Upping the Ante in ODT Formulations – Characterization of ODT Formulations as a Function of Drug Loading

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INTRODUCTION

Orally Disintegrating Tablets (ODTs) are a well-established dosage form that improves patient convenience through a rapid oral disintegration and ease in swallowing. Formulation challenges for ODTs increase significantly in drugs with doses greater than 100 mg. The formulator often strives to meet a critical quality attribute (CQA) for robustness while simultaneously seeing impacts to disintegration time and the organoleptic aspects of the dose form. This study investigates the relationship between drug loading and tablet CQAs, specifically linking them to practical targets that go beyond those discussed in the FDA Guideline[1]. This novel research provides guidance for the specific challenge related to higher dose API tablet formulation.

AIMS AND OBJECTIVES

The current study aims to give insight into the formulation of robust, high dose ODTs. In order to have a viable product, the formulator connects the functional limitations of the excipients being used and how they relate to the final product CQAs. We have investigated the impact of API dose using formulations developed with Pharmaburst® 500 and Actimask® 92M, a commercially available ODT platform and taste masked paracetamol respectively. At active loads of 250 mg and 500 mg, the tablet sizes are at or exceed the upper limit considered in the FDA Guideline. However, these objectives represent a realistic formulation challenge for ODTs with larger doses.

The Disintegration Time (DT) and Tablet Robustness (in terms of Tensile Strength (TS) and Friability) were compared for different doses of a challenging taste masked API and the excipient only system. In addition, other important tableting parameters such as the porosity of the tablets and the energy of compaction were obtained and compared to values reported elsewhere[2,4,7].

MATERIALS AND METHODS

ODT formulations containing the commercial platform Pharmaburst 500 and different loadings of the taste masked API paracetamol (Actimask 92M) were compressed on a Styl'One™ evolution, a fully instrumented single punch tableting instrument. The experimental results, giving the compression characteristics from the Styl'One, was processed using the Analis™ software. The software calculated values for Compaction Energy (Plastic and Elastic) as well as Elastic Recovery and Ejection Force. The true density of each formulation, used to obtain out of die tablet porosity, was measured using a helium pycnometer.

The formulations for the different paracetamol doses are given in Table 1. A level of 2.5% of the lubricant sodium stearyl fumarate (Lubripharm® SSF) was chosen. Other workers [2, 3] have investigated this lubricant in ODT formulations at levels ranging from 1 to 3 %. A lubricant level at 2.5 % is at the higher limits typically used, however, previous in-house data suggests this level of Lubripharm evenly minimized ejection force over experimental conditions without significantly increasing DT. The materials were blended together for 10 minutes in a Turbula Mixer prior to the compression studies.

The formulations were compressed using 11.28 mm flat face tooling. Resulting tablets were then assessed for the CQAs. TS was calculated by measuring thickness, diameter, and hardness on a WHT tester. Friability and DT were measured according to the respective USP Methods.

Table 1 – Formulation details

Formulation	1	2	3	4	5
Material and level	% w/w	% w/w	% w/w	% w/w	% w/w
Pharmaburst 500	97.5	72.5	58	44.9	37
Lubripharm SSF	2.5	2.5	2.5	2.5	2.5
Actimask paracetamol	0	25	25	52.6	51.3
Mannogem® 2080	0	0	14.5	0	9.2

RESULTS AND DISCUSSION

Results given in Figures 1 and 2 show a clear relationship between drug loading and tablet robustness as measured by TS and Friability. While there are a number of published studies on the physical attributes of dose forms made using ODT platforms [2,3,4,5] the majority of the data is generated using placebo formulations or for formulations with API that has not been taste masked. A sparsity of data exists for taste masked ODT formulations with drug loads that exceed 20%.

Figure 3 shows the relationship between drug loading, porosity, and DT. Compared to values of placebo Pharmaburst 500 tablets, these results demonstrate how tablet robustness changes when the taste masked drug loading approaches 50%. While robustness is impacted by the drug load, both friability and DT values are within the acceptable ranges for ODTs under a range of compression forces. This shows that there is a payoff between obtaining a target TS and meeting a 30 second DT. As expected, these contradicting effects are an industry challenge when the drug loading exceeds 50%. Higher DT values result from both the decreased tablet porosity given by the API as the drug loading is increased and the higher compression needed to obtain TS.

The porosity values we report for Pharmaburst 500 containing formulations are close to those reported elsewhere[4,6] and are significantly higher than porosity results reported for other ODT platforms with and without drug loadings[4]. Tablet porosity is a key consideration in the development of ODTs as it is directly related to DT. From the results, we found that a target porosity for tablets containing a high loading of taste masked API (25 – 50%) and Pharmaburst 500 should be a final out of die porosity of around 9 – 12% in order to achieve the requisite balance of acceptable robustness and low DT.

Another important characteristic in any DC formulation is to understand the compaction energy and how it relates to the final dose form attributes. The area under the force displacement profile represents the energy or work done during the compaction process and the plastic energy represents the degree to which plastic deformation is being undertaken. Yaakub et al[7] showed the influence that different levels of lactose and super-disintegrants had on plastic energy across a range of compaction pressures. Their research found that plastic energy increases as a function of compression pressure and is influenced to a different extent by different excipients. Similarly, it is possible with the Analis software to capture compaction energy in the form of both Plastic and Elastic Energy. Figures 4 and 5 show Plastic and Elastic Energy across the different formulations as well as for the individual components. Plastic energy for the pure excipients falls in the range of between 10 and 23 J for the compression forces used (10-35 kN).These values are similar to values reported by Yaakub et al[7] for formulations based on super-disintegrants and lactose but are lower than those obtained for microcrystalline cellulose generated at similar compression forces (in house unpublished data). The relatively low Compaction Energy seen compared to conventional binder systems highlights the specific challenge in generating a robust ODT system that meets the conflicting requirements of tabletability, low DT, and organoleptic acceptability. The values for the taste masked drug loaded formulations are lower, as expected, at 5-16 J and proportionally decrease as the drug loading increases.

The Elastic Energy of the pure taste masked API, formulations with taste masked API, and pure excipients are given in Figure 5. This data shows that the taste masked drug contributes negatively to Elastic Energy which must be addressed through the formulation approach to achieve a suitably robust tablet. The positive influence of the excipients, like Mannogem 2080, demonstrate that their incorporation into the Pharmaburst formulation may overcome the negative Elasticity of both the API and other ODT components. Interestingly, the incorporation of the larger particle size mannitol into the formulation (Formulation 3) not only reduced the Elastic Component of the compaction but decreased the DT to 45 seconds versus 81 second for tablets of equivalent thickness (3.96 mm) without having an overly detrimental effect on the robustness of the tablets (Figure 6). The tablet porosities were equivalent between Formulation 2 and 3. The explanation could be that the increased hydrophilic nature of the additional mannitol may enhance the wettability of the system, reducing overall DT, useful in situations with large dose drugs where the DT is marginally too long.

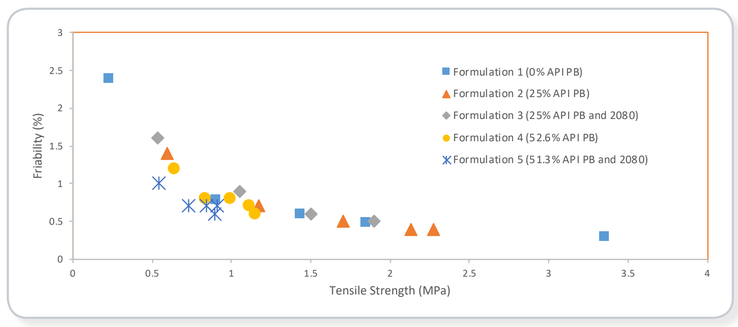

Figure 1: Relationship between Tensile Strength and Friability for Formulations with a range of API loading

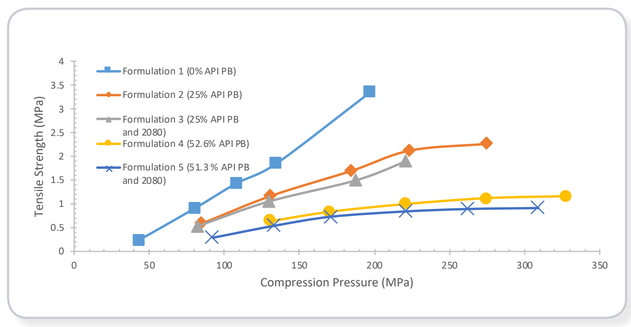

Figure 2: Relationship between Tensile Strength and Compression Pressure for a range of Formulations with different API loading

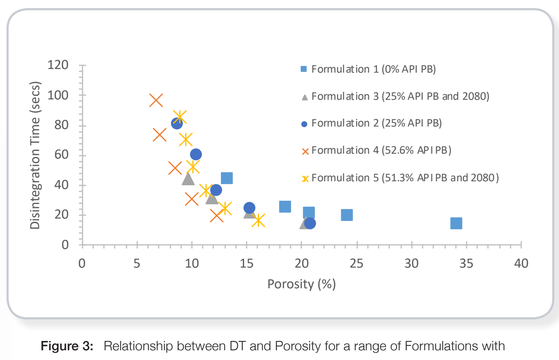

Figure 3: Relationship between DT and Porosity for a range of Formulations with different API loading

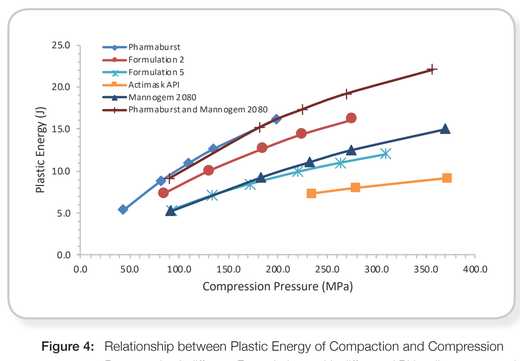

Figure 4: Relationship between Plastic Energy of Compaction and Compression Pressure for 2 different Formulations with different API loading compared with API and excipient (2.5% SSF as lubricant in all cases)

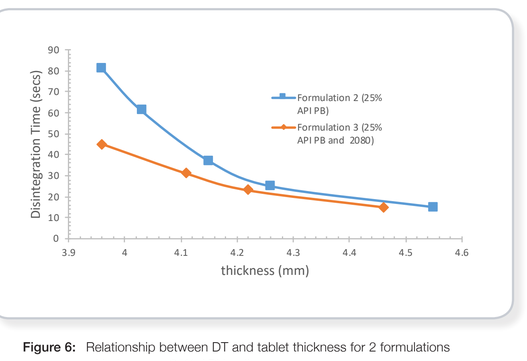

Figure 6: Relationship between DT and tablet thickness for 2 formulations with the same 25% API loading

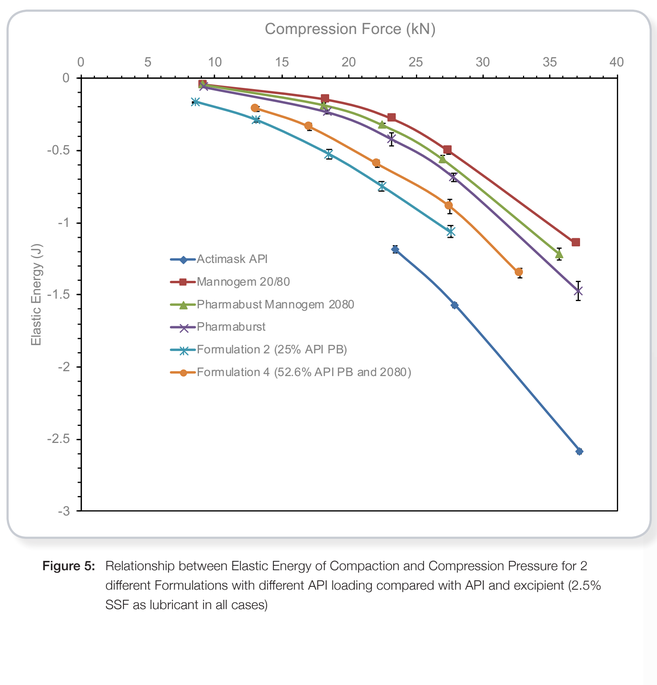

Figure 5: Relationship between Elastic Energy of Compaction and Compression Pressure for 2 different Formulations with different API loading compared with API and excipient (2.5% SSF as lubricant in all cases)

CONCLUSIONS

Full mechanical and physical characterization of a formulation can help in the design of ODTs with higher drug loading (> 20%). The development of a direct compression ODT formulation requires a balance between achieving the requisite tablet robustness and meeting a low DT. We have shown that by using Pharmaburst 500 as a co-processed ODT platform an acceptable balance between all CQAs are possible at drug loadings up to 50% while maintaining acceptable organoleptics. This formulation strategy is useful for both larger tablets with higher drug loads or decreasing tablet size for patient compliance.

The Styl'One tableting instrument proved an efficient and flexible tool to enable rapid screening, characterization of the formulation components and to help in the development and understanding of an optimized formulation.

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