



International Journal of ChemTech Research CODEN(USA): IJCRGG ISSN : 0974-4290 Vol.1, No.3 , pp 476-482, July-Sept 2009

Comparative Tabletting behavior of Carbamazepine granules with spherical agglomerated crystals prepared by spherical crystallization technique

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ABSTRACT : The aim of this study was to prepare Spherical agglomerates of Carbamazepine by Quesi-Emulsion Solvent Diffusion system (QESDS) with Ethanol-Chloroform-Water system. Granules were prepared by wet granulation method with different excipients. The prepared agglomerates were evaluated for flowability, compressibility, wettability, packability and solubility. Tablets were prepared and evaluated for tensile strength, hardness, friability, disintegration time and dissolution rate. Formulate, evaluate and compare the tablet dosage form prepared from agglomerated crystals, granules and physical mixture of drug with excipients. The prepared agglomerates were white, free flowing and spherical in shape. The yield of agglomerates was 95% and showed 90-95% drug content. Prepared agglomerates were also improved in compressibility, packability and solubility. The tablet dosage form prepared from agglomerated crystals showed improvements in tensile strength, hardness, friability, disintegration time and dissolution rate as compared to tablets prepared from granules. Thus this technique is simple, less expensive, may be an advantages for developing it on a commercial scale for manufacturing of tablets.

KEY WORDS: Carbamazepine, agglomerated crystals, packability, compressibility, tensile strength, solubility.

INTRODUCTION:

The formulation and manufacturing of solid oral dosage forms particularly tablets, the most convenient pharmaceutical dosage forms and hence widely used in the chemotherapeutic field should comprise only a few working steps (1). The material used for the production of tablet should be in physical form that flows smoothly, directly compressible and physically stable so as to achieve rapid production capability of tablet formulation.

One of the most important changes in the manufacturing of tablet in the last decade is the large-scale introduction of direct compression of tablets (direct tabletting method). The traditional method involves first making granules and then compressing them into tablets by way of indirect (granule) tabletting. However the need in recent year for process validation, GMP and automation of production process has focused renewal attention on direct tabletting method which involved few steps. Direct tabletting in pharmaceuticals has been successfully industrialized by formulation with higher amount of fillers. However it is desirable to reduce amount of filler there by reducing the size of dosage form and in production cost. To achieve these goals, the macromeritic properties like Flowability, packability, compressibility of the drug must be improved without aid of fillers and binders. Direct Tabletting necessitates an active ingredient powder that excels in flowability, bindiability, and mechanical strength.

There are currently limited pharmaceutical tablets on commercial production that can be made by direct tabletting for that reason development of the design method of active ingredient crystals that can be directly tabletted has been waited (2). Most powders cannot be compressed directly into tablet because they lack the proper characteristics of binding or bonding together into a compact entity. For these reasons particle design is done to improve the properties of particle like flowability, packability and solubility to impart a new function to formulation and to guarantee more stable and reliable powder processing (3). In 1986, Kawashima, Y., 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 into compact spherical forms during the crystallization process." It also enables coprecipitation of drug and encapsulating polymer in the form of spherical particle (4).

This technique could enable subsequent process such as separation, filtration, drying etc to be carried out more efficiently. Furthermore the resultant agglomerated crystals could be easily compounded with other pharmaceutical powders due to their spherical shape (5). The recent advances in tabeletting technology especially the introduction of number of directly compressible excipients has made the process cost-effective due to faster operation, less machinery and fever personnel requirements in this technology. Physicochemical properties of pharmaceutical crystals could be dramatically improved for pharmaceutical process i.e. milling, mixing and tabletting because of their excellent flowability and packability (6).

Carbamazepine is an anticonvulsant and also used for the treatment of pain associated with trigeminal neuralgia. It is white or yellowish white crystalline powder and exists as stone shaped crystals having poor flow properties and compressibility. It has limited aqueous solubility as well as slower dissolution rate, which get absorbed slowly and erratically after oral administration and required higher dose for its effect.

So as to overcome the problems related to Flowability, compressibility, solubility, dissolution rate, the spherical agglomeration of Carbamazepine has been prepared by spherical crystallization technique. The compressed tablets were prepared from agglomerated crystals of Carbamazepine, the physical mixture of Carbamazepine directly compressible excipients with and the conventional granulation method. The performance characteristics of these tablets via hardness, tensile strength, friability, porosity, disintegration time and dissolution rate have been studied and compared.

MATERIAL AND METHOD : Materials:

Materials:

Carbamazepine was obtained as gift sample from Bajaj Health Care Pvt. Ltd. (Mumbai, India). Its purity was confirmed by testing its melting points and by examining its IR spectrum.

All the solvents were pure laboratory grade purchased from Loba chemicals.

Solubility study:

Solubility study of carbamazepine in different solvents was done by adding an excess amount of Carbamazepine (5gm) to 10ml of various solvents such, ethanol, chloroform, and water in 50ml conical flask. The suspension was shaken at room temperature for 12 hour in a flask. The samples were centrifuged, 5ml aliquots of the supernatants was evaporated and residue was diluted with 1% SLS up to 100ml, from that 1 ml was taken and diluted again up to 100 ml with 1% SLS and assayed spectrophotometrically at 288nm (7).

Selection of solvent quantity:

Selection of quantity of solvent for spherical crystallization was done by using SCHEFFE third degree incomplete model (8-9). Optimized the different critical conditions before the preparation of spherical agglomerates of Carbamazepine like Selection of temperature difference between the drug solution and dispersion medium and Selection of agitating speed for spherical agglomeration crystals.

Preparation of carbamazepine agglomerates:

Qasi-Emulsion solvent diffusion technique (QESD Method)

Carbamazepine (2.5gm) was dissolved in the mixture of good solvent ethanol (15ml) and bridging agent chloroform (5ml) thermally controlled at 55° C so as to form the saturated solution of drug. The solution was poured into 80ml of distilled water (poor solvent) with stirring rate at 1000 ± 50 rpm by using paddle type of agitator at room temperature. After agitating the system for 5 min the prepared agglomerates were collected by filtration through Whatman filter paper no.42 under the vacuum, washed the spherical crystals with distilled water and placed at 60° C for drying in hot air oven and stored in desiccators (10-11).

Preparation of granules:

Wet Granulation method: Wet Granules were prepared by wet granulation method using povidone as granulating agent.

Dry granulation method: granules were prepared by slugging method. Slugges were prepared by using compression machine equipped with 20mm standard concave punches.

Evaluation of spherically agglomerated crystals: *Solubility study:*

Solubility study was carried out in distilled water and by using flask shaker. Excess Carbamzepine and different spherical agglomerated crystals were introduced into a 25 ml bottle containing 10 ml distilled water (pH 7 ± 0.1). All suspensions were protected from the light by wrapping the flask with aluminum foil. The flasks were shaken for 24 hours at room temperature. The content of each flask was then filtered through a Whatman filter paper. The filtrate was then diluted in distilled water and assayed spectrophotometrically at 285nm in water. (Double beam spectrophotometer). Each solubility was determined in triplicate (n =3).

Content determination:

Three samples of 100mg equivalent of Carbamazepine agglomerates was accurately weighed, crushed & transferred to 100ml standard conical flask to this 10ml of ethanol was added to dissolve the drug & polymer. The volume was made up to 100ml with 1% SLS & filtered through Whatman filter paper. From resulting filtrate, 1ml solution was taken & diluted to 50 ml, so as to form $20\mu g$ /ml & absorbance was taken at

288nm.Calculate the content of the spherical agglomerates by using calibration curve.

Dissolution study

Using USP –II Apparatus (rotating basket method) carried out the dissolution test.900ml of distilled Water with 1% SLS maintained at $37 \pm 1^{\circ}$ C was used as dissolution medium .The rotation speed of basket was kept at 75 rpm.

Flow property

Flowability of Carbamazepine and their agglomerated crystals were determined in terms of following parameters viz. Angle of Repose, Carr's Compressibility Index and Hausnar ratio.

Particle size distribution: Measured by using mechanical sieve shaker.

Density and porosity:

Density like Bulk Density (ρ_b), Granular Density (ρ_g), True density (ρ_t) and porosity like Intraparticle porosity (1- ρ_g / ρ_t), Interparticle porosity (1- ρ_b / ρ_g), and Total porosity (1- ρ_b / ρ_t) of agglomerated crystals were calculated.

Packability:

Packability was assessed by analysis of the tapping process with the Kawakitas (I) and Kunos (II) method and using the parameter a, b, k in the equation:

N/C = 1/(ab) + N/a....I

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

$$\rho_{\rm f} - \rho_{\rm n} = (\rho_{\rm f} - \rho_{\rm o}) \cdot \exp((-kn) \dots \Pi)$$

Where,

N =Number of tapping.

C =Difference in volume (degree of volume reduction.) a and b = constant for packability and flowability.

Vo = Initial volume.

Vn = Final volume after nth tapping.

 $V\infty$ = Powder bed volume at equilibrium.

 $\rho_{f_{n}} \rho_{o_{n}} \rho_{n}$ = Apparent densities at equilibrium, nth tapped, initial state respectively

From the graph of N/C verses N, then the compactability \mathbf{a} , constant of Flowability b and cohesiveness $1/\mathbf{b}$ are obtained from the slop $1/\mathbf{a}$ and the intercept $1/\mathbf{ab}$ of the plot of modified Kawakitas equation and value of k in Kunos equation was determined directly putting the values of densities (14-16).

Formulation and preparation of tablets from agglomerated crystals, granules and direct compression method:

- Sift the prepared agglomerated crystals or granules through sive no # 30.
- Mix the agglomerated crystals or granules with sifted quantity of microcrystalline cellulose and croscarmellose sodium mix in polybag for 5 minutes.
- To the above-prelubricated blend add sifted quantity of magnesium stearate mix in polybag for 3 minutes.
- Use this lubricated blend for compression of tablets using 8 -station compression machine equipped with 10.5mm standard concave punches tooling.

 For direct compression method, compress the carmamazepine raw crystals with directly compressible excipients (microcrystalline cellulose and croscarmellose sodium) by lubricating the blend with magnesium stearate.

Evaluation of prepared tablets

Dissolution study:

Using USP –II Apparatus (rotating basket method) carried out the dissolution test.900ml of distilled Water with 1% SLS maintained at 37 ± 1^{0} C was used as dissolution medium .The rotation speed of basket was kept at 75 rpm.

Disintegration study:

Disintegration test was carried out as described under procedure for uncoated tablets in USP.

Drug content:

Drug content was determined as per the mentioned in compendial procedure.

Friability test:

Twenty tablets were weighted and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighted again. The percentage friability was measured using the formula,

% $F = \{1-W / W_0\} X 100....III$

Where, %F = Friability in percentage.,

 W_0 = Initial weight of tablets.

W = Weight of tablet after revolution.

Thickness:

Three tablets selected randomly from each batch and thickness was measured by using vernier caliper.

Hardness:

Hardness was measured by using Pfizer hardness tester; hardness values are given in Kg.

Tensile strength test:

Measured by using the following formula,

 $T = 2F / \pi DL....IV$

Where, T = Tablet tensile strength.

- D = Tablet diameter (mm).
 - L = Thickness (mm).

$$F = Hardness (Kg/cm^2).$$

Porosity study of compacted tablet:

Twenty-four hours after ejection of compacted tablet of Carbamazepine and their agglomerated crystals measured the volume of the compacted tablet by measuring thickness and diameter. The %Porosity (ϵ) was calculated from the following equation (18).

$$\varepsilon = \{(v-v_0) / v\} \times 100 \dots$$

Where, v = Tablet volume(r X h.),

r = Radius of the compacted tablet,

h = thickness of the compacted tablet,

 v_o = the volume of material at zero porosity (true volume)

RESULTS AND DISCUSSION:

The method used for the preparation of agglomerated crystals was Quasi-Emulsion Solvent Diffusion method (QESD), in which droplets of solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible. Crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets.

From the solubility data of Carbamazepine, the good solvent (ethanol), bridging agent (chloroform) and poor solvent (distilled water) were selected for the spherical crystallization process. Chloroform was chosen as bridging liquid because of its excellent wettability with the drug and immiscibility with the dispersion medium (poor solvent).

The average diameter of the agglomerated crystals increased with increasing content of chloroform in the system due to the enhanced agglomeration of powdery crystals. The diffusion rate of ethanol and chloroform from the droplets were enhanced with increasing the content of ethanol in the system. The increase in diffusion rate of chloroform from droplets shortens the agglomeration process of the crystals produced in the droplets. Decreases in chloroform content of droplets reduce the agglomeration force of the crystal due to increase in the unwaited part of the crystals with chloroform in the agglomerates resulting in formation of flocks produced with pendular bridges of water. Thus diameter and recovery of agglomerates decreased with increasing the ethanol content in the system. Agglomerated crystals showed drug content between 95-97%.

Table: 2 represent the all evaluation parameters of prepared agglomerates crystals. Solubility study of Carbamazepine in different solvents revealed that it is (98.93mg/ml), soluble in chloroform ethanol (49.52mg/ml), water (0.161mg/ml).Quantities of the were determined by using Scheffe selected solvents third degree incomplete model. The selection of optimized temperature difference between drug solution and dispersion medium was 25^oC and agitation speed 1000 ± 50 rpm.

Solubility profile of prepared agglomerates:

The solubility study was carried out in distilled water and in 1% SLS. The solubility of Carbamazepine in distilled water was 0.161 mg/ml and in 1% SLS was 0.466 mg/ml. There is significant increase in the solubility of spherically agglomerated crystals in distilled water 0.293 mg/ml, and in 1 % SLS 0.618 mg/ml as compared to carbamazepine. The improvement in solubility may be due to changing the crystal forms, different habit, structure, surface modification. In some instances solvents included into the crystals forms solvates changing the surface properties and the reactivity of drug particles and internal energy of the molecules playing an important role in increasing solubility of drug.

Particle size distribution:

The agglomerated crystals have wider particle size distribution than that of raw crystals of Carbamazepine.The agglomerated crystals size was easily controlled by adjusting agitating speed, temperature of the system and chloroform content in the system and residence time. Agglomerate crystal size decreased with increasing agitation speed and decreased chloroform content. Increasing the temperature difference between the chloroform-ethanol drug solution and poor solvent water result in decrease in agglomerate size.

Flow properties of agglomerated crystals:

Flowability parameters of the spherically agglomerated crystals were studied in term of Angle of repose, Carr index and Hausnar ratio. The Carr index revealed that the flowability of the Carbamazepine was significantly poor (** P<0.01) than that of the agglomerated crystals i.e. the agglomerates had lower Carr index than carbamazepine raw crystals. Hausnar ratio of agglomerated crystals was less than 1.25 that also indicates improvement in flowability of agglomerated crystals. Carbamazepine crystals were found to have significantly higher angle of repose in comparison to the spherical agglomerates, which could be due to the irregular shape of the crystals, which hindered in the uniform flow of crystals from funnel. The reason for the excellent flowability of spherical crystals might be the significant reduction in interparticle friction because of the perfect spherical shape and the larger size of crystals

Porosity study:

From the porosity profile of agglomerated crystals. The interparticle, intraparticle and total porosity of agglomerated crystals showed significantly higher as compared to the raw crystals of Carbamazepine. To a minor degree, agglomerates porosity gives them good wettability and faster dissolution properties.

Density:

From the bulk, granular, and true density of the agglomerated crystals, the results indicated that all densities of the agglomerated crystals showed decrease value because of the increased in volume and the total porosity of agglomerated crystals.

Packability study:

Represent the packability profile of agglomerated crystals. From Kawakitas equation the agglomerated crystals showed significantly smaller value of parameter **a** (** P<0.01) & significantly higher value (** P<0.01) of parameter **b**, 1/b as compared to raw crystals of Carbamazepine. From Kenos equation agglomerates showed significantly larger value (** P<0.01) of parameter **k**.

From the values of these all packability parameters it proved that the agglomerated crystals showed higher packability then that of raw Carbamazepine crystals. The increasing packability of agglomerated crystals may be due to lower surface & wider particle size distribution of spherical crystals, during tapping process smaller particle might have infiltrated into the voids between the larger particles & resulted in improved packability.

Tablet formulation:

Table: 3 represent the formulation of the tablets of agglomerated crystals, granules, raw crystals of Carbamazepine. The prepared tablets were evaluated and compared with each other and the marketed tablet.

Evaluation of prepared tablet formulation:

Figure: 1 represent the dissolution profile of the tablet formulation. The tablet prepared from agglomerated

crystals of Carbamazepine with the polymer showed higher dissolution rate as compared to the other tablet formulation. The order of dissolution profile of tablet formulation within 30 min. CBZ-SCT > CBZ-SGT > CBZ-WGT. Table: 4 represent the evaluation of prepared tablets from agglomerated crystals and granules.

As carbamazepine is not directly compressible, tablet manufacturing gives significant problems. Severe sticking, capping, lamination occur during direct compression along with directly compressible excipients. Therefore tablets were not prepared by direct compression method and further evaluation was not done. Prepared tablets from agglomerated crystals showed significantly improved in disintegration time, tensile strength, porosity, hardness as compared to the tablets prepared from granules. A hardness study of tablets showed that the tablets prepared from agglomerated crystals had greater mechanical strength than those prepared from granules may be due to stronger bonds formed between the newly formed crystals of agglomerates. The formation of stronger bonds may be due to increase fragmentations of the large size fraction should result in increased bonding due to the formation of fresh surface. The smaller fragment particles would tend to occupy the interparticular voids and thus increase the

CONCLUSION:

From the present work we can conclude that spherical agglomerates have improved solubility, dissolution rate, flowability, porosity of the Carbamazepine. Prepared tablets from the directly compressible agglomerates showed improvements in dissolution profile, disintegration time, mechanical strength, porosity, friability as compared to tablets prepared from raw Carbamazepine crystalline powder and granules. Thus this technique is simple, less expensive, may be an advantages for developing it on a commercial scale for manufacturing of tablets.

ACKNOWLEDGMENTS:

The authors express their gratitude to Bajaj Health Care Pvt. Ltd. (Mumbai.) for providing Carbamazepine as gift sample for this research work.

 Table 1: Codes for prepared Carbamazepine Spherical agglomerated crystals and granules.

Sr.No	System	Code for agglomerates or	
•		granules	
1	Commercial Carbamazepine crystals	CBZ	
2	Carbamazepine granules prepared by wet granulation technique	CBZ-WG	
3	Carbamazepine granules prepared by slugging method	CBZ-SG	
4	Carbamazepine spherical agglomerates prepared by Quasi- Emulsion solvent diffusion method	CBZ-SC	

Table 2: Evaluation parameters of Carbamazepine and their agglomerated crystals.

Agglomerates code	CBZ*	CBZ-WG*	CBZ-SC*
Bulk density	0.437 ± 0.86	0.312 ± 0.35	0.142 ± 0.96
Granular density	1.250 ± 0.69	1.110 ± 0.26	0.660 ± 0.28
True density	1.295 ± 0.47	1.171 ± 0.79	0.730 ± 0.81
Interparticle porosity	0.034 ± 0.89	0.052 ± 0.63	0.095 ± 0.81
Interparticle porosity	0.644 ± 0.98	0.672 ± 0.53	0.737 ± 0.49
Total porosity	0.657 ± 1.07	0.690 ± 0.66	0.763 ± 0.73
Angle of Repose	37.69 ± 0.28	29.93 ± 0.50	24.62 ± 0.63
Carr's Index	20 ± 0.33	18.75 ± 0.98	17.14 ± 0.54
Hauser Ratio	1.229 ± 0.68	1.250 ± 0.60	1.104 ± 0.46
a	0.390±0.285	0.335±0.305	0.217±0.259
b	0.0165±0.345	0.0204±0.268	0.0603±0.267
1/b	60.60±0.345	49.01±0.268	16.58±0.267
K	0.01955±0.268	0.02298 ± 0.60	0.02407±0.265

Results represent means of replicate determinations with the standard deviation (n = 3)

Ingredients (Mg.)	Tablets Batch code				
	CBZ-T	CBZ-SCT	CBZ-WGT	CBZ-SGT	
CBZ	200				
CBZ-SC		200			
CBZ-WG			200		
CBZ-SG				200	
Microcrystalline cellulose	90	90	80	90	
Croscarmellose sodium	24	24	24	24	
Povidone			10		
Magnesium stearate	6	6	6	6	
Total weight(mg)	320	320	320	320	

Table 3: Formulation of tablets from spherically agglomerated crystal and granules of Carbamazepine.

CBZ-T: Tablets prepared by direct compression method, **CBZ-SCT:** Tablets prepared from spherical agglomerated crystals, **CBZ-WGT:** Tablets prepared by wet granulation method, **CBZ-SGT:** Tablets prepared from dry granulation method.

Table 4: Evaluation of tablet formulation

Tablet code	Drug content (%)	Disintegration time (min: sec.)	Friability (%w/w)	Thickness (mm)	Hardness (Kg)	Tensile strength (Kg /cm²)
CBZ-WGT	98.30	1:15	0.90	5.26±0.19	4.5±0.11	5.44±0.19
CBZ-SGT	99.00	1:50	0.59	4.80±0.17	6±0.11	6.03±0.26
CBZ-SCT	98.75	0:30	0.29	4.65±0.17	8.5 ±0.15	7.96±0.26

Each value represents mean \pm S.D. (n = 3)



Figure 1: Dissolution Profile of Tablets Prepared From Spherically Agglomerated Crystals, Granules and Marketed Tablets.

REFERENCES:

- 1. Chouracia M.K., Jain A., Valdya S. and Jain S.K., Utilization of spherical crystallization for preparation of directly compressible materials, Indian Drugs. 2004, 41 (6), 319-29.
- 2. Kawashima Y., Imai M., Takeuchi H., Yamamoto H and Kamiya K., Development of agglomerated crystals of Ascorbic acid by the spherical crystallization techniques, KONA. 2002, 20 (3), 251-61.
- 3. Chouracia M.K., Vijay S., Jain S.K. Jain, S., Jain N and Jain N.K., Preparation and characterization of spherical crystal agglomerates for direct tabletting by the spherical crystallization technique, Indian Drugs. 2004, 41(4), 214-20.
- 4. Goczo H., Szabo R.P., HasznosNezdei M. and Farkas B., Development of spherical crystals of Acetyl salicylic acid for direct tablet making, Chem.Pharm.Bull. 2000, 48(12), 1877-1881.
- 5. Kawashima Y. Yang, L., Nito M. and Takenaka H., Direct agglomeration of sodium theophylline crystals produced by salting out in the liquid.Chem.Pharm.Bull. 1982, 30 (5), 1837-43.
- 6. Morshima K., Kawashima Y., Takeuchi H., Niwa T. and Hino T.,Tabletting properties of Bucillamine agglomerates prepared by the spherical crystallization technique, Int.J.Pharm. 1994,105,11-18.
- 7. Hector G.P. Jorge, B., Carlo A., Preparation of Norfolxacin spherical agglomerates using the ammonia diffusion system. J. Pharm. Sci, 1998, 87(4), 519-23.
- 8. Kulkarni P.K. and Nagavi B.G., Spherical crystallization, Ind. J. Pharm. Edu. 2002,36 (2), 66-73.
- 9. Martino P.D., Barthelemy C., Piva F., Joiris E., Marthelemy C., Improved dissolution behavior

of Fenbufen by spherical crystallization, Drug Dev.Ind.Pharm. 1999, 25 (10), 1073-1081.

- 10. Jbilou M., Ettabia A., Guyot-Hermann A.M. and Guyot J.S., Ibuprofen agglomeration prepared by phase separation, Drug. Dev. Ind. Pharm. 1990, 25(3), 297-305.
- 11. Kawashima Y., Niwa T. and Handa T., Preparation of controlled release microspheres of Ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method, J. Pharm. Sci. 1989,78(1),68-72.
- 12. Bhadra S., Kumar M., Jain S., Agrawal S. and Agrawal G.R., Spherical crystallization of Mefenamic acid, Pharmaceutical Technology. 2004,66-76.
- 13. Kawashim Y., Niwa T., Handa T., Takeuchi H. and Iwamoto T.,Preparation of controlled release microspheres of Ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method, J. Pharm. Sci. 1989,78(1),68-72.
- 14. Kawashima Y., Aoki S., Takenaka H. and Miyake Y., Preparation of spherically agglomerated crystals of Aminophylline, J.Pharm.Sci. 1984, 73 (10), 1407-10.
- 15. Ueda M., Nakamura Y., Makita H., Imasato Y. and Kawashima Y., Particle design of Enoxacin by spherical crystallization technique II, Characteristics of agglomerated crystals, Chem.Pharm.Bull.1991,39 (5),1277-1281.
- 16. Nokhodehil A., Bolourtchian N. and Dinarvand R., Crystal modification of Phenytoin using different solvents and crystallization conditions, Int. J. Pharm. 2003, 250, 85-97.
