TABLETTING OF COATED MULTIPARTICULATES: EFFECT OF FORMULATION COMPOSITION, PROCESS VARIABLES ON DRUG RELEASE AND TABLET PROPERTIES

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ABSTRACT SUMMARY

Tabletting of the coated multiparticulates is a challenging task. The coated multiparticulates react differently to compaction and consolidation than powders or granules of the same material. Also the application of the compaction pressure can lead to structural changes in the coating or the particulates and may alter drug release after compaction. A tablet formulation can offer significant advantages over a bead-filled capsule for specific purposes. This study summarizes the optimization of the tablet formulation and process parameters for the successful production and performance of tablets containing multiparticulates.

INTRODUCTION

Controlled release dosage forms are available as single unit dose (e.g., matrix tablets) or multiparticulate drug delivery systems. The multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits, typically consisting of spherical particles with diameter of 0.05 to 2.0 mm. The main advantages of these systems over the single unit dose are the more predictable gastric emptying and dispersion in the GI tract, reduced risk of dose dumping, increased bioavailability with minimum intra and inter-subject variability. To deliver the total recommended dose, these subunits are either encapsulated or compressed into tablets for the final dosage form. The tablet formulation may be the preferred final dosage form as it offers various advantages over capsules. These potential advantages include higher patient compliance, higher dose strength administration, high production rate and less cost compared to capsules. Only a few products exist in the market due to the inherent challenges involved in the compression of these multiparticulates despite the advantages listed for multiparticulates contained within a tablet.

Ideally, the compacted tablet should disintegrate into individual particulates in the GI tract and drug release rate profile of the compacted multiparticulates should not be affected by the compaction force. In order to achieve these properties excipients with so-called cushioning or protective, properties are usually incorporated in the tablet formulation. The compression-induced changes of the structure of coating may depend on the formulation factors such as type and amount of coating and incorporation of excipients particles. The primary goal will be the achieving the desired release rates from the multiparticulates before considering the final dosage. The formulation scientist focuses on tabletting these pellets with additional excipients once the desired release rate is achieved from the multiparticulate pellets formulation. At this stage of development, the optimization of the tablet formulation and compaction process parameters play an important role in successful production and functioning of the tablet dosage forms.

EXPERIMENTAL METHODS

The core pellets for this study are prepared from a powder blend containing water soluble model drug, binder and microcrystalline cellulose in appropriate quantities. The blend was dry-mixed and aqueous granulated in a high shear mixer, extruded and then spheronized. The core pellets were coated with Eudragit RS 30 D and Eudragit RL 30 D (9:1) controlled release polymers at 50% weight gain for the desired release rate and finally coated with Eudragit® L enteric polymer at two different coating levels, 20% and 30% weight gains. The pellets were cured in an oven for 18 hrs after the modified and enteric release coatings were applied.

The enteric coated pellets were used for the tabletting trials. The enteric coated pellets were dry mixed in a v-blender with additional tablet diluents such as microcrystalline cellulose, lactose, croscarmellose sodium, hypromellose, sodium lauryl sulfate and magnesium stearate. The blend was compressed into tablets using three different compression forces of 11, 22 and 45 kN. The tablets were evaluated for hardness, friability, weight variation and disintegration time during the compression run. The compressed tablets were also evaluated for assay, content uniformity and for the drug release. The drug release studies were conducted using USP II apparatus in 900 ml of 0.1N HCl for 2 hrs followed by pH 6.8 phosphate buffer for 12 hrs.
RESULTS AND DISCUSSION

The core pellets that were produced were approximately 0.8 mm in size diameter and spherical in shape. It was found that the type and amount of excipients had a crucial role for the successful tablettting of the pellets. The cushioning effect of the excipients was dependent upon the particle size and its compactable properties. Microcrystalline cellulose was found to be a suitable diluent because of its compaction properties, in which plastic deformation is the predominant volume reduction mechanism. MCC PH 102 (D<sub>50</sub>: 100 µ) alone helped in compacting the pellets, however segregation of the pellets in the blend was observed. Blending with a higher proportion of MCC PH 200 (D<sub>50</sub>: 180 µ) showed chipping and failed in friability. The combination of MCC PH 102 and MCC PH 200 at 4:1 ratio was found to be optimal for successful compression and to avoid pellet segregation.

Adding sodium lauryl sulfate in addition to magnesium stearate decreased the hardness significantly from 14 kp to 5 kp. The tablets disintegration reduced significantly from > 2 hrs to less than 60 minutes with the addition of 2.5% disintegrant.

The hardness of the compressed tablets with optimized composition at 11, 22 and 45 KN compression force was found to be 4, 10 and 14 Kp respectively. The tablets weight, hardness, friability and disintegration time during in-process testing were within the acceptable limits. The assay and the % RSD for content uniformity of the tablets were 102.7% and 4.6% respectively. Figure 1 shows the dissolution profile of enteric coated uncompressed pellets. Both 20% and 30% enteric coated pellets showed similar profiles. The dissolution profile of the compressed pellets from tablets is shown in Figure 2. Slight increase in dissolution rate from tablets over uncompressed pellets was observed. This might be due to the slight deformation of the pellets from compression. Interestingly from the tablets we observed almost zero-order release profile which is an added advantage for this controlled release formulation.

CONCLUSION

The 0.8 mm sized pellets were successfully compressed in the tablet with acceptable hardness content uniformity and dissolution profiles. There was little to no affect of compression force on the dissolution profiles for tablets and a slight increase in dissolution rate from pellets alone compared to tablets due to deformation of the pellets.

REFERENCES


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