

## CHAPTER 1

### INTRODUCTION

#### 1.1 Research Background

The oral modified-release pharmaceutical dosage form is designed to enhance the properties of therapeutic ingredients that can be delivered in a single-unit or multiparticulate dosage form (Sandberg *et al.*, 1988; Bodmeier, 1997). In recent years, there has been rising interest in preparing a multiparticulate system owing to its effective therapeutic properties such as dose-flexibility, rapid onset of action, less affected by gastric emptying, and lower chance of dose-dumping (Ghebre-Selassie, 1994; Bodmeier, 1997; Yang *et al.*, 2016; Al-Hashimi *et al.*, 2018). Multiparticulate is the composition of a plurality of small discrete subunits, commonly pellets, granules, microparticles, or mini-tablets (Bodmeier, 1997; Abdul *et al.*, 2010; Sun *et al.*, 2012).

Since the 1970s, pellets have been the most popular subunits for preparing oral multiparticulate dosage form (Ghebre-Selassie, 1994; Tan and Hu, 2015; Deb and Ahmed, 2016; Stegemann, 2016), namely Multiple Unit Pellet System (MUPS). The MUPS is an ideal platform for delivering the active pharmaceutical ingredient (API) with a short biological half-life and a narrow therapeutic index. Moreover, an API could be dispersed uniformly in the matrix or loaded in the pellet's core to modify the release efficiently (Ghebre-Selassie, 1994; Stegemann, 2016; Tan and Hu, 2016). A layer of release-controlling coating could be applied to each pellet to sustain the release of the API hence enabling a uniform distribution over the gastrointestinal tract (Ghebre-Selassie, 1994; Sun *et al.*, 2012). Coated pellets can be either filled in capsules or compressed into tablets (Sandberg *et al.*, 1988; Hosseini *et al.*, 2013). Compaction of functionally coated pellets is gaining preference over pellet-filled capsules due to its greater benefits such as the lower likelihood of oesophageal ulceration, easy swallowing tablets by geriatric and paediatric patients, and cost-effectiveness (Marvola *et al.*, 1983; Millinder, 1994; Hu, 2016).

Nonetheless, preparation of pellet-containing tablet is technically challenging as the polymeric film may be incapacitated to resist the detrimental effect from compaction, impairing its function as a diffusion barrier, and thus the desired *in-vivo* drug release (Altaf *et al.*, 1998; Dreu *et al.*, 2011; Choudhary and Avari, 2013; Al-Hashimi *et al.*, 2018). Earlier approaches have been focused on the modification of the flexibility of the

coating layer to reduce the compaction-induced damage, such as the addition of plasticizer (Bécharde and Leroux, 1992; Wagner *et al.*, 2000; Fukui *et al.*, 2001), modifying the amount of coating used (Maganti and Çelik, 1993) and using an acrylic polymer with flexible extensibility to withstand deformation during compression (Bodmeier and Paeratakul, 1994; Abdul *et al.*, 2010; Yang *et al.*, 2016). Other studies have evaluated different coating techniques, including organic solvent coating (Sun *et al.*, 2012), top-coating with highly plasticized polymers (Osei-Yeboah *et al.*, 2017) to increase the flexibility of the polymer coat. On the other hand, Yang *et al.* (2016) has mentioned that both the pellet core and the film coat should be plastically deformable to confer protection against compaction.

Apart from the techniques mentioned above, several studies have incorporated excipient functioning as a filler and a cushioning agent to absorb the deleterious effect of the tablet compaction. Such excipient can be in the form of powder or beads (Yao *et al.*, 1997; Habib *et al.*, 2002). As revealed by Yao *et al.* (1997), compaction of coated pellets with excipients of average particle size below 20  $\mu m$  can effectively prevent the coating layer from rupturing. Numerous researches have credited that porous excipient has a well-defined cushioning effect in MUPS tableting (Lin *et al.*, 2011; Xu *et al.*, 2016; Elsergany *et al.*, 2020a). In addition, Elsergany *et al.* (2020a) has posited that particle size difference between the cushioning excipients and coated pellets can induce segregation issues. On the contrary, the density and strength of excipients are the other parameters that need to be considered if cushioning agents of the same size as the polymer-coated pellets are adopted as the only way to tackle the segregation problem (Aulton *et al.*, 1994).

A good cushioning agent should deform more readily than the coated pellets at low compaction pressure (Aulton *et al.*, 1994). Consequently, compaction force will be distributed more evenly in the plastic deforming cushioning agent rather than transmitted on coated pellets to reduce the damage on the polymeric coatings of pellets. A material that deforms plastically should possess a yield pressure ( $P_y$ ) of less than 80. A more porous excipient is easier to compress, facilitating the formation of a greater inter-particulate bonding capacity and consequently a closed packed tablet (Johansson *et al.*, 1995; Elsergany *et al.*, 2020a). Besides, a porous excipient is needed to facilitate liquid penetration to the tablet during both the disintegration and dissolution process (Yihong *et al.*, 2017). Microcrystalline cellulose (MCC) is considered to be beneficial in the MUPS formulation owing to its plastic deformity nature (Beckert *et al.*, 1996; Katdare and

Chaubal, 2006; Kucera *et al.*, 2012). However, using MCC alone would not produce a good cushioning effect, as cracks were observed on pellets solely made of MCC powder. This is due to the rough surface of MCC with an abundance of large crystals contributing to the damage on the layers of the pellet (Li *et al.*, 2016; Zheng *et al.*, 2018).

Therefore, further modification is required to reduce the particle size and smoothen the edge of MCC crystals. MCC with such desired properties can be achieved through the particle size reduction process. The most appropriate method to achieve it is via wet beads milling since the attrition and impaction process in conjunction with the wetting process will effectively reduce and smoothen the MCC particles. However, the main problem observed during the wet process of MCC is the reduction in plastic deformation of MCC, causing the MCC deformation to be less plastic and more brittle. Siow *et al.* (2018), Lestari and Heng (2021) have posited that an equilibrium between plastic and brittle deformation must be established among the cushioning excipients to protect coated pellet from compression-induced damage.

A brittle material will initially undergo fragmentation to surrounding drug-loaded compact and concisely occupy the spaces between them, whereas a strong compact can be produced when the cushioning excipients deform plastically (Habib *et al.*, 2002). This can be achieved by co-processing plastic and brittle materials which is usually used to produce a novel composite of filler-binder in pharmaceutical fields (Celik, 2011). Co-processed MCC and polyvinylpyrrolidone (PVP) will be adopted as a cushioning agent in this study to increase the plasticity during deformation and overcome the brittle nature of MCC after co-processing. This is because co-processed PVP possesses a porous structure in an orderly arrangement and has the lowest Py among the other polymers, indicating it can improve the plastic deformability of cushioning agent (Siow *et al.*, 2018). Unprocessed PVP K30 deforms plastically with a Py value as low as 35.7, whereas unprocessed MCC has a Py value of 62.5 (Badwan *et al.*, 2015). Hence, it is hypothesized that PVP can increase the plastic deformation of cushioning agents on account of its high plastic deformability during compaction. Furthermore, it was also reported by Siow *et al.* (2018) that co-processed partially pregelatinized starch (PGS) has the tendency to balance the brittleness of incorporated excipients and lead to the formation of less brittle cushioning agent. PGS deforms plastically during compaction and has a Py value of 75.1 which is close to the Py value of the unprocessed MCC (Badwan *et al.*, 2015; Svačinová *et al.*, 2021). Another finding by Pan *et al.* (2010) has revealed that PGS readily forms aggregate upon contact with water and might be

adhesive on coated pellets. Therefore, it will be co-processed with MCC as it might potentially increase the plastic deformity nature of cushioning agent, which can consequently absorb more compaction pressure and confer better protection on coated pellets.

The goal of performing co-processing in this study is to develop an ideal composite of a cushioning agent with (i) a smooth surface morphology to reduce friction-induced when embedded between coated pellets, (ii) re-establish an equilibrium of deformation between plastic and brittle excipients to reinforce the protection on polymeric coatings of pellet during compression, (iii) being smaller than coated pellets, and ultimately (iv) maintain the sustained-release kinetic from the drug-loaded pellet. Hence, this study will use a combination of wet beads milling and freeze-drying as the co-processing method to prepare cushioning agent. Wet beads milling will be performed to produce cushioning excipients with less size variation to pack more orderly and prevent segregation, whereas freeze-drying can increase the degree of deformability by inducing a porous structure.

Metformin hydrochloride, the model drug in the current study, is an oral antihyperglycemic agent for type II diabetic patients (Scheen, 1996; ADA, 2006). A twice-daily oral dosing regimen is needed as metformin HCl does not bind to plasma protein and has a mean plasma elimination half-life between 4.0 and 8.7 hours (Scheen, 1996). Metformin HCl is classified as a BCS Class III drug with low membrane permeability and is highly soluble in water (Chou, 2010). In this study, Metformin HCl is layered on pellet cores then coated again with ethyl cellulose to sustain the therapeutic effect. In the present work, ethyl cellulose, which ruptures easily at low compression pressure (Bansal *et al.*, 2013), is coated on drug-loaded pellets to evaluate the effectiveness of cushioning agent in protecting the coated pellet from the loss of sustained-release properties.

## 1.2 Research Problems

1. Are the co-processed cushioning agents, MCC-PVP and MCC-PGS, able to deform plastically and protect the coated pellets during the compaction of MUPS?
2. Which combination of co-processed cushioning agent could produce a stronger MUPS tablet at low compaction pressure and achieve similar dissolution profile as the uncompacted pellet?

### **1.3 Research Objectives**

1. To determine the effect of both co-processed cushioning agents MCC-PVP and MCC-PGS on protecting the coated pellets during the compaction of MUPS.
2. To determine the ideal combination of cushioning agent that could produce a stronger MUPS tablet at low compaction pressure with dissolution profile similar to the uncompacted pellets.

### **1.4 Research Outcomes**

#### **1.4.1 Theoretical Outcome**

The theoretical outcome of this research could give further theoretical basis on the development of co-processed MCC-PGS and MCC-PVP as cushioning agent on to the degree of protection of release-controlling coating in MUPS tablet during compaction.

#### **1.4.2 Practical Outcome**

The cushioning potential of each combination of cushioning agents in protecting ethyl cellulose-coated pellets would have practical benefits in another polymer-coated pellets from compaction-induced damage in future studies.