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Spherical Agglomeration – An Innovation in Tablet Technology

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ABSTRACT

Direct tabletting technique is modern and efficient technology used in tablet manufacturing and it has been successfully applied for various poorly soluble and drugs with poor micromeritic properties. Spherical crystallization is a particle engineering technique which involves the transformation of fine crystals into spherical shape which enhances the micromeritic properties such as bulk and tapped densities, compressibility, porosity, packability, solubility and dissolution. The present review gives a glimpse on spherical crystallization technique and its utility in direct compression of tablets. It also provides comprehensive review on merits of direct compression over granulation technique. It provides information about methods and mechanisms of spherical crystallization techniques such as solvent change method, quasi emulsion solvent diffusion method, ammonia diffusion method and neutralization methods, how to optimize conditions such as crystallization solvent medium, temperature, speed of agitation, amount of bridging liquid and how micromeritic properties improved with this techniques. This review emphasis principle steps involved in the process of spherical crystallization such as flocculation zone, zero growth, fast growth zone and factors curbing the process of agglomeration such as solubility profile, mode and intensity of agitation, amount of bridging liquid and temperature, advantages and disadvantages of spherical agglomeration and evaluation of agglomerates.

Keywords: Spherical crystallization, Bridging liquid, Zero growth zone, Micromeritic properties.

INTRODUCTION

Formulation and manufacturing of solid oral dosage forms and tablets in particular, have undergone rapid change and development over decades. Direct compression is a modern method in tablet manufacturing. The direct compression method indulges the compaction of tabletting without a step of granulation, provided the tabletting mixture should have enough flow properties to form robust tablets. The success of direct compression tabletting method is strongly affected by the quality of crystals used in process. When the mechanical properties and micromeritic properties of the drug particles are deficient and preliminary granulation is necessary, spherical crystallization technique is an efficient technique for getting particle obtained for direct tabletting (Nokhodchi, 2007). Manufacturing of tablets with direct compression eliminates many processing steps such as granulation, drying etc (Shangraw, 1989).

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The preparation of spherical agglomerates by spherical crystallization recently came into the forefront of interest because the habit of the particles (form, shape, particle size distribution, surface, etc.) can be modified by the crystallization process. It is well known that the morphology of crystal strongly depends upon the crystal growth conditions. One of the crystal growth processes is the development of crystal agglomerates by spherical crystallization (Puechagat, 1998). The novel spherical crystallization technique is an efficient technique in designing of particles for direct tableting, during which crystallization and agglomeration can be carried out in one-step**.** The quality of solid formulations is influenced by primary micromeritic characteristics such as the shape and size of drug crystals, especially when large amounts of poorly soluble drugs are formulated (Sano, 1987).

This review emphasizes the following.

Merits of Direct Compression (Shangraw, 1990)

1. Direct compression is more efficient when compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

2. Direct compression is cost effectiveness due to reduced labor costs, fewer manufacturing steps, and less number of equipments. Less process validation and reduced consumption of power leads to reduced tablet production cost.
3. Direct compression is suitable for moisture and heat sensitive active pharmaceutical ingredients.
4. Particle size uniformity.
5. Prime particle dissolution. In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.
6. The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
7. Chemical stability problems for API and excipient would be avoided.
8. Provides stability against the effect of aging which affects the dissolution rates.

Direct compression is affected by particle size and size distribution of the materials such as active pharmaceutical ingredient (API) and excipients, flowability, compressibility of the crystalline powder (Szabo-Revesz, 2001).

Spherical agglomeration

Spherical crystallization is a particle design technique, in which crystallization and agglomeration can be carried at simultaneously in one step (Paradkar, 1994). In this technique, fine crystals are produced which are directly converted into the spherical shape. These are designated as the spherical agglomerates (Chourasia, 2003). Some of crystalline drugs exhibit very poor flowability and compressibility (Tanguy, 1996). Crystal habit and polymorphic form of a crystalline solid influences its physicochemical, mechanical and biological performance (Subhramanyam, 2002). A crystal can be defined as a solid particle, which is formed by the crystallization process in which structural units are arranged by a fixed geometric pattern or lattice. Crystalline forms are having some physico-chemical advantages over amorphous forms. They are having definite shape and an orderly arrangement of units. These are incompressible and showing definite melting points. By determining the melting points we can determine whether any polymorphic modifications occurred during crystallization. In amorphous forms molecules are arranged randomly the liquid state and are isotropic. They do not have specific shape and structural units are arranged randomly in the solid. They do not have definite melting points and may exhibit better therapeutic activity than the crystalline form (Brittain, 2001). The isomorphic forms by alteration only in the crystal habit influence the particle orientation and play a vital role in the flowablility, packing, compaction and dissolution characteristics of a powder drug (Tiwary 2001). Regularly shaped spherical particles have been found to be free flow and exhibiting better compressibility. An alternative approach is obviously to control the crystallization of the drug such that agglomerates of fine drug particles are formed during precipitation from solution (Viswanathan, 2006). Various steps involved in the crystallization of organic and other compounds, including agglomeration and crystallization. For example, ibuprofen and ascorbic acid whether compactibility is improved for the agglomerates compared to the original particles used in the preparation of crystallization solution. Customized agglomerates showed improved compatibility and reduced capping propensity compared to the original unagglomerated particles (Alander, 2003). Paracetamol agglomerates formed by crystallization in water, in which agglomerate size and distributions are affected by crystallization method and which had effect on compactibility. Two types of secondary particles of paracetmol were prepared. The degree of deformation and fragmentation during compression varied between agglomerates and granules. The granules varied in comactibility due to particle strength while agglomerates due to fragmentation. Spherical crystallization of drug particle design has emerged as one of the active research in manufacturing. In recent pasts spherical crystallization is the research interest or gained great importance due to the fact that crystal habit is being modified during the process (Alander, 2004). Spherical crystals can be obtained by two different techniques, either by typical crystallization technique or non-typical spherical crystallization technique. Non typical spherical crystallization technique can also be considered as the traditional crystallization process (salting out, cooling, precipitation) (Kallies, 1993) which is carried out by controlling the physical and chemical factors.

Wet spherical agglomerates or solvent change method

Many researchers have attempted differently to obtain optimized shaped crystal agglomerate with various solvents. Solvents were selected based on the miscibility of the solvents and solubility of the drug in individual solvents. To select the best solvent composition, a ternary diagrams were also envisaged. The solvents used in wet spherical agglomeration are good solvent, bridging liquid and poor solvent. The good solvent is also designated as perfect solvent and it is based on the solubility of drug in the solvent (Szabo-Revesz, 2001). For forming the liquid bridges and the wetting property bridging liquids are used (Yadav 2009). Another solvent is bad solvent or poor solvent or antisolvent which is immiscible with the drug (Yadav, 2009). It was observed that the properties of agglomerates are quite sensitive to the amount of bridging liquid (Kawashima 1995). The agglomerating solvents was chosen in a manner that it is immiscible with anti solvent (Gordon, 1990) and the drug has limited solubility in it (Chorasia, 2003). The poor and good solvents are freely miscible and the affinity between the drug and the good solvent is more. The bridging liquid should not be miscible with the poor solvent and should perfectly wet the precipitated crystals. Due to interfacial tension effect and capillary forces, the bridging liquid acts to adhere the crystal to each other (Kawashima, 1984) by promoting the formation of liquid bridges

between the drug crystals to form spherically crystal agglomerates (Rosetti, 2003). Spherical crystals are formed by coalescence of these dispersed crystals (Gupta, 2007). The choice of bridging liquid, stirring speed and concentration of solids are important. The agglomeration rate was reduced with increasing stirring because of increasing disruptive forces (Bos, 1987). When the stirring rate is high agglomerates produce which are less porous and mere resistant to mechanical stress and the porosity decreases when the concentration of solid increases (Bladin 2003). Spherical agglomeration of benzoic acid by solvent change method showed that bridging liquid (diethylether) has significant influence on product properties in which no agglomerates were formed. It was reported that solvents such as chloroform, toluene, heptanes and pentane have produced spherical agglomerates. With increasing amount of the bridging liquid, particle size, strength and morphology of particle were also improved. Celecoxib spherical agglomerates were prepared with PVP, acetone, water and chloroform as crystallization medium have exhibited improved micromeritic properties, solubility and dissolution rate (Venkadari Rammohan, 2007). Whereas ibuprofen had exhibited poor solubility and poor flow. Isopopylalcohol, water, isopropyl acetate used as crystallization medium.Ibuprofen agglomerates exhibited decreased crysatllinity and improved micromeritc properties (Mudit Dixit, 2010). Ketoprofen spherical agglomerates were prepared by solvent change method in which crystallization medium is composed of alcohol, water and chloroform. Spherical agglomerates exhibited improved dissolution compared to pure drug (Mudit Dixit, 2010). Zaltoprofen spherical agglomerates were prepared by spherical crysallizaion technique in which medium is composed of acetone, water, bridging liquid and sodium carboxymethylcellulose was also used to enhance the dissolution rate. In this instance spherical agglomerates have good flow properties when compared to pure drug due to reduction in inter-particle friction because of spherical shape of crystals (Harikrishna, 2012).

Quasi emulsion solvent diffusion method

As shown in above Fig. 1, this method is also known as transient emulsion method. In the emulsion solvent diffusion the affinity between drug and good solvent is stronger than that of the good solvent and poor solvent (Chow 1996). In a good solvent, drug is dissolved and that solution is dispersed into poor solvent, producing droplets (quasi), even if solvents are normally miscible. This is due to an increase in interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion drops into the outer poor solvent phase and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. This method is simpler than solvent change method method, but it is difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase (Mudit dixit 2010). In case of carvedilol spherical crystals, drug along with poloxamer is dissolved in the methanol and dichloromethane acts as bridging liquid. Then the resulting solution was poured into the distilled water (poor solvent) containing aerosil. The affinity between the carvedilol and methanol is stronger than that of methanol and water. Then methanol diffuses gradually out of the emulsion drops into the water surrounding phase and water diffuses into the droplets by which the carvedilol crystallizes inside the droplets (Tapas 2009). In another case (etoricoxib) acetone was acted as a good solvent because the drug is soluble in acetone and chloroform act as bridging liquid and water is poor solvent. The counter diffusion of the poor solvent into the droplets induces the crystallization at the drug within droplet due to the decrease in drug's solubility in droplet containing water. In preparation of spherical crystal agglomerates of loperamide hydrochloride, polymers such as polyethyleneglycol and Eudragit were used to enhance the solubility. Solubility markedly increases with Eudargit when compare to PEG due to presence of quaternary group in Eudragit. Spherical crystal agglomerates showed good flowability due to reduction in inter-particle friction because of spherical shape and large size of the crystals. Higher packability was observed due to low surface and width particle size distribution.

Ammonia diffusion method

In this technique (Figure.2) ammonia-water system is used as the good solvent and solvent is selected based upon the drugs solubility in that solvent. Here, ammonia water also acts as bridging liquid. This technique is applicable to amphoteric drugs such as enoxacin, ampicillin trihydrate, norfloxacin which cannot be agglomerated by conventional procedures. Acetone is water miscible but a poor solvent, thus drug precipitate without forming ammonium salts (Sano, 1990). Drug dissolved in ammonia water precipitated while the droplets collect the crystals and simultaneously ammonia in the agglomerates diffuses to the outer organic solvent. Agglomeration by ammonia diffusion method, norfloxacin is an antibacterial agent with zwitteronic molecular structure, during process of agglomeration a new pseudopolymorph (trihydrate norfloxcin) was observed. This enable to enhance the better micromeritic and macromeritic properties because of agglomerates with flat rhomboidal structures arranged in a spherical like crystalline structure whereas pure drug possess hexagonal structure (Puechagut 1997).

Neutralization method

This technique involves the formation of fine crystals by neutralization and agglomeration by bridging liquid. Micromeritic properties of crystals were drastically changed due to markedly different crystal habit leading to variant contact points, frictional, cohesive forces between the crystals. The above factors affect the sliding of particle against each other leads to different packing geometry. During the process of compression fresh surfaces are formed by fracturing crystals which may leads to superior compressibility. The agglomerates prepared by this method found to have

more specific area, as compared to other methods. The reason for the superior wettability of agglomerated crystals was due to the fact at the time of agglomeration the hydrophilic polymer in crystallization adheres firmly to the agglomerated crystals (Mudit dixit 2010).

Principle steps involved in the process of spherical crystallization

Flocculation zone

In flocculation zone bridging liquid displace the liquid from the surface of the crystals and tends to agglomerates with agitation. The absorbed bridging liquid links particles by forming bridges between them, due to which loose floccules are formed. Mutual attraction of particles brought about the surface tension of the liquid and liquid bridges. Capillary stage is reached when all the void space within agglomerates is filled with liquid.

Zero growth zone

This zone is characterized by converting the loose flocs into tightly packed pellets or agglomerates during which entrapped fluid is squeezed out, followed by squeezing of bridging liquid on to surface of small flocs causing poor space in the pellets. The driving force for transformation is provided by agitation of slurry causing liquid turbulence, pellet-pellet, pellet-stirrer collision.

Fast growth zone

The growth of agglomerates takes place as bridging liquid get squeezes out from 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 slightly access moisture, which imparts plasticity nucleus. The growth of agglomerates also takes place due to successive addition of materials on formed nucleus.

Factors controlling the process of agglomeration

Solubility profile

Solvent selection depends upon the solubility characteristics of drug. Three solvent system consisting of good solvent, poor solvent and bridging liquid are necessary. The physical form of product whether microagglomerate or irregular macroagglomerate can be controlled by selection of solvent proportions. The selection criteria and proportion of solvents to be used is determined by carrying out solubility studies and constructing the ternary phase diagram. In case of enoxcin sesquihydraates forms in acetone where solubility is more and it s converted into anhydrous form in alcohols where solubility is lower than in acetone (Masumi Ueda 1990). In mefanamic acid case tetrahydrofuran acts as a good solvent to obtain a very concentrated drug solution which increases the densification of material during the crystallization. The addition of poor solvent (water) caused drug precipitation. Isopropyl acetate (bridging liquid) favours the transfer of drug to emulsified phase which results in crystal agglomeration (Mudit Dixit 2011).

Mode and intensity of agitation

High speed agitation is necessary to dispose the bridging liquid throughout the system but in some cases increasing stirring rate may cause reduction in agglomerate formation due to increased disruptive forces. With increasing agitation speed, shear force applied to the droplets increases leads to more dispersed at consolidated droplets resulting in reduction of particle size. Beyond the speed limits, the agglomerates tend to be more resistant and less porous. Agitation leads to consolidation of the agglomerates. Lower stirring rate reduces the possibility of obtaining agglomerates due to slow circulation of droplets in the medium and slight collision between the particles. For instance in roxythromycin spherical agglomeration method agitation speed was maintained as 1000 rpm (Venkat Yadav 2010) whereas in case of celecoxib was at 500 rpm (Venkadari 2007) and for flurbiprofen it was 600 rpm (Jain 2002). Hence it require optimize the agitation speed.

Amount of bridging liquid

In many cases, it has been observed that properties of spherical agglomerates were much sensitive to amount of bridging liquid. The diameter of agglomerated crystals increases with decrease in the amount of bridging liquid in a three solvent system. Insufficient bridging liquid produces plenty of fines and excessive produces coarse particle. In case of mefenaimic acid 15% of bridging liquid with drop-wise manner produces spherical agglomerates, wherein naproxen case it was 10 % only (Mudit Dixit 2011). The amount of bridging liquid depends on interfacial tension and capillary forces and solubility and was evidenced with benzoic acid spherical agglomeration. When less amount of bridging liquid is available there was no agglomeration because a little amount was available for solubulisation. When large amount of bridging liquid was used, poor agglomerates were formed due to localization (Jyothi Thati 2011).

Temperature

Temperature has a significant influence on the shape, size and texture of the agglomerates. The average size of agglomerate was smallest at the crystallization temperature 10°C. At higher temperature, the larger agglomerates were produced initially and equilibrium attained more rapidly than at lower temperature. At lower temperature, it was characteristic that the growth rate of crystals was slow at initial stage but become faster at later stage. At low temperature, the initial number of crystals produced were greater than high temperature, number of nuclei increased with decreased crystallization temperature. In case of carbamazpine, at 25° C irregular shaped large entities were formed whereas at 45° C improved particle morphology. Achievement of more regular agglomerates were observed because of high temperature and result the dispersion of bridging liquid by formation of small droplets with more surface area

which can increasing wetting rate of crystals and consequently promotion of nucleation step (Yadav, 2009). Naproxen spherical agglomerates' optimum temperature was 20°C because at 10° C there was reduced solubility of drug (Mudit dixit 2011).

Advantages of spherical crystallization

Sustained-release nitrendipine microspheres with Eudragit RS and pH-dependent gradient-release microsphere system for nitrendipine were the products of crystallization. Roxithromycin, a bitter tatse drug was processed as polymeric microspheres for taste masking. Numerous applications of spherical crystallization were recorded with many researches such as complex formation and crystallo-coagglomerates on ibuprofen-paracetamol and ibuprofen-talc was reported. Similarly ibuprofen reservoir-type microcapsules for were developed for lysozyme protein; ketoprofen and benzoyl peroxide microsponges; riboflavin-containing microballoons for floating controlled drug delivery system; hollow microballoons of aspirin, salicylic acid, ethoxybenzamide, indomethacin, riboflavin; PLGA nanospheres for pulmonary delivery of insulin to prolong hypoglycemic effect; PLGA nanospheres with chitosan for gene delivery; Cystatin PLGA, cefuroxime axetil (CFA) nanoparticles; and also to improve the physicochemical properties of drugs such as propyphenazone, aceclofenac and benzoic acid were developed.

Disadvantages

It provides low yield because the drug show significant solubility in the crystallization solvent due to cosolvency effect.

Further spherical crystals can be characterized by

Compressibility or Carr's index, Hausner ratio, porosity, friability test, mechanical strength, optical microscopy, Electron scanning microscopy, X- ray powder diffraction and Fourier transform-infrared spectrometer (FT-IR).

Figure.1 Schematic representation of Quasi emulsion solvent diffusion method

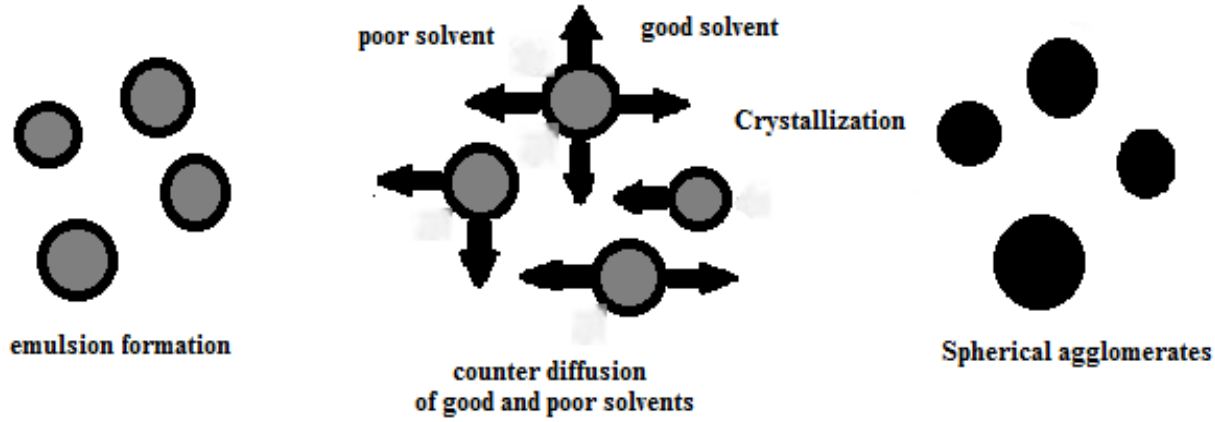
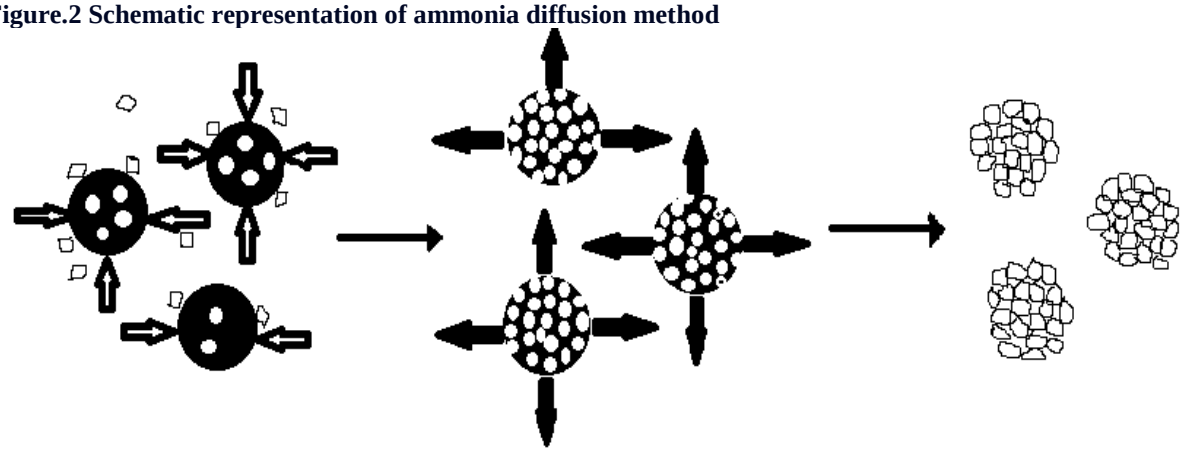


Figure.2 Schematic representation of ammonia diffusion method



CONCLUSION

The spherical crystallzation could shorten the manufacturing process in tabletting, so that the cost and time of manufacturing of the tablets could be reduced. Spherical crystal agglomerates were prepared by solvent change method, quasi-emulsion solvent, diffusion method, ammonia diffusion system and neutralization method. These methods are applicable to poorly water soluble drugs and drugs have poor flow properties. Due to its crystal shape and nature irregular crystals have different contact points, frictional, cohesive forces between the single crystals which affect the sliding of particle against each other lead to poor flow. By using spherical agglomerates flow properties, packability. compressibility, mechanical strength, wettability, dissolution can possibly be enhanced. Flowability is also

increased due to increase in inter-particle friction due to their spherical shape and large size of crystals. Spherical agglomerates exhibited superior compressibility due to the fact that during the process of compression fresh surfaces are formed leads to enhance the inter particle bonding resulting in the lower compressional forces. Mechanical strength of agglomerates can be increased due to plastic deformation of the agglomerates. Wettability depends upon the crystallinity and elementary crystal size of the crystals. As the contact angle decreases wettability increases. Here, spherical agglomerates have low crystallinity and more wettability. Thus, it was concluded that this review provides information about that what are the drugs and pharmaceutical ingredients suitable to carryout spherical crystalliztion. What are the techniques followed to get spherical agglomerates and what are the criteria that have to be followed during agglomerate preparation. How parameters such as time, speed of agitation, bridging liquid concentration shows its effect during agglomeration process. How micromeritic properties enhanced for agglomerates compared to pure and crystals with irregular shape. Finally, application of spherical crystallization in the preparation of tablets by direct compression and in other pharmaceutical preparations was emphasized clearly.

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