Technical Information

Kolliphor® RH 40

Macrogolglycerol Hydroxystearate (Ph. Eur.)
Polyoxyl 40 Hydrogenated Castor Oil (USP/NF)

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1. Introduction

Kolliphor® RH 40 is a solubilizer, emulsifier and primary surfactant used in a multitude of pharmaceutical formulations.

2. Technical properties

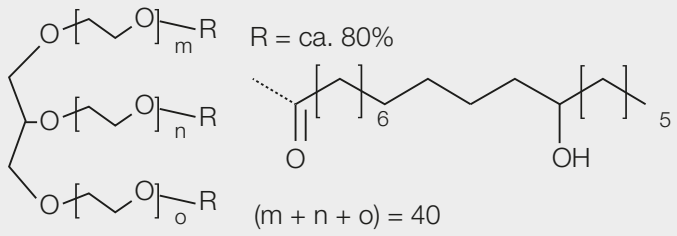
Description

Structural formula

Kolliphor® RH 40 is a nonionic solubilizer and emulsifying agent obtained by reacting 1 mole of hydrogenated castor oil with 40 moles of ethylene oxide.

The main constituent of Kolliphor® RH 40 is glycerol polyethylene glycol hydroxystearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate.

A diagram of the molecular formula is listed below:



Kolliphor® RH 40 is a white to yellowish paste at 20 °C. The HLB value lies between 14 and 16.

Particular features are that it has very little odor and in aqueous solutions is almost tasteless.

Composition

The rough composition of the product is as follows:

Compound	Content
Glycerol - Mono-(PEG - 12 - Hydroxystearate)*	approx. 20%
Glycerol - Di-(PEG - 12 - Hydroxystearate)*	approx. 12%
Glycerol -Tri-(PEG - 12 - Hydroxystearate)	approx. 6%
PEG - 12 - Hydroxystearate	approx. 7%
PEG	approx. 18%
Glycerol - PEG	approx. 35%

CAS number

61788-85-0

Solubility

Kolliphor® RH 40 forms clear solutions in water, ethanol, 2-propanol, n-propanol, ethyl acetate, chloroform, carbon tetrachloride, toluene and xylene.

Solutions become cloudy as the temperature increases.

Kolliphor® RH 40 can be mixed with all other Kolliphor® products. At elevated temperatures it forms clear mixtures with fatty acids and fatty alcohols.

Critical micelle concentration

The critical micelle concentration (CMC) is 0.03% w/w @ 37°C.

Micelles are typically in the range of 10 – 15 nm in diameter (dynamic light scattering) and slightly larger (up to 25 nm) when loaded with API. There is a sharp increase in micelle size at temperatures greater than 60.

Stability

Pure Kolliphor® RH 40 is chemically very stable. Prolonged exposure to elevated temperatures can cause physical separation into a liquid and a solid phase on cooling but the product can be restored to its original form by homogenization. Kolliphor® RH 40 is stable in aqueous alcohol and purely aqueous solutions.

However, it must be noted that strong bases or acids should not be added, as otherwise the ester components may be saponified.

Aqueous Kolliphor® RH 40 solutions can be sterilized by heating to 120 °C. Allowance must be made for the fact that this can cause a slight decrease in the pH value. The phases may also separate during sterilization, but this can be remedied by agitating the solution, particularly while it is still warm.

Preservatives common to the pharmaceuticals industry may be added to the aqueous solutions. The requisite concentrations should be determined in tests.

Kolliphor® RH 40 is largely insensitive to water hardness.

Dispensing

It is recommended that Kolliphor® RH 40 be heated to between 50 and 60 °C and lightly agitated prior to use. Kolliphor® RH 40 exhibits complex melting behavior, and phase separation is known to occur depending on the shipping and storage conditions. This is easily overcome via melting and light mixing.

In order to ensure product stability during reheating, heat cycling was performed on Kolliphor® RH 40. Commercial material was heated to 60 °C and held for 24 hours, then cooled and held at room temperature for a further 24 hours; this was repeated 20 times in total. The results of this stress test on the stability indicating parameters of Kolliphor® RH 40 are shown below, no significant deviation was noted.

Stability Indicating Parameter	Spec	Release	Test 1	Test 2	Test 3
Congealing temperature [°C]	16 to 26 °C	24	25	25	25
Acid value [mg KOH/g]	≤ 0.8 mg KOH/g	0.1	0.3	0.3	0.3
Hydroxylvalue [mg KOH/g]	60 to 75 mg KOH/g	71	72	72	72
Iodine value [g I_2/100 g]	≤ 1.0 g I/100g	0.3	0.3	0.3	0.3
Saponication value [mg KOH/g]	50 to 60 mg KOH/g	54	54	54	54
Water [g/ 100g]	N.A.	1.00	0.80	0.82	0.80
Sulfated ash [g/100g]	≤ 0.25g/100g		0.18	0.19	0.18

3. Handling

Please refer to the individual Material Safety Data sheet (MSDS) for instructions on safe and proper handling and disposal.

4. Example apllication

Solubilization

Kolliphor® RH 40 is the industry standard pharmaceutical surfactant used primarily as a solubilizer and emulsifier.

Most notably the product is used in the following types of formulations (common concentration show):

- Softgel Capsules – 400 mg per dose
- Opthalmics 0.5 % w/w
- Oral Solutions 0.5 – 45%
- Tablets – 50 mg
- Creams – 1% w/w

In softgel applications, Kolliphor® RH 40 is soluble in PEG 400 (Kollisolv® PEG 400) up to 20% w/w, up to 30% w/w in Medium Chain Triglycerides (Kollisolv® MCT 70), 20% w/w in Propylene Glycol (Kollisolv® PG)

Kolliphor® RH 40 is fully miscible in aqueous formulations.

Solubilization and bioavailability enhancement

Kolliphor® RH 40 may be use very effectively in Lipid-Based Drug Delivery Systems, for example, Self-Emulsifying Drug Delivery Systems (SEDDS). In order to effectively make such formulations, high concentrations of primary surfactant, secondary surfactant, oil and aqueous phase are mixed. The resultant formulations are clear, low-viscosity, isotropic and suitable for encapsulation into softgels, hard shell capsules and other liquid formulations. Once the formulations are released inside the GIT, they emulsify into nanoscale (15 – 80 nm) droplets, which are further digested and absorbed, significantly increasing bioavailability.

In Vivo, it has been shown that Kolliphor® RH 40 digests slowly and can retain drug in solution (micelles) for a long period of time allowing for absorption to take place.

Note: Water or Ethanol is used as an aqueous phase – this is to account for atmospheric water that is absorbed from the environment or during encapsulation, thus maintaining stability and integrity of the system.

Example SEDDS Formulation 1 (High solubility, slow digestion, small droplets).

This example shows high concentrations of Kolliphor® RH 40, this will result in small droplet sizes upon self-emulsification (20 nm) and slow digestion. Ethanol may be used in place of water to increase drug content.

Compound	Content
Kolliphor® RH 40	68 %
Kollisolv® MCT 70	10 %
Glyceryl Monooleate	12 %
Water / Ethanol	10 %

Example SEDDS Formulation 2 (Faster digestion, larger droplets).

This example shows higher oil concentrations, which will result in faster digestion and larger oil droplets (40 nm). Ethanol may be used in place of water to increase drug content.

Compound	Content
Kolliphor® RH 40	42.5 %
Kollisolv® MCT 70	40.0 %
Glyceryl Monooleate	7.5 %
Water / Ethanol	10.0 %

Miscellaneous solubilizer applications

Clear, aqueous solutions of hydrophobic substances other than vitamins can be obtained with Kolliphor® RH 40. Examples are essential oils and certain drugs for oral and topical application. A feature of the solutions thus obtained is their good stability. The following substances serve as examples:

Hexachlorocyclohexane	Miconazole
Hexeditine	Gramicidin
Levomepromazine	Eucalyptol
Thiopental	Azulene
Benzocaine	Oil of anise
Clotrimazole	Oil of sage
Diazepam	

Kolliphor® RH 40 shows little tendency to foaming, which is particularly important for solutions in aqueous ethanol.

Use as emulsifier

Kolliphor® RH 40 is also very suitable as an emulsifying agent. It will emulsify a wide range of hydrophobic substances, e. g. fatty acids, fatty alcohols and drugs.

Phase	Ingredients	Description	Mass (Weight%)
A	Kollicream® OA	Emollient	20.00
	Kolliwax® GMS II	Consistency factor, co-emulsifier	2.08
	Kolliphor® RH 40	Emulsifier	2.92
B	Deionized Water	Continuous phase	73.80
	Carbopol Ultrez 21	Viscogen	0.20
C	Triethanolamine	Neutralizing Agent	Drops to pH = 7
D	Euxyl K 350	Preservative	1.00

5. Safety data sheet

Safety data sheets are available on request and are sent with every consignment.

6. Retest date and storage conditions

Please refer to Quality & Regulatory Product Information (QRPI).

7. Specification

For current specification, please speak to your local BASF sales or technical representative.

8. Regulatory status

Please refer to Quality & Regulatory Product Information (QRPI).

9. Toxicological data

For information on toxicological issues please refer to the tox abstract which can be supplied on request.

More/detailed toxicological information for Kolliphor® RH 40 is available on request under Secrecy Agreement.

10. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging	
30555082	Kolliphor® RH 40	50259811	0.5 kg	Plastic bottle
		50581348	60 kg	Steel drums

* BASF's commercial product number.

11. Publications

http://pharmaceutical.basf.com/en.html

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