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Granulation of indomethacin and a hydrophilic carrier by fluidized hot melt method: The drug solubility enhancement

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ABSTRACT

Fluidized bed hot melt granulation is an interesting alternative for preparing pharmaceutical solid dosage forms with functional properties such as sustained release and enhanced solubility. The aim of this work was to study indomethacin granulation by the FBHMG process. Fifteen granulates were prepared using indomethacin as a model drug, polyethylene glycol 4000 as a hydrophilic carrier, and spray-dried lactose as a fluidising substrate. The binder used for spray granulation in the FBHMG technique was a mixture of molten PEG 4,000 and indomethacin. The effects of the nozzle air flow rate, the binder flow rate and the weight of the binder used were studied using a Box–Behnken design. The dependent variables studied were the mean particle size (D_{50}) and the flow properties, which were determined from the angle of repose. The D_{50} values ranged from 479 to 824 μm, and the analysis of variance by a response surface methodology showed that the granule size was affected by the nozzle air flow rate at a significance level of 5%. The D_{50} value was also affected by the weight of binder/drug used and the interaction between the binder/drug flow rate and the weight of binder/drug used at a significance level of 10%. The angle of repose was not affected by the factors studied. Lower spray nozzle air flow rates (45 to 25 L/min) produced granules with excellent flow properties. The granule properties and the drug/binder/substrate interactions were comprehensively characterized using differential scanning calorimetry, scanning electron microscopy, Fourier transform infrared spectroscopy, X-ray powder diffraction and *in vitro* drug dissolution. Thermal and infrared spectroscopy analyses showed that there was no drug interaction during the process. The X-ray diffraction and scanning electron microscopy results showed that indomethacin crystals were present on the surface of the granules. Granulation enhanced the dissolution profile of indomethacin remarkably. Unprocessed indomethacin released only 45% of the drug in 120 min, whereas the granule released 100% of the drug in 20 min in a phosphate buffer media (pH 7.2). Therefore, the results confirmed the high potential of the FBHMG technique to produce granules with enhanced drug solubility and release rates.

1. Introduction

Coating and granulation of pharmaceutical solid dosage forms are important operations in the pharmaceutical industry for improving the mechanical, chemical and biological properties of the final product [1]. The key characteristics of granulates and coated forms include the size, density, flowability, compactability, and capability for slow or pH-dependent release [2]. Granulates containing active ingredients are usually prepared by successive operations of blending, drying, and sieving, which are each carried out using a different piece of equipment [3], thereby increasing the process time and the risk of contamination. Fluidized beds are an effective alternative for pharmaceutical granulation, because some of these operations, such as blending and drying, may be carried out simultaneously during fluidisation [4]. However, the conventional method of fluidized bed granulation involves the spraying of a binder solution. Recent regulatory restrictions on organic solvents have limited the use of conventional granulation in which solvents are used to prepare binder solutions [2]. However, aqueous solutions also present the risk of microbial contamination, drug hydrolysis and other difficulties that are related to residual moisture [2].

Recently, fluidized bed hot melt granulation (FBHMG) has received attention as a technique for processing pharmaceutical powders. The primary advantage of the hot melt method is that solvent use is eliminated [5–8]. The process of FBHMG, has been previously used to prepare acetaminophen granules with polyethylene glycol [9], white beeswax microcapsules containing potassium chloride [10], theophylline granules with Compritol® 888 Ato [11], chlorpheniramine maleate microparticles with beeswax [12], propanolol hydrochloride using Gelucire® 50/02 and Precirol® ATO5 [13].

Although FBHMG has been most commonly used for sustained release formulations [9–12], it has also an served as an alternative means of enhancing the solubility of weakly water soluble drugs [13] in spray freeze drying [14], spray congealing [15,16], supercritical fluids

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[17] and spray drying [18–20]. The solubility of drugs in water is directly related to their bioavailability and has recently received attention because of the increasing number of low-solubility active pharmaceutical ingredients, APIs, [13].

Indomethacin, IND, is an example of a drug with low water solubility. IND is a non-steroidal anti-inflammatory drug that was discovered in 1963 and inhibits the production of prostaglandins. Following its approval by Food and Drug Administration (U.S.A) in 1965, IND has been used to treat pain, fever, swelling and stiffness [21]. Despite its low water solubility, IND is classified as a class II drug in the Biopharmaceutical Classification System, BCS [22], because of its high permeability through the intestinal membrane. Consequently, many efforts have been made to increase the solubility of IND in aqueous media to improve its bioavailability. One option is to prepare a solid dispersion containing IND using a hydrophilic carrier. A solid dispersion is a useful means of dispersing drugs at the molecular level using a hydrophilic carrier.

The aim of this work was to study the fluidized bed granulation of IND by the hot melt method using a mixture of molten PEG 4000 and IND as a binder and spray-dried lactose as a substrate. The key FBHMG factors that were investigated included the nozzle air flow rate, the binder/drug atomisation rate and the total weight of the binder/drug applied to the substrate. A fractional factorial design of the Box–Behnken type was used in the experimental study. Box–Behnken factorial design is a tool that reduces the number of experimental runs by avoiding the execution of unnecessary experiments under extreme conditions. This design also enables first-order, second-order, and interaction coefficients to be efficiently estimated to characterize and/or optimize a process [23]. The granule quality was evaluated from the size distribution and the flow properties. The granule properties and the drug/carrier/substrate interactions were also comprehensively characterized using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRPD), and *in vitro* drug dissolution.

2. Material and methods

2.1. Materials

The substrate used in the granulation experiments was spray-dried lactose DCL-11 (Selectchemie, Brazil), which was supplied by Selectchemie Ltda (São Paulo, Brazil). Indomethacin was purchased from Henrifarma Ltda (São Paulo, Brazil), and the hydrophilic carrier was polyethylene glycol 4000, which was supplied by Vtech Ltda (São Paulo, Brazil).

2.2. Fluidized bed granulation

The equipment used was a fluidized bed, model LM FBD 3.0 (Labmaq do Brasil Ltda, Ribeirão Preto, SP, Brazil) that consisted of three stainless steel parts: a cylindrical column that was 35 cm in diameter and 25 cm in height, which was coupled with a conical base with a 60° included angle that was 35 cm in height and a top section that was 35 cm in diameter and 15 cm in height. The air inlet had a diameter of 9.5 cm and a stainless steel screen mesh of 270. Fluidising air was supplied by a 2-HP radial compressor, for which the mass flow rate was measured by a Pitot probe and calibrated with a turbine anemometer model MDA 11 (Minipa Ltda, Manaus, AM, Brazil). The pneumatic spray nozzle was centered at the top of the cylindrical column on an assembly that allowed the vertical position to be varied. A bag filter with an automated pneumatic self-cleaning system was also installed at the top of the cylindrical body to retain and return elutriated fines to the chamber. A PID controller and an electrical heater were used to set the process temperature. The air temperature and the humidity at the outlet were measured using a thermo hygrometer, model MTH 1380 (Minipa Ltda, Manaus, AM, Brazil). The spray nozzle consisted of a double fluid with external mixing and a liquid outlet orifice with a 1-mm diameter (Labmaq do Brasil Ltda., Ribeirão Preto, SP, Brazil). The spray nozzle was connected to a jacketed extensor that allowed a heating fluid to be circulated at 110 °C to prevent the solidification of IND/PEG 4000. The fluidized bed is shown Fig. 1.

Three hundred and forty grams of spray-dried lactose was weighed and loaded into the chamber; the minimum fluidisation air flow rate was checked and then adjusted according to the experimental design. When the set temperature was stable, the mixture of molten PEG 4000 and IND was atomized at predetermined spraying conditions. The following conditions were maintained constant for all of the experiments: the spray nozzle air temperature and pressure were 80 °C and 4 bar, respectively; the spray nozzle was located at a vertical distance of 55 cm from the bottom of the bed, the temperature of binder/drug feed was 110 °C, the pump head and the tubing temperature were 80 °C, and the self-cleaning filter purging interval was 30 s. The fluidisation air velocity was varied linearly to maintain the solid motion at 10% above the minimum spouting velocity, in accordance with the methodology developed by Mathur and Epstein [24]. The IND content in molten PEG 4000 (binder/drug) was 25% (*w*/*w*) for all of the granulation experiments. After completion of the experiments, the granules were collected for characterization.

The experiments followed a Box–Behnken design [25] with 3 factors and 3 levels. The factors chosen were the spray nozzle air flow rate (Q_{NA}), the binder/drug feed flow rate (Q_{MD}) and the total weight of binder/drug (W_{MD}) applied to the substrate. The levels and factors studied are presented in Table 1, which shows the coded and non-coded values of the factors. The formula applied to decode the factor levels is given by Eq. (1).

$$X_i = \frac{(value - 0.5 \times (high \cdot value + low \cdot value))}{0.5 \times (high \cdot value - low \cdot value)} \quad (1)$$

An analysis of variance on experimental data was performed using a surface response methodology with the Visual General Linear Model (VGLM) module from the software Statistica 7 (Statsoft Inc., Tulsa,

Fig. 1. Fluidized bed FBD 3.0 with 3-kg capacity (reproduced with permission of Labmaq do Brasil Ltda, Ribeirão Preto, SP, Brazil).