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ScienceDirect
Powder Technology 175 (2007) 73–81
POWDER TECHNOLOGY
www.elsevier.com/locate/powtec

Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients

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Received 31 August 2006; received in revised form 23 January 2007; accepted 24 January 2007
Available online 2 February 2007

Abstract

Agglomerates of naproxen, carbamazepine and lactose were developed by two spherical crystallization techniques, i.e., a spherical agglomeration method for carbamazepine and an emulsion diffusion method for naproxen and lactose. Physical characteristics of the crystals were studied for the morphology of crystals using scanning electron microscope, for the identification of polymorphism by X-ray powder diffraction (XRPD) and for thermodynamic properties using differential scanning calorimetery (DSC). The results showed that the flow and packing properties of agglomerates, represented in terms of the angle of repose and changes in tapping density, were much improved by these techniques compared with those of conventional crystals. This may be due to the spherical shape of agglomerated particles, since the area of contact in the powder bed for spherical agglomerates was smaller than that for other crystal shapes. Under static compression the acceptable tablet with a sufficient strength was produced successfully without capping, although the capping occurred with the original unagglomerated crystals. The improved compactibility of agglomerates was attributed to their structural characteristics. Scanning electron microscope showed that the agglomerates were comprised of small crystals and this particular structure was responsible for large relative volumes change which occurred during the early stage of the compression process, as a consequence of fragmentation. XRPD and DSC results showed that during the agglomeration process, naproxen did not undergo any polymorphic changes. XRPD and DSC results for carbamazepine and lactose revealed that during the agglomeration process, carbamazepine Form III changed to Form I and some of α-lactose monohydrates were converted to anhydrous β-lactose.

Keywords: Spherical agglomeration; Flow; Compactibility; Packability

1. Introduction

Particle design for solid pharmaceutical dosage forms involves improving the efficiency of the manufacturing processes and giving a high degree of functionality to the drug or excipient particles. The direct compression is a modern method in tablet manufacturing. Many processing steps *mainly granulation and drying* are omitted in direct compression, and additionally, wet technology cannot be used with sensitive agent (e.g., in effervescent tablet making). The direct compression of a powder depends on its particle size, flowability, mechanical properties such as hardness and Young's modulus [1–4] and bulk density. It should be kept in mind that, throughout the manuscript the terms compressibility and compactibility were used to describe the ability of a powder bed to be compressed due to the application of a given pressure and the ability of a powder bed to cohere or to form a compact, respectively. Some drug crystals exhibit appropriately such properties, but many materials have very poor flowability and compactibility [5]. For tablet making from the latter materials, possible solutions may be the use of wet granulation [6] or the use of direct tablet making with "good" excipients which promote direct compression. Another solution is to directly generate spherical agglomerates of drug crystals with good flowability and compactibility properties during the crystallization step. The latter method recently came into the forefront of interest because the properties of the particles such as shape, size, size distribution, specific surface area can be changed by crystallization processes.

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doi:10.1016/j.powtec.2007.01.030

It is difficult simultaneously to design multiple particle functions, so particle design is usually conducted in several steps. The compressibility, solubility and bioavailability of pharmaceuticals can be improved by the mechanical micronization of crystals. This, however, leads to a decrease in some other properties such as flowability and packability. Therefore, it becomes necessary to process microcrystals through a series of additional steps, e.g., mixing with fillers and granulation, for ease of handling. It would be more efficient to transform the microcrystalline drugs or excipients into an agglomerated form during the crystallization process.

Two methods are reported in the literature for generating spherical agglomerates: the spherical agglomeration (SA) method and the quasi-emulsion solvent diffusion (QESD) technique also known as the transient emulsion (TE) method. They are essentially distinguished by the miscibility of the drug solvent complex with the nonsolvent [7,8].

Spherical agglomeration is a novel agglomeration technique that can directly transform the fine crystals produced in the crystallization or in the reaction process into a spherical shape. This method was originally developed by Amaro-Gonzalez and Biscans [9]. Size enlargement processes to upgrade fine particulates are becoming increasingly important as it is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously. SA method proceeds in three steps. The first step is the selection of the crystallization method to precipitate crystals from solution, i.e., thermal method (temperature decrease or evaporation), physicochemical methods (addition of another solvent, salting out) and chemical reaction. The second step is the choice of the wetting agent that will be immiscible with the solvent of crystallization. Finally, the third step is the hardening of the agglomerates.

In QEDS method, a quasi-emulsion is formed by droplets of solvent containing the drug. The continuous phase is a liquid in which the drug is immiscible. Crystallization occurs inside the droplets because of the counter diffusion of the solvents through the droplets [9].

Carbamazepine and naproxen crystals are unsuitable for direct tableting due to their poorly compactible properties [10], although strongly demanded in commercial production by direct tableting. Lactose monohydrate crystals are the most common filler in tablets. Crystals of lactose monohydrate are large enough to flow reasonably well for direct compression, however, they are not particularly compactible [11]. For a good compactibility of lactose powders, small particle sizes are required. However, this will lead to poor flow properties due to high surface area of small particles making it a poor candidate as direct compression filler. So, the main aim of the present study is to produce agglomerated particles of carbamazepine, naproxen and lactose with improved compressibility and compactibility by spherical crystallization technique. Thus, the present study evaluates the suitability of agglomerates prepared by this technique for direct tableting together with the attempt to elucidate any differences with agglomerates and conventional crystals in flow, packing and compression characteristics.

2. Materials and methods

2.1. Materials

In this work three different materials are used: carbamazepine, naproxen and lactose which were supplied by Arasto Pharmaceutical Chemical Inc, Iran; Shasun Chemicals, India and Merch, Germany, respectively. Hydroxypropylcellulose and magnesium stearate were purchased from Nisso, Japan and BDH, UK, respectively. All other reagents and solvents (ethanol, acetone and isopropyl acetate) were purchased from Merck, Germany.

2.2. Development of spherical carbamazepine crystals by SA method

In order to produce spherical agglomerate of carbamazepine, 5 g of original sample was dissolved in ethanol (100 ml) at 60 °C to make quasi-saturated solution. The resultant solution (5% w/v) was poured into mixture of water (840 ml) and isopropyl acetate (60 ml) thermally controlled at temperature 20 °C, with stirring at 400 rpm. The precipitated crystals were collected after 20 min by vacuum filtration. The obtained crystals were dried in an oven at 60 °C for 3 h. The dried crystals were stored in a desiccator at room temperature before use. The above process was repeated several times in order to obtain enough carbamazepine for flow and particle size analysis tests.

2.3. Development of spherical naproxen crystals by QESD method

In order to produce spherical agglomerate of naproxen, 10 g of original sample was dissolved in 40 ml of acetone at 50 °C. This solution was added to 500 ml distilled water (20 °C) containing 0.25% w/v of hydroxypropylcellulose under fixed stirring conditions 200 rpm, paddle type agitator with 4 blades. The precipitated crystals were collected after 10 min by vacuum filtration onto a sintered glass filter then were placed in a thin layer in an oven at 60 °C for 3 h. The dried crystals were stored in a desiccator at room temperature before use. The above process was repeated several times in order to obtain enough materials for flow and particle size analysis tests.

2.4. Development of spherical lactose crystals by QESD method

In order to produce spherical agglomerate of lactose, 33 g of original sample was dissolved in distilled water (50 ml) at high temperature (80 °C). Then the solution was left to cool to 40 °C. Crystallization took place by the addition of various volumes of ethanol (100, 120 or 140 ml) at room temperature via a peristaltic pump (JMS, SP-500, Japan) at 300 ml/h. After the addition of ethanol, stirring was continued for 15 min, thereafter the crystals were collected by vacuum filtration. The obtained crystals were dried in an oven at 60 °C for 3 h. The dried crystals were stored in a desiccator at room temperature before use. The relative proportion of lactose/water has been chosen in accordance with the solubility of lactose in pure water. The solvent/nonsolvent ratio was 0.7.