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# Formulation and process strategies to minimize coat damage for compaction of coated pellets in a rotary tablet press: A mechanistic view

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ABSTRACT

Compaction of multiple-unit pellet system (MUPS) tablets has been extensively studied in the past few decades but with marginal success. This study aims to investigate the formulation and process strategies for minimizing pellet coat damage caused by compaction and elucidate the mechanism of damage sustained during the preparation of MUPS tablets in a rotary tablet press. Blends containing ethylcellulose-coated pellets and cushioning agent (spray dried aggregates of micronized lactose and mannitol), were compacted into MUPS tablets in a rotary tablet press. The effects of compaction pressure and dwell time on the physicomechanical properties of resultant MUPS tablets and extent of pellet coat damage were systematically examined. The coated pellets from various locations at the axial and radial peripheral surfaces and core of the MUPS tablets were excavated and assessed for their coat damage individually. Interestingly, for a MUPS tablet formulation which consolidates by plastic deformation, the tablet mechanical strength could be enhanced without exacerbating pellet coat damage by extending the dwell time in the compaction cycle during rotary tableting. However, the increase in compaction pressure led to faster drug release rate. The location of the coated pellets in the MUPS tablet also contributed to the extent of their coat damage, possibly due to uneven force distribution within the compact. To ensure viability of pellet coat integrity, the formation of a continuous percolating network of cushioning agent is critical and the applied compaction pressure should be less than the pellet crushing strength.



## 1. Introduction

Multiparticulates are small discrete particulates such as pellets, granules, minitablets and microparticles. Coating of multiparticulates is commonly employed for various reasons, including improving product appearance, masking bitter taste and modifying drug release (Porter, 2013). Multiparticulate dosage forms comprise coated and/or uncoated multiparticulates, filled into hard gelatin capsules, or less commonly, compressed into tablets. To date, development of tablets containing coated pellets, generally referred to as multiple unit pellet system (MUPS) tablets, have seen growing interest. This could be attributed to the reduced risk of product tampering, lower production cost and higher productivity of the tablet compaction process (Bodmeier, 1997). MUPS tablet is designed to liberate individual pellets upon oral administration, with their coat functionality uncompromised by the compaction force needed to prepare tablets (Abdul et al., 2010). After oral administration, the disintegration of MUPS tablets and subsequent release of individual coated pellets are essential to maintain the advantages of MUPS tablets as multiparticulate drug delivery systems. The uniform distribution of pellets over a large surface area throughout the gastrointestinal tract contributes to optimized drug absorption, improved bioavailability and reduced risk of local irritation to the gastrointestinal mucosa.

Despite the advantages, preparation of MUPS tablets remains a challenge due to the need for compaction. The compaction force exerted on the coated pellets during tableting often damages their functional polymer coat, compromising their desired drug release attribute (Altaf et al., 1998; Miller et al., 1999). Upon compaction, the coated pellets may also fuse into a non-disintegrating matrix due to inter-particle adhesion. Hence, cushioning agents which deform preferentially and function as surrogates to absorb the energy of compaction are generally included in the MUPS tablet formulations. It has been shown that plastically deforming cushioning agents with lower yield pressure than the pellets and the pellet coats were more desirable than those that consolidate by fragmentation (Yao et al., 1998). Ideally, the cushioning agent should bring about rapid disintegration of MUPS

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tablets with the overall dissolution profile unaffected by the compaction process. The MUPS tablets should also possess sufficient mechanical strength for subsequent handling and packaging. Therefore, formulation and process related factors, including the size and physical integrity of the pellet core, amounts of coating material and plasticizer, type and amount of cushioning agent, compaction pressure and speed, are critical variables to be judiciously considered during development of a MUPS tablet formulation (Yao et al., 1997; Lundqvist et al., 1997; Nicklasson et al., 1999; Habib et al., 2002; Chambin et al., 2005; Altaf et al., 1999; Dashevsky et al., 2004; Torrado and Augsburger, 1994).

Ethylcellulose (EC)-based film coating is often used to produce membrane-controlled drug delivery systems (McConnell and Basit, 2013). However, EC film is known to be brittle and when applied onto pellets, the resultant film coats are prone to be ruptured by the compaction force during tableting. As a result, the controlled drug release function was severely compromised after compaction of EC-coated pellets (Bansal et al., 1993; Bodmeier and Paeratakul, 1994). Excipients with small particle size have been shown to confer better protective effect for coated pellets (Yao et al., 1997). For instance, micronized lactose (ML) was evaluated as a cushioning agent and it was shown to exhibit greater flexibility for particle rearrangement than coarse lactose. Unlike coarse lactose, ML would not fragment into sharp-edged fragments when compacted with EC-coated pellets. Moreover, ML was postulated to adhere to the surfaces of coated pellets as an elastic powdery coat and helped to dissipate compaction force by a lubricative effect on the coated pellets (Chin et al., 2014). However, ML in large proportion is not ideal for routine rotary tablet production due to its poor flowability and compactability. Co-spray drying ML with polymeric additives was subsequently developed by Lin et al. to improve the physicomechanical performances of ML during tableting (Lin et al., 2011). These spray dried particles showed porous structures containing fine ML particles connected together by amorphous lactose and would collapse rather than undergo fragmentation during compaction. Therefore, aggregation by spray drying of ML was recognized as a promising approach to produce cushioning agents.

The rotary tablet press is commonly used to produce commercial tablets (Picker-Freyer, 2015) and for MUPS tableting, it would be necessary to critically examine the events during the four-stage compression model: volume reduction with pellet rearrangement, surface deformation, bulk structure deformation and densification, and bond formation due to reduced compact porosity (Johansson and Alderborn, 1996). To date, most of the studies that investigated pellet coat damage caused by compaction were conducted using a single punch tablet press or a compaction simulator. The knowledge obtained from such studies might not be directly translated to the rotary tableting process, due not only to the material feeding process but also to differences in their modes of force application and compaction mechanism (Palmieri et al., 2005). Clearly, studies on compacts containing coated pellets prepared by a rotary press are limited and the mechanism by which the pellet coats are damaged by compaction remains unclear (Wagner et al., 2000, 1999). To assess the extent of coat damage sustained, the change in drug release rate of coated pellets before and after compaction has been the most commonly used approach. However, the bulk dissolution properties of MUPS tablets are often influenced by the tablet disintegration time. Moreover, the change in the overall dissolution rate alone does not provide insight into the mechanism of pellet coat damage under compaction. Therefore, the primary aim of this study was to investigate formulation and process strategies to minimize coat damage during compaction in a rotary tablet press. A spray dried blend of ML and mannitol was prepared and evaluated as a plastically deforming cushioning agent. Two compaction process parameters, dwell time and applied pressure, were examined for their effects on the physicomechanical properties of resultant MUPS tablets and the extent of damage to the EC coats on the pellets. In order to elucidate the extent and mechanism of coat damage caused by compaction, the crushing strength of the coated pellets and degree of coat damage of excavated individual pellets from different locations in the MUPS tablet were investigated. In addition, changes in pellet volume fraction in MUPS tablets under different compaction pressures and with different cushioning agent/pellet ratios were examined and correlated with the extent of pellet coat damage.

## 2. Materials and methods

### 2.1. Materials

Lactose (Granulac 200, Meggle Pharma, Germany), mannitol (Man; Mannitol 35, Roquette, France), sugar cores (355–425 μm; Pharm-a-spheres, Hanns G. Werner, Germany), hydroxypropyl methylcellulose (VLV, Dow Chemical, USA), polyvinylpyrrolidone (Plasdone C-15, Ashland, USA), ethylcellulose (EC) dispersion (Surelease, Colorcon, USA), magnesium stearate, cross-linked polyvinylpyrrolidone (Polyplasdone XL, Ashland, USA) and isopropyl alcohol (IPA, Aik Moh Paints and Chemicals, Singapore) were used as supplied. Deionized water (Milli-Q, Millipore Corporation, USA) was used when water was needed and metformin hydrochloride (USP grade, Granules India, India) was the model drug.

### 2.2. Preparation of micronized lactose (ML)

Granulac 200 was air jet milled (100 AFG, Hosokawa Alpine, Germany) to produce ML of median diameter, 7.83 μm in filtered IPA as determined by laser diffractometry (LS-230, Coulter Corporation, USA).

### 2.3. Preparation of spray dried ML-mannitol particles

The preparation method is as reported by Lin et al. (2011). ML was first dispersed in a beaker of ice-cold lactose saturated aqueous solution containing 4%, w/w mannitol on an ice bath. The ratio of dispersed ML to dissolved lactose and to dissolved mannitol in the feed dispersion was fixed at 2:1 (w:w) and 10:1 (w:w), respectively. The dispersion was immediately spray dried (Mobile Minor, GEA-Niro, Denmark) after preparation using a rotary atomizer with inlet temperature, 140 °C; outlet temperature, 80 °C; atomizing air pressure, 1.5 bar and feed rate, approximately 30 mL/min. The spray dried product (sML-Man) was collected, sealed in plastic bags and then stored in a desiccator until required. The particle size of sML-Man (46.58 ± 1.74 μm) was determined by laser diffractometry (LS-230, Coulter Corporation, USA) in filtered IPA as the dispersing medium.

### 2.4. Preparation of coated pellets

The sugar cores were first coated with the drug layer followed by the release-controlling membrane in an air suspension coater (FlexStream module, MP-1, GEA Aeromatic-Fielder, UK). For drug loading, 2 kg cores were coated under the following conditions: airflow rate, 140 $m^3$/h; atomizing air pressure, 2.5 bar; spray rate, 20 g/min and inlet air temperature, 65 °C. The side spray nozzle was fitted at 10 mm away from the powder bed. A 7331.4 g drug layering solution containing 6%, w/w hydroxypropyl methylcellulose, 1%, w/w polyvinylpyrrolidone and 20%, w/w metformin hydrochloride, was sprayed using a two-fluid nozzle. The theoretical percent increase in dry weight of cores after drug