SPHERICAL AGGLOMERATION A NOVEL FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT: A CRITICAL REVIEW

[1]Harsha V Sonaye ,[2]Mohmad Rafik Shaikh ,[3] Kiran Sing
[1] *Assistant Professor,[2]Project Officer at KEMHRC, Pune,[3]Student
[1] Department of Pharmaceutics, [1]Taywade College of Pharmacy , Koradi, Nagpur , India

Abstract : Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties and physicochemical properties can also be modified .As this technique forms the spherically agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage form. Therefore it is necessary to evaluate and characterized these spherically agglomerated crystals by using the different parameters so as to differentiate it from the raw crystals.

Keywords: Spherical crystallization, flowability, compactability, physicochemical properties.

I. INTRODUCTION

Agglomeration: Particle size enlargement

Agglomeration is a phenomenon in particles technology which includes smaller crystals adheres to form bigger particles. Poor physical and mechanical properties of drug particles have been traditionally covered by various granulation methods. Enlargement of particle size is an important procedure during manufacturing of tablets. There are different techniques for enlargement of particle size such as wet granulation, dry granulation, extrusion spheronization and spherical crystallization methods. These techniques have important role in modifying primary and secondary properties of pharmaceutical substances. Spherical agglomeration is one such technique to improve micromeritic properties and dissolution of drug. Kawashima and Capes (during the 1970 decade) suggested enlargement of particles size during the crystallization process. According to their report, controlling the crystal's agglomeration leads to spherical agglomerates with accorded properties. [1]

In 1986, Kawashima et al used the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Spherical crystallization was defined by Kawashima as "An agglomeration process that transforms crystals directly in to a compact spherical forms during the crystallization process." It also enables co precipitation of drug and encapsulating polymer in the form of spherical particle. [2]

Agglomeration is a size enlargement process used in the chemical process industries to impart better functionality to a product, thus avoiding common processing problems, and providing the consumer with a better product experience. Agglomeration is an important process used in many industries to improve the characteristics of a material; giving benefits to the end user in the form of improved quality and function of the final product. [3]

An agglomeration process that transform crystalline drug directly into compacted spherical form for improving the flowability, solubility and compatibility. It is non- conventional particle size enlargement techniques that involve crystallization and agglomeration using a bridging liquid. This technique enables crystalline form of a drug to be converted into different polymorphic form having better bioavailability. It also improves the dissolution behaviour of drug with low water solubility. Physicochemical properties (flowability, solubility, dissolution rate, bioavailability and stability) and micromeritic properties (bulk density, flow properties and compatibility) are modified during the crystallization process. [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 and poorly soluble drugs. [5]

Spherical agglomeration is a novel method of particle engineering that can directly shift the fine crystals produced in the crystallization into a spherical shape. It is a versatile procedure that enables to control the type and the size of crystals. It also enables co precipitation of the drug and the encapsulating polymer in the form of spherical particle. Quasi-emulsion solvent diffusion system (QESDS) is most commonly used. Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvent i.e. good solvent bridging liquid-poor solvent. [6]

In present time, one of the particle design technique such as spherical crystallization is widely used in pharmaceutical industries to modify primary properties of powder like particle size, particle shape, crystal form, crystal habit, density, porosity etc. In such modification in the crystal habit certain "Micromeritic properties" like bulk density, flow properties, compatibility, 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 the pharmaceutical dosage form. Solubility in the 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 fluid and its potential contribution to bioavailability issue. [7]

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. [5]

Poor physical and mechanical properties of drug particles have been masked by various wet granulation method, such as high-shear and fluid bed granulation, which generally involves mixing, atomization, and spraying of granulation liquid on powders, drying steps, sieving, and so on. Both agglomeration methods are an energy-consuming process. Other agglomeration technique 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 solution for improving the physical and mechanical properties of drug particles; however, they are still less economical than direct compression tabletting. Spherical agglomeration is the most commonly used method and involve the use of polymer and bridging liquid to simultaneously crystallize and agglomerates. Spherical agglomeration technique improves flow properties and compression characteristics of the drug which can be directly compressed into tablet. A number of drugs such as salicylic acid, naproxen, celecoxib, ibuprofen, mefenamic acid and nabumetone are reported in literature that has been processed using spherical agglomeration technique. [8]

Purpose:

- Improve flow properties
- Improve dispersion/dissolution properties
- Ensure composition uniformity (segregation)
- Reduce dustiness
- Improve visual appeal
- Dosage uniformity

MECHANISM:

- "Dry" agglomeration (compaction)
- "Wet" agglomeration

PHENOMENON:

- Rearrangement
- Elastic deformation
- Plastic deformation and viscous flow
- Brittle failure
- Elastic recovery

Table 1: Agglomerate equipment designs and usual application [3]

Method	Typical application
Tumbling granulation -Drums -Discs	Fertilizers, iron ore, non-ferrous ore, agricultural chemicals
Mixer and planetary granulators -Continuous high shear -Batch high shear	Chemicals, detergents, clays, carbon black, pharmaceuticals, ceramics
Fluidized granulators -Fluidized beds -Spouted beds	Continuous: fertilizers, inorganic salts, detergents, Batch;pharmaceuticals, agricultural chemicals, nuclear waste
Centrifugal granulators	Pharmaceuticals, agricultural chemicals

As can be seen from Table 1 there is a significant number of granulation processes that involve 'wet' granulation (i.e. granulation with the use of a liquid binder) as opposed to more traditional 'dry' granulation techniques which use the duct ability of a solid in order to produce agglomerates from the process. [3]

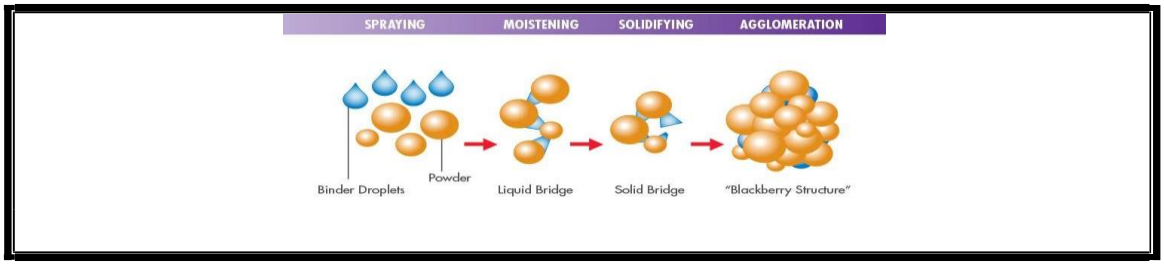


Figure 1: The Process of Agglomeration

Fundamental agglomeration principles:

a) Tumble agglomeration (growth or agitation agglomeration) pelletizing
b) Press agglomeration (compaction)
- Continuous sheet
- Solid forms (tablets, briquettes)

c) Sintering (thermal process) [10]

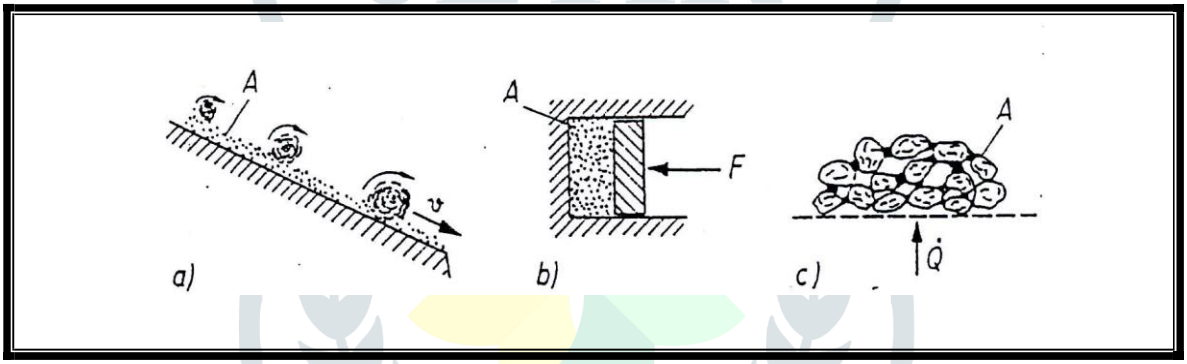


Figure 2: A – feed material (for agglomeration), heat flow-Q

Using CCA with proper selection of excipients/polymers, drug release can also be modified from drug loaded agglomerates or compacts of agglomerates. CCA technique involves simultaneous crystallization and agglomeration of drug particles with or without excipients from good solvent and bridging liquid by addition of a poor solvent. Sometimes, good solvent also serves as bridging liquid. Presence of suitable excipient greatly affects the properties of agglomerates. Utilization of CCA in designing spherical agglomerates having excellent micromeritic and compression properties with satisfactory mechanical strength has been revealed in various studies. The technique has been successfully utilized for improving process ability via enhancement in flow, compaction and packing properties. So far the technique has been applied for preparation of directly compressible sustained release agglomerates by few scientists it is further required to study successful utilization of technique for the same. [11]

The low aqueous solubility of drug molecule may potentially lead to slow dissolution in biological fluid, insufficient and in consistent systemic exposure and consequently less optimal efficacy in patients, particularly when delivered via oral route of administration. It is accepted that drug substance 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.[7]

Bioavailability of drug depends on its solubility and permeability in a given medium. At present, about 40% of drugs in the development phase and approximately 70% of drugs coming from synthesis or high through put screening are poorly water soluble, and also lots of drugs are not soluble in organic solvents1. Limited aqueous solubility of drugs is becoming increasingly prevalent in the drug product development scenario. According to the Biopharmaceutical Classification System (BCS) aqueous solubility and permeability are the most significant parameters affecting drug bioavailability. [6]

Spherical Agglomeration

Spherical Agglomeration- Direct Tabletting Method

Spherical crystallization can be defined as "a novel agglomeration technique that can transform 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. [7]

It is the versatile process that enables to control the type and the size of crystals. [2] In an enhanced spherical crystallization technique so-called crystallo-co-agglomeration, the active substance is crystallized and agglomerated with either excipient or another drug, which may or not be crystallized in same systems. In general, in this technique, a particulate substance dispersed in water can be aggregated by immiscible liquids which wet the particles and form bridges between them as well as, in the course of mixing, gather the particles. Under favourable conditions spherical agglomerates can be formed. If the active substance is firstly dissolved in a good solvent, and then poured into a poor solvent in which the crystallization occurs, and then agglomeration of particles is caused by various mechanisms, this technique belongs to crystallization processes. Spherical crystallization has many applications in the pharmaceutical industry such as improving flowability and compressibility of poorly compressible active substances, masking bitter taste of drugs and bettering solubility and disintegration of poorly soluble drugs. [12]

Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. [13]

Crystallization is important phenomenon which is used for both separation and purification in pharmaceutical industries. This process leads to the crystal formation which has chemical stability and convenience in transportation, packing and storage. Most of active pharmaceutical ingredients have different sizes. Active pharmaceutical ingredient particles with less than 10 μm size have the advantage of increased dissolution rate and better bioavailability. [1]

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 exhibit poor bioavailability. Therefore improve water solubility or dissolution of these types of drug molecules in great challenge for scientist to formulate or to design a delivery system which provides required oral bioavailability. [7]

This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties (bulk density, flow property, compactability) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified. It is also possible to prepared novel particulate drug delivery system like microsponges, microspheres and nanospheres, microballons, nanoparticles and micro pellets by using these techniques. This technique may enable crystalline form of a drug to be converted into different polymorphic form and thus attain better bioavailability and improving the dissolution behaviour of some drugs that are characterized by low water solubility and a slow dissolution profile. [2] Spherical agglomeration belongs to a group of spherical crystallization processes and has been successfully applied in the pharmaceutical industry in the drugs preparation. A quasi emulsion solvent diffusion method (QESD) is one more modification of spherical crystallization, in which the drug dissolved in a good solvent and dispersed in a poor one producing quasi-emulsion. Then, the good solvent step by step diffuses out of the emulsion droplets into the surrounding phase, and the poor solvent diffuses into the droplets. As a result, the drug crystallizes inside the droplets. In another technique called ammonia diffusion method (AD), the mixture of three partially immiscible solvent can be used as a crystallization system. In this system the ammonia solution acts as a bridging liquid as well as the good solvent. The drug precipitated by the solvent changes without forming ammonium salt. The water immiscible solvent promotes liberation of liquid ammonia. [12]

BENEFITS OF SPHERICAL CRYSTALLIZATION TECHNIQUE:

1) A spherical shape of the final product formed drastically improves the micromeritics property of the drug crystals.
2) Improvement in wettability and dissolution rate of some drug were found by utilization of this process
3)ThistemplatThis technique could enable subsequent process such as separation, filtration, drying etc to be carried out more efficiently.
4) Furthermore the resultant agglomerated crystals could be easily compounded with other pharmaceuticals powders due to spherical shape.[15]

SPHERICAL AGGLOMERATES ARE PREPARED TO:

- Improve the flowability and compressibility.
- Mask the bitter taste of drugs.
- Increase the solubility and dissolution of poorly soluble drugs.

Spherical crystallization is preferred mainly due to less no. of steps involved and the following other reasons:

- Less equipment and space
- Lower labour costs
- Less processing time
- Lower energy consumption[4]

PRINCIPLE OF SPHERICAL CRYSTALLIZATION:

The saturated solution of the drug in a good solvent is poured into a poor solvent. A third solvent known the bridging liquid is added in small amounts to wet the crystal surface and promote the formation of liquid bridges between the drug crystals for forming spherical agglomerates [14]. In this process the poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between drug and the good solvent. Furthermore, the bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. [1]

This process involves pouring the saturated solution of the drug in good solvent (first solvent) into poor solvent (second solvent).Third solvent called the bridging liquid is added in small amounts to promote the formation of agglomerates. Bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals for forming spherical agglomerates. Poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between drug and the good solvent. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. [4]

NEED OF SPHERICAL CRYSTALLIZATION TECHNIQUE:

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. [7]

ADVANTAGES OF THE SPHERICAL CRYSTALLIZATION:

- The micromeritic properties of the drug crystals shall be drastically improved by inducing spherical shape to th crystals.
- Utilization of this process improves wettability and dissolution rate of some drugs.
- 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.
- This technique could be used for masking of the bitter taste of drugs. (ATH & enoxacin)[5]
- 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.
- Pharmaceutical process improved i.e. milling, mixing, and tabletting by using third technique.
- Agglomerated crystals can be easily compounded with other pharmaceutical powder due to its spherical shape.
- It avoid granulation step.[7]
- Preparation of microsponges, microspheres and nanospheres, microballoons, nanoparticles and micro pellets as novel particulate drug delivery system is possible by it
- Use of this technique leads to conversion of crystalline forms of a drug into polymorphic form that may have better bioavailability.[1]
- It improves flow property and compression characteristics of the drug which can be directly compressed into tablet.
- The bioavailability of hydrophobic drug is improved by this technique; the crystalline form of the drug is converted into different polymorphic form having higher solubilities and hence resulted in better bioavailability.
- Due to the spherical shape of the agglomerated crystals they are easily compounded with the pharmaceutical powders.

DISADVANTAGES OF SPHERICAL CRYSTALLIZATION:

- Selection of suitable solvents is a tedious process.
- Optimization of processing parameters (temperature, agitation) is difficult. [1]
- This process requires careful selection of suitable solvent for processing.
- Processing parameters like (temp, agitation, speed, amount, and mode of bridging liquid) are required to be optimized. [14]

APPLICATION

- By this technique solubility, dissolution and hence bioavailability of poorly soluble drug can be enhanced.
- Flowability and compressibility of drug can be improved by this technique.
- Taste masking of bitter drugs.
- Used in preparation of other novel drug delivery system like microparticle, microsponges, microballons, micropellets etc.
- Used for the preparation of control drug delivery dosage form.

FACTORS INFLUENCING THE PROCESS OF SPHERICAL CRYSTALLIZATION:

The technique of spherical crystallization depends upon the several factors which contribute to the physico-chemical characteristics of the drug. During the crystallization the parameters like stirring rate, temperature, pH, selection of solvent

system, addition rate of bridging liquid etc. need to be optimized to get maximum amount of spherical crystals. How to optimize the processing parameters and how these parameters affect on ideal spherical crystals is discussed as follows.

- Selection of Good, Poor Solvent and Bridging Liquid
- Addition Mode of Bridging Liquid
- Interfacial tension
- Mode and Intensity of Agitation
- Temperature
- pH
- Residence Time
- Concentration of Polymers (or) Stabilizers
- Particle Size and Shape (Crystal habit)
- Density

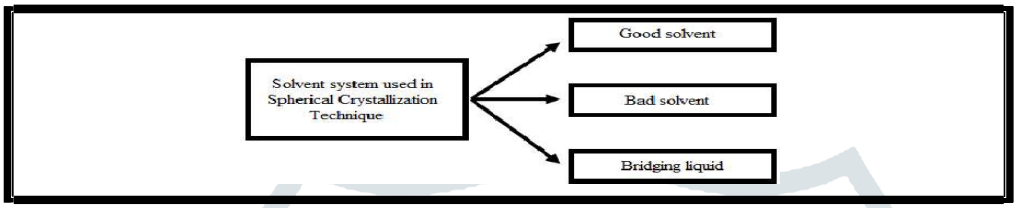


Figure 3: Solvent used in spherical crystallization

SOLVENT USED IN SPHERICAL CRYSTALLIZATIONTECHNIQUE:

In Spherical Crystallization Technique mainly three types of solvent are involve as per follow:

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 BADSOLVENT

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. [7]

TABLE NO. 2: SOME OF THE EXAMPLES ENLISTING DIFFERENT TECHNIQUES AND SOLVENTS USED IN PREPARING SPHERICAL AGGLOMERATION OFDRUGS.[1]

DRUG	SOLVENTSYSTEM			TECHNIQUE
	Good solvent	Bad solvent	Bridging liquid	
Antibiotic				
Enoxacin	Ammonia-water	Acetone	Ammonia-water	ADS
Norfloxacin	Ammonia-water	Acetone	Ammonia-water	ADS
NSAIDS				
Aspirin	Acid buffer	Methanol	Chloroform	SA
Aceclofenac	Acetone	water	Dichloromethane	SA

SA= Spherical Agglomeration, ADS= Ammonia Diffusion System

STEPS INVOLVED INTHE 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 the particles by forming a lens bridge between them [Fig No 1 (a)]. In this zone, loose open flocks of particles are formed by pendular bridges. 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.

Zero Growth Zone:

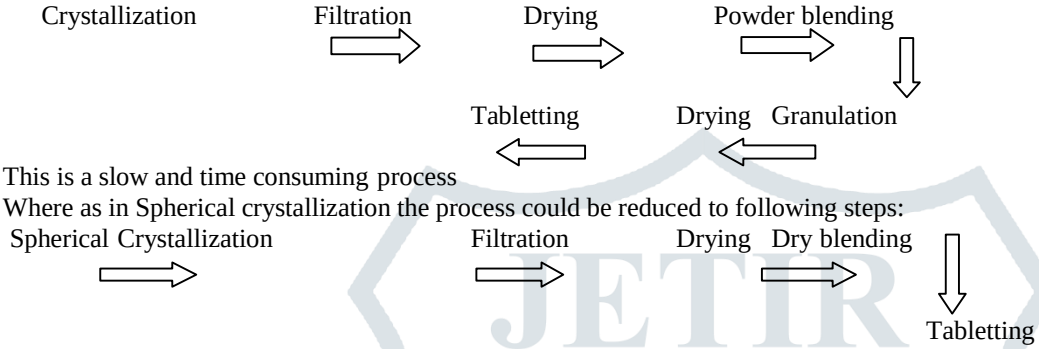
Loose floccules get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocks causing poor space in the pellet of completely filled with the bridging liquid [Fig No 1 (b)].
The driving force 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 [Fig No 1 (c)].

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 [Fig No 1 (d)]. The size reduction may be due to attrition, breakage and shatter.[1]



This is a slow and time consuming process
Where as in Spherical crystallization the process could be reduced to following steps:

Figure 5: Traditionally drug manufacturing procedure involves 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 tabletting manufacturing process step and agglomerated crystal showing significant effect on the formulation and manufacturing of pharmaceutical dosage form.[7]

METHODS OF SPHERICAL CRYSTALLIZATION:

1. Conventional method
2. Solvent change method
3. Quasi emulsion solvent diffusion method
4. Ammonia diffusion method
5. Salting out method

CONVENTION METHOD:

In these methods spherical agglomerates are produced by controlling the physical and chemical characteristics of drug particles. This method is so called non-typical spherical crystallization. These are:

- Addition of non-solvent resulting in salting out of drug.
- Controlled crystallization method like change in temperature and pH change
- Crystallization of drug under melting

SPHERICAL AGGLOMERATION:

This method is also called solvent change method. Three type of solvent are implicated in this system: good solvent in which drug is soluble; a poor solvent in which drug is not soluble but good solvent should be immiscible with poor solvent and third solvent is a bridging liquid which is added in small amount after the formation of crystal to agglomerate them. The bridging liquid is added under continuous agitation.
Steps involved in the formation of spherical agglomerates are shown below:

1. Selection of solvent and drug.
2. Formation of saturated solution and good solvent.
3. Pour the solution into poor solution under controlled condition of temperature and speed. Fine crystals are formed.
4. Bridging liquid is added in small amount to promote the formation of agglomerates. Bridging liquid is added under continuous agitation, it act as wetting agent for the fine crystals. Bridging liquid should not be miscible with the poor solvent. Due to the interfacial tension and negative capillary forces and by the action of bridging liquid the crystals adhere to each other to form the spherical agglomerates.
5. Enlarged spherical agglomerates are formed. [14]

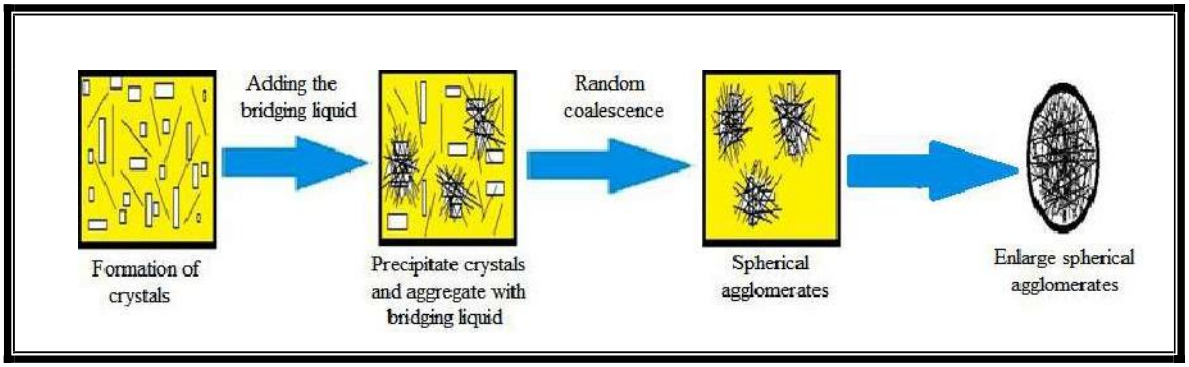


Figure 6: Schematic representation of spherical agglomeration process [7]

QUASI EMULSION SOLVENT DIFFUSION METHOD:

The affinity between good solvent and drug is more than the affinity of drug with poor solvent [35]. The drug is dissolved in good solvent and then dispersed in poor solvent, (quasi) emulsion droplets are produced, even though the pure solvent is missicible. Good solvent diffuse out gradually out of the emulsion droplets due to the interfacial tension between the two solvent into the poor solvent and the poor solvent diffuses into the droplet by which drug crystallize inside the droplet. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. The residual good solvent present in the droplet act as a bridging liquid to agglomerate the generated crystals. In this process the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization. [14]

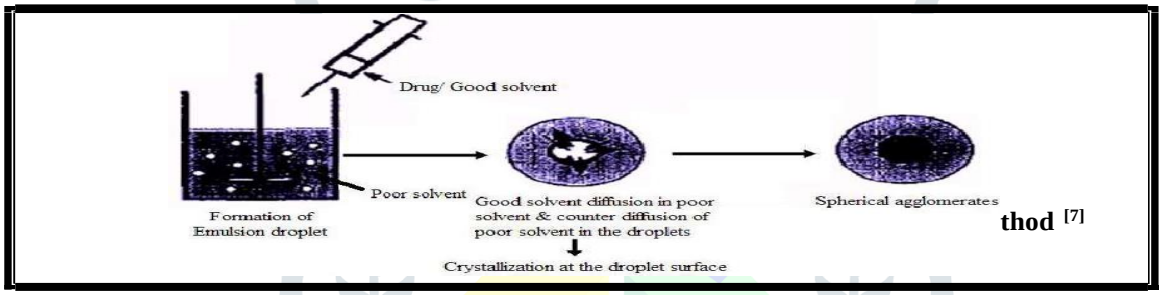


Figure 7 : Schematic representation of quasi emulsion Solvent diffusion method [7]

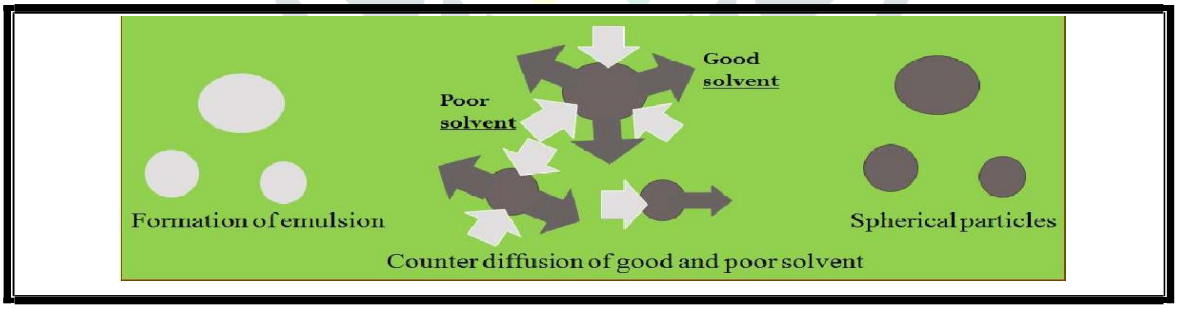


Figure 8: Steps involved in Quasi emulsion solvent diffusion method [7]

Ammonia diffusion method:

In this method three solvents are used i.e. acetone, ammonia water and dichloromethane. Ammonia water acts as a bridging liquid as well as good solvent. Drug is dissolved in ammonia water which acts as a good solvent; the solution is then added to the acetone. Acetone (a hydrocarbon derivative) is missicible with the system but it reduces the miscibility of ammonia with the poor solvent. The ammonia water exists as immiscible phase forming droplets. The counter diffusion process across the process involves movement of poor solvent into and ammonia out of the droplet. Agglomeration take place inside the droplet as the drug precipitate slowly in ammonia water and causes growth of crystals .Dichloromethane is added slowly which induce liberation of ammonia. Spherical agglomerates are formed. This technique is mainly applicable for amphoteric drugs. [14]

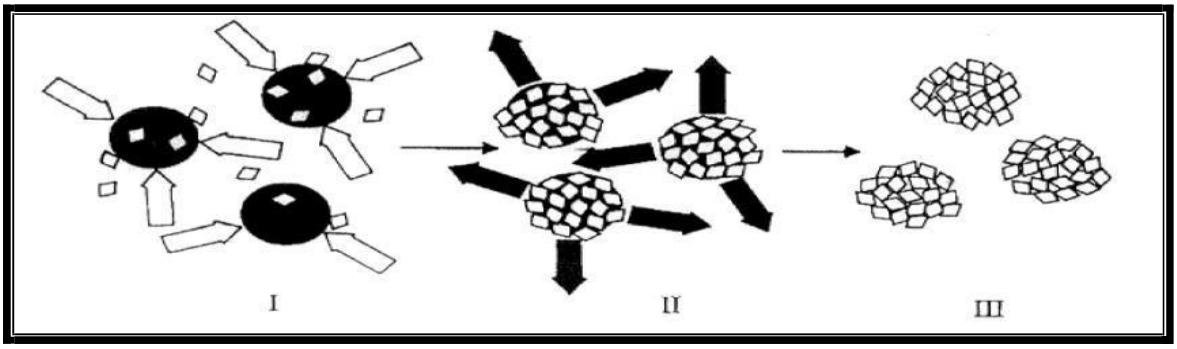


Figure 9: Steps involved in ammonia diffusion method [7]

Steps involved in Ammonia Diffusion Method: [4]

Drug + ammonia water

↓

Added Acetone

↓ Dichloromethane added dropwise

Spherical agglomerates

NEUTRALIZATION

In this method a neutral solution is added in the drug and good solvent solution neutralize the good solvent. Drug is first dissolved in good solvent and placed it in cylindrical vessel with constant stirring. With continuous agitation an aq. polymer solution and one neutral solution is added which neutralize the good solvent, the drug crystallize out. Bridging liquid is added dropwise at a definite rate, the crystals of the drug start to agglomerate and form spherical crystals. [14]

Steps involved in Neutralization technique

Drug + goodsolvent

↓ Added in Neutralizing solution

Crystallization

↓ Adding bridging liquid Dropwise

Spherical agglomerates

CRYSTAL CO-AGGLOMERATION TECHNIQUE:

Spherical crystallization technique is restricted to only water insoluble large dose drug because excipients like disintegrating agent and diluents are hydrophilic in nature hence addition of these excipients in the agglomerates with the help of organic bridging liquid is difficult. To overcome the limitation of spherical crystallization developed a novel technique known as crystallo-co-agglomeration. It is a modification of spherical crystallization technique and used for size enlargement of all low dose, high dose, poorly compressible drugs and combination of drug with or without diluents. In this technique spherical agglomerates are generated in a single step and recently it is utilized to improve micromeritic, mechanical and compression properties in design of multiple unit particulate drug delivery systems. In this technique drug is directly crystallize and agglomerated in combination with an excipient or with another drug with the help of bridging liquid. [14]

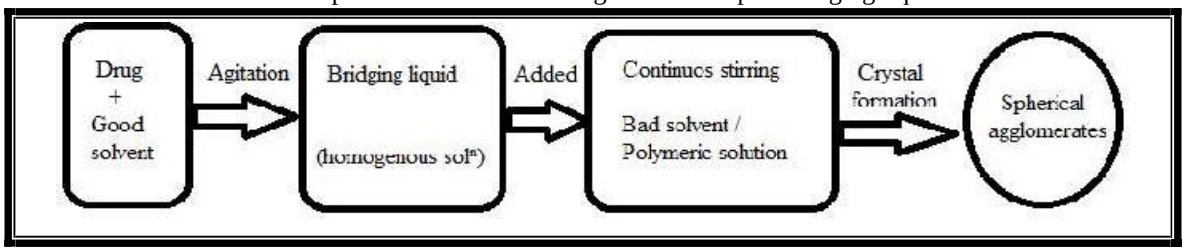


Figure 10: Steps involved in Crystallo-co-agglomeration technique.

EVALUATION PARAMETER OF SPHERICAL AGGLOMERATES:

Drug content and percentage yield:

The drug content is defined as the ratio of experimentally measured drug content value to the theoretical measured value, which 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 following Equation. The averages of three determinations will be considered as mean value for both parameters.

%Yield = Total weight of agglomerates / Total weight of excipients*100

Particle size measurement:

The size of pure drug particles and prepare agglomerates will be measure by optical microscope, sieve analysis method or by master size. 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.

Flow characteristics:

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 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 pile of powder and horizontal plan. The angles of repose for the powder of each formulation will be determined by the funnel method. The powder will be made to allowed 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 are continued until the pile touch 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.

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

Where, θ = 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.

Bulk density (g/ml) = weight of powder in gm/ 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 tapped from height of 2 inches until a constant volume get obtained. Volumes occupied by the powder after tapping will be recorded and tapped density are calculated as following equation.

Tapped density (g/mol) = weight of powder in gm / 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 inters particulate interactions. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Tapped density and bulk density will measure and the Hausner's ratio will be calculated using the following equation.

Hausner's ratio = tapped density / 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.

Carr's index = tapped density-bulk density / tapped density*100

Porosity:

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.

Porosity = bulk volume – tapped volume / bulk volume*100

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. [7]

Wettability:

Wettability of the crystals is determined by accessing the contact angle. Wettability depends on 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 crystals with high crystallinity.

Moisture uptake study:

The study indicates the behaviour 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+10C and 75% + 3% respectively. The gain in weight of drug and spherical crystals were measured. [14]

.

CONCLUSION:

The technique of spherical crystallization is simple and inexpensive, can be successfully applied to modify the micromeritic and physico-chemical properties of the drug. The spherical crystallization can also be applied for manufacturing spherical crystals of poorly soluble drugs in order to improve wettability, solubility there by bioavailability and dissolution rate with or without using polymers. Method used for preparation of spherical crystals is needed to be optimized for various processing parameters to get ideal spherical agglomerates. On the whole, spherical crystallization technique seems to be promising technique in which the drug crystals are changed by applying different solvents for obtaining direct compressible spherical agglomerates

REFERENCES:

1. S. K. Putta and P. Srikumar J. 2016, Spherical crystallization and its process optimization. Journal of Chemical and Pharmaceutical Research , Res. 8(7):611-623.
2. Paridar R G,2010,Evaluation parameters for Spherical Agglomeration formed by Spherical Crystallization Technique.Int J Pharma Bio Sci. 1(3)
3. R. P. J. Sochon and A.D. Salman, Particle growth and agglomeration process. Chemical Engineering and chemical process technology- Vol. II
4. Janika Garg, Sadhna Khatry, Sandeep Arora,. 2012, Spherical Agglomeration: An overview, IJPT Vol. 4, Issue No.1,1909-1928..
5. Patil Pradnya B et al. 2011,. Spherical Agglomeration- Direct Tabletting Technique. IRJP 2 (11), 30-35.
6. Rashmi Bhosale et al. 2017,Acyclovir spherical agglomerates for enhancement of solubility and dissolution rate. Int. Res. J. Pharm.
7. Suryabali K. Yadav, Abhirajsinh J. Solanki, Jitendra J. Jaiswal.2016. Spherical Agglomeration: A Novel Particle Design Technique to Improve Micromeritic and Dissolution Properties. J Pharm Sci Bioscientific Res. 2016 6(4):499-508.
8. Parmar Shital S, Mishra Rakesh, Shirolkar S. V, 2016. Spherical Agglomeration A Novel Approaches for Solubility and Dissolution enhancement of Simvastin. Asian Journal of pharmaceutical and clinical
9. Reseacrch 9(6).
10. Prof. Dr. J. Tomas, chair of Mechanical Process Engineering.2013
11. Shah and Sorathia, 2017, Design and evaluation of sustained release spherical agglomerates of Fluvastatin sodium by crystallo-co-agglomeration. Journal of Applied Pharmaceutical Science 7 (09); 099-108.
12 Izabela Polowczyk, and Karolina Szczesniak. 2016, Spherical agglomeration of acetylsalicylic acid. Wroclaw, Poland. E3S Web of Conferences 8, 0101
13. Mudit Dixit, Dr. P. K. Kulkarni, Shahnawazanis and Ashwini G Kini, 2010, Preparation and characterization of Spherical Agglomerates of Ketoprofen by Neutralization Metho, Inter J of Pharm & life Sci,1(4).
14. Parul Saini, Anoop Kumar and Sharad Vishta, 2013, Spherical Agglomeration: A Novel Technique of Particulate Modification & Developing Niche Drug Delivery System. IJBR Vol.6 No.2
15. S Mahanty, J. Sruti, Ch. Niranjan Patra, M.E. Bhanoji Rao.2010, Particle Design of Drug by Spherical Crystallization Technique, International Journal of Pharmaceutical Science and nanotechnology. Vol 3 Issue 2..