

PREPARATION AND CHARACTERIZATION OF SPHERICAL AGGLOMERATES OF KETOPROFEN BY NEUTRALIZATION METHOD**MUDIT DIXIT*, DR. P. K. KULKARNI, SHAHNAWAZ ANIS AND ASHWINI G KINI**

Department of Pharmaceutics, J.S.S College of Pharmacy, S.S Nagar, Mysore-570015, India.

Corresponding Author* muditdixit911@yahoo.comABSTRACT**

Ketoprofen, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Spherical agglomerates were prepared by neutralization method. Crystallization medium used for spherical agglomerates of ketoprofen consisted of 1 M Sodium hydroxide; 0.25 M hydrochloric acid; chloroform (bridging liquid) in the ratio of 20:55:25, respectively. Spherical agglomerates were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. Micromeritic and dissolution behavior studies were carried out. Process variables such as amount of bridging liquid, stirring time and duration of stirring were optimized. Dissolution profile of the spherical agglomerates was compared with pure sample and recrystallized sample. Tablets were prepared using spherical agglomerates by direct compression and evaluated for tablet properties. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared with pure sample. The dissolution profiles of ketoprofen tablets prepared using spherical agglomerates exhibit greater dissolution behaviour than tablets prepared by powder raw material.

KEY WORDS

spherical agglomerates, ketoprofen, dissolution.

INTRODUCTION

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression¹. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tableting method, it is necessary to increase flowability and compressibility of the bulk powder in order to

retain a steady supply of powder mixture to the tableting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spherical agglomeration is one of such techniques to improve the micromeritic properties and dissolution of drug.

Spherical agglomeration process is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously in one step. The

resultant crystals can be designated as spherical agglomerates².

Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges². The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The properties of the particles so designed vary greatly as compared to the fine crystalline material. These agglomerates were found to have good flowability and compressibility. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs³⁻⁵. These modifications allow for the practice of more efficient manufacturing methods that could save time and reduces economic risk. Ketoprofen exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties⁶. Various methods were used to increase the flow properties of ketoprofen⁶, e.g., Spheronisation, Direct compression, coating, granulation etc.

MATERIALS AND METHODS

Ketoprofen was obtained as a gift sample from Micro labs, Bangalore, India. Chloroform was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of spherical agglomerates of ketoprofen

Ketoprofen (6.357 gm) was dissolved in 20 ml of 1 M sodium hydroxide and heated at 45^oC until a clear solution was obtained. The drug solution was poured quickly in to 55 ml of 0.25 M hydrochloric acid to neutralize the sodium hydroxide of ketoprofen and crystallize out and maintained at 20^oC, under continuous stirring at 500 rpm with a propeller. When fine crystals of ketoprofen begun to precipitate (5-10 min), 20 ml of chloroform (bridging liquid) was added drop wise. After 10 min of stirring, 5 ml of chloroform was added again. The temperature was reduced to 5^oC, after about 1 hour stirring; spherical

agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^oC for 12 hours.

Drug content

Spherical agglomerates⁷ (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, measured at 258.5 nm. Drug content was determined from standard plot.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (2 θ).

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel-LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

Micromeritic properties

Particle size of recrystallized samples and pure samples were determined by microscopic method using calibrated ocular micrometer and size of spherical agglomerates was determined by sieving method. Apparent particle densities of agglomerated and unagglomerated crystals were measured using a Pycnometer. Carr's index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electrolab, Mumbai). The angle of repose of agglomerated and commercial crystals was measured by fixed funnel method.

Mechanical Properties

Mechanical Properties⁸⁻¹⁰ like tensile strength of spherical agglomerates was determined by compressing 500 mg of crystals using hydraulic press at different ton/cm² for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (ton/cm²) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.

Crushing strength

Crushing strength of agglomerates was determined using modified Jarosz and Parrot's mercury load cell method¹⁴. It was carried out using a 10 ml glass hypodermic syringe. The modifications include removal of the tip of the syringe and the top end of the plunger. The barrel was used as a hollow support and guide tube with close fitting to the plunger. A window was cut at the lower end of the barrel to facilitate placement of the agglomerate on the base plate. Mercury was added to the plunger at a rate of 10 g/s from a separating funnel, from a fixed height. The total weight of mercury plus that of plunger required to break the agglomerate was the crushing strength (g).

Friability

For friability studies, 2 g (Wo) of spherical agglomerates (particle size 250-600 μm) was

placed in a friabilator, and this was subjected to the impact test at 50 rpm for 2 min. After passing this through a sieve having a mesh size 125 μm , the weight (W) of the material which did not pass through the sieve was determined, and friability (X) was calculated using equation

$$X = \frac{W_o - W}{W_o} \times 100$$

Solubility studies¹²

The solubility of ketoprofen spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates in 50 ml to screw-capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 258.5 nm.

Dissolution studies of agglomerates⁷

The dissolution of ketoprofen pure sample, spherical agglomerates and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 258.5 nm.

Preparation of tablets¹³:

Ketoprofen conventional tablets were prepared by mixing the pure sample and spherical agglomerates with microcrystalline cellulose and sized silica for a period of 10 min in a cubic mixer. The mixture was mixed with sodium starch glycolate and lactose for 10 min. The mixture was compressed on a tableting machine (Rimek, Mumbai), having a punch diameter of 10 mm and equipped with strain gauge (10-400 kg/cm²). Sufficient compression load between 80-100 kg/cm² was applied in order to produce tablets hardness of 5-6 kg/cm². The formulation prepared with pure sample and spherical agglomerates was denoted as F and F* respectively and each tablet contains 25 mg ketoprofen, 100 mg of

coarse granular microcrystalline cellulose, 5 mg of nm-sized silica(Aerosil), 5 mg sodium starch glycolate and 65 mg lactose. The punched tablets were subjected to dissolution study as described under dissolution study of agglomerates.

RESULTS AND DISCUSSION

1 M Sodium Hydroxide is miscible in any proportion with water and chloroform. The 0.25

hydrochloric acid was added to neutralize the 1 M Sodium hydroxide of ketoprofen. The proportions of 1 M Sodium hydroxide; 0.25 M hydrochloric acid; chloroform (bridging liquid) in the ratio of 20:55:25 were chosen for the study.

Other process parameters like amount and mode of addition of bridging liquid, stirring speed and time and temperature were considered for optimization (Table 1).

Table 1
effect of variables on formulation of spherical agglomerates of ketoprofen

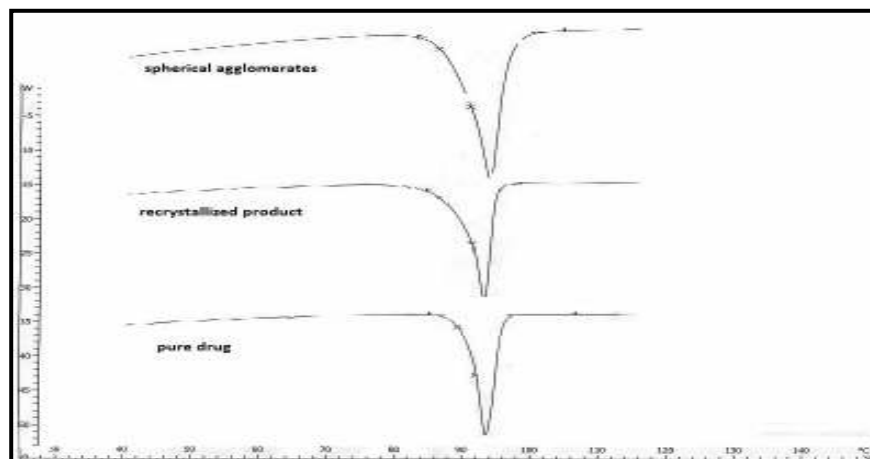
Parameter	Variables	Observation
Conc. of bridging liquid (Chloroform)	2%	No agglomeration
	8%	No agglomeration
	15%	Agglomeration
Agitation speed	300±25	Clumps
	400±25	Spherical & large
	500±25	Spherical
	600±25	Spherical & small
	700±25	Irregular shape & small
Agitation time	20 min	Incomplete agglomerates
	45 min	Spherical agglomerates
Temperature	5±1 ⁰	Agglomeration
	20 ⁰ ±1 ⁰	Loose Spherical agglomerates
	45±1 ⁰	Very large agglomerates
Mode of addition of bridging liquid	Whole at a time	Crystals of irregular geometry
	Drop wise	Spherical agglomerates

Uniform distribution of bridging liquid was achieved when it was added dropwise with continuous stirring of agitator, resulting in formation of spherical agglomerates due to efficient agglomeration. Addition of whole amount of bridging liquid at a time to agglomerating vessel produced spherical agglomerates of irregular geometry. This may be due to localization of bridging liquid and hence its unavailability for efficient agglomeration. The yield obtained was in the range of 94.3±1.54%, with the drug content of 97.17± 1.32% .

The DSC thermograms (fig. 1) shows a sharp endothermic peak for all the ketoprofen

crystals. This one step melt might be due to only one crystal form (Triclinic) of the ketoprofen formed during the crystallization process, thus indicating that ketoprofen did not under go any crystal modification. The temperature range of the endothermic peak of all the ketoprofen crystals lies in the range of 94⁰ to 96⁰. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated ketoprofen was 96.58° with decreased enthalpy of (175.01 J/g) indicating decreased crystallinity.

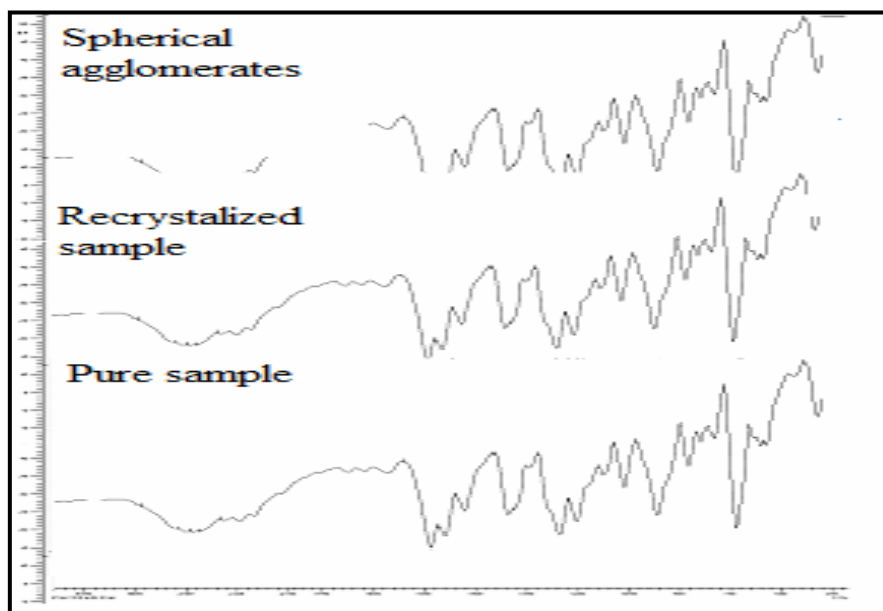
Fig. 1
DSC thermograms of Ketoprofen



All the crystals have exhibited general characteristic peaks at $2983\text{-}2930\text{ cm}^{-1}$ (Aromatic C-H stretch carboxylic acid O-H stretch), $1695\text{-}1649\text{ cm}^{-1}$ (C=O stretch), 1595 cm^{-1} (Aromatic C=C stretch), 1437 cm^{-1} (CH-CH₃ deformation), 2891 cm^{-1} ((C-H) stretch plus O-H deformation), 1690 cm^{-1} (Carboxylic O-H out of plane deformation), $860\text{-}640\text{ cm}^{-1}$ (C-H out of plane deformation for substituted aromatic) (fig. 2).

Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of a solvent of crystallization.

Fig. 2
FT-IR spectra of Ketoprofen



All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of ketoprofen was ruled out. However relative intensities of XRD peaks were modified (fig. 3). This could be attributed to the markedly different crystal habits of the samples

(Table 2). Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes.

Fig. 3
X-ray diffraction spectra of Ketoprofen.

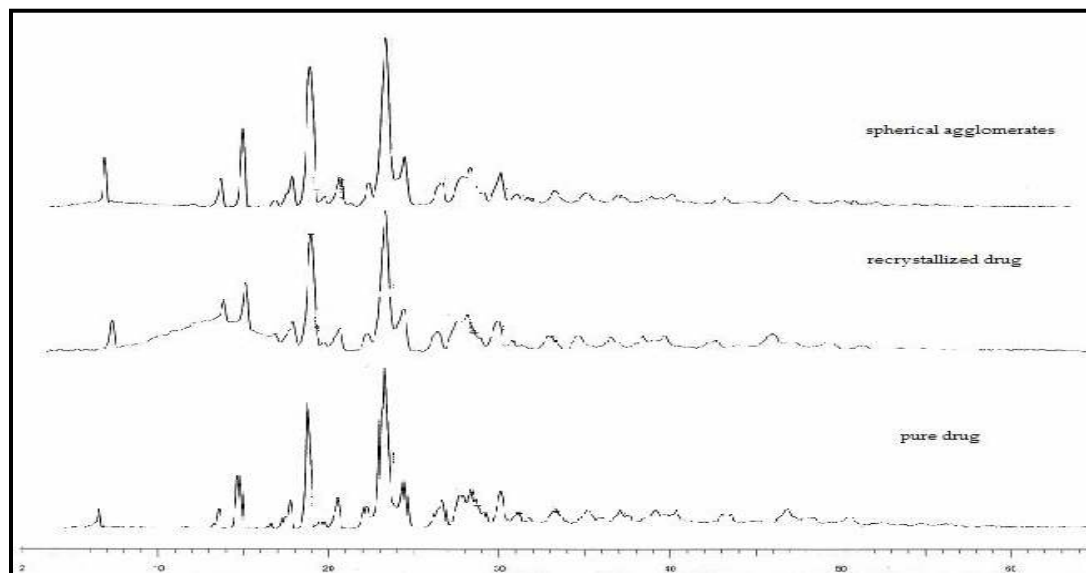


Table 2
different cell parameters obtained for ketoprofen crystals from xrd data.

	A	B	C	α	β	γ	Unit cell volume
Pure sample	12.0807	12.213	16.227	94.22	71.76	145.4	1214.19
Spherical crystals	6.8634	10.890	14.494	96.27	83.42	54.97	863.67
Recrystallized Sample	6.8795	7.4789	15.890	92.88	64.57	81.94	721.50

a, b, c – three sides of cell expressed in \AA .

α, β, γ - three angles of the cell expressed in degrees

Crystals of pure sample are of the smallest size (5-10 μm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (9-16 μm). The agglomerates were formed by coalescence of the

microcrystalline precipitates, so the resultant agglomerates had a rough surface (fig's. 4-7). Agglomerates obtained were spherical in shape with size 350-825 μm .

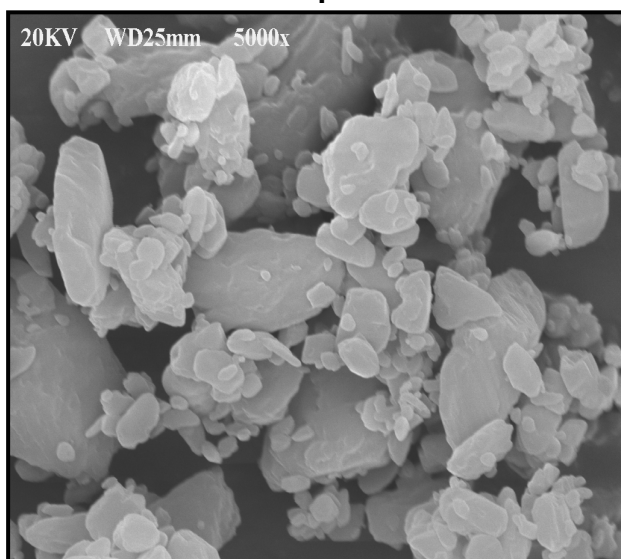


Fig. 4

SEM of Ketoprofen pure sample sample in mixture of 1M Sodium Hydroxide: chloroform:

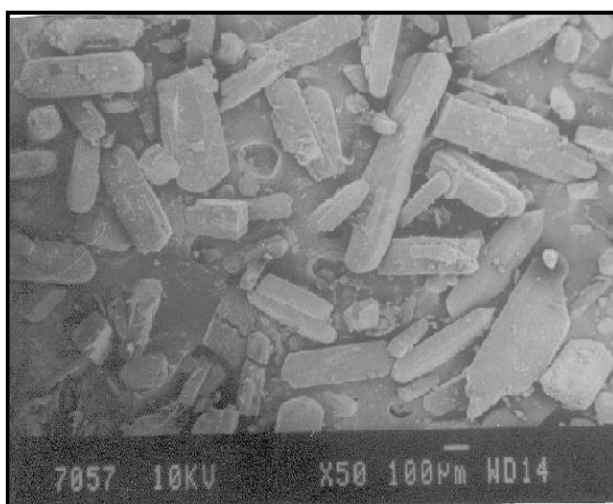


Fig. 5

SEM of ketoprofen-recrystallized 0.25 Hydrochloric acid.

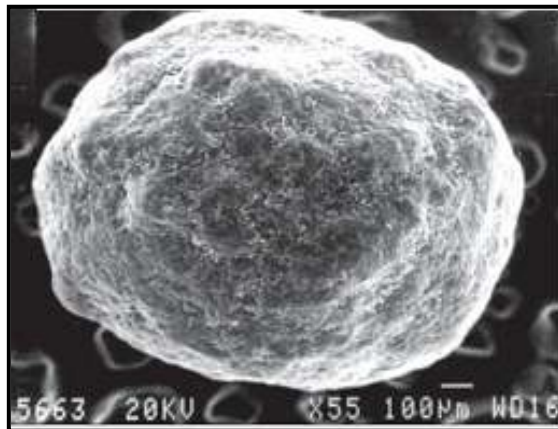


Fig. 6
SEM of Spherical agglomerate at 55X

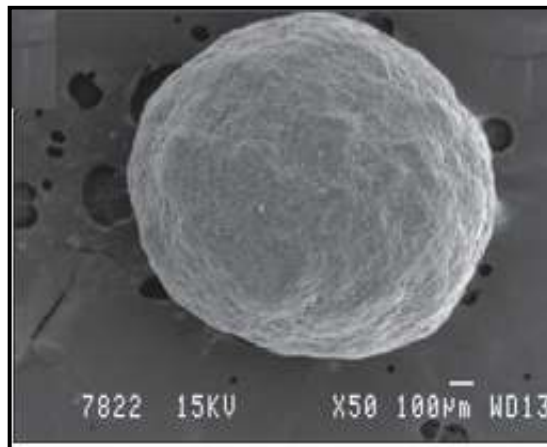


Fig. 7
SEM of spherical agglomerate at 50X

The Micrometrics properties of Pure Sample, Recrystallized Sample and Spherical agglomerates of ketoprofen shown below: (Table 3).

Table 3
micromeritic properties of ketoprofen pure sample and spherical agglomerates obtained by solvent change method.

Properties	Pure sample	Recrystallized Sample	Spherical agglomerates
Particle size (μm)	5-10	9-16	350-825
Flow rate (gm/Sec)	No flow	No flow	8.31
Angle of repose	41.31	32.61	28.07
Tapped density (gm/ml)	0.9302 \pm 0.006	0.5753 \pm 0.043	0.2459 \pm 0.05
Bulk density(gm/ ml)	0.6692 \pm 0.0034	0.4178 \pm 0.06	0.1892 \pm 0.004
Carr's index	28.05	27.37	12.37
Porosity (%)	0.3944	0.7052	0.9286
Friability (%)	-	-	0.7439 \pm 0.32

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (fig. 8). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower

compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal. The crushing strength of agglomerates was in the range of 90-102 g and was unaffected by the process variables.

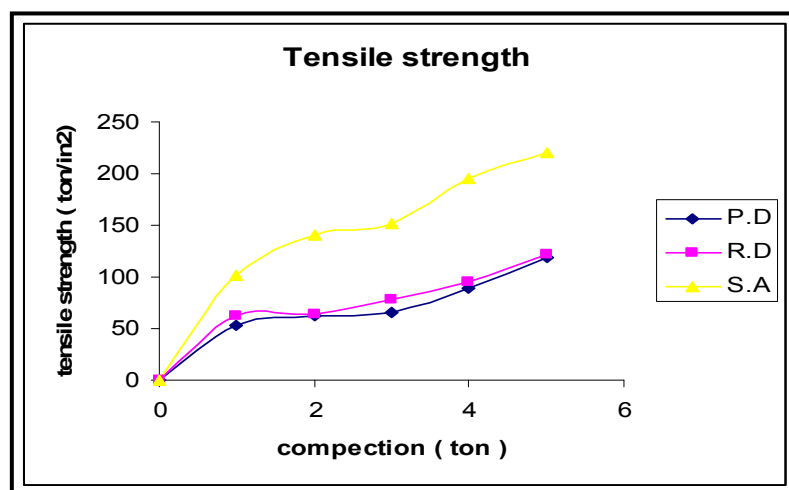


Fig. 8
Tensile strength of spherical agglomerates Pure sample and Recrystallized Sample as a function of compaction pressure

The dissolution profiles of ketoprofen (fig. 9) exhibited improved dissolution behaviour for spherical agglomerates than pure sample. The reason for this faster dissolution could be linked to

the better wettability of the spherical agglomerates. The amount of drug dissolved in 60 min greatly varied for spherical agglomerates.

P.D-Pure drug, R.D- Recrystallized drug , S.A- Spherical agglomerates.

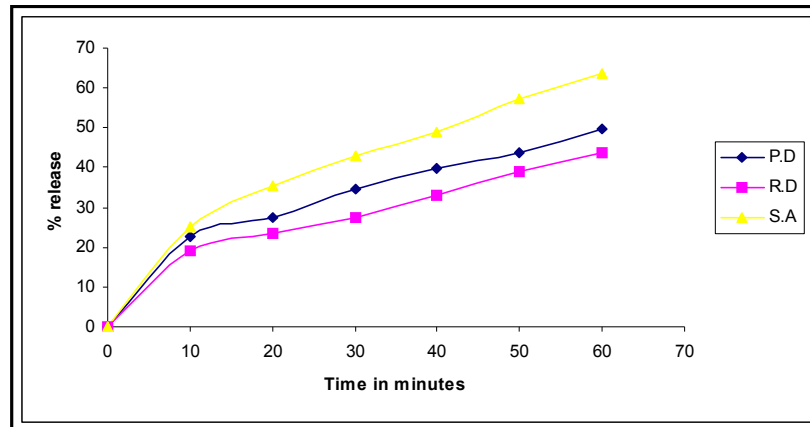


Fig. 9
Dissolution profile of Ketoprofen crystals.

The dissolution of ketoprofen tablets (fig. 10) containing spherical agglomerates exhibited improved dissolution behaviour than tablets prepared by powder raw material.

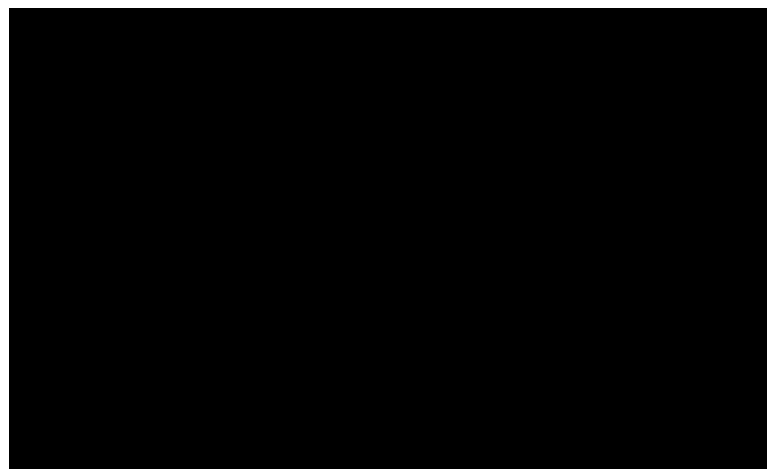


Fig. 10
Dissolution profile of Ketoprofen from tablets

F-1=pure sample, f-1*=Spherical agglomerates,
F- Tablets prepared by pure raw material
F*- Tablets prepared by spherical agglomerates

Spherical crystals of Ketoprofen were prepared by Neutralization spherical crystallization technique. Spherical crystals exhibited decreased crystallinity and improved micromeritic properties. Amount of bridging liquid, speed of agitation and duration of agitation affects the mechanical and micromeritic properties of spherical crystals. DSC and XRD studies showed that there is no change in the crystal structure of ketoprofen during the crystallization process i.e., polymorphism has not occurred. The dissolution of the spherical crystals was improved compared with pure sample. Hence

this spherical agglomeration technique can be used for formulation of tablets of ketoprofen by direct compression with directly compressible tablet excipients.

ACKNOWLEDGEMENTS

The authors are thankful to Micro labs, Bangalore, India for the gift sample of Ketoprofen, Dr. H. G. Shivakumar, Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carryout this work.

REFERENCES

1. Chourasia MK, Vaidya S, Jain N, Jain SK, Jain S. and Jain A., Utilisation of spherical crystallization for preparation of directly compressible materials. *Indian Drugs*, 41(6): 319-329, (2004)
2. P.K.Kulkarni and B.G.Nagavi., Spherical crystallization. *Indian J Pharm Edu*, 36:66-73, (2002)
3. Di Martino P, Barthelemy C, Piva F, Joiris E, Palmieri G F and Martelli S., Improved dissolution behaviour of Fenbufen by spherical crystallization. *Drug Dev Ind Pharm*, 25(10): 1073-1081, (1999)
4. 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. *J Pharm Sci*, 76(Jun): 471-474, (1987)
5. Sano A, Kuriki T, Kawashima Y, Takeuchi H, Niwa T.and Hino T., Particle design of tolbutamide by spherical crystallization technique. V. Improvement dissolution and bio availability of direct compressed tablets prepared using tolbutamide agglomerated crystals. *Chem Pharm Bull*, 40(11):3030-3035, (1990)
6. Janos Bajdik, Klara Pintye-Hodi, Odon Planinsek, Zsofia Tuske, Ljiljana Tasic, Geza Regdon Jr., Stane Srcic, Istavan Eros., Surface treatment of indomethacin agglomerates with eudragit. *Drug Dev Ind Pharm*, 30(4):381-388, (2004)
7. Indian Pharmacopoeia, Controller of publications, New Delhi, 1996.
8. Paradkar AR, Pawar AP, Chordiya JK, Patil VB and Ketkar AR. Spherical crystallization of celecoxib. *Drug Dev Ind Pharm*, 28(10):1213-1220, (2002)
9. Chourasia MK, Vijaya R, Jain N, Jain SK, Jain S. and Jain NK., Preparation and characterization of Spherical crystal agglomerates for direct tableting by spherical crystallization technique. *Indian Drugs*, 41(4):214-220, (2004)
10. Takeo Kuriki, and Kawashima.Y, Hirofumi Takeuchi, Tomoaki Hino, and Toshiyuki Niwa. Modification of tolbutamide by solvent change technique. III. Micromeritic properties, dissolution rate of tolbutamide spherical agglomerates prepared by QESD method and SC method. *Chem Pharm Bull*, 38(3):733-739, (1990)
11. Piera Di Martino, Roberta Di Cristofaro, Christine Barthelemy, Etienne Joiris, Giovanni Palmieri Filippo and Martelli Sante. Improved compression properties of propyphenazone spherical crystals. *Int J Pharm*, 197(1-2):95-106, (2000)
12. Nocent M, Bertocchi L, Espitalier F, Baron M, Courraze G. Definition of a solvent system for spherical crystallization of salbutamol sulfate by quasi-emulsion diffusion (QESD) method. *J Pharm Sci*, 90(10):1620-1627, (2004)

13. Yousef Javadzadeh, Mohammad Reza Siahi-Shadbad, Mohammad Barzegar-Jalali. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Sci, 8(1):18-25, (2005)