Comparison of Orally Disintegrating Technologies in High Dose Acetaminophen Tablets.

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Introduction

The majority of currently formulated orally disintegrating tablets (ODT's) available on the market have a relatively low dose of active pharmaceutical ingredient (API content < 50mg). The major reason for this is the difficulty associated with the formulation and manufacture of high-dose ODT's. The formulation of high-dose ODT's presents all the challenges of manufacturing low-dose ODT's, most notably the balancing of rapid disintegration with both tablet robustness and pleasing organoleptics. However, in high-dose ODT manufacture these difficulties are more pronounced, due to the increased proportion of API relative to other igredients in the formulation. For this reason, any pre-formulated ODT system that is being considered for the manufacture of high dose ODT's should be precisely optimized to provide robust tablets with rapid disintegration characteristics.,

This study compared three commercially available, ODT systems for direct compression: Pharmaburst® 500, Technology A, and Technology B with regard to their performance in manufacturing a high-dose ODT. Acetaminophen was selected as the model API due its popularity as an orally disintegrating dosage form.

Tablet Manufacture

500g blends were manufactured for direct compression according to the formula presented in table 1. All ingredients were passed through a #20-mesh screen prior to blending. Subsequently, each respective ODT technology was blended with the taste-masked acetaminophen in an 8-quart V-blender for 15 minutes at 25 rpm. Next, the Lubripharm® SSF(SPI Pharma) was added to the resultant blend and mixed for 5 minutes at 25 rpm. Each blend was compressed into 1200 mg tablets (containing 500 mg of acetaminophen) on a GP-8 rotary tablet press outfitted with 0.625" FFBE "type D" punches at compression forces of 10, 15, 20, 25, and 30 kN with 1.5 kN of pre-compression force. The press was operated at 25rpm. The measured tablet characteristics were tablet hardness, friability, and USP/EP disintegration time.

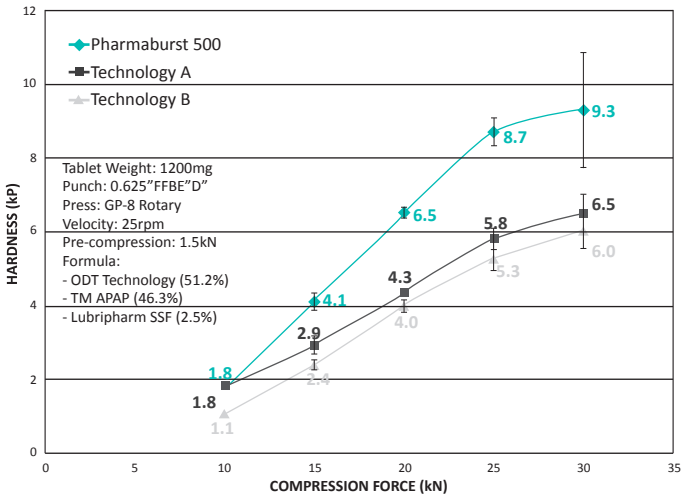
Table 1: High-Dose ODT Formulation

Ingredient	%	mg/tablet
Taste-masked APAP (90.0%)	46.3	555.6 (equivlant to 500mg APAP)
ODT Technology	51.2	614.4
Lubripharm SSF	2.5	30
Totals	100.0	1200

Results

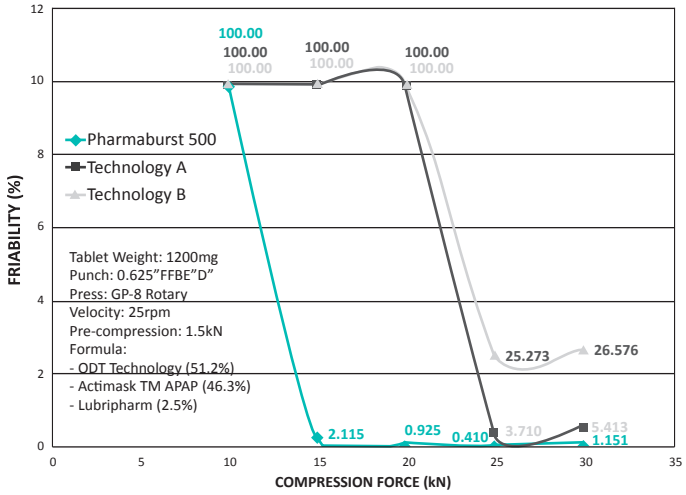
As seen in figure 1, over the studied compression force range, Pharmaburst 500 provided for greater compaction as determined by tablet hardness. This greater compaction is required for the manufacture of robust (high hardness and low friability), high-dose ODT's. The greater compaction is typically associated with a higher dilution capacity which is necessary in order to consolidate less potent API's into high-dose ODT's.

Figure 1: Tablet Hardness



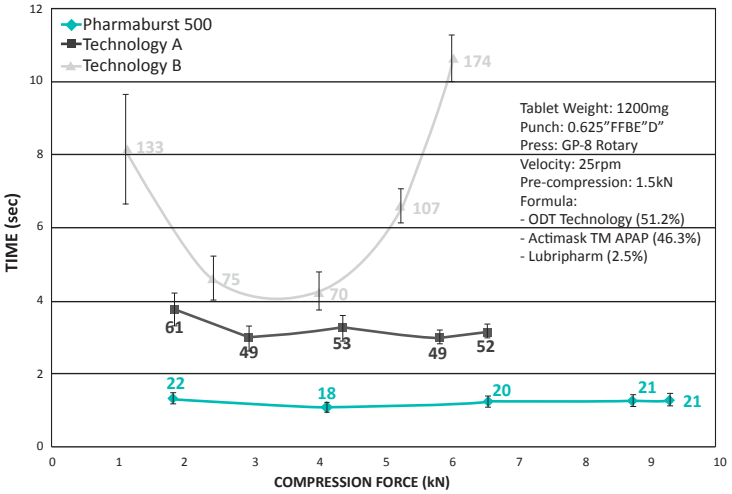
As seen in figure 2, over the studied compression force range, Pharmabust 500 provided for lower overall friability than technology A or technology B. At 20 kN and 25 kN, for ODT's manufactured with Pharmaburst 500, friability was below 1.0%. Comparatively, both technology 1 and technology 2 exhibited friability in excess of 1.0% over the entire compression force range studied. This indicates that Pharmaburst 500 provides for superior tablet robustness, with regard to friability, even when incorporating large quantities of API.

Figure 2: Tablet Friability



As seen in figure 3, over the compression force range studied, Pharmaburst 500 provided for lower USP/EP disintegration times than technology 1 and technology 2. Additionally, all disintegration times for Pharmaburst 500 were under 30 seconds, which is the current limit in the FDA's guidance on ODT's. Conversely, the USP/EP disintegration times for both technology A and technology B are above 30 seconds at all stations of the compression force range. In order to meet the FDA guidance on ODT's (FDA-CDER, Guidance for Industry-Orally Disintegrating Tablets, December 2008), formulations using Technology A or B would require the addition of super disintegrants, which would increase the overall formulation cost.

Figure 3: USP/EP Tablet Disintegration Time



Conclusion

Pharmaburst 500 provides an efficient, optimized platform for the manufacture of high-dose ODT's. In a comparative high-dose, ODT formulation evaluation against two other marketed ODT, drug-delivery technologies, Pharmaburst 500 was found to be more compactable, less friable, and more rapidly disintegrating. In this study, Pharmaburst 500 was the only technology which obtained acceptable friability (<1.0%) and acceptable USP/EP disintegration times (<30 seconds) in association with a high-dose, acetaminophen ODT.

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