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Review Article

SPHERICAL AGGLOMERATION – DIRECT TABLETTING TECHNIQUE

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ABSTRACT

Direct tabletting technique is the modern and the most efficient process used in tablet manufacturing and has been successfully employed for various poorly soluble and poorly compressible drugs. Spherical agglomeration is particle engineering technique which involves the transformation of fine crystals into spherical shape particles which enhances the powder properties such as particle size, shape, flow properties, solubility and bioavailability of pharmaceutical drug substances. This technique can also be applied to sustain the drug release from solid dosage forms. The present article is on the detailed comprehensive review about advantages and disadvantages, mechanism, different manufacturing methods of spherical agglomerates and characterization of spherical agglomerates.

Key Words: Direct tabletting technique, Spherical crystallization, flowability, bioavailability, flocculation zone, poorly compressible.

INTRODUCTION

Tablet is known to be the most popular dosage form of all pharmaceutical preparations for oral route of administration because of easy administration by patient, least content variability and great precision. Apart from these advantages, formulation and manufacturing of tablets is most convenient and easy process. One of important factor which influences the success of tablet is flowability and compressibility of materials. Direct compressibility is one of the best, simple, economical techniques for manufacturing of tablets. This facilitates processing without the need of moisture, heat and involves small number of processing steps. But, the technique depends on, the flowability, particle size, the particle size distribution, bulk density and the compressibility of the crystalline drug substances. Most of the drugs like NSAIDs exhibiting poor compressibility and flowability and were not suitable for direct compression. For enhancing the flow properties and compressibility of such drug substances several methods have been introduced by the researchers. Recently pharmaceutical companies have adopted modified crystalline techniques for reducing the production cost as well as enhancing the production process. Spherical agglomeration is one among those techniques.

Formulation of tablets by spherical crystallisation method was developed by Kawashima in 1986 which enlightened the size enlargement of the drug in the field of pharmacy[1]. The traditional drug manufacturing procedure (granulation) is a slow and time consuming process. Contrary to this, spherical crystallization involves lower labor costs, less processing time, lower energy consumption, less equipment, space and appears to be more advantageous technique in the direct tabletting process[2]. This technique has been applied to improve the wettability, bioavailability, and dissolution rate of some poorly soluble drugs like celecoxib and fenbufen[3, 4]. There are various parameters to be optimized in this technique to produce spherical crystals such as amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. Besides being producing spherical crystals it also enables co-precipitation of drugs and encapsulating polymers in the form of spherical particles of poorly compressible drug like celecoxib (Gupta et al., 2007). Spherical crystallization has been applied to several drugs which are high dosed, poorly compressible and poorly soluble drugs. The advantages of this technique are as follows.

Advantages of the spherical crystallization process

- The micromeritic properties of the drug crystals shall be drastically improved by inducing spherical shape to the crystals.[5]
- Utilization of this process improves wettability and dissolution rate of some drugs.[5]
- The processes such as separation, filtration, drying etc to be carried out more efficiently by application of this technique.[6]
- The resultant agglomerated crystals could be easily compounded with other pharmaceutical powders due to their spherical shapes.[7]
- This technique could be used for masking of the bitter taste of drugs. (ATH & enoxacin)[8,9]
- This technique could be used in the preparation of microsponges, microspheres, nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery systems.[10]

Disadvantages

- Selection of the suitable solvents is tedious process.
- Maintenance of processing parameters (temperature, agitation, etc) is difficult.

METHODS OF SPHERICAL CRYSTALLIZATION

Various methods are available for preparation of spherical crystals which are as follows.

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

Traditional crystallization process

Spherical agglomerates shall be produced in these methods by controlling the physical and chemical properties and can be called as the non typical spherical crystallization processes[11]. These are

- Salting out precipitation
- Cooling crystallization
- Crystallization under melting.

Solvent change method (SC)

Solvent change method[12] involves simultaneous crystallization and agglomeration of two or more drugs from a good solvent and bridging liquid by addition of a non-solvent. To obtain fine crystals the solution of the drug and a good solvent is poured into a poor solvent under controlled condition of temperature and speed. The bridging liquid is used for agglomeration of the crystals. The poor solvent has miscibility with good solvent but has low solubility with solvent mixture, so that, during agitation of the solvent system the crystals are formed. The drawback of this system is that it provides low yield, due to co-solvency effect of crystallization solvent. The bridging liquid, the stirring speed and the concentration of solids are the influencing factors for the spherical crystallization.

Lesser amount of bridging liquid will yield fine particles where as larger amount of bridging liquid will produce coarse particles[13]. By increasing stirring rate the agglomeration get reduced because of increasing disruptive forces[14]. Higher stirring rate produces agglomerates that are less porous and more resistant to mechanical stress. The porosity decreases when the concentration of solid increases[15]. 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 also on the strength of the agglomerates.

Steps involved in solvent change method

Good solvent +drug
↓ In bad solvent
Formation of crystals
With addition of bridging liquid (Drop wise)
&continuous agitation
↓
Precipitated crystals and aggregation with bridging liquid
↓ Random coalescence
Spherical agglomerates
↓
Enlarged spherical agglomerates

Quasi emulsion solvent diffusion method (QESD)

In the case of quasi emulsion solvent diffusion method[16], affinity between the drug and a good solvent is stronger than that of the drug and poor solvent. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. Due to the interfacial tension between the two solvents, the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent.

In this process, the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization. In the droplets, the process of solidification proceeds inwards and the liquid is not maintained on the surface and the agglomerate formed without coalescence.

Steps involved in QESD method

Drug +good solvent
↓ Into poor solvent
Formation of emulsion
↓ (With agitation)
Good solvent which acts as a bridging liquid diffuses out into poor solvent phase
↓
Formation of spherical agglomerates
↓ Polymeric solution
Stabilized Spherical crystals

Ammonia diffusion method (AD)

In this method, the mixture of acetone, ammonia water and dichloromethane shall be used as a crystallization system. In this system ammonia water acts as bridging liquid as well as good solvent. The other components of the system, like poor solvent and a hydrocarbon derivative are selected depending upon the drug's solubility in that solvent. Acetone (hydrocarbon derivative) is miscible with the system but it reduces the miscibility of ammonia water with poor solvent. The ammonia water exists as immiscible phase forming droplets. The counter diffusion process across the droplet involves movement of poor solvent into and ammonia out of the droplet. Inside the droplet agglomeration takes place as the drug precipitates slowly in ammonia water and causes growth of crystal[17]. The technique is mainly applicable for amphoteric drugs, which have the same properties as enoxacin.

Drug +ammonia water
↓ Added
Acetone
↓ Dichloromethane added drop wise
Spherical agglomerates

Neutralization method

The method consists of dissolving the drug in the good solvent and placing in the cylindrical vessel with constant stirring. During stirring an aqueous polymer solution and one neutral solution was added to neutralize the good solvent, which crystallizes out the drug. The bridging liquid shall be added drop wise at a definite rate. The agglomeration of the crystal form of the drug takes place[18].

Steps involved in neutralization method

Drug + good solvent
↓ Added in
Neutralizing solution
↓ Crystallization
Add bridging liquid
↓ Drop wise
Spherical agglomerates

Crystal-co-agglomeration technique (CCA)

Applications of spherical crystallization to obtain directly compressible agglomerates without diluents are restricted to water insoluble large-dose drugs only. Most of the excipients, such as diluents and disintegrating agents, are hydrophilic in nature. Hence incorporation of these excipients in the agglomerates formed by using organic bridging liquid is difficult. Due to this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials[19]. To overcome these limitations of spherical crystallization Kadam et al. developed the crystallo-co-agglomeration (CCA) technique. It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing two drugs (Mahadik et al., 2004) or a low-dose[20] or poorly compressible drug in combination with diluents[21, 22]. The difference in the physicochemical properties of the drug molecules and the excipient become the major challenge in the selection of a solvent system for the crystal-co-agglomeration technique.

Steps involved in crystal-co-agglomeration technique

Drug+ good solvent
↓ Agitation
Bridging liquid (homogenous solution)
↓ Added continuous stirring
Bad solvent /polymeric solution
↓ Crystal's formation
Spherical agglomerates

CHARACTERIZATION OF SPHERICAL AGGLOMERATES

Particle Size and Size Distribution

Particle size and distributions can be determined by sieve analysis. With the help of Ro-Tap sieve shaker, particle size analysis can be determined. In advance technology image-analyzer is used to determined size and volume of the particle.

Density

Density[23] of the spherical crystals is the mass per unit volume.

Density = Mass/Volume

Densities such as true density, granular density, apparent bulk density, tapped density shall be evaluated.

Porosity

Porosity of granules affects the compressibility. Porosities are of two types "intragranular and intergranular" and these are measured with the help of true and granular densities.

Intra granular porosity = 1- Granular density /True density.

Inter granular porosity = 1- Bulk density / Granular density

Flowability- The flow properties of spherical agglomerates were characterized by following methods.

a) Angle of repose

Flow property of the material depends on the particle size, shape, distribution, surface texture or roughness, surface area and applied force. The angle of repose can be determined by using the following equation.

$$\text{Tan } \theta = h/0.5d$$

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

Values for angle of repose ≤ 30 usually indicate free flowing material and angle ≥ 40 suggested a poor flowing material.

b) Compressibility or Carr index

The ease with which a material can be induced to flow is given by application of compressibility index.

$$I = (1\text{-}V/Vo)*100$$

Where V = the volume occupied by a sample of the powder after being subjected to a standardized tapping procedure and V_O = the volume before tapping.

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

c) Hausner ratio

It is calculated from bulk and tapped densities.

Hausner ratio = Tapped density / 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.). If it is between 1.25-1.5 add the glident to improve flow.

Packability

Sample packability was assessed by analysis of the tapping process with the Kawakita and Kuno methods, and using the parameters a, b, and k in the equations.

$$n/C = 1/(ab) + n/a$$

$$C = (Vo\text{-}Vn)/Vo,\ a = (Vo\text{-}V\infty)/Vo.$$

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

Where, a is the degree of volume reduction when the tap number is infinity, b and k are constants for the apparent packing rate, V_0 and Vn are the volume in the initial loosely packed and the n^{th} tapped state, and ρo, ρn, and ρf are the apparent density in the initial state, the n^{th} tapped state, and the most densely packed state.

The angle of friction, shear cohesive stress and shear indexes of spherical agglomerates should be less than the pure drug which can improve the packability of the agglomerates.

Compression Behavior Analysis

For direct compression the particles must possess good compatibility and compressibility. The compaction behavior of the spherical agglomerates and the pure drug can be studied by using the plots constructed between the relative volume and compression pressure.

The inter particle plastic bonds and compression force are inversely proportional to each other. The inter particle plastic bonds are more in spherical agglomerates rather than the pure drug. During compression the particles get broken down which results in the formation of new surfaces which improves the inter particle plastic bonds. This is more in agglomerates than the pure drug crystals which results in requirement of lower compression force in agglomerates when compared to that of pure drug crystals.

Compaction behavior of agglomerated crystals were evaluated by using following parameters-

a) Heckel Analysis

The following Heckel's[24,25] equation used to analyze the compression process of agglomerated crystals and assessed their compactibility.

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

Where: D is the relative density of the tablets under compression Pressure K is the slope of the straight portion of the Heckel Plot, the reciprocal of K is the mean yield, the mean yield pressure (Py). The following equation gives the intercept obtained by extrapolating the straight portion of the plots

$$\mathbf{A = 1n\ [1/(1\text{-}D0)] + B}$$

Where: D0 is the relative density of the powder bed when P=0.

The following equation gives the relative densities corresponding to A and B.

$$\mathbf{DA = 1\text{-}e\text{-}A}$$

$$\mathbf{DB = DA\text{-}D0}$$

b)Stress Relaxation Test

In this test, specific quantity of spherical crystals sample has to be placed in a die of specific diameter whose surface was coated with magnesium stearate in advance and the sample is to be compressed using universal tensile compression tester at a constant speed. After attaining the desired pressure limit, the upper punch should be held in the same position for 20 min, during which measure time for the reduction amount of the stress applied on the upper punch. The result was corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions. The following equation finds the relationship between relaxation ratio Y(t) and time t, calculated the parameters As and Bs, and assessed relaxation behavior.[19,20]

$$t/Y(t) = 1/AsBs\text{-}t/As$$

$$Y(t) = (P0\text{-}Pt)/P0$$

Where: P0 is the maximum compression pressure, and Pt is the pressure at time t.

Mechanical Properties

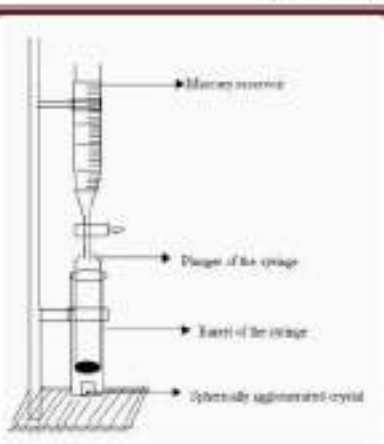
Mechanical Properties[26-31] like tensile strength of spherical agglomerates shall be determined by compressing 500 mg of spherical crystals using hydraulic press at different ton/cm^2 for 1 min. The compact should be stored in desiccator for overnight to allow elastic recovery. The thickness and diameter should be measured for each compact. The hardness of each compact shall be measured using Pfizer hardness tester. The tensile strength (σ) of the compact (ton/cm^2) shall be calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm) respectively.

Crushing Strength

Crushing strength[32] is determined by using hypodermic glass syringe which consists of hallow plunger. The syringe has to be modified slightly by making a window at the lower end of the barrel and by removing the top end of the plunger as shown in the figure. The hallow plunger with open end serves as load cell in which mercury has to be placed. The crystal has to be placed in the barrel which was on base plate. The plunger acts as movable plate and should be set directly on the granules positioned on the base plate 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 to be 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.



Friability

For friability studies, 2 g (Wo) of spherical agglomerates (particle size 250-600 µm) shall be placed in a friabilator, and subjected to the impact test at 50 rpm for 2 min. After passing this through a sieve having a mesh size 125 µm, the weight (W) of the material which did not pass through the sieve shall be determined, and friability (X) was calculated using equation

$$X = Wo - W/W_O \times 100$$

Wettability

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. By determing the contact angle, one can assess the wettability of the agglomerates.

Solubility

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

Dissolution Rate and Bioavailability

Dissolution rate and bioavailability of the API from pure crystals and agglomerates can be determined by performing dissolution test using USP Dissolution apparatus and in vivo studies in animal models respectively.

Moisture Uptake Study

The study indicates the behavior of uptake of moisture by drug and the prepared spherical crystals, which affect the stability. The weighed quantity of drug and spherical crystals were placed in crucible at accelerated condition of temperature and humidity, $40^0 \pm 1^0$ C and 75% ± 3% respectively. The gain in weight of drug and spherical crystals should be measured [3].

Table 1: Equipments to be used for characterization of spherical crystals

S.No	Parameters to be studied	Name of the equipment
1	Size, shape, dimensions of the spherical crystals	Optical microscopy, Scanning Electron Microscopy (SEM)
2	Polymorphism existence	X-ray powder diffraction
3	Structure and Compatibility studies	Fourier Transform Infrared spectrometer (FTIR)
4	Dehydration, Dissociation, Decomposition, Phase transfer, Purity, Glass transition, Heat capacity	Differential scanning calorimeter (DSC)
5	Drug and the polymer interaction and stability of drug in solvents	Thin layer chromatography

Factors Controlling the Process of Agglomeration

Solubility profile

The selection of solvent is dictated by solubility characteristic of drug. A mutually immiscible three solvent system consisting of a poor solvent suspending liquid, good solvent and bridging liquid are necessary. Physical form of product i.e. whether micro agglomerates or irregular macro-agglomerates or a paste of drug substance can be controlled by varying 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.

Mode and intensity of agitation

High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would affect the shape of agglomerate. So the extent of mechanical agitation and mode of addition and the amount of bridging liquid determines the rate of formation of agglomerate and their final size.

Temperature of the system

Studies revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. Indirectly it affects on the solubility of drug substances.

Residence time: The time for which agglomerates remain suspended in poor solvent affects its strength.

Role of bridging liquid

Agglomerates are formed by agitating the crystals in a liquid suspension on adding a bridging liquid, which is immiscible with reaction mixture is capable of aggregating the particles to form agglomerates. Bridging liquid preferentially wets the crystal surface to cause binding. The addition of bridging liquid promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals.

THE PRINCIPLE STEPS INVOLVED IN THE PROCESS OF SPHERICAL CRYSTALLIZATION

Bermer and Zuider Wag proposed four steps in the growth of agglomeration.

Flocculation Zone

In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation, the adsorbed bridging liquid links particles by forming bridges or lens between them. In these zones, loose open flocs of particles are formed by pendular bridges. At this stage of agglomeration process, particles are brought by mutual attraction due to surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void spaces within the agglomerate is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure.

Zero Growth Zone

Loose floccules get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing pore space in the pellet to be completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

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. The other reason for the growth of agglomerates size is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

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 floccules 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 bridging liquid and solid substances.

Table 2-List of drugs on which spherical agglomeration technique has been carried out

Drug	Method	Property improved	Solvents used	Reference
Roxythromycin	SC	Flowability and Compressibility	Methanol,chloroform,water	34
Aminophylline	SC	Flowability and Compressibility	Ethanol,chloroform,water	35
Naproxen	SC	Flowability and Compressibility	Acetone, ethanol, chloroform, water	36
Aspirin	SC	Flowability and Compressibility	Acid buffer, ethanol, chloroform	37
Salicylic acid	SC	Flowability and Compressibility	Water,ethanol,chloroform	38
Valsartan	SC	Flowability, and compressibility	Methanol, water, dichloromethane	39
Ibuprofen	ESD	Flowability and Compressibility	ethanol,water with sucrose, fatty acid ester	40
Acebutalol HCl	ESD	Flowability and Compressibility	Water,ethanol,Isopropyl acetate	41
Indomethacin	ESD	Flowability, packability, and wettability	Methanol, dichloromethane, distilled water	42
Norfloxacin	ADM	Flowability and Compressibility	Ammonia water,actone,dichloromethane	43
Mefenamic acid	ADM	Flowability and Compressibility	Ammonia water, acetone, dichloromethane	44
Mefanamic acid	Neutralisation	Flowability, compressibility and dissolution behavior	1 M Sodium hydroxide; 0.7 M hydrochloric acid; iso propyl acetate	45
Ibuprofen	Neutralisation	Flowability, compressibility and dissolution behavior	1 M Sodium hydroxide; 0.07 M hydrochloric acid; iso propyl acetate	46
Ketoprofen	Neutralisation	Flowability, compressibility	1 M Sodium hydroxide; 0.25 M hydrochloric acid; chloroform	47

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