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## Spherical Agglomeration: A Novel Particle Design Technique to Improve Micromeritic and Dissolution Properties

Suryabali K. Yadav\*, Abhirajsinh J. Solanki, Jitendra J. Jaiswal

Department of Pharmaceutics, Rofel Shri G.M. Bilakhia College of Pharmacy, Vapi-396191, Gujarat, India

### ABSTRACT:

Tablet is most popular solid oral dosage form. It boosts stability, portability and acceptable patient compliance. The quality of solid oral dosage form is primarily affected by poor micromeritic properties such as size, shape, flowability, compressibility of drug crystal, mostly in case of poorly water soluble drugs. The poor flow property and compressibility give rise difficulty in pharmaceutical preparation meant for oral use and the poor aqueous solubility limits its effective absorption and bioavailability. Spherical agglomeration of drug particle induce spherical shape, enlarge the size, improve porosity and improve wettability, which in turn improve the dissolution and micromeritic properties like flow property and compressibility of drug. The resulting spherically agglomerated crystals can be directly compressed into a tablet, thus direct tableting saves time and reduces cost.

**KEYWORDS:** Spherical crystallization, agglomerates, flowability, direct compression, Solubility, Dissolution rate.

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### INTRODUCTION:

Solubility in different solvent is an intrinsic property for defined molecule. To achieve a pharmacological activity, is must that molecule exhibit certain solubility in physiological gastro-intestinal fluids and to be present in dissolved state at the site of absorption. Aqueous solubility of material is greatly indicate the solubility in intestinal fluids and its potential contribution to bioavailability issues.<sup>(1)</sup>

The low aqueous solubility of drug molecule may potentially lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequently less optimal efficacy in patients, particularly when delivered via oral route of administration.

It is accepted that drug substance solubility especially low aqueous solubility is become an issue for the drug discovery and it can provide number of challenges in the early stage screening studies of new chemical entities as well as in late stage pharmaceutical formulation design and development process.<sup>(2)</sup>

More than 40% of new chemical entities having low aqueous solubility means they poorly soluble in water, which leads to pharmacokinetic variability after oral administration and thereby exhibits poor bioavailability. Therefore improve water solubility or dissolution of these types of drug molecules is great challenge for scientist to formulate or to design a delivery system which provides required oral bioavailability.<sup>(3)</sup>

### \*For Correspondence:

Mr. Suryabali K. Yadav,

Department of Pharmaceutics, Rofel Shri G.M. Bilakhia College of Pharmacy, Vapi-396191, Gujarat, India.

(www.jpsbr.org)

Direct tableting is most desirable, easy and simplest technique of manufacturing tablet. Such manufacturing process of tablets involve simple mixing and compression of powder, which result in number of overall benefits including time, cost and energy savings. Direct compression of drug into tablet requires good micromeritic properties, such as good flowability, and good reproducible compressibility. In addition to increasing efficiency of manufacturing oral dosage form it is also important to increasing solubility of bulk drug powder, thereby improve dissolution rate, release profile of drug and may increasing bioavailability of drug.<sup>(4)</sup>

In present time, one of the Particle design technique such as Spherical crystallization is widely use in pharmaceutical industries to modifies primary properties of powder like particle size, particle shape, crystal form, crystal habit, density, porosity etc. In such modifications in the crystal habit certain "Micrometric properties" like bulk density, flow property, compactability, packability and "Physicochemical properties" like solubility, dissolution rate, and stability can be improved. Therefore, Spherical agglomeration is a multiple unit process in which crystallization, agglomeration, spheronization can be carried out simultaneously in one

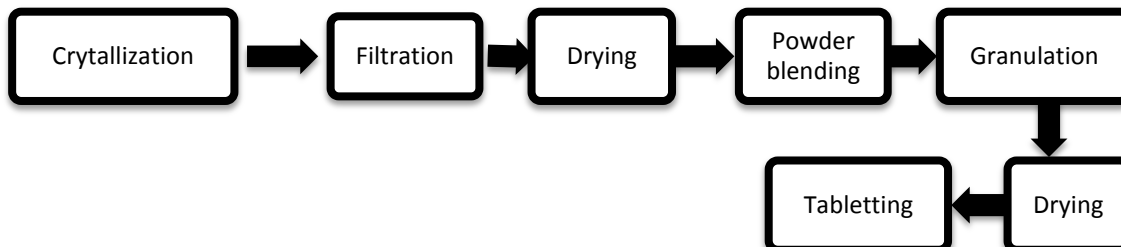
step and agglomerated crystal showing significant effect on the formulation and manufacturing of pharmaceutical dosage form.<sup>(5)</sup>

**Spherical Crystallization Technique**

Spherical crystallization can be defined as "a novel agglomeration Technique that can transforms the fine crystals obtained during crystallization directly into Spherical agglomerates." It is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step, which has been successfully utilized for improvement of Flow property, compact ability and solubility of crystalline drugs.<sup>(6)</sup>

Spherical agglomeration technique is employ to improve micromeritic properties and dissolution of drug. Kawashima used Spherical crystallization technique for size enlargement of drug particle in the field of pharmaceutical manufacturing by controlling crystal agglomeration with control properties and to exhibit that Spherical crystal agglomerates produced and were suitable to direct tableting.<sup>(7)</sup>

Traditionally drug manufacturing procedure involves following steps:



This is a slow and time consuming process.

➤ Where as in Spherical crystallization the process could be reduced to following steps:



It means by applying Spherical Crystallization the process of tablet manufacturing could be reduced, and it require less equipment and space, lower labour costs, less processing time, and lower energy consumption in the direct tableting manufacturing process.<sup>(8)</sup>

**Need of Spherical Crystallization technique<sup>(9)</sup>**

Developing novel methods to increase the Solubility and dissolution rate of drugs that inherently have poor aqueous solubility is a great challenge to formulate in solid dosage form. The two techniques are more commonly used to improve the solubility and dissolution of poorly soluble drugs i.e. Mechanical micronization of

crystalline drugs and incorporation of surfactants during the crystallization process.

When applying micronization process it alters the flowability and compressibility of crystalline powders and cause formulation problems. While Addition of surfactant usually led to less significant increase in aqueous solubility. When applying wet granulation, it cannot be used with moisture sensitive drugs.

To overcome this problem Kawashima developed a spherical crystallization technique that led to improving the Flow property, compact ability of crystalline drugs. Then spherical crystallization further developed use with hydrophilic polymers to enhance dissolution rate of poorly water soluble drugs.

#### Advantages of spherical crystallization technique:<sup>(10, 11)</sup>

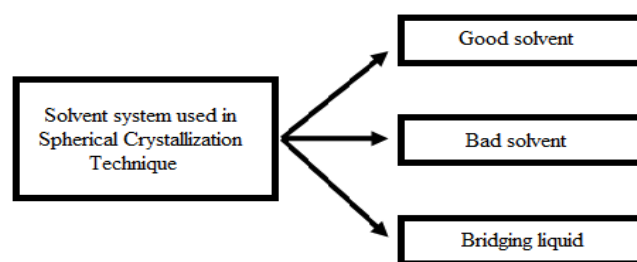
- Spherical crystallization technique is a simple and inexpensive process enough for scaling up to commercial level.
- It reduces time as well as cost by faster operation, and requires less machinery and fewer personnel's.
- The "Micromeritic properties" i.e. flowability, compressibility, and packability of the drug crystals improved by inducing spherical shape to the crystals.
- By Utilization of this process improved wettability, Solubility, and dissolution rate of drugs.
- Pharmaceutical process improved i.e. milling, mixing and tableting by using this technique.
- By Use of this technique may leads to conversion of crystalline forms of a drug into amorphous form that may have better bioavailability.
- Agglomerated crystals can be easily compounded with other pharmaceutical powders due to its spherical shape.
- It is avoid granulation step.
- For the masking the bitter taste of drug.

#### Disadvantage of spherical crystallization technique:

- Selection of suitable solvent for spherical crystallization is tedious process.
- Optimization of process parameter i.e. temperature of system, mode and intensity of agitation, is difficult.

#### Solvent used in Spherical Crystallization technique

In Spherical Crystallization Technique mainly three types of solvent are involve as per follow:<sup>(12, 13)</sup>



#### Good solvent

The solvent which solubilise the drug particle is called good solvent for drug. It should be volatile in nature. Example of good solvent included, Acetone, Ethanol, Ethyl acetate, Dichloromethane, THF, Ammonia-water, etc.

#### Poor solvent or bad solvent

The solvent which cause precipitation or crystallization of drug particle is called poor solvent or bad solvent. It is immiscible with drug substance. Example of poor solvent included, Ethyl acetate, water, etc.

#### Bridging liquid

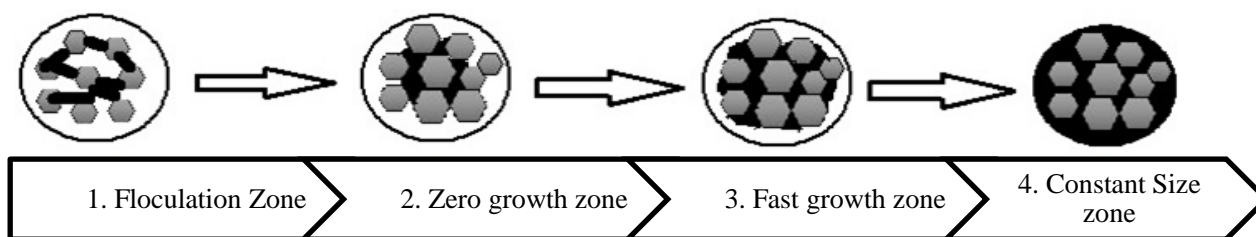
During process the Bridging liquid causing preferentially wetting of crystals and forms a liquid bridge between the drug crystals for forming spherical agglomerates. It partially dissolved the drug particle. Example of bridging liquid includes dichloromethane, isopropyl acetate, chloroform, hexane, etc.

#### Common excipients used in spherical crystallization technique

Mainly used excipients in spherical crystallization technique are polymers and surface active agent. Presence of excipients or additives like polymers and surface active agents whose surfaces are different to the crystal surfaces can influence molecular aggregation during crystallization. Viscosity of the medium and surface tension is reduced by the surfactants which affect the nucleation process. The studies have revealed that crystallization and agglomeration of pure drugs shows poor handling qualities. Addition of polymers such as HPMC, PEG and PVP has improved the properties of spherical agglomerates.<sup>(14)</sup>

#### Principle steps involved in the process of spherical crystallization

Berner and Zudier Wag identified following four steps, which involved in Spherical Crystallization:<sup>(15)</sup>



**Figure 1 Steps involved in Spherical crystallization**

### **Flocculation zone**

In flocculation zone the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in closer by agitation process, the adsorbed bridging liquid links the particles by forming bridge or lens between them. The loose open flocs of particles are formed by forming pendular bridges between particle and at this stage of agglomeration where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular stage. Mutual attraction of particles is due to the surface tension of the liquid and the liquid bridges. The capillary stage is reached when all void space within the agglomerate is completely filled with the liquid. A funicular stage is an intermediate state exists between the pendular and capillary stage. The cohesive strength of agglomerate is due to the bonding forces exerted by the pendular bridges and capillary suction pressure.

### **Zero growth zone**

In this zone loose floccules get converted 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 and causing poor space in the pellet which is completely filled with the bridging liquid. The agitation is provided the driving force to the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision by which transformation is occurred.

### **Fast growth zone**

The fast growth zone is takes place when sufficient bridging liquid has squeezed out on the surface of the small agglomerates. Forming a large size particle following random collision of well formed nucleus is known as coalescence. The successful collision occurs only if the nucleus has slight excess of surface moisture. This imparts plasticity on the nucleus and enhances particle deformation and subsequent coalescence.

### **Constant size zone**

In constant size zone agglomerates cease the growth of particle or even show slight decrease in size. The size reduction may be due to attrition, breakage and shatter. The zero growth zones is a rate determining step in agglomeration growth when bridging liquid is squeezed out of the pores as the initial floccules are transformed into small agglomerates. 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.

### **Factor controlling the process of agglomeration**

The factor which affect the Spherical crystallization technique are as per follow:<sup>(16)</sup>

#### **Solvent system**

Selection of solvent depends upon the solubility characteristics of the drug. The proportion of solvent to be used is determined by carrying out solubility studies and constructing a ternary phase diagram. Water has been reported as a bad solvent or external phase medium and organic solvents relatively nontoxic as a good solvent or internal phase and bridging liquid in the system design.

#### **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.

#### **Mode and intensity of agitation**

Optimum speed of 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. It has been reported that, the speed of the agitation affects size, sphericity, and strength of agglomerates. The extent of mechanical agitation and the concentration of bridging liquid determine the rate of formation of agglomerates and their final size.

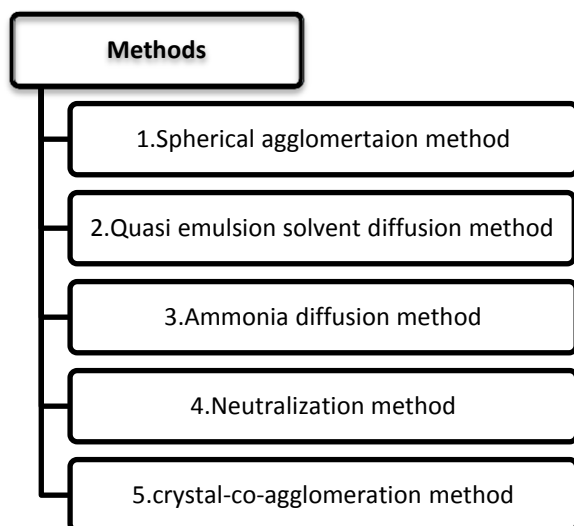
#### Amount of bridging liquid

The amount of bridging liquid is a critical factor in the spherical crystallization method. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates. There are some studies about the enlargement of agglomerates by increasing the amount of bridging liquid. Insufficient bridging liquid produces plenty of fines and excess produces very coarse particles.

#### Residence time

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

#### Methods of Spherical Crystallization Technique



#### Spherical agglomeration method

There are three main stages for spherical agglomeration method. The first step is Formation of precipitate crystals from saturated solution of drug. In this stage mainly the thermal method (temperature decrease or evaporation), physico-chemical method (addition of another solvent, salting out) or chemical methods may be used in this stage. The second step is the choice of the wetting agent

or bridging agent that should be immiscible with the poor solvent of the crystallization. The third step is the hardening of agglomerates.<sup>(17)</sup>

Three solvent called the good solvent, poor solvent and bridging liquid is used in the spherical agglomeration method. Prepared a nearly 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. To 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, there for crystals will precipitate immediately. Under agitation, the bridging liquid 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 by promoting the formation of liquid bridges between the drug crystals to form spherical agglomerates shown in Fig.<sup>(21)</sup> The spherically agglomerated crystals are formed by coalescence of these dispersed crystals.

Spherical Agglomeration method has been applied to numbers of drugs, and it has been found that the agglomerates properties are quite sensitive to the amount of the bridging liquid. Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles. As well as the choice of bridging liquid, the stirring speed and the concentration of solids are of importance.<sup>(18)</sup>

The agglomerate size distribution was affected by both the size of raw particles and the amount of bridging liquid used that observed in case of lactose. 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. 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.<sup>(19)</sup>

#### Quasi emulsion solvent diffusion method

Quasi emulsion solvent diffusion method is also known as transient emulsion method. In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the

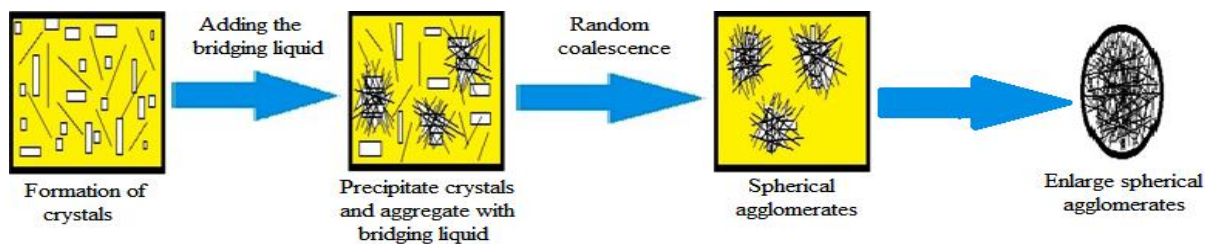


Figure 2 Schematic representation of spherical agglomeration process

poor solvent. Firstly the drug is dissolved in a mixed solvent of good solvent and bridging liquid, the solution is dispersed into the poor solvent, producing quasi emulsion droplets, even though the solvents are 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<sup>(20)</sup> and finally nucleation, growth, and agglomeration of crystals inside the droplets. This is known as the emulsion solvent diffusion (ESD) process.

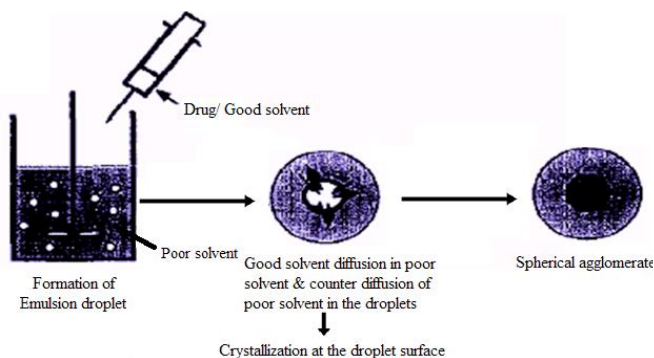


Figure 3 Schematic representation of Quasi emulsion Solvent diffusion method

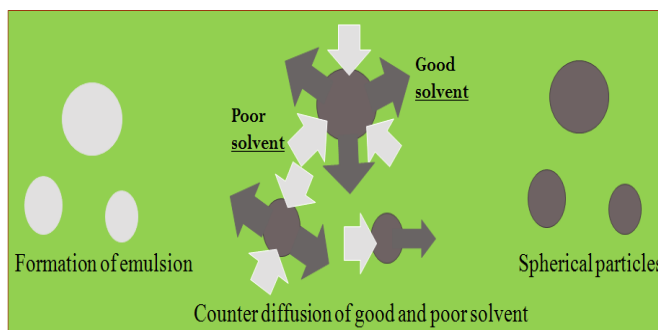


Figure 4 Steps involved in Quasi emulsion solvent diffusion method<sup>(21)</sup>

In this process, the continuous phase (generally aqueous phase) is formulated with polymer which avoids

secondary agglomeration by steric effect. 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.<sup>(21)</sup>

**Ammonia diffusion method**

In Ammonia diffusion method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In which ammonia water acted as bridging liquid as well as good solvent and water miscible Acetone acted as 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.<sup>(22)</sup>

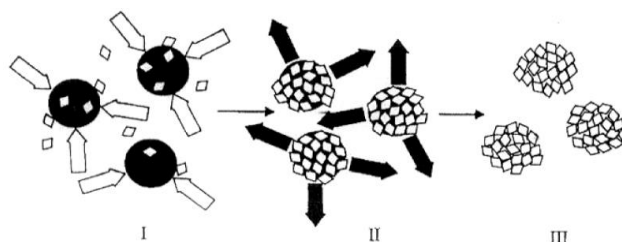


Figure 5 Steps involved in ammonia diffusion method

**Neutralization method**

Neutralization method involves the formation of fine crystals and their agglomeration by bridging liquid. First the drug dissolved in alkaline solution and poured in acidic solution containing polymers and added bridging liquid under constant agitation. Drug crystals precipitated out by neutralization of base with acid. Then the precipitated crystals were simultaneously agglomerated with co-operated polymer through wetting action of bridging liquid.

For example, the spherical agglomerate of non-steroidal anti-inflammatory drug (NSAID) Ibuprofen was reported by this technique. The drug was dissolved in 1N sodium

hydroxide solution. Aqueous solution of hydrochloric acid was added to neutralize sodium hydroxide solution of Ibuprofen, and isopropyl alcohol was added as bridging liquid. Prepared Spherical agglomerates showed improved micromeritic properties and dissolution rate.<sup>(23)</sup>

### Crystallo-co-agglomeration method

Because the hydrophobic nature of most excipients, incorporation of them in the formed agglomerates using organic bridging liquid is complicated. Then spherical agglomeration could not be employed for low-dose or poorly compressible materials. Crystallo-coagglomeration technique is an extension of spherical crystallization technique developed by Kadam *et al* in which drug is crystallized and agglomerated with an excipients or with another drug and technique could be able to overcome the mentioned limitation of spherical crystallization.<sup>(24)</sup>

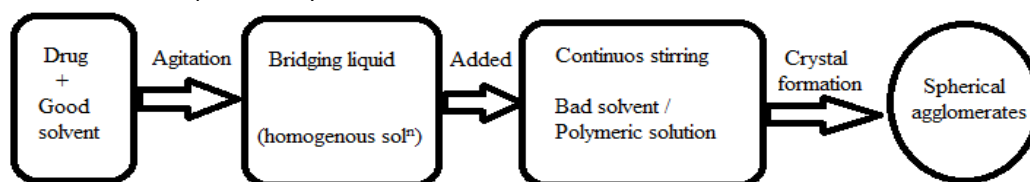


Figure 6 Steps involved in Crystallo-co-agglomeration technique.

### Evaluation parameter of spherical agglomerates:

#### Drug content and percentage yield<sup>(25)</sup>

The drug content is defined as the ratio of experimentally measured drug content value to the theoretical measured value, which is expressed as percentage (%). Accurate weighed quantity of prepared agglomerates will be dissolved in a sufficient quantity of a suitable solvent in which they get easily soluble. Solutions will be appropriately diluted and drug content will be determined by previously validated UV method. The percent (%) yield of samples will be calculated using the following Equation. The averages of three determinations will be considered as mean value for both parameters.

$$\% \text{Yield} = \frac{\text{Total weight of agglomerates}}{\text{Total weight of drug and excipients}} \times 100$$

#### Particle size measurement

The size of pure drug particles and prepared agglomerates will be measured by optical microscope, sieve analysis method or by mastersizer.

This process includes continuous stirring of drug and excipients in liquid medium. The continuous stirring is necessary for loading of the drug consistently in the agglomerates. In expansion concept, crystallo-co-agglomeration technique involves simultaneous crystallization and agglomeration of drug substance with or without excipients from good solvent and or bridging liquid by the addition of a poor solvent. The formed crystal of drug has minuscule form and therefore the drug dissolution and bioavailability are improved by using this method. Sometimes bridging liquid also serves as a good solvent. To overcome drug loss due to co-solvency, the good solvent should be volatile and immiscible with poor solvent.<sup>(24)</sup>

### Flow characteristics<sup>(26, 27)</sup>

Determination of angle of repose, Carr's index, Hausner's ratio will be used to characterize flow properties of the solid powder system. The flowability of a powder is a critical parameter important in production of pharmaceutical dosage form in order to get uniform feed as well as reproducible filling of the tablet dies.

#### Angle of repose:

Angle of repose is defined as the maximum angle possible between the surfaces of a pile of powder and horizontal plane. The angles of repose for the powder of each formulation will be determined by the funnel method. The powder will be made to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. After this gradual addition of the powder from the funnel mouth is done which forms a pile of powder at the surface, this is continued until the pile touches the tip of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone will be measured. Angle of repose will be calculated with the use of the following equation. Relationship between angle of repose and flowability is shown in table 6.1.

$$\tan \theta = h/r$$

Where,  $\theta$  = Angle of repose,

h= height of the pile, r = average radius of the powder cone

### Bulk density

Bulk densities of the powder will be determined by pouring gently 10 g of powder through glass funnel into a 50 ml graduated cylinder. The volume occupied by the powder will be recorded. The bulk density will be calculated as following equation.

$$\text{Bulk Density} \left( \frac{\text{g}}{\text{ml}} \right) = \frac{\text{weight of powder in grams}}{\text{volume occupied by the powder}}$$

### Tapped Density

10 g of powder will gently pour through a glass funnel into a 50 ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume is obtained. Volumes occupied by the powder after tapping will be recorded and tapped density is calculated as following equation.

$$\text{Tapped Density} \left( \frac{\text{g}}{\text{mol}} \right) = \frac{\text{weight of powder in grams}}{\text{volume occupied by the powder}}$$

### Hausner's ratio

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Tapped density and bulk density will be measured and the Hausner's ratio will be calculated using the following equation.

$$\text{Hausner's Ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

### Carr's index

The important measure that can be obtained from bulk density and tapped density is determination of the percentage compressibility or the Carr's index, which will be determined by the following equation.

$$\text{Carr's Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

### Porosity<sup>(28)</sup>

The State of packing of powders can be described by its porosity. Porosity may be defined as the ratio of void volume to the bulk volume of the packing

$$\text{Porosity} = \frac{\text{Bulk volume} - \text{Tapped volume}}{\text{Bulk volume}} \times 100$$

### Measurement of Packability<sup>(25)</sup>

**Kawakita analysis:** The packability of sample will be investigated by tapping them into a measuring cylinder using a tap density apparatus. The packability of sample will be calculated by the following equation.

$$\frac{n}{c} = \frac{1}{ab} + \frac{n}{a}$$

Where, n is the tap number, a and b are constant, and c is denotes the volume reduction which again calculated according to following equation.

$$c = \frac{v_0 - v_n}{v_0}$$

Where,  $v_0$  and  $v_n$  are the agglomerate bed volume at initial stage and at  $n^{\text{th}}$  stage respectively.

**Kuno analysis:** The relationship between the change in apparent density and the number of tappings was described by Kuno as per following equation

$$\ln(\rho_t - \rho_n) = -Kn + \ln(\rho_t - \rho_0)$$

Where,  $\rho_t$  infinity state taps density,  $\rho_n$  at nth state tapped density,  $\rho_0$  at initial state tapped density, and K represent rate of packing process.

### Solubility studies

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

### Dissolution studies

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

### Scanning electron microscopy<sup>(29)</sup>

The surface morphology and shape of both agglomerates and drug will be determined by using scanning electron

microscopy. The agglomerates will be observed at various magnifications in order to analyze the effect of additives on surface morphology and agglomeration efficiency.

#### **Differential scanning calorimetry analysis**<sup>(25)</sup>

DSC spectra of pure drugs, polymers and optimized agglomerates will be recorded using differential scanning calorimeter. That will be previously calibrated with indium standard. Sample (~5–10 mg) will hermetically sealed in an aluminium crucible and subjected to a purging of nitrogen gas at a flow rate of 50 mL/min. The heating at a rate of 10 °C/min. Empty sealed aluminium pan will be used as reference. The spectra obtain will be analyzed for endothermic and exothermic transitions in drug agglomerates. The change in physical and chemical properties of agglomerates can be studied with DSC.

#### **X- ray powder diffraction**<sup>(30)</sup>

The form of crystallinity and intensity of drug crystals in agglomerates will be determined using X-ray powder diffraction. The XRPD patterns of pure drugs and optimized agglomerates will be recorded using diffractometer system with a copper target and scintillation counter detector.

#### **Gas Chromatography**<sup>(25)</sup>

Residual solvents may be a critical impurity in excipients, drug sub-stances and ultimately drug products, because they may cause toxicity and safety issues, and affect physicochemical properties of drug substances and drug products. Generally, the solvents are not completely removed by practical manufacturing techniques. Hence, the solvent may sometimes be a critical parameter in the process. The general procedure of European Pharmacopoeia for residual solvent determination in pharmaceutical products included analysis of many solvents by GC.

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