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Influence of process parameters on fluidised hot-melt granulation and tablet pressing of pharmaceutical powders

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Abstract

This study investigates the influence of process parameters on the fluidised hot melt granulation of lactose and PEG 6000, and the subsequent tablet pressing of the granules. Granulation experiments were performed to assess the effect of granulation time and binder content of the feed on the resulting granule properties such as mass mean granule size, size distribution, granule fracture stress, and granule porosity. These data were correlated using the granule growth regime model. It was found that the dominant granule growth mechanisms in this melt granulation system were nucleation followed by steady growth (PEG 10–20% w/w). However, with binder contents greater than 20% w/w, the granulation mechanism moved to the "over-wet massing" regime in which discrete granule formation could not be obtained. The granules produced in the melt fluidised bed process were subsequently pressed into tablets using an industrial tablet press. The physical properties of the tablets: fracture stress, disintegration time and friability were assessed using industry standards. These analyses indicated that particle size and binder content of the initial granules influenced the mechanical properties of the tablets. It was noted that a decrease in initial granule size resulted in an increase in the fracture stress of the tablets formed.

Keywords: Fluidised hot melt granulation; Growth regime theory; Tablet pressing; Breakage strength

1. Introduction

Fluidised hot melt granulation (FHMG) is a developing process for the preparation of pharmaceutical granules for tableting. Several process parameters of the FHMG system, such as binder content and properties, particle size and air flow rate, have been shown to influence the physical properties of the resulting tablets (Kidokoro et al., 2002; Abberger, 2001). Melt granulation offers several advantages compared to the conventional wet granulation process. It is a good alternative to wet granulation for water-sensitive materials. Also, the wetting and drying phases are eliminated, making the entire process less consuming in terms of energy and time, as well as improving the quality of the granules (drying tends to make granules porous, bulky, and in some cases fragile) (Aulton, 1992). Because there is no solvent used in melt granulation, there are no solvent recovery issues and hence safety and environmental considerations are also reduced.

In melt granulation, mixing with the drug may be performed by addition of the molten excipient to the drug powder or by heating both components together; in either case the system is cooled to the solid state with the molten excipient acting as a binder. This process may allow the generation of granules of a suitable size and compression profile for subsequent processing into solid dosage forms (Kristensen and Schaefer, 1993; Passerini et al., 2002).

There may also be advantages to melt granulation in terms of the nature of the product, as the absence of extraneous liquid may result in a more favourable binder/substrate ratio and may also result in a higher granule density and reduced porosity due to the absence of a liquid phase that is subsequently removed. That said, some granule porosity is

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required in order to allow water to penetrate in during disintegration (Crowley et al., 2000). A further significant advantage of melt granulation is that judicious choice of the granulation excipient may enable the formulator to manipulate the drug dissolution rate from the corresponding dosage form. This may be performed in terms of producing slow release formulations, whereby daily dosing can be reduced and plasma blood levels rendered more steady over a 24 h period. In this case hydrophobic excipients such as stearic acid or triglycerides may be utilised (Crowley et al., 2000; Thies and Kleinbudde, 1999; Voinovich et al., 2000). Alternatively, hydrophilic materials such as polyethylene glycol (Voinovich et al., 1999; Hengh et al., 2000) or poloxamer 188 may be used (Passerini et al., 2002). These polymers may enhance the dissolution rate of poorly soluble drugs, thereby yielding the possibility of enhanced bioavailability (Craig, 2002). However, these benefits must be weighed against the possibility of degradation of thermolabile drugs and the absence of a core knowledge base within the pharmaceutical industry with regard to the optimisation of the melt-granulation process. Indeed, while the wet granulation process has been studied extensively in pharmaceutical and bulk chemical manufacture (Krycer et al., 1983), there is a paucity of information available with regard to the predictability and modelling of the melt granulation process.

FHMG has received considerable attention in recent years with the majority of these processes involving the spraying of molten binder onto a bed of fluidised particles. Abberger et al. (2002) have shown that the granule growth mechanism was dependent on the ratio of binder droplet size to powder particle size. A low ratio led to a nucleation mechanism, which then gave rise to coalescence and further granule growth. Kidokoro et al. (2002) have shown that the increase in granule size during FHMG is influenced by viscosity of the binder melt. They further indicated that the physical properties of tablets pressed from the fluidised hot melted granules were influenced by the properties of the binder material. This study, although drawing on the experience of previous researchers, is novel in that the binder is not sprayed on but is initially present as discrete particles within the fluidised bed which are co-melted with increase in fluidisation temperature.

1.1. Granule growth behaviour

A considerable amount of work has been performed in order to understand and model growth behaviour during granulation. Two significant contributions to this field have been made by Ouchiyama and Tanaka (1975) and by Ennis et al. (1991). Ouchiyama and Tanaka's (1975) model assumes that granulation takes place due to the deformation of particles when they come in contact, hence whether or not granulation occurs depends on the bond formed by the granule dumbbell and the forces it encounters. Ennis's model does not take into account particle deformation, but views particles as rigid spheres coated with a finite layer of binder. The model assumes that two granules stick when the viscous dissipation in the binder layer is equal to the relative kinetic energy of the two colliding particles. These two models assume different behaviour of the particles, i.e. surface-dry, deformable granules and rigid granules with a liquid layer at the surface. In addition, Iveson and Litster (1998) proposed a regime map for granule growth. They proposed a general framework in which the two extremes, as posed by Ouchiyama and Tanaka and by Ennis et al. (1991), were combined. Based on two properties of the granulating system, the growth regime map predicts what type of growth will occur. The two main types of growth that can be distinguished on the map are steady growth and induction-type growth. Steady growth occurs when particles are deformable and is characterised by a steady increase of the granule size with time; the growth rate increases when more binder is present in the system. In contrast, induction behaviour occurs when the granules possess low deformability and is characterised by no growth occurring during the first stage of granulation, known as the induction stage. During this stage, the granules are compacted and liquid is squeezed from the interior on to the surface of the granules. Once the pores of the granules are saturated, they become surface wet and the liquid layer at their surface renders further growth possible. Increasing the amount of binder results in a shorter induction period (Ennis et al., 1991). In their work, Iveson and Litster (1998) cited a number of examples from several authors of both induction-type behaviour as well as steady growth behaviour and they explain the differences using their regime map. In summary, their regime map provided a plausible explanation for the different growth types, using both Ouchiyama and Tanaka's theory as well as that of Ennis, Tardos and Pfeffer. The aim of the current study is to examine the applicability of these approaches to the melt-granulation of pharmaceutical powders in order to better understand the processes associated with granule growth.

1.2. Effect of process variables on granulation

Effect of initial particle size and size distribution: it has been shown that a narrow distribution of feed particles to the granulator increases the sphericity and decreases the porosity of the granular products (Walker et al., 2000). Porosity, and its shape, orientation and size distribution have a large effect on the breakage behaviour and strength of granules. Walker et al. (2003) have shown how a high granule porosity results in lower the granule strength. The pores can be regarded as crack release zones, where the highest local tensile stress is generated and where fracture initiates (Bika et al., 2001).

The effect of binder content: Correlations have been developed to estimate the required binder content, but these have proved unsuccessful for powder mixtures with more than one component, or with powders that have varying diameter and particle shape. Moreover during granulation,