Developing Robust Chewable Tablet Formulations

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INTRODUCTION

Chewable tablets are an increasingly popular oral dosage form, with market growth particularly in the branded Rx segment. Chewable tablets offer flexibility for pediatric and geriatric patients who may have difficulty swallowing large tablets or who suffer from dysphagia. The FDA has recently issued a guidance[1] regarding the Critical Quality Attributes (CQAs) related to chewable tablets. The guidance highlights the importance in designing robust dose forms with the patient in mind. The organoleptics of the dose form should be considered to improve patient acceptance, which may include incorporating taste masked actives if necessary. In this work we aim to further explore the limitations and opportunities in developing robust chewable tablets that meet the FDA guidance principles.

BACKGROUND

Paracetamol is a widely used drug for the treatment of pain and elevated temperature in children. Aside from its reported bitter taste[2], paracetamol was used in this study as a model compound due to its poor compressibility and large particle size (300 µm average). Initial development activity for a chewable tablet formulation was undertaken on a Styl'One Evo™ tableting instrument. The goal was to understand the relationship between coated and uncoated active and the tabletability of the mannitol binder to give a final dose form of requisite CQAs such as tensile strength, hardness, disintegration time, and friability. The binder compared in this work is a standard spray-dried mannitol versus Mannogem® XL Mannitol, which is designed for higher tabletability. For this work, a target active dose of 120 mg of paracetamol was used in the pure form, as well as in the taste masked form with the goal to understand the influence of the drug, taste masking, and filler/binder system on the tablet CQAs. Formulation details are given in Table 1. In the second part of the investigation, the formulation was scaled up to a development scale and work was undertaken on a Globe Pharma 8 station rotary press to optimize the formula based on the findings from the initial lab development to improve the overall tablet characteristics. For this work, the target dose was adjusted downward to 80 mg for the US market and inclusion of mcc was investigated to understand its role in improving the overall robustness of the tablet. At the same time the different grades of mannitol that were used in Phase 1 were investigated to see if the same findings remained valid.

MATERIALS AND METHODS

In Phase 1, the formulations used were two different grades of mannitol, non-taste masked and non-DC paracetamol, the taste masked paracetamol (Actimask® 92M), super disintegrant (AcDiSol), and lubricant (Lubripharm® SSF). These formulations were compressed on a Styl'One Evo fully instrumented single punch tableting instrument. The Analis™ software was used to record all the relevant parameters from each compression. Compression was undertaken at a slow speed (25 rpm, ~45-50 msec dwell time) for the majority of the study, but for each formulation a run at fast speed (80 rpm, ~5-6 msec dwell time) was undertaken to investigate what influence speed had on tablet characteristics, if any. Results were obtained through a simulated compression profile of a Fette 1200 Euro D tablet press. A pre-compression force of around 6 kN was used for each compression. Formulations were blended in a Turbula® mixer for 10 minutes; then lubricant was added, followed by another 2 minutes of blending before they were compressed. The formulations were compressed using 11.3 mm flat faced tooling. The resultant tablets were then assessed for the CQAs. Tensile strength was calculated by measuring thickness, diameter and hardness on a WHT tester. Friability and disintegration time were obtained according to the USP Methods. Table 1 shows the formulation details.

Table 1. Target quantity of each material in each tablet for each formulation in mg per tablet for Phase 2 of the study

Material	Form 1	Form 2	Form 3	Form 4
Paracetamol	120	120	-	-
Actimask®	-	-	120	120
Mannogem® XL	453	-	453	-
Standard Spray Dried Mannitol	-	453	-	453
AcDiSol	18	18	18	18
Lubripharm®	9	9	9	9

For Phase 2 of the study, the materials were first passed through a #20 MESH sieve. They were then blended in a Vcone blender for 15 mins. The lubricant was then added and blending continued for a further 2 minutes. The compression blends were then compressed on a Globe Pharma 8 station rotary tablet press with a target tablet weight of 800 mg using 14 mm flat faced beveled edge tooling run at an RPM of 25, equivalent to a dwell time of 70 msec.

Table 2. Target quantity of each material in each tablet for each formulation in mg per tablet for Phase 2 of the study

Material	Form 1	Form 2	Form 3	Form 4
Paracetamol	86	-	86	-
Actimask®	-	86	-	86
Mannogem® XL	580	-	-	580
Standard Spray Dried Mannitol	-	580	580	-
Crospovidone	40	40	40	40
Avicel PH102	80	80	80	80
Magnesium stearate	14	14	14	14

RESULTS AND DISCUSSION

The FDA guidance proposes an upper limit for tablet hardness in chewable tablets of 12 kp (equivalent to 117.7 N). One of the purposes of the study was to understand the practicality of this limit in terms of tablet robustness as demonstrated by friability and tensile strength and to relate that to the FDA guideline recommendations. Although a defined hardness is given in the FDA guidance, tensile strength is used here since reporting hardness is not relatable across the wide variety of shapes and sizes used in commercial products. In addition, flat faced tooling was chosen to eliminate the impact of tablet shape and create ease in determining tensile strength. Another advantage of using flat faced tooling is that it produces tablets prone to edge damage[3] during friability testing. Flat faced tablets are also a common design for chewable tablets. This enabled us to highlight relative differences in robustness of formulations during early development (Phase 1). In Phase 1, it was clear that Mannogem XL produces tablets of a higher hardness and tensile strength with lower friability compared to standard spray dried mannitol compacted with both non-taste masked and taste masked paracetamol. In addition, tablet friability improves significantly with the use of the taste masked Actimask 92M paracetamol versus uncoated API alone. The data generated in Phase 1 suggests it is challenging but possible to achieve the targeted CQAs of an upper limit of 12 kp = 117.7 N for hardness but a desired friability of less than 1%. Formulation 3, which uses Mannogem XL and Actimask, hits these CQA targets, although the design space is relatively small. Disintegration times were all acceptable and short, generally below 50 seconds, for all formulations. Additionally, no significant differences were seen in tablet properties for tablets compressed at long or short dwell times, suggesting relative robustness of the formulations to compression speed. In order to meet the target friability and maintain a target hardness below 12 kp, a small amount of MCC (10%) was incorporated in the formulations in Phase 2 to widen the design space. Figures 3 and 4 show the relationship for Compression Force versus tablet hardness, and friability versus hardness respectively for the formulations detailed in Table 2. The results show that incorporating MCC does not improve the desired CQAs for tablet hardness and friability when both non-taste masked APAP and standard spray dried mannitol (Formulation 3) are used. Using the standard spray dried mannitol gives tablets within the target limits for friability at hardness values that were above the FDA recommended upper target of 12 kp for chewable tablets. However, the optimum approach to have the widened design space is shown in the data for Formulation 4 which had the taste masked APAP (Actimask 92M), Mannogem XL and a small amount of MCC. Only the taste masked paracetamol (Actimask 92M) gave tablets free of unacceptable bitter aftertaste. Another important outcome from this work is the need for formulators to consider using tensile strength as a target for tablet robustness as opposed to the use of hardness in Newtons (N) or Kiloponds (kp). Targeting an upper hardness for chewable tablets makes little sense as it does not take into account any change in tablet dimension or shape that may occur during development. From our findings here, we would suggest an upper target Tensile Strength of 1.1 MPa for chewable tablets would give tablets of requisite robustness (low friability) but that would still remain relatively easy to chew (low Chewing Difficulty Index).

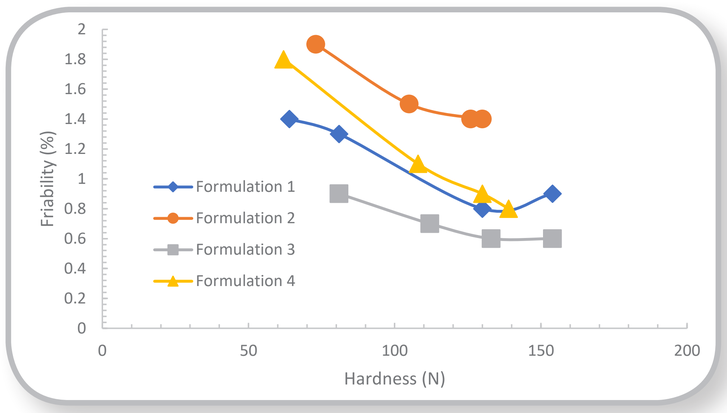

Figure 1. Tablet hardness versus friability across all formulations studied in Phase 1

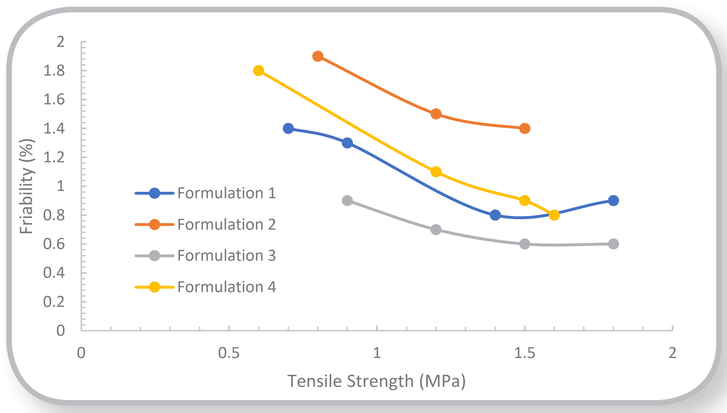

Figure 2. Tensile strength versus friability across all formulations studied in Phase 1

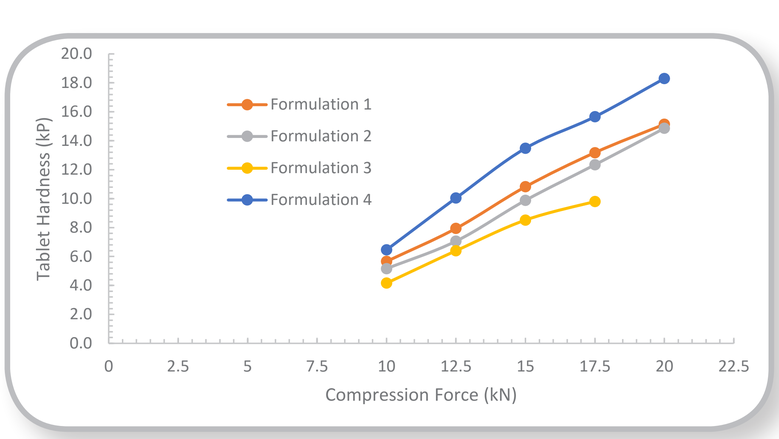

Figure 3. Tablet hardness versus compression force for the four formulations given in Table 2

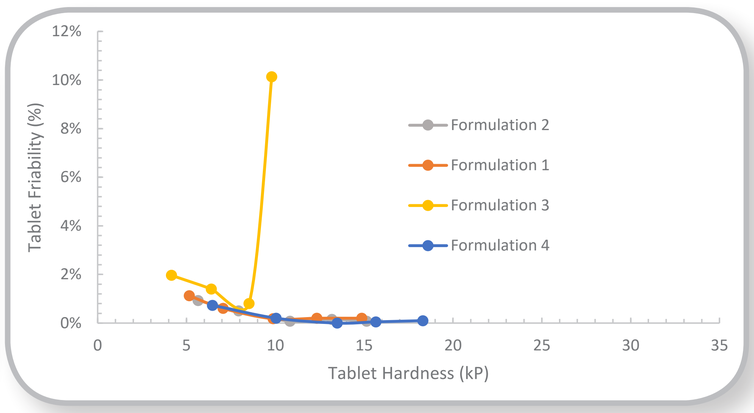

Figure 4. Friability versus tablet hardness for the four formulations given in Table 2

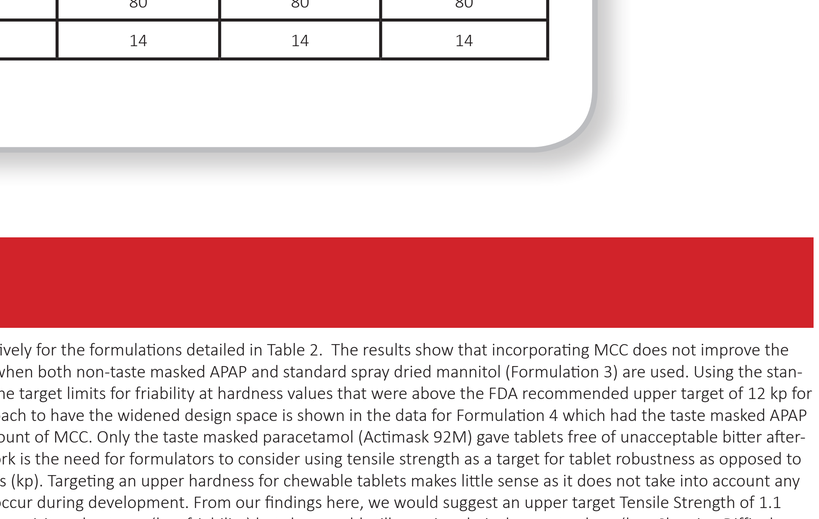

Figure 5. The relationship between compression force and tensile strengths for the 4 formulations investigated in Phase 2

CONCLUSIONS

Development of robust formulations for chewable tablets requires some detailed understanding of the tabletability of both the excipients used and of the API (in both raw and taste masked form). Numerous factors including taste, mouthfeel, robustness, and chewability must be considered to achieve an optimized formulation.

Use of higher compactible grades of mannitol, such as Mannogem XL, and taste masked APIs that have enhanced tabletability, such as Actimask, help the formulator achieve the requisite requirements and enable a robust formulation to be developed. Use of a flexible tableting instrument like the Styl'One Evo equipment helps screen formulations in a rapid manner speeding up development time and helps scientists to understand the fundamentals of their formulations.

References

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