International Journal for Pharmaceutical Research Scholars (IJPRS)

V-2, I-4, 2013 ISSN No: 2277 - 7873

REVIEW ARTICLE

Spherical Crystallization: A Distinctive Practice in Pharmaceutical Processing

Ghodake PP[*1], Bhosale RR[1], Osmani RA[1], Harkare BR[1], Shaikh SM[2]

[*1]*Department of Pharmaceutics, Satara College of Pharmacy, Satara- 415004, (M.S.) India.*

[2]*Department of Pharmaceutics, Appasaheb Birnale College of Pharmacy, Sangli- 416416, (M.S.) India.*

Manuscript No: IJPRS/V2/I4/00202, Received On: 18/11/2013, Accepted On: 26/11/2013

ABSTRACT

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to formulate solid dosage form. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs. The micronization process alters the flow and compressibility of crystalline powders and cause formulation problems. Addition of surfactant generally led to less significant increase in aqueous solubility. To overcome this problem many researchers developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of microcrystalline drugs. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. By using this technique, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical processes.

KEYWORDS

Crystallization, Micronization, Agglomeration, Spherical crystallization

INTRODUCTION

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"[1]. It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape.

***Address for Correspondence:**
Prasanna P. Ghodake
Department of Pharmaceutics,
Satara College of Pharmacy, Satara.
A/P Degaon, Satara- 415004, (M.S.) India.
E-Mail Id: ghodakeprasanna2@gmail.com

It is the versatile process that enables to control the type and the size of the crystals. 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 (form, surface, and 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 nanaospheres, microbaloons 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. By using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability[2]. The process is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel. It gives important advances in tableting technology; especially the introduction of number of directly compressible excipients. The spherically agglomerated crystals can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation.

Advantages of Spherical Crystallization

1) Spherical crystallization technique has been successfully utilized for improving of flowability and compressibility of drug powder.
2) This technique could enable subsequent processes such as separation, filtration, drying etc. to be carried out more efficiently.
3) By using this technique, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tableting because of their excellent flowability and packability [3].
4) This technique may enable crystalline forms of a drug to be converted into different polymorphic form having better bioavailability.
5) For masking of the bitter taste of drug.
6) Preparation of microsponge, microspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system.

Techniques of Spherical Crystallization

1) Spherical agglomeration method (SA)
2) Quasi-emulsion solvent diffusion method (QESD, Transient emulsion)
3) Ammonia diffusion System (ADS)
4) Crystal-co-agglomeration technique (CCA)
5) Neutralization technique

Spherical Agglomeration Method (SA)

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. WSA method proceeds in three steps as shown in Figure 1. 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 hardening of the agglomerates[4].

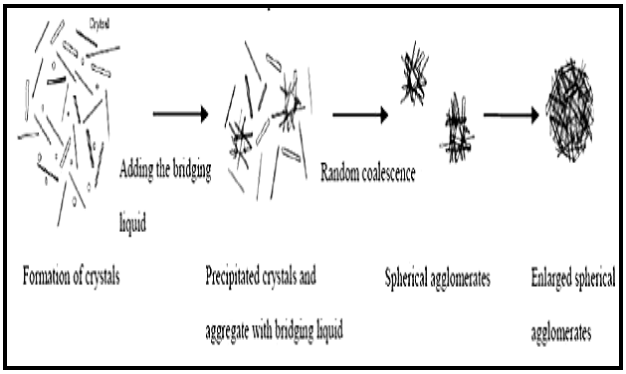

Figure 1: Steps involved in spherical agglomeration

Quasi-Emulsion Solvent Diffusion Method (QESD)

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 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 2[5].

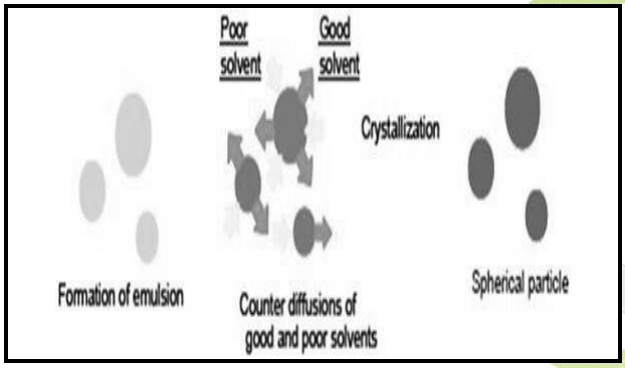

Figure 2: Steps involved in Quasi emulsion Solvent Diffusion (QESD)

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 .This technique usually meant for amphoteric drugs which cannot be agglomerated by conventional procedures. The whole process is completed in three stages. First, the drug dissolved in ammonia water is precipitated while the droplets collect the crystals. Simultaneously, ammonia in the agglomerate diffuses to the outer organic solvent. Its ability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed.

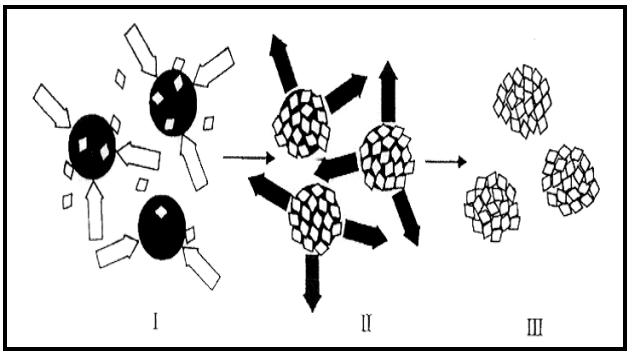

Figure 3: Steps involved in Ammonia Diffusion System (ADS)

Crystal-Co-Agglomeration Technique (CCA)

Applications of spherical crystallization to obtain directly compressible agglomerates without diluents are restricted to water insoluble large-dose drugs only. Most of the excipients, such as diluents and disintegrating agents, are hydrophilic in nature; hence, incorporation of these excipients in the agglomerates formed using organic bridging liquid is difficult. Because of this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials[6]. To overcome these limitations of spherical crystallization Kadam et al. developed the crystallo-co-agglomeration (CCA) technique. It is a modification of the spherical crystallization technique in which a drug is crystallized and agglomerated with excipients or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing two drugs or a low-dose or poorly compressible drug in combination with diluents.

Neutralization Technique (NT)

This technique involves the formation of fine crystals by neutralization and consequently their agglomeration by a bridging liquid. Spherical crystallization of tolbutamide and phenytoin were reported by this technique. The drug was dissolved in alkaline solution and then poured into an acidic solution containing polymers and bridging liquid under constant agitation[7]. The drug crystals are precipitated out by

neutralization of the base with acid. Then the precipitated crystals were simultaneously agglomerated with the incorporated polymer through the wetting action of the bridging liquid.

Steps of Spherical Crystallization

Flocculation Zone

In this zone the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation, the adsorbed bridging liquid links the particles by forming bridge or lens between them. In this zone, loose open flocs of particles are formed by pendular bridges and this stage of agglomeration process where the ratio of liquid to the void volume is low and air is the continuous phase, is known as the pendular state. Mutual attraction of particles is brought about by surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerate is completely filled with the liquid. An intermediate state known as funicular state exists between the pendular and capillary stage. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure[8].

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 causing pore space in the pellet to be completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision[9].

Fast Growth Zone

The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size particle following random collision of well formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances article deformation and subsequent coalescence.

Constant Size Zone

In this zone agglomerate ceases to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomerate. The size reduction may be due to attrition, breakage and shatter. The rate-determining step in agglomeration growth occurs in zero growth zone when bridging liquid is squeezed out of the pores as the initial flocs are transformed into small agglomerates[10].

Factors Affecting the Process of Spherical Crystallization

Temperature of the System

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

Mode and Intensity of Agitation

The extent of mechanical agitation along with the amount of bridging liquid determines the rate of formation and size of agglomerates. The stirring speed must be optimized. High speed agitation is necessary to disperse the bridging liquid through the system. But in some cases increasing stirring rate, may cause reduction in agglomerate formation due to increased disruptive forces. Higher stirring rate produces agglomerates that are less porous and more resistant to mechanical stress[11].

Amount of Bridging Liquid

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

Choice of Solvent

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

The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility by using ternary diagram[12].

Residence Time

The time for which agglomerates remain suspended in reaction mixture affect their strength.

Evaluation of Spherical Crystals

Particle Size and Size Distribution

Particle size and shape of pharmaceutical ingredients can be changed with this method. Generally a large size and spherical shape particle are formed. Size of particles are improved due to the aggregation if particles influenced by the bridging agent. Similarly, agitation of solvent system during process results in the spherical shape of particles. Size of the particle and their distributions can be determined by simply sieve analysis. Now with the help of Ro-Tap sieve shaker, particle size analysis can be determined. In advance technology image-analyzer is used to determined size and volume of the particle[13].

Particle Shape or Surface Topography

Following methods are used:

Optical Microscopy

The shape of the spherical crystals is studied by observing these under an optical microscope. The observations are made under the observation like 10X, 45X, 60X etc[14].

Electron Scanning Microscopy

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

X-ray Powder Diffraction

This is an important technique for establishing batch to- batch reproducibility of a crystalline form. The form of crystal in agglomerates determine by using technique. An amorphous form does not produce a pattern[15]. The X-ray scattered in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a compound.

Mechanical Strength

Spherical crystals should posse's good mechanical strength as that directly reflects the mechanical strength of compact or tablet. This may be due to increased intraparticle force within spherical agglomerated crystals. It is determine by using the following two methods:

Tensile Strength

Tensile strength of spherical crystals is measured by applying maximum load required to crush the spherical crystal. This method is a direct method to measure the tensile strength of spherical crystals.

Crushing Strength

It is measured by using 50ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel is then used as hallow support and the guide tube with close fitting tolerances to the Plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). Mercury is introduced from reservoir into the upper chamber at the rate of 10 gm/sec until the single granule crushed; loading time should be <3 minutes. The total weight of the plunger and the mercury required to fracture a granule is the crushing load[16].

Flow Property

Flow property of the material depends on the force developed between the particle, particle size, particle size distribution, particle shape, surface texture or roughness and surface area. The improvement in the flowability of spherical crystals could be attributed to the significant

reduction in inter-particle friction, due to their spherical shape and a lower static electric charge Following are the methods used to determine of flow property

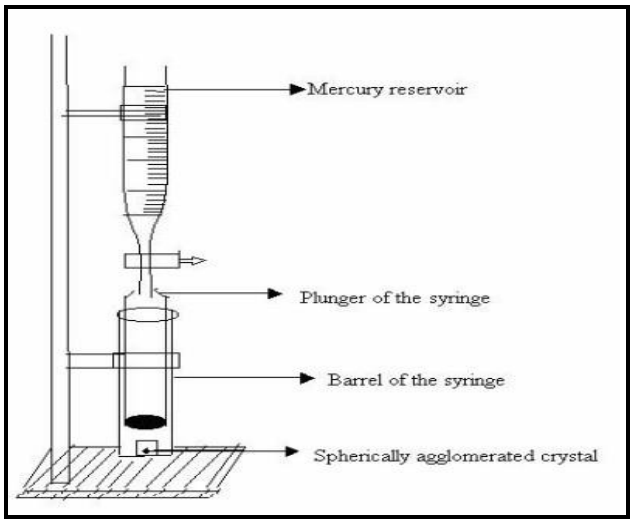

Figure 4: Crushing strength apparatus

Angle of Repose

This is the common method used for determination of flow property. The angle of repose is the angle between the horizontal and the slop of the heap or cone of solid dropped from some elevation. Values for angle of repose ≤ 30 usually indicate free flowing material and angle ≥ 40 suggested a poor flowing material. The angle of repose can be obtained from equation:

$$\mathbf{Tan\ \theta = h/0.5d}$$

Where h = height of the cone and d = diameter of the cone

Compressibility or Carr's Index

A simple indication of ease with which a material can be induced to flow is given by application of compressibility index:

$$\mathbf{I = (1\text{-}V/Vo) *100}$$

Where, v = the volume occupied by a sample of powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping.

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

Hausner Ratio

It is calculated from bulk density and tap density.

Hausner ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow (20% Carr Index) and the value greater then

1.25 indicates poor flow (33% Carr Index).

Density

This method involve the size enlargement therefore volume of powder get increase and density get decrease. Density of the spherical crystals is the mass per unit volume.

$$\mathbf{Density = M/V}$$

Where M= mass and V= volume of powder.

Packability

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower than that of single crystals, which can improve the packability of the agglomerates. The packability of agglomerates improved compared with those of the original crystals and that the agglomerated crystals are adaptable to direct tableting. The packability assessed by analysis of the tapping process with the Kawakita method and using the parameters a, b, 1/b, k in the equation:

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

$$C = (Vo\text{-}Vn)/Vo,$$

$$a = (Vo\text{-}V\infty)/Vo.$$

Where, N =Number of tapping, C =Difference in volume (degree of volume reduction.) and a, b are constant.

Compression Behaviour Analysis

Good compatibility and compressibility are essential properties of directly compressible crystals. The compaction behaviour of agglomerated crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Spherical

agglomerates possess superior strength characteristics in comparison to conventional crystals. It is suggest that the surface are freshly prepared by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals. Compaction behaviour of agglomerated crystals can evaluated by Heckel analysis and Stress relaxation test[17].

Friability Test

The friability of the spherical crystals is the combination of the attrition and sieving process in to a single operation. Granules along with the plastic balls placed on a test screen. The sieve is then subjected to the usual motion of a test sieve shaker provided the necessary attrition on the granules. The weight of powder passing through the sieve is recorded as function of time. The friability index is determined from the slope of the plot of % weight of granules remaining on the sieve as a function of time of shaking[18]. Friability of agglomerates determined by using formula

$$\textbf{Friability(X)} = \{1\text{-}W/Wo\} \times 100$$

Where Wo = Initial weight of the crystalline agglomerates placed in sieve

W = Weight of the material which does not passed through sieve after 5 min.

Moisture Uptake Study

The study indicates the behaviour of uptake of moisture by drug and the prepared spherical crystals, which affect the stability. The weighted quantity of drug and spherical crystals placed in crucible at accelerated condition of temperature and humidity, $40^{o}C \pm 1^{0}C$ and 75% ± 3% respectively. The gain in weight of drug and spherical crystals is measured.

Dissolution Rate and Bioavailability

The dissolution rate and bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the agglomerated crystals. It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases[19]. Tabletting compacts partially breaks the agglomerated crystals and thus the average particle size is reduced. But compression also increases the particle density, which may adversely affect dissolution. Specific surface area of crystals is found to depend on the method used for spherical crystallization.

Applications of Spherical Crystallization in Pharmaceuticals

To Improve the Flow Ability and Compressibility

Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage form. Tablet is the most stable readily portable and consumed dosage form. The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products[20].

For Masking Bitter Taste of Drug

Microcapsules are prepared to mask the bitter taste of the drug. They are suitable for coating granules, since spherical material can be uniformly coated with a relatively small amount of polymer.

For Increasing Solubility and Dissolution Rate of Poorly Soluble Drug

Spherical crystallization has been described as a very effective technique in improving the dissolution behaviour of some drugs having low water solubility and a slow dissolution profile.

CONCLUSION

The spherical crystallization technique is a simple and inexpensive for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel because it eliminates most of

the steps which are required in granulation technology of tablet manufacturing. The spherical crystallization process can be used successfully to manufacture spherical crystals of poorly soluble drugs to improve flow ability and compatibility. So the spherical crystallization method may be an attractive approach for the improvement of direct tableting technique.

REFERENCES

1. Gupta MM, Sharma M, "Spherical crystallization: A tool of particle engineering for making drug power suitable for direct compression", International Journal of Pharmaceutical Research and Development, 2010, 1(12), 1-9.
2. Mahanty S, Niranjan P, Bhanoji ME, **"**Particle Design of Drugs by Spherical Crystallization Techniques", International Journal of Pharmaceutical Sciences and Nanotechnology, 2010, 3(2), 918.
3. Patil SV, Sahoo SK, "Pharmaceutical overview of spherical crystallization", Der Pharma Let, 2010, 2 (1), 421-426.
4. Goyal N, Sharma N, Sharma PK, "Spherical crystallization: A method for improving powder and tablet characteristics", Der Pharma Let, 2010, 2(4), 246-254.
5. Katta J, Rasmuson A, "Spherical crystallization of benzoic acid", International Journal of Pharmaceutics, 2008, 61-69.
6. Lieberman HA, Lachman L, Pharmaceutical Dosage Forms, Tablets, 1st Edition, Marcel Dekker, New York Publisher, 1989, 195-246.
7. Kawashima Y, "New processes application of spherical crystallization to particulate design of pharmaceuticals for direct tabletting and coating and new drug delivery systems", In: Powder Technology and Pharmaceutical Processes. Handbook of Powder Technology, 9th Edition, 1994, 493-512.
8. Kawashima Y, Okumara M, Takenaka H, "Spherical Crystallization: Direct Spherical Agglomeration of Salicylic Acid Crystals during Crystallization", Science Magazine, 1982, 216(4550), 1127-1128.
9. Chourasia, MK, Jain SK, Jain S and Jain NK, "Preparation and characterization of agglomerates of Flurbiprofen by spherical crystallization technique", Indian Journal of Pharmaceutical Sciences, 2003, 287-291.
10. Bhadra S, Kumar M, Jain S, Agrawal S and Agrawal GR, "Spherical crystallization of Mefenamic acid", Pharmaceutical Technology, 2004, 66-76.
11. Rasenack N, Hartenhauer H, Muller BW, "Microcrystal for dissolution rate enhancement of poorly water soluble drugs". International Journal of Pharmacy, 2003, 254, 137-145.
12. Gordon RE and Amin SI, Europian patent No.0120587, 1984.
13. Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y, "Particle design of Tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: improvement of dissolution rate", Journal of Pharmaceutical Sciences, 1987, 76, 471-474.
14. Jarosz PJ and Parrott EL, "Compression of granule strength and tablet tensile strength", Journal of Pharmaceutical Sciences, 1983, 72(5), 530-534.
15. Kuriki ST, Handa T, Takeuchi H, Kawashima Y, "Particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: Improvement of dissolution rate", Journal of Pharmaceutical Sciences, 1988, 76(6), 471-474.
16. Yadav AV, Yadav VB, "Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique", Journal of Pharmacy Research, 2008, 1(2), 105-112.
17. Jain SK, Chourasia MK, Jain NK, Jain S, "Preparation and characterization of agglomerates of flurbiprofen by spherical

crystallization technique", Indian Journal Pharmaceutical Sciences, 2008, 65(3), 287-291.

18. Dixit M, Kulkarni PK, "Spherical agglomeration of Indomethacin by solvent change method", International Journal of Pharma Research and Development, 2005, 2(9), 33-43.
19. Gohle MC, Parikh RK, Shen H, Rubey RR, "Improvement in flowability and compressibility of Ampicilline Trihydrate by spherical crystallization", Indian Journal Pharmaceutical Sciences, 2003, 634-637.
20. Nokhodchi A, Maghsoodi M, Hassanzadeh D, "An Improvement of Physicomechanical Properties of Carbamazepine Crystals", Indian Journal Pharmaceutical Research, 2007 6(2), 83-93.

