Technical Information

Ludiflash®

Direct compression excipient for fast-disintegrating solid oral dosage forms.

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1. Introduction

Ludiflash® is a formulation for fast disintegrating solid oral dosage forms.
The formulation of co-processed ingredients consists of three compendial ingredients: A sugar alcohol, crospovidone and a polymer dispersion based on polyvinyl acetate. It is tailored to disintegrate readily on the tongue with a pleasant creamy mouth-feel without a chalky or sandy sensation.

Ludiflash® is suitable for direct compression manufacturing by simply blending the excipient with the active and a lubricant, and is thus applicable for a very cost efficient production pathway.

2. Technical properties

Composition

Ludiflash® consists of D-mannitol, crospovidone, polyvinyl acetate and small amounts of povidone. Polyvinyl acetate is incorporated into the system as Kollicoat® SR 30 D, a polyvinyl acetate dispersion stabilized with povidone.

The used D-mannitol fully complies to the monographs of the European Pharmacopeia, USP/NF and Japanese Pharmacopeia.

CAS numbers

D-Mannitol	69-65-8
Crospovidone (Kollidon® CL-SF)	9003-39-8
Polyvinyl acetate (Kollicoat® SR 30 D)	9003-20-7
Povidone (Kollidon® 30)	9003-39-8

Description

Ludiflash® is a white to off-white powder with good flowability. The angle of repose was determined to be ~38 °.

Sorption isotherm

The product has a very low hygroscopicity, driven by the specific character of D-mannitol.

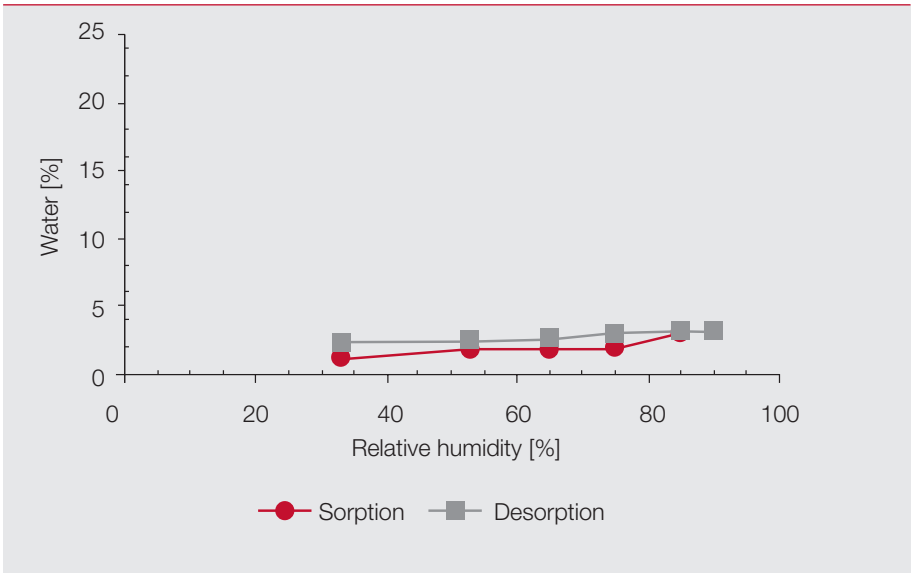

Figure 1: Sorption isotherm at 23 °C

Solubility

Due to the content of crospovidone and polyvinyl acetate, the product does not dissolve completely in water, nor is it entirely soluble in organic solvents.

Properties

The properties described in the following paragraph are considered to be typical values.

Particle size distribution (determined)	> 0.400 mm	max. 20%
	< 0.200 mm	max. 90%, min. 45%
	< 0.063 mm	max. 45%, min. 15%
Bulk density (DIN ISO 697, Apparatus from Coesfeld, no specification parameter)	0.42 – 0.58 g/ml	
Typically batches show a bulk density between	0.53 – 0.58 g/ml	
pH value (5% in water, partially dissolved)	5.5 – 6.5	

Notice: As the product contains D-mannitol it can have a mild laxative effect.

3. Application

General remarks

To achieve fast disintegrating solid oral dosage forms, it is important to have tablets with high porosity which allows water to penetrate very fast. The careful control of the compression force is thus very important. 50 MPa to 90 MPa tabletting pressure, which corresponds to 3 – 6 kN compression force for a 10 mm tablet are most suitable.

Furthermore the control of humidity throughout tablet manufacturing and the use of vapor resistant packaging materials for the finished tablets should be considered. The storage temperature for Ludiflash® and formulations with Ludiflash® should not exceed 25 °C, to avoid an undesired increase of disintegration times.

Recommendations for Lubricants

Detailed tests revealed magnesium stearate and sodium stearyl fumarate to be appropriate lubricants for fast disintegrating formulations based on Ludiflash®.

Recommendations for Taste Optimization

Tablets with optimum properties can be achieved when the following excipients are applied in the ranges given:

1. Sweeteners like aspartame in concentrations ranging from 0.3 to 0.7% or saccharine sodium in a concentration ranging from 0.05% to 0.1% were tested in various formulations and can be recommended.
2. To achieve an effervescent effect the combination of citric acid with sodium hydrogen carbonate can be formulated. Both compounds are applied in quantities of 0.5%.
3. To control the acidity of a tablet ascorbic acid or combinations of ascorbic acid and sodium ascorbate in concentrations, as well as citric acid can be used.
4. Vanilla flavor in a concentration of around 0.5% or L-Menthol in the range of 0.1% to 0.3% can be used with good tabletting results for aroma purposes.

Recommended API Loading

Possible drug loads depend very strongly on the properties of the API. Most APIs can easily be formulated in concentrations of up to 20%. Several APIs, like for example Acetaminophen, can be formulated at even higher concentrations of up to 60% and still disintegrate and dissolve very quickly.

Formulation 1

To demonstrate the basic properties of the excipient Ludiflash®, placebo tablets were manufactured and checked for their properties.

Ludiflash® placebo formulation

Ludiflash®	(BASF)	98%
Sodium stearyl fumarate	(JRS Pharma)	2%

Manufacturing
All components were blended in a Turbula blender for 10 minutes, passed through a sieve with a mesh size of 0.8 mm and compressed into tablets.

Tabletting equipment	Korsch XL 100 rotary press
Tablet size/shape	10 mm, flat
Total tablet weight	300 mg

Even at very low compression forces (figure 2) in the range of 5 kN to 10 kN, which still allow very porous tablets, it is possible to achieve tablets sufficiently stable and showing a low friability. The disintegration time is in the range of less than 30 seconds when determined in a disintegration tester (figure 3).

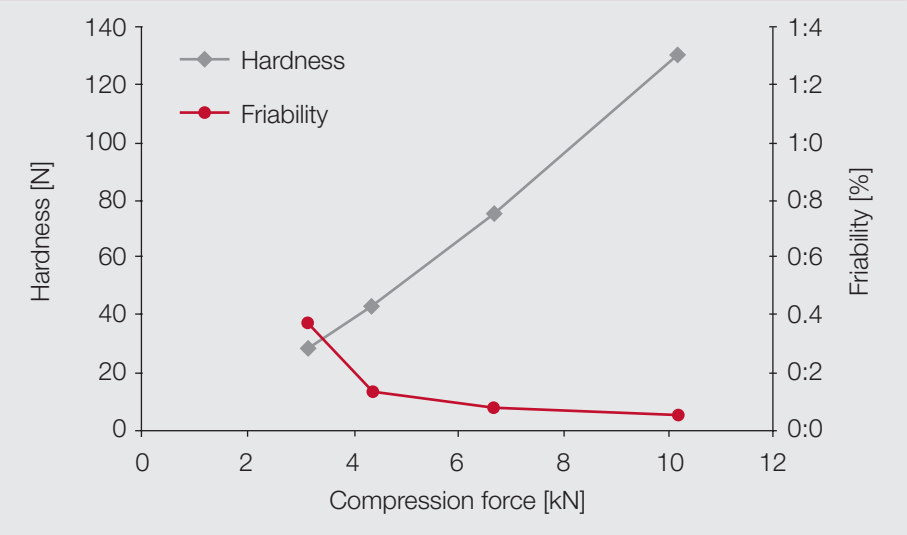

Figure 2: Hardness and friability as function of compression force

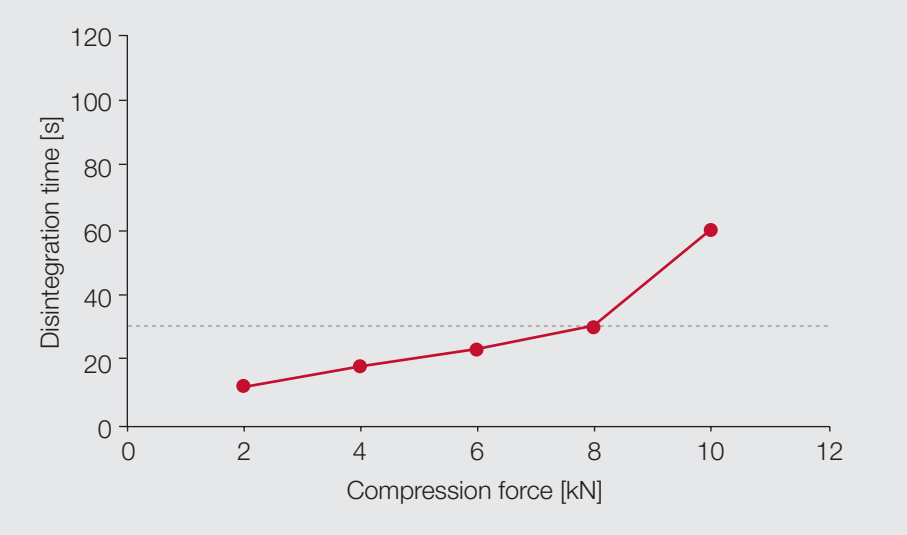

Figure 3: Disintegrations time as function of compression force

In long time production runs the influence of tabletting speed on the uniformity of mass, hardness and friability was checked. For the tests rotation speeds of 20 rpm, 40 rpm and 60 rpm were used. The uniformity of mass (tested on 20 tablets) is well within the compendial ranges (figure 4).

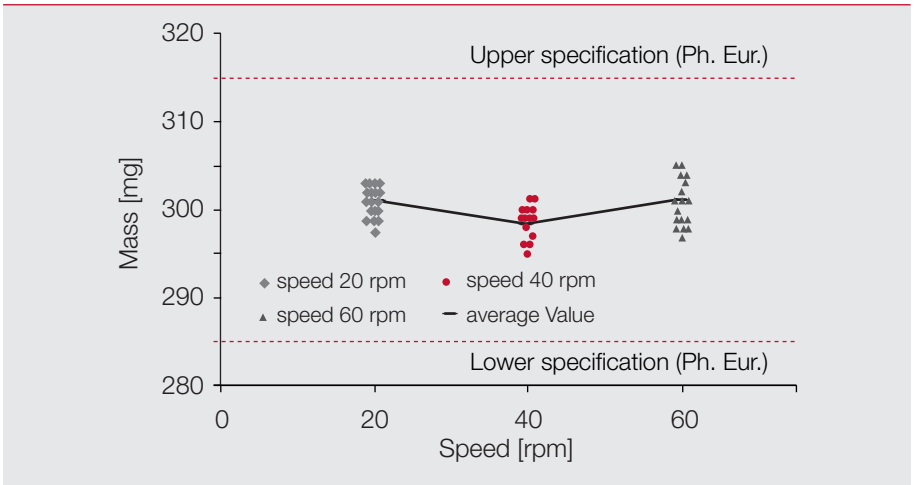

Figure 4: Uniformity of the tablet mass as function of rotation speed

Formulation 2

Loperamide fast disintegrating tablet: 2 mg

Loperamide HCl	(Select Chemie)	2.0 mg
Ludiflash®	(BASF)	94.5 mg
Kollidon® CL-SF	(BASF)	1.0 mg
Chocolate aroma	(Symrise)	1.5 mg
Sodium stearyl fumarate	(JRS Pharma)	1.0 mg
Total tablet weight		**100.0 mg**

Manufacturing
All components were blended in a Turbula free fall blender for 10 minutes, passed through a sieve with a mesh size of 0.8 mm and compressed into tablets at 3.8 kN.

Tablet properties

Tablet weight	100.0 mg
Form	7 mm concave
Hardness	32 N
Friability	0.09%
Disintegration time (phosphate buffer pH 7.2)	11 s
Dissolution (0.01 N HCl/100 rpm)	94.7% (30 min)
Taste	quickly disintegrating in the oral cavity, slightly bitter, chocolate taste, very smooth mouth-feeling

The content uniformity (figure 5) and the dissolution profile (figure 6) of the Loperamide tablets are shown in the following figures:

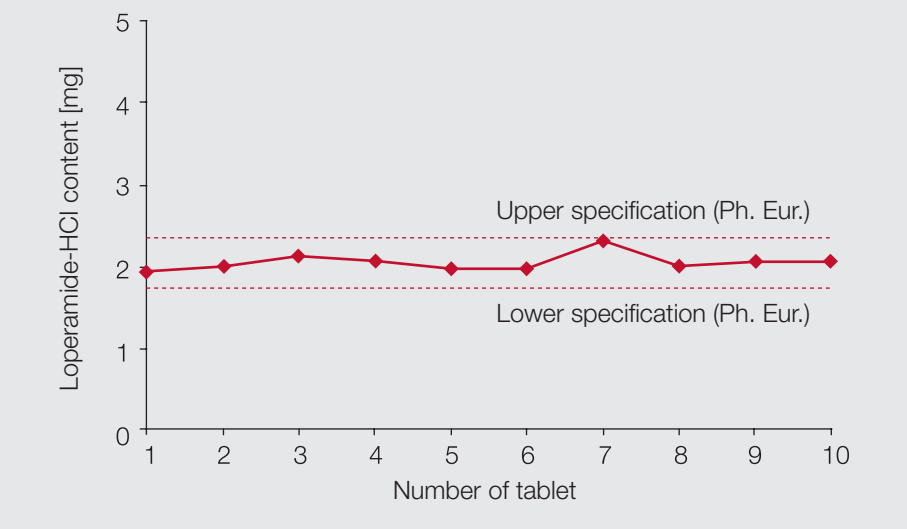

Figure 5: Content uniformity of Loperamide Tablets (2 mg)

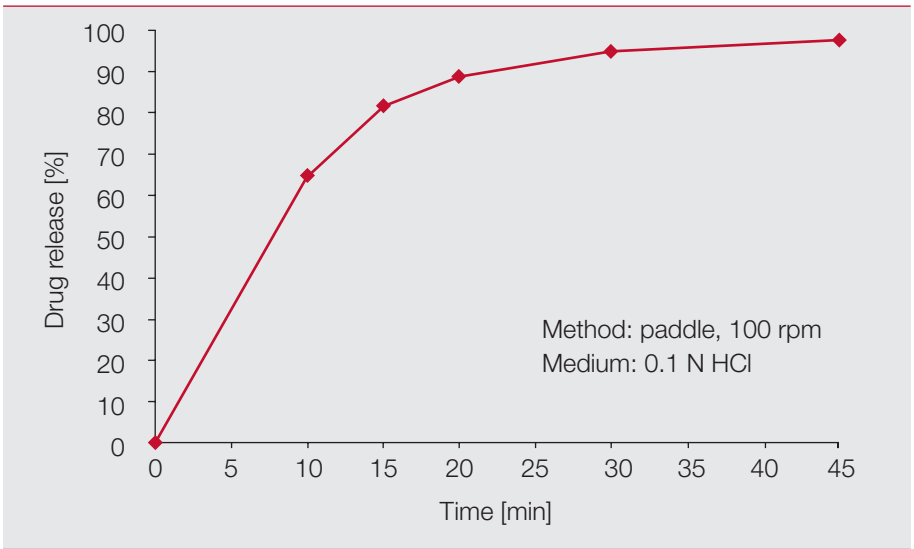

Figure 6: Dissolution profile of Loperamide tablets (2 mg)

Formulation 3

Loratadine fast disintegrating tablet: 10 mg

I	Loratadine	(Select Chemie)	10.00 mg
	Ludiflash®	(BASF)	39.70 mg
	Saccharin-Sodium	(Merck)	0.26 mg
II	Kollidon® 25	(BASF)	1.02 mg
III	Ludiflash®	(BASF)	142.02 mg
	Peppermint-aroma	(Bell Flavours & Fragrances)	3.00 mg
	Magnesium stearate	(Baerlocher)	4.00 mg
	Total tablet weight		**200.00 mg**

Manufacturing

The components of I were granulated with a 6.5% aqueous solution of II in a Glatt GPC G3 fluid bed granulator (atomizing pressure 0.5 bar, inlet air temperature 45 – 50 °C, outlet air temperature 30 °C). The resulting granules were blended with III in a Turbula blender for 10 min, passed through a 0.8 mm sieve and compressed into tablets at 2.8 kN.

Tablet properties

Tablet weight	200.0 mg
Tablet form	8 mm, flat
Hardness	37.0 N
Friability	0.25%
Disintegration time (phosphate buffer pH 7.2)	38 s
Dissolution (0.1 N HCl/50 rpm)	98.8% (10 min)

The content uniformity and the dissolution profile of the Loratadine tablets are shown in the following figures:

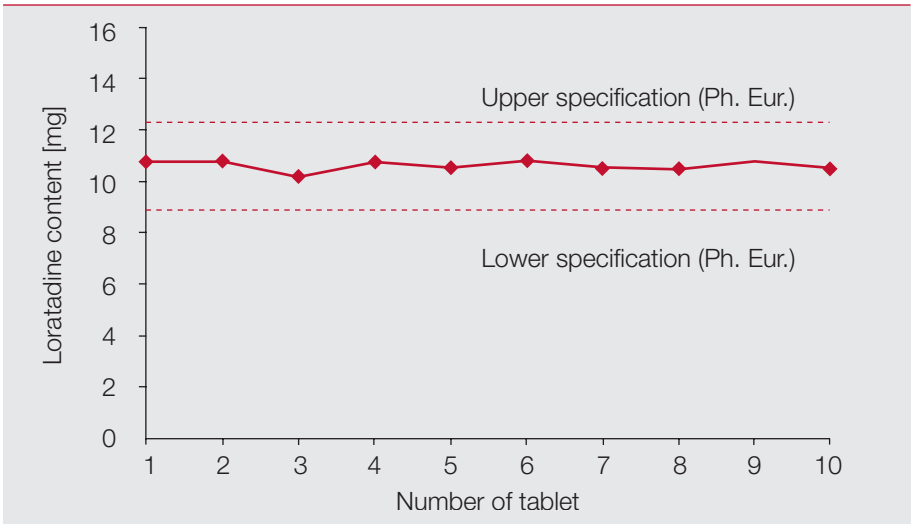

Figure 7: Content uniformity of Loratadine tablets (10 mg)

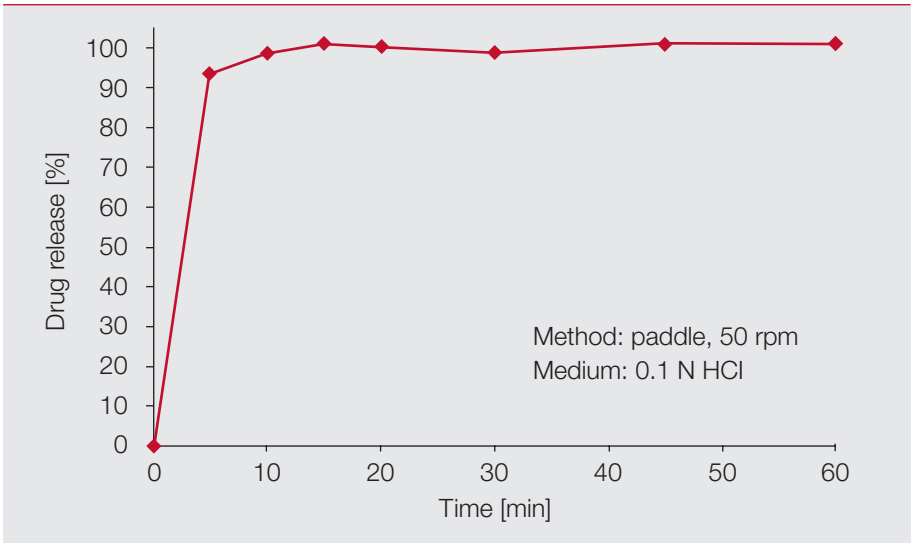

Figure 8: Dissolution profile of Loratadine tablets (10 mg)

Formulation 4

Famotidine fast disintegration tablet: 20 mg

Famotidine	(Various sources)	20.0 mg
Ludiflash®	(BASF)	267.1 mg
Aerosil 200	(Degussa)	3.0 mg
L-Menthol	(Symrise)	0.9 mg
Aspartame	(Ajinomoto)	4.5 mg
Sodium stearyl fumarate	(JRS Pharma)	4.5 mg
Total tablet weight		**300.0 mg**

Manufacturing

All components were blended in a Turbula free fall blender for 10 minutes, passed through a sieve with a mesh size of 0.8 mm and compressed into tablets at 0.8 ton/cm^2, corresponding to ~10 kN for a 10 mm tablet.

Tablet properties

Tablet weight	300 mg
Tablet form	10 mm, 10 R
Rotation speed	40 rpm
Hardness	51 N
Friability	<0.2%
Disintegration time (phosphate buffer pH 7.2)	27 s
Dissolution (n=10); 0.05 mol/l acetic acid/Na-acetate buffer pH 4.0, 50 rpm	98.8% (10 min)

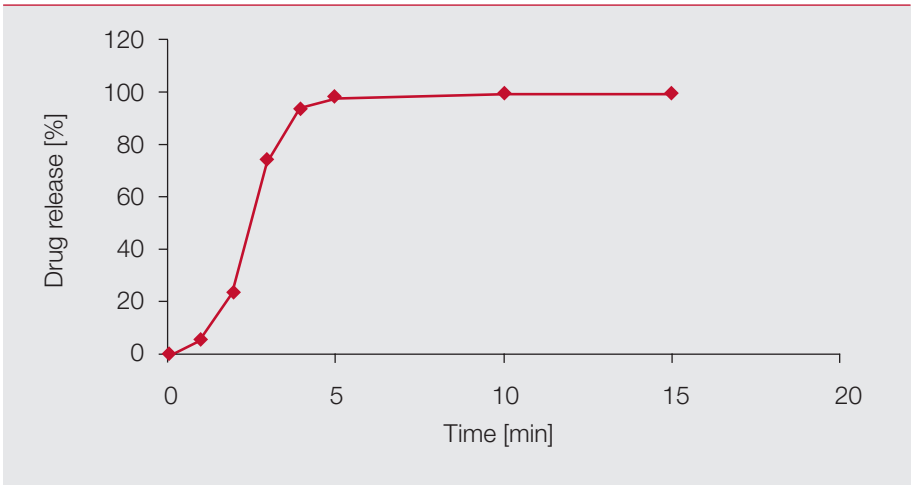

Figure 9: Dissolution of Famotidine

Content uniformity (n=10)
Ave.= 100.5%
Max= 101.5%
Min = 97.4%
SD = 1.2%

Formulation 5

Cetirizine fast disintegration tablet: 5 mg

Cetirizine	(Daito)	5.0 mg
Ludiflash®	(BASF)	163.4 mg
Aerosil 200	(Degussa)	2.0 mg
Avicel PH 101	(FMC)	20.0 mg
Grapefruit powder	(Symrise)	2.0 mg
L-Menthol	(Takasago International)	0.6 mg
Aspartame	(Ajinomoto)	4.0 mg
Sodium stearyl fumarate	(JRS Pharma)	3.0 mg
Total tablet weight		**200.0 mg**

Manufacturing
All components were blended in a Turbula free fall blender for 10 minutes, passed through a sieve with a mesh size of 0.8 mm and compressed into tablets at 0.8 ton/cm^2, corresponding to ~14 kN for a 8.5 mm tablet.

Tablet properties

Tablet weight	200 mg
Tablet form	8.5 mm, 12 R
Rotation speed	40 rpm
Hardness	51 N
Friability	<0.2%
Disintegration time (phosphate buffer pH 7.2)	32 s
Dissolution (n=10); water, 50 rpm	98.8% (10 min)

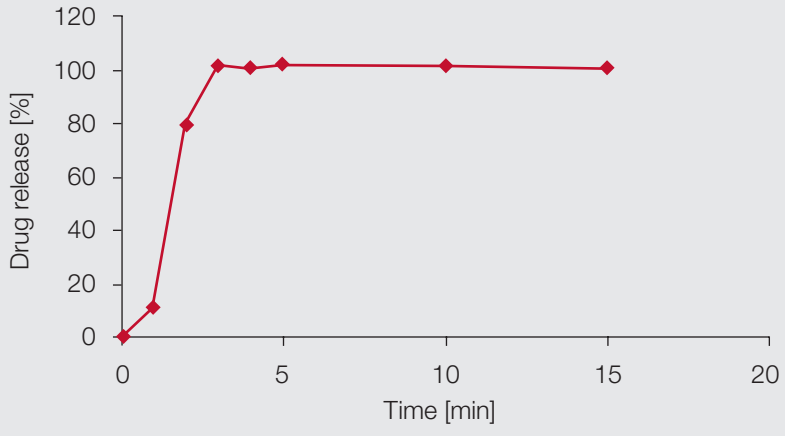

Figure 10: Dissolution of Cetirizine

Content uniformity (n=10)
Ave. = 101.4%
Max = 102.7%
Min = 98.6%
SD = 1.6%

4. Handling & Safety

Please refer to the individual material safety data sheet (MSDS) for instructions on safe and proper handling and disposal. Material safety data sheets are available on request and are sent with every consignment.

5. Product specification

The current version of the product specification is available on BASF WorldAccount, or from your local BASF sales representatives.

6. Regulatory & Quality

Please refer to the individual document quality & regulatory product information (QRPI), available on BASF WorldAccount and from your local sales representative. The QRPI document covers all relevant information including retest periods and storage conditions.

7. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging
30280988	Ludiflash®	56513304	20 kg Corrugated fiberboard box with PE liner
		53269227	1 kg Plastic bottle**

* BASF's commercial product number.
** Free non-GMP samples for testing purposes are available on request.

8. Publications

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

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