Spherical Crystallization as Particle Engineering Technique to Improve Processability of Poor Flowing Furosemide

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ABSTRACT

The pharmaceutical industry is focusing on developing simple and economical formulations to meet desired drug delivery challenges. Tablet continues to be the most popular dosage form. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage forms. The formulation of tablet must be optimized to achieve desired goals. Poor flow of active pharmaceutical ingredient may raise issues like loss of tablet hardness and weight variation. This may restrict the formulator to use granulation techniques or higher levels of lubricants and glidants to impart the flow, which may adversely affect dissolution and compaction. Furosemide is a class IV drug from BCS classification and possesses poor flow properties. The main objective of study was to improve the flow properties of furosemide and thereby improve its solubility leading ultimately improvements in its bioavailability. We used two different techniques of spherical crystallization to improve the flow properties of furosemide. Our results reveal that the spherical crystallization by neutralization technique is better method than wet spherical crystallization to improve the flow properties of furosemide. Flow properties of excipients also affect the compression process. In conclusion, spherical crystallization technique could be used to enhance the flow properties of furosemide.

KEYWORDS: Spherical crystallization; wet spherical crystallization; neutralization technique; bridging liquid; flow properties; tableting.

Introduction

The basic requirement for commercial production of tablet is a particulate solid with good flowability, mechanical strength and compressibility. These micrometric properties of pharmaceutical powders are very important for the handling and improving the bioavailability of active pharmaceutical agent (API) from product. Hence is necessary to evaluate and modify the said properties. To improve flow property, one can add glidant, a hydrophobic material which in turns delays the disintegration and dissolution profiles of the tablets. To improve these properties, the APIs are subjected to particle engineering techniques such as spherical crystallization. There are other methods also to improve flow property of powders such as granulation techniques, extrusion and spheronization, but solubility cannot be modified by these methods. The spherical crystallization is a nonconventional particle- size enlargement technique that involves crystallization and agglomeration using bridging liquid and give evidences of improved solubility (Gupta et al., 2007).

Amongst the dosage forms, tablets are the most popular and convenient dosage form. As an intermediate step in production of tablets out of the powder; often granulation is used, by which the powder is converted into a material with improved handling properties. However, the granulation step is time consuming, and adds to the manufacturing costs, and this could be avoided if the micro crystals are agglomerated directly in the crystallization step. Spherical crystallization is a size enlargement method in which limited quantities of an agglomeration promoting liquid are added directly during the crystallization in order to get spherical agglomerates. These agglomerates can be directly compressed into a tablet form without intermediate processing steps (Kawashima et al., 1995).

Spherical crystallization can be carried out by different methods such as spherical agglomeration (SA) (Mahanty et al., 2010), emulsion solvent diffusion (ESD), ammonia diffusion system (ASD) and neutralization technique (NT) (Kawashima et al., 1986). Chow and Leung (1996) showed that agglomeration takes place as the wetted particles collide and the bridging liquid hold the particles together by forming liquid bridges between them. The selection and the amount of the bridging liquid, the agitation rate, concentration of the solid and feeding rate are the most critical parameters in spherical crystallization. Depending upon the amount of bridging liquid the particles can either form loose flocs or compact pellets.

Furosemide, 4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoyl-benzoic acid, is a drug with a diuretic action. The major problem associated with the formulation and effectiveness of the furosemide is its poor flowability and variable oral absorption of about 11–90% (Christensen 1971) due to insufficient aqueous solubility at gastrointestinal pH, thus making solubility the rate-