

**A New Excipient
for
Fast Disintegrating
Oral Dosage Forms**

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Pharma Ingredients & Services
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 **BASF**
The Chemical Company

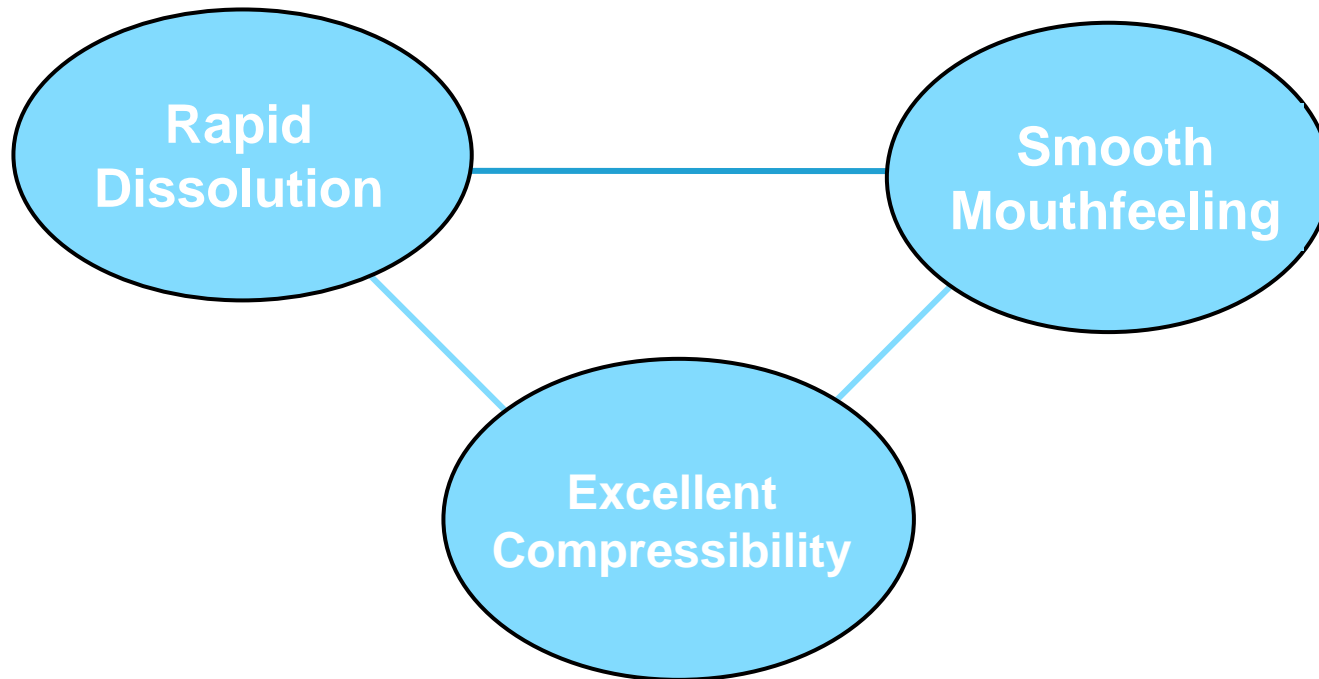
The Starting Point

- ❖ **What do you do if a tablet is simply too big?**
- ❖ **Or you don't have a glass of water at hand?**
- ❖ **Or you would like to take your medication without drawing attention to yourself?**

- ➔ **Demand grows for products that don't need to be swallowed, but rapidly disintegrate in the mouth.**

- ➔ **That is precisely how Ludiflash® works: with a smoother, creamier texture than any other excipient to date.**

Property Triangle for Orally Disintegrating Tablet (ODT)



Parameters to be taken in mind:

Hydrophilicity, water uptake capacity, surface area, outer surface, inner surface, porosity, mechanical strength, hardness, compression force, taste and taste masking etc., but also manufacturing parameters, intellectual property etc.

Composition and Production

This co-processed product consists of three ingredients.

- **90% Mannitol**
 - **Fast-dissolving filler with a mildly sweet taste**
- **5% Kollidon[®] CL-SF (Crospovidone)**
 - **A superior tablet disintegrant**
- **5% Kollicoat[®] SR 30D (Polyvinyl acetate)**
 - **Hydrophobic binder for enhanced disintegration**

Ludiflash[®] is prepared by patented and validated process in accordance with cGMP guidelines. Its properties are superior to the simple physical mixture.

Suitable API categories for Orally Disintegrating Tablets

Analgesics (non steroidal and opioids)

Antianginal drugs

Antidiarrheal

Antiemetics

Antihistaminics

Antimigraine drugs

Antitussives

Glucocorticoids

Hypnotics/Sedatives

Tranquillizers

Vasodilators

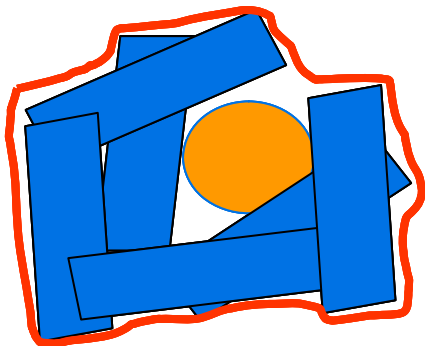
Antispasmodics

Antipsychotics

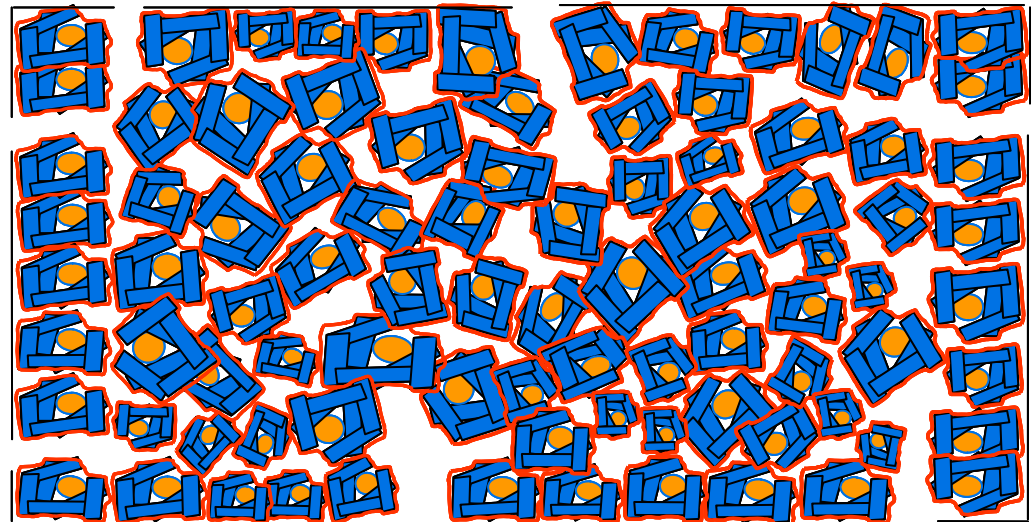
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- ➔ ODT especially suitable for...
 - ➔ regular or emergency medication
 - ➔ people with swallowing difficulties
 - ➔ people „on the move“ (discreetness, convenience)

Granule



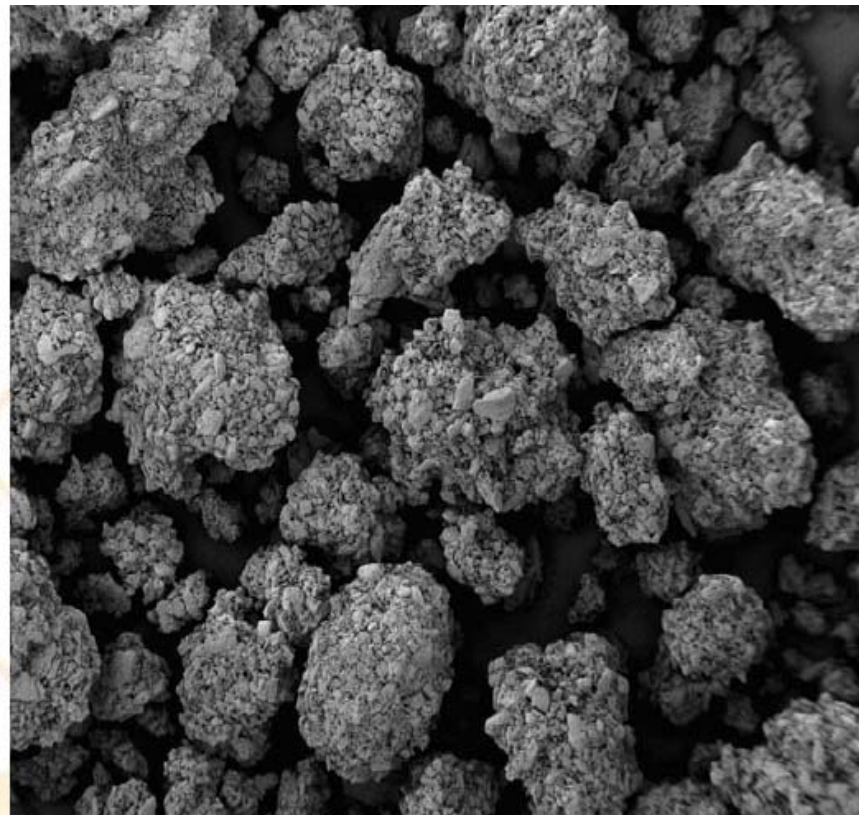
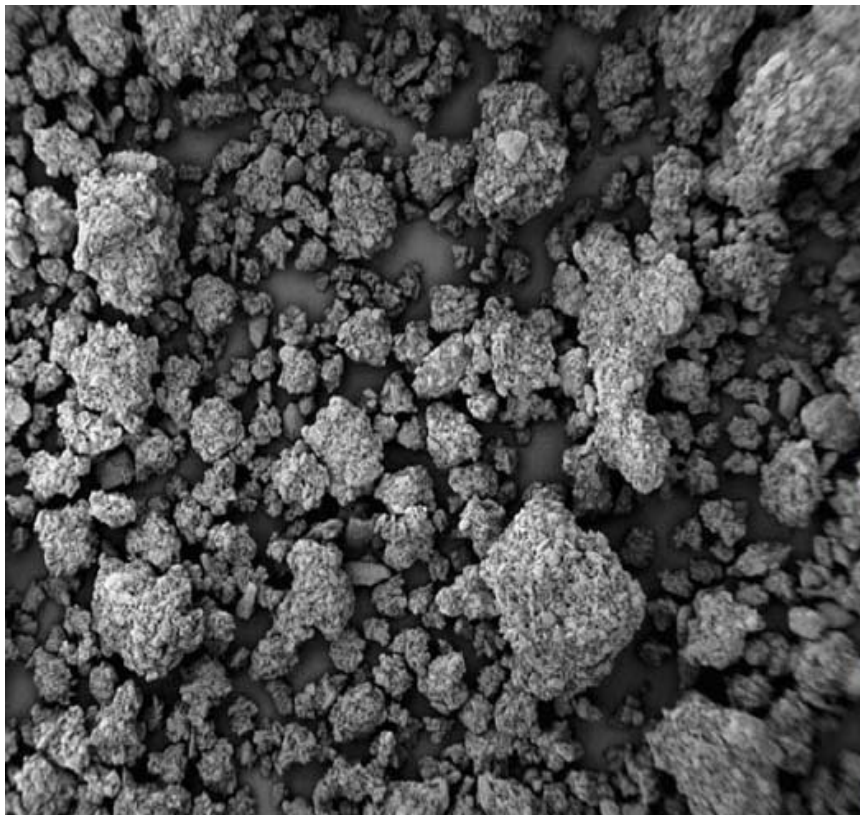
Tablet



High porosity and quick penetration of water deeply into the tablet

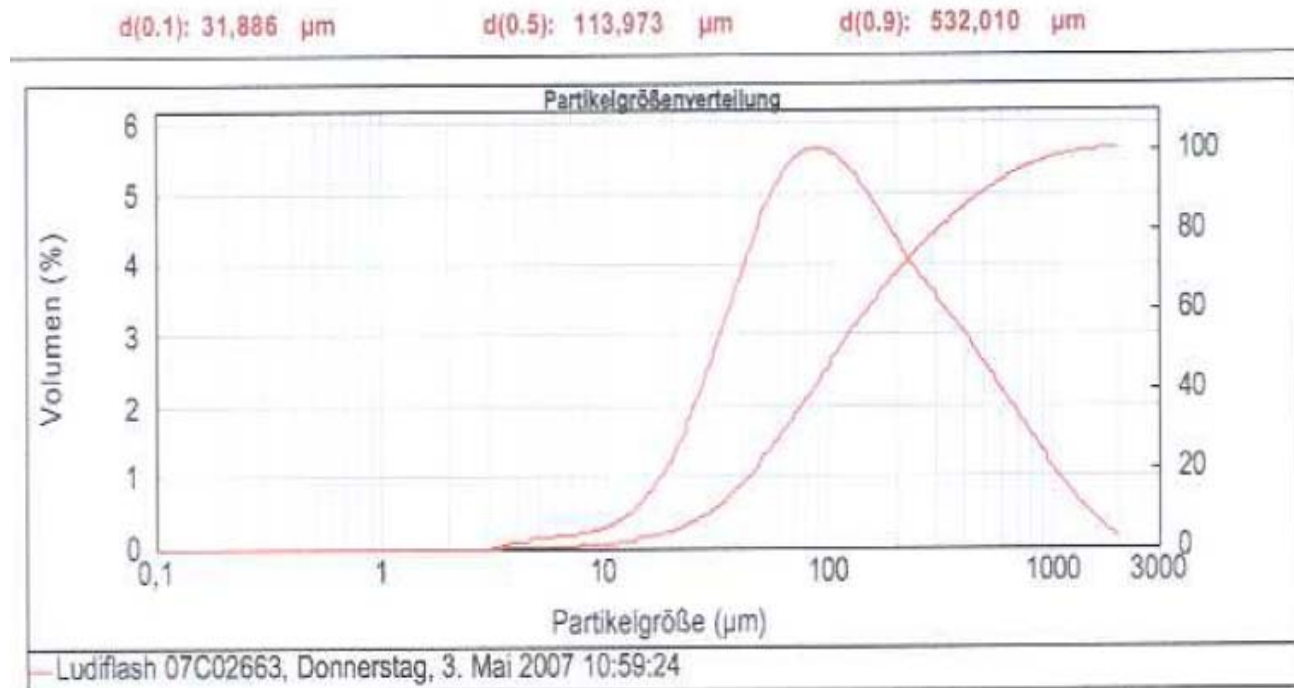
No blocking of pores  Quick action of disintegrant

Ludiflash[®] - Particle Shape SEM Pictures



Powder Characteristics of Ludiflash® (Characteristic Values)

Bulk density (g/ml)	0.4-0.5
Tap density (g/ml)	0.5-0.65
Particle size (D4,3) [μm]	170-210
Appearance	White to off-white powder
Water (Karl-Fischer-Titr.), %	Max.: 4.0 (typical values: 1.5-2%)



Why Kollidon® CL-SF?

- ❖ **Due to very small particles, CL-SF is superior to the other Crospovidone grades to provide fast dispersion and pleasant mouthfeeling**

No chalky or sandy sensation, but creamy consistency

- ❖ **Very high absorption rate and retention capability of water**

- ❖ **Very fast swelling in contact with water or saliva**

	Kollidon CL	Kollidon CL-F	Kollidon CL-SF
Mean particle size (µm)	118	29	17
Swelling volume (ml/g)	4.3	5.9	9.0
Hydration capacity (g/g)	3.9	5.9	8.1

Monograph: EP, USP, JPE

Why Kollicoat® SR 30D?

- ❖ **Hydrophobic EP-monographed film-former acts as a binder**
- ❖ **Prevents D-Mannitol to block tablet pores when dissolved after first contact with water/saliva**
- ❖ **Although it is of hydrophobic character, the functionality exceeds all water soluble binders tested**

- ❖ **Monograph: EP**
- ❖ **US-DMF: No. 15055, Type IV**

Why D-Mannitol?

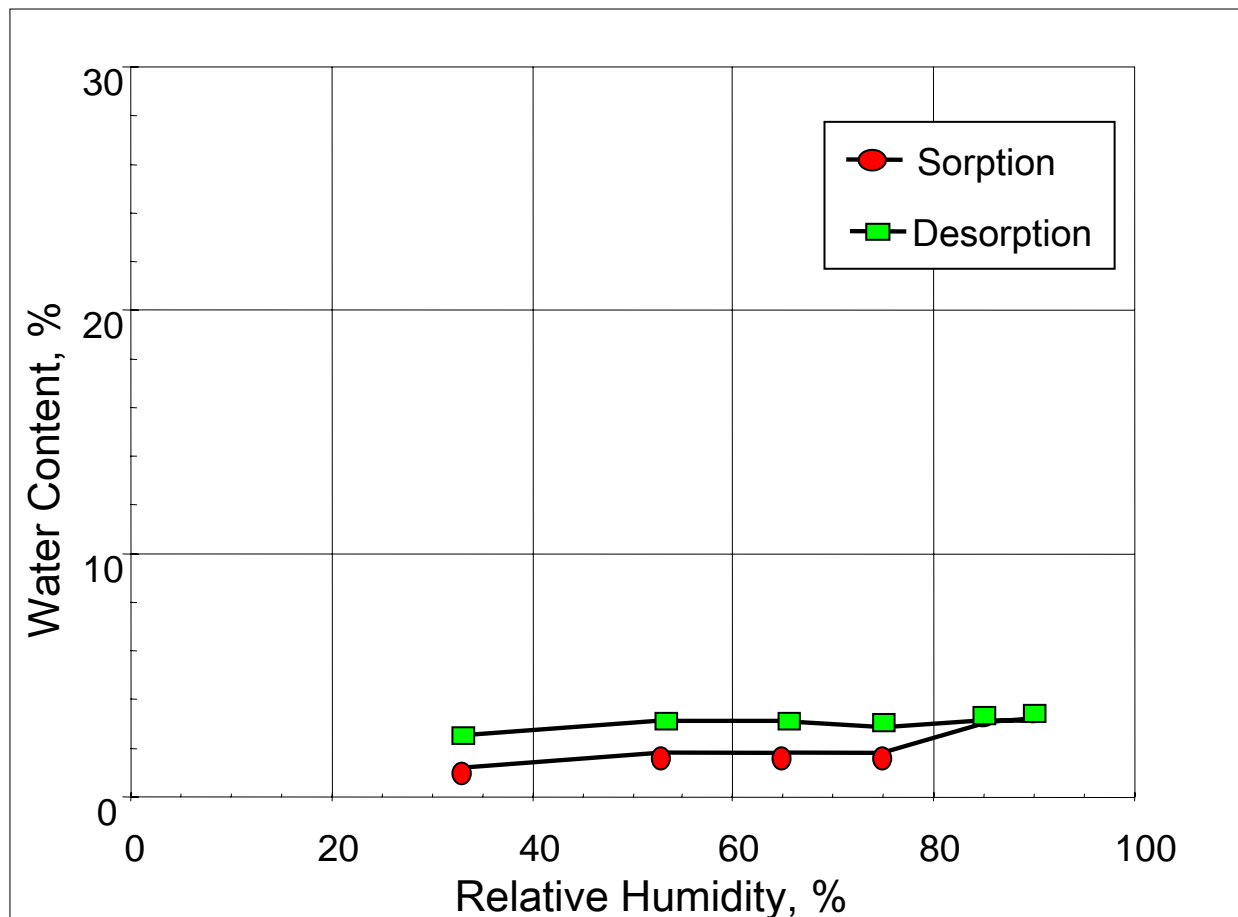
D-Mannitol is a compendial excipient, which

- **is non-hygroscopic**
- **dissolves easily**
- **is available in different powder grades**
- **has a cooling effect**
- **is non-carcinogenic and**
- **has a low caloric content.**

Mannitol is not considered to be a „sugar“ → Ludiflash is „sugar-free“.

- **Monograph: EP, USP, JP**

Sorption Isotherm at 23°C of Ludiflash®



Basic Placebo Formulation (lab and production scale)

Ludiflash® (BASF) 98%

Sodium stearyl fumarate (JRS Pharma) 2%

Blending: Turbula blender

Equipment: Korsch XL 100 rotary press (lab)

Fette 1200 rotary press (production; 160 000 tablets/h)

Tablet dimensions: 10 mm, flat

Tablet weight: 300 mg

Ludiflash[®]-Based Placebo

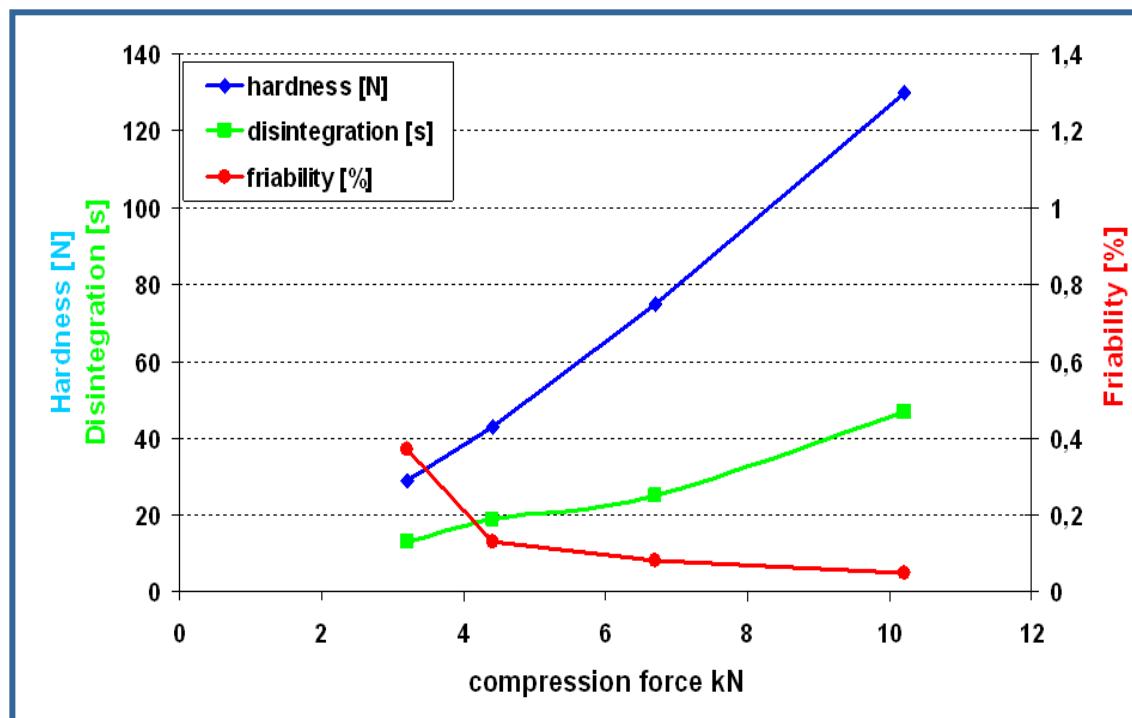
Composition, Properties, Production (Lab Results)

■ Formulation

Ludiflash	294.0 mg
Sod. stearyl fumarate	6.0 mg
Total weight	300.0 mg

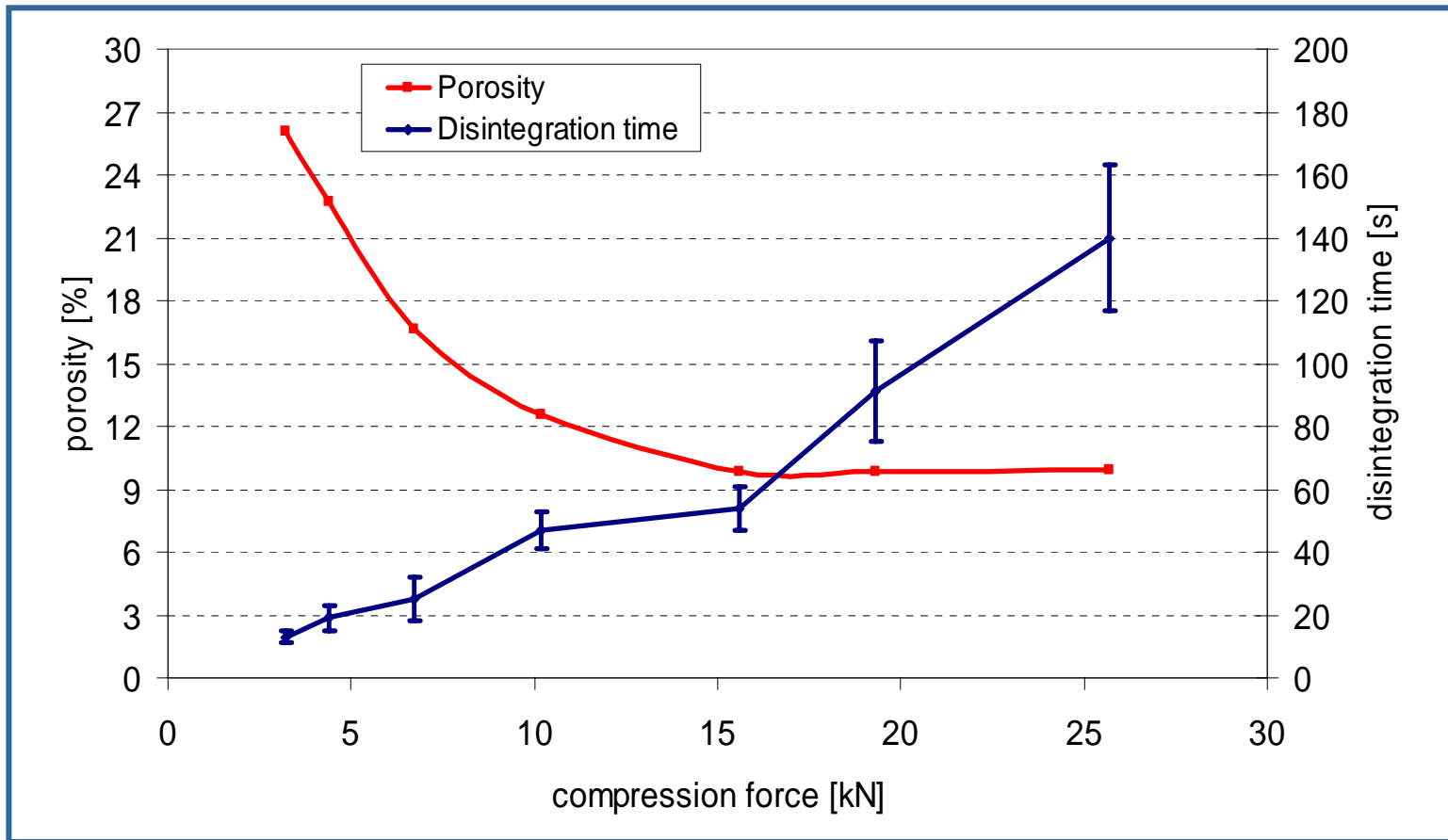
■ Tablet properties

Weight:	300.0 mg
Form:	10 mm flat
Hardness:	44 N
Friability:	< 0.2 %
Disintegration time (phosphate buffer pH 7.2):	19 s
Disintegration (oral cavity):	~15 s
Taste: extremely pleasant mouth-feel	



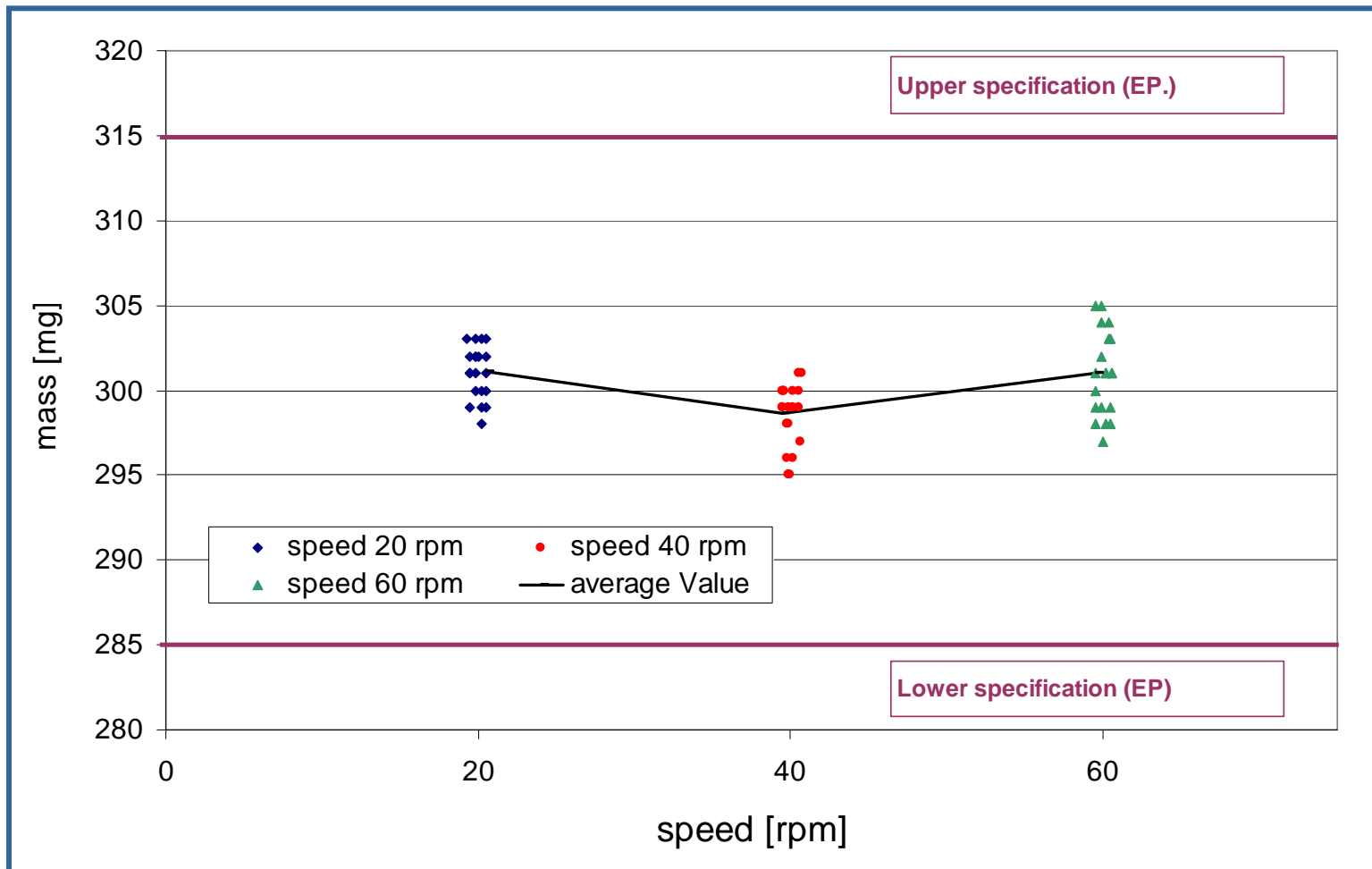
- Production process
free-fall mixer, 10 minutes blending, 0.8 mm sieve,
compression force 4.8 kN, Korsch XL-series press

Disintegration Time as a Function of Compression Force / Porosity



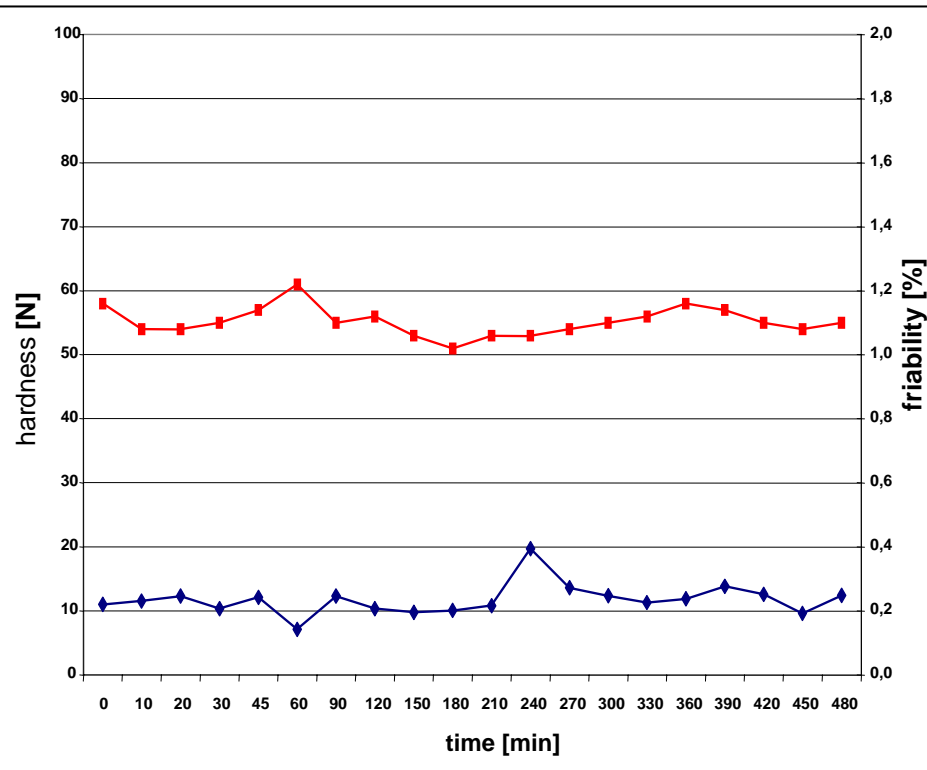
Note: Porosity is calculated

Uniformity of Mass Related to the Specification of Ph.Eur. (n=20)

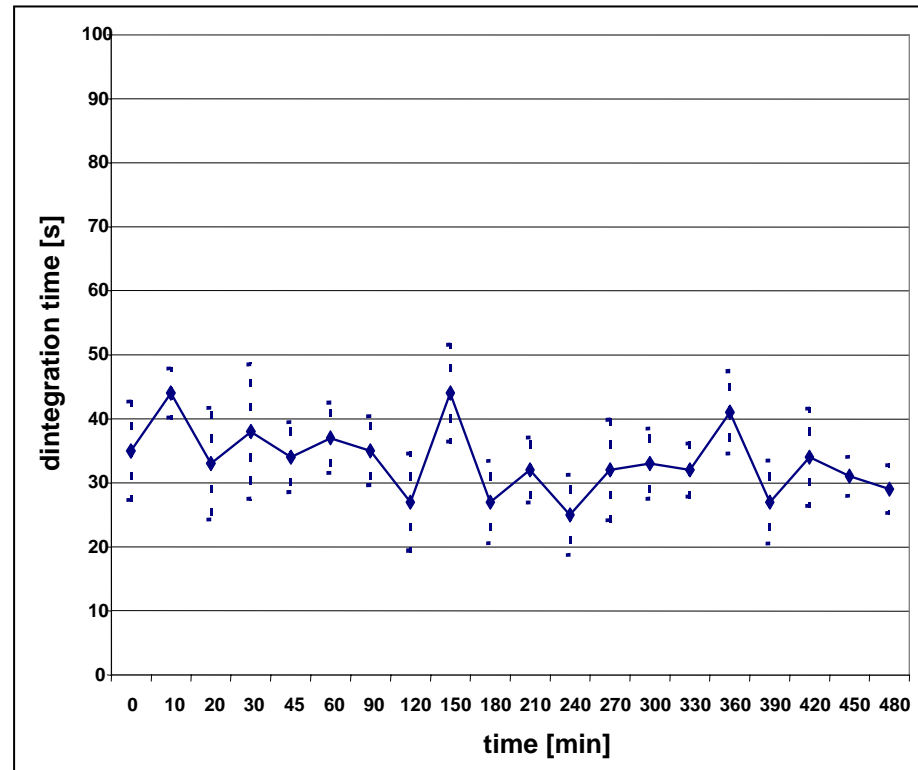


Long Term Tableting Trials– Hardness, Friability and Disintegration (lab results)

Hardness



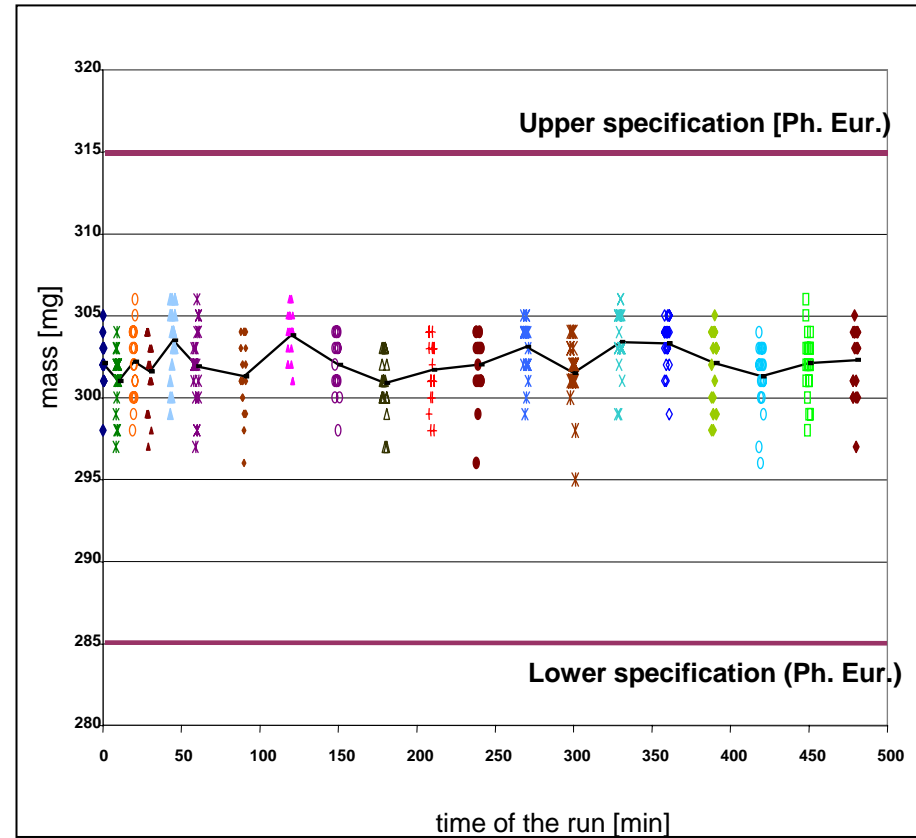
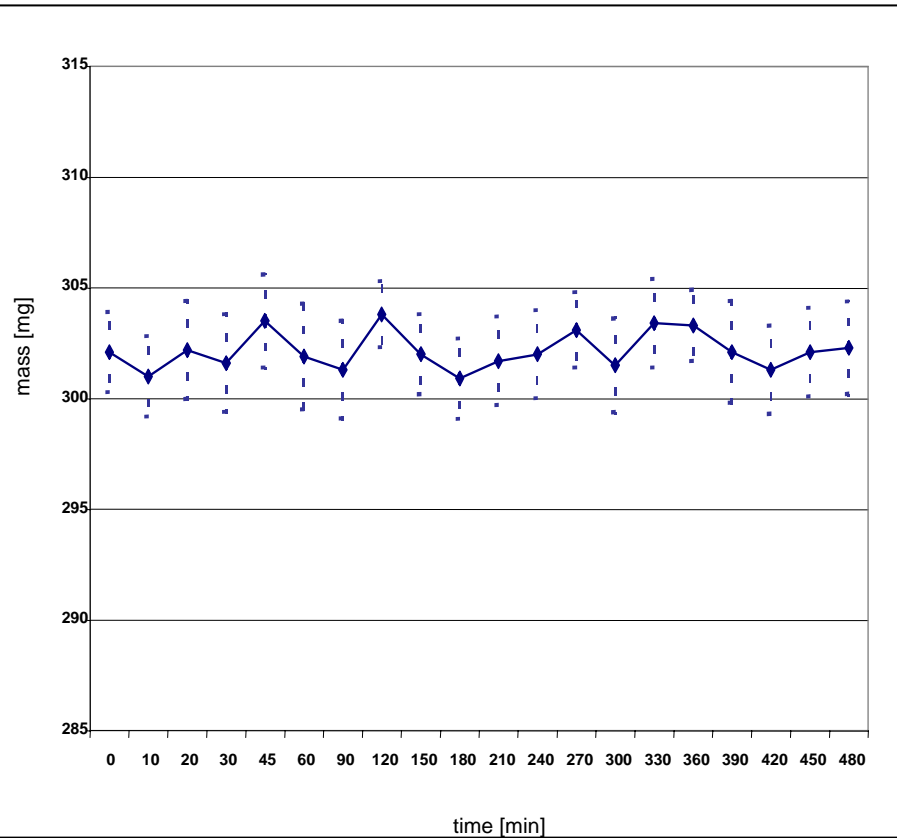
Disintegration Time



- No adjustments necessary
- Very stable and robust tableting process

Development of standard deviation of mass at a long time run

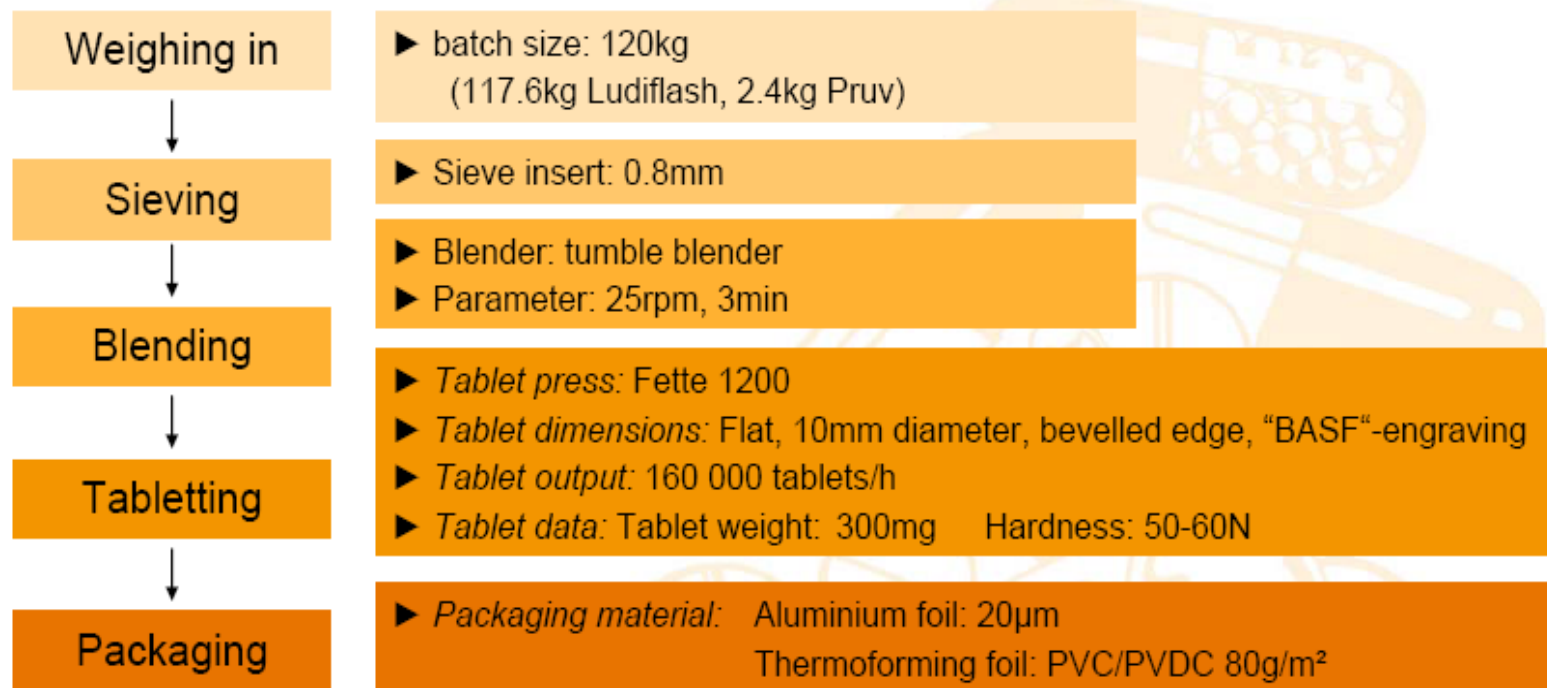
Uniformity of mass related to the specification of the Ph. Eur. (20 single values)



- **Low or insignificant tablet mass variations**
- **Robust process**

Scale-up at Toller

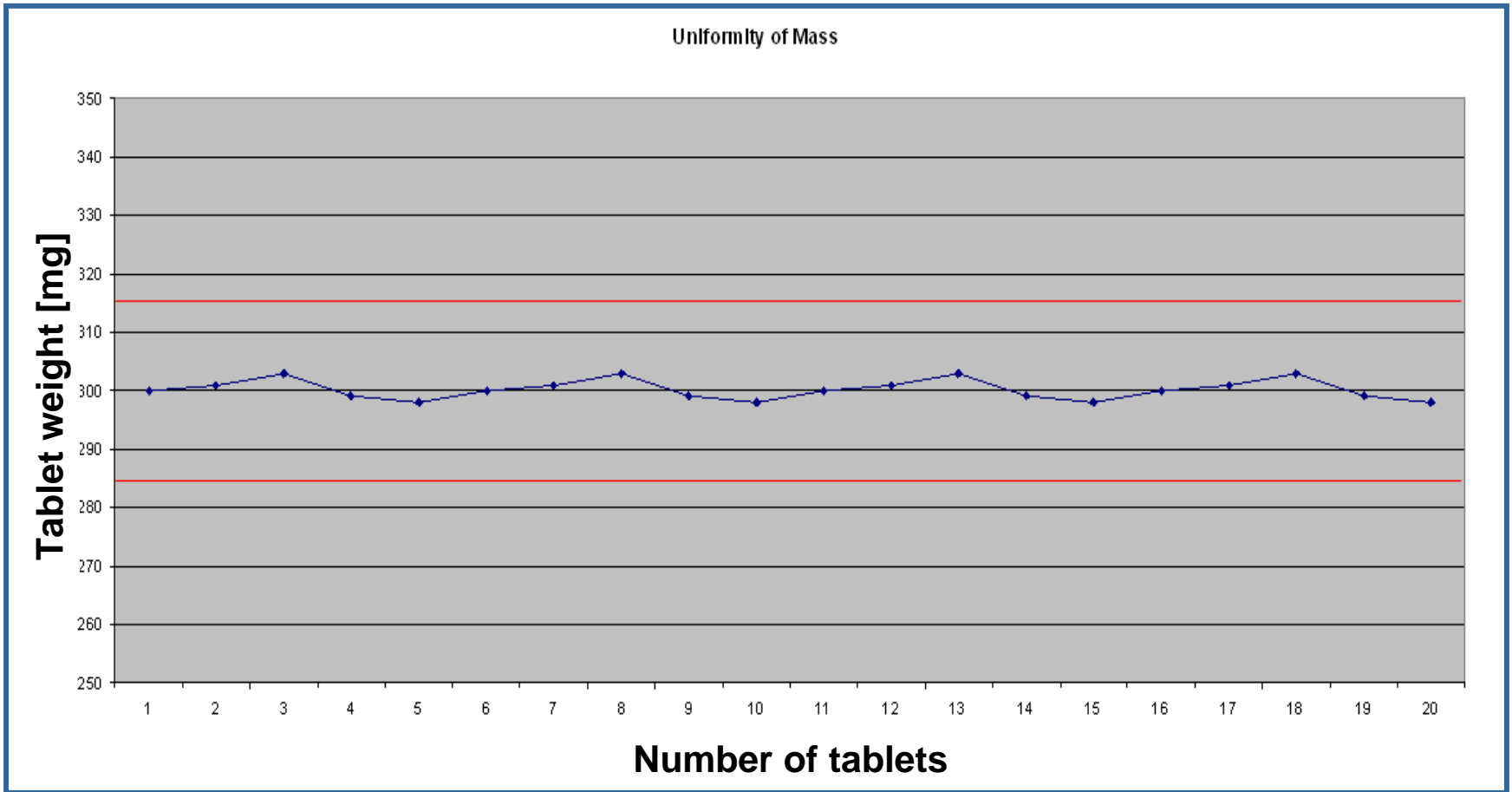
Flow Chart and Parameters



Scale-up at Toller Tablet Properties

Parameter	Production	Laboratory
Tablet weight:	300mg	300mg
Thickness:	3.5mm	3.5mm
Diameter:	10.1mm	10mm
Hardness	55N	44N
Disintegration Time:	ca. 20s	ca.15s
Friability	<0.25%	<0.2%

Scale-up at toller Dragenopharm: Uniformity of Mass 160.000 tablets/hour



Risperidone formulation with Ludiflash®

Formulation, Properties, Production, Content Uniformity

Formulation

● Risperidone	1.0 mg
● Ludiflash	96.0 mg
● Aerosil 200	0.5 mg
● Lemon powder	0.5 mg
● Aspartame	1.0 mg
● Magnesium stearate	1.0 mg
● Total weight	100.0 mg

Tablet properties

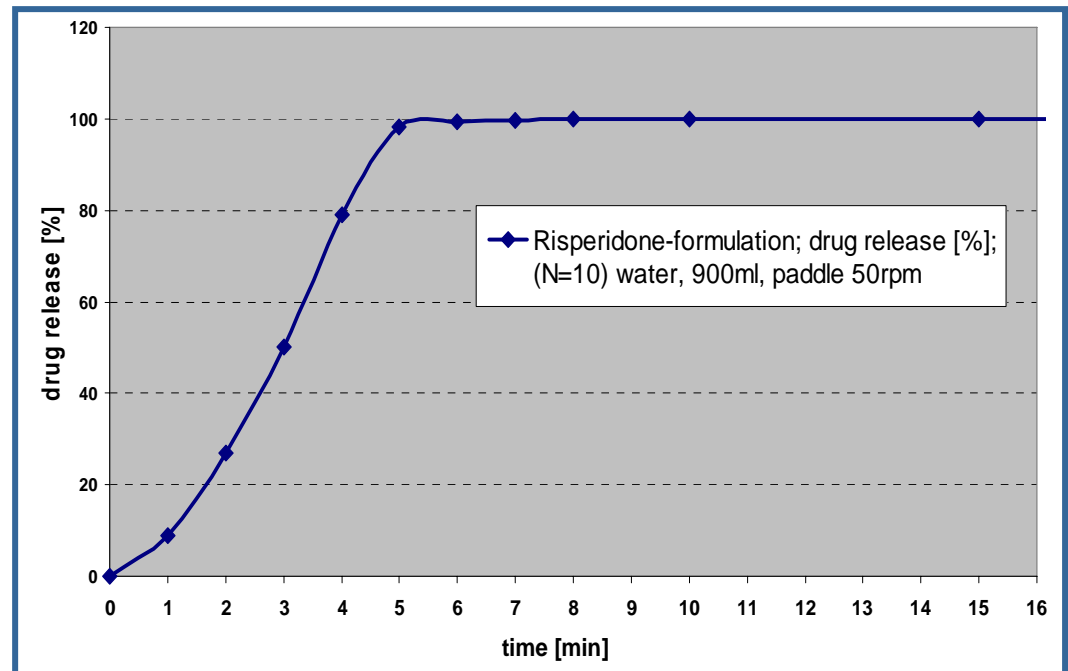
● Weight:	100.0 mg
● Form:	6.5 mm
● Hardness:	56 N
● Friability:	< 0.2 %
● Disintegration time (water):	27 s
● Release rate (water, 900 ml, 50 rpm):	98.2 % (5 min.)

Content uniformity (N-10)

- Mean = 98.8 %
- Maximum = 102.1 %
- Minimum = 97.7 %
- Standard deviation = 2.2

Production process

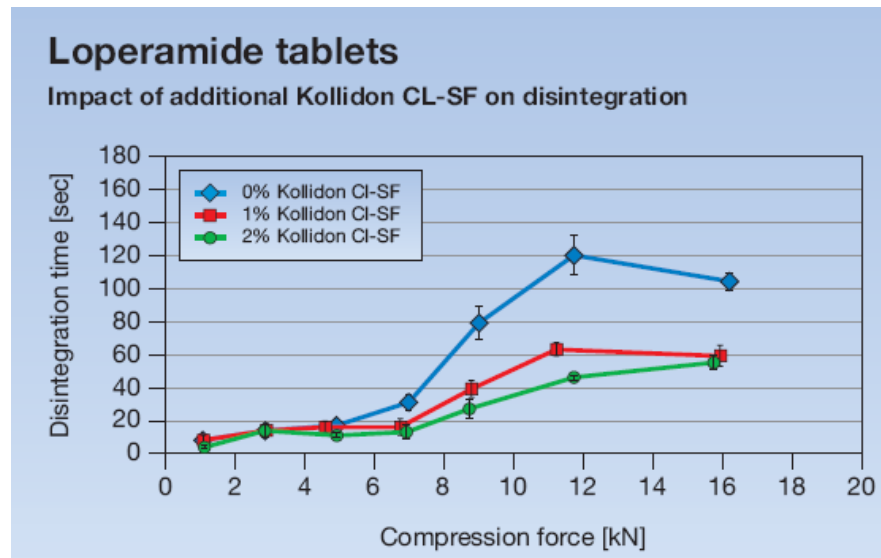
- free-fall mixer, 10 minutes, 0.8mm sieve, compression force 4 kN at 40 rpm



Additional Disintegrant

Adding small amounts of BASF's **Kollidon® CL-SF** further accelerates disintegration. (up to 15 wt% if desired, recommended: 0.5 to 1%, max 3%)

- ➔ Reduces disintegration time without compromising the smooth and creamy mouthfeel of Ludiflash
- ➔ Ensures that even tablets of superior hardness begin to disintegrate within seconds



Lubricants

Lubricants and amounts tested:

	Possible wt.%	Recommended wt.%
<input type="checkbox"/> Mg stearate	(1 –) 2	1.5 / 2
<input type="checkbox"/> Na stearyl fumarate	1 – 2	1/ 1.5/ 2
<input type="checkbox"/> Stearic Acid	Possible	
<input type="checkbox"/> Lutrol F68 Micro (BASF)	Possible	
<input type="checkbox"/>		

Packaging recommendations

- ❑ **Push-through blisters (PVC/PVDC/Alu* recommended)**
- ❑ **Polyethylene containers**
 - **Desiccant recommended**
 - **Limited package size (less opening, faster use-up)**

Test:

- ❑ **Stability test with Blister (PVDC/PVC/Alu) and PE-container initiated**
- ❑ **Stability test at uncontrolled conditions: Tablets being stored in glass vials/bottles for > 6 months → disintegration increases slightly from ~15 sec. To ~18-20 sec.**

***Aluminum foil: 20 μm ; Thermoforming foil: PVC/PVDC 80g/m²**

Loperamide Formulation with Ludiflash[®] and additional Kollidon[®] CL-SF

Formulation, Properties, Production

Formulation

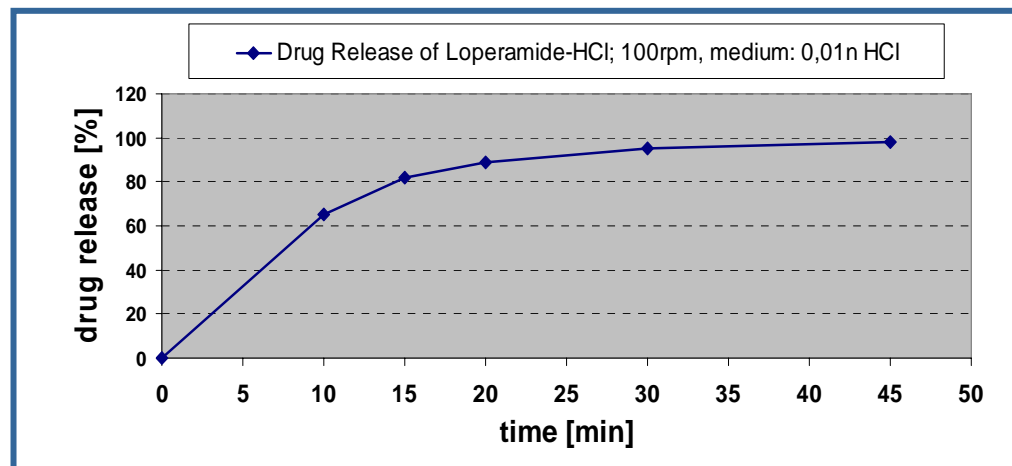
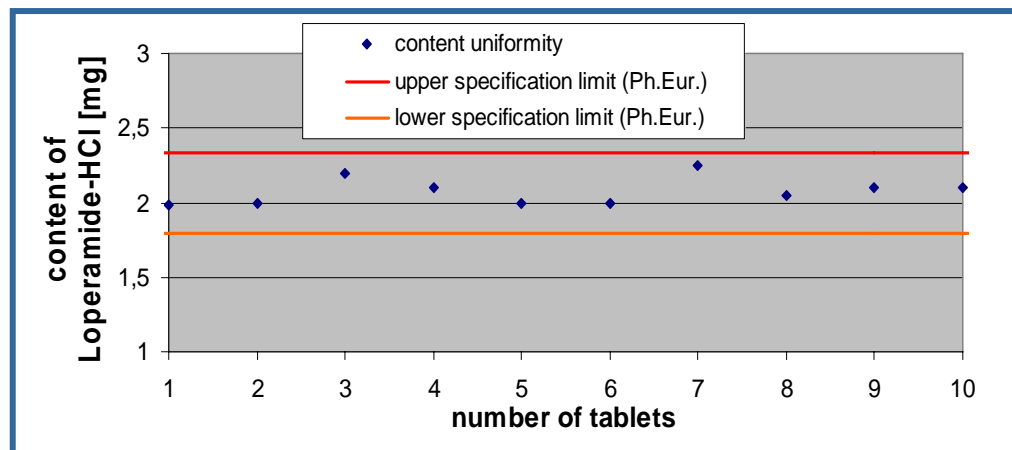
● Loperamide HCl	2.0 mg
● Ludiflash	94.5 mg
● Kollidon CL-SF	1.0 mg
● Chocolate flavoring	1.5 mg
● Sodium stearyl fumarate	1.0 mg
● Total weight	100.0 mg

Tablet properties

● Weight:	100.0 mg
● Form:	7 mm, concave
● Hardness:	30 N
● Friability:	0.09 %
● Disintegration time	
● (phosphate buffer pH 7.2):	11 s
● Release rate:	94.7 % (30 min.) (0.01N HCl/100 rpm)

Production process

free-fall mixer, for 10 minutes, 0.8 mm sieve, compressed at a force of 3.7 kN



Wet Granulation

Attention needs to be directed towards:

- Amount of water**
 - as little as possible per time period**
 - reduce dissolution of Mannitol during wet-granulation**
 - reduce thereby increase in disintegration time**

**Disintegration time can be lowered by additional Kollidon CL-SF
(1 to 3 wt.% or more if necessary)**

Recommendation:

- Fluidized-bed granulation is recommended**
- Pre-granulation of API with small amount of Ludiflash**
- Blending of granulate with more Ludiflash**
- Tabletting via direct compression**

Ludiflash®-Formulations

Loratadine (10 mg) – Pre-Granulation of API



Formulation

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

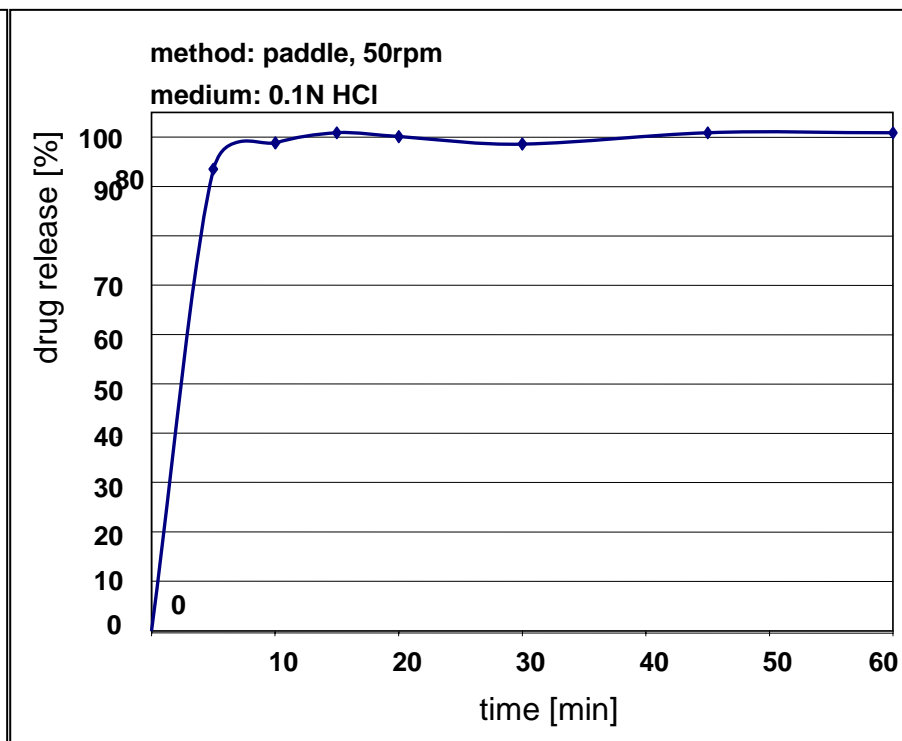
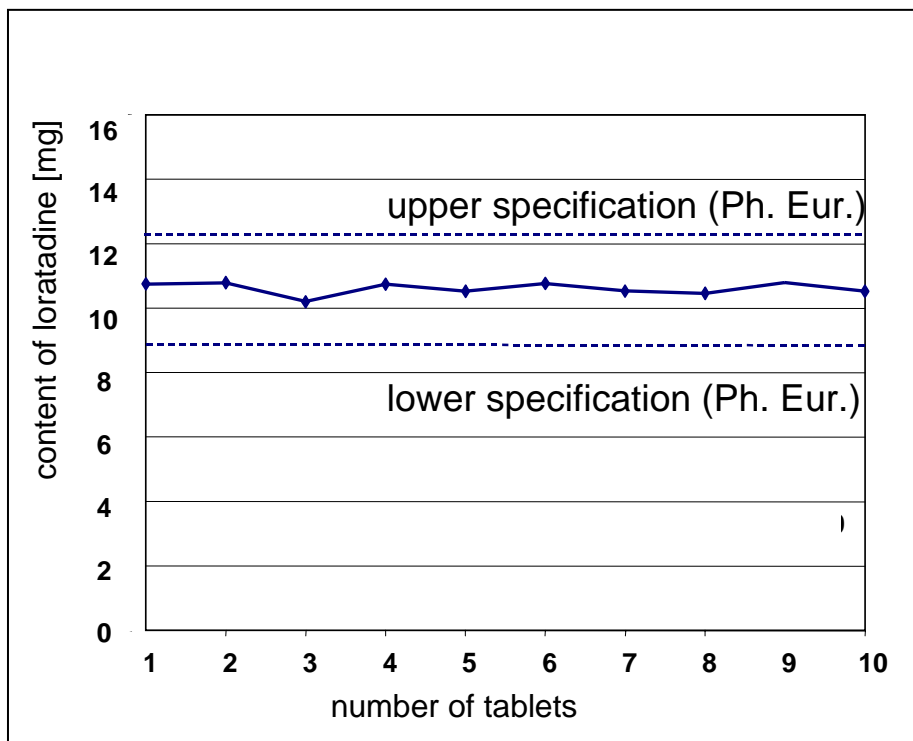
Tablet properties

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

Ludiflash®-Formulations

Loratadine (10 mg)

Content Uniformity of Loratadine-Tablets Dissolution of Loratadine-Tablets



Ludiflash® : Unique Value Proposition

- ❑ **Superior product performance:**
 - ❖ **Creamy and smooth mouth-feel**
 - ❖ **Tablets with exceptional tensile strength and hardness and extremely low friability, low hygroscopicity**
- ❑ **High compression speeds without compromising tensile strength**
- ❑ **Flexibility in processing: direct compression, roller-compaction or wet- granulation**
- ❑ **All-in-one system: filler, binder and disintegrant**
- ❑ **Low lubricant levels for tableting process**
- ❑ **Compatible with other typical ingredients, no segregation**

Ludiflash® : Unique Value Proposition

- ❑ **Faster product development, and faster process validation**
 - ❑ **Easy Scale-up**
 - ❑ **Standard high-speed tableting and standard packaging equipment**
 - ❑ **Packaging possible in standard push-through blisters and PE containers**

 - ❑ **Life-cycle extension**
 - ❑ **Value-added application (ODT, FDDF)**
 - ❑ **No license/ confidentiality/ royalty: full control over formulation, Manufacturing process and intellectual property**
- ➔ **Independence from supplier**

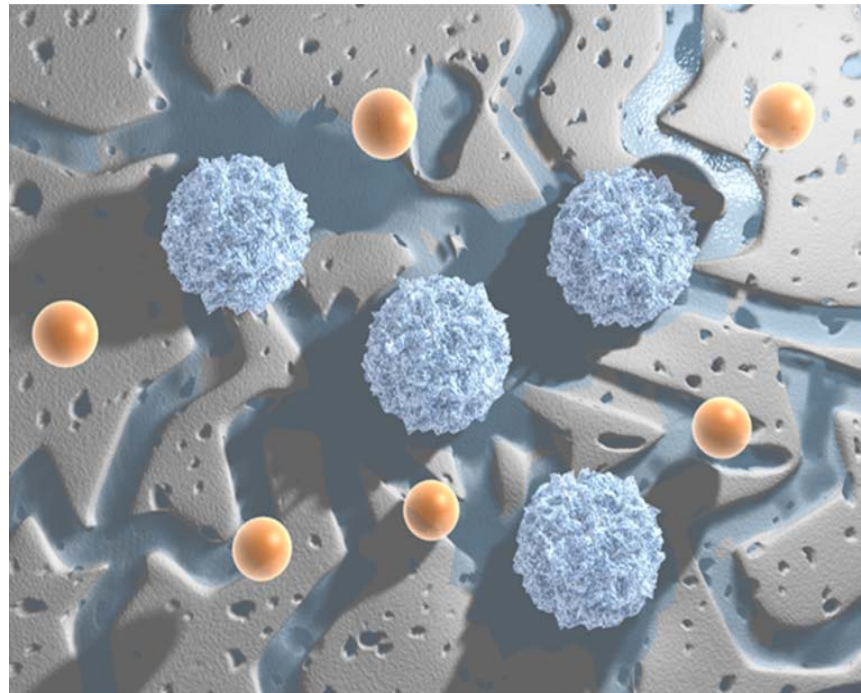
Product Performance: Disintegration

Ludiflash®

– Excipient of Choice for
Orally Fast-Disintegrating
Formulations for Rapid
Relief

- Fast-Disintegrating
- Fast-acting

MOVIE



↪ ...and releases the active ingredients extremely rapidly.

Thank you very much for Your kind attention!