Ludiflash® as Excipient for Paediatric Use

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Abstract Summary

Ludiflash® is a formulation for fast disintegrating solid oral dosage forms. The formulation consists of three compendial excipients: D-mannitol, crospovidone (Kollidon® CL-SF), and a polymer dispersion based on polyvinyl acetate (Kollicoat® SR 30 D). It is designed to disintegrate readily within a few seconds in the oral cavity with a pleasant mouthfeel. Ludiflash® formulated as orally disintegrating mini-tablet (ODMT), is especially suitable for the paediatric use and may be considered as innovative technology platform for paediatric formulations: Considering the recent development and current regulations on paediatrics and/or concept paper on the development of a quality guideline on pharmaceutical development and medicines for paediatric use, BASF decided to support its customers by creating a special safety report for Ludiflash®.

Introduction

The experimental design, preparation and methods for Ludiflash® formulated as orally disintegrating mini-tablet (ODMT) have been published by Ines Stoltenberg and Jörg Breitkreutz, Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany (7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Malta 2010: *Orally Disintegrating Mini-Tablets for Paediatric Use with the new Excipient Ludiflash®*).

Ludiflash® formulated as orally disintegrating mini-tablet (ODMT): Ludiflash® (BASF SE, composition see Table 1), sodium stearyl fumarate (Pruv®, JRS Pharma), magnesium stearate (Baerlocher GmbH).

Ingredients	Quantity [%]
Mannitol, Ph.Eur.	84.0–92.0 %
Kollidon® CL-SF, BASF SE (Crospovidone, Ph.Eur.)	4.0–6.0 %
Kollicoat® SR 30 D, BASF SE (Poly[vinylacetate] dispersion 30 per cent, Ph.Eur.)	3.5–6.0 %

Table 1: Ludiflash® formulation

All ingredients were blended in a Turbula blender (Bachofen AG) for 10 minutes and directly compressed into biconvex mini-tablets of 2 mm diameter using a rotary tablet press (Pressima MX-EU-B/D, IMA Kilian GmbH & Co KG) with one 19-tip mini-tableting tool (Ritter Pharmatechnik GmbH).

A compression force between 5 and 8 kN (approx. 80–130 MPa) should be applied to achieve ODMTs with sufficient crushing strength (above 8 N). Excellent SWT times of less than 4 seconds were obtained using 2–3.5 % sodium stearyl fumarate. Ludiflash® – ODMTs can be obtained with sizes as low as 1 mm diameter. Disintegration of such small ODMT can be realized within a second or less than 10 seconds, depending on size and formulation.

Ludiflash® formulated as orally disintegrating mini-tablet (ODMT), is especially suitable for the paediatric use and may be considered as innovative technology platform for paediatric formulations.

Considering the recent development and current regulations on paediatrics* BASF decided to support its customers by creating a special safety report for Ludiflash® [2].

* Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 and/or Concept paper on the development of a quality guideline on pharmaceutical development and medicines for paediatric use, EMEA/138931/2008

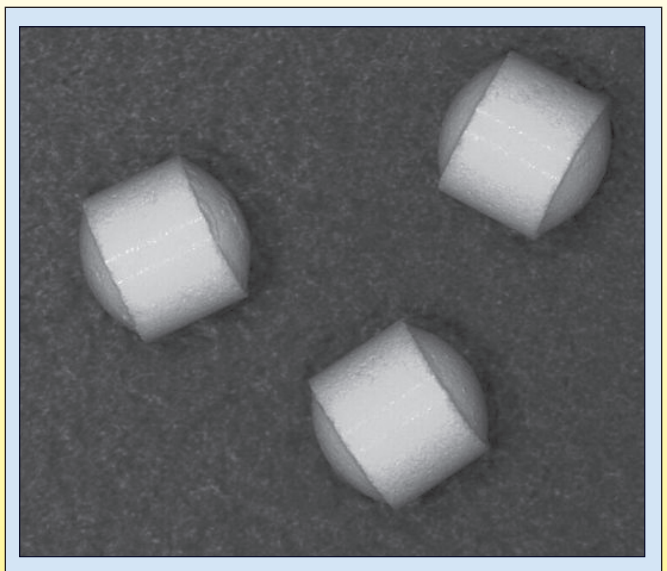

Figure 1: ODMTs made from Ludiflash® and 3 % sodium stearyl fumarate (2 mm diameter) (Ines Stoltenberg, Jörg Breitkreutz, Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany)

Regulatory Discussion

Many medicinal products are currently not available in formulations suitable for administration to the paediatric population.

Criteria for drug dosage forms appropriate for children [1]

1. sufficient bioavailability (despite children's particularities)
2. nontoxic excipients regarding age group and administration
3. palatable or acceptable organoleptic properties
4. acceptable dose uniformity
5. easy and safe administration
6. socio-cultural acceptability (no stigmatisation)
7. precise and clear product information
8. must be convenient to parents

Ludiflash® provides a solution for paediatric ODMTs with unique characteristics (i.e. very fast disintegration, direct compression and crushing strength of sizes as low as 1 mm diameter). The European Medicines Agency (EMA) considered orodispersible dosage forms to hold great promise for children as they are easy to administer, do not require additional water and, as long as dispersion is rapid, are difficult to spit out and could provide a range of dosages appropriate for use in younger children [3].

Mannitol representing the major component of Ludiflash® is used as an inactive ingredient in a number of orally administered drugs that were specifically approved for newborns, infants and children, e.g. SINGULAIR® chewable tablets or granules (Merck & Co. Inc., from 6 months onwards) containing montelukast sodium as active ingredient. Moreover, sufficient clinical experiences in the paediatric population are available after oral administration of hyperosmolar solutions of mannitol, for example in dialyzed children (e.g., a 20 % solution) for the acute treatment for fluid overload [4] or in paediatric patients (150 g mannitol/L at a median volume of 300 mL/patient before MRI) with clinical suspicion of inflammatory bowel disease [5]. Individual patients received single oral doses up to 75 g mannitol; diarrhea was observed most frequently in these patients [5].

Intravenous doses of mannitol are also of well-established clinical use in paediatric patients, e.g. M.V.I.® Paediatric for Infusion (ASTRA Pharmaceuticals), a daily multivitamin maintenance dosage, is approved for infants weighing less than 1 kg. Administration of mannitol via intermittent bolus doses ranging from 250–1000 g/kg has become a cornerstone in the treatment of paediatric patients with severe head injury and elevated intracranial pressure [6], [7] that is also recommended as first line of therapy after fluid restriction by a consensus statement from the American Diabetes Association and The European Society for Paediatric Endocrinology/Lawson Wilkins Paediatric Endocrine Society (ESPE/LWPES) [8].

Crospovidone is also used in drug products that are approved for paediatric use, e.g. as disintegrant in Viracept® tablets and oral powder (Agouron Pharmaceuticals) or Metoprolol Succinate extended-release tablets (AstraZeneca).

Moreover, polyvinyl acetate is used in a prescription drug product approved in USA for the treatment of children of 6 years or older.

Conclusion

Orally disintegrating mini-tablets are supposed to be perfectly suitable dosage forms for the treatment of young children and may be considered as a new technology platform in paediatrics. With ODTs like Ludiflash®, the criteria of the World Health Organization (WHO) such as the use of standard excipients and conventional techniques, are fully met [9].

A summary of the relevant safety data in the scientific literature and BASF's own safety data with focus on paediatric use have been compiled [2]. This safety data sheet is available upon request. Extensive safety and toxicological reports performed by BASF are available under a secrecy agreement.

References

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