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Melt granulation of pharmaceutical powders: A comparison of high-shear mixer and fluidised bed processes

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ABSTRACT

The main aim of this research was to compare *in situ* melt granulation process in high-shear mixers and fluidised bed equipments with particular attention to the final properties of granules. In addition, the study evaluated the suitability of melt granulation in fluidised bed for improving the dissolution rate of drugs. Agglomerates having identical composition (10%, w/w, of ibuprofen or ketoprofen, 20%, w/w, of PEG 6000 and 70%, w/w, of lactose monohydrate) were produced using both equipments and their morphology, particle size, flowability, friability, drug loading, dissolution behaviors at pH 1.2 and 7.4 and physicochemical properties (DSC and XRD analysis) have been evaluated and compared. The results showed that melt granulation can be successfully performed in both granulators. The utilization of a different equipment had strong impact on the particle size distribution of the granules and on their morphology, while the effect on others physical properties was little, as all the granules possess low friability and excellent flowability. Moreover both the solid state characteristics of the products and the dissolution behaviors of ibuprofen and ketoprofen granules were found to be practically independent of the equipment and all granules showed a significant increase of the drug dissolution rate in acidic conditions. In conclusion *in situ* melt granulation in fluidised beds could be considered a suitable alternative to the melt granulation in high-shear mixers.

1. Introduction

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a substance which melts at relatively low temperature (50–80 °C). This substance can be added to the powders either in the form of a molten liquid (spray-on procedure) or in the form of a solid that melts during the process (*in situ* melt granulation or melt-in procedure) (Wong et al., 2005). In both cases, the molten substance acts like a liquid binding and the dry granules are obtained as the molten binder solidifies by cooling.

In recent years, the interest in melt granulation has increased due to the numerous advantages of this technique over traditional wet granulation. In fact the melt granulation does not require the use of organic or aqueous solvents: the advantages of not using organic fluids are the absence of any risk originating from residuals solvents in the final dosage form and the absence of problems associated with environmental requirement of solvent capture and recycle, while the absence of water results in the elimination of the wetting and drying phases, making the entire process less consuming in terms of time and energy as compared to wet granulation. A further significant advantage of melt granulation is that by an appropriate selection of meltable binders, this technique can be used either to prepare controlled release or enhanced release granules. Examples of hydrophilic binders used to prepare improved-release dosage forms include polyethylene glycols and poloxamers, while hydrophobic binders such as waxes, fatty acids, fatty alcohols and glyceride can be utilized for prolonged-release formulations (Wong et al., 2005).

Utilizable equipments for melt granulation are high-shear mixer and fluidised bed. The first studies on melt granulation in high-shear mixers date back to early 1990s, when the group of Shaefer and Kristensen published a series of papers that extensively investigated the effect of process and formulation variables on melt agglomeration and the mechanisms involved in the growth of the agglomerates (Schaefer et al., 1992a,b,c, 1993a,b). Since then, beside the Shaefer and Kristensen group, others researchers have examined the melt granulation process in high-shear mixer demonstrating that this process can be usefully employed both to enhance the dissolution rate of poorly water soluble drugs (Passerini et al., 2002, 2006; Perissutti et al., 2003) and to control the release of short half-life drugs (Thies and Kleinebudde, 1999; Voinovich et al., 2000a,b).

The interest on melt granulation of pharmaceutical powders in fluidised (or fluid) bed is more recently; the earliest papers, at least at our knowledge, were published by Abberger (2001) and Kojima

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and Nakagami (2001) in 2001. In the period thereafter, considerable amount of work has been performed by Shaefer's group at the Danish University of Copenhagen (Abberger et al., 2002; Seo et al., 2002; Vilhelmsen and Schaefer, 2005), Hounslow' s team at University of Sheffield (Boerefijn and Hounslow, 2005; Tan et al., 2005, 2006), Walker's group at The Queen's University of Belfast (Walker et al., 2005, 2006, 2007a,b, 2009; Zhai et al., 2009) and finally Ansari and Stepanek (2006, 2008) at the Imperial College of London; the four research groups mainly focused their efforts on investigating the detailed mechanism of granule growth and on identifying the overall kinetics during the process. The majority of the works of melt granulation in fluidised bed has been performed using placebo formulations and only very few papers (Walker et al., 2007a) have examined granules containing drugs. Moreover, up till now no paper has demonstrated the potential of melt granulation in fluidised bed for modifying the release behaviors of drugs.

Although high-shear mixers and fluidised beds are suitable equipment for melt granulation of powders, and that the mechanisms of granule formation are different, a comparison of the two processes in terms of granule properties has not been carried out.

The main aim of this research was to compare high-shear mixers and fluidised bed processes with particular attention to the final technological, physicochemical and biopharmaceutical properties of granules. In addition, the study evaluated the suitability of melt granulation in fluidised bed for improving the dissolution rate of drugs. Agglomerates having same composition (a non-steroidal anti-inflammatory agent, ibuprofen or ketoprofen, as model drug, PEG 6000 as hydrophilic meltable binder and lactose as diluent) were produced by *in situ* melt granulation using both equipment and their morphology, particle size, flowability, friability, drug loading, dissolution behaviors and physicochemical properties have been evaluated and compared.

2. Materials and methods

2.1. Materials

Ibuprofen [2-(4-isobutylphenyl)-propionic acid] (Ibu) and ketoprofen [(3-benzoylphenyl)-propionic acid] (Ket) were used as model drugs; both were in the micronized form. Lactose (α-lactose monohydrate) 200 mesh was used as diluent and polyethylene glycol (PEG) 6000 was used as meltable binders; PEG 6000 was in a powder form and the size fraction 250–355 μm was obtained by sieving. All the materials were supplied by Polichimica s.r.l, Bologna, Italy.

2.2. Production of the granules

2.2.1. Melt granulation in fluidised bed (FB)

The experiments were performed using a Mini-Glatt fluidised bed (Glatt GMbH, Binzen, Germany). The conical vessel volume was 0.75 l; the granulator was equipped with three metallic filters, a timing filter blowing (out time fixed set 3 s) and a product temperature probe (±0.1 °C). A single granulation process (batch size 200 g) consisted of three steps: mixing, heating–kneading and cooling. The powders (10% drug, 20% fractionated PEG 6000 and 70% lactose) were placed at the centre of the bottom grid and were mixed by fluidising air with an inlet flow rate of 16.6 m^3/h at ambient temperature; the mixing phase lasted for 5 min. The flow rate of the inlet air was then increased to 23.9 m^3/h and its temperature was raised to 80 °C; as a consequence, the temperature of the powders gradually increased as well (heating phase). Once the product temperature reached 58 °C, the timing of the kneading phase started; after 3 min, the granulation end point was reached. Finally the flow rate of the inlet air was kept constant, while its temperature was decreased to 25 °C to achieve the consolidation of the granules; this cooling phase lasted until the product temperature reached 40 °C. At the end of the granulation process (total processing time was 15 min), the granules were discharged, collected and sieved as described in a following section. The phases and the main process parameters are summarised in Table 1.

2.2.2. Melt granulation in high-shear mixer (HSM)

The granules were prepared in a laboratory scale high-shear mixer (Rotolab®, IMA-Zanchetta, Lucca, Italy), equipped with an electric heated jacket, three blades impeller, a top chopper and a product temperature probe (±1 °C); the vessel volume was 2 l and the batch size was 400 g. The process consisted of three steps: mixing, heating–kneading and cooling. The powders (drug, PEG 6000 and lactose) were mixed in the high-shear mixer for 5 min, using an impeller speed of 120 rpm. Then the impeller speed was increased to 400 rpm and the heating jacket was heated to 70 °C (heating phase): due to the frictional forces and to the heating jacket, the product temperature increased till 57 °C, which was considered the starting point of the kneading phase. After 3 min, the granulation end point was reached. Finally the cooling phase was performed utilising the bowl tilt system and setting an automatic impeller cycle (10 s on, 60 s off) at 120 rpm for 10 min.

At the end of the granulation process (total processing time was 45 min), the granules were collected and sieved as described in a following section. The phases and the main process parameters are summarised in Table 1.

2.3. Characterization of the granules

2.3.1. Granule size analysis

The size distribution of granules was evaluated by sieves analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) and six standard sieves (Scientific Instruments s.r.l., Milano, Italy) in the range 100–1400 μm. The mass of the granules used for the analysis was 100 g and the sieving time was 10 min. The fractions were then collected and stored in a closed glass container at 25 ± 2 °C.

Table 1
Process parameters of the melt granulation in fluidised bed (FB) and high-shear mixer (HSM) granulator.

Phase	Parameters for FB				Parameters for HSM			
	Inlet air flow rate (m^3/h)	Inlet air temperature (°C)	Product temperature (°C)	Time (min)	Impeller speed (rpm)	Jacket temperature (°C)	Product temperature (°C)	Time (min)
Mixing	16.6	25	25.0–30.0	5	120	25	25–30	5
Heating	23.9	80	25.0	4	400	70	25	27
Kneading			58.0	3			57	3
Cooling	23.9	25	58.0–40.0	3	120[a]	70–25	57–40	10
Total time				15				45

[a] Automatic impeller cycle: 10 s on–60 s off.