Rapid Development of Robust, Large Dose, Direct Compression ODTs

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INTRODUCTION

Orally Disintegrating Tablets (ODTs) are a well-established dosage form that improve patient convenience, enabling patients to take their medicines without resorting to the need for a glass of water to facilitate swallowing. Hence, they are particularly targeted at specific patient groups; e.g paediatric, geriatric and dysphagic. Many APIs have been formulated into ODTs and successfully commercialized. Most of these products are low dose and/or reasonably palatable without need for substantial taste masking; with drug taste overcome by the appropriate use of excipients, flavours and sweeteners. The increased use of ODTs resulted in the FDA issuing a Guidance Paper[1] in 2008 regarding typical Critical Quality Attributes (CQAs) of ODTs. Unfortunately, this Guidance did not go into great detail regarding ODTs that incorporated high doses of APIs. The wide use of ODTs to treat pain and inflammation, particularly in an OTC format, mean that there is a need to understand achievable targets in terms of CQAs when developing these formulations. Additionally, as incorporation of taste masked APIs at higher dose levels becomes increasingly challenging particularly for this type of dose form it is important to be able to characterize these systems more fully.

AIMS AND OBJECTIVES

The current study aims to give insight into the formulation of robust ODT's based on Pharmaburst® 500, a commonly used ODT excipient platform supplied by SPI Pharma. We aim to understand the compressibility, compactability and tabletability of formulations with paediatric dose loadings of the taste masked paracetamol (Actimask® 92M). Such active loadings leads to tablet sizes at the upper limit or beyond the 500mg level considered in the FDA Guideline. However, these formulations represent a common formulation challenge for this type of product. The relationship between Disintegration Time (DT) and tablet robustness (assessed in terms of Tensile Strength (TS) and Friability) were evaluated for the higher dose of a poorly compactible API (taste-masked paracetamol) with the goal to determine the relationship seen for the excipient system only. In addition, the porosity of the tablets were compared to values reported elsewhere[2].

MATERIALS AND METHODS

Simple ODT formulations were compressed on a Styl'One™ evolution fully instrumented single punch tableting instrument. Styl'One enables rapid evaluation of tablet mechanical properties of different formulations using small quantities of powder. A study of the compression characteristics was performed on Styl'One using the Analis™ software. The software also obtains values for Elastic Recovery (ER) and Ejection Force (EF). The true density of each formulation was measured using a helium pycnometer. Together with the other dimensional data obtained in the investigation the skeletal density enabled tablet porosity to be calculated and analysed.

The formulations are given in Table 1. A level of 2.5% of the lubricant sodium stearyl fumarate (Lubripharm®) was chosen. Other works[2,4,5] have investigated this lubricant in ODT formulations at levels ranging from 1 to 3%. 2.5% is at the higher limits normally seen but previous in house data had suggested this level minimized ejection force without significantly increasing DT. The materials were blended together for 10 minutes in a Turbula Mixer prior to the compression studies. Both fast and slow compression speeds were investigated the slow speed being approximately 25% of the fast speed. The intent was to see whether any difference was observed that would indicate scale up challenges. The formulations were compressed using 11.28mm flat face tooling, and a profile consisting of a main compression that gave a compression time of around 100ms and a dwell time of 15ms and was intended to mimic a tableting speed routinely used for development scale (this was the 25% setting). The resultant tablets were then assessed for the CQAs. TS was calculated by measuring thickness, diameter and hardness on a WHT tester. Friability was measured according to the USP Method. DT was obtained again according to the USP Method.

Table 1 – Formulation Details

Formulation	1	2	3
Material	% w/w	% w/w	% w/w
Pharmaburst 500	97.5	72.5	58
Lubripharm SSF	2.5	2.5	2.5
Actimask paracetamol	0	25	25
Mannogem® 2080	0	0	14.5

RESULTS AND DISCUSSION

Figure 1 shows the relationship between TS and CP for the 3 formulations. Although a target TS of >1.7MPa is widely acknowledged as a must-have CQA for conventional 'swallow' tablets[3], with a Relative Density of around 0.85, no such consensus exists for ODTs. Several studies have been undertaken assessing ODTs formulated from different excipients by DC. However the majority of them have focused on the excipient only[4] or with the incorporation of low dose actives, such as hydrochlorothiazide in orally disintegrating minitablets[5] (ODMTs). Forster et al[4] studied a range of DC ODT excipient platforms and highlighted the importance of achieving acceptable tablet robustness whilst targeting DT of less than 30 seconds but only considered placebo systems. In that study, they demonstrated the performance of different ODT excipient platforms and attributed varying performance to the compositional differences between the platforms, highlighting the superior performance of Pharmaburst 500 in achieving the required tablet robustness combined with fast DT.

Figure 1

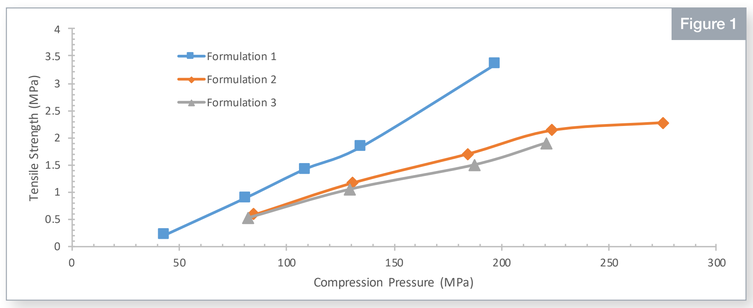


Figure 2

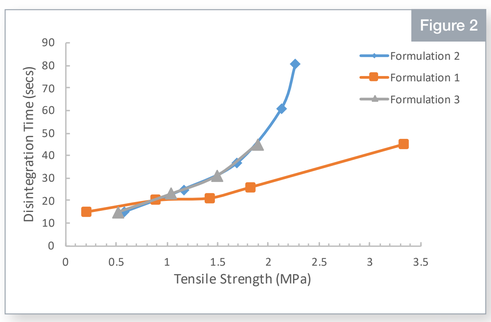
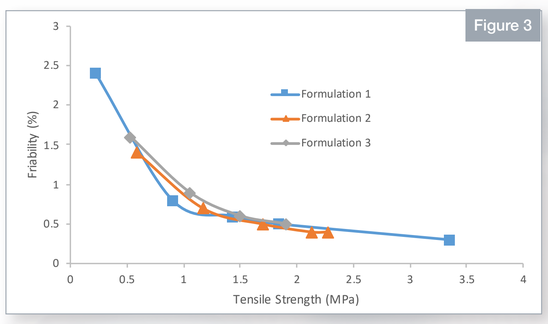


Figure 2 shows that for these current formulations hitting the desirable target of DT's less than 30 secs and TS > 1.7MPa is more challenging. There is a clear difference in the excipient only formulation when compared to formulations containing 25% taste masked API both in terms of TS achievable and resultant DT From the data obtained in our current study (Figures 1 and 2) a TS greater than 2MPa is still achievable at routine Compaction Pressures (< 250MPa for the API containing formulations). However, there exists an obvious play off between achieving adequate TS and retaining a fast disintegration time. Although TS is an important parameter to characterize a tablet formulation's robustness, friability should also be considered. Figure 3 shows that although significant differences are seen in terms of TS between the excipient only and drug loaded formulations these differences do not translate to significant differences in terms of friability with all 3 formulations lying on essentially the same line in a friability versus TS plot.

Figure 3



As well as the need to formulate a robust tablet the formulator must ensure an ODT has an acceptable DT. Brniak et al.[6] highlighted the variability in ODT excipient platforms in terms of their ability to wick water and the subsequent alternative mechanisms of disintegration associated with these different systems. Although they looked at some formulations containing ibuprofen and highlighted differing performance in terms of DT between placebo and active systems, they did not show a detailed relationship between TS, DT and friability in their drug loaded formulations.

In our current work we clearly see a much faster DT is achieved when an excipient only is used. Incorporation of taste masked API significantly retards DT. To meet the FDA Guideline of a 30sec DT a maximum TS of around 1.5MPa can be achieved for the formulations containing API (Figure 2). This still seems an adequate TS given that Friability was well below 1% for these formulations (Figure 3). Conversely, targeting a shorter DT comes with the risk that the tablet may not be robust enough to withstand downstream processes such as packaging (Figures 2 and 3). This conundrum is more challenging when one considers ODTs where the drug loading is higher and when the API is taste masked so it has to retain coating integrity during compaction. Larger tablets also have a proportionally longer DT simply due to the smaller surface area to volume ratio.

Very recent work by Draskovic et al.[2] considered dynamic compaction analysis for a range of DC ODT systems. They observed significant porosity differences between the commercial ODT platforms and the relation to tablet TS and the influence of the inclusion of the poorly compactible API ibuprofen at various weight loadings. They found formulations containing Pharmaburst 500 retained higher porosity than the other ODT excipient platforms studied, even at significant weight loadings of ibuprofen. This translated to shorter DT's with the tablets retaining adequate TS. Figures 4 and 5 shows the relationship of porosity to TS and porosity to DT for the 3 formulations investigated. Porosity values are lower than those reported previously[2] but were higher than values they observed for other ODT platforms. The inclusion of a different API that in our case is taste masked with a gelatin coating may explain the differences seen in absolute porosity values but confirm the importance of optimization of porosity and TS to obtain acceptable DT's.

Interestingly, incorporation of a large particle size mannitol (Mannogem 2080) into Formulation 3 enhanced DT (45sec versus 81sec for tablets of equivalent thickness (3.96mm) without having an overly detrimental effect on the robustness of the tablets (Figure 6). The porosity of the tablets were about equivalent between Formulation 2 and 3 so that cannot explain this difference. Potentially, the increased hydrophilic nature of the additional mannitol may enhance the wettability of the system, reducing overall DT. This is likely useful in situations with large dose drugs where the DT is marginally too long.

Figure 4

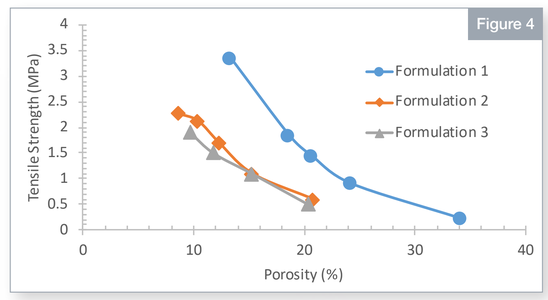


Table 2 – Elastic Recovery Data

Formulation	E.R at low speed high Force (22kN) (%)	E.R at high speed high Force (22kN) (%)
1	7.8	9.9
2	8.2	10.6
3	7.1	10.2

Assessment of elastic recovery data (Table 2) revealed minimal increase in ER versus Force seen for all formulations at the low speed. ER for all formulations at low speed was around 7-8%, which is close to the value reported by Draskovic[2] at lower compaction pressures. At high speed all formulations showed higher ER at high compaction Forces (around 22kN), although this increase was minimal (around 2-3%) with the peak value of around 10% significantly lower than was reported. Clearly ER will vary depending on a number of factors including the formulation and the compaction speed being used. Compaction speed did not significantly affect any of the other CQA's such as TS or DT.

Figure 5

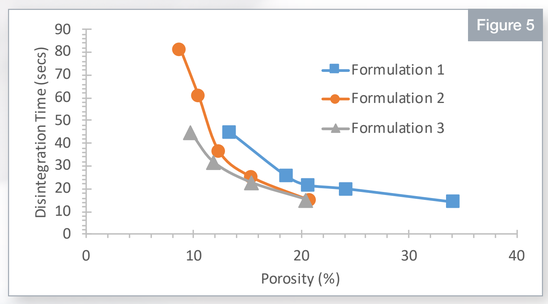
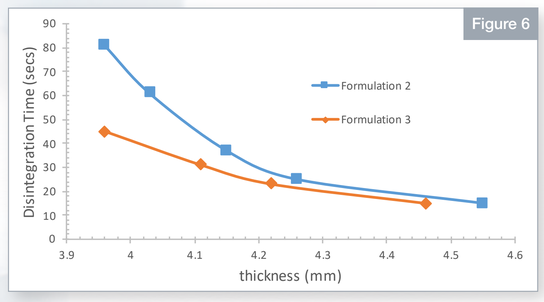


Figure 6



CONCLUSIONS

Formulation of higher drug loading ODTs (25%) of poorly compressible taste masked APIs by Direct Compression requires a payoff between achieving the requisite tablet robustness and meeting the DT requirements as laid out in the FDA Guideline. Simple, palatable, taste masked ODTs were achieved using the ODT platform Pharmaburst and the taste masked paracetamol API Actimask. These formulations had sufficient robustness in terms of meeting friability requirements despite having lower TS than typically targeted for conventional 'swallow' tablets. An insight into as many compression characteristics as possible including TS, friability, porosity, and ER should be gained when developing ODTs in order to ensure target CQAs are met. This becomes increasingly important as the drug loading of taste masked APIs is increased. The Styl'One tableting instrument proved an efficient and flexible tool to enable rapid screening, characterisation and development of an optimized formulation and process.

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