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A REVIEW ON SPHERICAL AGGLOMERATION FOR IMPROVEMENT OF MICROMERITIC PROPERTIES AND SOLUBILITY

PANCHAL HARDIK K, MRS. KINJAL SANGHVI
Arihant School of Pharmacy & Bio Research Institute, Gujarat, India.

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Abstract: The present study has been satisfactory attempt to improve flow characteristics, solubility and dissolution characteristics of poorly soluble drug as it has low aqueous solubility. Spherical crystals were prepared with or without polymers. There are many techniques can be used to improve solubility of poorly soluble drug but spherical agglomeration technique having more advantages. Spherical agglomeration technique usually used to improve flow characteristics of crystallized materials and solubility by incorporation of hydrophilic polymer. Spherical agglomerates were characterized by IR, XRD and SEM. Micromeritic properties and dissolution behaviour studies. Process variables such as amount of bridging liquid, stirring speed, duration of stirring and temperature were optimized. Dissolution profile of the spherical agglomerates was compared with pure sample and recrystallized sample.

Keywords: Spherical agglomerates, Poorly soluble drugs, Dissolution

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Corresponding Author: MR. PANCHAL HARDIK K

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INTRODUCTION

Kawashima et.al developed spherical agglomeration as a method of novel particulate design. It is the particle engineering technique by which the crystallization and agglomeration can be carried out simultaneously in one step.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 temper proof nature[1]. 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[2]. Spherical crystallization is one of such particle design technique in which crystallization and agglomeration process are carried out simultaneously. Kawashima et al, in 1990, developed spherical crystallization technique[3]. Spherical Crystallization process transforms the fine crystals obtain during crystallization into spherical agglomerates.

Agglomerates formed further improves the flowability and compressibility of pharmaceutical ingredient which enables direct tabletting of drug instead of further processing like mixing , granulation, seiving, drying etc. There are certain parameters which have to be optimized in order to obtain the maximum amount of spherical crystals. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone[4]. Direct tableting has been renewed as a preferred process by simply mixing and comprising powder to save time and cost in comparison with granule tableting. The direct tableting technique has been successfully applied to numerous drugs on the industrial scale. The success of any direct tableting procedure and resulting mechanical properties of tablets are strongly affected by the quality of the crystals used in this process. When the mechanical properties of the drug particles are inadequate and preliminary granulation is necessary, spherical crystallization technique appears to be an efficient alternative for obtaining particle destined for direct tableting. In the spherical crystallization process, crystal formation, growth and agglomeration occur simultaneously within the same system. In this method, a third solvent called the bridging liquid is added in a smaller amount to purposely induce and promote the formation of agglomerates. Crystals are agglomerated during the crystallization process and large spherical agglomerates are produced. A near saturated solution of the drug in a good solvent is poured into a poor solvent. The poor and good solvents are freely miscible and the “affinity” between the solvents is stronger than the affinity between drug and good solvent, leading to precipitation of crystals immediately. Under agitation, the

bridging liquid (the wetting agent) is added, which is immiscible with the poor solvent and preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid acts to adhere the crystals to one another and facilitates them to agglomerate[5-8].

Spherical agglomeration is carried by below Methods:-

- Spherical agglomeration method
- Quasi emulsion solvent diffusion method
- Ammonia diffusion method
- Neutralization method
- Traditional crystallization process
- Crystallo-co-agglomeration

Wet spherical crystallization method: Here the good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, which leads to precipitation of crystals immediately. Bridging liquid collects the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid. Spherical agglomeration proceeds in three steps as shown in Figure 1.1.

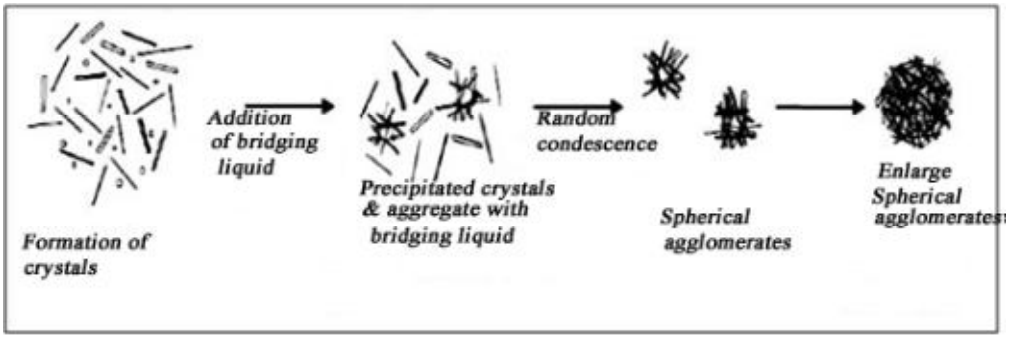

Figure 1.1: Steps involved in wet spherical crystallization (WSA).

The first one is the selection of the crystallization method to precipitate crystals from solution, i.e., thermal method (temperature decrease or evaporation), physicochemical methods (addition of another solvent, salting out) and chemical reaction. The second step is the choice of the wetting agent that will be immiscible with the solvent of crystallization. Finally, the third step is the hardning of the agglomerates.

Quasi-Emulsion Solvent Diffusion method (QESD, Transient emulsion): This technique is usually applied for the preparation of microspheres. Here interaction between the drug and the good solvent is stronger than that of the good and poor solvents hence the good solvent and

drug solution is dispersed in the poor solvent, producing quasi emulsion droplets, even if the solvents are normally miscible. This is because of an increase in the interfacial tension between good and poor solvent. Then good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent. The steps involved in QESD are shown in Figure 1.2.

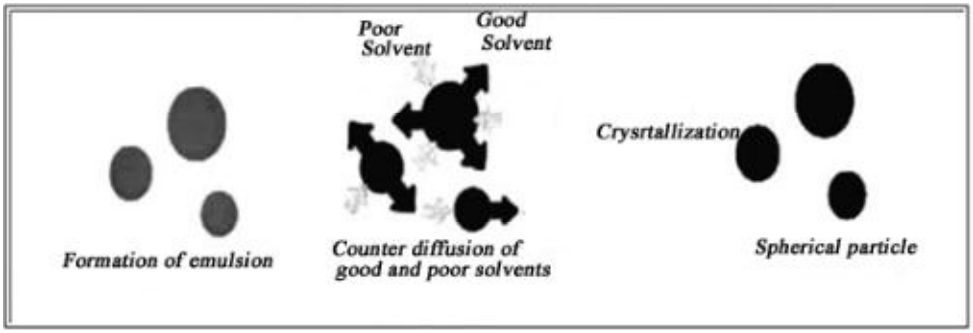

Figure 1.2: Steps involved in quasi emulsion solvent diffusion (QESD).

As previous studies have shown, solvent transfer is particularly influenced by two basic parameters. One of them is the difference in temperatures *T*1 - *T*2, with *T*1 being the temperature of the good solvent with dissolved drug before dispersion and *T*2 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 co-workers, 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 *T*1 and *T*2 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 co-workers. At higher temperatures, the agglomerated silybin particles were larger and more spherical which was explained by a higher diffusion rate, increased interfacial tension and higher kinetic energy of the droplets.

Ammonia diffusion system (ADS): In this technique ammonia-water system is used as the good solvent and bad solvent is selected depending upon the drugs solubility in that solvent. The ammonia-water also acts as a bridging liquid. The whole process is completed in three stages. First, the drug dissolved in ammonia water is precipitated while the droplets collect the crystals

(Figure 1.3 I). Simultaneously, ammonia in the agglomerate diffuses to the outer organic solvent (Figure 1.3 II). Its ability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed (Figure 1.3 III).

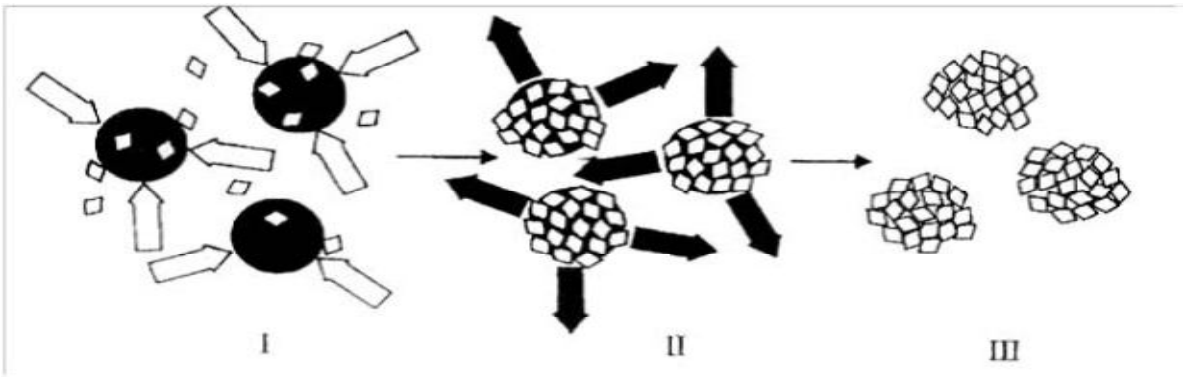

Figure 1.3: Steps involved in ammonia diffusion system (ADS).

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 spherical agglomeration or the quasi emulsion solvent diffusion method.

Neutralization method: In this method, the drug dissolved in the good solvent and placed in the cylindrical vessel with constant stirring. While stirring an aqueous polymer solution and One neutral solution was added which, neutralize the good solvent and crystallize out the drug. Then bridging liquid was added drop wise at a definite rate, followed by crystallization of the crystal form of the drug takes place.

Traditional crystallization process: Heat some solvent to boiling. Place the solid to be recrystallized in an Erlenmeyer flask. Pour a small amount of the hot solvent into the flask containing the solid. Swirl the flask to dissolve the solid. Place the flask on the steam bath to keep the solution warm. If the solid is still not dissolved, add a tiny of amount more solvent and swirl again. When the solid get dissolved in solution, set it on the bench top. Do not disturb it. After a while, crystals should appear in the flask. Simultaneously bridging liquid was added drop wise at a definite rate, followed by crystallization of the crystal form of the drug takes place.

Crystallo-co-agglomeration: Crystallo-co-agglomeration was invented by Kadam and coworkers as an attempt to 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 excipient 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.

Techniques There are two different methods used in spherical crystallization, i.e. typical and non-typical methods. Non typical technique is also called as traditional crystallization method which involves different steps as salting out, cooling and precipitation. The controlling factors are physical and chemical properties. Typical technique employs three solvents:

a. Good solvent (dissolution medium).
b. Bridging liquid (partially dissolves the drug and have wetting property).
c. Bad solvent (immiscible with the drug substance).

Spherical agglomeration is a novel agglomeration technique involving agglomerate formation based on addition of bridging solvent. In typical spherical agglomeration method the drug dissolved in a good solvent is poured in a poor solvent under controlled condition of agitation with the addition of bridging solvent which wets the crystal surface to form agglomerate. The bridging liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The obtained particles so designed to improve the bulk density, flow properties, compressibility, cohesivity, solubility and dissolution rate. The agglomerates were also characterized by differential scanning calorimetry (DSC), Fourier transforms infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The DSC showed a decrease in the melting enthalpy indicating disorder in the crystalline content. FTIR study revealed that no chemical changes in prepared recrystallized agglomerates[9].

Chow et al[10] postulated some general guide lines for the spherical crystallization of drugs.

- For compounds that are water soluble, a water immiscible organic solvent is used as the external medium and salt solutions of high concentration without common ions can be used as the bridging liquid.
- For compounds that are soluble in one or more organic solvents water is employed as the external phase and a water-immiscible organic solvent as the bridging liquid.

- For compounds that are only soluble in water-miscible organic solvents a saturated aqueous solution of the compound can serve as the external phase and an organic solvent mixture as the bridging solvent.
- For compounds that are insoluble in water or any organic solvents a water immiscible organic solvent can act as the external phase and a 20% calcium chloride solution as the bridging liquid. In addition, a binding agent such as PVP or PEG is required for crystallization since the powders are not sufficiently soluble in the bridging liquids to allow binding through re-crystallization and fusion.

Principle of spherical agglomeration

This process involves pouring the saturated solution of the drug in good solvent and then into poor solvent. Third solvent called the bridging liquid is added in small quantity to promote the formation of agglomerates. Bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drugs for forming spherical agglomerates. Poor solvent and good solvent should not be miscible and the affinity between both solvents must be stronger than the affinity between drug and good solvent. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the agglomerates.

Steps of Spherical agglomeration

1) Flocculation zone

In this zone the bridging liquid displaces the liquid from the surface of the agglomerates and these agglomerates 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 flocs of particle 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 by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerates is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerates is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure.

2) Zero growth zone

Loose flocs 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 cuasing pore space iin 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.

3) Fast growth zone

The fast growth zone of the agglomerates takes place when sufficient bridging liquid has squeezed out of the surface of 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 in the nucleus and enhances particle deformation and subsequent coalescence. Another reason for the growth of agglomerates size is attributed to growth mechanism that describe the successive addition of the material on already formed nuclei.

4) Constant size zone

In this zone agglomerates ceases to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may be due to attrition, breakage and shatter. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial floccules are transformed into small agglomerates. The rate determining step is the collision of particle with the bridging liquid droplets prior to the formation of liquid bridges. The rate is governed by the rate of agitation. The strength of the agglomerates is determined by interfacial tension between the bridging liquid and the continuous liquid phase, contact angle and the ratio of the volumes of the bridging liquid and solid particles.

Need for Spherical agglomeration

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 commonly used techniques to improve the bioavailability of poorly soluble drugs. The micronization process alters the flow and compressibility of crystalline powders and cause problem in formulation. Addition of surfactant generally led to less significant increase in aqueous solubility. To overcome this problem Kawashima developed spherical agglomeration technique that led to improving the flow and direct compressibility of drugs.

Advantages of spherical crystallization

- Spherical crystallization technique has been successfully utilized for improving of flowability and compressibility of drug powder.

- This technique could enable subsequent processes such as separation, filtration, drying etc. to be carried out more efficiently.
- By using this technique, physicochemical properties of pharmaceutical crystals are improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability.
- This technique can convert crystalline forms of a drug into different polymorphic form having better bioavailability.
- For masking of the bitter taste of drug.
- Preparation of microsponge, microspheres and nanospheres, nanoparticles and micropellets as novel particulate drug delivery system[1].

CONCLUSION

Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared to pure sample.Spherical agglomerates having better compactability and flow property.

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