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## Optimising excipient properties for ODT formulation

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**Orally disintegrating tablets (ODTs), also known as orodispersible tablets, are unique dosage forms formulated to improve their *in vivo* disintegration and dissolution rates. It is a big challenge to ODT producers to achieve a minimum disintegration time while keeping formulation simple and robust. The required advances in pharmaceutical manufacturing occurred when excipient suppliers developed multi-functional types for direct compression. Roquette's PEARLITOL® Flash, a combination of mannitol and starch, is a ready-to-use excipient for orodispersible tablets. This article describes its application to formulation and how this delivers advantages like robustness and rapid disintegration time. PEARLITOL® Flash means problem-free ODT formulation.**

Oral drug delivery remains the preferred route for the administration of various drugs<sup>1</sup>. Orally disintegrating tablets are becoming increasingly popular around the world. In the European pharmacopoeia the term "orodispersible tablet" is defined as a tablet intended "to be placed in the mouth where it disperses rapidly before swallowing"<sup>2</sup>. The US Food and Drug Administration (FDA) has issued a special Guidance for Industry: Orally Disintegrating Tablets, in which it recommends that ODTs "disintegrate rapidly in the oral cavity with an *in vitro* disintegration of approximately 30 seconds or less and the weight should not exceed 500mg"<sup>3</sup>. Disintegration rate and robustness of ODTs are critical to success.

Numerous reports have been published regarding the technologies to prepare ODTs, such as lyophilization and moulding<sup>1,4-7</sup>. However, to achieve their rapid disintegration rates the resulting ODTs have high porosity, low density and low hardness. This can lead to problems like extremely brittle tablets, a requirement for special equipment, and difficult handling<sup>8</sup>. Direct compression is a simple, cost-effective solution to producing robust tablets that retain the appropriate disintegration properties. The basic direct compression approach in the development of ODTs is to blend and compress a filler, a superdisintegrant, a lubricant and the active pharmaceutical drug<sup>9-12</sup>. To further simplify the formulation of ODTs, a new

generation of co-processed mannitol-based excipient has been developed by ROQUETTE. PEARLITOL®Flash is a combination of mannitol and starch, both of which are pharmacopoeia-compliant. Mannitol is commonly used as a diluent or a bulk excipient in the formulation of ODTs<sup>13-14</sup>. In fact, directly compressible mannitol grades exhibit an attractive balance of sweetness, mouthfeel, solubility, compressibility and rapid dispersibility<sup>15</sup>. PEARLITOL®Flash is specially designed to achieve the latter, providing a smooth texture without the addition of superdisintegrant. The formulations used to evaluate PEARLITOL®Flash disintegration and robustness properties are shown in **Table 1**.

**Table 1: Formulas (%w/w).**

Formula	F1	F2	F3	F4
PEARLITOL® Flash	99.6	89.6	79.6	69.6
Microcrystalline Cellulose (MCC) (Avicel PH102 FMC Biopolymer)	-	10.0	20.0	30.0
Magnesium Stearate	0.4	0.4	0.4	0.4

Placebo ODTs were made by blending PEARLITOL® Flash for 5 minutes with microcrystalline cellulose (MCC). Then the lubricant was added to the earlier mixture or PEARLITOL® Flash alone (F1) and blended for 5 minutes. The tablets were prepared by direct compression using a single-punch tablet press (Korsch XP1) set to obtain a fixed tablet weight (500mg) while increasing the compression force (10-25kN) using 13mm flat beveled-edge punches. Hardness, weight, friability and *in vitro* disintegration time were evaluated according to the USP method. Roquette developed a predictive *in vivo* disintegration time test for ODTs formulated with mannitol by using a texture analyzer instrument (Instron<sup>16</sup>). Only a small number of excipients are necessary for an ODT formulation. The association of starch and mannitol results in a powder characterized by good wettability that allows the formulation of orodispersible tablets without the need for adding a superdisintegrant. Thanks to the glidant properties of starch<sup>17</sup> the lubricant

level required (0.4%) is low. The hardness of the tablets increased with compression force (**Figure 1**).

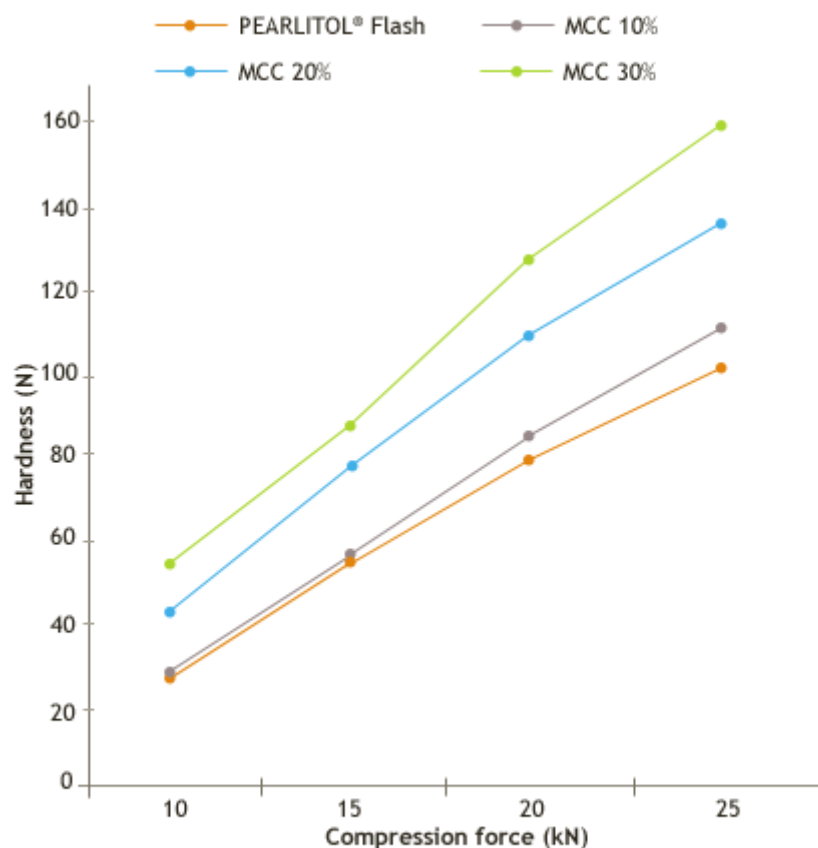


Figure 1: Compression profile of different formulations showing impact of addition of microcrystalline cellulose on tablets hardness.

A 15kN compression force is sufficient to obtain tablets with acceptable hardness and disintegration time (**Tables 2 and 3**). It is the combination of starch and mannitol that gives this compound its disintegration advantages.

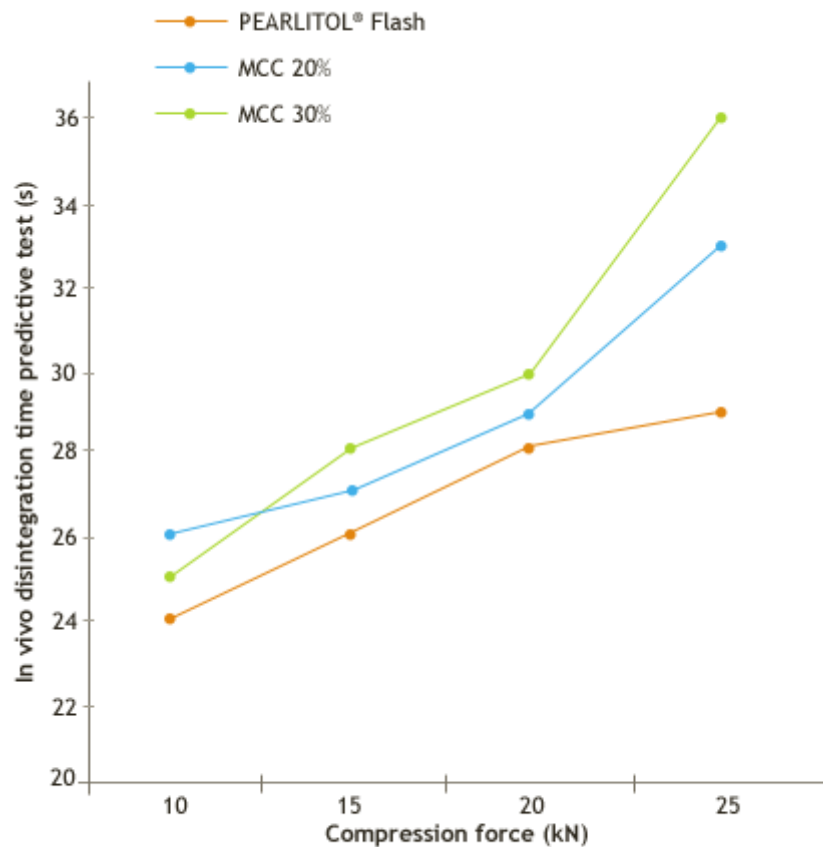
Table 2: In vitro disintegration time of PEARLITOL®Flash tablets (m ± SD, according to USP method).

	10	15	20	25
F1	68 ± 20	75 ± 26	69 ± 23	74 ± 20
F2	68 ± 17	74 ± 20	78 ± 15	80 ± 14
F3	40 ± 9	42 ± 8	50 ± 8	48 ± 8
F4	22 ± 4	28 ± 4	32 ± 5	31 ± 5

**Table 3: Predicted in vivo disintegration time of PEARLITOL®Flash tablets ( $m \pm SD$ , according to internal method).**

	10	15	20	25
F1	24 ± 0.4	26 ± 0.3	28 ± 0.3	29 ± 0.6
F3	26 ± 0.4	27 ± 0.0	29 ± 0.6	33 ± 1.2
F4	25 ± 0.4	28 ± 0.6	30 ± 0.4	36 ± 1.2

The hardness of the tablets can be significantly improved by adding 20% of microcrystalline cellulose (MCC) (**Figure 1**). ODTs made with PEARLITOL® Flash have a rapid predicted oral disintegration time (less than 1 minute) whatever the compression force (**Figure 2**).



**Figure 2: Impact of addition of microcrystalline cellulose on predicted in vivo disintegration time.**

Surprisingly, the disintegration time is not significantly influenced by the tablet hardness. In the presence of MCC, an increase in disintegration time was observed with the application of a high compression force (25kN) but the increased time (36 seconds) still remains acceptable to consumers. *In vitro* Pharmacopoeial disintegration time was measured at below three minutes (**Table 2**).

## CONCLUSION

PEARLITOL<sup>®</sup>Flash has been developed as a self-disintegrating mannitol compound for the formulation of ODTs by direct compression. Thanks to its specific composition, a very low level of lubricant is necessary (0.4%). For the tablets made exclusively with PEARLITOL<sup>®</sup>Flash, predicted *in vivo* disintegration time (below 30 seconds) is not dependent on compression force and hardness. To improve the robustness of the formulation and obtain greater production flexibility, a compression binder such as microcrystalline cellulose can be added to the formulation without significant impact on disintegration time. PEARLITOL<sup>®</sup>Flash facilitates formulation of ODTs.

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