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Spherical agglomeration: a tool of particle engineering for making drug powder suitable for direct tabletability

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ABSTRACT

Direct tabletting technique is the modern and the most efficient process used in tablet manufacturing which has been successfully used for various drugs. But the process strongly depends upon the quality of the crystals used. Spherical agglomeration, a novel crystallization technique that can transform directly the fine crystals produced in the crystallization or in the reaction process in to a spherical shape agglomerates, was developed by Yoshiaki Kawashima and coworkers in 1986. There are currently four methods to accomplish the conversion of drug particles into spherical agglomerates. Spherical agglomeration technique can transform directly the fine crystals, produced in the crystallization process into a spherical shape. Spherical agglomeration is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step. Spherical crystallization is a versatile process that enables to control the type and size of the crystals. Agglomerates exhibit improved secondary characteristics like flowability and compressibility. Drug release from these spherical crystals can be improved or can be controlled. This technique will be an invaluable technology in future, if it is scaled-up to manufacturing level. In this review we will discuss about the advantages, method and parameters which can be improved by spherical crystallization process. In addition current and future prospects of spherical crystallization are also discussed.

Introduction

Formulation and manufacture of solid oral dosage forms, and tablets in a particular, have under gone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. It is economical, facilitates the processing without the need of moisture, heat and involves small number of processing steps. In the direct tabletting method, it is necessary to increase the flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing the efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder [1].

Depending on the process, which the particles will undergo, particle sizes may be suitable or they may be too big or too small. If the particles are too big, their surface can be reduced by crushing or by micronization. If they are too small, they can be adjusted using particle enlargement technique. This is particularly true for compression [1].

There are many different ways of obtaining grains ranging from 100-1500 □m. The method selected will depend on the ultimate manufacturing process retained, i.e. dry compaction, wet granulation, extrusion-spheronization, atomization, prilling etc [2].

Spherical crystallization has been developed by Yoshiaki Kawashima and co-workers as a novel particulate design technique to improve both the processability such as mixing, filling, and tabletting characteristics, and the bioavailability of pharmaceuticals. Size enlargement processes to upgrade fine particulates are assuming ever-increasing importance today, because, it is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously in one step. The resultant crystals can be designated as spherical agglomerates. Due to the improved characteristics of crystals, the micromeritic properties such as flowability, packability and compressibility of the resultant crystals are dramatically improved, so that direct tabletting or coating is possible without further processing (mixing, agglomeration, sieving, etc.).One of the prominent features of the spherical agglomeration process is versatility in controlling the type and size of the crystals [2, 3].

The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression. [3, 4] 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 compactability of crystalline drugs. Spherical crystallization technique was used in 1986 by Kawashima Y, et al for size enlargement of the drug. According to Kawashima “An agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process is spherical crystallization”. [5]

Spherical crystallization makes the pharmaceutical ingredients suitable for direct compression by altering the physical properties [6, 7]. This technique involves the designing of particles by which crystallization and agglomeration are carried out for the improvement of powder and tableting

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parameters of various pharmaceuticals and biopharmaceuticals by changing the crystal habit (form, surface, size and particle size distribution). This technique involves the rearrangement of crystal lattice in controlled manner to get desired parameters of pharmaceutical ingredients. Moreover this modification of crystal habit also results in the modification of certain physicochemical properties as solubility, bioavailability and stability of pharmaceutical ingredients. Hence, this method may also be used to increase the solubility of poor water soluble drug [6].

The objective of this article is to present a review on spherical crystallization techniques applied to pharmaceuticals, different methods and its applications. Spherical agglomeration process was developed in the early 60's at the National research council of Canada as a general process for selective separation of one kind of particulate from a liquid suspension containing several different solids. One of the prominent features of the spherical agglomeration process is its versatility in controlling the type and size of the product [6, 2].

Need of spherical agglomeration

Powder can rarely be compressed directly in to the tablets and generally requires pretreatment to ensure tablet formation. The pretreatment involves modification and design of pharmaceutical powder drugs so as to improve the properties, such as flowability and packability of the product.

Most of the drugs exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties. Various methods are applied to increase the flow properties of drugs, e.g., coating, granulation etc. It is more desirable to crystallize the pure drug directly into spherical particles that exhibit good properties by spherical agglomeration technique [2.7, 8].

Theory of spherical crystallization

The principle of agglomeration was initially applied to coal and minerals. Owing to the naturally hydrophobic properties of coals, the agglomerate with ease and separate from the ash constituents by applying virtually any mode of agitation in the presence of sufficient hydrocarbons as bridging liquids. But the process cannot achieve commercialization due to high cost of the bridging oils. Since 1980 spherical crystallization has been studied as a size enlargement operation in the field of pharmacy [2.9].

Finely divided solids in liquid suspension can be agglomerated and separated from the suspending liquid by the addition of a small amount of bridging liquid, which preferentially wets the surface of the solid. Thus surface properties of the crystals and nature of the bridging liquid play an important role in the agglomeration process. Smith and Puddington studied the mechanical agglomeration of Barium sulphate in benzene and inferred that hydrophilic surface, is preferentially wetted and agglomerated by using bridging liquid of polar nature like water [3, 7, 8, 9].

Principal steps involved in the process of spherical crystallization

Preferential wetting of lipophilic/hydrophobic particles by bridging liquid forms the fundamental basis for the separation of particulate material from aqueous suspension by agglomeration. In the presence of adequate amount of bridging liquid and sufficient mechanical agitation the particle coated with bridging liquid collide with each other and form into agglomerates due to the interfacial tension of the bridging liquid and capillary attraction of liquid bridges between the particles. The behavior of suspension of fine particles that are formed during crystallization process, to which small amount of bridging liquid is added is controlled by three main factors, in order of importance [8-10];

- Free energy relationships at the liquid-liquid-solid interface
- The amount of second liquid (Bridging liquid) used in relation to the amount of solids and
- The type and intensity of mixing employed.

Agglomeration mechanism of particle by emulsion solvent diffusion technique involves three steps.

Droplet formation: Size of the droplet depends mainly on the flow conditions, on string and on the surface tension between the droplet and the solution.

Super saturation: When a hot droplet comes in contact with the cold solution (water) super saturation occurs which is more marked on the surface than at the center. The solid therefore tends to appear on the surface of the droplet.

Crystallization: Small crystalline agglomerates (<300□m) were produced when the small droplets subjected to cooling at (T1 – T2) > 350 C.

Agglomerates were hollow grains with single outside layer. Larger sized droplets (about 450□m) which undergo less rapid cooling (T1 – T2 □ 250 C) also start nucleating where the heat transfer takes place, since circulation is quite marked, it inhibits radial diffusion and favors tangential movement, so that crystals grow at right angle to the radius until circulation is stopped. Agglomerates were hollow grains with two outside layers. Large sized droplets (> 450□m) originate from competition between the internal circulation and miscible solvent transfers from the droplets. Under these conditions, when the nuclei appear, they were well dispersed, very fine and cluster together forming a network of micropores. The grains were homogenous.

Kinetics

Capes and Kawashima3 described the spherical crystallization kinetics in terms of the rate of decrease in the residual concentration of drug in crystallization solvent. It was found that the rate of decrease in residual concentration was a function of agitation speed of the system and of the concentration difference between the initial and the equilibrium state.

They concluded that spherical agglomeration is a first order process whereas Vanangamudi and Tadimeti Rao proposed it to be second order kinetics with two constants describing the growth kinetics [2, 10, Factors controlling the Process of agglomeration

Solubility profile

The selection of solvent is dictated by the solubility characteristic of the drug. Solvent system for spherical crystallization consisting of a poor solvent (suspending liquid), good solvent and bridging liquid for a drug. The Physical form of the product i.e. whether micro-agglomerates or irregular macro-agglomerates or a part of the drug substance can be controlled by the selection of proper solvent proportions. The proportion of the solvents to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility [13].

a. Ternary diagrams

The drug substance in solvent, bridging liquid and medium yields a phase diagram with distinct zones or regions. In the example shown in Figure1, the monophasic drug substance/acetone/ water liquid region is in equilibrium with different phases as a function of the mass ratio of acetone in the water/acetone mixture [9-14].

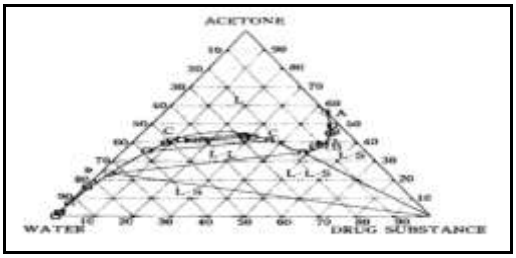


Figure 1: Ternary diagram

In region A drug is highly soluble in acetone; in region B drug substance is even more soluble. Solubility of drug substance decreases markedly in the region C. Regions between A and C, the monophasic region is in equilibrium with biphasic liquid/solid region (crystallization of drug substance). A liquid with a high drug concentration which is non miscible in a liquid with a low drug concentration appears and forms an emulsion. In the region D, the aqueous medium limits the solubility of the drug substance so the liquid/liquid region disappears, yielding equilibrium between regions D and E (crystallization of drug substance). In the region above the phase separation curve the system is completely miscible, but in the region just below the separation curve will provide small quantity of bridging liquid.

b. Scheffe ternary diagrams

According to this model, compositions of solvents can be determined by identifying points on the ternary diagram. If the parallels to the three sides of the triangle are drawn through the middles of the sides, four new triangles are traced, on which seven points are determined in a same way as for the first triangle. As some points are Common to both triangles, 19 points can be identified (Figure –2)

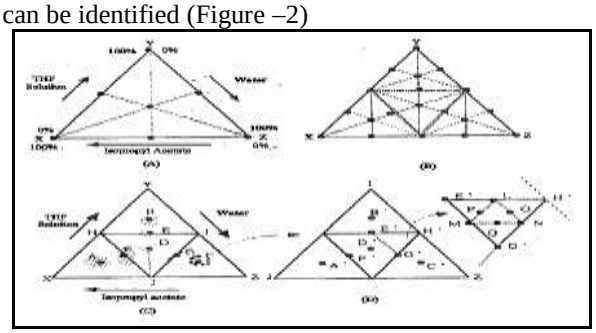


Figure 2: Scheffe ternary diagram

The points on the vertex correspond to a pure liquid; those on the sides correspond to a mixture of only two liquids. Since the presence of three liquids is necessary, these points must be excluded. Seven points remain for the experiments; A, B, C, D, E, F and G. A thorough study on the triangle and the points that enables to find the best proportions for spherical crystallization may be investigated [14].

Mode and intensity of agitation

High-speed agitation is necessary to disperse the bridging liquid throughout the system. The product of a high-speed shaker blender is usually in the form of irregular agglomerates. When tank is used as the reaction vessel, more irregular, but less spherical agglomerates could be prepared. An inclined pan and drum agglomerates facilitates the size enlargement process. Any change in agitation pattern or fluid flow would be reflected as a change in force acting on agglomerate, which ultimately affects the shape of agglomerate [14, 15, 16].

Mechanical agitation is the prime variable affecting the process and is necessary to bring the particles into proximity so that the force responsible for agglomeration may become operative. The extent of mechanical agitation in conjunction with the amount of bridging liquid determines the rate of formation agglomerates and their final size. High shear quickly forms agglomerates and reworks them by re-dispersion and reformation allowing cleaner particle to form, however, high shear limits the size of the agglomerates to small diameter [17].

Temperature of the system

Espitalier et al., have studied the spherical crystallization, modeling of the emulsion solvent diffusion technique. Study revealed that the temperature difference between the drug solution and crystallizing medium has a significant influence on the shape, size and texture of the spherical agglomerates. Large difference in the temperatures of crystallizing liquid and non-solvent (>350 C) produce small spherical crystals with thick outer crust and no preferential orientation of crystals. The core is hollow. These grains remain soft for long time, indicating that a high residence time in the crystallizer is required before filtration. If the temperature difference small (10-350 C) grains remains spherical, may have hallow core, but are made up of two layers. The outer crust is less dense and surface is covered with crystals. The internal layer is very porous and the crystals are oriented towards center. If the temperature difference is less than 100 C the outer crust is more porous [6].

The effect of temperature on spherical agglomeration is probably due to the effect of temperature on the solubility of the drug substance in ternary system. The average size of agglomerates was the smallest at the crystallization temperature 100 C, at temperature higher or lower than 100 C, the size and variation increased. At higher temperature, the larger agglomerates were produced initially and the equilibrium state attained more rapidly than at lower temperature. At low temperature, it was characteristic that the growth rate of crystal was slow at the initial stage but became faster at a later stage. At low temperature, the initial numbers of crystals produced were greater than at high temperature, the number of nuclei increased with decreased crystallization temperature [14].

Residence time

The time for which agglomerates remain suspended in reaction mixture affects their strength [2, 14].

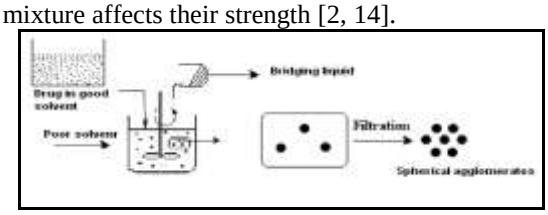


Figure 3: Simple spherical crystallization

Methods of Spherical crystallization

Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is purposely induced through the addition of a third solvent, termed the "bridging liquid." Crystal agglomeration, which is usually avoided during normal processing, is performed in a controlled fashion during spherical crystallization to bring about improved flow and compaction properties to the material. These properties are highly advantageous for pharmaceutical production[2, 14].

1. Spherical agglomeration method (SA)
2. Quasi-Emulsion solvant diffusion method (QESD)
3. Ammonia diffusion method
4. Neutralization method

Simple Spherical Crystallization Method

This process involves formation of fine crystals and their agglomeration. Crystallization is generally achieved by change of solvent or salting out. The solution of the material in a "good solvent" is poured in a "poor solvent" under controlled

conditions, so as to favors formation of fine crystals. Agitating the crystals in a liquid suspension and adding a "bridging liquid" which preferentially wets the crystal surface to cause binding forms the agglomerates Figure 3. The agglomerate may be spherical, if the amount of this bridging liquid and the rate of agitation are controlled.

Kawashima et al.carried out crystallization of salicylic acid by change of solvent, ethanol as good solvent and water as a poor solvent. The crystals were agglomerated using chloroform as a bridging liquid [7].

In solvent change method when bridging liquid was poured into DMF- water mixture, small amount of chloroform was liberated from the system. This precipitated microcrystal may initially form loose agglomerates held together by discrete bridges of chloroform.

These loose agglomerates in funicular state could coalesce with small particles and individual crystals. However, they would not be able to coalesce with other large agglomerates because they have no excess bridging liquid on the surface. On further agitation, the filling ratio of chloroform in agglomerates would increase under the sheer force, and finally agglomerates reach capillary state. These agglomerates could coalesce into larger agglomerates with a slight increase in the apparent density Figure 4.

Sodium theophylline was crystallized by salting out from the solution of theophylline in aqueous ethylenediamine solution by addition of equal volume of (15% w/v) sodium chloride solution. The agglomerate crystals were produced by addition of adequate amount of ethanol and chloroform.

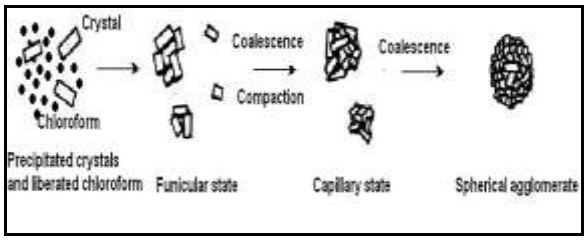


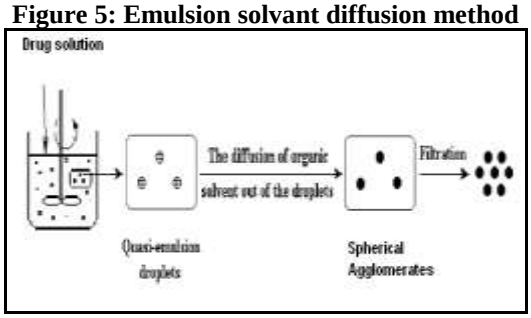
Figure 4: Mechanism of spherical agglomeration

Quasi - Emulsion Solvent Diffusion Method

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 the drug was poured into poor solvent (dispersing medium) under agitation, quasi emulsion droplets of bridging liquid or good solvent from the emulsion droplet into the dispersing medium induce the crystallization of the drug, followed by agglomeration Figure 5.

Antirheumatic drug Bucillamine was crystallized as spheres by emulsion solvent diffusion method using hydroxy propyl methyl- cellulose. Uniformly coated directly compressible crystal agglomerates were obtained.

Figure 5: Emulsion solvant diffusion method



Ammonia Diffusion System, Method

Kawashima et al.,developed a novel method for spherical crystallization of amphoteric drug substances. They carried out spherical crystallization of Enoxacin, an antibacterial, which is slightly soluble in water but soluble in acidic and alkaline solution [15].

A mixture of three partially immiscible solvents, Acetone - ammonia water - dichloromethane was used as a crystallization system. In this system, ammonia water was used as a bridging liquid, a good solvent for Enoxacin. Acetone is a water miscible but a poor solvent for drug, thus Enoxacin gets precipitated by solvent change without forming ammonium salt. Water immiscible solvents such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induce liberation of the ammonia water Figure 6.

Acetone in the solvent enters into droplets of ammonia water, which is liberated, from acetone-ammonia water-dichloromethane system, and consequently enoxacin dissolved in water is precipitated while the droplets collect the crystals. At the same time ammonia in the agglomerates diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker and the agglomerates are obtained. This technique is termed as 'A D S' and is useful in agglomeration of drugs, which are soluble only in an acidic or an alkaline medium.

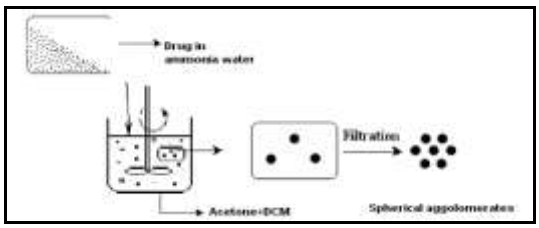


Figure 6: Ammonia diffusion method

Neutralization method

This process involves the formation of fine crystals and their agglomeration; the crystallization is generally achieved by neutralization method Figure 7.

The drug was dissolved in a sodium hydroxide solution and chloroform aqueous solution and hydrochloric acid was added to neutralize the sodium hydroxide solution of tolbutamide and crystallize out. The bridging liquid was added drop wise followed by agglomeration of the tolbutamide crystals [8, 10, 14].

Parameters of pharmaceutical ingredients improved by spherical crystallization technique

The condition under which crystallization is carried out determines the texture of the spherical crystals; it is this texture which then defines the functional properties of the powder bed. In order to control the reproducibility of the process, a certain number of physical properties are evaluated. Since the material methods are standard [18-24].

Particle Size and Size Distribution:

Particle size and shape of pharmaceutical ingredients can be changed with this method. Generally a large size and spherical shape particle are formed.

Size of particles are improved due to the aggregation if particles influenced by the bridging agent. Similarly, agitation of solvent system during process results in the spherical shape of particles.

Characterization of spherical agglomerates

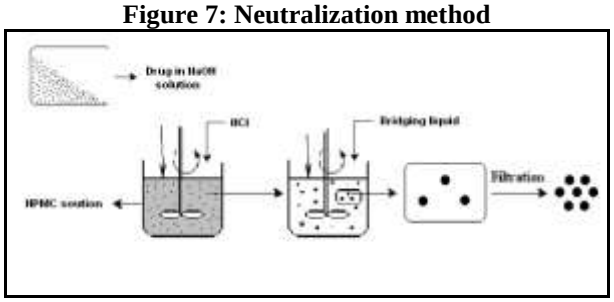
a) Optical Microscopy: The shape of the spherical crystals is studied by observing these under a optical microscope. The

observations are made under the observation like 10X, 45X, 60X etc.

b) Electron Scanning Microscopy: The surface topography, type of crystals (polymorphism and crystal habit) of the spherical crystals is analyzed by using scanning electron microscopy.

c) X-ray Powder Diffraction: This is an important technique for establishing batchto-batch reproducibility of a crystalline form. The form of crystal in agglomerates determine by using technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a compound.

Figure 7: Neutralization method



Mechanical Strength:

Spherical crystals should posses' good mechanical strength as that directly reflects the mechanical strength of compact or tablet. This may be due to increased intrapartical force within spherical agglomerated crystals. It is determine by using the following two methods,

a) Tensile strength: Tensile strength of spherical crystals is measured by applying maximum load required to crush the spherical crystal. This method is a direct method to measure the tensile strength of spherical crystals

b) Crushing Strength: It is measured by using 50ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel is then used as hallow support and the guide tube with close fitting tolerances to the Plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). Mercury is introduced from reservoir into the upper chamber at the rate of 10 gm/sec until the single granule crushed; loading time should be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is the crushing load.

Flow Property:

Flow property of the material depends on the force developed between the particle, particle size, particle size distribution, particle shape, surface texture or roughness and surface area. The improvement in the flowability of spherical crystals could be attributed to the significant reduction in inter-particle friction, due to their spherical shape and a lower static electric charge Following are the methods used to determine of flow property.

a) Angle of Repose: This is the common method used for determination of flow property. The angle of repose is the angle between the horizontal and the slop of the heap or cone of solid dropped from some elevation. Values for angle of repose ≤ 30 usually indicate free flowing material and angle ≥ 40 suggested a poor flowing material. The angle of repose can be obtained from equation:

$$\tan \theta = h/0.5d$$

Where h- height of the cone and d- diameter of the cone

b) Compressibility or Carr's Index: A simple indication of ease with which a material can be induced to flow is given by application of compressibility index:

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

Where v = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping. The value below 15% indicates good flow characteristics and value above 25% indicate poor flowability

Hausner Ratio: It is calculated from bulk density and tap density.

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density}$$

Values less than 1.25 indicate good flow (20% Carr Index) and the value greater than 1.25 indicates poor flow (33% Carr Index).

d) Density: This method involve the size enlargement therefore volume of powder get increase and density get decrease. Density of the spherical crystals is the mass per unit volume.

$$\text{Density} = M/V$$

Where, M and V are mass and volume of powder respectively.

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. The packability of agglomerates improved compared with those of the original crystals and that the agglomerated crystals are adaptable to direct tabletting. The packability assessed by analysis of the tapping process with the Kawakita(I) and Kuno(II) method and using the parameters a, b,1/b, k in the equation.

$$N/C = 1/(ab) + N/a \quad \text{.....I}$$

$$C = (Vo-Vn)/Vo,$$

$$a = (Vo-V\infty)/Vo.$$

$$\rho f - \rho n = (\rho f - \rho o) \cdot \exp(-kn) \quad \text{.....II}$$

Where, N =Number of tapping, C =Difference in volume (degree of volume reduction.) and a, b are constant.

Compression Behaviors Analysis:

Good compactibility and compressibility are 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. 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. Compaction behavior of agglomerated crystals was evaluated by using following parameters.

Friability Test:

The friability of the spherical crystals is the combination of the attrition and sieving process in to a single operation. Granules along with the plastic balls placed on a test screen. The sieve is then subjected to the usual motion of a test sieve shaker provided the necessary attrition on the granules. The weight of powder passing through the sieve is recorded as function of time. The friability index is determined from the slop of the plot of % weight of granules remaining on the sieve as a function of time of shaking. Friability of agglomerates determined by using formula

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

Where, Wo = Initial weight of the crystalline agglomerates placed in sieve

W = Weight of the material which does not passed through sieve after 5 min.

Moisture Uptake Study:

The study indicates the behavior of uptake of moisture by drug and the prepared spherical crystals, which affect the stability. The weighted quantity of drug and spherical crystals placed in crucible at accelerated condition of temperature and humidity, 40 C ± 10C and 75% ± 3%respectively. The gain in weight of drug and spherical crystals is measured.

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.

Advantages of spherical crystallization

The spherical crystallization technique can enable subsequent processes such as [22, 25,26] :

- Spherical crystallization technique has been successfully utilized for improving of 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.
- For masking of the bitter taste of drug.
- Preparation of microsponge, microspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system.

Applications

The spherical crystallization technique can enable subsequent processes such as

1. To improve the flowability and compressibility:

Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. 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. 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 tabletting 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 [27]. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired [29]. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression [30, 31]. Due to different crystal habit many drugs show inconvenient flowability and compressibility. So these problems can be solved by converting them into a agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility. Various drugs of which flow and compressibility are improved were listed in table 1.

2. For masking bitter taste of drug:

Microcapsules are prepared to mask the bitter taste of the drug. They are suitable for coating granules, since spherical material can be uniformly coated with a relatively small amount of polymer. Microcapsules of following drugs were prepared for masking of bitter taste [32]. Various drugs of which taste masking has done were listed in table 1.

3. For increasing solubility and dissolution rate of poorly soluble drug:

Spherical crystallization has been described as a very effective technique in improving the dissolution behavior of some drugs having low water solubility and a slow dissolution profile [33-37]. Various drugs of solubility and bioavailability is improved were listed in table 1.

4. Prolonged release systems

The spherical crystallization technique can be modified to a simple and less expensive process to prepare spherical matrices of prolonged release drugs as an alternative to spray-congealing method. The advantage of this technique includes the avoidance of harmful organic solvents and additives such as isobutylene used in the process of micro-encapsulation phase separation.

This process does not require elevation of temperature of the system as in phase separation method and finally resultant matrix spheres obtained are directly compressible [42-46].

Microencapsulation studied spherical crystallization of ibuprofen involving, spheronization and drug loading with acrylic polymer [42] were prepared. Ibuprofen was formulated as small spherical cores for subsequent coating in an attempt to develop a competitor microencapsulated product to the commercially available sustained-release tablet. Optimum spherical crystallization conditions yielded cores of loosely adhering crystals of active, with highly irregular surface morphology and poor mechanical strength during pan coating. Aqueous spheronization yielded satisfactory cores in high yield when microcrystalline cellulose and liquid paraffin were used. However, application of large amounts of controlled-release coatings based on Eudragit RL and RS failed to produce a product with retarded drug dissolution comparable to the commercial product. Drug loaded non-pareils were easily formed [46], but required application of about 20 per cent Eudragit RL/RS coating to achieve adequate prolonged-release properties. Application of 10 per cent hydrogenated castor oil/ethylcellulose based coating gave acceptable in-vitro release only if the microcapsules formed were tableted and annealed. All products investigated rapidly discoloured during storage and none were considered to represent a realistic alternative to tableting technology for the production of a sustained-release oral dosage form. Preparation of microcapsules to mask the bitter taste of the drug they are suitable for coating granules, since spherical materials can be uniformly coated with a relatively small amount of polymer.

Current and future prospects of spherical crystallization method. Several pharmaceutical ingredients have been converted into spherical crystals for the improvements of several

parameters. Yadav VA, et al. prepared Spherical Crystal of Carbamazepine by using Qussi emulsion solvent diffusion method taking Ethanol (Good Solvent), Chloroform (Bridging Agent) & Water (Poor Solvent) as solvent system and concluded that spherical crystals of CBZ with different hydrophilic and hydrophobic polymers showed an improvement in direct tabletting behaviour as well as bioavailability of the dosage form. [47, 48] Other investigations related to this technique by using different methods are given in table -1.

This technique can be applied to; design novel drug delivery devices like micro-baloons – hallow micro-spheres loaded with drug in their outer polymer cells and micro-sponges.

Although several investigation have been done in spherical crystallization method, but still a Method is required to be investigated to remove some limitations related to existing spherical crystallization method. Percentage yield of recovery is the main concern, as it is very low in other method. Large amount of pharmaceutical ingredients are not recovered during the process.

Another problem is the selection of solvent system, which is quite problematic to design the system. Again controlling of several factors as agitation speed, amount of bridging liquid and temperature, make these method quite difficult to produced spherical crystals. Hence, there is a promising need to develop a new method for the minimization of above problems associated with existing methods so that spherical crystallization methods can be used in regular manner for the development of direct tabletting technique.

Conclusions

There are about four methods to achieve spherical agglomeration of drugs. Spherical agglomerates exhibit improved secondary characteristics like flowability and compressibility.

This crystal modification technique can be used to enhance the dissolution and hence the bioavailability of the drugs or to control the drug release from the granules. If the process can be scaled-up to manufacturing level, this technique has the potential to develop into an invaluable technology in future.

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Table 1: List of drugs on various spherical agglomeration techniques have been tried for improving physicochemical properties

Drug	Method	Property improved	Reference
Salicylic acid	SA	Flowability and Compressibility	[7]
Ibuprofen	NM	Flowability and Compressibility	[8]
Indomethacin	SA	Solubility and Bioavailability	[9]
Mefenamic acid	NM	Flowability and Compressibility	[10]
Ibuprofen	SA	Solubility and Bioavailability	[11]
Mefenamic acid	SA	Solubility and Bioavailability	[12]
Ketoprofen	SA	Solubility and Bioavailability	[13]
Ketoprofen	NM	Flowability and Compressibility	[14]
Enoxacin	ADM	Taste masking	[15]
Aspirin	SA	Flowability and Compressibility	[18]
Fenbufen	SA	Solubility and Bioavailability	[30]
Celecoxib	SA	Flowability and Compressibility	[31]
Aminophylline	SA	Flowability and Compressibility	[32]
Ibuprofen	SA	Flowability and Compressibility	[42]
Acebutalol HCl	ESD	Flowability and Compressibility	[43]
Carbamazepine	SA	Flowability and Compressibility	[47]

SA: Spherical agglomeration, ESD: Emulsion solvent diffusion, ADM: Ammonia diffusion method, NM: Neutralization method.