Asian J. Pharm. Res. Vol 2, Issue 2, 113-121, 2012.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

A REVIEW ON SPHERICAL CRYSTALLIZATION: A NOVEL PARTICLE DESIGN TECHNIQUE FOR DIRECT COMPRESSION OF PHARMACEUTICAL POWDERS

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ABSTRACT

Direct compression of powders is simplest and easiest way of making tablets. Good flowability and compressibility plays a major role for direct compression of drugs. There are several techniques available to impart desired compressibility to drugs. Spherical crystallization techniques are reliable techniques in which the drug crystals are modified using different solvents to directly compressible spherical agglomerates, which less economical and time saving. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression. Spherical crystallization is a particle design technique, by which crystallization, agglomeration and spheronization can be carried out simultaneously in one step.

Key words: Direct compression, Spherical crystallization, Spherical agglomerates crystallization, Agglomeration, Spheronization.

INTRODUCTION

Tablet is very specific dosage form, accounting for 50 % of all oral drug delivery system and 70 % of all pharmaceutical preparations produced [1]. Formulation and manufacture of solid dosage forms and tablets in particular, have undergone rapid change and development over several decades. One of the revolutionary technologies is of direct compression [2]. Direct compression involves simple mixing and compression of powders which is economical and time saving[3]. Compressing a drug directly requires good micromeritic properties, such as flowability, and a good reproducible compressibility. Especially, the flowability of needle-shaped or plated-shaped crystals is very poor and these crystals are difficult to handle [4]. In addition to increasing efficiency of manufacturing process it is also important to increase the bioavailability of drug by increasing solubility of bulk drug powder [5].

Spherical agglomeration is one such techniques to improve micromeritic properties and dissolution of drug.Kawashima suggested obtaining the size enlargement of particles during the crystallization step by controlling crystal agglomeration with controlled properties [6]. He introduced this technique into pharmaceutical manufacturing and showed that spherically dense agglomerates could be produced and were suitable for direct tabletting and defined it as spherical crystallization. The traditional drug manufacturing procedures (granulation) involves following steps: crystallization → filtration → drying → formulated powders blending → granulation → drying → tabletting, This is a slow and time consuming process, where as in spherical crystallization the process could be reduced to: crystallization → filtration → drying → dry blending → tabletting. It means less equipment and space, lower labor costs, less processing time, and lower energy consumption in the direct tabletting process [7]. This technique is also reputed to improve the wettability, bioavailability, and dissolution rate of some poorly soluble drugs like celecoxib and fenbufen [8, 9].

So spherical agglomeration is a multiple unit process in which crystallization, agglomeration, spheronization can be carried out simultaneously in one step [10]. The resultant crystals can be designated as spherical agglomerates [11]. Due to characteristic shape, micromeritic properties such as flowability, packability and compressibility of resultant crystals are dramatically

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improved so that direct tabletting or coating is possible without further processing [12].

Methods of spherical crystallization

I. Wet Spherical agglomeration

A near saturated solution of the drug in the good solvent is poured into the poor solvent. Crystals will precipitate immediately. In the spherical agglomeration method a third solvent called the bridging liquid is added in a smaller amount to promote the formation of agglomerates [13].The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid makes the crystals to adhere one another [14].

The SA method has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid [15]. Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles [16]. Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance.

In the case of lactose, the agglomerate size distribution was affected by both the size of raw particles and the amount of bridging liquid used. At increasing stirring rate the agglomeration was reduced because of increasing disruptive forces [17]. Higher stirring rate produce agglomerates that are less porous and more resistant to mechanical stress, and the porosity decreases when the concentration of solid increases [18]. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates.

Chow et al postulated some general guide lines for the spherical agglomeration of drugs [19].

• For compounds that are water soluble, a water-immiscible organic solvent is used as the external medium and salt solutions of high concentration without common ions can be used as the bridging liquid.

• For compounds that are soluble in one or more organic solvents water is employed as the external phase and a water-immiscible organic solvent as the bridging liquid.

• For compounds that are only soluble in water-miscible organic solvents a saturated aqueous solution of the compound can serve as the external phase and an organic solvent mixture as the bridging solvent.

• For compounds that are insoluble in water or any organic solvents a water-immiscible organic solvent can act as the external phase and a 20% calcium chloride solution as the bridging liquid. In addition, a binding agent such as PVP or PEG is required for agglomeration since the powders are not sufficiently soluble in the bridging liquids to allow binding through recrystallization and fusion.

II. Quasi-Emulsion Solvent Diffusion method (QESD, Transient emulsion)

This technique is usually applied for the preparation of microspheres [20]. Here interaction between the drug and the good solvent is stronger than that of the good and poor solvents; hence the good solvent drug solution is dispersed in the poor solvent, producing quasi emulsion droplets, even if the solvents are normally miscible [21]. This is because of an increase in the interfacial tension between good and poor solvent [22]. Then good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent.

III. Ammonia diffusion method [23]

In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water.

IV. Neutralization Method [24]

Drug crystals are precipitated by neutralization of the base with acid and then poured into an acidic solution containing polymers and bridging liquid under constant agitation Spherical crystals of tolbutamide and phenytoin has been prepared by this technique.

V. Crystal-co-agglomeration technique [25]

It is a modification of the spherical crystallization technique in which drug is crystallized and agglomerated with an excipient or with another drug. This process enables design of agglomerates containing two drugs or poorly compressible drug in combination with diluents and is restricted to water insoluble large-dose drugs only. Difference in the physicochemical properties of drug molecules and excipient is a major challenge in the selection of the solvent system for the Crystal-co-agglomeration technique.

Steps involved in the process of spherical crystallization

Flocculation zone, zero growth zone, fast growth zone and constant size zone [26]

A) Flocculation zone

In this zone, bridging liquid displaces the liquid from the surface of the crystals and these crystals are

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brought in close proximity by agitation. The adsorbed bridging liquid links the particles by forming bridge between them.

B) Zero growth zone

During this growth phase, the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocks. Loose floccules are transformed into tightly packed pellets

C) Fast growth zone

The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size particle after random collision of well formed nucleus is known as coalescence.

D) Constant size zone

In this zone agglomerates cease to grow or even show slight decrease in size. Here thefrequency of coalescence is balanced by the breakage frequency of agglomeration. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial floccules are transformed into small agglomerates.

Factors controlling the process of agglomeration [27]

1. Solubility profile

Selection of solvent depends upon the solubility characteristics of the drug. The proportion of solvent to be used is determined by carrying out solubility studies and constructing a ternary phase diagram.

2. Mode and intensity of agitation

High speed agitation is necessary to disperse the bridging liquid throughout the system. Change in the agitation pattern or fluid flow will affect the shape of agglomerates. The extent of mechanical agitation and the concentration of bridging liquid determine the rate of formation of agglomerates and their final size.

3. Temperature of the system

It has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to its effect on the solubility of drug substance.

4. Residence time

It is defined as the time for which agglomerates remain suspended in the reaction mixture. Residence time affects the strength of agglomerates.

5. Amount of bridging Liquid

Median diameter of agglomerated crystals increases with decrease in the amount of bridging liquid in the three-solvent system. Insufficient bridging liquid produces plenty of fines and excess produces very coarse particles [28]

The common excipients used in spherical crystallization (polymers and surfactants)

Presence of additives like polymers and surface active agents whose surfaces are not similar to the crystal surfaces can influence molecular aggregation during crystallization. The viscosity of the medium and surface tension is reduced by the surfactants which affect the nucleation process. Studies have revealed that crystallization and agglomeration of pure drugs shows poor compressibility and handling qualities. Addition of polymers such as HPMC, PEG and PVP has improved the properties of spherical agglomerates. It has been reported that PVP improved the micromeritic properties, solubility and dissolution rate of spherical crystals of Celecoxib.

Evaluation of spherical agglomerates

1. Micromeritic properties

Improvement in the flowability of agglomerates could be attributed to thesignificant reduction in inter-particle friction due to their spherical shape and lower static electric charge [29]

Methods used for determination of flow properties are:

a) Angle of repose (θ)

It can be obtained from the equation:

$$\theta = \tan^{-1} h/r$$

Where "h" is height of the cone, "r" is radius of cone.

Values for angle of repose: ≤ 30 indicate free flow and ≥40 indicate poor flow.

b) Compressibility or Carr index

Compressibility index calculated by:

$$I = (1-V/Vo)\ 100$$

Where

V = Volume occupied by a sample of the powder after being subjected to standardized tapping procedure

Vo = the volume before tapping.

Value below 15% indicates good flowability and value above 25% indicate poor flowability

c) Hausner ratio

It is calculated from bulk density and tap density.

Hausner ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow and the value greater than 1.25 indicates poor flow.

2. Friability test:

Tak Ho and John A Hersy method is used and determined by formula

$$\text{Friability (X)} = \{1-W/Wo\}/100$$

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Where
Wo = Initial weight of the crystalline agglomerates placed in sieve
W = Weight of the material retained on sieve after 5 minutes.

3. Mechanical Properties

Tensile strength of spherical agglomerates is determined by compressing 500 mg of crystals using hydraulic press at different forces (kg/cm2) for 1 min. The hardness of each compact is measured using Pfizer hardness tester. Crushing strength of agglomerates is determined by using modified Jarosz and Parrot's mercury load cell method [30]

4. Wettability

Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. The methods used to determine wettability are:

- Determination of density: Density of saturated solution of drug and spherical crystals in water is determined by using a relative density bottle.
- Determination of surface tension: Surface tension of saturated solution of drug and spherical crystals in water is determined by employing a stalagmometer.
- Determination of porosity: Thickness and diameter of prepared tablet of drug spherical crystals is determined by using vernier callipers. Porosity of tablet is calculated from the apparent density of the tablet.

5. Solubility studies

Solubility studies are carried out in distilled water and dissolution medium by using Flask shaker method. Spherical agglomerated crystals are introduced into a flask containing distilled water and dissolution medium. The flasks are shaken for 24 hours at room temperature. The filtrates are then diluted with the respective medium and content is determined by a suitable analytical [31].

6. Dissolution studies

Dissolution of spherical agglomerates is determined by using the official dissolution apparatus and comparative studies are done for agglomerated crystals and non agglomerate [32]. Dissolution rate and bioavailability depends on the particle size and density and specific surface area of the agglomerated crystals.

7. Particle Size and Size Distribution

Size of the particle and their distributions can be determined by simple sieve analysis with the help of a Ro-Tap sieve shaker.

8. Compression Behavior Analysis

Good compactibility and compressibility are the essential properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Compaction behavior of agglomerated crystals can be evaluated by using following parameters:

Heckel Analysis

The following Heckel's equation is used to analyze the compression process of agglomerated crystals and assessed their compactibility.

$$\mathbf{In\ [1/\ (1\text{-}D)]=KP+A}$$

Where:
D is the relative density of the tablets under compression Pressure and K is the slope of the straight portion of the Heckel Plot.

9. Moisture uptake study

This study indicates the behaviour of uptake of moisture by drug and the prepared spherical crystals which affects their stability. Weighed quantity of drug and spherical crystals are placed in crucibles at accelerated conditions of temperature and humidity, 40 0C ± 1 0C and 75% ± 3% respectively. Gain in weight of drug and spherical crystals is measured [33].

Characterization of Spherical Agglomerates

Optical microscopy

The shape of spherical agglomerates is studied by observing them under optical microscope.

Electron scanning microscopy

The surface topography, type of crystals (polymorphism and crystal habit) of the spherical agglomerates is analyzed by using a scanning electron microscopy.

Thin layer chromatography

TLC studies are carried out and the Rf value is determined. Rf value of drug and spherical crystals are compared. This study is carried out to check if there is any interaction between the drug and the polymer. It also helps in determining the stability of drug in different solvents.

X-ray powder diffraction

Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound. The form of crystals in agglomerates is determined by using X-ray powder diffraction technique**.** This is an important technique for establishing batch-to-batch reproducibility of a crystalline form.

Fourier Transform Infrared spectrometer (FTIR)

It is mainly used for identification of drug and its different polymorphic forms. It is also used for distinguishing solvates and anhydrous form of drug.

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Differential scanning calorimeter (DSC)

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. It is also useful to determine thermal degradation, purity, polymorphism and drug-excipient compatibility [34].

Advantages [35]

1. This technique improves the flowability and compressibility of crystalline drugs.
2. Masks the bitter taste of drug.
3. Physicochemical properties of drug are dramatically improved for pharmaceutical processes like milling, mixing and tabletting because of their excellent flow and packability.
4. This technique enables crystalline form of a drug to be converted into different polymorphic form thus attaining better bioavailability.
5. It enables subsequent processes such as separation, filtration, drying to be carried out more efficiently.
6. It is also used in preparation of microsponges, microspheres and nanospheres, nanoparticles and micropellets as novel particulate drug delivery system.
7. The agglomerated crystals can be easily compounded with other pharmaceutical powders due to its spherical shape.

Disadvantages

1. Selection of suitable solvents is a tedious process.
2. Optimization of processing parameters (temperature, agitation) is difficult

Table 1. Some of the examples enlisting different techniques and solvents used in preparing spherical agglomeration of drugs

DRUG	SOLVENT SYSTEM			TECHNIQUE	REFERENCE
	Good solvent	Poor solvent	Bridging liquid		
Antibiotics					
Enoxacin	Ammonia-water	Acetone	Ammonia-water	ADM	[36]
Ampicillin Trihydrate	Ammonia water	Acetone	Dichloromethane	ADM	[37]
Norfloxacin	Ammonia-water	Acetone	Ammonia-water	ADM	[38]
Cefuroxime Axetil	Acetone	Water	Dichloromethane	ESD	[39]
Roxythromycin	Methanol	Water	Choroform	SA	[40]
NSAIDS					
Aspirin	Acid buffer	Methanol	Chloroform	SA	[41]
Aceclofenac	Acetone	Water	Dichloromethane	SA	[42]
Acetylsalicyclic acid	Ethanol	Water	Carbon tetrachloride	SA	[43]
Celocoxib	Acetone	Water	Chloroform	SA	[44]
Flubiprofen	Acetone	Water	Hexane	SA	[45]
Fenbufen	THF	Water	Isopropyl acetate	SA	[46]
Ibuprofen	Ethanol	Water	Ethanol	SA	[47]
Ibuprofen-Paracetamol	Dichloromethane	Water	Dichloromethane	CCA	[48]
Ibuprofen-Talc	Dichloromethane	Water	Dichloromethane	CCA	[49]
Indomethacin	Dimethyl formamide	Water	Chloroform	SA	[50]
Indomethacin Mepirizole	Ethyl acetate	Water	Ethyl acetate	CCA	[51]
Ketoprofen	Isopropyl acetate	Water	Choroform	SA	[52]
Ketoprofen-Talc	Dichloromethane	Water	Dichloromethane	CCA	[53]
Mefenamic acid	Ammonia-water	Acetone	Ammonia-water	ADM	[54]
Naproxan	Acetone-ethanol	Water	Chloroform	SA	[55]
Nabumetone	Ethanol	Water	Cyclohexane	SA	[56]
Piroxicam	NaOH	HCl	Chloroform	NT	[57]
Propylphenazone	Ethyl alcohol	Water	Isopropyl acetate	SA	[58]
Bronchodialators					
Aminophylline	Ethanol	Water	Chloroform	SA	[59]
Theophylline	Ethylenediamine	Sodium Chloride	Water	SA	[60]
Antidiabetic drugs					
Glibenclamide	Dichloromethane	Water	Chloroform	SA	[61]
Tolbutamine	Ethanol	Water	Isopropyl acetate	ESD,NT	[62]

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Antiallergic drugs					
Tranilast	Acetone	Water	Dichloromethane	SA	[63]
Anti hypertensive drugs					
Felodipine	Acetone	Water	Dichloromethane	ESD	[64]
Valsartan	Methanol	Water	Dichloromethane	ESD	[65]
Antihelmenthic drugs					
Mebandazole	Acetone	Water	Hexane	SA	[66]
Antiepileptic					
Carbamazepine	Ethanol	Water	Chloroform	ESD	[67]
Antifungal					
Gresiofulvin	Dichloromethane	Water	Dichloromethane	ESD	[68]
ß-adrenergic blockers					
Acebutalol HCl	Ethanol	Water	Isopropyl acetate	ESD	[69]
Other drugs					
Ascorbic acid	Water	Ethyl Acetate	Ethyl Acetate	SA, ESD	[70]
Aspartic acid	Methanol	Water	-	SA	[71]
Bromohexin HCl	Dichloromethane	Water	Dichloromethane	CCA	[72]
DCP (`Dibasic calcium Phosphate)	Citric acid	Water	Phosphoric acid	SA	[73]

SA = Spherical Agglomeration, ESDS = Quasi-Emulsion Solvent Diffusion System, ADS = Ammonia Diffusion System, NT = Neutralization Technique, CCA = Crystal-co-agglomeration technique

CONCLUSION

Spherical crystallization reduces time and cost by enabling faster operation, less machinery and fewer personnel because of less number of the steps when compared to conventional granulation technology of tablet manufacturing. But the residues of organic solvent after the formation of agglomerates have to be monitored for passing the regulatory requirements. Agglomerates exhibit excellent physicochemical and micromeritic properties, solubility, dissolution rate, stability and *in vivo* (preclinical and clinical) performance when compared with pure drug as well as marketed formulation besides exhibiting no preclinical toxicity. Even Spherical agglomeration is a particle size enlargement technique the increase in solubility may be due to porosity of the agglomerates. The spherically agglomerated crystals can be compounded directly into a pharmaceutical system without further processing such as granulation.

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