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Review Article

REVIEW ARTICLE- SPHERICAL CRYSTALLIZATION– A NOVEL DRUG DELIVERY SYSTEM

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Abstract

Spherical crystallization is the novel agglomerated technique that can directly transform the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. Spherical crystallization of drugs is the process of obtaining larger particles by agglomeration during crystallization. The most common techniques used to obtain such particles are spherical agglomeration and quasi-emulsion solvent diffusion. Ammonia diffusion systems and crystalloid- co-agglomeration are extensions of these techniques. Today, the tablet is the most popular dosage form, covering around 50% of total oral drug delivery system and accounting 75% of all pharmaceutical preparation produced. To improve the dissolution rate of poorly soluble drugs, fine crystals are referred and this micronisation can change drug powder properties such as wet ability, compressibility, packability and flow. General methods of spherical crystallization are spherical agglomeration, emulsion, solvent diffusion method, ammonia diffusion method, neutralization method. The principle steps involved in the process are flocculation zone, zero growth zone, fast growth zone, constant size zone. There is a wide application of spherical crystallization. Improvement of flow ability, compressibility of poorly compressible drug, masking bitter taste of drug, improving solubility and dissolution rate of poorly soluble drug and thus improve bioavailability of drug.

Keywords: Spherical crystallization, Drug Techniques, agglomeration, solvent diffusion.

Introduction

The solid state properties of pharmaceutical compounds have a decisive impact on dosage form development, stability, and in vivo performance of the drug. Many pharmaceutical drugs are problematic per sedue to their inappropriate physical and mechanical properties and poor aqueous solubility. The micrometrics properties of drug particles, such as shape and size, are of essential importance for the formulation of solid high dose units. The particle size of poorly soluble drugs is always an issue due to its impact on dissolution properties. Micronized drug particles (smaller than 10 mm) have a large specific area and provide a way to improve the dissolution rate, but high energy input during the micronization process gives rise to increased free surface energy, electrostatic tendencies, and thus poor flow ability and/or compressibility of powders and low bulk density, which makes them difficult to use in downstream processing in the pharmaceutical industry such as direct tablet-making or capsule-filling processes. In addition, micronized drug substances tend to agglomerate and the increase in surface area is not always reflected in improved dissolution.

Spherical crystallization of drugs is the process of obtaining larger particles by agglomeration during crystallization. The most common techniques used to obtain such particles are spherical agglomeration and quasi-emulsion solvent diffusion. Ammonia diffusion systems and crystalloid- co-agglomeration are extensions of these techniques.

By controlling process parameters during crystallization, such as temperature, stirring rate, type and amount of solvents, or incipient selection, it is possible to control the formation of agglomerates and obtain spherical particles of the desired size, porosity, or hardness.

Researchers have reported that the particles produced have improved micromeritic, physical, and mechanical properties, which make them suitable for direct compression. In some cases, when additional recipients are incorporated during spherical crystallization, biopharmaceutical parameters including the bioavailability of drugs can also be tailored.

Presently, particle design techniques are widely used in pharmaceutical industries to modify primary properties like particle shape, size, crystal habit, crystal form, density, porosity etc. as well a secondary properties like flow ability , compressibility, compact ability, reduction In air entrapment, etc. Spherical crystallization is one of such particle design technique in which crystallization and agglomeration process are carried out simultaneously. Kawashima et al, developed spherical crystallization technique .Spherical Crystallization process transforms the fine crystal obtain during crystallization into a spherical agglomerates.

Agglomerates formed further improves the flow ability and compressibility of pharmaceutical ingredient which enables direct tableting of drug instead of further processing like mixing , granulation, sieving, drying etc. There are certain parameters which have to be optimized in order to obtain the maximum amount of crystals spherical.

It is also known that the particle shape or crystal habit can influence the packing, flow ability, compressibility, dissolution, and sedimentation properties of pharmaceutical powders. For example, it has been demonstrated that symmetrically shaped crystals of ibuprofen possess better compaction and flow properties than needle-shaped crystals. Physico-mechanical properties of crystals, such as melting point, solubility, true density, dissolution profile, flow ability and compatibility, can be modified by re-crystallizing the drug in different ways that affect the physical and chemical properties of formed particles. For example, ibuprofen crystals were grown from various solvents and, by using various crystallization conditions, it was shown that various crystal forms with various crystal shapes were obtained: cubic, needle-shaped, and plate-shaped crystals. Differences in true density, flowing properties, and tabletability were determined for these different particles.

Poor physical and mechanical properties of drug particles have been traditionally masked by various granulation methods, such as the conventional and widely used wet granulation, which produces agglomerates with higher bulk density, better flow ability, and compressibility/compatibility. Most common techniques of wet granulation are high-shear and fluid bed wet granulation, which generally involve mixing, atomization, and spraying of granulation liquid on powders, drying steps, sieving, and so on. Both agglomeration methods are energy-consuming process steps in dosage form production and can impair the stability of moisture- or heat-sensitive drugs or can cause transformation of the physical form of drugs. Other agglomeration techniques, such as dry granulation, hot-melt granulation, melt extrusion, spray congealing, or melt solidification have been introduced in recent years, and have yielded some innovative solutions for improving the physical and mechanical properties of drug particles; however, they are still less economical than direct compression tableting.

Kawashima and Capes introduced the concept of obtaining larger particles by agglomeration during the crystallization step. Silica sand dispersed in agitated carbon tetrachloride and agglomerated with calcium chloride aqueous solutions was used as a model system. Some years later, Kawashima used the spherical crystallization method for increasing the size of drug particles and defined it as an agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process.

Using this method, the precipitated crystals can be agglomerated during the final synthesis step (recrystallization) into more or less spherical particles with sizes between 300 and 500 mm without any binders. This paper describes spherical crystallization methods and outlines the potential of the particles obtained.

The oral route of administration is the most impor-

tant method of administering drugs for systemic effects. In this, the solid dosage form, particularly, tablets are the dosage form of a choice because of their special characteristics like unit dosage form with greatest dose precision and least content variability, lower cost, easy administration by a patient and temper proof nature.

The formation of solid oral dosage forms and tablets in particular, have undergone rapid changes and development over the last several decades and one of the most revolutionary technologies in that of direct compression. It is economical, facilitates processing without the need for moisture and heat and small number of processing steps are involved The basic requirement for commercial production of tablet is a particulate solid with good flowability, mechanical strength and compressibility. Hence is necessary to evaluate and manipulate the above said properties. To impart these properties the drugs are subjected to particle design techniques, spherical crystallization is one the techniques of particle design. The particle size can be enhanced by the help of wet granulation method, dry granulation method, extrusion spheronization and by spherical crystallization methods. The spherical crystallization is a nonconventional particle size enlargement technique that involves crystallization and agglomeration using bridging liquid. The solid state properties of pharmaceutical compounds have a decisive impact ondosage form development, stability, and *in vivo* performance of the drug. Many pharmaceutical drugs are problematic due to their inappropriate physical and mechanical properties and poor aqueous solubility. The micrometrics properties of drug particles, such as shape and size, are of essential importance for the formulation of solid high-dose units.

The particle size of poorly soluble drugs is always an issue due to its impact on dissolution properties. Micronized drug particles (smaller than 10 mm) have a large specific area and provide a way to improve the dissolution rate, but high energy input during the micronization process gives rise to increased free surface energy, electrostatic tendencies, and thus poor flow ability and/or compressibility of powders and low bulk density, which makes them difficult to use in downstream processing in the pharmaceutical industry such as direct tablet-making or capsule-filling processes. In addition, micronized drug substances tend to agglomerate and the increase in surface.

Crystallization is a process of forming solid crystals that occurs when molecules start aggregating and precipitating from solution or melt. The rate and mechanisms by which crystals are formed from liquid solutions are determined by many factors: thermodynamic (*e.g.*, solubility, solid-liquid interfacial tension, solvent activity, temperature, *etc.*), kinetic (*e.g.*, super saturation, molecular mobility, meta-stable zone width), and molecular recognition (hydrogen bonds, non-covalent bonds, molecular networks). The driving force for crystallization is super saturation, which describes the exceeding of the saturated equilibrium concentration of solute.

Super saturation can be created by increasing the solute concentration (solvent evaporation) or decreasing the solute solubility (*e.g.*, temperature change, anti-solvent addition, pH change, salting out). The concentration threshold above which crystallization (nucleation) is observed is determined by the kinetic stability of supersaturated states and is regulated by nucleation mechanisms (homogenous, heterogeneous) and kinetics. The next step in crystallization is the formation of macroscopic crystals from stable nuclei, called crystal growth. Crystal growth is controlled by internal and external factors (temperature, impurities, super saturation and solvent type) and determines the particle morphology.

The most commonly used spherical crystallization techniques are spherical agglomeration and quasi-emulsion solvent diffusion. In both processes, a good solvent that dissolves the compound to be crystallized is used, and a poor solvent that acts as an anti-solvent is used to generate the required super saturation. Other extensions of these techniques are crystalloid-co-agglomeration and the ammonia diffusion system.

Various authors give this kind of agglomeration process different names. It is usually called spherical agglomeration when the process is aimed at producing final particulate material with special characteristics.

When its aim is to facilitate manufacturing processes such as filtration or handling, the term agglomeration in suspension is used. The term

selective agglomeration is employed when it is used to separate a solid component from a mixture or oil(assisted) agglomeration when oil or some other organic liquid is used as a bridging liquid to facilitate the agglomeration process.

In addition to being used in producing spherical particles of pharmaceutical powders with improved physical properties, this kind of agglomeration is also useful for selective collection of one dispersed phase among many, such as may be desired in coal purification and mineral beneficiation or de-inking toner on printed paper for secondary fiber recovery where hydrophobic particles are agglomerated to a sufficient size and then effectively removed by filtration or air flotation.

Presently tablet is the most popular dosage form of all pharmaceutical preparations produced .Tablet is the most stable readily portable and consumed dosage form. 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 tablet over recent years since in comparison to the used at the more traditional granulation process. Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to solid dosage form formulators. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs.

The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone 1.Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. The oral route of administration is the most important method of administering drugs for systemic effects. In this, the solid dosage form, particularly, tablets are the dosage form of a choice because of their special characteristics like unit dosage form with greatest dose precision and least content variability, lower cost, easy administration by a patient and temperature proof nature. The formation of solid oral dosage forms and tablets in particular, have undergone rapid changes and development over the last several decades and one of the most revolutionary technologies in that of direct compression. It is economical, facilitates processing without the need for moisture and heat and small number of processing steps are involved.

The basic requirement for commercial production of tablet is a particulate solid with good flow ability, mechanical strength and compressibility. Hence is necessary to evaluate and manipulate the above said properties. To impart these properties the drugs are subjected to particle design techniques. Spherical crystallization is one the techniques of particle design. The particle size can be enhanced by the help of wet granulation method, dry granulation method, extrusion spheronization and by spherical crystallization methods.

The first step in the formulation is often milling or granulation, in order to provide for better properties for the final tableting or to increase bioavailability. Often very small particles are required in order to increase the dissolution rate, and reach sufficient bioavailability. However, micronisation by milling is extremely inefficient, can cause physical and chemical instability, and produces powders with a wide size distribution and poor flow ability. The alternative is to produce quite small crystals directly in the crystallization. In some cases thin needles are produced having a high surface area to volume ratio, but likewise may be quite difficult to handle.

Crystals could be generated employing any of the conventional techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding. One of method called Spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired.[14]

Need for spherical crystallization:

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to formulate solid dosage form. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques

commonly used to improve the bioavailability of poorly soluble drugs. The mercerization process alters the flow and compressibility of crystalline powders and cause formulation problems. Addition of surfactant generally lead to less significant increase in aqueous solubility.[19]

Theory [1,4,19]

Methods of Spherical Crystallization

The methods of spherical crystallization are categorized

1. Solvent Change Method (SC)
2. Quasi Emulsion Solvent Diffusion Method (QESD)
3. Ammonia Diffusion Method (AD)
4. Salting Out Method (SO)
5. Spherical Agglomeration (SA)

Spherical agglomeration:

In the spherical agglomeration method, a solution of a compound in a good solvent is poured into the poor solvent, which is miscible with the good solvent. The affinity between the solvents must be stronger than the affinity between the good solvent and the compound, which causes immediate precipitation of crystals. In the spherical agglomeration method, a third solvent called the bridging liquid is also added in a smaller amount and acts as an antiparticle binder that promotes agglomeration.

The bridging liquid, which should not be miscible with the poor solvent and should wet the precipitated crystals, collects the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure.

Surfactants are usually avoided because the strength of liquid bridges is proportional to the interfacial tension between the bridging liquid and the solid Some authors have reported that the amount of bridging liquid has an impact on particle size distribution, but there is no general rule regarding how the quantity of bridging liquid affects the size of agglomerates and it seems to vary on a case-by-case basis.

Some researchers report on the enlargement of agglomerates with increasing amounts of bridging liquid , whereas in another study of the spherical agglomeration process the addition of a smaller amount of bridging liquid produced larger particles of acebutolol (up to 1,000 mm) and vice versa larger amount of bridging liquid produced smaller particles (around 600 mm).

Kati and coworkers noticed no change in the particle size of agglomerated benzoic acid with an increased volume of bridging liquid. However, it can be concluded from other studies that if the quantity of bridging liquid is too small, there is no significant agglomeration and when too much bridging liquid is used, the agglomerates become soft and pasty. Some authors emphasize the importance of the choice of bridging liquid and suggest how to determine the optimal one for spherical agglomeration.

Regarding the importance of the bridging liquid wetting properties during the spherical agglomeration process, Amado-Gonzales and Buskins proposed a study of the capillary uptake of liquid in a powder medium using Washburn's test. The best results during crystallization tests on lobenzarit disodium were obtained in the presence of *n*-hexane wetted solid crystals better.

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1. For compounds that are water soluble, a water-miscible organic solvent is used as the poor solvent and salt solutions of high concentration without common ions can be used as the bridging liquid.

2. For compounds that are soluble in one or more organic solvents, water is employed as the poor solvent and a water-immiscible organic solvent as the bridging liquid.

3. For compounds that are only soluble in water-miscible organic solvents, a saturated aqueous solution of the compound can serve as the poor solvent and an organic solvent as the bridging solvent.

4. For compounds that are not sufficiently soluble in water or any organic solvent, a water immiscible organic solvent can act as the poor solvent and salt solutions of high concentration without common ions as the bridging liquid. In addition, a binding agent such as PVP (*M*r. 40000) or PEG (*M*r. 10000) is required for agglomeration because the powders are not sufficiently soluble in bridging liquids to allow binding through recrystallization and fusion. Proposed mechanism of spherical agglomeration.

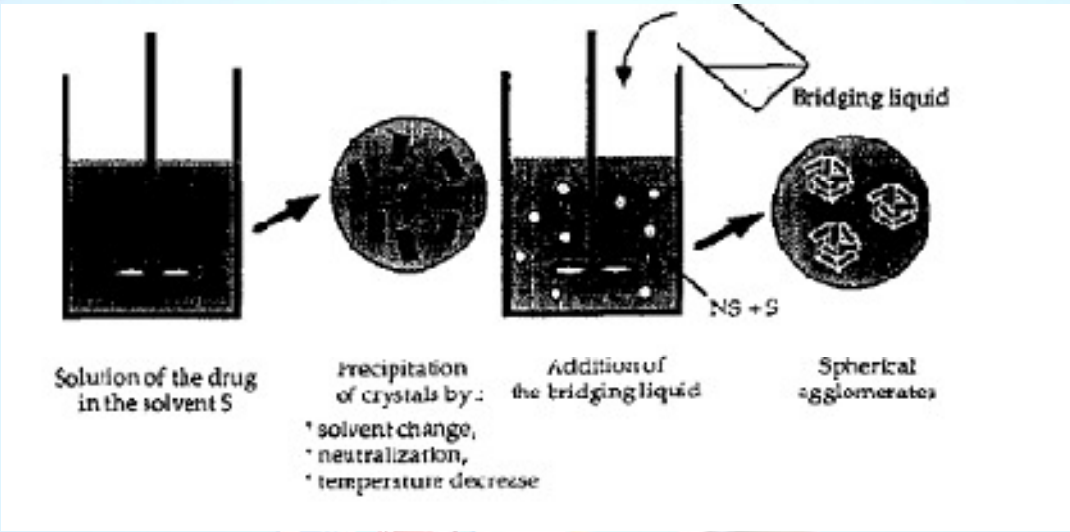


Fig.no.1. Principle of Spherical Agglomeration

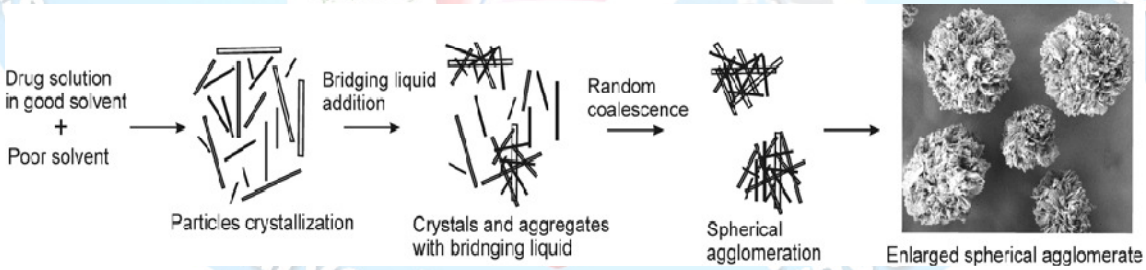


Fig. no. 2. Proposed mechanism of spherical agglomeration

Solvent change method:

The solution of the drug in a good solvent is poured in a poor solvent under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent but low solubility with solvent mixture so during agitation of the solvent system the crystals formed. The Drawback of this system is that it provide low yield because the drug shows significant solubility in the crystalliza-

tion solvent due to co solvency effect. This method is not applicable for water insoluble drugs

Quasi emulsion solvent diffusion method (QESD):

In addition to the amount and choice of bridging liquid, other process parameters during crystallization are also important for agglomeration kinetics and particle properties. One of the important process parameters is the agitation rate during the agglomeration process. It has been shown that increasing stirring speed makes the agglomeration process less efficient due to the shearing rate, disruptive forces, and higher probability of agglomerate collisions, which preferentially tear them apart.

It has also been demonstrated that higher stirring speed at the same time results in decreased porosity and greater mechanical resistance of the agglomerates produced. Another important process parameter is the proportion of good solvent to poor solvent. Zhang and coworkers have recently reported that the mean particle size of cefotaxime sodium spherical agglomerates increased with an increase of the poor solvent chloroform content in the crystallization system, and at the same time the particle size distribution became narrower, which can be ascribed to higher super saturation and more effective crystallization and agglomeration. In that study, the temperature and agitation speed had no notable impact on the agglomerated particle size, while in another study higher temperature resulted in smaller particle size and increased density of agglomerated carbamazepine.

The quasi-emulsion solvent diffusion (QESD) was first mentioned in 1989 by Kawashima and Coworkers the prerequisite of this method is that the interactions between the drug and the good solvent are stronger than the interactions between the good solvent and the poor solvent. The drug is dissolved in the good solvent and when the solution is dispersed into the poor solvent, quasi-emulsion droplets are created, even though good and poor solvents are miscible. Formation of an unstable emulsion is induced by the increase in interfacial tensions between both solvents.

The good solvent gradually diffuses out of the emulsion droplets into the outer poor solvent phase, and the poor solvent diffuses into droplets, which reduces the solubility and eventually causes drug crystallization inside the droplets. Residual good solvent in the droplet Acts as a bridging liquid to agglomerate the generated crystals. Spherical agglomerates of crystals are then formed if the process parameters are set accordingly.

As previous studies have shown, solvent transfer is particularly influenced by two basic parameters. One of them is the difference in temperatures $T1$ - $T2$, with $T1$ being the temperature of the good solvent with dissolved drug before dispersion and $T2$ the initial temperature of the poor solvent.

A smaller difference in initial temperatures between the two phases accelerates the mass transfer of solvents and consequently the rate of crystallization is increased. The second parameter that influences the rate of solvent transfer is the initial mass ratio of good solvent to poor solvent and, as shown by Espitalier and coworkers, mass transfer of the good solvent (acetone) into the poor solvent's phase (water) increased when the ratio between the good solvent and the poor solvent was high. At the same time, by increasing the initial ratio of good to poor solvents, the apparent density of the ketoprofen particles produced decreased. In a later study, the median diameter of particles produced was reduced using the higher temperature difference between $T1$ and $T2$ and a low ratio of good solvent to poor solvent. The results were explained by more intense creation of super saturation.

The effect of the overall temperature of the dispersed system on particle shape and size has been demonstrated by Zhang and Coworkers. At higher temperatures, the agglomerated sallying particles were larger (0.89, 1.74, and 2.48 mm at 15, 23, and 30 °C, respectively) and more spherical (Fig. 3), which was explained by a higher diffusion rate, increased interfacial tension, and higher kinetic energy of the droplets. Some authors reported that an emulsifier must be used for the QESD method. Nocent and Coworkers conducted a study of spherical crystallization of salbutamol sulfate using the QESD method and tested several emulsifiers with different HLB (hydrophilic/ lipophilic balance). Only the use of the most lipophilic emulsifier in the study.

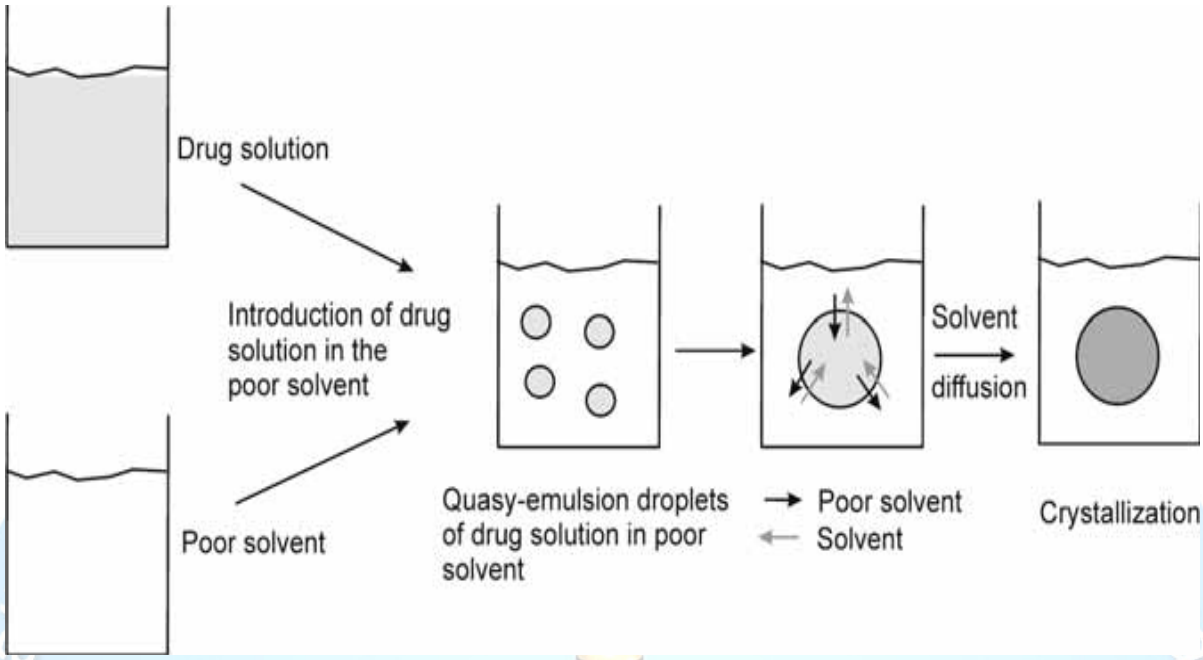
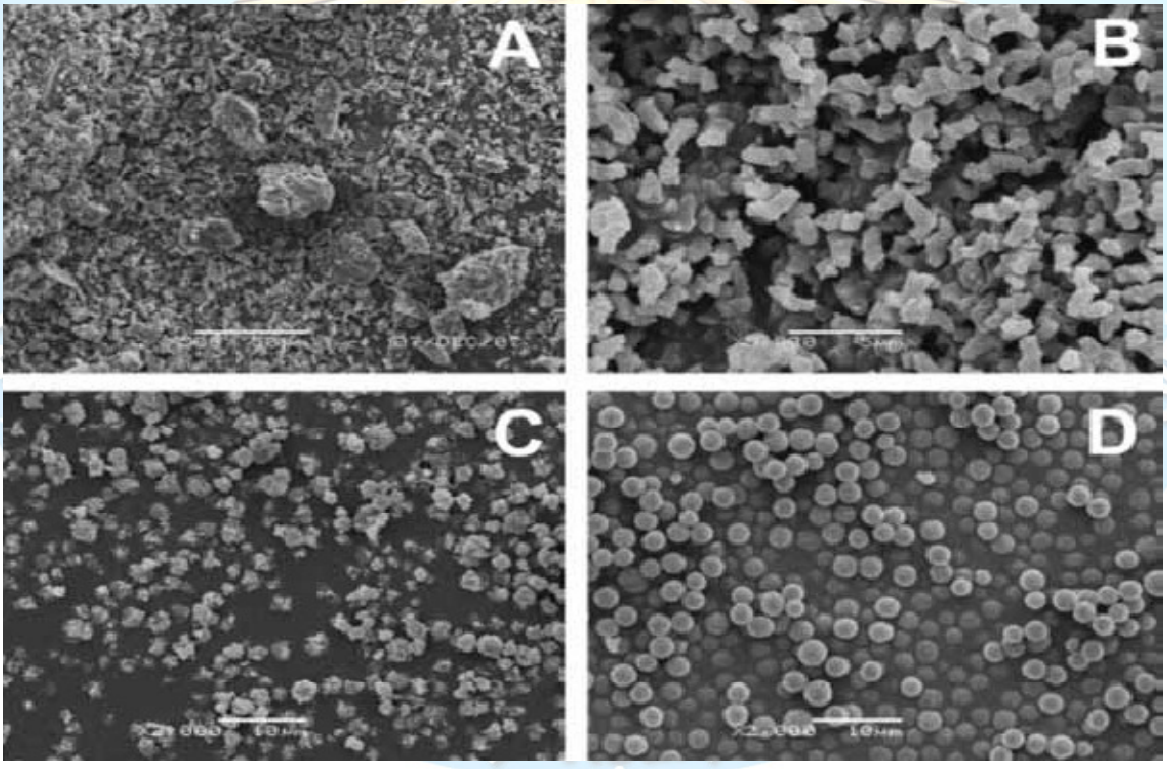


Fig.no.3 Proposed mechanism of QESD

Fig .No. 4. SEM images of: A) commercial sallying powder; sallying particles prepared at: B)15 °C; C) 23°C; D) 30 °C



Bail EM 90 (polysiloxane poly alkyl polyether co-polymer; HLB = 5), yielded spherical Particles. A larger amount of emulsifiers dispersed in the poor solvent can cause a coalescence of particles and

increase their surface roughness, whereas a lower proportion of emulsifier increases the apparent density of particles. In a study by Zhang and co-workers, a trial without surfactant resulted in relatively large spherical particles of sallying (6.68 mm) with coarse surfaces, and trials with lower or higher concentrations of surfactant yielded smaller particles (2.97 mm, 2.49 mm, and 2.48 mm at 0.01, 0.02, and 0.10 % SDS concentration, respectively) with narrower particle size distribution.In this study spherical crystallization was utilized in an attempt to improve the solubility and dissolution rate of Mel. Mel spherical agglomerates were prepared with or without different polymers (PEG 4000, Intec SP1, PVP k30, pluronic F127 and HPßCD) at three different concentrations (0.0125 %, 0. 025 % and 0.05 % w/v) using quasi emulsion solvent diffusion and neutralization techniques. The processed meloxicam crystals were evaluated for yield, particle size, solid state, dissolution in simulated gastric (SGF) and saliva fluids (SSF) and finally for ant nociceptive effect.

Ammonia diffusion method

This is a modified spherical crystallization technique applicable to amphoteric substances, which are only soluble in acidic or alkaline aqueous solutions and insoluble in neutral aqueous solutions or organic solvents. It is therefore impossible to agglomerate them using conventional spherical crystallization techniques such as sphericalthe surface the agglomerate formed without coalescence, agglomeration or the quasi-emulsion solvent diffusion method. In this technique, an aqueous ammonia solution is used as the good solvent and it also acts as a bridging liquid.

In this method ammonia water act as a good solvent and bridging solvent, other components of this method are bad solvent and hydrocarbon/halogenated hydrocarbon (acetone). The hydrocarbon is miscible with the system but it reduces the miscibility of ammonia water with bad solvent. The fraction of ammonia water is the system that exists as an immiscible phase forms droplet. The counter diffusion process across the droplet involves movement of bad solvent into and ammonia out of the droplet. The droplet collects the crystals as a drug in ammonia water precipitates slowly and growth of agglomerates occurs.

The poor solvent is selected on the basis of the drug solubility in that solvent and good miscibility with ammonia and water. Water-immiscible solvents such as hydrocarbons or halogenated hydrocarbons are a third component in the system, inducing liberation of the ammonia. The drug is dissolved in an aqueous ammonia solution and poured into a mixture of a poor solvent and a water-immiscible solvent.

It is assumed that the poor solvent enters the droplets of aqueous ammonia solution and causes drug precipitation without forming ammonium salts. Simultaneously, the ammonia diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker, which then determines the final size of agglomerates. It is important to find a suitable combination of solvents in order to attain a high crystallization rate. When too much immiscible or poor solvent is applied, the resultant agglomerates form a large solid mass or a paste and with too little solvent, drug crystals form without agglomeration.

Salting out method

This method involves the addition of suitable salt for drug to crystallize out in the presence of bridging liquid.

Crystallo-co-agglomeration

Crystallo-co-agglomeration was invented by Adam and coworkers as an attemptto overcome the limitations of spherical crystallization techniques, which were restricted to size enlargements of single high-dose drugs only. It is a modification of the spherical crystallization techniques described above, in which a drug is crystallized and agglomerated with an incipient or with another drug. Similar to spherical agglomeration, a good solvent is used in this method to solubilize the drug, a poor solvent to cause drug crystallization and the bridging liquid, which is immiscible with the poor solvent, to form liquid bridges during the agglomeration process.

Crystallo-co-agglomeration is a complex process and is influenced by many formulation and process variables. The majority of drugs are hydrophobic, soluble in organic solvents, and poorly soluble in water, whereas many recipients, such as diluents, disintegrate or giants are hydrophilic.

Therefore the difference in the physical and chemical properties of drug molecules and the incipient is a major challenge in selecting a solvent system for the crystalloid-co-agglomeration and dictates the yield of the process.

Maghsoodi and coworkers prepared spherical co-agglomerates with naproxen and disintegrates, either starch or sodium starch glycol ate. Acetone was used as a good solvent and the bridging liquid, whereas water with dispersed disintegrate and a small amount of hydroxyl propyl cellulose served as a poor solvent. Disintegrate was present in the acetone and aqueous phases during the agglomeration process, and so losses of disintegrate could not be avoided and final yields of the agglomerates prepared were within a range of 68 to 70 %.

Addition of various polymers such as polyethylene glycol, ethyl cellulose, or hydroxyl propyl methylcellulose can improve the tensile strength or compressibility of agglomerates. Properties of the finished product are simultaneously affected by polymer- -induced properties such as the interfacial tension, viscosity, and the rate of vaporization.[10]

Principles of Spherical Crystallization [18]

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 the particles by forming bridge or lens between them. In this zone, loose open flocks of particles are formed by pendular bridges and this stage of agglomeration process where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular state.

Mutual attraction of particles is brought about by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space 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 flocks get transferred into tightly packets pellets, during which the entrapped fluid is squeezed out followed by the squeezing of the bridging liquid on to the surface of the 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

4.2.3. Fast growth zone:

The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size article 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 article deformation and subsequent coalescence.

4.2.4. Constant size zone:

In this zone agglomerate ceases to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomerate. The size reduction may be due to attrition, breakage and shatter. [12]

5. Factors Controlling The Process of Agglomeration[1]

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

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

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

3. **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.

4. **Polymer types and their concentration:** Plain drug agglomerates (without recipients) have showed poor resistance to breaking, poor compressibility and low compatibility due to inherent poor cohesiveness of drug/s. Agglomerates obtained by optimum addition of polymers imparts sufficient mechanical strength and sphericity to the agglomerates.[21]

6. Factors affecting the process of spherical crystallization.[12]

Temperature of the system

Temperature has significant influence on the shape, size and texture of the agglomerates .The solubility of drug is affected by the temperature change.

Mode and intensity of agitation

The extent of mechanical agitation along with the amount of bridging liquid determines the rate of formation and size of agglomerates. The stirring speed must be optimized. High speed agitation is necessary to disperse the bridging liquid through the system. But in some cases increasing stirring rate, may cause reduction in agglomerate formation due to increased disruptive forces. Higher stirring rates produces agglomerates that are less porous and more resistant to mechanical stress.

Amount of bridging liquid

The spherical agglomeration method has been applied to plenty of drugs,and it has been observed that the properties of spherical agglomerates were very muchsensitive to the amount of bridging liquid.

Choice of solvent

The choice of solvent depends on the solubility profile of drug. A mutually immiscible three solvent system consisting of good solvent, poor or anti-solvent and bridging liquid are necessary. 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 solutions.[4]

7. Advantages of Spherical Crystallization.[6]

1. Spherical crystallization technique has been successfully utilized for improving of flow ability and compressibility of drug powder.
2. This technique could enable subsequent processes such as separation filtration, drying etc. to be carried out more efficiently.
3. By using this technique, physicochemical properties of pharmaceutical crystal as are dramatically improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flow ability and pack ability.
4. This technique may enable crystalline forms of a drug to be converted into different polymorphic form having better bioavailability.
5. For masking of the bitter taste of drug.
6. Preparation of micro sponge, microspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system.
7. Spherical crystallization techniques have been successfully applied to produce compact spherical particles of drug substances that possessed improved micrometrics properties, such as uniform shape and size of particles, lower bulk density, and better flow ability
8. For Particle shape/surface topography optical microscopy and Electron scanning microscopy are used.
9. X-ray powder diffraction: X-ray powder diffraction is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystals in agglomerates was determined by using this technique. An amorphous form does not produce a pattern. Each diffraction pattern is characteristics

of a specific crystalline lattice for a given compound.

10. Fourier Transform Infrared spectrometer (FTIR): It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the salvation.
11. Differential scanning calorimeter (DSC): DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC.
12. By using this technique, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flow ability and packability, flow ability and compressibility of drug powder.
13. This technique may enable crystalline forms of a drug to be converted into different polymorphic form having better bioavailability.
14. Preparation of microsponge, micrspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system 3.[5,8,9]

Table no.1.List of solvents used in spherical crystallization of drugs. [8]

Drugs	Good solvent	Bridging liquid	Poor solvent
Celecoxib	Acetone	Water	Chloroform
Benzoic acid	Ethanol	Water	Chloroform
Mefenamic acid	Dimethylformamide	Water	Chloroform
Aceclofenac	Acetone	Water	Dichloromethane
Ascorbic acid	Water	Ethyl acetate	Chloroform
Aspirin	Acid buffer	Methanol	Chloroform
Roxythromycin	Methanol	Chloroform	Water
Aminophylline	Ethanol	Cloroform	Water
Nabumetone	Ethanol	Water	Cyclohexane
Acetyl salycilic	Ethanol	Water	CCL4
Salicylic acid	Water	Ethanol	Chloroform
Dibasic	Water	Phosphoric a	Citric acid
Calciumphosphate	Ethanol	Water	Isopropylacetate

Drugs	Method	Solvent
Ibuprofen	ESD	Ethanol, water with sucrose,fatty acid ester
Norfloxacin	ADM	Ammoniawater,acetone,dichloromethane
AcebutalolHCL	ESD	Water,ethanol,Isopropylacetate
Mefenamic acid	ADM	Ammonia, water, acetone, dichloromethane

Table no.2 - List of some drugs on which Emulsion Solvent Diffusion (ESD) and Ammonia Diffusion Method (ADM)[16]

Table.no. 3. Pharmaceutical drugs with improved physical and mechanical properties prepared using various. [6]

Drug	Method	Improved property
Acetylsalicylic acid	SA	Flow properties, compatibility
Cefotaxime sodium	SA	Flow properties, compressibility
Lobenzarit disodium	SA	Particle shape and size distribution
Tolbutamide	QESD	Particle shape, flow properties
Bucillamine	SA, QESD	Flow properties, compressibility
Ascorbic acid	SA, QESD	Flow properties, compatibility
Salbutamol sulfate	QESD	Particle shape and size distribution
Ketoprofen	QESD	Flow properties, size distribution
Mefenamic acid	ADM	Flow properties, compressibility
Norfloxacine	ADM	Particle shape and size
Naproxen	CCA	Flow properties, compatibility
Aspartic acid	SA	Compressibility, compatibility
Naproxen	QESD	Compressibility, compatibility

- SA – spherical agglomeration, QESD – quasi-emulsion solvent diffusion, ADM – ammonia diffusion method, CCA – crystalloid-co-agglomeration
- Consequently, the physical and mechanical properties (compressibility, compatibility)were also improved and the particles obtained were suitable for direct tableting (Table I).Spherical crystallization techniques can be also exploited to incorporate various recipientsinto agglomerates, such as colloidal silica, surfactants, or polymers. In this case as well, the physical and mechanical properties drugs are improved and the incorporated recipients also affect the wetting properties, solubility, dissolution rate, and hence the bioavailability of pharmaceutical drugs (Table II).

Application of spherical crystallization in pharmaceuticals:

1.For increasing solubility and dissolution rate of poorly soluble drug.

2. For masking bitter taste of drug.

3. Improve flow ability and compressibility.

4. Reduces cost of production.

Evaluation of Spherical Crystals

As these spherical agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage forms so it is necessary to evaluate them by using different parameters. [16]

Particle shape & surface topography:

Geometrical properties of agglomerates

Geometrical properties of spherical crystals can be determined by image processing system. Around 300 particle of different range size fraction were run over with an optical pen. The system determines the smallest (Dmin) and the largest (Dmax) diameter of each individual particle. A Parameter R was developed, which indicates the roundness of the particles sovereignty of the size of the particle. A value of R near 1 is indicative of perfectly spherical agglomerate.

Electron Scanning Microscopy

The surface topography, type of crystals (polymorphism and crystal habit) of the spherical agglomerates & the conventional crystals is analyzed by using scanning electron microscopy. Using an image analyzer micrographs ofmore than 100 particles were transformed into the software and the shape factor is specified as 4π (area/perimeter).

X-ray Powder Diffraction

This is an important technique for establishing batch-to-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. X-ray diffractometer is operated at 40kV, 30mA, and a scanning speed of 0.06°/min over the range of 5-40 2θ using Cu kα1 radiation of wavelength of 1.540A°.

Parameters determining the spherical crystals behavior:

Particle size, Particle shape & Size distribution:

Change of crystal habit of pharmaceuticals gives different physicochemical properties. Size & crystal habit of pharmaceuticals changes on recrystallization in spherical crystallization.

Using advance technology, Size & volume of particles can be determined by image analyzer

Size of particles & their distributions can be determined by simple sieve analysis.

Particle size analysis can be determined by Ro-Tap sieve shaker.

Density:

Density of spherical crystals is mass per unit volume. Different type of densities such as true density, granular density, apparent bulk density, tapped density can be evaluated.

True density = M / Vt.

Granular density = M / Vg.

Bulk density = M / V b.

Tap density = weight of sample in gm/tapped volume of sample in ml.

When compared to original drug crystals the size of agglomerates is more. Therefore, with increase of agglomerates, density of drug substances decreases.

Amorphous form:

It is developed by addition of polymers during recrystallization which have enhanced solubility compared to crystalline form.

Flowability:

1. Angle of repose: It is determined by following equation

Tan ɵ = h/0.5 d

Where h-height of pile

d-Diameter of pile

Value

≤ 30→free flowing materials

≥ 40→poor flowing materials

2. 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

$$I = (1-V/V_0)* 100$$

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

The value below 15% indicates good flow characteristics and value above 25% indicate poor flow ability

3. Hausner's ratio: Calculated from bulk & tapped densities.

HR = Tapped density/Bulk density

Value < 1.25-good flow (20% Carr's index).

> 1.25-poor flow (33% Carr's index).

Between 1.25-1.5 –to improve the flow glidant must be added.

Porosity:

Porosity affects the compressibility in granules. Porosity is of two types intra granular & intergranular. These are measured with the help of true & granular densities.

Intergrannular Porosity = 1 - granular density/ true density

Intergrannular Porosity= 1 - bulk density/ granular density

Total Porosity= 1 - bulk density/ tapped density

Packability:

Shear cohesive stress, shear indexes & angle of friction are lower than that of single crystals which can be improve packability of agglomerates. Simple packability was assessed by tapping process with kawakita & kuno methods & using parameters a, b & k in equations.

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

$C=(V_0-Vn)/ Vo$, $a=(V_0-V\infty)/ Vo$.

$\varrho f - \varrho n = (\varrho f - \varrho o). exp. (-kn)$

N =Number of tapping.

C =Difference in volume (degree of volume reduction.)

at and b = constant for packability and Flowability

Vo = Initial volume.

Vn = Final volume after n the tapping.

$V\infty$ = Powder bed volume at equilibrium.

ϱf, ϱn, ϱo = Apparent densities at equilibrium, nth tapped and initial state respectively.

Wettability:

Density was determined by using relative density bottle. Surface tension was determined by employing stalagmometer. Wettability can be determined by following formula.

$B=\varrho g/2\gamma$

γ = surface tension of saturated solution of formulation in water; dyne/cm;

ϱ = density of saturated solution of formulation in water, gm/cm 3,

ε = porosity of tablet, h = height of liquid drop in cm.

Moisture uptake study:

The moisture uptake is determined by taking the weighed quantity of drug & spherical crystals & placing them in crucible at accelerated conditions of temperature & humidity i.e., 40±10⁰ C & 75±3% respectively. The weight gain of drug & spherical crystals is measured.

Mechanical strength:

1. 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.

2. 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). At the rate of 10 gm/sec, mercury is introduced from reservoir into the upper chamber 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.

Compression Behavior Analysis:

Good compatibility and compressibility are the fundamental properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting a graph by taking the relative volume against the compression pressure. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. The surface are freshly prepared by fracture during compression of agglomerates, which intensifies the plastic inter particle bonding, resulting in a lower compression force obligatory for compressing the agglomerates under plastic deformation compared to that of single crystals. Compaction behavior of agglomerated crystals were evaluated by using following parameters

1. Heckel Analysis: The following Heckel's equation used to analyze the compression process of agglomerated crystals and estimated their compatibility.

$In [1/(1-D)]=KP+A$

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 is the mean yield pressure (Py).

The following equation gives the intercept obtained by extrapolating the straight portion of the plots [22].

A=1n [1/ (1-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.

DA=1-e-A

DB=DA-D0

Stress Relaxation Test: Impose specific quantity of spherical agglomerated crystals sample in a die of specific diameter, magnesium stearate was coated on the surface of die in advance, then used the universal tensile compression tester to compress the samples at a constant speed. After the certain limit of pressure attained, the upper punch held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch. The result corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions.

The relationship between relaxation ratio Y (t) and time t, calculated the parameters As and Bs, and assessed relaxation behavior is

t / Y (t) =1/AsBs-t/As

Y (t) = (P0-Pt)/P0

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

Particle Shape / Surface Topography

Following methods are used

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.

Electron Scanning Microscopy

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

X-ray Powder Diffraction

This is an important technique for estin reaction mixture effect the agglomerates strength.

Advancement in Spherical Crystallization Process

Use of polymers and surfactants

The presence of additives like polymeric material and surface active agents, whose surfaces are not similar to the crystal surfaces, can influence molecular aggregation during crystallization.

The viscosity of the medium and surface tension is reduced by the surfactants which affect the nucleation process. Spherical agglomeration in the presence of these additives may reduce the processing time,improves the bioavailability of drug, and improves the micrometric properties of drug. Use of polyvinyl pyrrrolidine in preparing spherical crystals of Celecoxib, improved micromeritic properties, as well as improved solubility and dissolution rate. However, in vivo studies are required to confirm these results. Studies revealed that crystallization and agglomeration of pure drugs (without recipients)shows poor compressibility and handling qualities. Addition of polymers such as HPMC, PEG, EG, AND PVP has shown the improved properties.

Crystal-co-agglomeration (CCA) technique

Spherical crystallization has been restricted to size enlargement of single large dose drugs. Crystal-co-agglomeration technique is one of the novel particles designing technique developed by Adam et al, to overcome the limitations of spherical crystallization. It is a single step process enlarging the size of single, two or more drugs, may be of small does or large doses and in combination or without combination of diluents. CCA has been applied for spherical agglomeration of - By using talc, placebo beads have been prepared by Limzerwala. Broom hexane hydrochloride-talc: Gadekar and Judah have developed the process for size enlargement of low dose bromhexine hydrochloride (BXH) using talc as a diluents. Ibuprofen-talc: use of talc has been made by Paxar in the agglomeration of ibuprofen, a high a blishing batch-to-batch reproduci-

bility 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.[9]

Physicochemical characterization of Agglomerates:

Thin layer chromatography:

TLC study was carried out in mentioned mobile phase and the Fro value was determined and compared the Fro value of drug with the spherical crystals. This study was carried out to check the interaction between the drug and the polymer and also to confirm the stability of drug in solvents.

Fourier Transform Infrared spectrometer:

It was done for identification of the drug present and also to identify whether the drug has undergone polymorphism. It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the salvation

Differential scanning calorimeter:

DSC measures the heat loss or gain resulting due to physical or chemical changes within a sample could be obtained from thermograms using instrumental software. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC. It is also useful to determine thermal degradation, purity, polymorphism, salvation, Dehydration, Dissociation, Decomposition, and Phase transfer, Glass transition, Heat capacity and drug-recipients compatibility. Crystal of samples age heated (25-200°C) at the rate of 10°C/min in crimped hermetically sealed aluminum pans under nitrogen atmosphere. Calorimeter was calibrated using Indium & lead standards. [11]

Summery and Conclusion:

The spherical crystallization technique is a simple and inexpensive for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel because it eliminates most of the steps which are required in granulation technology of tablet manufacturing. It gives important advances in tableting technology, especially the introduction of number of directly compressible recipients. The spherically agglomerated crystals can be prepared into tablet form or compounded directly into a pharmaceutical system without further processing such as granulation.

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