Review Article

Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique

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ABSTRACT

In 1986, Kawashima and their coworkers developed the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Kawashima defined spherical crystallization as "An agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process." It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that 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, compactability) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified. The process is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel.

Key Words: Spherical crystallization, crystal habit, physicochemical properties, compactability, agglomeration

INTRODUCTION

The quality and efficiency of a solid pharmaceutical preparation is influenced by primary micrometric properties (shape, size of crystals etc) and micrometric properties (bulk density, Flowability.) of active medical substances and inactive substances especially when the large amounts of non water-soluble drug with poor rehologic properties are formulated. The formulation and manufacturing of tablet, the most convenient and widely used pharmaceutical dosage form should comprise only a few working steps. The material used for the production of tablet should be in physical form that Flow smoothly and uniformly, have bindability / compressibility and physically stable, so as to achieve rapid production capability of tablet formulation. Therefore one of the most important changes in the manufacturing of tablet in the last decade is the large-scale introduction of direct compression of tablets (direct tabletting method). The main tabletting method involved first making granules and than compressing them into tablets by way of indirect (granule) tabletting, but the need in recent years for process validation, GMP and automation of production process has focused renewal attention on direct tabletting method, which involve few steps.

There are currently limited pharmaceutical tablets on commercial production that can be made by direct tabletting. There fore the development of the active ingredient crystals design that can be directly tabletted has been waited.[1] Most powders cannot be compressed directly into tablet because they lack the proper characteristics of binding or bonding together into a compact entity. Directly tabletting technique is quite simple but depends on, the flowability, particle size, the particle size distribution, bulk density and the compressibility

Table: 1 Following are the other examples of drugs improving its physicochemical properties by spherical crystallization techniques.

METHOD	DRUG	SOLVENT	RESEARCH FINDINGS
SA	**Aminophylline** Kawashima,Y.,et al.[13]	Chloroform Ethanol Water	The resultant Aminophylline agglomerates were free flowing and directly compressible due to their spherical shape.
SA	**Naproxen** Gorodon,M.S.,et al.[14]	Acetone Water Hexinol, octanol Toluene	Improved the intrinsic compressibility and flow characteristic of agglomerates, which is directly compressible.
SA	**Aspirin** Deshpande, M.C., et al.[15]	Acid buffer Methanol Chloroform	Significantly improved flow property, compressibility and stability.
ADS	**Ampicillin trihydrate** Ghol.M.,et al.[16]	Ammonia water Acetone Dichloromethane	Improved micromeritic properties, compressibility, and compaction property. Tablet prepared from agglomerates showed comparable drug release with that of obtained from marketed product.
SA	**Salicylic acid** Kawashima Y.,et al.[17]	Water Ethanol Chloroform	Agglomerates are having excellent flow ability used directly for the compression of tablet.
SA	**Aspartic acid** Szabo-Revesz,P.,et al.[1]	Water (solvent)Methanol (salting out agent)	Agglomerates showed very good flowability and faster rearrangement
ADS	Norfloxacin Puechagut, H.G., et al.[18]	Ammonia water Acetone Dichloromethane	Improved micrometric and micrometrics properties.
SA	**Ibuprofen** Jbilou , M.,et al.[19]	Water Ethanol	Increased compressibility, dissolution rate
SA	**Acetyl salicylic acid** Goczo Hajnalka.,et al.[20]	Ethanol Water Carban-tetrachloride	Agglomerates are having excellent flow properties and favorable compact ability, cohesiveness and tablettability value
SA / QESDS	**Ascorbic acid** Kawashima Y.,et al.[21]	Purified water Ethyl acetate Methanol	Improved the micrimeratic and compaction properties of the original Ascorbic acid crystals.
ADS	**Enoxacin** Ueda Masumi.,et al.[22]	Ammonia water Acetone Dichloromethane	Improved flowability, packability without much delay in their dissolution rate.
SA / QESDS	**Bucillamine** Morshima, K., et al.[3]	Ethanol Dichloromethane water	Agglomerates show excellent compatibility, Packability.
QESDS	**Ibuprofen** Kawashima Y.,et al.[23]	Ethanol Water with sucrose fatty acid ester	Improved Flowability, packability Compressibility of the resultant microspheres

of the crystalline powder. For these reasons, particle design is done to improve the properties of particle i.e. flowability, packability, solubility, particle size, size distribution and bulk density to impart a new function to preparation and to guarantee more stable and reliable powder processing in solid dosage form preparation.

Direct compression is the modern and the most efficient process used in tablet manufacturing because of free flowing property and able to form stable compacts at low punch forces. It is fastest, simplest and least expensive tablet compression procedure in which many processing steps (granulation, drying) are eliminated. Moreover is used for moisture sensitive drugs for which wet granulation technology cannot be used.

If the API (Active Pharmaceutical Ingredients) or Tablet excipient does not show such properties than the tablet is formed by the following method

1.By Granulation

2.By using direct compressible excipients

3.By Spherical crystallization method

Granulation:

Granulation is the generic method for particle size enlargement that refers to the accumulation of small particle gathered together into larger. But the granulation step is time and energy intensive and exposes the formulation to water or solvent and heat. Various granulation methods are widely used in pharmaceutical industries, common granulating methods includes

1.Dry granulation (slugging):

2.Wet granulation method:

3.Fluidized bed granulation:

4.Melt granulation

By using directly compressible excipient:

By using directly compressible excipients it is possible to prepare directly compressible tablet but if the drug or the excipients are having different crystal habit it may mostly affect the flow properties of the final powder blend, which are feed to die cavity.

Spherical crystallization:

In 1986, Kawashima, Y., et al 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 into compact spherical forms during the crystallization process." It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle.[2] this technique involved selective formation of agglomerates of crystals held together by liquid bridges.

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that 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, compactability) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified. It has been also described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compression ability of some powders so that critical steps involved in wet granulation can be avoided.

Advantages of Spherical Crystallization:

1.Spherical crystallization technique has been successfully utilized for improvement of flowability and compressibility of crystalline drug.

2.This technique could enable subsequent processes such as separation, filtration, drying etc to be carried out more efficiently.

3.By using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tabletting because of their excellent flowability and packability.[3]

METHOD	DRUG	SOLVENT	RESEARCH FINDINGS
NT	**Tolbutamide** Sano A.,et al.[24]	NaoH solution Aqueous solution with polymer or surfactant 1M HCl.	Increased dissolution rate, flowability, and solubility of agglomerated crystals.
SA	**Dibasic calcium phosphate** Takami, K.,et al.[25]	Water Aqueous solution of phosphoric acid Citric acid	Free flowing, porous directly compressible agglomerated crystals formed.
SA	**Tranilast** Kawashima,Y.,et al.[8]	Ethanol Acetone Water Chloroform Dichloromethane	Improved in vitro availability as well as micromeratic properties such as flowability, packability.
QESDS	**Acebutalol Hcl** Kawashima Y.,et al.[26]	Water Ethanol Isopropyl acetate	Agitation speed is an main factor for controlling diameter, improved flowability, compressibility of prepared agglomerated crystals
SA	**Naproxen** A. Nokhodchi[27]	Acetone–water containing hydroxypropyl Celloluse (HPC) and disintegrant croscarmellose sodium (Ac–Di–Sol)	Good flow, packing Properties and improved compaction properties of prepared agglomerates. The dissolution rate of naproxen from tablets made of naproxen–(Ac–Di–Sol) agglomerates was enhanced significantly because of including the disintegrant in to the particles. This was attributed to an increase in the surface area of the practically water insoluble drug is exposed to the dissolution medium.
QESDS	**Propyphenazone** Piera Di Martino[28]	Ethyl alcohol-demineralized water-isopropyl acetate	To improve the compression properties of propyphenazone. The improvement in flowability contributes to making the filling of the die easier and more precise and thus gives more reproducible results.

SA = Spherical Agglomeration method, ESDS = Quesi-Emulsion Solvent Diffusion System., ADS = Ammonia Diffusion System., NT = Neutralization Technique

4. This technique may enable crystalline form of a drug to be converted into different polymorphic form and thus attain better bioavailability.
5. For masking of the bitter taste of drug
6. Preparation of microsponges, microspheres and nanaospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system.

The process is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel. It gives important advances in tabletting technology, especially the introduction of number of directly compressible excipients. The spherically agglomerated crystals can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation.

Solvents for spherical crystallization:

1. First is substance dissolution medium (Good solvent).
2. Second is partially dissolution medium for the substance (Bridging liquid).
3. Third one is immiscible with the substance.(poor solvent)[4]

Role of bridging liquid in the spherical crystallization technique:

The spherical crystallization technique involved the selective formation of agglomerated crystals held together by liquid bridges. The agglomerates were formed by agitating the crystals in the liquid suspension in the presence of the bridging liquid. The bridging liquid should be immiscible in the suspending medium but capable of cementing the particle to be agglomerated. The finally divided solid crystals in the liquid suspension initially separated from each other but by adding small amount of bridging liquid which preferentially wets the surface of solids, form the bridges between the solid crystals and finally agglomerate into spherical form. Thus the nature of bridging liquid and surface properties of crystals play important role in agglomeration process.[5]

METHODS OF SPHERICAL CRYSTALLIZATION

Following are the methods used to prepare the spherical crystals.

1.Spherical Agglomeration method (SA)

2.Quasi-Emulsion Solvent Diffusion method (QESD)

3.Ammonia diffusion system (ADS)

4.Neutralization Technique (NT).

5.Traditional crystallization process.

Spherical Agglomeration method (SA):-

The process involves the formation of fine crystals and their agglomeration. Crystallization is generally achieved by the change of solvent system or salting out. The solution of material in good solvent is poured in a poor solvent, so as to favor formation of fine crystals. Agitating the crystals in a liquid suspension and adding the bridging liquid, which preferentially wets the surface crystals to cause binding, form the agglomerates. The agglomerates may be spherical if the amount of bridging liquid and the rate of agitation are controlled.

Martino, D., et al.[6] produced spherical propyphenazone crystals by an agglomeration technique using a three solvent system.

2. Quasi-Emulsion Solvent Diffusion Method (QESD)

By this method, spherical crystallization can be carried out using a mixed system of two or three partially miscible solvents, i.e. bridging liquid-poor solvent system or good solvent-bridging liquid-poor solvent system. When bridging liquid (or plus good solvent) solution of drug is poured in to poor solvent (dispersion medium) under agitation, quasi emulsion droplets of bridging liquid or good solvent forms the emulsion droplet in to the dispersing medium and induce the crystallization of drug followed by agglomeration.

Sano et al.[7] prepared Tolbutamide spherical agglomerates using emulsion solvent diffusion method

3. Ammonia Diffusion System Method (ADS)

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.[8]

Mechanism of the ammonia diffusion system method**:** It involves the three steps

1.Invasion of acetone into ammonia water droplets.

2.Diffusion of ammonia in the agglomerates to the outer solvent.

3.Agglomeration ending.

The spherical crystallization of Enoxacin, an antibacterial agent and Norfloxacin was carried out using the ammonia diffusion method. [9, 10]

4. Neutralization Method (NT):

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug tolbutamide was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous solution of Hydroxypropyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide, which was then, crystallized out.[11]

5. Traditional crystallization process:

These methods also can be used to produce spherically crystallized agglomerates, which are carried out by controlling the physical and chemical properties and can be called as the non-typical spherical crystallization process. These are

a) Salting out precipitation.

b) Cooling crystallization.

c) Crystallization from the melting.

Improvement of physicochemical properties of drug substances by spherical crystallization technique:

The spherical crystallization can enable subsequent process such as separation, filtration and drying to be carried out more efficiently. It exhibits high flowability, packability, compressibility and wettability of the materials.

Following physicochemical properties were improved by spherical crystallization technique:[12]

Particle size and shape (Crystal habit):

The size and the crystal habit of the pharmaceuticals changes during recrystallization process in spherical crystallization method. The change in crystal habit of pharmaceuticals gives different physicochemical properties.

Density:

In spherical crystallization process recdrystallization of drug agglomeration occur at same time and size of the agglomerates increases as compared to original crystals of drug substances. There fore volume of the agglomerates increaseas and density of the drug substances decreases.

Amorphous Form:

If the polymers are added during recrystallization of pharmaceuticals amorphous form is developed which are having more solubility comparative to crystalline form.

Stability:

Due to change in their polymorphism during recrystallization process there is change in stability of drug substances. As the spherical agglomerates is the agglomeration of small recrystallized crystals it reduces the surface area and improvement in stability

Flowability:

Flowability of the agglomerates is much improved as the agglomerate exhibits lower angle of repose than that of single crystals. This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction, due to their spherical shape and a lower static electric charge.

Packability:

Improve packability has been reported for agglomerates prepared by spherical crystallization. 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.[13]

Compaction Behavior of Agglomerated Crystals:

Good compactibility and compressibility are essential properties of directly compressible crystals. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. It is suggest that the surface are freshly prepared by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals.

Mechanical strength of resultant tablets:

The tablets compressed with the agglomerated crystals exhibit higher tensile strength than that of compressed original crystals. The tensile strength of tablets prepared from agglomerated crystals is higher than the tablets prepared from single crystal at the same compression pressure and porosity of the tablet. This was due to plastic deformation of the agglomerated crystals resulting in greater permanent antiparticle contact and stronger bond force than in case of the original crystals.

Wettability:

Wettability of agglomerated crystals by water is investigated by measuring the contact angle of water to the compressed crystals .The wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. As the contact angle decreases the wettability increases. Crystals with low crystallinity are more wettable than crystals with higher crystallinity.

Solubility:

The improved solubility in spherical agglomerates may be due to changing the crystal forms, different habit, structure, surface modification & in some instances, solvents included into the crystals forms solvets or clathrates can changes the surface properties and the reactivity of drug particles .The change in internal energy of the molecules play an important role to increase solubility.

Some polymers used showed increased intraparticle porosity suggested the absence of polymer deposition in the empty spaces between micro crystals in the agglomerates. The agglomerated crystals prepared by incorporating of water-soluble polymers like polyethylene glycol can improve solubility.

Dissolution Rate and Bioavailability:

The dissolution rate and bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the agglomerated crystals. It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases. Tabletting compacts partially breaks the agglomerated crystals and thus the average particle size is reduced. But compression also increases the particle density, which may adversely affect dissolution. Specific surface area of crystals is found to depend on the method used for spherical crystallization.

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