TECHNICAL INFORMATION 1426

RXCIPIENTS® FM 1000

A versatile excipient for orally disintegrating tablet (ODT) formulations

EVONIK
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1 Introduction

Certain patient groups, specifically elderly and infant patients, experience difficulties with swallowing oral dosages of medication. Orally disintegrating tablets (ODTs) are one approach to ease the intake, helping patients to comply with their prescription plans.

A conventional disintegrant pulls water into the tablet and swells, resulting in the delamination of the tablet. Our new excipient RXCIPIENTS® FM 1000 boosts the function of the disintegrant, causing the tablet to breakdown into small particles rather than to just delaminate. By adjusting the concentration of RXCIPIENTS® FM 1000 in combination with the disintegrant, formulators can target different disintegration times of the ODT. RXCIPIENTS® FM1000 calcium silicate can thereby be combined with a broad range of other ingredients.

2 Mode of action and advantages of RXCIPIENTS® FM 1000

RXCIPIENTS® FM 1000 channels moisture to the disintegrant due to its hydrophobic nature. The disintegrant absorbs that moisture, swells and thereby breaks the tablet.
Typically, 5–15 wt.-% of RXCIPIENTS® FM 1000 are used in the formulation.

Advantages of using RXCIPIENTS® FM1000 include:

- Promotion of faster tablet disintegration, breaking the tablet down into easy to swallow fine particles
- Durability of tablets, with low friability even at low compression forces
- Support of bulk packing instead of expensive blister packing
- High level of flexibility in formulation due to compatibility with many different disintegrants and fillers

3 Case studies

The following examples illustrate the benefits of RXCIPIENTS® FM 1000.

3.1 Example 1 – Placebo ODT formulation

Formulations

Table 1 Formulations of placebo ODT

	Formulation 1 wt.-%	Formulation 2 wt.-%
Mannitol (SPI Mannogem EZ)	76.8	67.8
MCC (Avicel PH-102 NF)	15	15
RXCIPIENTS® FM 1000	–	**9.0**
PVP-XL (ISP)	5.0	5.0
AEROSIL® 200 Pharma (Evonik)	1.0	1.0
Sucralose (Tate and Lyle)	1.5	1.5
Mg Steaarate (Ligamed MF-3-K, Peter Grevis)	0.7	0.7
Total	**100.0**	**100.0**

Mixing

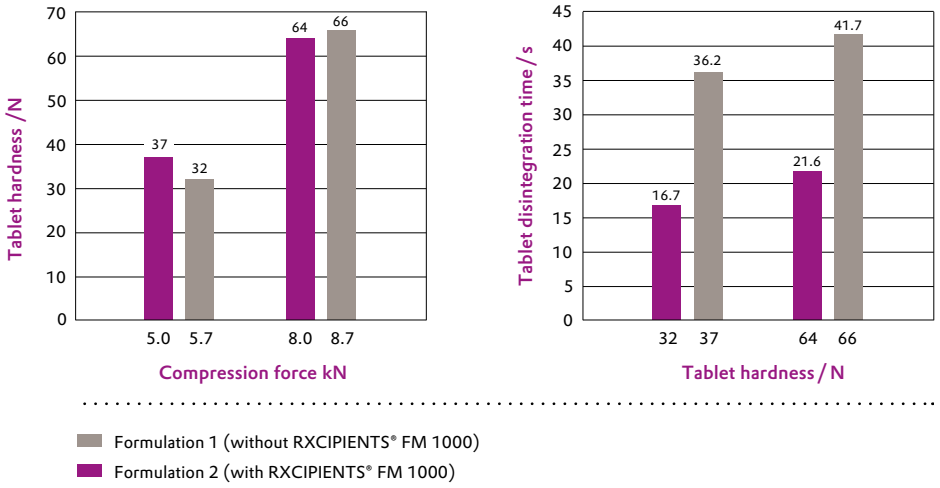
- All components except magnesium stearate were passed through a sieve (840 µm)
- Mixing in a V blender for 10 min at 27 rpm
- Addition of magnesium stearate after passing through a sieve (400 µm)
- Mixing in V blender for 5 min at 27 rpm

Tabletting

- SMI – Piccola rotary press, Model 8
- Turret speed: 30 rpm
- Compression force: 5–9 kN
- Tablet diameter: 10 mm
- Tablet mass: 450 mg

Results

Figure 1 Tablet hardness and disintegration time for placebo ODT formulations



RXCIPIENTS® FM 1000 drastically reduced the disintegration time at a low concentration and at the same time improved compressibility of the formulation leading to tablets with equivalent mechanical stability at a significantly lower compression force. The following pictures illustrate the quick disintegration.

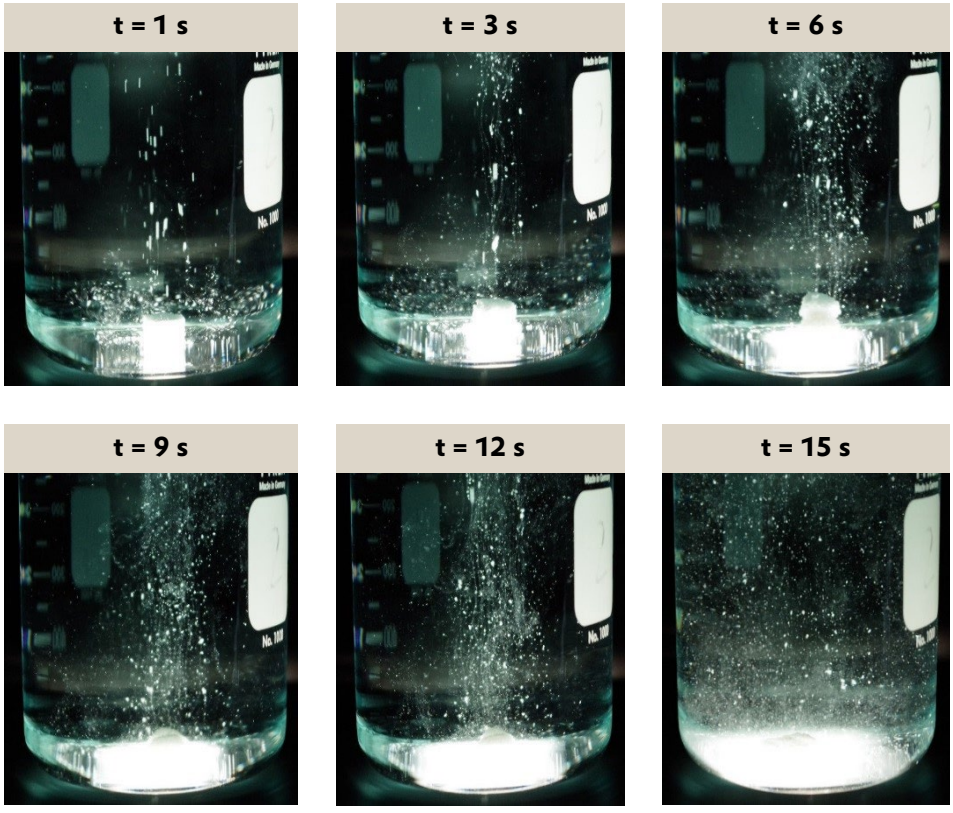


Figure 2 Disintegration of placebo ODT formulation with RXCIPIENTS® FM 1000

3.2 Example 2 – Acetaminophene ODT formulation

Formulations

Table 2 Formulations of acetaminophene tablets

	Formulation 1 wt.-%	Formulation 2 wt.-%	Formulation 3 wt.-%
Acetaminophene 02216101, Rhodia	43.0	43.0	43.0
Microcrystalline cellulose Vivapur 102, JRS Pharma	43.5	41.5	43.5
RXCIPIENTS® FM 1000	**0**	**10**	**10**
Starch DC7134, National Starch	10.0	5.0	0
Sodium Starch Glycolate 9690, Penwest	3 .0	0	3.0
Magnesium stearate Type 2256, Malinckrodt	0.5	0.5	0.5

Mixing

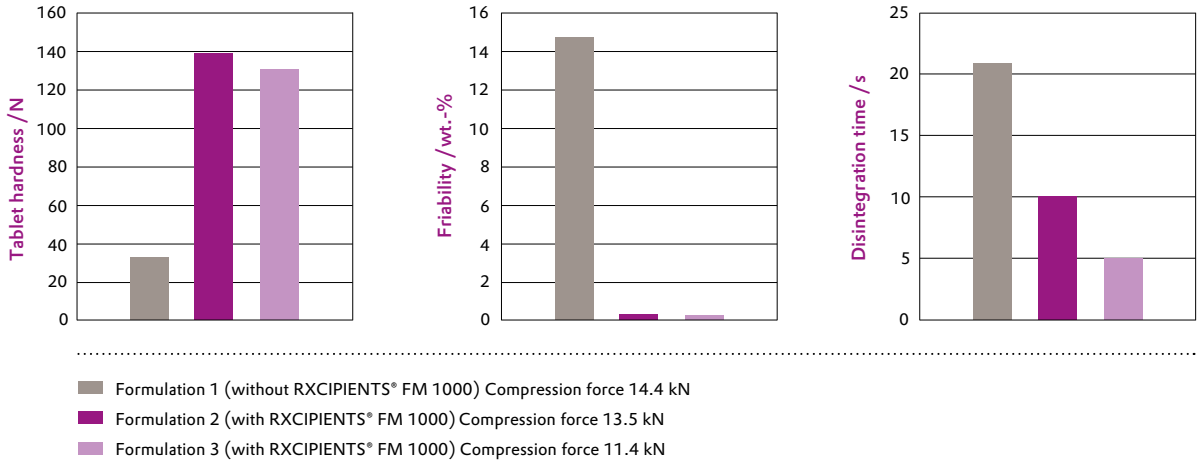
- All components except magnesium stearate were passed through a sieve (840 µm)
- Mixing in a V blender for 10 min at 27 rpm
- Addition of magnesium stearate after passing through a sieve (400 µm)
- Mixing in V blender for 5 min at 27 rpm

Tabletting

- SMI – Piccola rotary press, Model 8
- Turret speed: 30 rpm
- Compression force: 11–14 kN
- Tablet diameter: 10 mm
- Tablet mass: 400 mg

Results

Figure 3 Compression force, tablet hardness, friability and disintegration time for acetaminophene tablets



Acetaminophene tablets that only relied on the sodium starch glycolate for disintegration (Formulation 1) had slow disintegration time and insufficient mechanical stability. When only RXCIPIENTS® FM 1000 was employed (Sample 2) the resulting tablets had an average hardness of 138.9 N and disintegration time was halved compared to the sodium starch glycolate alone. The use of RXCIPIENTS® FM 1000 as a disintegration promoter decreased tablet disintegration times and minimized friability when used in conjunction with a super disintegrant.

3.3 Example 3 – COX-2 inhibitor ODT formulation

Formulations

Table 3 Formulations of acetaminophene tablets

	Formulation 1 wt.-%	Formulation 2 wt.-%	Formulation 3 wt.-%
Nonsteroidal anti-inflammatory active	25.0 (1)	25.0 (1)	25.0 (1)
Dextrates Emdex, JRS Pharma	5.0 (1) 22.0 (2)	5.0 (1) 32.0 (2)	5.0 (1) 37.0 (2)
Microcrystalline cellulose Vivapur 102, JRS Pharma	5.0 (1) 10.0 (2)	5.0 (1) 10.0 (2)	5.0 (1) 10.0 (2)
RXCIPIENTS® FM 1000	**5.0 (1)** **15.0 (2)**	**5.0 (1)** **5.0 (2)**	**5.0 (1)** **5.0 (2)**
ZEOPHARM® 600	2.0 (2)	2.0 (2)	2.0 (2)
Aspartame, Tate and Lyle	1.5 (2)	1.5 (2)	1.5 (2)
Flavor, Fona International	2.0 (2)	2.0 (2)	2.0 (2)
Crospovidone Polyplasdone, ISP Pharmaceuticals	7.0 (2)	7.0 (2)	2.0 (2)
Magnesium stearate Type 2256, Malinckrodt	0.5 (2)	0.5 (2)	0.5 (2)

Mixing

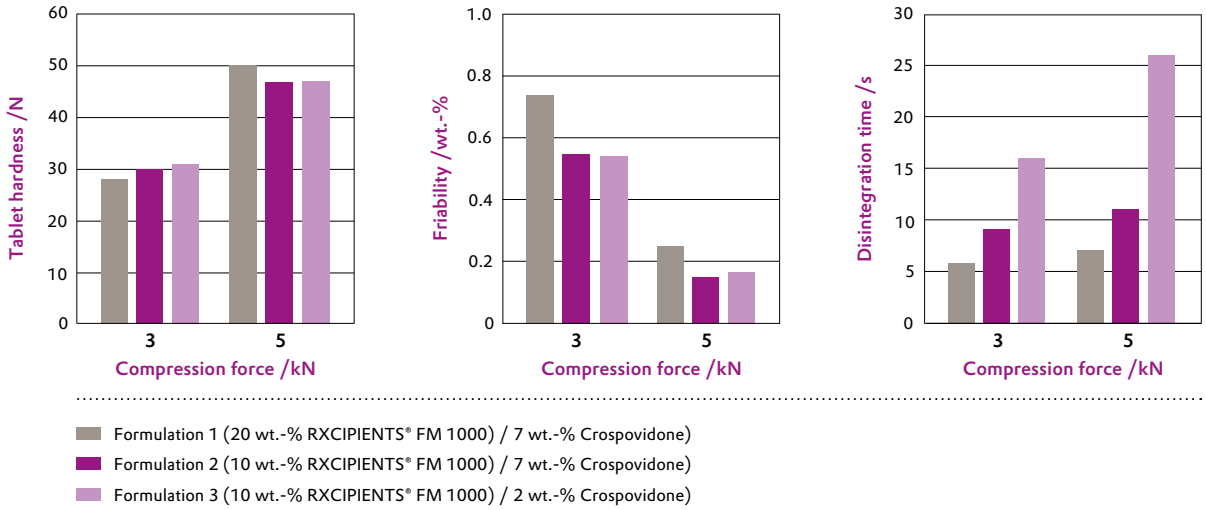
- Two stage mixing process:
  Stage 1: API; part of RXCIPIENTS® FM 1000, MCC, Dextrate
  Stage 2: Stage 1 mix with the other components
- All components except magnesium stearate were passed through a sieve (840 µm)
- Mixing in a V blender for 10 min at 27 rpm
- Addition of magnesium stearate after passing through a sieve (400 µm)
- Mixing in V blender for 5 min at 27 rpm

Tabletting

- SMI – Piccola rotary press, Model 8
- Turret speed: 30 rpm
- Compression force: 3.5 kN
- Tablet diameter: 10 mm
- Tablet mass: 300 mg

Results

Figure 4 Tablet hardness, friability and disintegration time for Cox-2 inhibitor tablets



The ratio of RXCIPIENTS® FM 1000 to PVP-XL plays a critical role in the disintegration time of the tablets. The results show that a loading level of 20 wt.-% of RXCIPIENTS® FM 1000 along with 7 wt.-% of PVP-XL resulted in a 6–7 second disintegration time. If a slower disintegration time is required, a ratio of 10 wt.-% RXCIPIENTS® FM 1000 to 2 wt.-% PVP-XL is recommended. Changing the RXCIPIENTS® FM 1000 to PVP-XL ratio provides the formulator a great deal of flexibility to adjust the disintegration time to a specified target.

4 Chemical identity, regulatory and registration information

Calcium silicate, physical and chemical properties

Appearance	Off-white powder
Median particle size	~ 4 µm
Bulk density	~ 530 g/l
Loss on drying	~ 0.1 wt.-%
Ca content	~ 24 wt.-%
pH (5 wt.-% in water)	~ 9.8

Pharmacopoeia compliance

USP/NF	Complies to monograph "Calcium Silicate"
Ph. Eur.	No monograph for calcium silicates. EMA accepts compliance to USP/NF monographs for products for which no Ph. Eur. monograph exists (see Guideline on excipients in the dossier for application for marketing authorization of a medicinal products)

Chemical inventory status

Chemical name	Australia AICS	Canada DSL	Europe REACH	Korea KECI	USA TSCA
Calcium silicate	registered	registered	exempted*	registered	registered

* *Pharmaceutical excipients are exempted from REACH registration. However, if RXCIPIENTS® FM 1000 is used in applications requiring REACH registration, the user needs to take care of the compliance with the REACH regulation.*

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