Excipient Compositions to Support a Capsule to Tablet Development Approach

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Introduction

The race for new drug product development can be very challenging, with capsule drug product formulations remaining the most convenient for early safety and dose ranging studies. However, for later stages of development tablets are still preferred due to their simplicity and cost effectiveness1. In this work we explore a pragmatic approach to early formulation development, where multifunctional excipients can be utilised to speed up formulation development; and not only provide excellent encapsulation performance, but also enable essentially the same qualitative composition to be utilised for both early phase encapsulation and subsequent commercial tablet manufacture.

Objectives

The main objective of this project is to study the material attributes (flow behaviour, encapsulation and tabletability) of physical mixtures of microcrystalline cellulose (MCC), mannitol and StarTab® and to predict the correct ratios of these three excipients for developing robust and scalable capsule/tablet formulations.

Methods

A total of 13 physical mixtures of StarTab®, MCC and mannitol at 10 to 80% level with 0.25% magnesium stearate were manufactured by blending in a Turbula blender. Flow analysis/cohesive index of these blends was measured using GranuDrum™ powder tester. Encapsulation of the blends was assessed with an IMA Minima dosator and compression behaviour was determined using Gamlen press and Phoenix compaction simulator. Data analysis was performed using Fusion Pro QbD software.

Results

Figure 1 shows the ternary phase diagram of cohesivity index and excipient composition ratios. A cohesive index value of ≤ 20 value indicates good flow. Compositions containing high StarTab® amounts (blue zone) indicates low cohesivity demonstrating good powder flow behaviour, where high mannitol and MCC (red zone), indicates poor flow. Figure 2 demonstrates the relationship between capsule fill variability (standard deviation) at various excipient ratios. Higher StarTab® quantities in the blend provide lower capsule fill variability, whereas higher mannitol levels lead to increased encapsulation fill weight variability. Figure 3. shows the tabletability profiles of three excipient blends of StarTab® with microcrystalline cellulose and mannitol in various combination. StarTab® when mixed with these excipients produced tablets of tensile strength > 1.8 MPa and ≤25% strain rate sensitivity (SRS); indicating robust tablets that would be suitable for scale-up manufacture. The SRS of these formulations for compression was determined at low speed (2 mm/sec) and high speed (300 mm/sec). The composition, SRS values and disintegration time of these formulations is given in Table 1.

Figure 1. Ternary Phase diagram showing relationship between cohesive index and excipient ratios

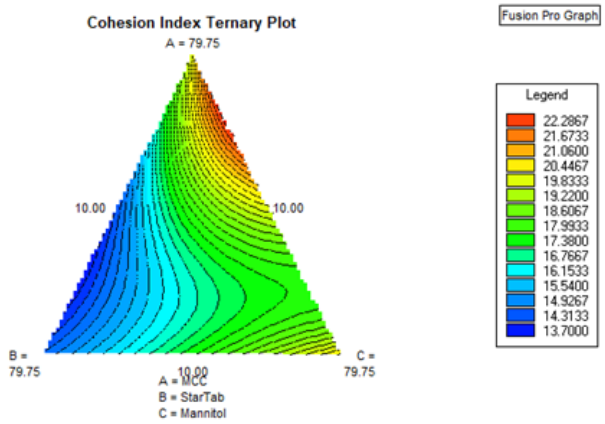


Figure 2. Ternary Phase diagram demonstrating fill weight variation in the encapsulation process

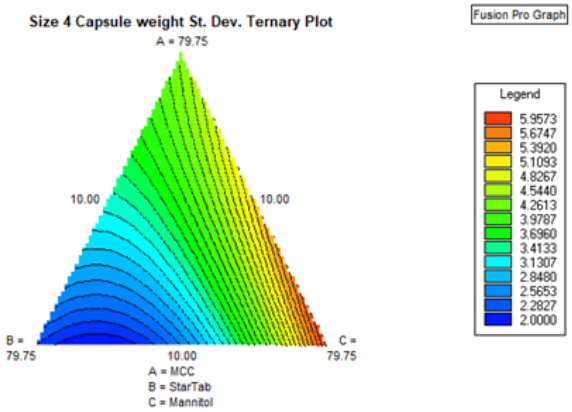
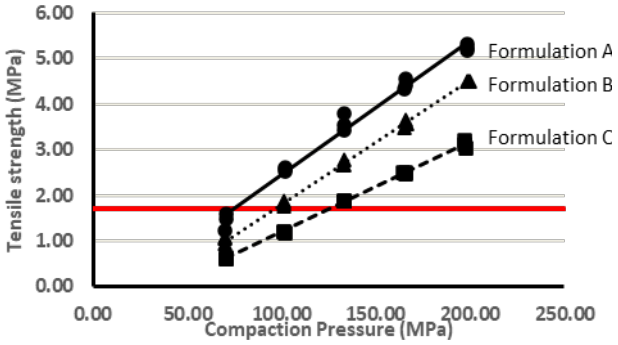


Figure 3. Tabletability profile of various blend ratio of StarTab® with MCC and mannitol



Conclusions and Discussion

The main purpose of this study design is to demonstrate the use of excipient compositions with multifunctional ingredients to accelerate early screening with flexible manufacturability capability built in. For a particular drug dose strength this concept includes the testing of the drug substance for flow behaviour, and the compressibility as a starting point. Based on the compressibility, dose and flow data, a starting formulation recommendation can be prepared, with a recommended customised excipient composition suitable for both capsule and tablet formulations.
The starting excipients for this study were selected based on physical attributes, include three parts:

a. Plastically deforming multifunctional material - StarTab® (disintegrant/filler/flow aid/binder)
b. Plastically deforming compression enhancer - microcrystalline cellulose (filler/dry binder)
c. Brittle deforming material - mannitol (soluble filler).

By choosing suitable ratios of these excipients, a novel customised excipient composition for formulation development that could help in rapid prototyping of the capsule to tablet formulation can be prepared. A matrix of starting compositions with these model excipients were explored in an experimental design with range 10 to 80%w/w. The inclusion of StarTab® in these concepts provides disintegration and binder effects, microcrystalline supports additional tablet tensile strength, and mannitol, which fractures at compression pressures mitigates risk of tablet delamination associated with plastically deforming materials at high tablet compression speeds.

Table 1. Compositions of the formulation blends

Formula	MCC % w/w	arTab % w/w	Manni-tol % w/w	MgST % w/w	SRS %	Disintegration Time (min)
A	56.5	21.63	21.62	0.25	16	NMT 2
B	44.87	44.88	10.0	0.25	25	NMT 2
C	44.88	10.0	44.87	0.25	9	NMT 2

One of the strategies to help de-risk drug product development and the subsequent transition from capsule to tablet formulations, is to ensure reliable, established suppliers are used that provide high-quality, consistent excipients. While encapsulation and tabletting both require good powder flow, there are differences in terms of formulas that promote good powder compactability, and then the need for a disintegrant to ensure the tablet falls apart in-vivo. Ideally excipients will provide multiple functionalities. An example of this would be the Starch family of excipients from Colorcon, which can act as a diluent, binder and disintegrant combined with moisture scavenging functionality. The concept of using customised blends with multi-functional excipients could not only accelerate formulation development process but would have the ability to easily transfer from a capsule to tablet formulation.

The use of excipient compositions that have been developed based on drug substance properties can accelerate formulation development and reduce the risk of issues on scale-up of the manufacturing process. In addition, incorporating multifunctional excipients like StarTab® can offer further advantage, as a qualitatively equivalent formula could be used in both wet or dry granulation processes without concern about drug substance compatibility, thus offering added benefits for manufacturing flexibility.

References

1. Graham Cole, Evaluating Development and Production Costs: Tablets Versus Capsules; Pharmaceutical Technology Europe; Vol. 5, Pgs. 17 – 26 (1998)

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