Review Article

SPHERICAL CRYSTALLIZATION: A METHOD TO IMPROVE PHYSICOCHEMICAL PROPERTIES

Srinivasarao. Prathipati *, V.Ganesan,
Department of Pharmaceutics, The Erode College of Pharmacy And Research Institute, Veppampalayam, Erode, TN, India.
***Corresponding author's E-mail:** pvlsr123@gmail.com

Accepted on: 19-11-2010; **Finalized on:** 15-01-2011.

ABSTRACT

Spherical crystallization is "An agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process." Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. In this spherical crystallization good solvent, bridging liquid and poor solvents are used. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time. This crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties (bulk density, flow property, compatibility) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified. Spherical crystallization is having wide applications in pharmaceuticals like improvement of flowability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the solubility and dissolution rate of poorly soluble drug. Characterization of spherical crystals determine by Optical microscopy, studied shape of the spherical crystals, X-ray powder diffraction, Electron scanning microscopy, Fourier Transform Infrared spectrometer (FTIR), Differential scanning calorimeter (DSC).

Keywords: Spherical crystallization, physicochemical properties, Agglomeration, emulsion solvent diffusion, ammonia diffusion method, characterization.

INTRODUCTION

In 1986, Kawashima used the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Spherical crystallization was defined by Kawashima as "An agglomeration process that transforms crystals directly in to a compact spherical forms during the crystallization process." Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone [1].

Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. The oral route of administration is the most important method of administering drugs for systemic effects. In this, the solid dosage form, particularly, tablets are the dosage form of a choice because of their special characteristics like unit dosage form with greatest dose precision and least content variability, lower cost, easy administration by a patient and temperature proof nature. The formation of solid oral dosage forms and tablets in particular, have undergone rapid changes and development over the last several decades and one of the most revolutionary technologies in that of direct compression. It is economical, facilitates processing without the need for moisture and heat and small number of processing steps are involved The basic requirement for commercial production of tablet is a particulate solid with good flowability, mechanical strength and compressibility. Hence is necessary to evaluate and manipulate the above said properties. To impart these properties the drugs are subjected to particle design techniques[2]. spherical crystallization is one the techniques of particle design. The particle size can be enhanced by the help of wet granulation method, dry granulation method, extrusion spheronization and by spherical crystallization methods. The spherical crystallization is a non-conventional particle- size enlargement technique that involves crystallization and agglomeration using bridging liquid[2]. Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compatibility of crystalline drugs the various parameters optimized were type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk density), wettability (contact angle) and compressibility. It was revealed from the studies that spherical agglomerates exhibited improved flowability, wettability and compaction behavior [3].

ADVANTAGES OF SPHERICAL CRYSTALLIZATION

- By using this technique, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability, flowability and compressibility of drug powder.
- This technique may enable crystalline forms of a drug to be converted into different polymorphic form having better bioavailability.
- Preparation of microsponge, micrspheres and nanospheres, microbaloons, nano-particles and micro pellets as novel particulate drug delivery system [3].

METHODS

The methods of spherical crystallization are categorized

- Solvent Change Method (SC)
- Quasi Emulsion Solvent Diffusion Method (QESD)
- Ammonia Diffusion Method (AD)
- Salting Out Method (SO)

Solvent change method

The solution of the drug in a good solvent is poured in a poor solvent under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent but low solubility with solvent mixture so during agitation of the solvent system the crystals formed. The Drawback of this system is that it provide low yield because the drug shows significant solubility in the crystallization solvent due to co solvency effect. This method is not applicable for water insoluble drugs [3].

Quasi Emulsion Solvent Diffusion Method

It involves the formation of quasi- emulsion of solution of drug in good solvent with a non-solvent. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. In this process the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization [4].

Ammonia Diffusion Method

In this method ammonia water act as a good solvent and bridging solvent, other components of this method are bad solvent and hydrocarbon/halogenated hydrocarbon (acetone). The hydrocarbon is miscible with the system but it reduces the miscibility of ammonia water with bad solvent. The fraction of ammonia water is the system that exists as an immiscible phase forms droplet. The counter diffusion process across the droplet involves movement of bad solvent into and ammonia out of the droplet. The droplet collects the crystals as a drug in ammonia water precipitates slowly and growth of agglomerates occurs. List of various drugs on which Emulsion solvent diffusion, spherical agglomeration and Ammonia diffusion method has been tried for improving physicochemical properties in table No-1 [3, 4].

Table 1: List of various drugs on which Emulsion solvent diffusion and Ammonia diffusion method has been tried for improving physicochemical properties.

Drug	Method	Solvent used	Reference Articles No
Celecoxib	SA	Acetone, water, chloroform	6
Aspirin	SA	Acid buffer, methanol, chloroform	7
Aminophylline	SA	Ethanol, chloroform, water	8
Nabumetone	SA	Ethanol, water, cyclohexane/n-hexane	9
Ibuprofen	ESD	Ethanol, water with sucrose, fatty acid ester	10
Acebutalol HCl	ESD	Water, ethanol, Isopropyl acetate	11
Norfloxacin	ADM	Ammonia water, acetone, dichloromethane	12
Enoxacin	ADM	Ammonia water, acetone, dichloromethane	13
Mefenamic acid	ADM	Ammonia water, acetone, dichloromethane	14

SA: Spherical agglomeration, ESD: Emulsion solvent diffusion, ADM: Ammonia diffusion method, HCl: Hydrochloride DMF: Dimethyl formamide

IMPROVEMENT OF PHYSICOCHEMICAL PROPERTIES OF DRUG BY SPHERICAL CRYSTALLIZATION METHODS:

- **Particle size and shape**

  Spherical crystallization change in crystal habit of pharmaceuticals gives different physicochemical properties.

- **Density**

  Volume of the agglomerates increases as density of the drug substances decreases.

- **Stability**

  Due to change in their polymorphism during recrystallization process there is change in stability of drug substances.

- **Flowability**

  Flowability of agglomerates improved as it exhibits lower angle of repose than that of single crystals. Significant reduction in inter-particle friction, due to their spherical shape and a lower static electric charge.

- **Packability**

  The angle of friction, shear cohesive stress and shear indexes are lower than that of single crystals, which can improve the packability of the agglomerates.

- **Compaction Behavior of Agglomerated Crystals**

  Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals.

- **Wettability**

  Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. As the contact angle decreases the wettability increases.

- **Solubility**

  In the prepared spherical changes in internal energy of the molecules play an important role to increase solubility.

- **Dissolution Rate and Bioavailability**

  Prepared agglomerated crystals Particle size, solubility, particle density and specific surface area increases the dissolution rate and Bioavailability[4].

CHARACTERIZATION

Characterization of spherical crystals determine by

Optical microscopy **-** Studies on shape of the spherical crystals.

X-ray powder diffraction **-** Studies on polymorphism existence.

Electron scanning microscopy **–** Studies on shape, over view, dimensions of the spherical crystals.

Fourier Transform Infrared spectrometer (FTIR) – Studies on Structure and Compatibility studies of spherical crystals.

Differential scanning calorimeter (DSC) – Studies on Dehydration, Dissociation, Decomposition, and Phase transfer, Purity, Glass transition, Heat capacity[5].

CONCLUSION

In this study prepared spherical crystals were having excellent physicochemical and micromeritic properties, solubility, dissolution rate, stability and in vivo (preclinical and clinical) performance when compared with pure drug besides exhibiting no preclinical toxicities'. If this process can be scaled-up to manufacturing level, this technology has the potential to provide the directly compressed tablets with improved bioavailability. However, extensive long-term stability, toxicity and clinical pharmacokinetic studies are required before commercialization.

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