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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[1]. 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"[2]. 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"[3]. 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[1,4-7]. 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[8]. 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[9-12]. 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[13-14]. In fact, directly compressible mannitol grades exhibit an attractive balance of sweetness, mouthfeel, solubility, compressibility and rapid dispersibility[15]. 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[16]). 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[17] the lubricant

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

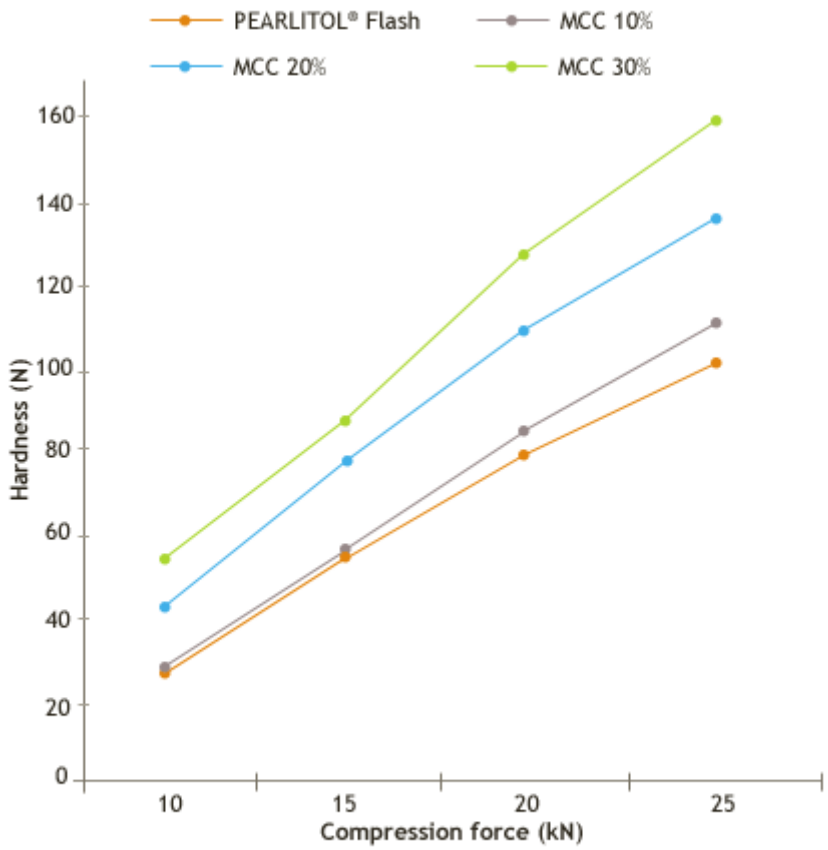

Figure 1: Compression profile of different formulations showing impact of addition of microcrystalline cellulose on tablets hardness.

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 ± 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**).

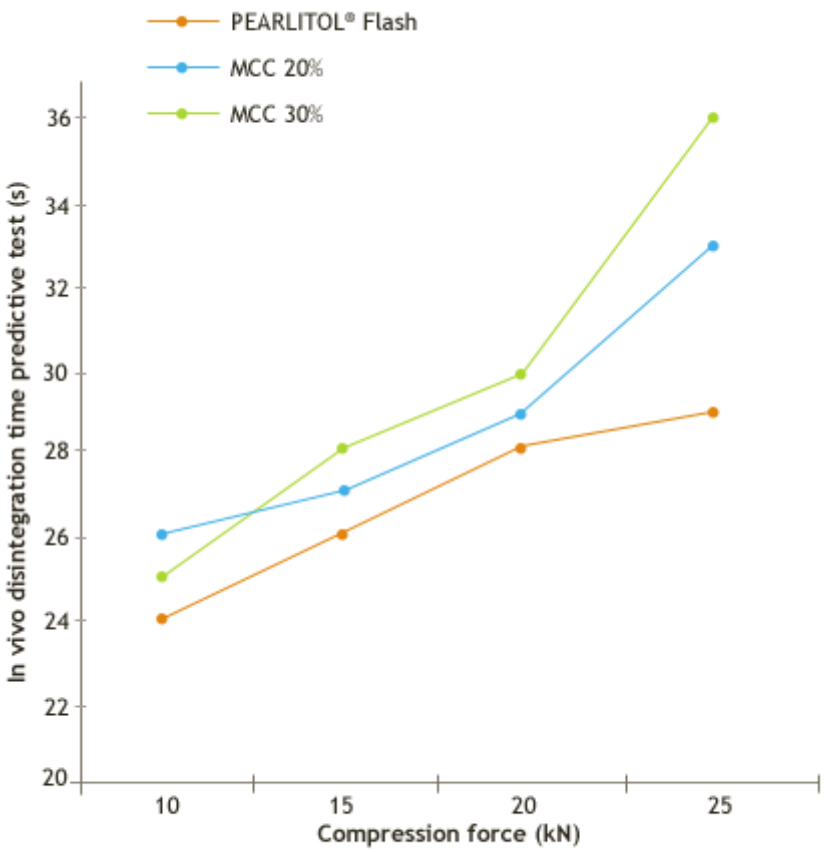

Figure 2: Impact of addition of microcrystalline cellulose on predicted in vivo disintegration time.

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. I*n vitro* Pharmacopoeial disintegration time was measured at below three minutes (**Table 2**).

CONCLUSION

PEARLITOL®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®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®Flash facilitates formulation of ODTs.

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