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REVIEW ARTICLE

Spherical Crystallization: A Novel Drug Delivery Approach

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ABSTRACT

Spherical crystallization is a fast developing technique of particle design in which crystallization and agglomeration can be achieved simultaneously in one step. It has been successfully utilized for improvement of flow ability and compactability of crystalline drugs. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone. General methods of spherical crystallization are emulsion solvent diffusion, spherical agglomeration, ammonia diffusion method and neutralization method. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time. Characterization of spherical crystals can be carried out using Optical Microscopy, Scanning Electron Microscopy, X-ray Powder Diffraction, Fourier Transform Infrared spectroscopy, Differential Scanning Calorimetry and Thin layer Chromatography.

KEYWORDS: Differential Scanning Calorimetry, Spherical crystallization, X-ray Powder Diffraction.

1. INTRODUCTION

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs [1].

Presently, particle design techniques are widely used in pharmaceutical industries to modify primary properties like particle shape, size, crystal habit, crystal form, density, porosity etc. as well a secondary properties like flow ability , compressibility, compact ability, reduction In air entrapment,etc Spherical crystallization is one of such particle design technique in which crystallization and agglomeration process are carried out simultaneously. Spherical Crystallization process transforms the fine crystal obtain during crystallization into a 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 [2].

ADVANTAGES OF SPHERICAL CRYSTALLIZATION [3]

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 tabletting because of their excellent flowability and packability.
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.

NEED FOR SPHERICAL CRYSTALLIZATION

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 two techniques commonly used to improve the bioavailability of poorly soluble drugs. The

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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 Kawashima developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of microcrystalline drugs [3].

THE PRINCIPLE STEPS INVOLVED IN THE PROCESS OF SPHERICAL CRYSTALLIZATION [4]

Bermer and Zuider Wag proposed four steps in the growth of agglomeration.

1. Flocculation Zone:

In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation; the adsorbed bridging liquid links the particles by forming a lens bridge between them. In these zones, loose open flocs of particles are formed by pendular bridges.

2. Zero Growth Zone:

Loose floccules get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing poor space in the pellet of 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 on the small agglomerates. This formation of large particles following random collision of well-formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances particle deformations and subsequent coalescence. Another reason for the growth of agglomerates size is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

4. Constant Size Zone:

In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. 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.

FACTORS CONTROLLING THE PROCESS OF AGGLOMERATION: [5]

1. Solubility profile: The selection of solvent is dictated by solubility characteristic of drug. A mutually immiscible three solvent system consisting of a poor solvent (suspending liquid), good solvent and bridging liquid are necessary. Physical form of product i.e.whether microagglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions. 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.

2. Mode and intensity of agitation: High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would be reflected as change in force acting on agglomerate, which ultimately affects the shape of agglomerate. The extent of mechanical agitation in conjugation with the amount of bridging liquid determines the rate of formation of agglomerate and their final size.

3. Temperature of the system: Study revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to the effect of temperature on the solubility of drug substance in the ternary system.

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

METHODS OF SPHERICAL CRYSTALLIZATION

1. Quasi emulsion solvent diffusion [6]

The drug is dissolved in the good solvent (solvent that readily dissolves the compound to be crystallized), and the solution is dispersed into the poor solvent (an antisolvent generating the required supersaturation), producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase.

2. Spherical agglomeration (SA method) [7]

In both processes is used a solvent that readily dissolves the compound to be crystallized (good solvent), and a solvent that act as an antisolvent generating the required supersaturation (poor solvent). In the SA method also a

third solvent called the bridging liquid is added in a smaller amount to promote the formation of agglomerates. A near saturated solution of the drug in the good solvent is poured into the poor solvent. Provided that the poor and good solvents are freely miscible and the "affinity" between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. Under agitation, the bridging liquid (the wetting agent) is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid act to adhere the crystals to one another. It has been found that the product properties are quite sensitive to the amount of the bridging liquid. [8] Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles [9] Also the choice of bridging liquid, the stirring speed and the concentration of sol

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3. Ammonia diffusion method

In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water [12].

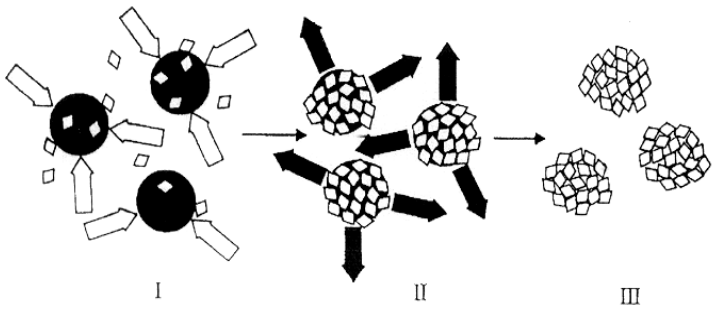

Figure 1: Steps involved in Ammonia Diffusion System (ADS).

4. Neutralization Method (NT):- This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug tolbutamide was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous solution of Hydroxypropyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide, which was then, crystallized out [13].

Besides above mentioned methods there are some other traditional methods for the crystallization which are carried out by controlling the physical and chemical properties and also called as the non-typical spherical crystallization process. These methods include Salting out precipitation, cooling crystallization and crystallization from the melting. [14]

EVALAUTION OF SPHERICAL CRYSTALS [14]

As these spherical agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage forms so it is necessary to evaluate them by using different parameters.

1. 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. Flow ability of the agglomerates is much improved as the agglomerate exhibits lower angle of repose then that of single crystals. This improvement in the flow ability of agglomerates 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.

(a) 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.

Tan θ = h/0.5d

Where h- height of the cone and,
d- diameter of the cone

(b) Compressibility or Carr index

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

I = (1-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.

(c) 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).

2. DENSITY

Density of the spherical crystals is the mass per unit volume.

Density = Mass(M)/ Volume(V)

3. POROSITY

Porosity of granules affects the compressibility. Porosities are of two types "intra granular and Intergranular and these are measured with the help of true and granular densities.
Intra granular porosity = 1- Granular density /True density.
Inter granular porosity = 1- Bulk density / Granular density
Total Porosity = 1- Bulk density/ True density

4. PACKABILITY:

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower then 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 tabletting. The packability assessed by analysis of the tapping process with the Kawakita (I) and Kuno (II) method and using the parameters a, b, 1/b, k in the equation

$$N/C = 1/(ab) + N/a \quad \text{.....I}$$

$$C = (Vo-Vn)/Vo,$$

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

$$Pf - \rho n = (\rho f - \rho o).\exp.(-kn) \quad \text{.....II}$$

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

5. COMPRESSION BEHAVIOUR ANALYSIS

Good compatibility and compressibility are essential properties of directly compressible crystals. The compaction behavior 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 were evaluated by using following parameters

(a) Heckel Analysis

The following Heckel's equation used to analyze the compression process of agglomerated crystals and assessed their compatibility.

In [1 / (1-D)] = KP+A

Where:
D is the relative density of the tablets under compression Pressure
K is the slope of the straight portion of the Heckel Plot
The reciprocal of K is the mean yield is the mean yield pressure (Py).
The following equation gives the intercept obtained by extrapolating the straight portion of the plots

A=1n [1 / (1-D0] +B

Where:
D0 is the relative density of the powder bed when P=0.
The following equation gives the relative densities corresponding to A and B.

DA=1-e-A

DB=DA-D0

(b) Stress Relaxation Test

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which is coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed. After the certain limit of pressure attained, the upper punch held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch. The result corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions.
The following equation finds the relationship between relaxation ratio Y (t) and time t, calculated the parameters As and Bs, and assessed relaxation behavior.

t/Y (t) = 1/AsBs-t/As

Y (t) = (P0-Pt)/P0

Where:
P0 is the maximum compression pressure, and Pt is the pressure at time t.

6. MECHANICAL STRENGTH

Spherical crystals should posses' good mechanical strength as that directly reflects the mechanical strength of compact or tablet. It is determine by using the following two methods,

(a) 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

(b) 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.

7. 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 slop of the plot of % weight of granules remaining on the sieve as a function of time of shaking.

Friability of agglomerates determined by using formula

Friability(X) = {1-W/Wo}/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.

8. PARTICLE SIZE AND SIZE DISTRIBUTION

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.

9. MOISTURE UPTAKE STUDY

The study indicates the behavior 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 C ± 10C and 75% ± 3%respectively. The gain in weight of drug and spherical crystals is measured

10. PARTICLE SHAPE / SURFACE TOPOGRAPHY

Following methods are used

(a) Optical Microscopy

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

(b) Electron Scanning Microscopy

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

(c) 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. 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.

(d) Fourier Transform Infrared spectrometer (FTIR) [3]:

It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the salvation.

(e) Differential scanning calorimeter (DSC) [3]:

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC.

(f) Thin Layer Chromatography (TLC): It determines the drug and polymer interaction of spherical agglomerates and also studies the stability of drug in different solvents.

APPLICATIONS OF SPHERICAL CRYSTALLIZATION IN PHARMACEUTICALS

1. To improve the flowability 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. Such manufacturing of the tablets involves simple mixing and compression of powders which gives benefits like time and cost saving [15]. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make suitable for direct compression tabletting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding [16]. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired [17]. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression [18,19]. Due to different crystal habit many drugs show inconvenient flowability and compressibility. So these problems can be solved by converting them into a agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility.

2. 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. Microcapsules of following drugs were prepared for masking of bitter taste [20].

3. For increasing solubility and dissolution rate of poorly soluble drug: Spherical crystallization has been described as a very effective technique in improving the dissolution behavior of some drugs having low water solubility and a slow dissolution profile.

4. Better Bioavailability: As spherical crystallization technique increases the solubility of poorly soluble drugs and promotes faster dissolution of drug in the intestinal fluid. Improved dissolution profile of drug causes increase in drug absorption and hence, greater will be the bioavailability of drugs [8].

5. To prepare novel drug delivery systems : It can be used to prepare microspheres and nanospheres, microbaloons, nanoparticles and micro pellets as novel particulate drug delivery system [21].

CONCLUSION:

The spherical crystallization technique is a new inexpensive technique for reducing time and cost by enabling faster operation, less machinery and fewer personnel because it removes most of the steps which are required in granulation technology of tablet manufacturing. It provides advances in tabletting technology by introduction of number of directly compressible excipeints. The spherically agglomerated crystals can be prepared into tablet form or compounded directly into a pharmaceutical system without further processing such as granulation. This technique of particle design of drugs has emerged as one the areas of active research currently of interest in pharmaceutical manufacturing.

REFERENCE

[1] A.R. Paradkar, A.P. Pawar, K.R. Mahadik, S.S. Kadam. Spherical crystallization: a novel particle design technique. Indian Drugs, 1994, 6: 229–233.

[2] Y Kawashima. Spherical crystallization as a novel particle design technique for oral drug delivery system. Chin. Pharm. J., 1989, 41: 163-172.

[3] M.M Gupta, B Srivastava, M Sharma, V Arya. Spherical crystallization: a tool of particle engineering for making drug powder suitable for direct compression. Int. J. Pharm. Res. Dev., 2010, 12: 1-10.

[4] M.K. Chouracia, A. Jain, S. Valdya, S.K. Jain. Utilization of spherical crystallization for preparation of directly compressible materials. Indian Drugs, 2004, 41(6): 319-329.

[5] P.K. Kulkarni, B.G. Nagavi. Spherical crystallization. Ind. J. Pharm. Eudc., 2002, 36(2): 66-73.

[6] K. Jyothi, A.C. Rasmuson. Spherical crystallization of benzoic acid. Int. J. Pharm., 2008, 348: 61-69.

[7] A. Ribardire, P. Tchoreloff, G. Couarraze, F. Puisieux. Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system. Int. J. Pharm., 1996, 144: 195 - 207.

[8] Y. Kawashima, M. Imai, H. Takeuchi, H. Yamamoto, K. Kamiya, T. Hino. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder Technol., 2003, 130: 283-289.

[9] A. Bausch, H. Leuenberger. Wet spherical agglomeration of proteins as a new method to prepare parenteral fast soluble dosage forms. Int. J. Pharm., 1994, 101: 63-70.

[10] A.S. Bos, F.J. Zuiderweg. Size of agglomerates in batch wise suspension agglomeration. Chem. Eng. Res. Des., 1987, 65: 187.

[11] A.F. Blandin, D. Mangin, A. Rivoire, J.P. Klein, J.M. Bossoutrot. Agglomeration in suspension of salicylic acid fine particles: influence of some process parameters on kinetics and agglomerate final size. Powder Technol., 2003, 130: 316-323.

[12] Y. Kawashima, F. Cui, H. Takeuchi, T. Hino, T. Niwa, K. Kiuchi. Parameters determining the agglomeration behavior and the micrometric properties of spherically agglomerated crystals prepared by spherical crystallization technique with miscible solvent system. Int. J. Pharm., 1995, 119: 139-147.

[13] A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi, T. Hino, T. Niwa. Particle design of Tolbutamide by the spherical crystallization technique IV, Improved of dissolution and bioavailability of direct compression tablets prepared using Tolbutamide agglomerated crystals Chem Pharm Bull., 1992, 40: 3030-3035.

[14] A.V. Yadav, V.B. Yadav. Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique. J. Pharm. Res., 2008, 1(2): 105-110.

[15] R.F. Shangraw. Compressed tablets by direct compression. In: Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets, vol. 1. Marcel Dekker, New York, 1989: 195–246.

[16] J.K. Guillory. Polymorphism in pharmaceutical solids. Marcel Dekker, New York, 1989:183-226.

[17] Y. Kawashima. Development of spherical crystallization technique and its application to pharmaceutical system. Arch. Pharm. Res., 1984, 7(2): 145-151.
[18] Y. Kawashima, H. Ohno, H. Takenaka. Preparation of spherical matrixes of prolonged release drug from liquid suspension. J. Pharm. Sci., 1981, 70(8): 913-916.
[19] Y. Kawashima, K. Furukawa, H. Takenaka. The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. Powder Technol., 1981, 30: 211.
[20] I. Eros, H. Goczo, P. Szabo-Revesz, B. Farkas, M. Hasznos-Nezdei, F.S. Serwanis, K. Pintye-Hodi, P. Kasa, I. Antal, S. Marton. Development of spherical crystals of acetyl salicylic acid for direct tablet making. Chem. Pharm. Bull., 2000, 48(12): 1877-1881.
[21] S. Mutalik, A.N. Usha, M.S. Reddy, A.K. Ranjith, P. Kushtagi, N. Udupa. Prepartion and invitro preclinical and clinical studies of aceclofenac spherical agglomerates. Eur. J. Pharm. Biopharm., 2008, 70: 674-683.

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