SPHERICAL CRYSTALLIZATION: AN ASPECT TO INCREASE THE PHYSICOCHEMICAL PROPERTIES OF DRUGS

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Abstract
Tablets are the significantly used formulations in the health care. In the area of tablet manufacturing control of particle size is important in achieving the appropriate flow property. Therefore sound knowledge of micromeritics must expect from today’s pharmacist and this property can be greatly affected by crystal habit. With spherical crystallization technique crystal habit can be significantly improves in terms of improvement of flow property and precise particle size control in cost effective and time saving manner. There by micromeritics property of drug is dramatically increased. Review throne the light on the detail description about mechanism of spherical agglomeration, factors affecting method including various methods of preparation and solvents systems. Need of this technique in the present scenario is well explain in review. Also various evaluation parameters are included.

Key Words- Spherical crystallization, principle, Agglomeration, Physicochemical Properties

INTRODUCTION
Today many different types of dosage forms are available in the health care market but, tablet dosage form still retains its popularity among the global population. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage form. Tablet is the most stable readily portable and consumed dosage form. The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. To achieve this one of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression tableting over recent years since in comparison to the used at the more traditional granulation process. Such manufacturing of the tablets involves simple mixing and compression of powders which gives benefits like time and cost saving. [1] Thus direct tableting technique has been widely used successfully for different drugs. But it strongly depends upon the

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physicochemical properties of the drugs used. When mechanical properties and micromeritics properties of the drug particles are not adequate a primary granulation is necessary. The final purification of the Active Pharmaceutical Ingredient (API) is usually a crystallization step, in which the product properties like the crystal size distribution, crystal shape, degree of agglomeration, and agglomerate properties, depend on how the process is operated. Temperature profile, solvent composition, method and rate of supersaturation generation, hydrodynamics, etc. often have a profound influence on these properties, and can be used to control the process in such a way that more specific solid state properties, suitable for formulation, are obtained.

The first step in the formulation is often milling or granulation, in order to provide for better properties for the final tableting or to increase bioavailability. Often very small particles are required in order to increase the dissolution rate, and reach sufficient bioavailability. However, micronisation by milling is extremely inefficient, can cause physical and chemical instability, and produces powders with a wide size distribution and poor flowability. The alternative is to produce quite small crystals directly in the crystallization. In some cases thin needles are produced having a high surface area to volume ratio, but likewise may be quite difficult to handle. Crystals could be generated employing any of the conventional techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding. [2]

One of method called Spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression.[3], [4]

Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired. [5] The definition of Spherical crystallization is given as 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 particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form [6] and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs. [7]

**SPHERICAL CRYSTALLIZATION**

In 1986, [Kawashima 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 in to a compact spherical forms during the crystallization process.” It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle. [8], [9]

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, 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 (solubility, dissolution rate, bioavailability and stability) can be improved. As this technique forms the spherically agglomerated crystal showing significant effect on the formulation and manufacturing of pharmaceutical dosage form. [6] It is also possible to prepare novel particulate drug delivery system like micro sponges, microspheres and nanoospheres, microbaloons, nanoparticles and micro pellets by using these techniques. This technique may enable crystalline form of a drug to be converted into different polymorphic form and thus attain better bioavailability and improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. [6] 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 micromeretic 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. [2]

Methods of Spherical Crystallization

1. Spherical agglomeration (SA):

In the spherical agglomeration method a third solvent called the good solvent, poor solvent and bridging liquid is used. A near saturated solution of the drug in the good solvent is poured into the poor solvent alone or containing polymer if added to impart strength to the generated crystals. [10] The agglomerating or bridging solvent was chosen in a manner that it is immiscible with the anti-solvent and the drug has limited solubility in it. [11] Provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. Under agitation, the bridging liquid (the wetting agent) is added. 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 act to adhere the crystals to one another [12] by promoting the formation of liquid bridges between the drug crystals to form spherical agglomerates shown in Fig. 1.[13] The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. [14], [15] 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. [16] Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles.[17] 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.[18] 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.[19] 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. Various drugs on which spherical agglomeration technique has been tried for improving tabletability are given in Table no.1

Figure-1. Schematic representation of the spherical agglomeration process

2. Emulsion solvent diffusion (ESD) or Quasi-Emulsion Solvent Diffusion method (QESD):
In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing quasi emulsion droplets, even if the solvents are normally miscible. This is due to an increase in the interfacial tension between good and poor solvent. Then the 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. This process is known as the emulsion solvent diffusion (ESD) process. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase.[20] Various drugs on which Emulsion solvent diffusion technique has been tried for improving tabletability are listed in Table no.2

3. Ammonia diffusion method
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. [20] Various drugs on which Ammonia diffusion method technique has been tried for improving tabletability are listed in Table no.2 [2]
Table - 1 List of Various Drugs on Which Spherical Agglomeration Technique Has Been Tried for Improving Tabletability

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SOLVENT USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxythromycin</td>
<td>Methanol, chloroform, water</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Ethanol, chloroform, water</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Acetone ethanol, chloroform, water</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Acid buffer, methanol, chloroform</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Water, ethanol, chloroform</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>Water, methanol</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Water, ethanol</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>Ethanol, water, carbon tetrachloride</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Water, ethyl acetate, chloroform</td>
</tr>
<tr>
<td>Dibasic calcium phosphate</td>
<td>Water, phosphoric acid solution, citric acid</td>
</tr>
<tr>
<td>Tranilast</td>
<td>Ethanol, acetone, water, chloroform, DCM</td>
</tr>
<tr>
<td>celecoxib</td>
<td>Acetone, water, chloroform</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>DMF, water, carbon tetrachloride/ chloroform</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>Acetone, water, dichloromethane</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Ethanol, water, cyclohexane/n-hexane</td>
</tr>
</tbody>
</table>

Table - 2 List of various drugs on which Emulsion solvent diffusion and Ammonia diffusion method has been tried for improving tabletability

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SOLVENT USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Ethanol, water with sucrose, fatty acid ester</td>
</tr>
<tr>
<td>Acebutalol HCl</td>
<td>Water, ethanol, Isopropyl acetate</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Ammonia water, acetone, dichloromethane</td>
</tr>
<tr>
<td>Ampicillin trihydrate</td>
<td>Ammonia water, acetone, dichloromethane</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Ammonia water, acetone, dichloromethane</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>Ammonia water, acetone, dichloromethane</td>
</tr>
</tbody>
</table>

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. [20]
5. Traditional crystallization process: [21]
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.

The Principle Steps Involved in The Process of Spherical Crystallization [22]
Following four steps in the growth of agglomeration was identified by Bermer and Zuider Wag [8].

1. Flocculation Zone: In this zone, the bridging liquid displaces the liquid from the surface of the crystals and brought crystals in close proximity by stirring; the adsorbed bridging liquid links the particles by forming a lens bridge between them. In these zones, loose open flocs of particles are formed by pendular bridges.

2. Zero Growth Zone: Loose flocules get transferred into tightly packed agglomerates, entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing poor space in the agglomerates of completely filled with the bridging liquid. The driving force for the transformation is provided by the stirring of the slurry causing liquid turbulence, agglomerates - agglomerates - stirrer collision.

3. Fast Growth Zone: The fast growth zone of the agglomerates takes place when sufficient bridging liquid has squeezed out of the surface on the small agglomerates. This formation of large particles following random collision of well-formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances particle deformations and subsequent coalescence. Another reason for the growth of agglomerates size is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

4. Constant Size Zone: In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may be due to attrition, breakage and shatter. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial flocules are transformed into small agglomerates. The rate determining step is the collision of particle with the bridging liquid droplets prior to the formation of liquid bridges. The rate is governed by the rate of agitation. The strength of the agglomerates is determined by interfacial tension between the bridging liquid and the continuous liquid phase, contact angle and the ratio of the volumes of the bridging liquid and solid particles.

APPLICATIONS OF SPHERICAL CRYSTALLIZATION

- Flow properties (flowability and compressibility) of crystalline drug improved.
Physicochemical properties of pharmaceutical drugs are dramatically enhanced for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability.[23]

Increasing solubility and dissolution rate of poorly soluble drug and obtained better bioavailability due to crystalline form of a drug to be transformed into different polymorphic form by this method [22].

Enable to use polymers and consequently use in preparation of microsponges, microspheres and nanospheres, microballoons, nanoparticles and micro pellets as novel particulate drug delivery system.

Successive procedure such as separation, filtration, drying etc to be carried out more efficiently.

Taste masking of bitter drugs [22]

FACTORS CONTROLLING THE PROCESS OF AGGLOMERATION

Agitation Speed
Optimum speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would be reflected as change in force acting on agglomerate, which ultimately affects the shape of agglomerate. [22] It has been reported that, the speed of the agitation affects size, sphericity, and strength of agglomerates [18]. Higher speed of agitation increases sphericity of agglomerates but reduces the strength of agglomerates. The time required for the completion of agglomeration process gets reduced with higher speed of agitation [24], [25].

Solvent system
The selection of solvent system depends on solubility and stability of drug/s in the solvent system. Water has been reported as a processing (bad solvent/external phase) medium, and organic solvents (relatively nontoxic) as a good solvent (internal phase) and/or bridging liquid in the system design.

Physical form of product i.e. whether microagglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions. The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility by using Ternary diagram.

Temperature of the system: Study revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to the effect of temperature on the solubility of drug substance in the ternary system.

Polymer Types and Their Concentration
Plain drug agglomerates (without excipients) have showed poor resistance to breaking, poor compressibility and low compactibility due to inherent poor cohesiveness of drug/s. Agglomerates obtained by optimum addition of polymers imparts sufficient mechanical strength and sphericity to the agglomerates.
Residence time: The time for which agglomerates remain suspended in reaction mixture affect their strength. Hence, judging the endpoint of agglomeration process becomes critical. End point of agglomeration process can be judged from clarity of supernatant, residual organic solvent and attainment of proper agglomerate size growth [24], [25]

EVALUATION PARAMETERS
It is necessary to evaluate and characterized these spherically agglomerated crystals by using the different parameters so as to differentiate it from the raw crystals.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Method/instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size distribution</td>
<td>sieve analysis, Microscopy</td>
</tr>
<tr>
<td>Shape and Surface</td>
<td>Optical and scanning electron microscopes (SEM).</td>
</tr>
<tr>
<td>Bulk &amp; tapped density</td>
<td>Manual method or Bulk density apparatus</td>
</tr>
<tr>
<td>Carr index &amp; Hausner’s ratio</td>
<td></td>
</tr>
<tr>
<td>Flow Properties</td>
<td>Angle of repose (0)</td>
</tr>
<tr>
<td>Packability</td>
<td>Kawakita (I) and Kuno (II) method [5]</td>
</tr>
<tr>
<td>Compactability</td>
<td>Heckel Analysis [27][28]</td>
</tr>
<tr>
<td>Crushing strength</td>
<td>Jarosz and Parrot’s mercury load cell method [22]</td>
</tr>
<tr>
<td>Sphericity</td>
<td>Stereomicroscope [29]</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Dissolution apparatus</td>
</tr>
<tr>
<td>XRD, DSC, FTIR,</td>
<td>Specific instruments</td>
</tr>
</tbody>
</table>

Developed spherical agglomerates also evaluated for other parameters such as Solubility, Friability test, Wettability, porosity, Moisture Uptake Study, Tablet Elastic Recovery Test, Tablet Tensile Strength Test etc.

NEED OF THIS TECHNIQUE
- It explains the potential benefits of the Spherical crystallization technique are as follows:
- It is a simple process and inexpensive enough for scaling up to commercial level.
- It reduce time and cost by involving faster operation, less machinery, and fewer personnel.
- Give great advancement in tableting technology, especially the introduction of a number of directly compressible excipients.
- Using this technology, micromeritics and physicochemical properties of pharmaceutical crystals are dramatically improved foe pharmaceutical processing like milling, mixing, and tableting because of their excellent flowability and packability. [23]
- Resultant agglomerates crystals could be easily compounded with other pharmaceutical powders due to their spherical shape. [26]
- Spherical crystals produced with minimum processing step like granulation in tablet dosage form is not required, so regulatory processes like GMP, process validation ,and automation linked to the that step is also not required.
REFERENCES
15. Chourasia MK, Jain NK, Jain S, Jain NK and Jain SK. Preparation


