CL-M [368]

1. Formulation:

I	Vitamin A/D dry powder CWD	19.0 g
	Thiamine mononitrate	2.6 g
	Riboflavin	3.3 g
	Nicotinamide	11.0 g
	Pyridoxine hydrochloride	2.2 g
	Calcium D-pantothenate	150.0 g
	Cyanocobalamin gelatin-coated 0.1 %	6.6 g
	Ascorbic acid powder	115.0 g
	Tocopherol acetate dry powder SD 50	21.0 g
	Sucrose, ground	2000.0 g
	Kollidon® CL-M	500.0 g
	Orange flavour	100.0 g
II	Kollidon® VA 64	200.0 g
	Ethanol 96 %	700 ml

Granulate Mixture I with Solution II in a fluidized bed granulator. If possible, the granules should be packaged under nitrogen.

2. Vitamin loss after 12 months at 23 °C (HPLC):

Vitamin A	below 5 %
Vitamin D	below 5 %
Vitamin B_1, B_6, B_{12}	below 5 %
Calcium pantothenate	not tested
Nicotinamide	below 5 %
Ascorbic acid	6 %
Vitamin E	below 5 %

The stabilization effect on the vitamins was particularly noticeable with vitamin B_1, calcium D-pantothenate and ascorbic acid in an accelerated test (Table 3.41). For this test, the formulation in Table 3.40 was produced in the laboratory once with, and once without Kollidon® CL-M and stored at 30 °C/ 70 % relative humidity or in sealed containers at 40 °C.
The stabilized vitamins are sensitive against hydrolisis and chemical interactions with other vitamins. Similar to povidone [569] the stabilization effect of Kollidon® CL-M could be described as desiccant action.

Table 3.41: Stabilization of vitamins in multivitamin drink granules with Kollidon® CL-M (formulation see Table 3.40)

1. Vitamin loss at 30 °C/70 % relative humidity:

	2 months	3 months	5 months
Vitamin B_1:			
Without Kollidon® CL-M	11 %	16 %	26 %
With Kollidon® CL-M	1 %	7 %	10 %
Vitamin C:			
Without Kollidon® CL-M	18 %	40 %	49 %
With Kollidon® CL-M	2 %	13 %	19 %
Calcium pantothenate:			
Without Kollidon® CL-M	8 %	21 %	50 %
With Kollidon® CL-M	10 %	10 %	15 %

2. Vitamin loss at 40 °C, airtight containers:

	2 months	3 months
Vitamin B_1:		
Without Kollidon® CL-M	1 %	7 %
With Kollidon® CL-M	0 %	1 %
Vitamin C:		
Without Kollidon® CL-M	19 %	18 %
With Kollidon CL-M	3 %	2 %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4 Kollidon® VA 64 grades (copovidone)

4.1 Structure, synonyms

The Kollidon® VA 64 grades are manufactured by free-radical polymerization of 6 parts of N-vinylpyrrolidone and 4 parts of vinyl acetate in 2-propanol according to the cGMP regulations. A water-soluble copolymer with a chain structure is obtained.

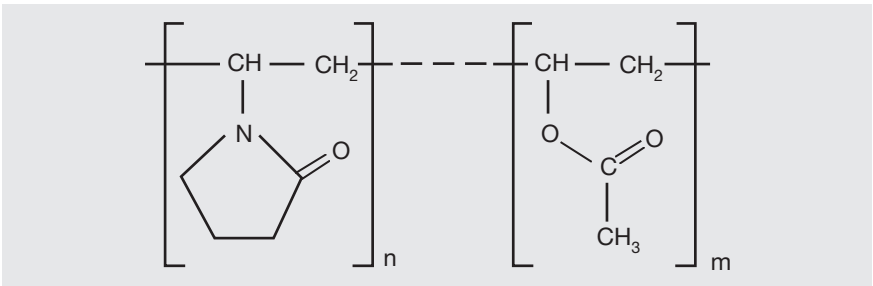

Fig. 4.1: Structural formula of Kollidon® VA 64 grades Mr = $(111.1)_n$ x $(86.1)_m$

In contrast to the soluble grades of Kollidon® (povidone) described in Chapter 2, the number 64 in the tradename Kollidon® VA 64 is not a K-value but the mass ratio of the two monomers, N-vinylpyrrolidone and vinyl acetate.

The K-value of Kollidon® VA 64 grades is of the same order of magnitude as that of Kollidon® 30 and is also used as a measure of the molecular weight here (see Section 4.2.3).

Table 4.1: BASF article and PBG numbers of Kollidon® VA 64 grades

Product	BASF article number (standard packaging)	PBG number
Kollidon® VA 64	50000781 (35 kg)	10095405.
Kollidon® VA 64 Fine	57071976 (15 kg)	10585104.

The CAS number of the copolymer Kollidon® VA 64/Kollidon® VA 46 Fine is 25086-89-9. It has the synonyms and abbreviations given in Table 4.2.

Table 4.2: Official names and abbreviations for soluble vinylpyrrolidone-vinyl acetate copolymer

Name/abbreviation	Source
Copovidone, Copovidonum	Ph.Eur., USP-NF
Copolyvidone	JPE
Copovidon	Deutsches Arzneibuch (former monograph 1997)
PVP-VAc-Copolymer	Literature

In the following, the pharmacopoeial term “copovidone” is used.

4.2 Product properties

4.2.1 Description, specifications, pharmacopoeias

4.2.1.1 Description

Kollidon® VA 64 grades are products of pharmaceutical purity. They are white or yellowish-white spray-dried powders which have a relatively fine particle size. They have a typical slight odour and a faint taste in aqueous solutions.

4.2.1.2 Specifications

The Kollidon® VA 64 grades fulfill the requirements of the "Copovidone" and "Copolyvidone" monographs in the current versions of the European Pharmacopeia (Ph.Eur.), United States Pharmacopoeia and Japanese Pharmaceutical Excipients (JPE).

The specifications of 2007 for Kollidon® VA 64/Kollidon® VA 64 Fine are listed in Table 4.3. Most of the parameters listed are included among the Ph.Eur. requirements. The actual specifications are available on request.

Table 4.3: Current specifications of Kollidon® VA 64 grades (Ph.Eur. methods)

Identity (IR spectrum, see Section 4.3.1.1):	Conforms
Colour (10 % in water):	Not darker than BY5, B5, R6
Clarity (10 % in water):	Not more opalescent than reference III
Relative viscosity (1 % in water):	1.178 – 1.255
K-value (nominally 28):	25.2 – 30.8
Monomers, iodometric (sum of VP + VAc):	≤ 0.05 %
N-Vinylpyrrolidone (HPLC, Section 2.3.3.2):	≤ 10 ppm
Vinyl acetate (HPLC, Section 2.3.3.2):	≤ 10 ppm
2-Pyrrolidone (HPLC, Section 2.3.3.2)	≤ 0.5 %
Loss on drying:	≤ 5 %
Nitrogen:	7.0 – 8.0 %
Saponification value:	230 – 270
Sulphated ash:	≤ 0.1 %
Heavy metals:	≤ 10 ppm
pH (10 % in water):	3 – 7
Peroxides (calculated as H_2O_2):	≤ 400 ppm
Hydrazine:	≤ 1 ppm
Acetaldehyde (enzymatic 2.3.3.3):	≤ 500 ppm
Polymerized vinyl acetate	35.3 – 41.4 %
Residual solvents (2-propanol* and acetic acid**)	Only class 3: ≤ 0.5 %
Microbial status (see below)	Passes test

** Method see Section 2.3.3.5*
*** Method see Section 4.3.2.6*

As an alternative to the iodometric titration, the monomers N-vinylpyrrolidone and vinyl acetate can be determined by HPLC (see Section 2.3.3.2).
The microbial status is tested by Ph.Eur. methods 2.6.12 and 2.6.13. The limits given in Ph.Eur. apply (Table 4.4). All the other parameters are specified in the methods given in the current Ph.Eur. monograph, "Copovidone".

Table 4.4: Microbial purity requirements (Ph.Eur. Chapter 5.1.4, Category 2 + 3A)

– Max. 10^2 aerobic bacteria and fungi/g
– No escherichia coli/g
– Max. 10^1 enterobacteria and other gramnegative bacteria/g
– No pseudomonas aeruginosa/g
– No staphylococcus aureus/g
Tests according to Ph.Eur. methods 2.6.12 and 2.6.13

Kollidon® VA 64 grades meet the ICH requirements on residual solvents according to Ph.Eur., chapter 5.4: Only Class 3 solvents (2-propanol, acetic acid) are likely to be present (≤ 0.5 %).

4.2.1.3 Pharmacopoeias

Up to now, monographs on copovidone are to be found in the European Pharmacopoeia Ph.Eur., the United States Pharmacopoeia USP-NF and in the Japanese Pharmaceutical Excipients JPE.
The Kollidon® VA 64 grades fulfill the requirements of all these monographs.

4.2.2 Solubility

Because of the ratio of N-vinylpyrrolidone to vinyl acetate in the Kollidon® VA 64 grades, they are almost as universally soluble as povidone (e. g. Kollidon® 30). They dissolve in extremely hydrophilic liquids such as water as well as in more hydrophobic solvents such as butanol.

Although nowadays the use of organic solvents such as methylene chloride or chloroform is largely avoided in the production of finished drugs, most pharmaceutical companies still use small quantities of ethanol, 1,2-propylene glycol or low-molecular polyethylene glycol (e. g. Lutrol® E 400). Both Kollidon® VA 64 grades are soluble in practically all proportions in these solvents and in water. Above a certain concentration, the viscosity of the solutions increases (see next Section 4.2.3.1).

Table 4.5 lists a large number of solvents in which the Kollidon® VA 64 grades dissolve in concentrations of more than 10 % or less than 1 %.

Table 4.5: Solubility of Kollidon® VA 64 grades

More than 10 % in:	Less than 1 % in:
Water	Diethyl ether
Methanol	Pentane
Ethanol	Cyclohexane
n-Propanol	Liquid paraffin
2-Propanol	
n-Butanol	
Chloroform	
Methylene chloride	
Macrogol 400 (Lutrol® E 400)	
1,2-Propylene glycol	
1,4-Butane diol	
Glycerol	

The dissolution behaviour and rate are typical for a polymer. It is recommended to add the powder slowly and in small portions to the solvent, which should be vigorously stirred. This ensures that the Kollidon® VA 64 grades dissolve rapidly without forming lumps. Lumps are relatively slow to dissolve.

4.2.3 Viscosity, K-value, molecular weight

4.2.3.1 Viscosity

The viscosity of copovidone in water depends on the average molecular weight. This can therefore be calculated from the viscosity, to give the viscosity-average of the molecular weight (see Section 4.2.3.3). Fig. 4.2 shows the typical dynamic viscosity of solutions in water and in 2-propanol of a batch of Kollidon® VA 64 as a function of their concentration. It can be seen that solutions of about 10 % have a low viscosity, which is an advantage in practice.

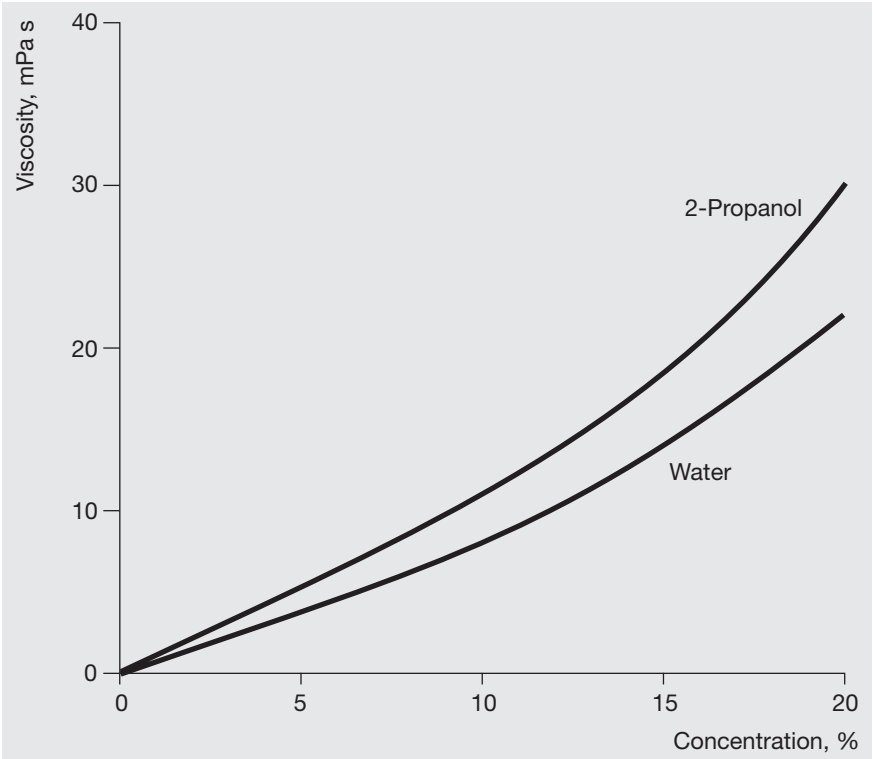

Fig. 4.2: Typical dynamic viscosity of Kollidon® VA 64 solutions in water and 2-propanol as a function of concentration (capillary viscometer, 25 °C)

The viscosity of solutions of copovidone of concentrations up to 10 % hardly changes between 20 °C and 40 °C. The temperature only affects the viscosity of solutions of higher concentration. The viscosity of a 20 % aqueous solution of Kollidon® VA 64 remains much the same over a wide range of pH values. If strongly acid or alkaline solutions are left to stand for a long time, the vinyl acetate may become saponified to some extent and the viscosity may change.

4.2.3.2 K-value

The average molecular weight of povidone is expressed in terms of the K-value, in accordance with the pharmacopoeias that apply in Europe and the USA. It is calculated from the relative viscosity in water [13]. The same method is also applied to the Kollidon® VA 64 grades, and they give K-values between the limits given in Section 4.2.1.2. They are based on the relative viscosity (kinematic) of a 1 % solution in water at 25 °C. The relationship between the K-value and the relative viscosity is shown in Fig. 4.3 for the range relevant for the Kollidon® VA 64 grades. The curve was obtained using the method of determination and calculation described in Section 2.3.2.1.

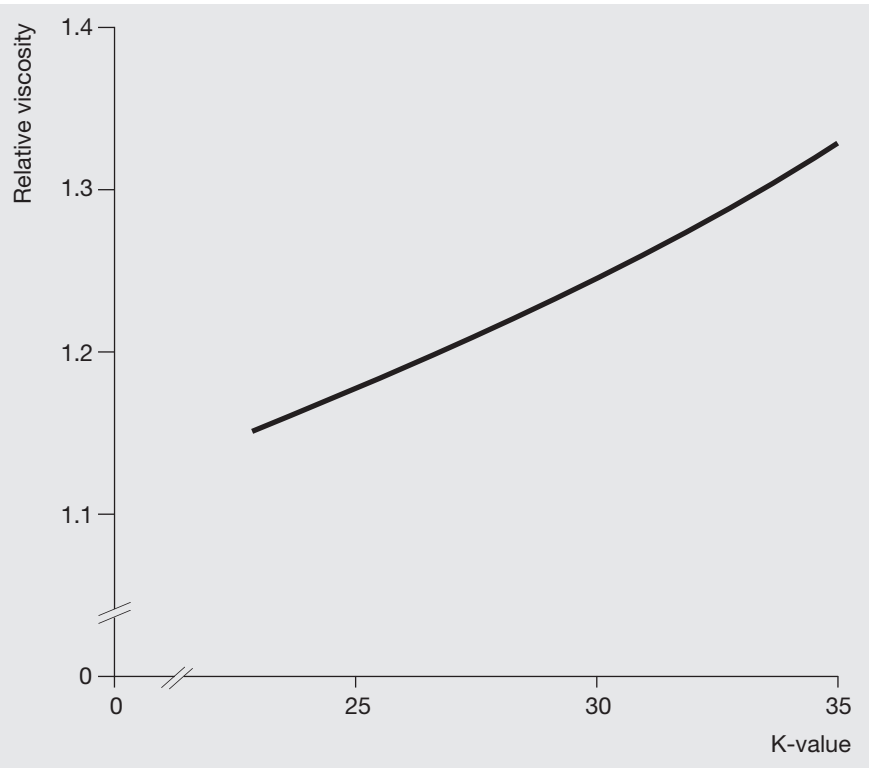

Fig. 4.3: Relationship between the relative viscosity (1 % in water) and the K-value over a range of 23–35

4.2.3.3 Molecular weight

The average molecular weight of a polymer can be viewed and measured in three different ways as indicated in Table 4.6.

Table 4.6: Average molecular weights of polymers and their methods of determination

Type of average molecular weight	Symbol	Method of determination
Weight-average	$\overline{M}w$	Light scattering, ultracentrifuge
Number-average	$\overline{M}n$	Osmometry, membrane filtration
Viscosity-average	$\overline{M}v$	Viscosity

As the methods of determining the average molecular weight are relatively time-consuming, that of the Kollidon® VA 64 grades is now expressed in terms of the K-value, in accordance with the European and U.S. Pharmacopoeia methods for povidone.

The weight-average of the molecular weight, $\overline{M}w$ is determined by methods that measure the weights of the individual molecules. The measurement of light scattering has been found to be the most suitable method for the Kollidon® grades [212]. Values determined by this method for Kollidon® VA 64 lie between 45 000 and 70 000, depending on the K-value. Recent results do not always agree well with older results, as the apparatus and method used have been improved significantly over the years.

The number-average of the molecular weight, $\overline{M}n$ is determined by methods that measure the number of molecules. Values of Kollidon® VA 64 recently determined by this method lie between 15 000 and 20 000.

The viscosity-average of the molecular weight, $\overline{M}v$ has attracted greater interest recently, as it can be calculated direct from the intrinsic viscosity (see Section 2.3.2.2).

However, it is simpler to calculate $\overline{M}v$ from the K-value determined by the USP or Ph.Eur. methods, with the following formula [212]:

$$\overline{M}v = 22.22\ (K + 0.075K^2)^{1.65}$$

The $\overline{M}v$ values obtained with this equation have been plotted in Fig. 4.4. They are significantly lower than the $\overline{M}w$ values, as the equation was developed for the homopolymer, povidone (e. g. Kollidon® 30).

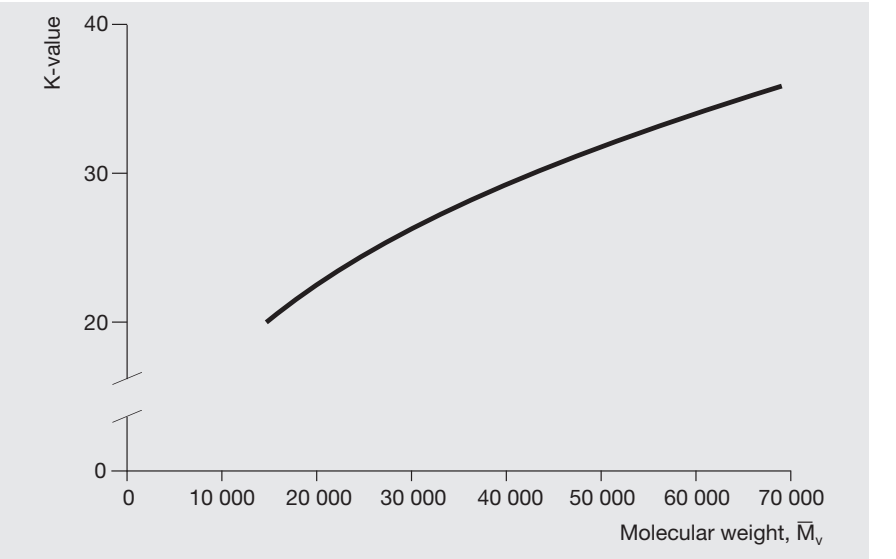

Fig. 4.4: K-value as a function of its viscosity-average molecular weight, $\overline{M}v$ [212]

4.2.4 Physical properties of Kollidon® VA 64 grades

4.2.4.1 Particle size, flowability

When processing auxiliaries such as the Kollidon® VA 64 grades in formulations for solid dosage forms, the particle size distribution can be of considerable importance. This particularly applies to the manufacture of tablets. However, it can also be important in solutions, e. g. film-coating solutions for tablets, as the dissolution rate and the dusting properties depend on the proportions of coarse and fine particles respectively.

Kollidon® VA 64 contains no coarse particles and very little fines and Kollidon® VA 64 Fine contains only a small percentage of particles coarser than 50 µm, so that the typical sieving values of Table 4.7 apply (air jet screen, 5 min, 20 mbar).

Table 4.7: Particle size of Kollidon® VA 64 grades measured by air jet screen (typical values)

Product	Smaller than 50 µm	Larger than 250 µm
Kollidon® VA 64	approx. 15 – 25 %	< 5 %
Kollidon® VA 64 Fine	> 80 %	< 1 %

When the particle size distribution of the Kollidon® VA 64 grades is determined by laser difraction the results depend on the solvent and the dispersing pressure. The typical volume-average diameters D [4.3] obtained with this method are the following:

- Kollidon® VA 64: 50 – 65 µm
- Kollidon® VA 64 Fine: 10 – 20 µm.

Figures 4.5 and 4.6 show the typical curves of the average of two laser diffraction measurements of each of both Kollidon® VA 64 grades with the application of a dispersing pressure of 1 bar and 3.5 bar respectively in air without any solvent. The equipement used was a Malvern Mastersizer 2000 (Malvern Instruments).

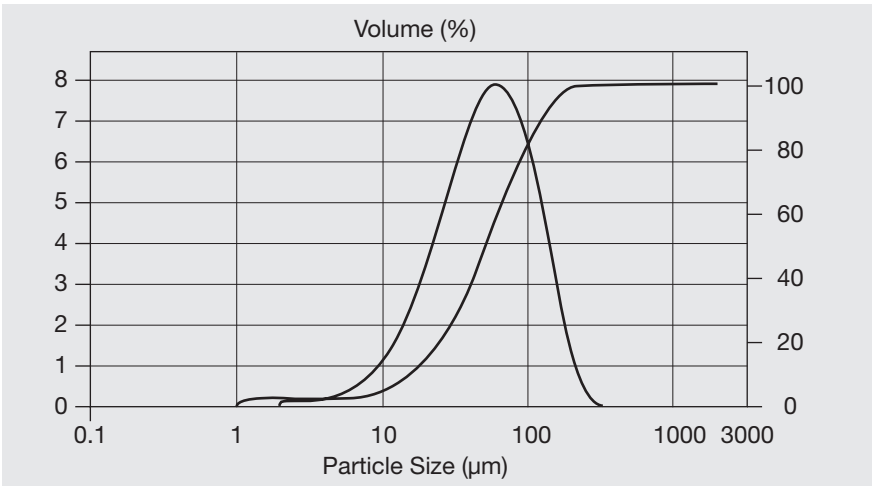

Fig. 4.5: Typical particle size distribution of Kollidon® VA 64 (laser diffraction measurement)

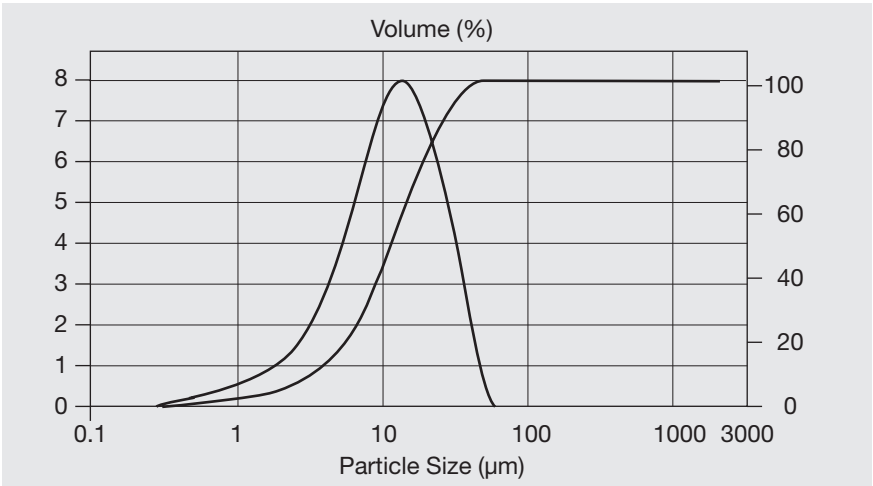

Fig. 4.6: Typical particle size distribution of Kollidon® VA 64 Fine (laser diffraction measurement)

The particle size distribution gives Kollidon® VA 64 good flow properties. Since Kollidon® VA 64 Fine contains much finer particles its flowability is not as good as in the case of Kollidon® VA 64. But added to a tabletting mixture in the usual binder concentration of 2–6 % Kollidon® VA 64 Fine shows good miscibility properties and enhances the flowability of such mixture by its sperical particle structure.

4.2.4.2 Particle structure

The Kollidon® VA 64 grades are spray dried products like Kollidon® 30. Therefore the structure of the particles is typical for this technology. But in the case of Kollidon® VA 64 the holow spherical particles are almost all broken as can be seen in the scanning electron micrograph (SEM) of Fig. 4.7.
The scanning electron micrograph of Fig. 4.8 has a different magnification to illustrates the structure of the finer hollow spheres of Kollidon® VA 64 Fine which are much more intact than the particles of normal Kollidon® VA 64.

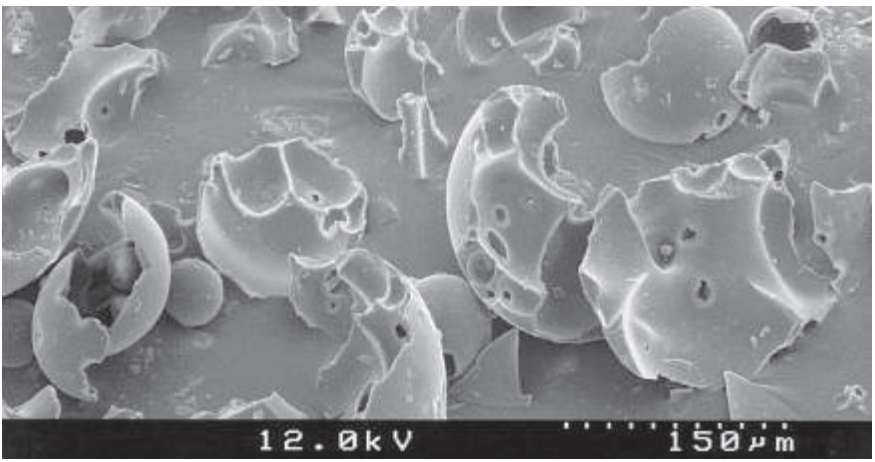

Fig. 4.7: Typical scanning electron micrograph of Kollidon® VA 64

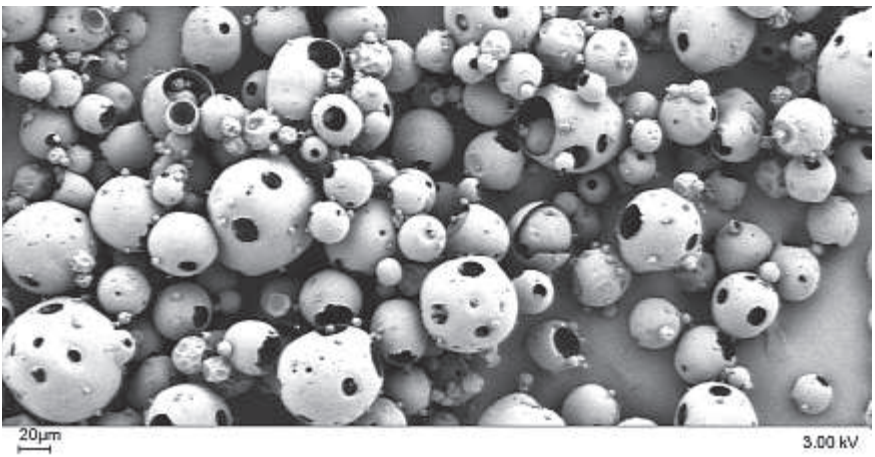

Fig. 4.8: Typical scanning electron micrograph of Kollidon® VA 64 Fine

4.2.4.3 Bulk density, tapped density

The bulk densities of the Kollidon® VA 64 grades are relatively low and do not increase very much with movement. Therefore the Haussner index is low and also the weight of the standard packaging is low. Table 4.8 shows typical values of the bulk and tapped densities of both products.

Table 4.8: Bulk and tapped densities of the Kollidon® VA 64 grades (typical values)

Product	Bulk density	Tapped density (500 taps)
Kollidon® VA 64	0.2–0.3 g/ml	0.30–0.45 g/ml
Kollidon® VA 64 Fine	0.08–0.15 g/ml	0.14–0.20 g/ml

4.2.4.4 Hygroscopicity

The importance of the hygroscopicity of the Kollidon® VA 64 grades depends on the application. When they are used as binder and granulating aid in tablets, a certain degree of hygroscopicity is useful, while in film-coatings, it is a nuisance. Overall, copovidone absorb about 3 times less water than povidone at a given relative humidity, as can be seen from Fig. 4.9.

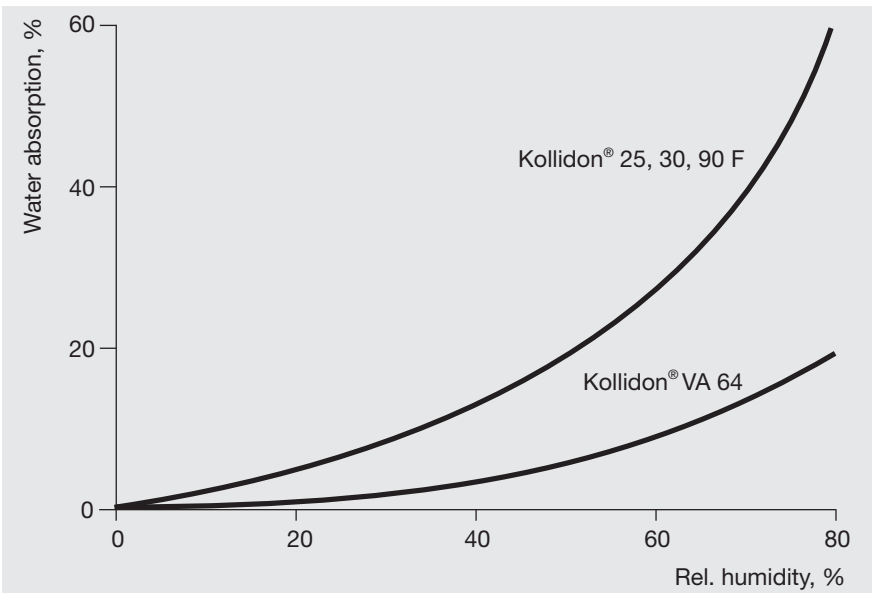

Fig. 4.9: Hygroscopicity of Kollidon® VA 64 and Kollidon® 25, 30 or 90 F for comparison, after 7 days at 25 °C

As the amount of water adsorbed from the air is particularly important in film-coating, this was determined with cast Kollidon® VA 64 films that contained 2.5 % glycerol as a plasticizer. Fig. 4.10 shows that a film of this type adsorbs significantly less water in 80 hours at 85 % relative humidity than the powder for which results are given in Fig. 4.9.

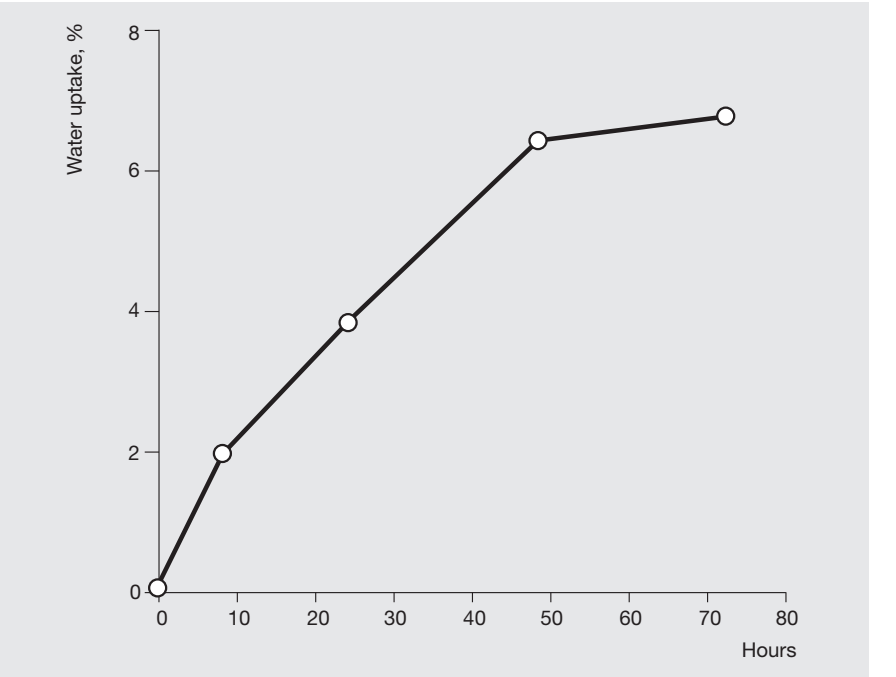

Fig. 4.10: Water uptake of Kollidon® VA 64 films containing 2.5% glycerol, over a period of 72 hours at 25 °C and 85% relative humidity

4.2.5 Stability, storage, packaging

Kollidon® VA 64 is very stable when it is stored as the pure product in the sealed, original containers (PE drums with PE inliners filled with 35 kg of Kollidon® VA 64) at room temperature (23–25 °C). It still meets the specifications given in Section 4.2.1.2 after more than 3 years.

Kollidon® VA 64 Fine has a more limited shelf life in the sealed, original containers (PE drums with PE inliners filled with 15 kg of Kollidon® VA 64 Fine) at room temperature (23–25 °C). It still meets the specifications given in Section 4.2.1.2 after more than 18 months.

As with povidone, the peroxide content of copovidone can increase slowly in the presence of atmospheric oxygen. However, the peroxide level increases much slower than in the case of povidone and it remains much below the specified value of 400 ppm, calculated as H_2O_2.

For the stability of solutions of Kollidon® VA 64 in water the only parameter sensitive during the storage is the colour. If an antioxidant like 0.5 % cysteine is added also the colour can be stabilized as can be seen in Table 4.9.

Table 4.9: Storage of solutions of 10 % of Kollidon® VA 64 in water at pH 6.4 in the dark during 3 months at 40 °C

Parameter	Initial values	Storage under air	Storage under nitrogen	Storage after addition of 0.5 % of cysteine
Colour (Ph.Eur.*)	$BY_6 - BY_7$	$BY_4 - BY_5$	$BY_3 - BY_4$	$BY_6 - BY_7$
Peroxides	< 20 ppm	< 20 ppm	< 20 ppm	< 20 ppm
Saponification value	25	25	25	26
Vinylpyrrolidone	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm
Clarity**	3.2 FTU	3.2 FTU	3.3 FTU	3.2 FTU

* *Reference solution BY = brown-yellow (the lower the number the stronger the colour intensity)*

** *FTU = Formazine Turbity Unit*

4.3 Analytical methods for Kollidon® VA 64 grades

4.3.1 Qualitative and quantitative methods of determination

4.3.1.1 Identification

Most of the colour and precipitation reactions described in the literature for soluble polyvinylpyrrolidone can also be used in the qualitative determination of Kollidon® VA 64 grades (Table 4.10).

Table 4.10: Detection reactions for Kollidon® VA 64 grades and Kollidon® 30 [18]

Reagent	Reaction
10 % aqueous barium chloride solution + 1 N hydrochloric acid + 5 % aqueous silicotungstic acid solution	White precipitate
10 % aqueous barium chloride solution + 1 N hydrochloric acid + 5 % aqueous phosphotungstic acid solution	Yellow precipitate
10 % potassium dichromate solution + 1 N hydrochloric acid	Orange-yellow precipitate
Saturated aqueous potassium iodide solution + 0.1 N iodine solution	Brown-red precipitate
Dragendorff's reagent + 1 N hydrochloric acid	Brown-red precipitate
Nessler's reagent	Yellowish-white precipitate
Aqueous ammonium-cobalt rhodanide solution + 6 N hydrochloric acid	Blue precipitate

The following further means of distinguishing between Kollidon® VA 64 grades and povidone, e. g. Kollidon® 30 are available:

1. Infrared spectrum

   The infrared spectrum provides the clearest identification of Kollidon® VA 64 grades. It differs significantly from that of Kollidon® 30, as can be seen in Figs. 4.11 and 4.12 (arrows indicate differences).

2. Thin-layer chromatography [17]

   Immerse a thin-layer chromatography plate in a 5 % solution of paraffin wax in petroleum ether for 5 seconds and dry in the warm. With a n-propanol + 2N ammonia solution (6 + 4 parts by volume) eluent, Kollidon® VA 64 grades give an Rf value of 0.64 – 0.75 and povidone an Rf value of 0.59 – 0.64.

Fig. 4.11: Infrared spectrum of Kollidon® VA 64 recorded in KBr [18]

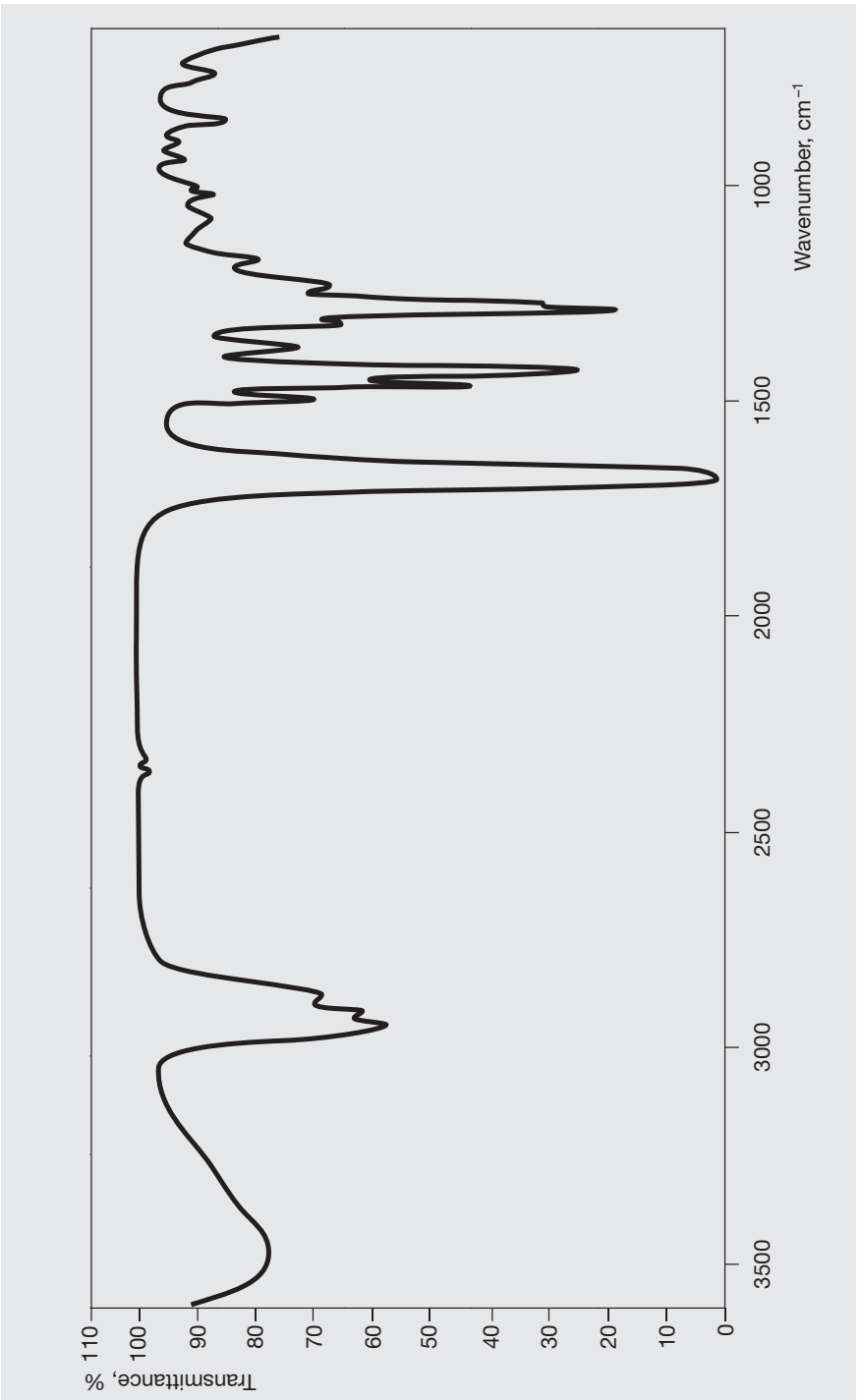

Fig. 4.12: Infrared spectrum of Kollidon® 30 in KBr [18]

3. Detection as hydroxamic acid [17]

Of all the Kollidon® grades, only Kollidon® VA 64 reacts with 3 M hydroxylamine solution to form hydroxamic acid, which reacts with iron(III) salts to give a violet colour, as described in the Ph.Eur. monograph, "Copovidone".

4. Electrophoresis [17]

The monographs of the European Pharmacopoeia (Ph.Eur.), USP-NF and of JPE give the identification reactions listed in Table 4.11.

Table 4.11: Identification reactions for copovidone/copolyvidone in pharmacopoeias

Reaction	Ph.Eur.	JPE	USP-NF
Colour reaction with iodine	+	+	+
Detection of vinyl acetate part as ethyl acetate	–	+	–
Detection as hydroxamic acid with iron(III) chloride	+	–	–
IR spectrum	+	–	+

4.3.1.2 Quantitative methods of determination

The photometric determination of the iodine complex used to determine povidone can also be used for Kollidon® VA 64 grades, though the colour intensity of the iodine complex only reaches its maximum after about 30 min, after which it slowly fades. Thus, it must be measured after 30 min, instead of 10 min, as in the determination of Kollidon® 25 [18].

Mix 50 ml of the sample solution, which must contain less than 50 µg of copovidone/ml with 25 ml of 0.2 M citric acid solution. Mix this with 10 ml of 0.006 N iodine solution (0.81 g of freshly sublimed iodine and 1.44 g of potassium iodide dissolved in 1000 ml of water), and measure the absorbance of this solution against that of a blank solution (50 ml of water + 25 ml of 0.2 M citric acid solution + 10 ml of 0.006 N iodine solution) at 420 nm after exactly 30 min.

A calibration curve must be established to determine the copovidone content from the absorbance (Fig. 4.13). The absorbance of the iodine complex obtained with Kollidon® VA 64 grades is slightly less than that of the povidone-iodine complex.

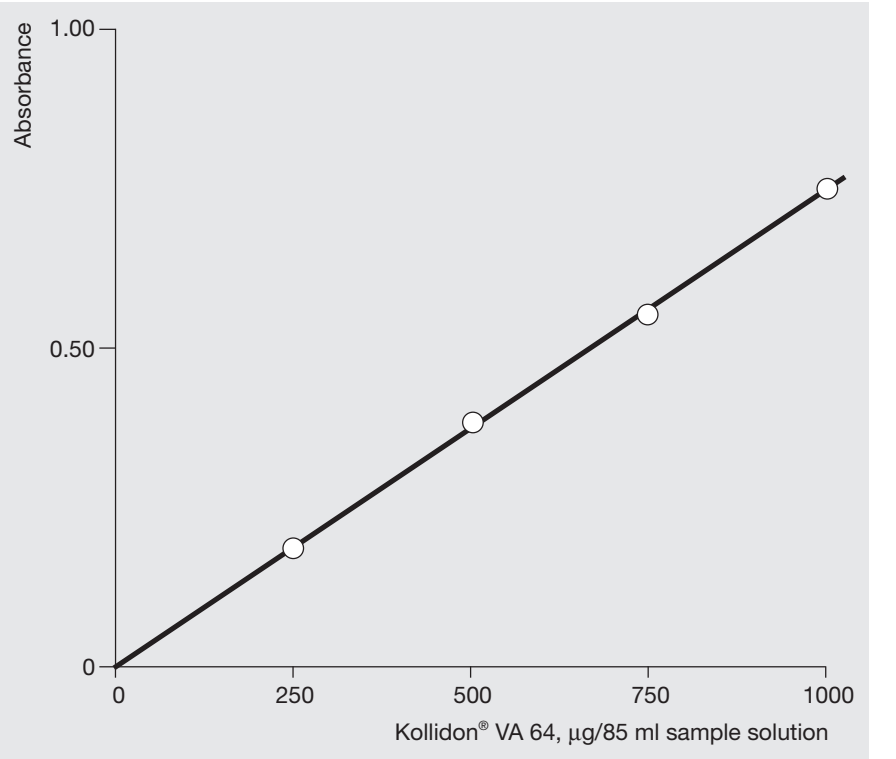

Fig. 4.13 Calibration curve for the photometric determination of Kollidon® VA 64 grades with iodine [18]

The method for the quantitative determination of copovidone given by the Ph.Eur. monograph as assay measures the nitrogen content (theoretical value 7.1 %) by the Kjeldahl method.

4.3.2 Methods for the determination of purity

4.3.2.1 Pharmacopoeia methods

Methods for determining the purity of copovidone are described in the corresponding monograph of Ph.Eur. The parameters measured are those given in Table 4.12.

Table 4.12: Purity test methods for Kollidon® VA 64 grades given in the pharmacopoeias

Acetaldehyde
Monomers (sum of N-vinylpyrrolidone + vinyl acetate)
N-Vinylpyrrolidone (= Impurity A of Ph.Eur. monograph)
Hydrazine
Peroxides
Nitrogen
Colour and clarity in solution
Loss on drying
Sulphated ash/residue on ignition
Heavy metals
K-value
2-Pyrrolidone
Polymerized vinyl acetate (Saponification value)
Residual solvents (2-Propanol and acetic acid)

Some of the pharmacopoeia methods are not always entirely relevant. This applies particularly to the titration test for the sum of N-vinylpyrrolidone and vinyl acetate monomers, as the method is not very specific and relatively inaccurate and therefore no longer do justice to the purity of Kollidon® VA 64 grades. For this reason, an alternative method for these two monomers are also described in this book (Section 2.3.3.2).

4.3.2.2 Method for the determination of the K-value

The K-value of Kollidon® VA 64 or Kollidon® VA 64 Fine is determined as an indication of the average molecular weight by the methods given in the monographs, “Povidone” and “Copovidone” in Ph.Eur. and USP in much the same way as the original method for cellulose derivatives [13], using the relative kinematic viscosity in water. An exact description of the method is to be found in Section 2.3.2.1.

The relationship between the relative viscosity and the K-value is shown in a graph in Section 4.2.3.2. However, it is preferable to use the mathematical formula for reasons of accuracy.

4.3.2.3 HPLC method for the determination of N-vinylpyrrolidone, vinyl acetate and 2-pyrrolidone in Kollidon® VA 64 grades

As Kollidon® VA 64 grades almost always contain residues of the monomers N-vinylpyrrolidone and vinyl acetate that are much lower than the detection limit of the titration method, it is recommended to use a more sensitive method such as high performance liquid chromatography (HPLC) for both monomers. The HPLC method described in Section 2.3.3.2 has proved to be precise with a detection limit of 2 mg/kg of N-vinylpyrrolidone and 10 mg/kg of vinyl acetate.

4.3.2.4 Determination of acetaldehyde in Kollidon® VA 64 grades

As the former potentiometric method for the determination of acetaldehyde is very unspecific and measures more than just aldehydes or acetaldehyde, the enzymatic method nowadays is used (Section 2.3.3.3).

4.3.2.5 GC Determination of 2-propanol in Kollidon® VA 64 grades

The determination of 2-propanol in copovidone can be done by the modified gaschromatographic method given in ISO 13741-1. The modifications of this method are described in Section 2.3.3.5.

4.3.2.6 HPLC method for the determination of acetic acid in Kollidon® VA 64 grades and Kollidon® SR

The content of the residual solvent acetic acid in the Kollidon® VA 64 grades is determined by the following HPLC method using acetic acid as external standard.

Sample solution:

Dissolve 200 mg of the sample in 3.0 ml of methanol, add 20 ml of water and 2 ml of water adjusted with phosphoric acid to pH 0.8 and shake for some seconds. Filtrate immediately about 2 ml of the obtained suspension through a 0.45 µm filter.

Table 4.13: Chromatographic conditions

Precolumn:	LiChrospher® 100 RP 18, 5 µm 25 mm x 4 mm (Merck)
Main column:	LiChrospher® 100 RP 18, 5 µm 250 mm x 4 mm (Merck)
Column temperatures:	30 °C
Mobile phase:	Water, adjusted with phosphoric acid to pH 2.4
Flow rate:	0.9 ml/min
Pressure:	about 150 bar
Injection volume:	10 µl
Detection wavelength:	205 nm
Retention time of acetic acid:	about 4.3 min

Calibration factor and linearity:

The linearity of the calibration of acetic acid was determined in the range of 2.8 – 22.1 mg/l. Fig. 4.14 shows the result.

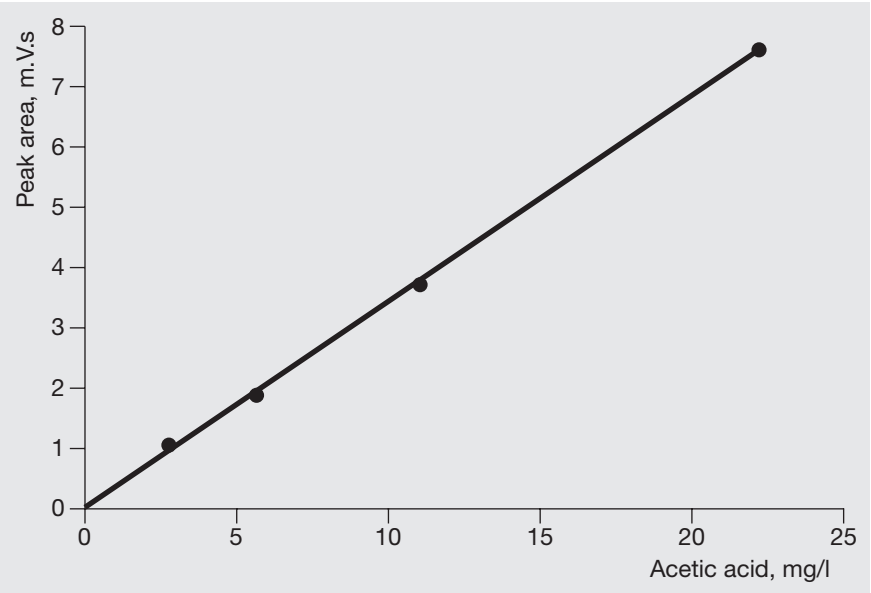

Fig. 4.14: Linearity of the calibration curve of acetic acid

The calibration factor is calculated by the following formula:

$$C = \frac{A_r}{W_r} \quad [\frac{mV \cdot s}{mg/100\ ml}]$$

A_r = Area of the peak of acetic acid reference sustance [mV · s]
W_r = Weight of acetic acid reference substance [mg/100 ml]

Calculation of the content of acetic acid in the sample

$$\text{Acetic acid (\%)} = \frac{A_s \times 100}{C \times W_S}$$

A_s = Area of the acetic acid peak of the sample solution [mV · s]
C = Calibraction factor
W_s = Sample weight [mg/100 ml].

A typical chromatogram obtained with this method is shown in Fig. 4.15.

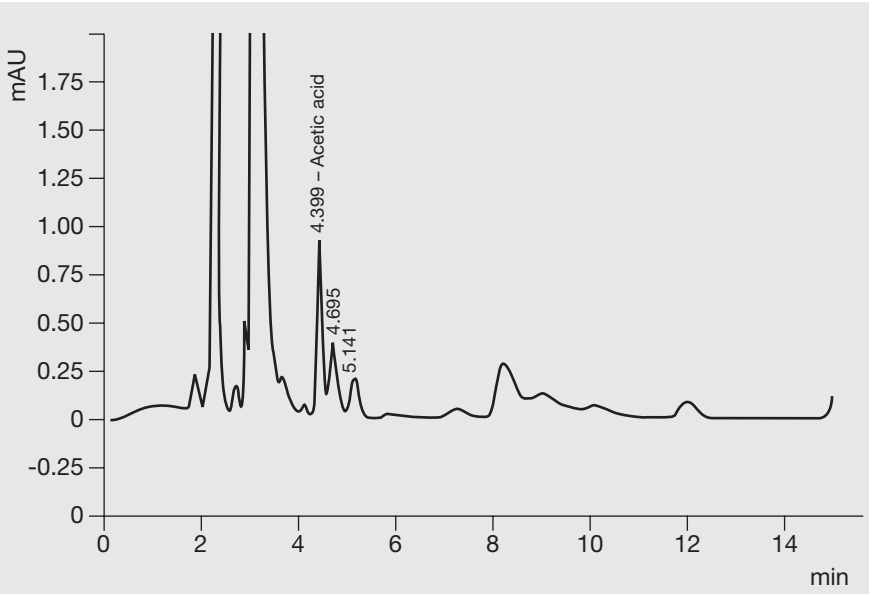

Fig. 4.15: Typical chromatogram of acetic acid in a sample

Validation

Linearity:

The linearity of the calibration curve of acetic acid in the concentration of 2 – 22 mg/l is shown in Fig. 4.14.

Reproducibility:

The content of acetic acid was determined 5 times in a sample and the following results were obtained (Table 4.14)

Table 4.14: Reproducibility of the determination of acetic acid in a sample of Kollidon® VA 64

Measurement	Acetic acid
1	0.274
2	0.262
3	0.257
4	0.251
5	0.255
Average	0.260

Recovery rate:

To the same batch of Kollidon® VA 64 used for the measurements of reproducibility different amounts of acetic acid were added. Table 4.15 shows the very good recovery of the method.

Table 4.15: Recovery of added acetic acid in a sample of Kollidon® VA 64

Added acetic acid, ppm	Theoretical content of acetic acid, %	Found acetic acid, %	Recovery rate, %
0	0.2600	0.260	–
103	0.2703	0.271	100.3
153	0.2753	0.274	99.5
204	0.2804	0.278	99.1

4.3.3 Determination of Kollidon® VA 64 grades in preparations

4.3.3.1 Qualitative determination

The detection reactions for pure copovidone given in Section 4.3.1.1 can also be used to detect Kollidon® VA 64 grades in most pharmaceutical preparations. Should these provide no clear results, the separation scheme shown in Fig. 4.16 can be used to detect copovidone in solid dosage forms, e. g. tablets, granules, capsules and coated tablets.

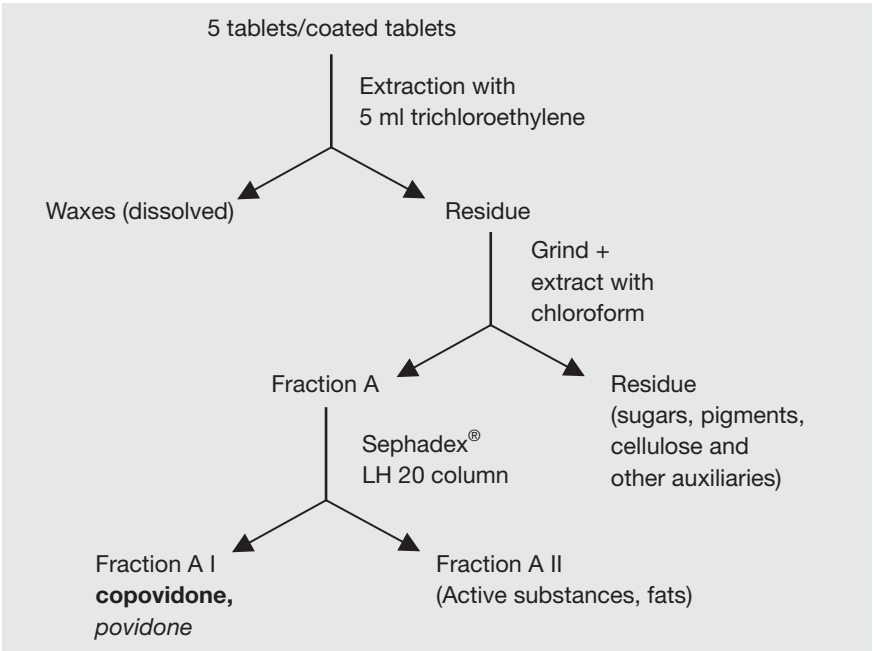

Fig. 4.16: Separation scheme for the detection of copovidone in solid dosage forms [17]

The detection and differentiation of povidone and copovidone obtained in Fraction A I in Fig. 4.16 is best carried out by thin layer chromatography on silica gel. A suitable eluent is a mixture of 6 parts n-propanol and 4 parts 2N-ammonia solution by volume, with which copovidone gives a higher Rf value than povidone (see Section 4.3.1.1).

4.3.3.2 Quantitative determination in preparations

The most versatile method for quantitatively determining Kollidon® VA 64 grades is probably the photometric measurement of the iodine complex described in Section 4.3.1.2. It has been successfully tested on samples that also contained a series of auxiliaries and active ingredients, to verify its suitability for preparations.

In these tests, aqueous solutions containing 50, 100 and 200 µg of Kollidon® VA 64 and 20 times the quantity of the tablet ingredients listed in Table 4.16 were prepared, and their Kollidon® VA 64 content determined.

Table 4.16: Recovery of Kollidon® VA 64 as the iodine complex in the presence of 20 times the quantity of active ingredients and auxiliaries [18]

Kollidon® VA 64 added µg	Thiamine hydrochloride	Caffeine	Acetphene-tidine	Lactose
50	49	48	49	48
100	102	100	102	96
200	203	201	203	198

4.4 Applications of Kollidon® VA 64 grades

4.4.1 General notes

Copovidone has been used by the pharmaceutical industry in Europe for decades [101, 114, 231, 409]. Up to about 1975, it was sold in this sector under the name, Luviskol® VA 64, which is now used exclusively for the technical/cosmetic grade of this copolymer. This is why the older publications often mention Luviskol® VA 64 for use in pharmaceutical products.

The applications of Kollidon® VA 64 grades rely mainly on its good binding and film-forming properties, their affinity to hydrophilic and hydrophobic surfaces and the relatively low hygroscopicity. Because of these properties, copovidone is used as a binder in the production of granules and tablets by wet granulation, as a dry binder in direct compression, as film former in coatings on tablets, as a protective layer and subcoat for tablet cores, as a film-forming agent in sprays and as a matrix.

The advantages of the Kollidon® VA 64 grades over Kollidon® 25 or Kollidon® 30 in solid dosage forms lie mainly in the lower hygroscopicity, the good dry binding properties and the higher plasticity. Kollidon® VA 64 is seldom used in liquid dosage forms, apart from sprays. The different applications are summarized in Table 4.17.

Table 4.17: Summary of the main applications of Kollidon® VA 64 grades

Function/dosage form	Kollidon® VA 64	Kollidon® VA 64 Fine
Dry binder in tablets (direct compression)	+	+
Binder in tablets, pellets and granules (wet granulation)	+	–
Dry binder in granules (roller compaction)	+	+
Film former for tablet film-coating and sugar coating	+	–
Film former for subcoating of tablets	+	–
Matrix former for melt extrusion of tablets	+	–
Film former in sprays	+	–

4.4.2 Kollidon® VA 64 grades as binders for tablets, granules and hard gelatin capsules

4.4.2.1 General notes on Kollidon® VA 64 grades as binders

The main area of application of the Kollidon® VA 64 grades is as binders in tablets and granules (including granules for hard gelatin capsules), regardless of whether they are made by wet or dry granulation or by direct compression, as they are equally effective in all three cases. They can also be used in extrusion [465] or in cocrystallization [463].

The usual concentration in which Kollidon® VA 64 grades are used as binders in tablets and granules lies between 2 % and 8 %.

4.4.2.2 Manufacture of tablets by wet granulation with Kollidon® VA 64 as binder

Granulation is still the most frequently used method of preparing a tabletting mixture. There are at least four different variations of the procedure (Table 4.18).

Table 4.18: Methods of wet granulation with a binder

1. Granulation of the active ingredient (+ filler) with a binder solution.
2. Granulation of the active ingredient (+ filler)-binder mixture with the pure solvent.
3. Granulation of a mixture of the active ingredient (+ filler) and a portion of the binder with a solution of the remaining binder.
4. Granulation of the active ingredient (+ filler) with the solution of a portion of the binder followed by dry addition of the remaining binder to the finished granulate.

Water is nowadays the most commonly used solvent in wet granulations. Sometimes, if water cannot be used, as with effervescent tablets, active ingredients that are prone to hydrolysis etc., ethanol or 2-propanol are used as solvents, though fluidized bed granulation is preferred.

There are a number of factors that dictate which of the methods in Table 4.18 must be used. With some formulations, Method 1 gives tablets with a shorter disintegration time and quicker release of the active ingredient than Method 2 [314]. In many cases, Method 1 gives somewhat harder tablets than Method 2. Method 3 in Table 4.18 is useful if Method 1 cannot be used, as when the tabletting mixture lacks the capacity for the quantity of liquid required for the total amount of binder. If the disintegration time of a tablet presents a problem, it is worth trying Method 4, mixing in about a third of the binder together with lubricant and, last of all, the disintegrant.

Methods 2 and 3 have proved best for active ingredients of high solubility, as the quantity of liquid can be kept small to avoid clogging the granulating screens.

As a typical example of wet granulation Fig. 4.17 shows that there are no significant differences in the compression diagrams for Kollidon® 25, Kollidon® 30 and Kollidon® VA 64 for lactose placebo tablets containing 3 % of each grade of Kollidon® as a binder. The results are only valid for the wet granulation technology because the use as dry binder gives a higher hardness in the case of Kollidon® VA 64 grades than of other binders (see Section 4.4.2.4).

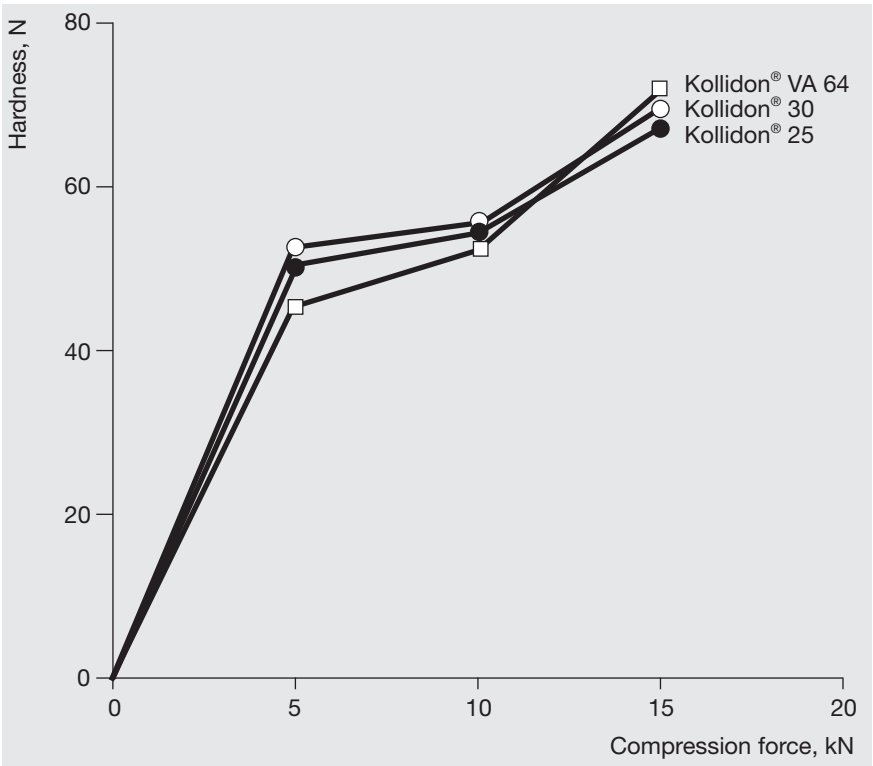

Fig. 4.17: Influence of the compression force on the hardness of lactose tablets containing 3 % Kollidon® VA 64 compared with tablets containing 3 % Kollidon® 25 or 3 % Kollidon® 30 (only valid for wet granulation)

In other cases of wet granulation it was also not possible to measure any major differences in the hardness of corn starch-lactose tablets granulated with Kollidon® VA 64 and Kollidon® 30, over the usual range of binder proportions. However, the hardness of tablets made with hydroxypropyl cellulose (Type L) was much lower. Similar results were obtained with calcium phosphate tablets.

As can be seen from Fig. 4.18 Kollidon® VA 64 has the advantage over Kollidon® 30 in Method 2 that small quantities of water used as granulation liquid give a higher tablet hardness.

The capacity of the powder mixture to bind liquid is one of the parameters that can be used to determine the quantity of Kollidon® VA 64 binder solution required in wet granulation. Every powder mixture to be granulated has a different binding capacity for Kollidon® VA 64 solutions, which most effectively minimizes the proportion of fines [483].

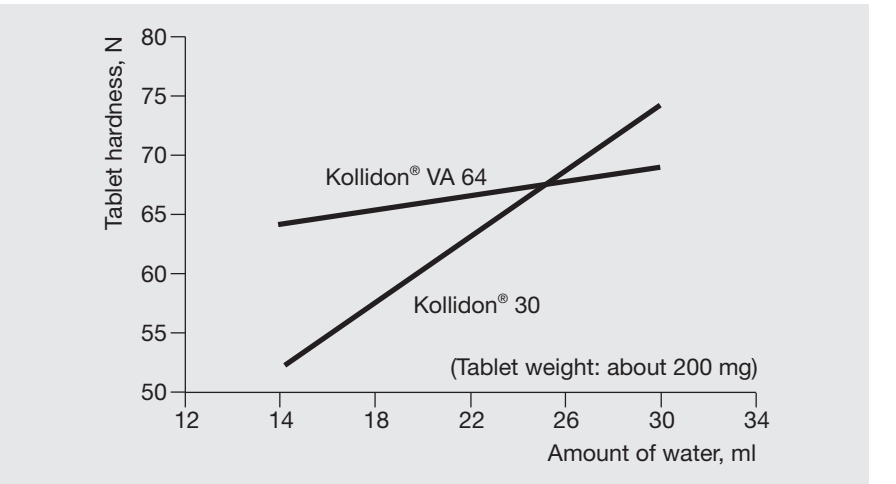

Fig. 4.18: Influence of the amount of water as granulation liquid on the tablet hardness (solvent granulation of tablets of 100 mg of aminophylline)

With all four of the granulating methods mentioned in Table 4.18, Kollidon® VA 64 usually gives hard tablets of low friability. Since Kollidon® VA 64 is soluble, the drug normally dissolves rapidly, whether in gastric or intestinal juice [132, 644] and frequently independently of the compression force, as can be seen in Fig. 4.19. Like in the case of Kollidon® 30 it can be expected that Kollidon® VA 64 enhances the dissolution of many active ingredients as shown with griseofulvin [528].

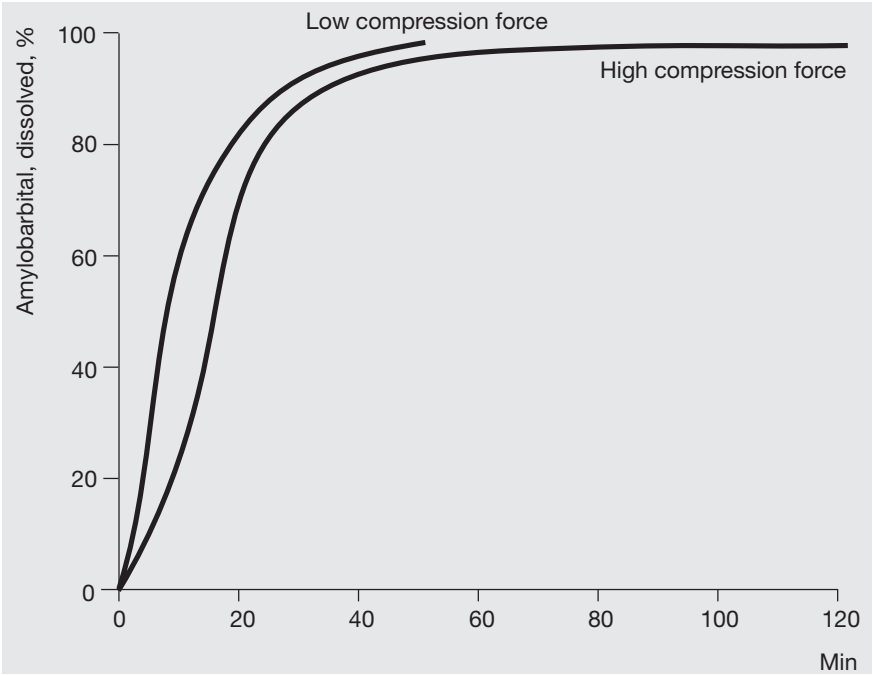

Fig. 4.19: Influence of the compression force on the dissolution of amylobarbital from tablets granulated with Kollidon® VA 64 [132]

An important property of the Kollidon® VA 64 grades, in the use as binders for tablets, is their plasticity [68c], a property that povidone does not possess (see Fig. 4.21). This property of Kollidon® VA 64 gives granules and mixtures that are less susceptible to capping during compression, and tablets that are less brittle. The tablets also have less tendency to stick to the punches when tabletting machines are operated under humid conditions.

Two formulations, for ampicillin and cimetidine tablets, that have been developed on a laboratory scale, are given in Table 4.19 as examples for the use of Kollidon® VA 64 in wet granulation.

Table 4.19: Ampicillin tablets (500 mg) and cimetidine tablets (400 mg) [615]

		Ampicillin tablets	Cimetidine tablets
Formulations:			
I	Ampicillin trihydrate	500 g	–
	Cimetidine	–	400 g
	Corn starch	242 g	170 g
II	Kollidon® VA 64	25 g	20 g
	2-Propanol or water	q. s.	q. s.
III	Kollidon® CL	15 g	–
	Magnesium stearate	10 g	3 g
	Aerosil® 200	8 g	–

Granulate mixture I with solution II, dry and sieve, mix with III and press into tablets with a low pressure.

Tablets obtained on a laboratory scale with a rotary tabletting machine had the following properties:

Tablet properties:

Weight	798 mg	601 mg
Hardness	170 N	91 N
Disintegration in gastric juice	5 min	4 min
Friability	0.35 %	0.5 %
Dissolution (USP)		
20 min	Not	91 %
30 min	tested	100 %

4.4.2.3 Manufacture of tablets and granules by dry granulation (roller compaction) with Kollidon® VA 64 grades as dry binders

Dry granulation is less widely used than wet granulation as a method for preparing tabletting mixtures. The best-known dry granulation technique is the roller compaction (see Fig. 4.20). It is the method of choice when-ever wet granulation cannot be used for reasons of stability and the physical properties of the drug components do not allow direct compression. Kollidon® VA 64 grades are very suitable as dry binders in this type of granulation [637, 653].

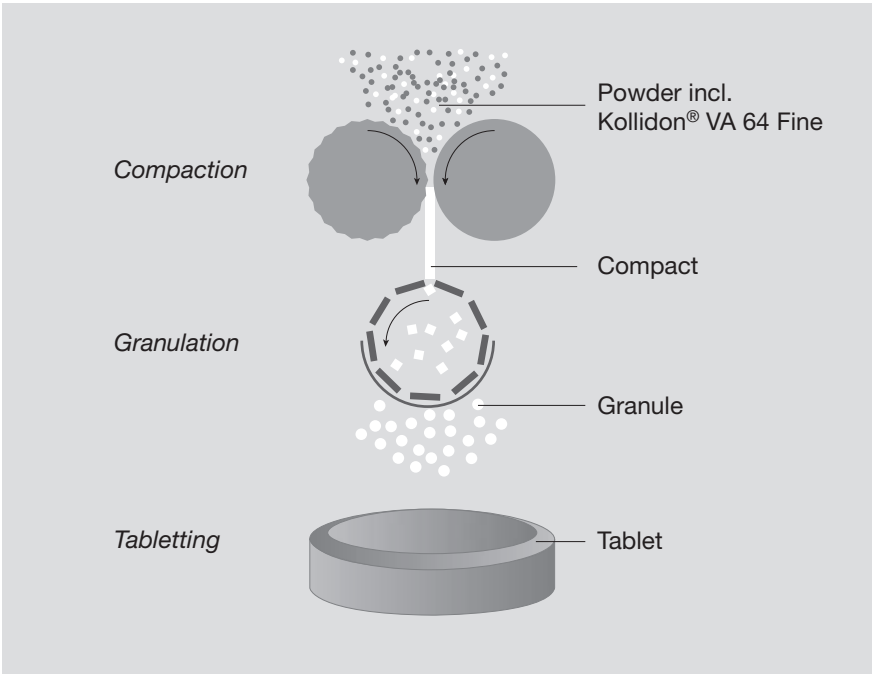

Fig. 4.20: Schematic roller compaction process with Kollidon® VA 64 Fine

Kollidon® VA 64 Fine was specially tailored for the application in roller compaction and is the material of choice in terms of particle size distribution and particle shape for this application. Due to the particle size it is able to cover a big surface area and to form numerous bridges in the tablet structure that lead to hard tablets with a reduced friability.

The formulations of allopurinol granules and tablets shown in Tables 4.20 and 4.21 are typical examples for the use of this technique with Kollidon® VA 64 Fine.

Table 4.20: Allopurinol granules obtained by roller compaction with Kollidon® VA 64 Fine

Formulation:	
Allopurinol	100 g
Ludipress®	50 g
Kollidon® VA 64 Fine	10 g
Kollidon® CL	6 g
Magnesium stearate	1 g
Compaction conditions:	
Roller compactor	Gerteis Type Mini-Pactor M1114
Roll width	25 mm
Compression force	2 kN/cm
Gap width	3 mm
Tamping/feeding ration	120 %
Roll speed	2 rpm
Mesh sizes	1.25 mm

After the compaction process the obtained allopurinol granules of the formulation of Table 4.20 were blended for 10 minutes with the tabletting excipients Ludipress® and magnesium stearate mentioned in Table 4.21 and pressed to tablets of 100 mg of active ingredient.

Table 4.21: Allopurinol tablets (100 mg) prepared with compacted allopurinol granules (Table 4.20)

Formulation:	
Allopurinol granules obtained by roller compaction	160 mg
Ludipress®	120 mg
Magnesium stearate	0.9 mg

Mix the components and press with the compression force of about 16 kN on a rotary press to tablets of the following properties:

Tablet properties:	
Diameter	8 mm
Weight	281 mg
Hardness	246 N
Disintegration time	9 min
Friability	< 0.1 %

4.4.2.4 Manufacture of tablets by direct compression with Kollidon® VA 64 and Kollidon® VA 64 Fine as dry binders

Direct compression is now becoming ever more widely used, even though most active ingredients cannot readily be directly compressed in the desired concentrations. For good tabletting properties, an active ingredient must fulfil a number of physical requirements. It must be free-flowing, it must not be prone to electrostatic charging, its crystals must not be too brittle and its compression characteristics must result in tablets of adequate hardness.

Although most active ingredients do not fulfil these criteria, they can be directly compressed with copovidone [68c, 213, 458, 459, 464, 615]. Kollidon® VA 64 grades could be considered as the best dry binders of all substances usually applied in drugs for this purpose. The main reasons of the excellent dry binder properties are the plasticity of Kollidon® VA 64 grades as shown in Fig. 4.21, the lower glass transition temperature (see Section 4.4.3.1) and the irregular structure of the particles (see Section 4.2.4.2).

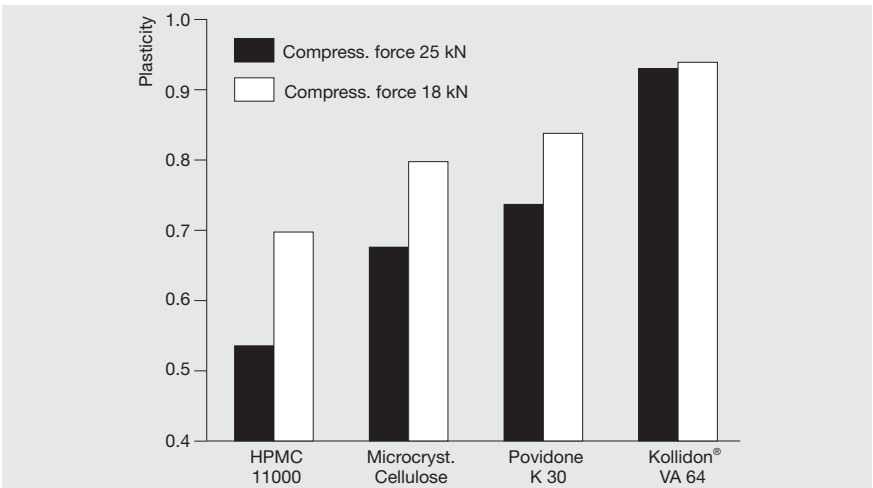

Fig. 4.21: Plasticity of different dry binders mixed with 0.5 % of magnesium stearate and pressed to tablets (Plasticity = plastic energy/total energy)

The hardness, friability, porosity and disintegration time of lactose and starch placebo tablets made with Kollidon® VA 64 by direct compression were directly related to the compression force used [458].

Excellent direct compression systems can be formulated with a combination of about 5 % Kollidon® VA 64 with fillers such as lactose, microcrystalline cellulose, sorbitol or mannitol, and, if required, a disintegrant, a glidant and/or a lubricant. These have been successfully tested in combination with more than 30 drugs [213, 464, 615].

These excipient combinations are also very good for single-vitamin or multi-vitamin tablets [368]. In tablets with several vitamins, they provide superior chemical stability, by avoiding the need for wet granulation, with equally good physical properties [615].

A general limit could be the concentration of the active ingredient in the tabletting mixture. High dosages could be problematic if the active substance has no good flowability. Therefore the physical properties of the active ingredient and the excipients should be fixed as specifications for such high dosage formulation.
Particulary in the case of Kollidon® VA 64 Fine it is recommended to add a flowability agent like Aerosil® 200 (Degussa).

It is normally difficult to produce tablets with normal ascorbic acid by direct compression, but as is shown in Table 4.22, they can be produced much more readily using Kollidon® VA 64. When this dry binder is added, the hardness of the tablets increases and the friability decreases much more than after the addition of Kollidon® 30 or hypromellose (HPMC) which had no effect on the hardness in this formulation.

Table 4.22: Dry binding effect of Kollidon® VA 64, Kollidon® 30 and hypromellose (HPMC) in ascorbic acid tablets

Formulations (direct compression):

	Without binder	Kollidon® VA 64	Kollidon® 30	HPMC 11 000
Ascorbic acid	200 g	200 g	200 g	200 g
Ludipress®	256 g	256 g	256 g	256 g
Kollidon® VA 64	–	25 g	–	–
Kollidon® 30	–	–	25 g	–
HPMC 11 000	–	–	–	25 g
Kollidon® CL	15 g	15 g	15 g	15 g
Aerosil® 200 (Degussa)	1.2 g	1.2 g	1.2 g	1.2 g
Magnesium stearate	2.5 g	2.5 g	2.5 g	2.5 g
Tablet properties (lab scale, rotary press):				
Hardness	56 N	73 N	59 N	57 N
Friability	3.2 %	0.4 %	1.1 %	0.9 %
Dissolution (30 min)	> 90 %	> 90 %	> 90 %	> 90 %

Using a formulation of acetylsalicylic acid tablets (composition: acetylsalicylic acid 500 mg, microcryst. celullose 200 mg, dry binder 60 mg, Kollidon® CL 25 mg, magnesium stearate 3 mg) even more dry binders including Kollidon® VA 64 Fine and hypromellose (HPMC) were compared. This comparison study demonstrated that the dry binding effect of Kollidon® VA 64 Fine is much higher than the effect of all other binders including normal Kollidon® VA 64 (Fig. 4.22).
The hardness of similar vitamin C tablets as shown in Table 4.22 and produced with Kollidon® VA 64 Fine was about the double in comparison with the hardness of the tablets obtained with povidone K 30, hypromellose (HPMC) or hydroxpropyl cellulose (HPC).

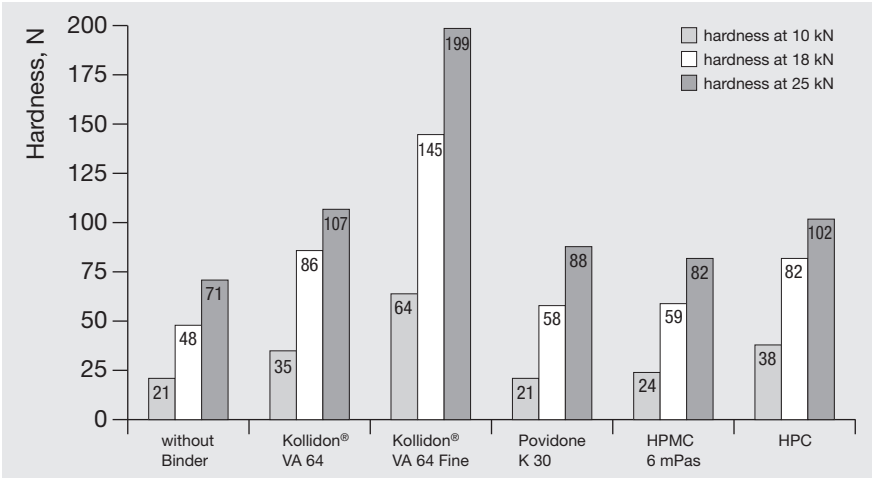

Fig. 4.22: Hardness of acetylsalicylic acid tablets (500 mg) obtained by direct compression with different dry binders

The combination of Kollidon® VA 64 with sucrose and microcrystalline cellulose is mentioned for vitamin C chewable tablets in the commentary to the German Standard Generic Formulations [460]. Table 4.23 shows the recommended formulation and the properties of these chewable tablets reproduced in the laboratory.

Table 4.23: Ascorbic acid chewable tablets (100 mg) with Kollidon® VA 64

Formulation (direct compression) [460]:

Ascorbic acid, powder	42.2 %
Sucrose, ground	13.0 %
Sucrose, crystalline	8.0 %
Microcrystalline cellulose	28.3 %
Kollidon® VA 64	2.4 %
Polyethylene glycol 6000, powder	2.0 %
Orange flavour + strawberry flavour (2 + 1)	1.2 %
Cyclamate sodium	2.4 %
Saccharine sodium	0.1 %
Aerosil® 200 (Degussa)	0.2 %

Tablet properties:

Tablets pressed on a rotary tabletting press in the BASF laboratories had the following properties:

Weight	250 mg
Diameter	8 mm
Hardness	157 N
Disintegration in water	15 min
Friability	less than 0.1 %

In Table 4.24 three different tablet formulations of atenolol (50 mg), acetylsalicylic acid (500 mg) and indomethacin (50 mg) produced with Kollidon® VA 64 Fine and different fillers are shown to demonstrate the application possibilities of this excipient in the direct compression technology for tabletting. All tablets produced with a relatively low compression force of about 10 kN have got hardnesses higher than 100 N, very low friabilities and normal disintegration times.

Table 4.24: Atenolol, acetylsalicylic acid and indomethacin tablets produced by direct compression with Kollidon® VA 64 Fine and different fillers

	Atenolol tablets	Acetylsalicylic acid tablets	Indomethacin tablets
Formulations:			
Active ingredient	50.0 mg	500 mg	50 mg
Ludipress®	135.7 mg	–	–
Avicel® PH102 (FMC)	–	200 mg	–
Di-Tab® (Innophos)	–	–	212 mg
Kollidon® VA 64 Fine	15.0 mg	60 mg	20 mg
Kollidon® CL	25.0 mg	25 mg	15 mg
Aerosil® 200 (Degussa)	1.3 mg	–	–
Magnesium stearate	3.0 mg	3 mg	3 mg

The individual components were sieved through a 0.8 mm sieve. After the blending time of 10 min the mixture is compressed on a rotary press with the compression force of about 10 kN and a rotation speed of 30 rpm.

Tablet properties:			
Diameter	8 mm	12 mm	8 mm
Weight	221 mg	777 mg	305 mg
Hardness	132 N	140 N	101 N
Disintegration time	4 min	8 min	< 1 min
Friability	< 0.1 %	0.2 %	< 0.1 %

Table 4.25 shows how it was possible to considerably improve the tabletting properties of an antacid tablet containing alginic acid, magnesium trisilicate, aluminium hydroxide and sodium hydrogen carbonate as active ingredients by the addition of Kollidon® VA 64. The hardness was doubled and the friability reduced by half.

Table 4.25: Improvement in the properties of antacid tablets with the addition of Kollidon® VA 64

Formulation (direct compression):		
Alginic acid	500 g	500 g
Magnesium trisilicate	25 g	25 g
Aluminium hydroxide dried gel	100 g	100 g
Sodium bicarbonate	170 g	170 g
Sorbitol, cryst.	160 g	160 g
Sucrose, cryst.	627 g	627 g
Ludipress®	900 g	900 g
Magnesium stearate	50 g	50 g
Vanillin	5 g	5 g
Kollidon® VA 64	–	70 g
Press to tablets on a rotary tabletting machine with a compression force of 30 kN.		
Tablet properties:		
Weight	2504 mg	2550 mg
Diameter	20 mm	20 mm
Hardness	67 N	120 N
Friability	3.0 %	1.3 %

In direct compression, particular attention must be paid to the moisture in the tabletting mixture, although under normal conditions the usual residual quantities of water in Kollidon® VA 64 grades suffice to provide an adequate binding effect between the particles

4.4.2.5 Granules and pellets obtained by wet granulation with Kollidon® VA 64

The properties of Kollidon® VA 64 described in Sections 4.4.2.1 and 4.4.2.2, that are of advantage in wet granulation, can, of course, also be used in the production of granules and pellets as final dosage form or for filling into hard gelatin capsules. The most important functions of Kollidon® VA 64 in granules are to enlarge the size of the granules, to achieve good flow properties and to avoid dusting. This makes the granules easier to handle when they are filled into containers or hard gelatin capsules.

Kollidon® VA 64 is also an excellent binder for the production of drug pellets provided for the sustained release coating with Kollicoat® SR 30D, Kollicoat® EMM 30D [662] or other sustained release polymers suitable for pellet coating. Typical examples of such drug pellets are spheronized pellets of diclofenac, propranolol or verapamil [615] and pellets of theophylline [479].
Table 4.26 illustrates such formulation of spheronized drug pellets of 48 % verapamil-HCl obtained by wet granulation and developed for the production of drug pellets for sustained release film-coating [662]. Kollidon® VA 64 is also highly suitable for producing multivitamin granules [368].

Table 4.26: Formulation of spheronized verapamil hydrochloride drug pellets [662]

Components	Amount (g)
I Verapamil-HCl (BASF)	480
Microcrystalline cellulose	300
Kollidon® VA 64	20
Talcum	175
Aerosil® 200 (Degussa)	25
II Water	400

Granulate mixture I with the water, pass through a sieve of 1.5 mm, round in a spheronizer for 10 minutes at 300 – 400 rpm and subsequently dry at 70 °C in a fluidized bed granulator

4.4.3 Tablet coatings with Kollidon® VA 64

4.4.3.1 Film-coatings

Kollidon® VA 64 forms soluble films, independently of the pH, regardless of whether it is processed as a solution in water or in organic solvents. Kollidon® VA 64 differs from povidone as a film-forming agent in that it is less hygroscopic (see Section 4.2.4.4) and has greater plasticity and elasticity. At the same time the films are also less tacky. The glass transition temperature depends on the moisture content, and at 103 °C for dry Kollidon® VA 64, is also below that of dry Kollidon® 30 (168 °C).

Pure isolated films of Kollidon® VA 64 were found to have a failure energy of only 1 J/m^2 at room temperature – a measure of their tack. The failure energy of Kollidon® 30 films was 45 J/m^2. As Kollidon® VA 64 usually absorbs too much water, it can seldom be used as the sole film-forming agent in a formulation. It is therefore recommended to combine it with less hygroscopic substances such as cellulose derivatives [101, 117], shellac, polyvinyl alcohol, polyethylene glycol (e. g. macrogol 6000) or sucrose. Plasticizers such as triethyl citrate, triacetin or phthalates are not normally required. The typical formulations with hypromellose and sucrose given in Tables 4.27 to 428 were tested in the laboratory on tablet cores of 9 mm diameter weighing 200 mg.

The properties of coatings can be significantly improved with copovidone, particularly when it is combined with cellulose derivatives [580, 620]. In the case of the tablet film-coating using HPMC 2910 the viscosity of the spray suspension containing 12 % of polymer can be decreased from about 700 mPa · s to 250 mPa · s if 60 % of the HPMC polymer is sustituted by Kollidon® VA 64 [615]. Since the viscosity of 250 mPa · s is considered as the usual limit for spraying of a coating suspension such substitution by Kollidon® VA 64 permits to apply this high polymer concentration and therefore to economize the spraying procedure. A formulation with this combination of HPMC and Kollidon® VA 64 is illustrated in Table 4.27.

Table 4.27: Film-coating with Kollidon® VA 64 and HPMC (Accela Cota® 24", Manesty)

I. Kollidon® VA 64	53 g
Macrogol 6000	12 g
HPMC 2910 (6 mPa·s)	79 g
Water	732 g
II. Titanium dioxide	36 g
Sicovit® Iron oxide red	18 g
Talcum	54 g
Water	216 g

Mix solution I with suspension II, pass through a disc mill and spray with 2 bar onto 5 kg of cores. The quantity of film former applied is about 3 mg/cm^2.

Inlet/outlet air temperature	60 °C/40 °C
Spraying rate	50 g/min
Spraying time (continuously)	34 min
Drying after spraying	5 min at 60 °C

A more recent and most interesting variation on the theme of film-coatings with Kollidon® VA 64 is its combination with sucrose to produce "sugar-film-coated" tablets. Here, Kollidon® VA 64 performs all the functions listed in Table 4.30, mainly film formation and inhibition of crystallization, to give a time and material-saving coating. Table 4.28 gives a formulation for such a sugar film-coating. Film-coated tablets with smooth films were obtained after only 50 min, as is shown in the photograph in Fig. 4.23.

Table 4.28: Sugar film-coating with Kollidon® VA 64 (Accela Cota® 24", Manesty)

Sucrose	40 g
Kollidon® VA 64	10 g
Macrogol 4000	8 g
Colour lake or Sicovit® Iron oxide	3 g
Titanium dioxide	6 g
Talc	10 g
Water	ad 240 g

1200 g of this suspension was sprayed continuously with the pressure of 2 bar onto 5 kg of tablet cores that contained 5 % Kollidon® CL as a disintegrant, under the following conditions:

Coating pan speed	15 rpm
Spraying nozzle	0.8 mm
Inlet/outlet air temperature	45 °C/36 °C
Spraying time	50 min
Quantity applied	Approx. 4 mg of film-forming agents/cm^2

Fig. 4.23: Tablets after sugar film-coating with Kollidon® VA 64 as described in Table 4.28

As an alternative to processing Kollidon® VA 64 in solutions in water and/or organic solvents, it can be applied to the tablet cores in powder form at 40 °C with the aid of a plasticizer such as triacetin to reduce the film-forming temperature [466]. Perhaps Kollidon® VA 64 Fine would be even better for the purpose.

In several cases an imcompatibility between Kollidon® VA 64 and dispersions of methacrylic acid – ethylacrylat copolymer (e. g. Kollicoat® MAE grades) was observed as the formation of agglomerates.

4.4.3.2 Subcoating of tablet cores as a barrier to water

As tablets are nowadays coated mostly with aqueous solutions or dispersions, it has become increasingly necessary to provide the tablet cores with a barrier layer prior to sugar or film-coating. This is mainly to protect water-sensitive drugs against hydrolysis and chemical interactions, e. g. between different vitamins, etc. and to prevent the swelling of high-performance tablet disintegrants like crospovidone that are very sensitive even to small quantities of water. Table 4.29 shows that Kollidon® VA 64 is also capable of hydrophilizing the tablet core surface, improving its adhesion properties and reducing dust formation [101].

Table 4.29: Reasons for subcoating tablet cores and the function of Kollidon® VA 64 in this application

Reasons for subcoating tablet cores	Function of Kollidon® VA 64
Instability of the active substance towards water (hydrolysis)	Formation of a barrier layer on the surface and in the pores
Chemical interactions between the active substances (e. g. vitamins)	Formation of a barrier layer on the surface and in the pores
Presence of high-performance disintegrants [541]	Formation of a barrier layer on the surface and in the pores
Hydrophobic surface of the tablet core	Improvement in adhesion of subsequent coatings by hydrophilization of the tablet surface
Dust formation (friability of the tablet cores)	Loose particles are bound to the surface of the tablet core

The subcoating of Kollidon® VA 64 is best applied in the same apparatus in which the subsequent sugar or film-coating is to be applied. An adequate barrier can be applied with less than 0.5 mg of Kollidon® VA 64/cm^2 of the warm tablet cores, using a 10 % solution of Kollidon® VA 64 in 2-propanol or ethanol.

4.4.3.3 Traditional sugar coating

Kollidon® VA 64 can be used in the same way as Kollidon® 30 in manual or automized sugar coating, in which it has the advantages of lower hygroscopicity and higher plasticity. Table 4.30 gives the most important properties and functions of Kollidon® VA 64 in sugar coatings.

Table 4.30: Important properties and functions of Kollidon® VA 64 for sugar coatings and sugar film-coatings

Property	Function
Film formation, plasticity	Prevention of hairline cracks/crazing
Adhesion	Adhesion of the sugar layer to the tablet core
Affinity to hydrophobic surfaces	Adhesion of the tablet coating to cores with hydrophobic substances
Dispersive effect	Homogeneous distribution of the colorant in the tablet coating suspension
	Stabilization of the coating suspension
Inhibition or retardation of crystallization	Slower and more homogeneous crystallization of the sugar

Sugar coatings are particularly susceptible to cracking when they are applied to large batches of tablet cores that are dried rapidly. As most active ingredients are hydrophobic, Kollidon® VA 64 is useful as an additive to prevent the tablet coating cracking away from the tablet core during manufacture.

Kollidon® VA 64 can certainly be used just as well as Kollidon® 30 in automatic sugar coating (see Section 2.4.4.1).

4.4.4 Film-forming agent in topical sprays

Because of its good film-forming properties, its bioadhesion and its good solubility in water, Kollidon® VA 64 can also be used as a film-forming agent in water-based sprays as final dosage form for human or veterinary topical administration. Table 4.31 gives a formulation developed on a laboratory scale for a wound spray containing polidocanol as the active ingredient.

As with film-coatings for tablets, a combination of Kollidon® VA 64 with a cellulose derivative can also be used for spray solutions, as this both improves the solubility and plasticity of ethylcellulose and reduces the hygroscopicity of a pure Kollidon® VA 64 film.

Table 4.31: Polidocanol wound spray [615]

Polidocanol-9	5 g
Lutrol® E 400	20 g
Kollidon® VA 64	50 g
Ethocel® 20 (Dow)	50 g
Ethyl acetate	675 g
2-Propanol	200 g

Fill the solution into spray cans with the necessary quantity of propellant (e. g. propane/butane).

The formulation in Table 4.32 is an example of an antimycotic film plaster spray containing the active ingredient, clotrimazole. Here, Kollidon® VA 64 is used as the sole film-forming agent.

Table 4.32: Clotrimazole plaster spray [467]

Clotrimazole	1.0 g
Benzyl alcohol	4.0 g
Isopropyl myristate	6.0 g
Copovidone (e. g. Kollidon® VA 64)	12.5 g
2-Propanol	ad 100.0 ml

Fill 6 – 8 parts of this solution with 2 – 4 parts of propellant, e. g. propane/butane, into spray cans.

Similar topical formulations containing steroids, antibiotics and antimycotics are described in patents [468, 469]. Nifedipine is an example of an active ingredient that is used in sublingual sprays with Kollidon® VA 64 [468].

For the veterinary application Kollidon® VA 64 is used as filmformer and bioadhesive in fipronil sprays.

4.4.5 Matrix-forming agent in instant release and controlled release dosage forms

4.4.5.1 Instant release preparations obtained by melt extrusion and other technologies

The most important newer technology for the application of Kollidon® VA 64 as matrix former is the melt extrusion [475, 663]. In this technology it also can be combined with surfactants. A drug containing Kollidon® VA 64 and the anti-HIV protease inhibitors lopinavir and ritonavir was the first co-formulated pharmaceutical compound to be successfully tabletted using a proprietary melt extrusion process. The melt extrusion appears to have overcome the poor solubility and negligible oral bioavailability of previous formulations of lopanavir/ritonavir [665]. Similar results of dissolution increase were found with lacidipine and indomethacin melt extruded with copovidone [668].

A typical example of an estradiol tablet was taken from the literature. Table 4.33 shows the formulations of the granules obtained by melt extrusion and the final tablets produced with these granules [667]. Kollidon® VA 64 has the advantage of its higher plasticity in comparison with other polymers like povidone or macrogol.

Table 4.33: Estradiol tablets produced by melt extrusion [667]

Formulation of the granules (melt extrusion):	
17ß-Estradiol hemihydrate	10.0 %
Kollidon® VA 64	50.0 %
Gelucire® 44/14 (Gattefossé)	40.0 %
Formulation of the tablets (direct compression):	
17ß-Estradiol hemihydrate melt extruded granules	8.3 %
Microcrystalline cellulose	45.6 %
Corn starch	45.6 %
Magnesium stearate	0.5 %
Tabet properties:	
Content of 17ß-estradiol hemihydrate	2 mg
Diameter	6 mm
Dissolution of the granules	see Fig. 4.24

Fig. 4.24 shows the almost 20-fold increase of the dissolution for the melt extruded estradiol granules produced with Kollidon® VA 64. The dissolution media was 0.1 N hydrochloric acid.

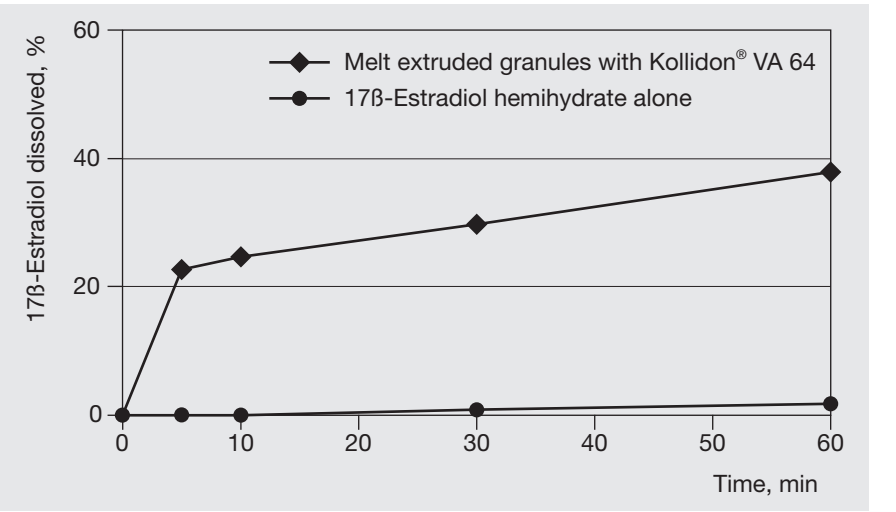

Fig. 4.24: Dissolution of 17ß-estradiol hemihydrate granules obtained by melt extrusion with Kollidon® VA 64 [667]

Kollidon® VA 64 can also be used as a matrix in other technologies for the production of instant release dosage forms in combination with other auxiliaries [112, 475]. This should be of particular interest for active ingredients with relatively poor bioavailability, as copovidone forms complexes with these active ingredients, increasing the dissolution rate in much the same manner as does povidone (see Section 2.4.3). Active ingredients whose dissolution rate can be increased in this way include carbamazepine [554], pseudoephedrine, diphenhydramine, propaphenon, nicotinic acid, biperiden [475], furosemide [548] and diclofenac.

Further, a Kollidon® VA 64 matrix can stabilize certain plant extracts such as valepotriate (valerian extract) [478].

4.4.5.2 Matrix in controlled-release preparations

Once it has been pressed as matrix into tablets or melted, Kollidon® VA 64 dissolves more slowly than Kollidon® 30. This property can be used to control or delay the release of some active ingredients, by embedding them in a matrix of mixtures containing also Kollidon® VA 64. There is mentioned a number of active ingredients in the literature, that are used with Kollidon® VA 64 as matrix component in sustained release preparations. Typical examples are bencyclane [473], captopril [411], dyphylline [474], imipramine [473], nitroglycerin [411, 473], propaphenone [476], theophylline [411, 473, 475, 476] and verapamil [477].

Kollidon® VA 64 has different functions in this application as matrix component in sustained release tablets:

1. As the main component, Kollidon® VA 64 provides the actual matrix to which lipophilic or water-insoluble auxiliaries such as stearic acid and stearyl alcohol [475–476], cellulose derivatives [476], starch [475] or calcium hydrogen phosphate [474] are added.

2. Kollidon® VA 64 forms an insoluble complex with polyacrylic acid, in the same way as povidone, (see Section 2.4.8.8) and thus provides the matrix [411, 473].

3. Kollidon® VA 64 can be used as pore former or hydrophilic component to adjust the release of the active ingredient when it is added to a lipophilic matrix such as stearyl alcohol or cetyl alcohol [471, 472] or to a matrix of a sustained release polymer such as Kollicoat® SR 30D.

The techniques for manufacturing controlled release preparations with Kollidon® VA 64 can vary widely. The simplest form of processing is direct compression [474]. Other processes involve fluidized bed granulation [411], melt granulation, melt extrusion [475–476] or melt compression [477] and powder extrusion.

4.4.6 Transdermal and transmucosal systems

Due to its higher plasticity, its lower hygroscopicity and its bioadhesion the film former Kollidon® VA 64 could be more suitable than povidone for transdermal or transmucosal systems. There is also described a crystallization inhibitory effect of Kollidon® VA 64 in transdermal or transmucosal systems of dihydroergotamine, melatonine, betamethasone and fusafungine [58, 590]. The bioadhesion of Kollidon® VA 64 is used for such systems of estradiol or levonorgestrel [414], and of flurbiprofen [593].

A typical basic formulation of mucoadhesive buccal tablets is given in Table 4.34. In this case the adhesive effect of Kollidon® VA 64 was much higher than the adhesion of Kollidon® 30 or Kollidon® 90F.

Table 4.34: Basic formulations of mucoadhesive buccal tablets

Formulations:

		No. 1	No. 2
I	Active ingredient	q. s.	q. s.
	Lactose monohydrate	76 g	76 g
	Carbopol® 934 (Goodrich)	4 g	–
	Carbopol® 980/981 1+1 (Goodrich)	–	4 g
	Kollidon® VA 64	19 g	19 g
II	Ethanol 96 %	15 g	10 g
III	Magnesium stearate	1 g	1 g

Mix intensively the components I, granulate mixture I with ethanol II, pass through a 0.8 mm sieve, dry, sieve again through a 0.5 mm sieve, mix with the component III and press with medium compression force to tablets.

Tablet properties (Formulations No. 1 and No. 2):

Diameter	8 mm
Weight	200 mg
Hardness	> 180 N
Disintegration	> 30 min
Friability	< 0.1 %

Buccal adhesive strength (in vitro):

One drop of human saliva was given to a glass plate and a tablet was put on this drop. After 7 min the force (N) needed to separate the tablet vertically from the glass plate was measured:
Formulation No. 1: about 7 N
Formulation No. 2: about 3 N


BASF
Kollidon® SR
BASF
Kollidon® SR

5. Kollidon® SR

5.1 Structure, composition

Kollidon® SR is a spray dried polyvinyl acetate containing also soluble polyvinylpyrrolidone (povidone) in the ratio 8 : 2.

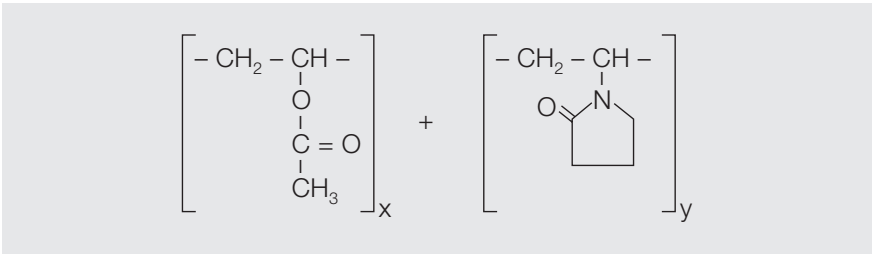

Fig. 5.1: Structural formula of Kollidon® SR, Mr = (86.1)$_{x = 5200}$ + (111.1)$_{y = 450}$

Kollidon® SR consists of a spray dried physical mixture of 80 % polyvinyl acetate having a weight-average molecular weight of about 450 000 and 19 % povidone Ph.Eur./USP (Kollidon® 30). About 0.8 % of sodium lauryl sulphate and about 0.6 % of silica are used as stabilizer and flowability agent.

Kollidon® SR has got the BASF article number 526 222 54 (20 kg) and the PBG number 10235112. The CAS number of polyvinyl acetate is 9003-20-7 and of povidone it is 9003-39-8.

5.2 Product properties

5.2.1 Description, specifications, pharmacopoeias

5.2.1.1 Description

Kollidon® SR is a product of pharmaceutical purity obtained according to the regulations of cGMP. It is a white to slightly yellowish free flowing powder.

5.2.1.2 Specifications

The specifications of 2007 are listed in Table 5.1. The actual specifications are available on request.

Table 5.1: Specifications of Kollidon® SR

Identification (IR spectrum, see Section 5.3.1)	conforms
pH (10 % suspension in water)	3.5 – 5.5
Loss on drying (140 °C, 60 min, vacuum)	≤ 5.0 %
Sulphated ash	≤ 2.0 %
Heavy metals	≤ 20 ppm
Vinyl acetate (HPLC, see Section 5.3.2)	≤ 100 ppm
Residual solvents (acetic acid, see Section 5.3.3)	≤ 0.5 %
Microbiological status (10 % in water)	conforms to Ph.Eur. categories 2 + 3A
Content of polyvinyl acetate (see Section 5.3.4)	75 – 85 %
Content of povidone (see Section 5.3.5)	18 – 21 %

Unless it is stated to the contrary the methods are taken from the current edition of the European Pharmacopoeia (Ph.Eur.).

Kollidon® SR meets the ICH requirements on residuel solvents according to Ph.Eur., chapter 5.4: Only class 3 solvents are likely present (acetic acid).

The microbiological status meets the requirements of the Ph.Eur. categories 2 and 3A given in Table 5.2.

Table 5.2: Microbial purity requirements (Ph.Eur. Chapter 5.1.4, Categories 2 and 3A)

– Max 10^2 aerobic bacteria and fungi/g
– No escherichia coli/g
– Max. 10^1 enterobacteria and other gramnegative bacteria/g
– No pseudomonas aeruginosa/g
– No staphylococcus aureus/g

Test methods according to Ph.Eur. Chapters 2.6.12 and 2.6.13.

5.2.1.3 Pharmacopoeias, registration

No pharmacopoeial monograph is available for Kollidon® SR as a physical mixture of two polymers.
The polyvinyl acetate dispersion Kollicoat® SR 30D used for the production of Kollidon® SR meets the requirements of the Ph.Eur. monograph 2152 *"Poly(vinyl) acetate Dispersion 30 Per Cent"*, published in the Supplement 5.8 and the Kollidon® 30 also used for the production of Kollidon® SR meets the requirements of the Povidone monograph in Ph.Eur., USP and JP.

For registration purposes a DMF was prepared and sent to the FDA (USA) and a short description of the production of Kollidon® SR is available on request.

Polyvinyl acetate is used in a variety of drugs for oral administration in numerous countries including Germany, France, Japan and USA.

Polyvinyl acetate also is allowed in the food industry in several countries like Germany, USA and Japan.

5.2.1.4 Molecular weight, K-value

The weight-average molecular weight of the polyvinyl acetate part is about 450 000 and of the povidone K 30 part it is about 50 000.

The average molecular weight of Kollidon® SR as mixture is expressed as K-value according to the method described in the USP and Ph.Eur. monographs “Povidone” and measured in a 1 % solution in tetrahydrofurane. The typical K-value is 60 to 65.

5.2.2 Physical properties

5.2.2.1 Solubility

Because Kollidon® SR only is used as powder in solid dosage forms it is no disadvantage that it does not dissolve in water. The povidone part is soluble but the polyvinyl acetate part is not soluble. It is very soluble in N-methylpyrrolidone.

5.2.2.2 Particle size and structure, flowability

The average particle size of Kollidon® SR is usually 80 – 100 µm. The form of the spray dried spheric particles is shown in form of an electron scanning micrograph (SEM) in Fig 5.2.

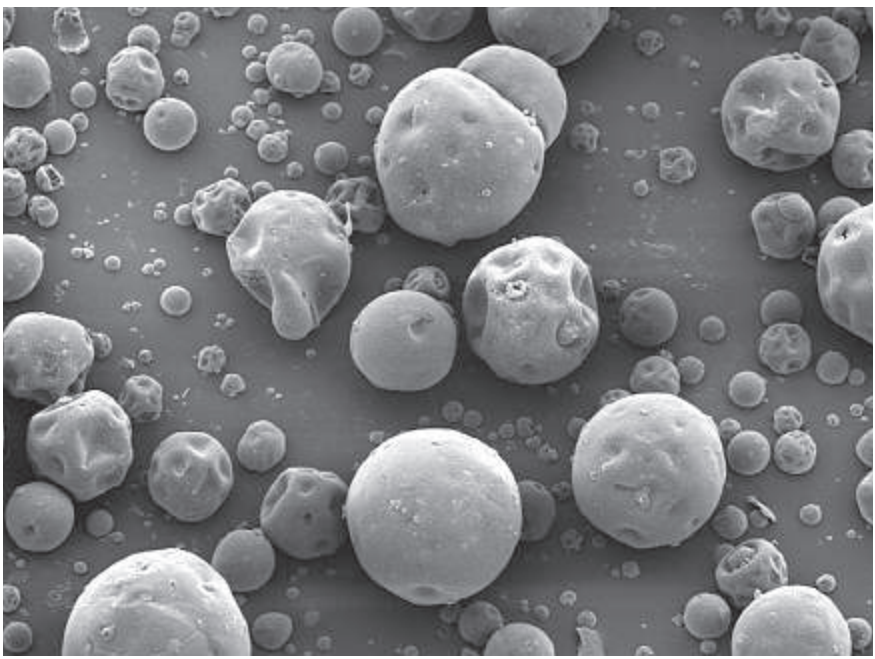

Fig. 5.2: Typical particles of Kollidon® SR (batch 55-3629)

As a spray dried powder the spherical particles of Kollidon® SR offer outstanding flow properties having a response angle well below 30° (see Fig. 5.3). It can enhance the flowability of other components added for a tablet formulation of direct compression.

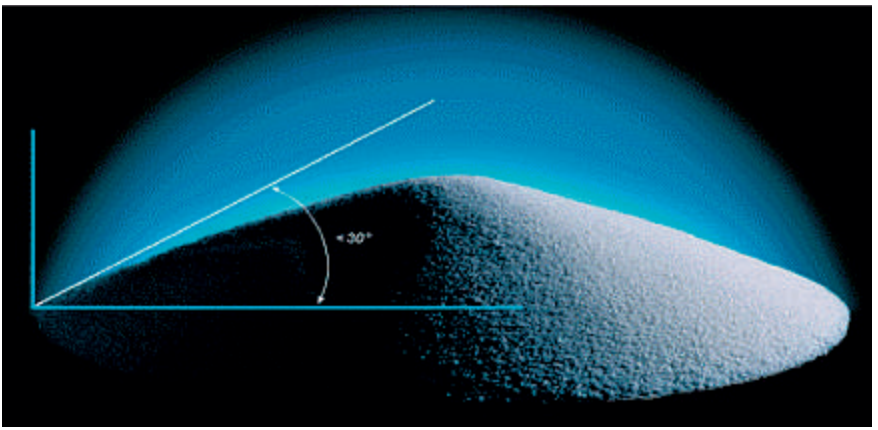

Fig. 5.3: Flowability of Kollidon® SR demonstrated by the repose angle

5.2.2.3 Bulk density

The bulk density is like the flowability an important parameter for the use of an excipient in the direct compression technology of tablets. In the case of Kollidon® SR it is about 0.45 g/ml and therefore in the same range as the bulk densities of many other ingredients used in this technology.

5.2.2.4 Hygroscopicity

The hygroscopicity and humidity uptake of Kollidon® SR is much less than that of povidone or copovidone. Fig. 5.4 shows the water sorption and desorption isotherms at room temperature after 14 days.

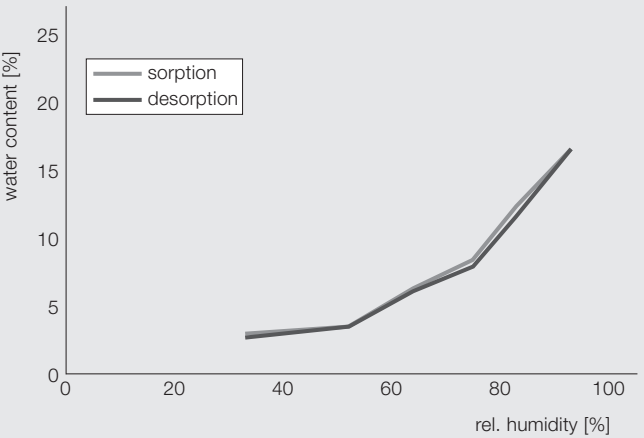

Fig. 5.4: Sorption and desorption isotherms of Kollidon® SR after 14 days

5.2.2.5 Compressibility

The high compressibility as an expression of the excellent dry binding properties is an other important parameter of Kollidon® SR for the use in the direct compression technology of tablets. Fig. 5.5 illustrates the extremely high tablet hardness levels obtained with different compression forces on propranolol tablets. This is due the combination of the very plastic polyvinyl acetate and the strongly binding povidone.

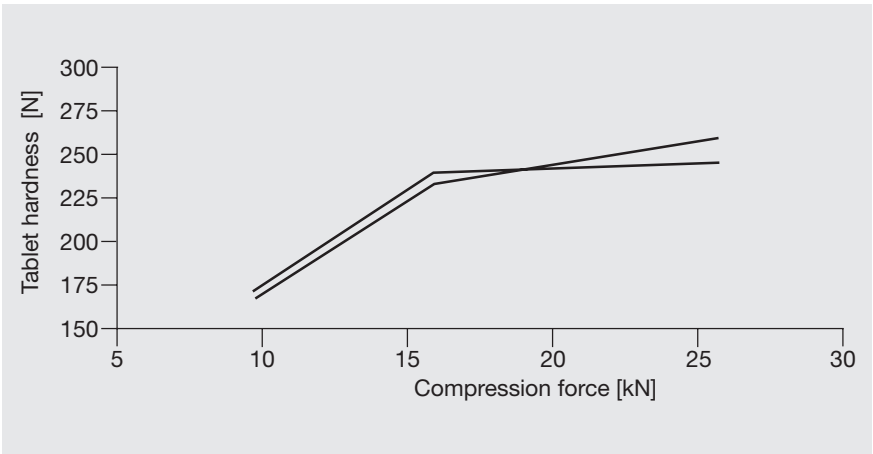

Fig. 5.5: Compressibility of two batches of Kollidon® SR in propranolol-HCl tablets

5.2.2.6 Glass transsition temperature

The glass transsition temperature (Tg) of Kollidon® SR is relatively low in comparison to povidone alone. The dried material showed a Tg of about 35 °C. This explains the plastic properties of Kollidon® SR in tablets.

The low glass transsition temperature can also have negative effects. This can be seen when tablets containing a matrix of Kollidon® SR are tested under accelerated storage conditions at increased temperature and high relative humidity (e. g. > 70 %). In such case the matrix properties and the drug release slowly could be modified. Particulary the high humidity reduces the glass transsition temperature.

5.2.3 Stability, storage, packaging

The spray dried powder Kollidon® SR is quite stable when it is stored at room temperature (20 – 25 °C) in the unopened original containers (20 kg PE drums with PE-inliners). It still meets the specifications given in Section 5.2.1.2 after more than 2 years under these conditions.

5.3 Analytical methods for Kollidon® SR

5.3.1 Identification

The best method for the identification of Kollidon® SR is the infrared spectroscopy. The infrared spectrum is measured in potassium bromide and a typical spectra is given in Fig. 5.6.

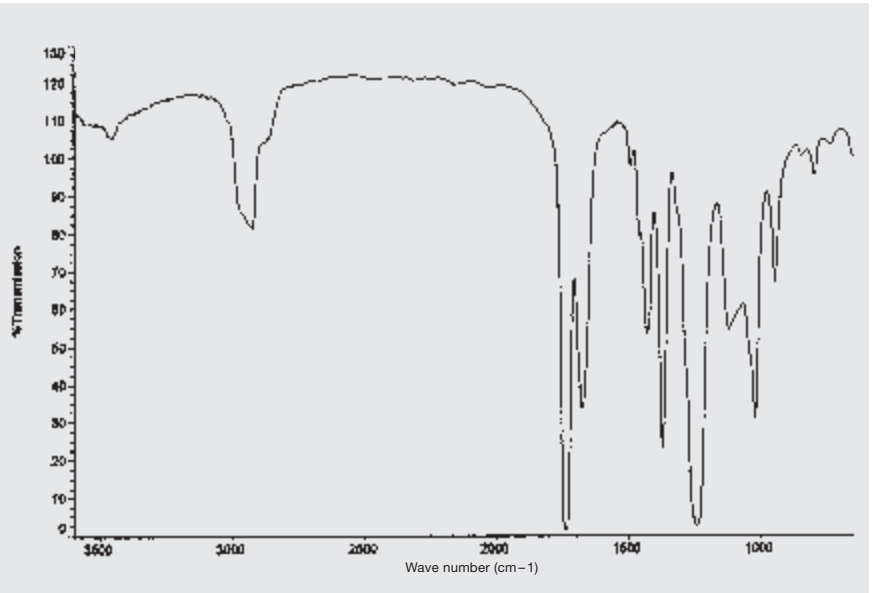

Fig. 5.6: Typical infrared spectrum of Kollidon® SR in KBr

5.3.2 Determination of free vinyl acetate

The content of the free vinyl acetate monomer in Kollidon® SR is determined by the following HPLC method:

Principle:

The sample is dissolved and separated by liquid reversed phase chromatography. The interfering polymeric components of the matrix are removed by a guard column and switching the columns. A UV detector operating at 205 nm and a calibration with an external standard are used to determine the level of vinyl acetate. The detection limit of this method is 20 ppm.

Sample preparation:

Weigh approx. 150 mg of Kollidon® SR accurately to 0.01 mg, into a 25-ml volumetric flask, dissolve in 10 ml of acetonitrile. Then make up the mark with the same solvent and shake for 30 minutes. Use aliquots of this solution for the HPLC analysis.

Preparation of the calibration solutions:

Weigh 40 – 50 mg of vinyl acetate, accurately to 0.01 mg, into a 50-ml volumetric flask and dissolve in about 20 ml of eluent. Then make up to the mark with eluent.
Prepare a series of dilutions from this stock solution to cover the expected range of vinyl acetate content in the sample of Kollidon® SR.

Table 5.3: Chromatographic conditions

Guard column:	25 x 4 mm cartridge packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Separation column:	250 x 4 mm steel column packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Eluent (mobile phase):	Water/acetonitrile 92 + 8 (% w/w)
Flow rate:	About 1.2 ml/min
Sample volume:	About 30 µl
Detection wavelength:	205 nm
Pressure:	About 200 bar
Column temperature:	40 °C
Retention time:	12 – 14 min

Column switching:

The analysis is started with the guard column and separation column in series. After about 1.2 minutes, the valves, controlled by the detector programme, switch over such that the eluent flows past the guard column, direct to the separation column. The columns are switched when the components to be determined, but not the interfering polymer, have already reached the separation column. Simultaneously, the guard column is washed out in the reverse direction by a second pump to remove the unwanted polymer components.

After about 18 minutes, the valves are reset to the starting position for the next analysis.
Fig. 5.7 shows a typical chromatogramm obtained under these conditions.

Calibration factor:

$$F = \frac{A_{ST}}{W_{St}}$$

A_{St} = calibration substance peak area [mV · s]
W_{St} = weight of calibration substance per 100 ml [mg/100 ml]

Calculation of vinyl acetate in the sample:

The content of the sample is calculated with the aid of an external standard:

$$\text{vinyl acetate (ppm)} = \frac{A \cdot 10^6}{F \cdot W_{Sa}}$$

A = peak area of vinyl acetate in the sample [mV · s]
W_{Sa} = sample weight [mg/100 ml]

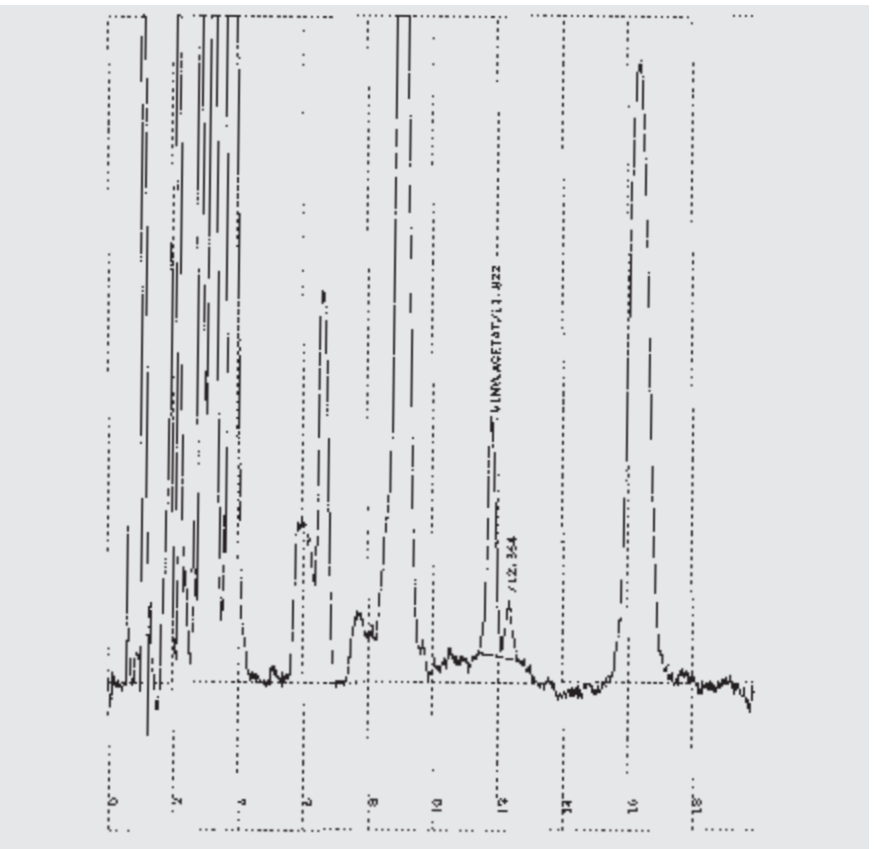

Fig. 5.7: Typical chromatogram of vinyl acetate in Kollidon® SR

Linearity:

The calibration curves were plotted from 5 points covering a concentration range of 0–1.0 µg/ml to check their linearity. A linear calibration curve was obtained.

5.3.3 Determination of acetic acid

The content of the residual solvent acetic acid in Kollidon® SR is determined by HPLC using acetic acid as external standard.
The detailed method is described in Section 4.3.2.6.

5.3.4 Determination of polyvinyl acetate

The polyvinyl acetate component of Kollidon® SR is determined by means of the saponification value which is measured according to the Ph.Eur. method 2.5.6 on 1.5 g of Kollidon® SR. The saponification value usually is 489 – 554. The content of polyvinyl acetate is calculated by the following formula:

Polyvinyl acetate in Kollidon® SR (%) = Saponification value x 0.1534

5.3.5 Determination of povidone

The povidone part of Kollidon® SR is determined by means of the nitrogen content measured according to the Ph.Eur. monograph “Povidone” (see section 2.3.3.6) in 1.0 g of Kollidon® SR. The nitrogen content usually is 2.3 – 2.6 %.

The content of povidone is calculated by the following formula:

$$\text{Povidone in Kollidon® SR (\%)} = \frac{\text{Nitrogen content (\%)}}{0.126}$$

5.4 Applications of Kollidon® SR

5.4.1 General notes

Kollidon® SR can be used for the production of the sustained release matrix preparations of tablets, pellets and granules.

The recommended technology for the production of sustained release matrix tablets based on Kollidon® SR is the direct compression. But also other technologies are possible to obtain such dosage form:
– Direct compression,
– Roller compaction,
– Melt extrusion,
– Wet granulation.
In the case of the wet granulation Kollidon® SR should be added to the extragranular phase.

Pellets and granules with Kollidon® SR can be produced by roller compaction or melt extrusion or also as mini-tablets by direct compression.

The excellent flowability and compressibility of Kollidon® SR are the main factors which makes this excipient particulary suitable for the manufacture of sustained release matrix tablets obtained by direct compression [647–649].

The required content of Kollidon® SR in the tablets, pellets or granules depends mainly on the particle size and the solubility of the active ingredient. The finer the particles the faster is the dissolution and the higher is the needed amount of Kollidon® SR. Table 5.4 gives an information about the influence of the solublity of the active ingredient on the needed amounts of Kollidon® SR to obtain a sustained release during 12–24 hours.

Table 5.4: Usual amounts of Kollidon® SR in sustained release tablets

Solubility of the active ingredient	Kollidon® SR in the tablet
Very slightly soluble to practically insoluble	15–25 %
Sparingly soluble to slightly soluble	25–40 %
Soluble to freely soluble	40–55 %

The sustained release characteristics can be modified by varying the Kollidon® SR content in the formulation. Fig. 5.8 shows the influence of the amount of Kollidon® SR on the release of caffeine as a example of a soluble active ingredient.

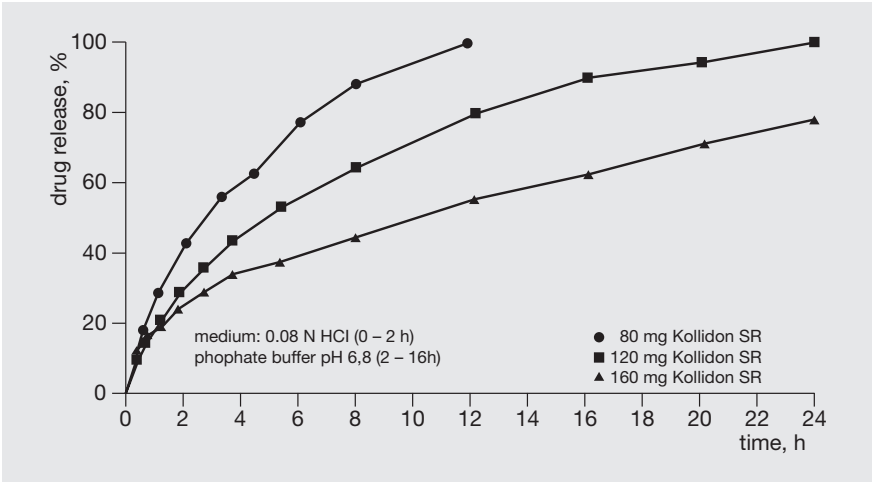

Fig. 5.8: Influence of the amount of Kollidon® SR on the release of caffeine sustained release tablets (160 mg caffeine)

In the case of slightly soluble or practically insoluble active ingredients the release can be accelerated not only by reducing the content of Kollidon® SR but also by the addition of hydrophilic substances like lactose monohydrate, granulated lactose monohydrate (Ludipress® LCE), Kollidon® 30 or even Kollidon® CL-M which act as pore formers.

An outstanding and important property of sustained release matrix tablets based on Kollidon® SR is their independency of the release from pH (Fig. 5.9), ionic strength (Fig. 5.9), usual compression force (Fig. 5.10) and tablet hardness (Table 5.6 and Fig. 5.10).

Table 5.5 gives an overview of possible influences on the release of matrix tablets based on Kollidon® SR. Only the storage and packaging conditions of the drug could modify the release of the active ingredient. Therefore it is recommended to store the matrix tablets containing Kollidon® SR at temperatures below 30 °C and in tightly closed containers to avoid the uptake of humidity which could modify the release profile of formulations containing a higher percentage of Kollidon® SR (see also Section 5.2.2.6).

Table 5.5: Possible influences on the release of matrix tablets

Parameter	Influence on release in the case of Kollidon® SR
pH of the dissolution medium	–
Ionic strength of the dissolution medium	–
Compression force	–
Tablet hardness	–
Humidity adsorption during storage of the drug	+
Temperatures over 35 °C during storage of the drug	+

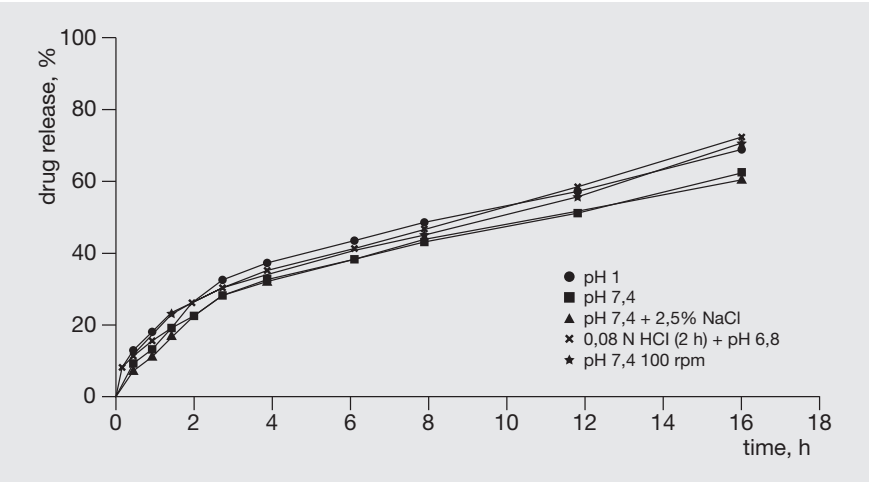

Fig. 5.9: Influence of the pH and the ionic strength of the dissolution medium on the release of caffeine matrix tablets (Caffeine + Kollidon® SR 1+1)

5.4.2 Matrix former for direct compression of sustained release tablets

For the production of sustained release tablets with Kollidon® SR as matrix the direct compression technology is recommended. This makes it possible to apply simple formulations and easy manufacture processes as can be seen in the examples mentioned in this Section.

In Tables 5.6 to 5.8 three typical examples of formulations with soluble and practically insoluble active ingredients are given in form of sustained release matrix tablets. Further formulations can be found in the "Generic Drug Formulations" [615].

The formulation examples of propranolol and theophylline (Tables 5.6 and 5.8) illustrate the high tablet hardness of 170 N reached with a low compression force of about 10 kN. If a high compression force was applied extremely hard tablets with more than 200 N were obtained without any change of the release of the active ingredient propranolol-HCl (Table 5.6 and Fig. 5.10).

Table 5.6: Propranolol-HCl sustained release matrix tablets (160 mg)

Formulation:

Propranolol-HCl (Powder 80, BASF)	160.0 mg
Kollidon® SR	160.0 mg
Aerosil® 200 (Degussa)	3.4 mg
Magnesium stearate	1.6 mg

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a mixer and then pressed to tablets on a rotary press with three different compression forces.

Tablets properties:

Diameter:	10 mm
Weight:	330 mg
Compression force:	10 kN / 18 kN / 26 kN
Hardness:	170 N / 235 N / 250 N
Friability:	0.1 %
Release of propranolol-HCl:	See Fig. 5.10

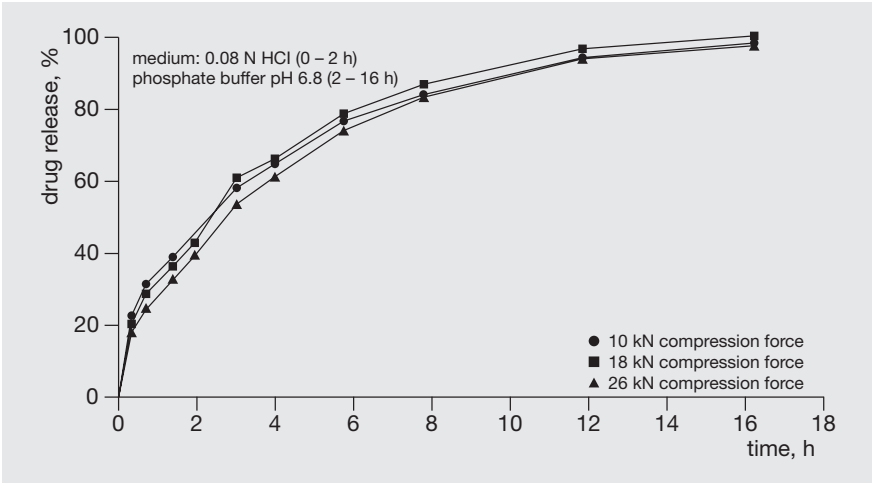

Fig. 5.10: Influence of the compression force on the release of propranolol-HCl sustained release tablets

In the formulation of Table 5.7 it was found that the particle size of the active ingredient has an strong influence on the release of the active ingredient. If finer particles of diclofenac sodium from an other supplier were used the release was much faster.

Table 5.7: Diclofenac sodium sustained release matrix tablets (100 mg)

Formulation:	
Diclofenac sodium (Irotec)	100 mg
Kollidon® SR	100 mg
Aerosil® 200 (Degussa)	3.4 mg
Magnesium stearate	3.4 mg

All ingredients are mixed, passed through a 0.8 mm sieve and pressed to tablets with a medium compression force on a rotary press.

Tablet properties:	
Diameter:	8 mm
Weight:	206 mg
Hardness:	195 N
Friability:	< 0.1 %
Release of diclofenac:	See Fig. 5.11

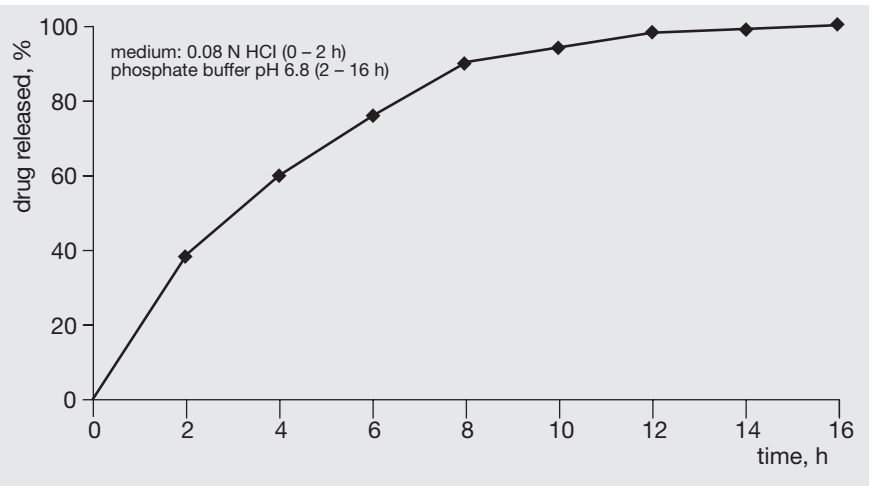

Fig. 5.11: Dissolution of diclofenac sodium sustained release matrix tablets

In the formulation of sustained release tablets of theophylline shown in Table 5.8 a relatively high amount of the pore former Ludipress® LCE is needed to adjust the release of this insoluble active ingredient to the requested profile.

Table 5.8: Theophylline sustained release matrix tablets (500 mg)

Formulation:

Theophylline gran. (BASF)	500 mg
Kollidon® SR	200 mg
Ludipress® LCE	225 mg
Magnesium stearate	3 mg

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a mixer and then pressed on a rotary press with the compression force of about 11 kN.

Tablet properties:

Diameter:	19.0 x 8.5 mm (football shape)
Weight:	928 mg
Hardness:	172 N
Friability:	< 0.1 %
Release of theophylline:	See Fig. 5.12

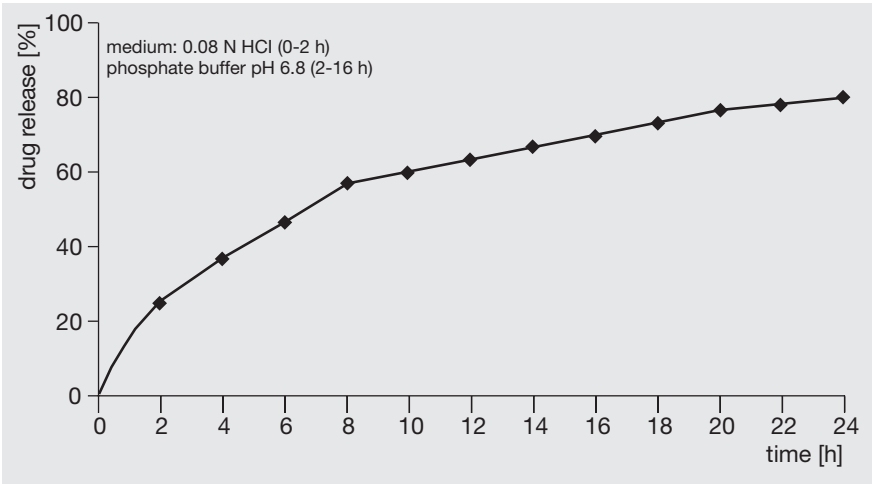

Fig. 5.12: Dissolution of theophylline sustained release tablets

5.4.3 Matrix former for the wet granulation of sustained release matrix tablets

If the wet granulation technology would be applied Kollidon® SR should be put in the extragranular phase by addition after the granulation to avoid the wetting of this spray dried polymer mixture. An example of this application is shown in the formulation of metoprolol tartrate controlled release matrix tablets given in Table 5.9. To increase the sustained release effect of this formulation the amount of Kollicoat® SR 30D should be even higher.

Table 5.9: Metoprolol controlled release matrix tablets obtained by wet granulation (200 mg)

Formulation:

I	Metoprolol tartrate (Moehs, Spain)	200.0 mg
II	Kollicoat® SR 30D	20.0 mg
III	Kollidon® SR	250.0 mg
	Magnesium stearate	2.5 mg

Granulate substance I in a top spray fluidized bed with dispersion II (Inlet air temperature 50 °C, outlet air temperature about 26 °C, nozzle 1.2 mm), mix with III and press to tablets with low compression force (9 kN) on a rotary press.

Tablet properties:

Diameter:	12 mm
Weight:	459 mg
Form:	biplanar
Hardness:	220 N
Friability:	< 0.1 %
Release of metoprolol tartrate	See Fig. 5.13

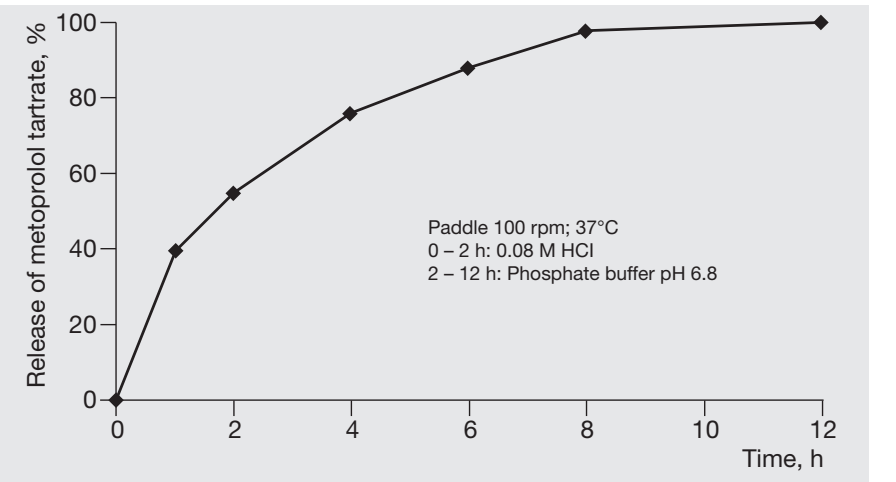

Fig. 5.13: Dissolution of metoprolol tartrate controlled release tablets

5.4.4 Matrix former for melt extrusion of sustained release tablets or pellets

Polyvinyl acetate is described in the literature as a matrix former in theophylline sustained release tablets obtained by hot-melt extrusion [646]. In a similar way Kollidon® SR can be applied for the production of tablets and pellets using its excellent flowability. In this case the pulverization of polyvinyl acetate by cryogenic grinding can be avoided and the mixture of the active ingredient with Kollidon® SR and other excipients are applied directly to the melt extruder.

2004
JAPANESE PHARMACEUTICAL
British Pharmacopoeia 2007
VOLUME IV
2007
USP
NF
USP 30
NF 25
U.S. Pharmacop
National Formulary
5.8
Supplement
European Pharmacopoeia
5.0
5th Edition
Volume 2
European
Pharmacopoeia
POVIDONE
Povidonum

6 Registration in drugs and approval in food

6.1 Pharmaceutical products

6.1.1 General

An auxiliary such as povidone or crospovidone cannot be registered as such by the authorities for use in pharmaceutical products. In Europe, Japan or America, it is always only possible to register a finished drug. There is no general positive or negative list of auxiliaries used in pharmaceuticals in Europe. It is only possible to state in which countries pharmaceuticals that contain povidone, copovidone, crospovidone and/or polyvinylacetate are registered or in which pharmacopoeia a monograph of these excipients is included.

6.1.2 Pharmacopoeias

In practice, a pharmaceutical preparation that contains povidone, copovidone and/or crospovidone can only be registered if these auxiliaries meet the analytical requirements of the monographs in the pharmacopoeias that are regarded as mandatory in the countries concerned. The Kollidon® grades meet these requirements and are produced according to the current cGMP regulations.

Table 6.1: Kollidon® grades covered by pharmacopoeias

Product	Ph.Eur.	USP-NF	J.P./J.P.E.
Kollidon® 12 PF	+	+	n. a.
Kollidon® 17 PF	+	+	+
Kollidon® 25	+	+	+
Kollidon® 30	+	+	+
Kollidon® 90 F	+	+	+
Kollidon® CL	+	+	+
Kollidon® CL-F	+	+	+
Kollidon® CL-SF	+	+	+
Kollidon® CL-M	+	+	+
Kollidon® VA 64	+	+	+
Kollidon® VA 64 Fine	+	+	+

n. a. = Monograph not available

The monograph “Povidone” to be applied for the soluble Kollidon® grades was world wide harmonized.

Mixtures of excipients usually are not included in a pharmacopoeia as monographs. Therefore there is no monograph of Kollidon® SR. But the components used for the production of Kollidon® SR meet the requirements of the corresponding pharmacopoeial monograph:
The polyvinyl acetate suspension Kollicoat® SR 30D which is mixed with Kollidon® 30 and the two other components for this production correspond all to the respective monograph in Ph.Eur. or USP-NF (e. g. “Poly(vinyl) acetate Dispersion 30 Per Pent” of the supplement 5.8 of Ph.Eur.).

6.1.3 Registrations in drugs in individual countries

Pharmaceutical products that contain Kollidon® have been registered in almost all countries for parenteral, oral and topical administration (Table 6.2).

Table 6.2: Countries in which Kollidon®-containing drugs are registered

Product	Country			
	Europe	USA	Japan	Latin America
Kollidon® 12 PF	+	+	+	+
Kollidon® 17 PF	+	+	+	+
Kollidon® 25	+	+	+	+
Kollidon® 30	+	+	+	+
Kollidon® 90 F	+	+	+	+
Kollidon® CL grades	+	+	+	+
Kollidon® VA 64	+	+	+	+

For parenteral use of povidone the following limitations apply to the information given in Table 6.2:

Since it was reported that medium-molecular povidone (K 30) was accumulated in the organism after parenteral administration the use of povidone in finished parenteral preparations was regulated in Germany by the Federal Health Ministry [214]:
– The K-value must be smaller than 18.
– The packaging and the package insert of the finished declaration must declare the quantity used.
– Attention must be drawn to the possibility of accumulation in the organism after frequent administration.
– For intramuscular administration a maximum of 50 mg of povidone is permitted per individual dose.

Similar regulations also apply in other european countries.

6.1.4 Drug Master File (DMF)

Separate Drug Master Files for Kollidon® SR and Kollidon® VA 64 (No. 6745) have been deposited with the Food and Drug Administration (FDA) in the USA for registration purposes. A Drug Master File for the other Kollidon® grades has not been required up to now and is not likely to be required for pharmacopoeial excipients.

6.2 Food

6.2.1 General

While there are no approval lists for pharmaceutical excipients, various countries have positive lists regulating the use of auxiliaries in food. These lists include soluble and insoluble polyvinylpyrrolidone, though in some cases only for certain applications.

6.2.2 FAO/WHO ADI value

In 1987 the World Health Organization (WHO + FAO) specified an Accepted Daily Intake (ADI) value for soluble polyvinylpyrrolidone in food of 0–50 mg/kg body weight [372]. For crospovidone the ADI value is "not specified" and therefore no limit is given for the application in foods [215].

6.2.3 Approval of povidone for use in food

In the European Union soluble polyvinylpyrrolidone having a nominal K-value of 25, 30, or 90 has got the E-number E 1201 for the use in dietary food supplements in (coated) tablet form and in sweetener preparations.

Povidone with an average molecular weight of 40 000 (e. g. Kollidon® 30) is approved for use in the USA in the manufacture of the foods listed in Table 6.3, subject to certain restrictions [487].

Table 6.3: Approval of povidone K 30 for use in food in the USA

Food	Purpose	Conditions of use
Wine	Clarifying agent	Residue < 60 ppm
Vinegar	Clarifying agent	Residue < 40 ppm
Vitamin, mineral and flavouring concentrates in tablet form	Tabletting auxiliary	Acc. to cGMP rules
Sweetener tablets	Tabletting auxiliary	Acc. to cGMP rules
Sweetener, vitamin and mineral concentrates in liquid form	Stabilizer, dispersant, thickener	Acc. to cGMP rules

In the USA, povidone with a number average molecular weight of 360 000 (e. g. Kollidon® 90 F) is permitted for use as a clarifying agent for beer. The amount remaining in the beer must not exceed 10 ppm.

6.2.4 Approval of crospovidone for use in food

In the European Union insoluble polyvinylpyrrolidone ("polyvinylpolypyrrolidone") has got the E-number E 1202 for the use in dietary food supplements in (coated) tablet form and in sweetener preparations.

Crospovidone is usually approved as "polyvinylpolypyrrolidone" or "PVPP" – in the USA for clarifying beverages and vinegar [488] and in the countries listed in Table 6.4 for stabilizing and clarifying beer and wine.

Table 6.4: Approval status of insoluble polyvinylpyrrolidone for the stabilization and clarification of wine and beer

Country	Beer	Wine
Argentina		x
Australia	x	x
Austria	x	–
Belgium	x	x
Brazil	x	x
Canada	x	–
Czechia	x	x
Denmark	x	x
Finland	x	–
France	x	x
Germany	x	x
Great Britain	x	x
Greece	x	x
Hungary	x	x
Italy	x	x
Netherlands	x	x
New Zealand	x	x
Norway	x	–
Philippines	x	x
Portugal		x
South Africa	x	–
South Korea	x	x
Spain	x	x
Sweden	x	–
Switzerland	x	x
USA	x	x


Die Tablette
PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone)
LEWIS
Lexikon der Pharma-Technologie
Polyvinylpyrrolidone Excipients for Pharmaceuticals
Kollicoat® Grades
Functional Polymers for the Pharmaceutical Industry
Fiedler
Encyclopedia of Excipients
6th Edition
Formulations
2nd edition
Generic Drug Formulations
European Pharmacopoeia
5th Edition
volume 2
5.0

7 Toxicological data

7.1 Soluble Kollidon® grades

There are a large number of publications on the good tolerance of polyvinylpyrrolidone [127–129, 131, 133–134, 201, 225]. A complete list with assessments is to be found in "A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone" by Robinson, Sullivan, Borzelleca and Schwartz, published in 1990 [225].

Because of the good tolerance of povidone, its Accepted Daily Intake (ADI) was adjusted to 0–50 mg/kg body weight by the FAO/WHO Joint Expert Committee for Food Additives (JECFA) [372].

In 1983, the JECFA awarded crospovidone an ADI status of "not specified", as on the basis of the available chemical, biochemical, toxicological and other data, the entire daily intake of the substance in the quantities to be expected did not represent any risk to health in the opinion of the JECFA. It therefore seemed unnecessary to set a numerical value for the ADI [215].

The following toxicological and biochemical studies have been carried out with the individual grades of soluble Kollidon®:

Kollidon® 12 PF
– Acute intravenous toxicity, mouse
– Four-week toxicity, intravenous, rat
– Prenatal intravenous toxicity, rabbit
– Kinetics (excretion), intravenous, rat
– Kinetics (determination of proportion absorbed), intraduodenal, rat
– Distribution and excretion, intramuscular, rat

There is also a study on renal elimination after intravenous administration in rats [97].

Kollidon® 17 PF
– Acute, oral toxicity, rat
– Acute, intraperitoneal toxicity, mouse
– Acute, intravenous toxicity, rat
– Primary skin irritation
– Primary mucous membrane irritation
– Kinetics (excretion), intravenous, rat
– Distribution and excretion, intramuscular, rat

There is also a study on renal elimination after intravenous administration in rats [97].

Kollidon® 25
– Acute, oral toxicity, rat
– Acute, intravenous toxicity, rat
– Primary skin irritation
– Primary mucous membrane irritation
– 2-year feeding study, rat
– Prenatal toxicity, oral, rat
– Kinetics (determination of proportions absorbed), intraduodenal, rat

Kollidon® 30
– Acute, oral toxicity, rat
– Acute, intravenous toxicity, mouse
– Primary skin irritation
– Primary mucous membrane irritation
– Epicutaneous test, man
– Test for mutagenic effects (dominant lethal test), intraperitoneal, mouse
– Cytogenetic studies (bone marrow chromosome analysis), intraperitoneal, Chinese hamster
– 2-year feeding study, rat
– 2-year feeding study, dog

Kollidon® 90 F
– Acute, oral toxicity, rat
– Primary skin irritation
– Primary mucous membrane irritation
– 4-week feeding study, dog
– 4-week feeding study, rat
– 90-day feeding study, rat
– 90-day feeding study, dog
– Metabolic study, rat
– 2-year feeding study, rat
– Prenatal, oral toxicity, rat

The following summary of toxicological properties is taken from the book mentioned at the beginning of this Section [225]:

Toxicology and Safety

An extensive body of toxicological data in animals supports the biological inertness of PVP. The acute, subchronic, and chronic toxicity of orally administered PVP is extremely low, with the only effect observed being diarrhea at high doses due to the osmotic action of PVP acting as a bulk purgative. Occasional observations of minimal absorption with storage in mesenteric lymph nodes seem to be of no toxicological importance. PVP is neither a sensitizer nor an irritant. There are no reported adverse effects following oral administration in humans. The currently permitted FAO/WHO ADI of 0–50 mg/kg body weight for food uses provides an adequate margin of safety. There would appear to be no reason to restrict its oral or topical pharmaceutical use or topical cosmetic use in any way. There have been no reports of adverse effects following its use intravenously as a plasma expander, even after the administration of very large amounts. The only toxicological problems have involved the repeated injection of large amounts of the higher molecular weight material into poorly perfused sites such as subcutaneously and into the breast. If the use of PVP in injectables for repeated use is restricted to PVP with a molecular weight less than K-18 in limited amounts (e. g. 50 mg/i. m. dose) and the injection sites are varied, and intramuscular or intravenous routes are used, then these problems should not occur. The repeated use of PVP in depot preparations, which could lead to excessive storage, is not to be recommended.

7.2 Kollidon® CL grades

The following toxicological and biochemical studies have been carried out with insoluble Kollidon® CL grades:

Kollidon® CL
– Acute, oral toxicity, rat
– Acute, oral toxicity, mouse
– Acute, oral toxicity, dog
– Acute, intraperitoneal toxicity, rat
– Acute, intraperitoneal toxicity, mouse
– Primary skin irritation
– Primary mucous membrane irritation
– 4-week feeding study, rat
– 4-week toxicity, oral, dog
– 6-month toxicity, oral, dog
– 90-day toxicity, oral, rat
– 90-day toxicity, oral, dog
– Pre, peri and postnatal toxicity, oral, rat
– Kinetics (excretion), oral, rat

7.3 Kollidon® VA 64 grades

Kollidon® VA 64 has no acute toxicity and does not irritate the skin or mucous membranes. Prolonged administration to rats and dogs was tolerated without recognizable undesirable side effects.

A prenatal toxicity test on rats gave no indication of adverse effects.

The following studies have been carried out:

– Acute, oral toxicity, rat
– Acute, oral toxicity, mouse
– Acute, oral toxicity, dog
– Acute, intraperitoneal toxicity, mouse
– 4-week feeding study, dog
– 13-week feeding study, dog
– 3-month feeding study, rat
– Prenatal, oral toxicity, rat
– Kinetics (determination of proportions absorbed), intraduodenal, rat

The results or the complete reports on the above studies are available on request.

Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve those to whom we supply our products from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.


Pharmaceutical Technology of BASF Excipients
BASF
Kollicoat® Grades
Kollidon® VA 64
Kollidon® VA 64 Fine
Kollidon® CL
Kollidon® CL-F
Kollidon® CL-SF
Kollidon® CL-M
Insoluble Kollidon®-grades
Soluble Kollidon® grades
Kollicoat® IR White
Volker Bühler
Polyvinylpyrrolidone Excipients for Pharmaceuticals
Kollicoat®

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