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Crystal Modification of Aceclofenac by Spherical Crystallization to Improve Solubility Dissolution Rate and Micromeritic Properties

R. R. Thenge*

Department of Pharmaceutics, IBSS College of Pharmacy, Malkapur-443101, Maharashtra, India

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ABSTRACT

Aceclofenac a non-steroidal anti-inflammatory drug widely used in the treatment of rheumatoid arthritis. The poor water solubility and poor micromeritic properties of aceclofenac lead to low dissolution rate and poor flow during tableting. The aim of present study was to improve dissolution rate and micromeritic properties of aceclofenac by spherical agglomeration techniques. The spherical agglomerate of aceclofenac was carried out by solvent change method in the presence of hydrophilic polymer in different concentration. The solvent system used was acetone, water and dichloromethane as good solvent, anti-solvent and bridging liquid respectively. The spherical agglomerates were characterized by FTIR spectroscopy, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. Also the agglomerates were evaluated for dissolution rate and micromeritic properties. The FTIR and DSC study showed no interaction between drug and polymer. XRD studies showed a slight decrease in crystallinity in agglomerates. The agglomerate showed significantly improved dissolution rate as well as micromeritic properties compared to pure drug. The SEM also showed that the agglomerate possess a good spherical shape.

Key words: Aceclofenac, spherical agglomerate, solubility, dissolution, micromeritic properties

INTRODUCTION

Spherical crystallization is the novel agglomeration technique that can directly transform the fine crystals produced in the crystallization or in the reaction process into a spherical shape[1]. 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 a compacted spherical form[2, 3]. This technique of particle designing of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size, and particle size distribution) can be modified during the crystallization process. As a consequence of such modifications in the crystal habit, certain micrometric properties (bulk density, flow property, and compactibility) and physicochemical properties (solubility, dissolution rate, bioavailability, and stability) can also be modified[4]. It had been described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile by using hydrophilic polymer during crystallization process[5,6]. It has also been applied to improve the flowability and the compression ability of some powders. Moreover, critical steps involved in wet granulation can be avoided. Aceclofenac, a non-steroidal anti-inflammatory drug (NSAID), is the selective cyclooxygenase-2 inhibitor used in the treatment of osteoarthritis and rheumatoid arthritis in adult patients. Aceclofenac exhibits poor flow and compression characteristics and is hence a suitable candidate for spherical crystallization process to improve the flow properties and compressibility. Also, aceclofenac shows incomplete and poor oral bioavailability due to low aqueous solubility[7, 8]. Hence, the improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. Spherical crystallization of aceclofenac was prepared in the presence of hydrophilic polymer polyvinyl pyrrolidone to improve the aqueous solubility, dissolution rate and micromeritic properties, compare with pure drug.

***Corresponding author.**
R. R. Thenge
Department of Pharmaceutics,
IBSS College of Pharmacy,
Malkapur-443101,
Maharashtra, India.

Materials and Method

Aceclofenac was a gift sample from Lupin pharmaceuticals Pvt ltd. Pune. PVP K-30 was purchased from S. D. Fine chemicals, Mumbai. All other chemicals and solvents used were of analytical reagent grade.

Spherical crystallization

The spherical agglomeration was carried out using solvent change method. The clear solution of aceclofenac (3.0 g) in acetone (20 ml) was added quickly to a 100 ml solution hydrophilic polymer (PVP-K30) in water at different concentration (2.5- 10.0 w/v). The mixture was stirred continuously at 500 rpm by using a mechanical stirrer. After 15 Min. fine crystals begun to precipitate then dichloromethane (bridging liquid) was added dropwise to obtain spherical agglomerates. The agglomerates were collected by filtration using Whatman filter paper and dried for 24 h at room temperature and store in desiccator.

Micromeritic properties[9]

Angle of Repose: Angle of repose was determined using Fix funnel method. The spherical agglomerates were poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (***?***) was calculated using the following formula,

$$q = \mathbf{Tan^{-1}\ (h / r)}$$

Where, *q*= angle of repose, r = radius of the pile, h = height of the pile
Bulk Density: Bulk density (B) was determined by pouring the spherical agglomerates into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density (B) was calculated using following formula,

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

Where, M= weight of the powder, V= bulk volume
Tapped Density: The measuring cylinder containing a known mass of spheri

cal agglomerates (M) was tapped for a fixed time (500 tapping). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (T) was calculated using following formula,

T= M / Vt

Where, M= weight of the powder**,** Vt = tapped volume

Compressibility Index: The simplest method of measurement of free flow of powder is compressibility, an indication of the ease with which material can be induced to flow is given by compressibility index (C.I) which is calculated as follows,

C.I (%) = Tapped density –Bulk density×100/Tapped density

Hausner's Ratio *(H):* This is an indirect index of ease of powder flow. It is calculated by the following formula,

H= T/ B

Where, T= tapped density, B= bulk density

Drug Content

Spherical agglomerates were weighed after drying, agglomerates (200 mg) were powdered, from which powder equivalent to 100 mg Aceclofenac was weighed and dissolved in phosphate buffer (pH 6.8) filter through whatman filter paper and volume was made to 100 ml. After appropriate dilution with same medium, samples were analyzed spectrophotometrically (Elico 190, Hyderabad, India) at 275 nm[10].

Solubility studies

The solubility of Aceclofenac spherical agglomerates in water was determined by weighing excess quantity of spherical agglomerates and adds to the 50 ml glass vials filled with phosphate buffer (pH 6.8). The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatman filter paper No.1, suitably diluted and the drug concentration was analysed spectrophotometrically at 275nm[11].

In vitro dissolution studies

In vitro drug release profiles of spherical agglomerates as well as pure drug were performed using USP type-2 dissolution apparatus (Labindia, Mumbai, India). Sample equivalent to 100 mg ofAceclofenac was added to 900 ml phosphate buffer (pH 6.8) at 37± 0.5ºC and stirred at 50 rpm. Aliquot of specified volume was withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min. The withdrawn volume was replaced with the same volume of fresh dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at 275 nm after suitable dilution if necessary, using appropriate blank[12].

Characterization of agglomerates

Fourier transforms infra red spectroscopy (FTIR)

FT-IR spectra of prepared spherical agglomerates and the pure drug were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Japan). Potassium bromide pellet method was used and the spectrum was scans over the range of 4000 – 400 cm^{-1}. Spectra were analysed for drug and polymer interaction.

Differential scanning calorimetry (DSC)

Differential scanning calorimetric (DSC) spectra of pure drug and spherical agglomerates (F4) were carried out by using differential scanning calorimeter equipped with computer analyzer (Mettler Toledo). Samples were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 20-350ºC.

Powder X-ray diffraction studies

Powder X-ray diffraction (PXRD) patterns were carried out by X-ray diffractometer (Philips PW 1729, Analytical XRD, Holland) for the samples using Ni filtered CuK, 40 KV, 30 mA . The samples were analyzed at 1 min/ second over the 1 to 50 diffraction angle (2?) range.

Scanning electron microscopy

The surface morphology of the spherical agglomerates was determined by scanning electron microscopy (SEM) (Model 840-A-Japan). The photomicrographs were taken at 25.0 kV and magnification at 50X, 200X, 500X.

RESULT AND DISCUSSION

Spherical agglomerates were prepared by solvent change method using three solvent system(acetone-dichloromethane, water) acetone a good solvent for aceclofenac, dichloromethane was used as a bridging liquid and water was anti-solvent. Agglomeration was initiated by the addition of dichloromethane as it acts as bridging liquid, it may be due to a adsorption of bridging liquid on the original crystals, subsequently bridging liquid diffused into dispersing medium as adsorbed layer on the crystal surface and cross contact point between particles which induces solubility change between in bridging liquid resulting in recrystallization of dissolved crystalline material which finally leads to formation of agglomerates. Moreover bridging liquid introduced into the dispersing medium after saturation point was immiscible and only coalescence of bridging liquid occurred, causing an increase in agglomerates. Generally hydrophilic materials are used to impart strength and sphericity to the agglomerates.

Micromeritic properties

The size of the agglomerates increased with an increase in the PVP concentration (from 2-5- 10 %). The shape of the agglomerate, when observed using an optical microscope was spherical in all the prepared formulations. The results of micromeritic properties are showed in the Table. l. These parameters were used to determine the packability and compressibility of the agglomerate. The bulk density and tapped density of pure drug (0.32 g/ml and 0.52 g/ml respectively) indicating that the pure drug is fluffy in nature and have more void space between particles, where as bulk density value of spherical agglomerate (0.38 - 0.40 g/ml) and the tapped density value (0.42- 0.44 g/ml) showed that the spherical agglomerates have good packability compared with pure drug. The, angle of repose, Hausner's ratio and Carr's index, was used to determine the flow properties and compressibility properties of the agglomerates. The Angle of repose Carr's index, Hausner's ratio, values for pure drug was 43.45^0, 38.46 %, 1.62 %, respectively, indicating that pure drug have poor flow, packability and compressional properties. Whereas spherical agglomerates exhibited lower Angle of repose Carr's index, Hausner's ratio indicating good flow, packability and compressibility compare to pure drug. The improved flowability and compressibility of spherical agglomerates may be due to the reduction in interpaticulate friction between spherical agglomerate. Due to the incorporation of hydrophilic polymer (PVP K-30) during the spherical crystallization may improved the wettability of spherical agglomerate, thus improved the solubility and dissolution rate. Among all the prepared spherical agglomerate, the agglomerates prepared with 10%, PVP exhibited good micromeritic properties, solubility and dissolution rate.

Drug Content

Drug content and percentage yield was carried out to know the any drug lose during formulation, the results were represented in Table.1. Yield for the formulations were within the range of (80.15- 85.12 %) and drug content was (92.50-97.2 %). These values showed that the crystal yield is increases as increase in PVP K-30 concentration during crystallization.

Table.1- Physicochemical Properties of pure drug and spherical agglomerates.

Formulation	Angle of repose	Bulk densit (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's Index (%)	Percent Yield (%)	Drug content (%)	Solubility (mg/ml)
Pure drug	43.45	0.32	0.52	1.62	38.46	-	-	10.6
F1 (PVP-2.5 %)	26.53	0.40	0.44	1.10	9.09	80.15	92.5	19.8
F2 (PVP- 5 %)	25.36	0.39	0.43	1.10	9.30	82.17	95.7	35.2
F3 (PVP-7.5 %)	25.29	0.39	0.44	1.12	11.36	85.12	96.3	58.4
F4 (PVP-10 %)	23.13	0.38	0.42	1.10	9.52	81.17	97.2	98.2

In vitro dissolution studies

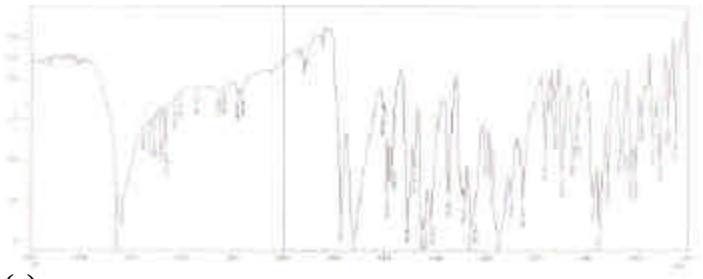
The results of in vitro dissolution studies are shown in Table.2. Pure drug solubility and dissolution rate of spherical agglomerates.

Table.2.Drug release pattern of pure drug and spherical agglomerate.

Time (Min.)	Pure Drug	F1	F2	F3	F4
05	5.84	23.31	30.13	32.50	35.45
10	17.50	31.41	41.30	46.32	48.20
15	27.46	42.10	52.65	56.27	60.31
30	35.45	50.47	63.25	68.65	72.65
45	39.40	59.42	71.35	75.45	81.74
60	45.64	66.45	75.60	79.60	86.60
90	52.75	71.73	81.36	86.25	95.72

IR, DSC, XRD and SEM Data

The possible interaction between the drug and the polymer was studied by FTIR spectroscopy and DSC. The results of IR spectra indicated that there is no interaction between aceclofenac and PVP-K30 shown in Fig.1. The DSC patterns of pure aceclofenac and spherical agglomerates are shown in Fig.2. Pure aceclofenac showed a sharp endotherm at 154 °C corresponding to its melting point. There was a slight change in the melting endotherm of the prepared spherical agglomerate compared to pure drug 147.45°C. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between the drug and polymer.



(a)

b)

c)

Fig.1. FTIR spectra of aceclofenac, PVP K-30 and spherical agglomerate
a) Pure aceclofenac b) PVP K-30 c) spherical agglomerate (10% PVP)

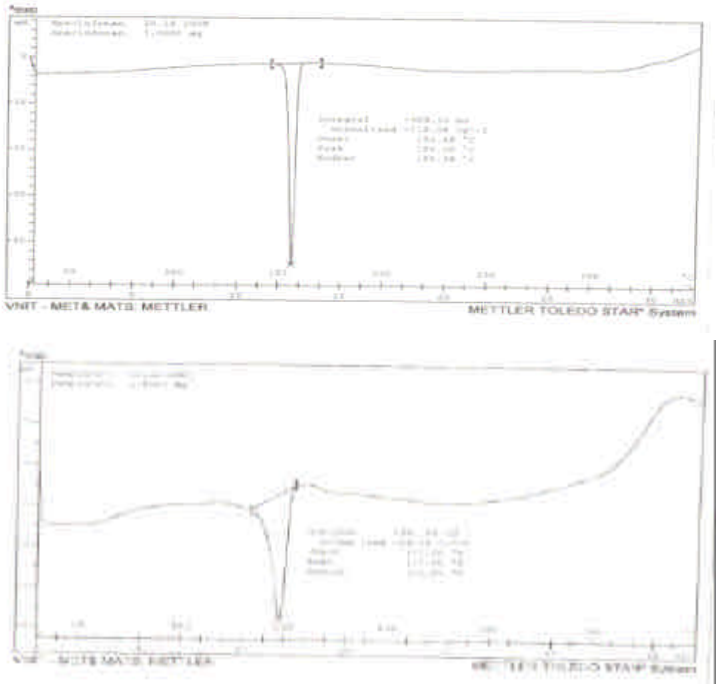
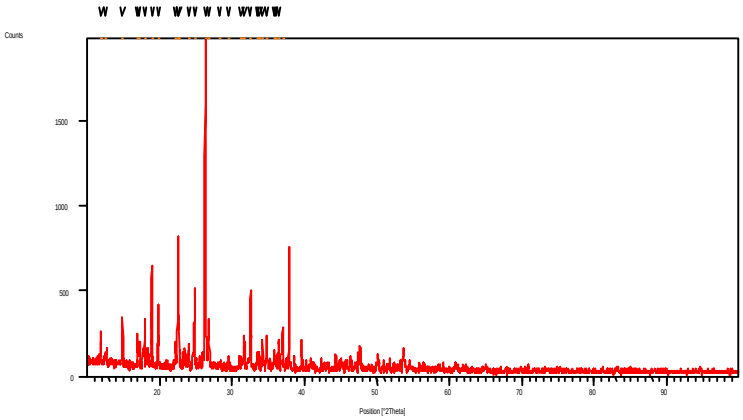
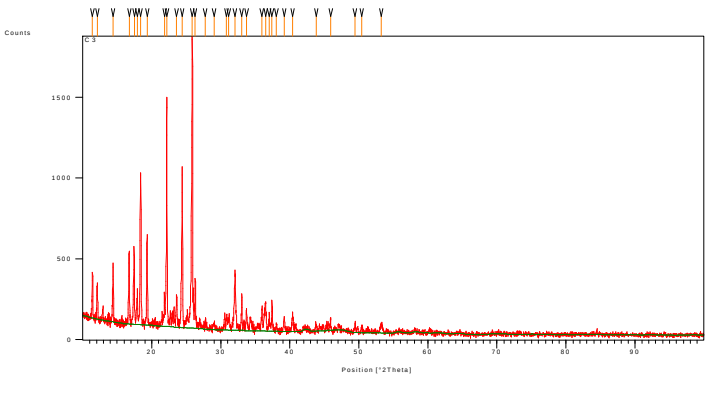


Fig. 2. DSC patterns of pure aceclofenac, and spherical agglomerate:
a) Pure aceclofenac, b) spherical agglomerate (10% PVP)



(a)



(b)

Fig. 3. X-ray diffraction spectra of aceclofenac, and spherical agglomerates
a) Pure aceclofenac b) spherical agglomerate (10% PVP)

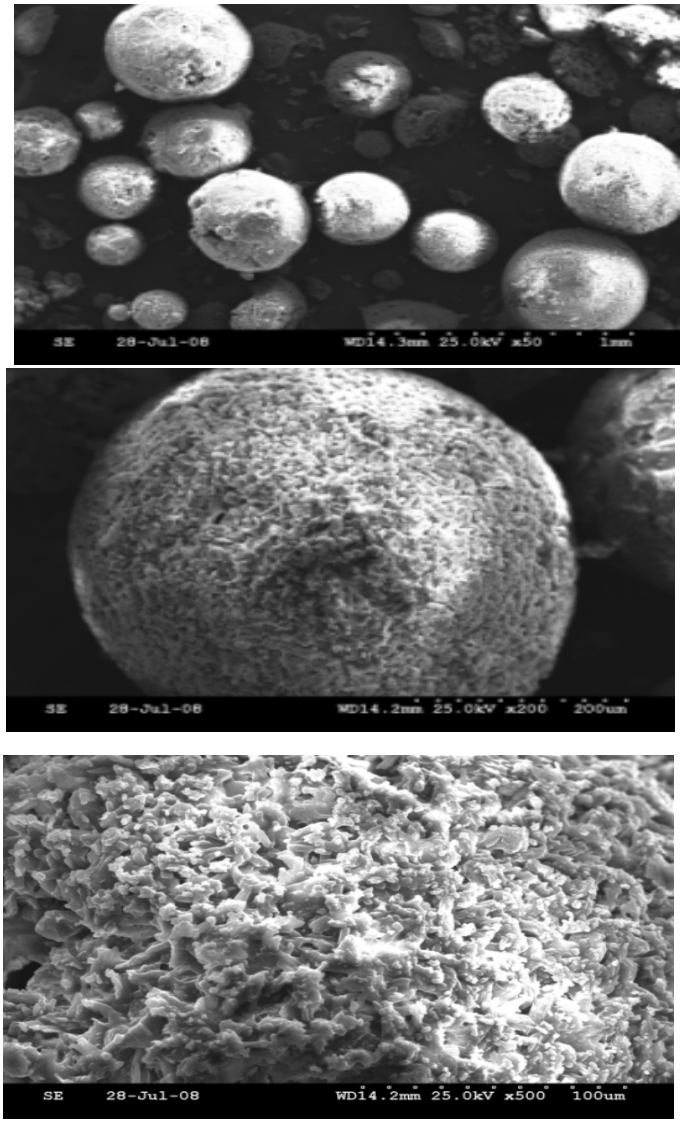


Fig.4. Scanning electron photographs of spherical agglomerate at magnification 50X, 200X and 500X.

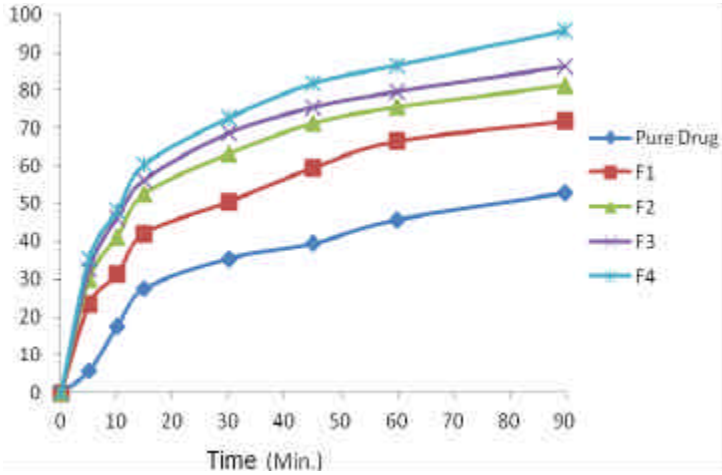


Fig.5. Dissolution Profile of pure drug and spherical agglomerates.

The results of the powder X-ray diffraction pattern of pure drug and spherical agglomerates are shown in Fig.3. Pure drug and the spherical agglomerate show the same peaks but the peak intensity was differ. Thus this indicates decrease in the crystallinity of spherical agglomerates compare to pure drug. Since all XRD peaks of the spherical agglomerates were consistent with the pattern of original drug crystals. The results of surface morphology studies are shown in Fig. 4. The pure drug have irregular crystal shape crystal form leads to very poor flow and compressional difficulties. The surface morphology of prepared agglomerates was shown at various magnifications such as 50X, 200X and 500X. These photo micrographs show that the prepared agglomerates were spherical in shape.

CONCLUSION

This techniques can significantly improves the dissolution rate and flow properties of aceclofenac without changing crystal forms thus the spherical crystallization technology will provide the directly compressible spherical agglomerates with improved properties.

REFERENCES

1. Kawashima Y. Development of spherical crystallization technique and its application to pharmaceutical System, Arch Pharm Res 1984; 7: 145-151.
2. Kulkarni P K and Nagvi B G. Spherical Crystallization: Indian J Pharm Edu, 2002; 36: 66-73.
3. A.R. Paradkar, K.R.Mahadik, and A.P. Pawar, "Spherical Crystallization a Novel Particle Design Technique," Indian Drugs, 1998 31, (6), 283–299.
4. Gupta M.M, Spherical crystallization: A tool of particle engineering for making Drug Powder Suitable for Direct Compression, International Journal of Pharma. Research and Development, 2005 1(12), 1-10.
5. Kawashima Y, Handa T, Takeuchi H, Okumura M, Crystal modification of phenytoin with polyethylene glycol for improving mechanical strength, dissolution rate and bioavailability by a spherical crystallization technique, Chem. Pharm. Bull., 1986,34,3376–3383.
6. Gupta VRM, Mutalik S, Patel MM and Jain GK.Spherical crystals of celecoxib to improve solubility, dissolution rate and micromeritic properties. Acta Pharm. 57; 2007: 173-184.
7. Alvarez-Larena A, Piniella JF and Carrasco E. Crystal structure and spectroscopic study of 2-[(2, 6-dichlorophenyl) amino] phenylace toxyacetic acid (Aceclofenac). J. Chem. Crystallography. 22; 1992: 323–328.
8. Shakeel F, Ramadan W and Shafiq S. Solubility and dissolution improvement of aceclofenac using different nanocarriers. J Bioequiv Availab, 1(2); 2009: 39-43.
9. Lachman L, Lieberman H A, The Theory and Practice of industrial Pharmacy, Varghese Publishing house, 3rd edition. 1990, 183-184.
10. Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagi P and Udupa N. Preparation and, in vitro, preclinical and clinical studies of aceclofenac spherical agglomerates.European Journal of Pharmaceutics and Biopharmaceutics. 70; 2008: 674–683
11. Gohel, M. C., Parikh, R. K., Shah, H., Dubey, R. R., Improvement in flowability and compressibility of ampicillin trihydrate by spherical crystallization**.** Indian Journal of Pharmaceutical Sciences, 2003, 65(6), 634-637.
12. Martino, P. Di., Barthelemy. C, Piva, F., Joiris, E, Palmieri, G.F, Improved dissolution behavior of fenbufen by spherical crystallization. Drug Development and Industrial Pharmacy, 1999, 25(10), 1073-1081.
13. Kawashima, Y., Furukawa, Keiko, Takenaka, Hideo, The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. Powder Technology, 1981, 30 (2), 211-16
14. Y. Kawashima et al., "The Development of an Emulsion- Solvent-Diffusion Preparation Method of Agglomerated Crystals for Direct Tableting and Evaluation of the Compressibility," J. Soc. Powder Technol. Japan 26, 1989, 659–665.
15. Kawashima, Y., Cui, F., Takeuchi, H., Niwa, T., Hino, T., Kiuchi, K., Improved static compression behaviors and tablettabilities of spheri cally agglomerated crystals produced by the spherical crystallization technique with a two-solvent system**,** Pharmaceutical Research, 1. 1995, 12 (7), 1040-4.

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