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Review Article

SPHERICAL CRYSTALLIZATION: A TOOL TO IMPROVE SOLUBILITY OF DRUGS

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ABSTRACT

Spherical crystallization is a technique in which crystallization and agglomeration are carried out synchronously in one step to form compact spherical form. The most common methods used in spherical agglomeration are quasi emulsion solvent diffusion method, ammonia diffusion system, neutralization technique and co-agglomeration. It succeeded to improve dissolution property of poorly soluble drugs. This can change drug powder properties such as flowability, wettability, packability, compressibility. It has wider applications in improvement of poorly compressible drugs; it has wider application in improvement of compressability of poorly compressible drugs, masking bitter taste of drugs, improving dissolution property, bioavailability and solubility of drugs. Agglomeration crystals converted into tablet forms thus helping us by saving time and reducing cost.

Keywords: Bioavailability, Agglomeration, Quasi Emulsion, Flowability, Compressible.

1. INTRODUCTION

Solid dosage forms such as tablets and capsules are used due to special features like unit dosage form with great dose precision, least content variability, lower cost and easy administration by patient. Direct compression is a simple and economical technique and solutions for manufacture of tablets [1]. Direct compression of drugs needs good micrometric properties of drug particles, such as shape and size, flow ability and honest reproducible compressibility are of crucial importance for formulation of highly solid dosage forms. Poor solubility of drugs depends on particle size which is always an issue due to its impact on dissolution properties. Micronized drug particles have a large specific area and provide a way to improve the dissolution rate [2]. Especially, the flow ability of crystals is very poor so these crystals are difficult to handle. During manufacturing, the bioavailability of drug can be enhanced by increasing solubility of bulk drug powder. Different novel methods are developing to increase the bioavailability of drugs that naturally have poor aqueous solubility; it is a great challenge to solid dosage form formulators [3]. Mechanical micronization of sparkling (crystalline) drugs and adding of surfactants during the process of crystallization are commonly used techniques to improve the bioavailability of poorly soluble drugs. Crystallization and agglomeration can be carried out at the same time in single step by spherical crystallization which is a particle design technique. Adding of surfactant normally led to slight increase in aqueous solubility to overcome this tissue. Kawashima developed a spherical crystallization technique. He used spherical crystallization technique in 1986 for size development of drugs in field of pharmacy. He determined the spherical crystallization as "The process of agglomeration that change crystalline drugs straight into a compacted spherical form.

Spherical agglomerates are prepared to Increase the flowability, compressibility, bioavailability of drugs and to mask the bitter taste of drugs [4].

Spherical crystallization utilizes three solvents: good solvent (dissolution medium for drugs); bridging liquid (drugs having wetting property dissolved by this medium) and bad solvent (drug substance immiscible the solvent) [5]. Spherical crystallization can be achieved by several methods such as simple spherical crystallization, emulsion solvent diffusion, ammonia diffusion and neutralization. The process of spherical crystallization principle involved in flocculation zone, zero growth zone, fast growth zone, and constant size zone [6].

2. NEEDS FOR SPHERICAL CRYSTALLIZATION

Developing novel procedure to improve the bioavailability of drugs that naturally have poor water solubility is a great challenge to formulate solid dosage form. The bioavailability of poorly soluble drugs can be increased by using the techniques such as, mechanical micronization of crystalline process. The micronization process makes a difference in the flow and compressibility of crystalline powders and causes formulation issues. Addition of surfactant generally led to reduce significant improvement in aqueous solubility. To control this issue, Kawashima developed a spherical crystallization procedure that led to improve the direct compressibility and flow of number of microcrystalline drugs [7].

3. IMPORTANCE OF SPHERICAL CRYSTALLIZATION

3.1. Advantages

- Spherical crystal agglomerates are very useful for preparing the solid dosage forms (e.g: capsules, tablets, etc.).
- This method is also useful in preparation of microspheres, microbaloons, micropellets, microsponges, nanoparticles, nanospheres as novel particulate drug delivery system.
- Physicochemical properties of pharmaceutical crystals are mainly improved for pharmaceutical process *i.e.,* milling, mixing and tableting by using this technique.
- Usage of this process enhances the wettability and dissolution rate of some drugs.
- Crystalline forms of a drug converted into different polymer forms that may have better bioavailability by using this technique.
- The micrometric properties of the drug crystals shall be hugely enhance.
- The agglomerated crystals are in spherical shape so that they can easily compounded with pharmaceutical powders.
- The method is mostly used helps to increase the stability of the pharmaceutical ingredients.
- No dose dumpin.
- Stirring of drug and excipients in liquid medium ensure homogeneity of drug.
- This technique could be used for masking of the better taste of drugs [8].

3.2. Disadvantages

- Maintenance of processing parameters is difficult.
- Selection of the suitable solvents is tedious process [9].

4. PRINCIPLE OF SPHERICAL CRYSTALLIZATION

This activity implies flowing the saturated solution of the drug in good solvent (first solvent) into poor solvent (second solvent). Third solvent called the bridging liquid is put in slight amount to wet the crystal surface and assist the formation of agglomerates. In this procedure poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between the drug and good solvent [10]. Moreover, the bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals.

This theory was proposed by Bermer and Zuider Wag, there are four steps which are included in growth of agglomeration [11].

4.1. Flocculation zone

In this zone, the bridging liquid replace the liquid from the surface of the crystals and these crystals are brought nearly closeness by agitation, the adsorbed bridging liquid connects the particles by forming a lens bridge between them (Fig. 1(a)). In this zone, by pendular bridges, the loose open flocks of particles are formed. By both the surface tension of the liquid and liquid bridges, the mutual attraction between the particles is done. After reaching the capillary stage all the void space within the agglomerate is completely filled with the liquid.

4.2. Zero growth zone

Loose flocules get carried into tightly packed pellets, throughout the process entrapped fluid is compressed out by crushing of the bridging liquid on to the surface of flocks causing poor space in the pellet of completely filled with the bridging liquid (Fig. 1(b)). The driving force for the transformation is provided by the agitation of slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

4.3. Fast growth zone

With the fast growth zone of the agglomeration takes place when plent bridging liquid has compressed out of the surface on the small agglomerates. Then the formation of large particles followed randomly collision of well-formed nucleus is known coalescence. Collision

of successful when the nucleus has small excess surface moisture [12]. This pass on plasticity on the nucleus and increases particle deformation and subsequent coalescence (Fig. 1(c)).

4.4. Constant size zone

In this zone, agglomeration end to grow and even show small decrease in size. Here, the breaking frequency of agglomeration is balanced by the frequency of coalescence of (Fig. 1(d)). By the attrition, breakage and shatter size reduction may takes place.

4.5. Requirements

Typical spherical crystallization employs three solvents: First one is the drug dissolution medium i.e., good solvent; another is medium which partially dissolves the drug and have wetting property i.e., bridging liquid; and the last one is immiscible with the drug substances i.e., bad solvent. Polarity of solvents and its interactions with hydrophobic phases of the growing crystals has an influence on shape, surface irregularity and roundness of the crystal agglomerates. Commonly three types of solvents are used in spherical crystallization; good solvent, bridging solvent and poor solvent [13].

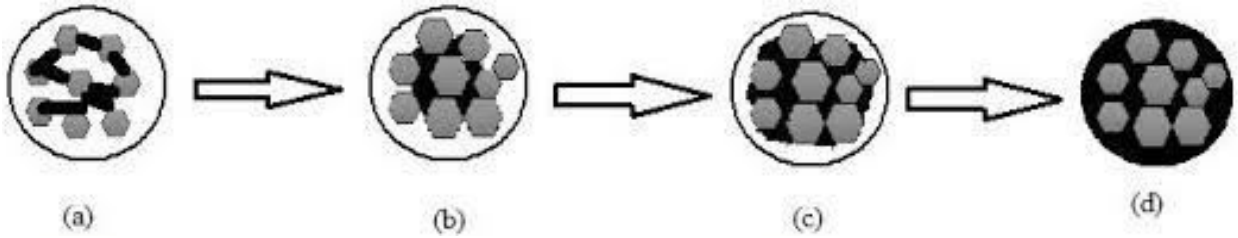
5. METHODS OF SPHERICAL CRYSTALLIZATION

5.1. Spherical agglomeration technique

This method involves at one and same time agglomeration and crystallization. Two or more than two drugs from compound in honest solvent, poured into bad solvent of controlled speed and temperature conditions. Third solvent is bridging liquid employed as antiparticle binder which promotes crystal agglomeration. Affinity of good and poor solvent should be stronger than interaction of drug with honest solvent [14]. Bridging liquid must not be soluble in bad solvent and only wet the crystal suspended in the system by liquid bridges between the two crystals, due to negative capillary pressure and inter facial physical phenomena.

Steps of the method include:

- Drug is dissolved in honest solvent
- Drug solution has to be poured in the poor solvent concurrently, crystallization of drug occurs.
- Bridging liquid which have good affinity towards drug and poor affinity towards bad solvent is added under controlled condition, as a result formation of bridges between particles occurs known as agglomerates.



(a) Flocculation Zone (b) Zero Growth Zone (c) Fast Growth Zone (d) Constant Size Zone

Fig. 1: Steps for Agglomeration Growth

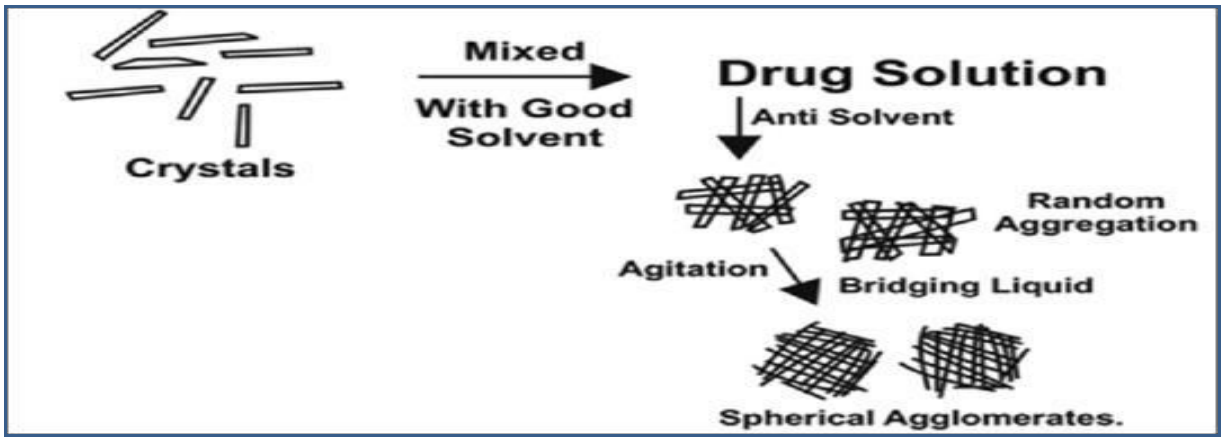


Fig. 2: Steps involved in spherical agglomeration

5.2. Quasi emulsion solvent diffusion method

Quasi emulsion solvent diffusion method was first introduced by Kawashion and co workers in 1989, where affinity of compound and honest solvent as stronger interaction of good solvent and bad solvent.

Steps of the method include:

- Compound (drug) is dissolved in honest solvent.
- The solution poured into the poor (or) bad solvent, due to which quasi emulsion droplets are formed.
- Formation of unstable emulsion
- Diffusion of honest solvent out of emulsion droplets into outer poor solvent.
- Poor solvent enters into the droplets due to which it affect solubility and cause crystallization of drug inside droplet.
- Residual of honest solvent inside the emulsion droplet act as bridging liquid, which result in agglomeration of crystals [15]. Reasons behind it include; inter-facial tension between solvent, a small difference of initial temperature between phases leads to mass transfer of solvent, increased rate of crystallization and rate of solvent transfer.

5.3. Ammonia diffusion method

In this method, partially immiscible solvents are used for system of crystallization. It is an alter method of spherical crystallization. Using suitable conventional procedures amphoteric substances are converted into agglomerates. In this method ammonia water acts as both, bridging liquid as well as honest solvent.

Other components of this method are hydrocarbons, poor solvent. Hydrocarbons are easily miscible with the system, but decrease miscibility of poor solvent with ammonia water. This segment or fraction of ammonia water exist as immiscible phases which form droplet. Synchronously, movement of poor solvent into and ammonia water out of droplet determines final size of agglomerates [16].

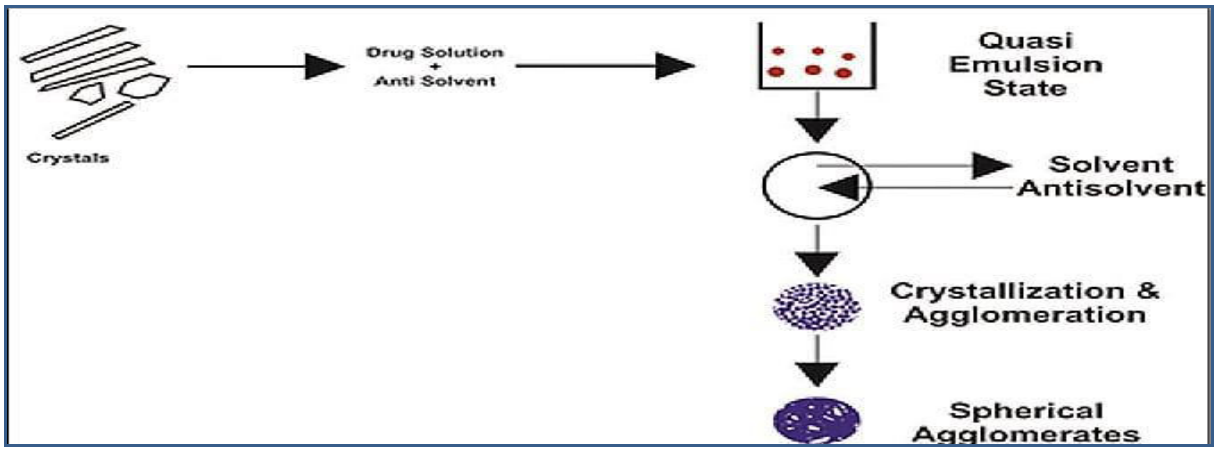


Fig. 3: Mechanism of quasi emulsion solvent diffusion method

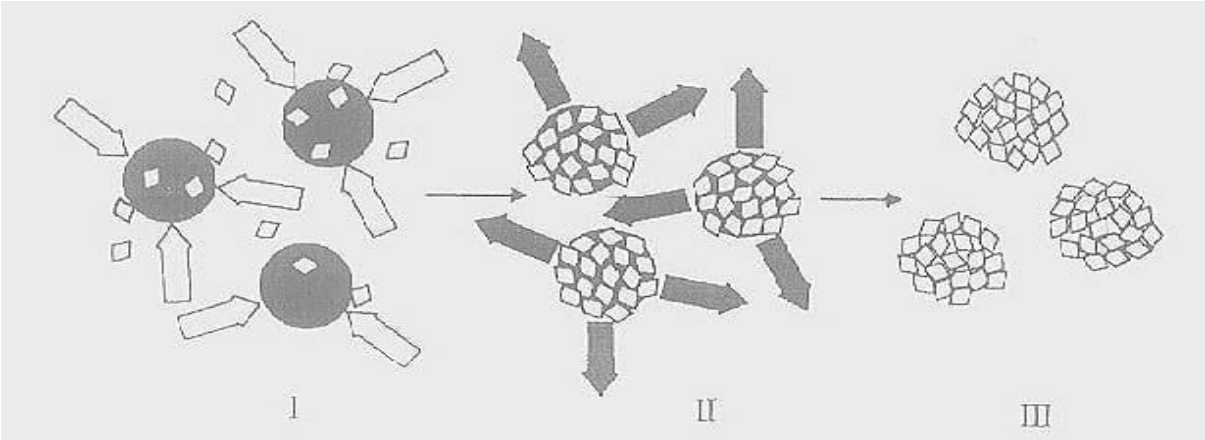


Fig. 4: Steps involved in ammonia diffusion method

5.4. Neutralization technique

This method includes 3 solutions; honest solvent, aqueous polymer solution and neutral solution. First step involves dissolving of drug in honest solvent, in which it is placed in the cylindrical vessel along with constant stirring. During this process of stirring, a polymer solution of aqueous phase is added and a neutral solution helps in neutralizing good solvent due to which crystallization of drug occurs. Lastly bridging liquid is added drop wise, crystals of drug converted into agglomerates [17].

5.5. Crystal co-agglomeration technique

It is also a process modification of spherical crystallization. During the process of spherical crystallization, agglomerates are obtained directly by compressible agglomerates without using dilutes. So, it is restricted for water insoluble drugs with large doses. However, dilutes and disintegration agent are hydrophilic in nature, hence difference in these properties of excipients formation of agglomerates using hydrophobic drugs are difficult [18]. To overcome this limitation, Kadam developed a method called crystal co-agglomeration. In this method drug is crystallized than agglomerated with another drug. Method is similar to spherical agglomerates; this process enables formation of agglomerates containing two drugs, poorly compressible drug or low dose drugs [19].

6. FACTORS AFFECTING THE PROCESS OF CRYSTALLIZATION

6.1. Agitation speed

To disperse the bridging liquid throughout the system, optimum speed agitation is necessary. Speed of agitation with circular motion find out the fluid flow in system. Any small change in fluid flow or agitation pattern would be reflected as change in force acting on agglomerate which finally influences the shape of agglomerate. As a result of this, it described that the size, sphericity, and strength of agglomerates are affected by the speed of agitation [20]. The spherical crystals at lower speed will give larger size where as at high speed will give smaller size of agglomerates. The speed mainly depends upon the rate of crystallization in the system some drugs need low speed for crystallization, whereas some required high speed. The time required for the achievement of agglomeration of procedure gets decreased with higher speed of agitation [21].

6.2. Temperature

Temperature has a significant effect on the shape, size and texture of the agglomerates. Compared to the smaller agglomerates, at higher temperature, larger agglomerates were produced initially and attain equilibrium rapidly [22]. At lower temperature, growth rate of crystals at initial stage was slow but becomes faster at later stage.

6.3. Addition mode of bridging liquid

The spherical nature of crystals is mainly affected by the rate of addition by bridging liquid in the system. By adding drug solution, drop by drop which is responsible for greater contact time of droplet in the system and after addition of solution, the residence time will decrease [23].

7. EVALUATION OF SPHERICAL CRYSTALLIZATION

7.1. Stability

There is a change in stability of drug substance due to change in their polymorphism during re-crystallization process [24]. The spherical agglomerate of the small recrystallized crystals reduces the surface area and improves its stability.

7.2. Wettability

Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. Wettability of agglomerated crystals by water is looked over by measuring the contact angle of water to the squeezed crystals. Decrease in the contact angle leads to increase in wettability [25]. Crystals with higher crystallinity are less wettable than crystals with low crystallinity.

7.2.1. Methods used to determine wettability

7.2.1.1. Determination of porosity

For prepared tablets of drug spherical crystals, the thickness and diameter can be found out by using vernier calliper. From the apparent density of the tablet, the porosity of the tablet is calculated.

7.2.1.2. Determination of Density

By using a relative density bottle, density of saturated solution of drug and spherical crystals in water is determined [25].

7.2.1.3. Determination of surface tension

By employing a stalagmometer, surface tension, spherical crystals in water and saturated solution of drug is determined [26].

7.3. Solubility

The enhanced solubility in spherical agglomerates may be due to substituting the crystal forms, different habit, structure, surface modification and in some cases, solvents added into the crystal forms solvent or clathrates can change the surface properties and the reactivity of drug particles [27]. In both distilled water and dissolution medium, solubility studies are carried out by using flask shaker method. Flask which contain dissolution method and distilled water, the spherical agglomerated crystals are added to it [28]. The flask is shaken for 24 hours at room temperature. The filtrated are then diluted with the regarded medium and content is determined by suitable analysis [29].

7.4. Flow ability

Agglomerates having flow ability is much increased as the agglomerates exhibits lower angle of response than that of unique single crystals [30]. This upgrade in the flow ability of agglomerates could be attributed to the significant depletion in inter particle friction, due to their spherical shape and a lower static electric charge [31].

7.5. Particle shape and size Determination

Change in crystal habit such as particle size and shape of pharmaceutical ingredients gives different physical and chemical properties [32]. The large size of particle is reduced by using of bridging liquid due to agglomeration of large size particles. This results in spherical shape of particles. Particle size and shape of agglomerates can be studied by different methods *e.g.* image analyzer, simple sieve analysis, Ro-tap sieve shaker, optical microscopy, electrons scanning microscope and X-ray power diffraction [33].

7.6. Packability

Agglomerates formed by spherical crystallization reported improved packing ability [34]. In general, it has the angle of friction, shear cohesive stress, compared to single crystal. The value of agglomerates indexes is low which improves packing ability of agglomerates.

8. APPLICATIONS

- Applicable for flow ability and compressibility.
- Better bioavailability.
- Reduces the cost of production [35].
- Spherical crystallization used for stability and toxicity.
- To mask the bitter taste.
- Better bioavailability [36].

Drug	Solvent	Method	Ref.
Enoxacin	Ammonia water, acetone, dichloromethane	Ammonia diffusion system	[37]
Ibuprofen	Ethanol, water with sucrose, fatty acid ester	Quasi emulsification solvent diffusion system	[38]
Aspirin	Acid buffer, methanol, chloroform	Spherical agglomeration	[39]
Tolbutamine	Ethanol, water, isopropyl acetate	Neutralization technique	[40]
Naproxen	Acetone, water hexinol, toluene	Spherical agglomeration	[41]
Tranilast	Acetone, water, dichloromethane	Spherical agglomeration	[42]
Mebandazole	Acetone, water, hexane	Spherical agglomeration	[43]
Theophylline	Ethylenediamine,sodium chloride, water	Spherical agglomeration	[44]
Norfloxacin	Ammonia water, acetone, ammonia water	Ammonia diffusion system	[45]
Acbutalol Hcl	Water, ethanol ,isopropyl acetate	Quasi emulsification solvent diffusion system	[46]

9. CONCLUSION

Spherical crystallization is a technique with reduced time, cost, simple, inexpensive, less machinery needed and few numbers of steps as compared to other technology manufacturing of tablets. It has excellent micrometric property, dissolution rate, physicochemical properties when compared to other marketed formulations. It is an advancement in tableting technology. Spherical crystallization technique is a promising technique which changes crystals of drug using different solvents for obtaining direct compressible spherical agglomerates.

Conflict of interest

None declared

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