SPHERICAL AGGLOMERATION OF KETOPROFEN BY SOLVENT CHANGE METHOD

Mudit dixit*, Dr.P. K. Kulkarni and Ashwini G Kini
Dept. of Pharmaceutics, J.S.S College of Pharmacy, S.S Nagar, Mysore-570015, India.
***Email:** muditdixit911@yahoo.com

ABSTRACT

Ketoprofen, an anti-inflammatory drug, exhibits poor water solubility and flow properties. Spherical agglomerates were prepared by solvent change method. Solvent composition for spherical agglomeration was determined by constructing ternary diagram. Crystallization medium used for spherical agglomerates of ketoprofen consisted of Isopropyl alcohol (good solvent); water (poor solvent); chloroform (bridging liquid) in the ratio of 25:60:15, 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. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared with pure sample.

Keywords: spherical agglomerates, ketoprofen, crystallinity, 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 compression[1]. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tabletting 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 tabletting 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 agglomerates[2]. Due to the characteristic shape, the micromeritic properties such as flowability, packability and compressibility of the resultant crystals are dramatically improved, so that direct tableting or coating is possible without further processing (e.g. mixing, agglomeration, sieving, etc.).

Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges[2]. 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 drugs[3-5]. 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 properties[6]. Various methods were used to increase the flow properties of ketoprofen[6], e.g., Spheronisation, Direct compression, coating, granulation etc.

MATERIALS AND METHODS

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

Preparation of spherical agglomerates of ketoprofen

Ketoprofen (4 gm) was dissolved in 25 ml of isopropyl alcohol (IPA) heated at 45^{0}C until a clear solution was obtained. The drug solution was poured quickly in to 60 ml of water maintained at 20^{0}C, under continuous stirring at 500 rpm with a propeller. When fine crystals of ketoprofen begun to precipitate (5-10 min), 10 ml of chloroform (bridging liquid) was added. After 10 min of stirring, 5 ml of chloroform was added again. The temperature was reduced to 5^{0}C, after about 1 hour stirring, spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^{0}C for 12 hours.

Drug content

Drug content[7] of Spherical agglomerates (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 absorbance of the

resulting solution was measured at 248.5 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).

X-ray analysis (XRD)

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.

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 (Electolab, Mumbai). The angle of repose of agglomerated and commercial crystals was measured by fixed funnel method.

Mechanical Properties

Tensile strength of spherical agglomerates was determined by compressing 500 mg of crystals using hydraulic press at different ton/cm^2 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[8-10]. The tensile strength (σ) of the compact (ton/cm^2) was calculated using following equation.

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

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

Solubility studies

The solubility[12] 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 twenty four hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 258.5 nm.

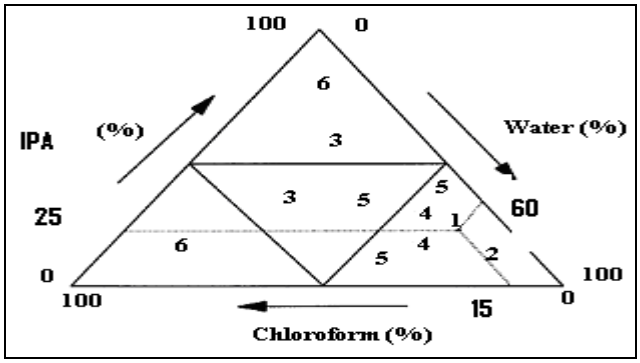
Dissolution studies of agglomerates

The dissolution[7] 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.

RESULTS AND DISCUSSION

Isopropyl alcohol (IPA) is miscible in any proportion with water and chloroform. If the ternary diagram is envisaged, to select the solvent composition, chloroform and water are like an emulsion in a large area of the diagram (fig. 1). The points on the vertex correspond to a pure liquid; those on the sides correspond to a mixture of only two liquids. Since the presence of three liquids is necessary (good solvent, bridging solvent and poor solvent) for spherical agglomeration, points on the sides of the triangle are excluded. 36 points remain for experiments. Each triangle in the ternary diagram was investigated for the crystallization. The optimal ratio for spherical agglomeration is found in zone (fig. 1). These proportions of IPA/water/chloroform (25: 60 : 15)were finally choosen for the study.

Figure 1: Ternary diagram



In this diagram results of different studies and the area for agglomerate formation are indicated.

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

The DSC thermograms (fig. 2) 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 undergo any crystal modification. The temperature range of the endothermic peak of all the ketoprofen crystals lies in the range of 94^0 to 96^0. 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.

All the crystals have exhibited general characteristic peaks at 2983-2930 cm^{-1} (Aromatic C-H stretch carboxylic acid O-H stretch), 1695-1649 cm^{-1} (C=O stretch), 1595 cm^{-1} (Aromatic C=C stretch), 1437 cm^{-1} (CH-CH_3 deformation), 2891 cm^{-1} ((C-H) stretch plus O-H deformation), 1690 cm^{-1} (Carboxylic O-H out of plane deformation), 860-640 cm^{-1} (C-H out of plane deformation for substituted aromatic) (fig. 3). 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.

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. 4). 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.

Table 1: Effect of variables on formulation of spherical agglomerates of ketoprofen

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

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

	A	B	C	A	β	γ	Unit cell volume
Pure sample	12.0807	12.213	16.227	94.22	71.76	145.4	1212.19
Spherical crystals	6.8634	10.890	14.494	96.27	83.42	54.97	860.67
Recrystallized Sample	6.8795	7.4789	15.890	92.88	64.57	81.94	725.50

a, b, c – three sides of cell expressed in A^0.

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

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)	5-11	9-17	350-830
Flow rate (gm/Sec)	No flow	No flow	8.37
Angle of repose	41.01	32.31	28.07
Tapped density (gm/ml)	0.9302±0.006	0.5753±0.043	0.2159±0.05
Bulk density(gm/ ml)	0.6692±0.0034	0.4178±0.06	0.1892±0.004
Carr's index	28.05	27.37	12.37
Porosity (%)	0.3844	0.6952	0.9086
Friability (%)	-	-	0.7439±0.32

Figure 2: DSC thermograms of Ketoprofen

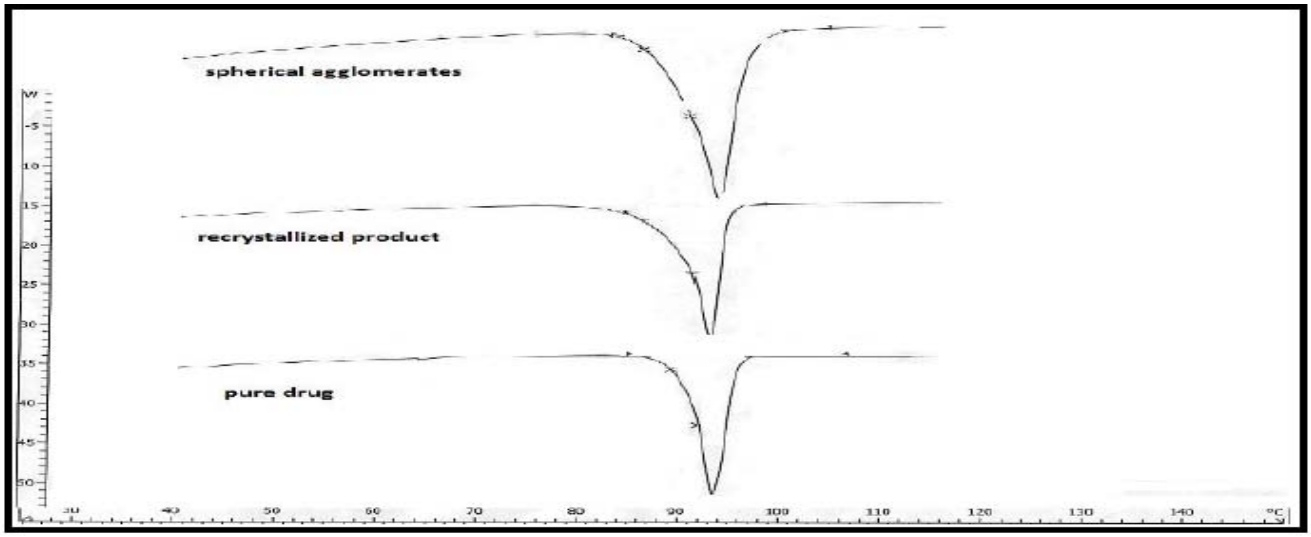


Figure 3: FT-IR spectra of Ketoprofen Samples

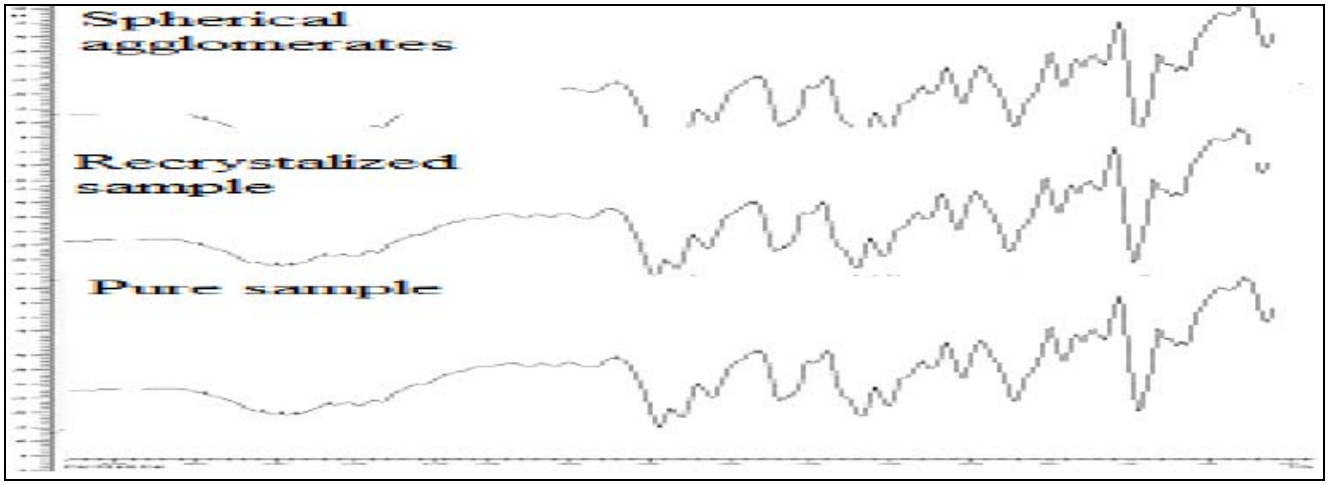


Figure 4:X-ray diffraction spectra of Ketoprofen

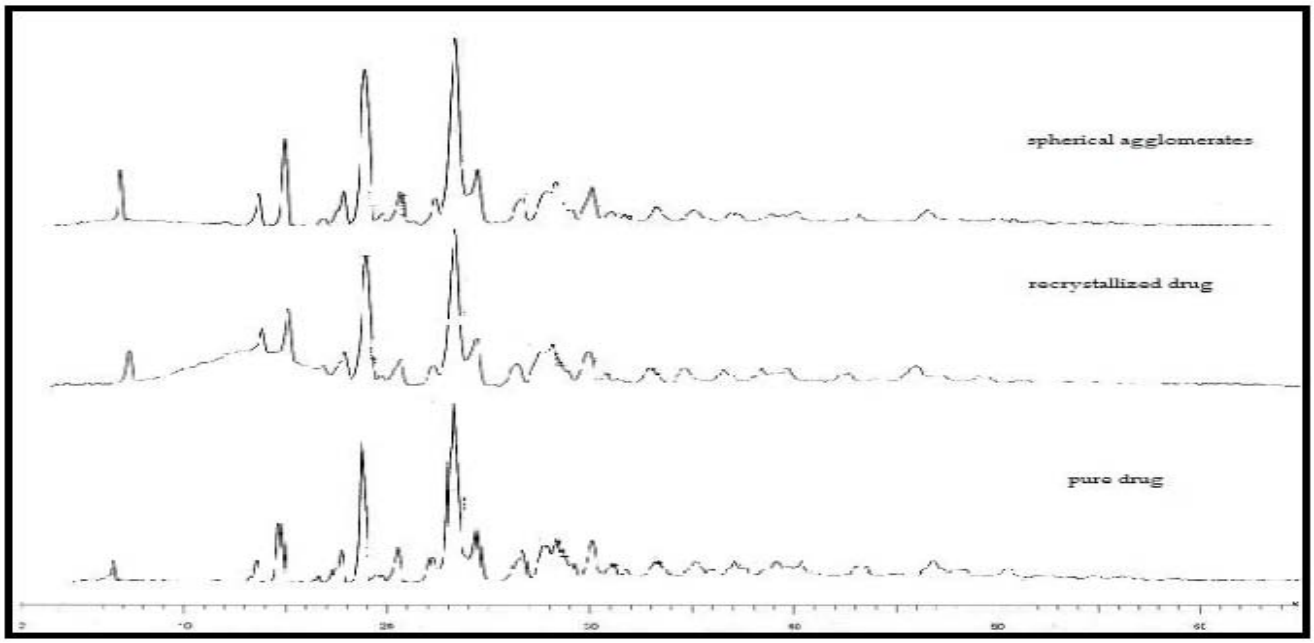


Figure 5: SEM of Ketoprofen pure sample.

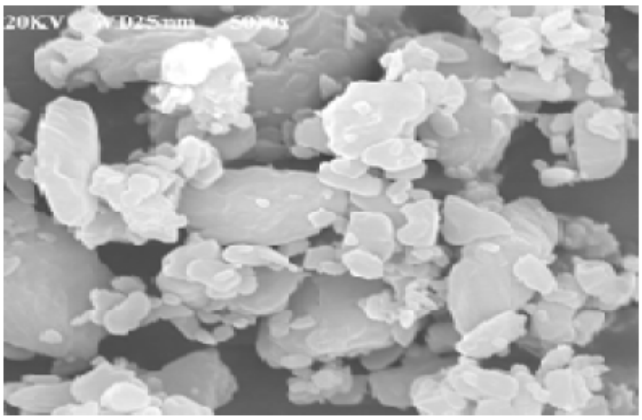


Figure 6: SEM of ketoprofen-recrystallize in mixture of Isopropyl alcohol: chloroform: water.

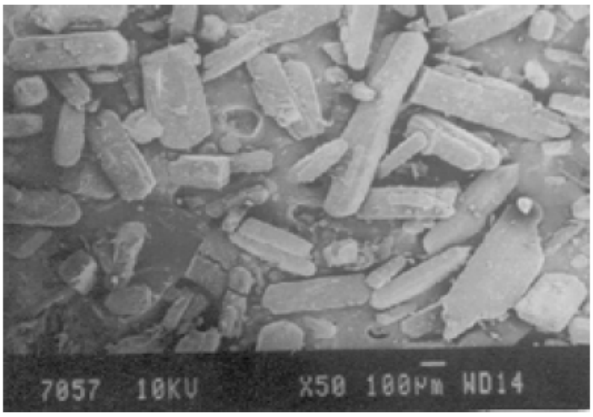


Figure 7: SEM of Ketoprofen spherical agglomerate at 55X

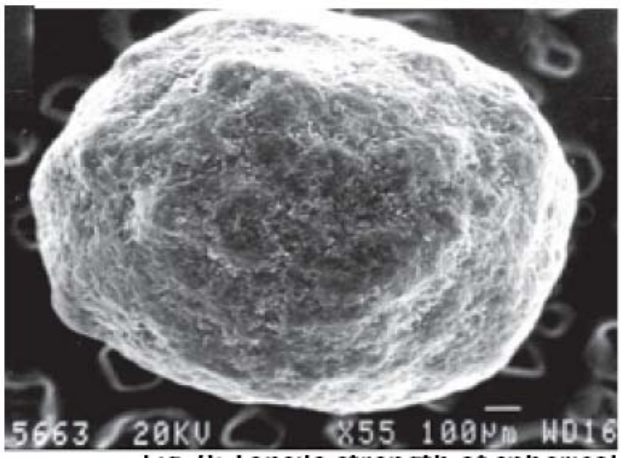


Figure 8: SEM of Ketoprofen spherical agglomerate at 50X

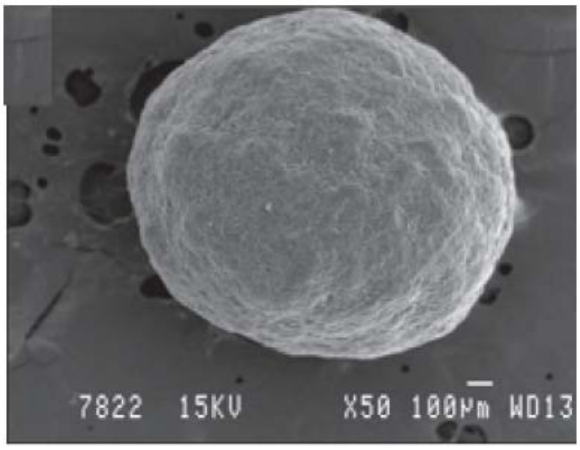


Figure 9: Tensile strength of spherical agglomerates pure sample and Recrystallized Sample as a function of compaction pressure

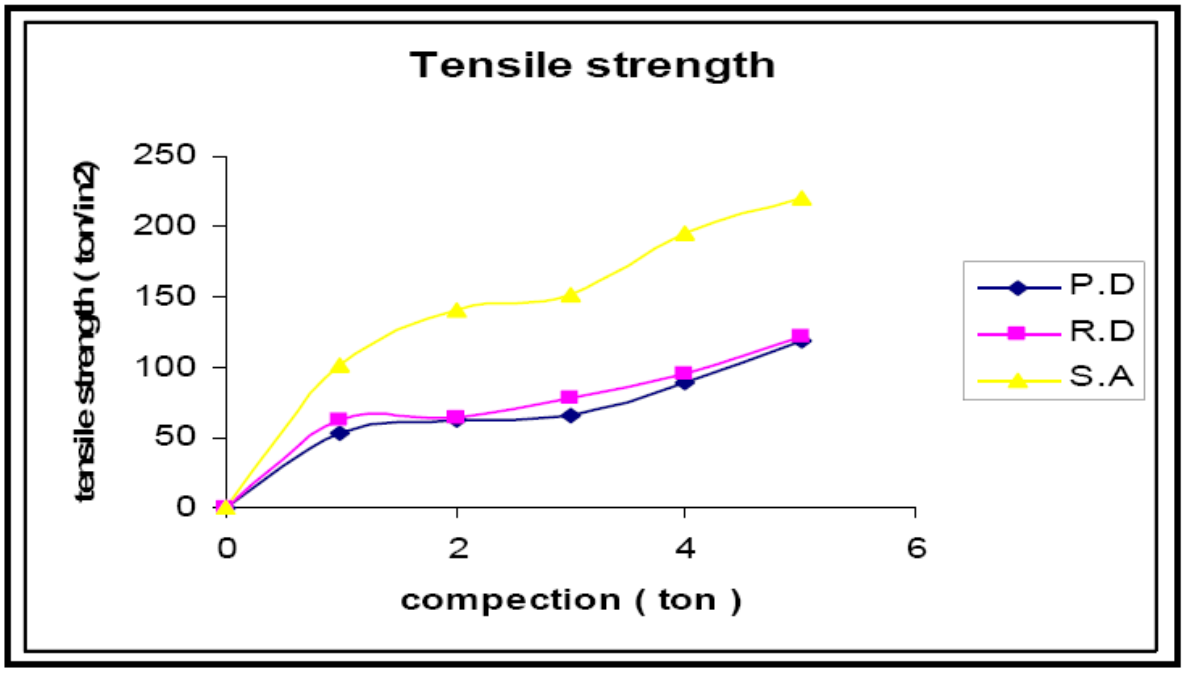
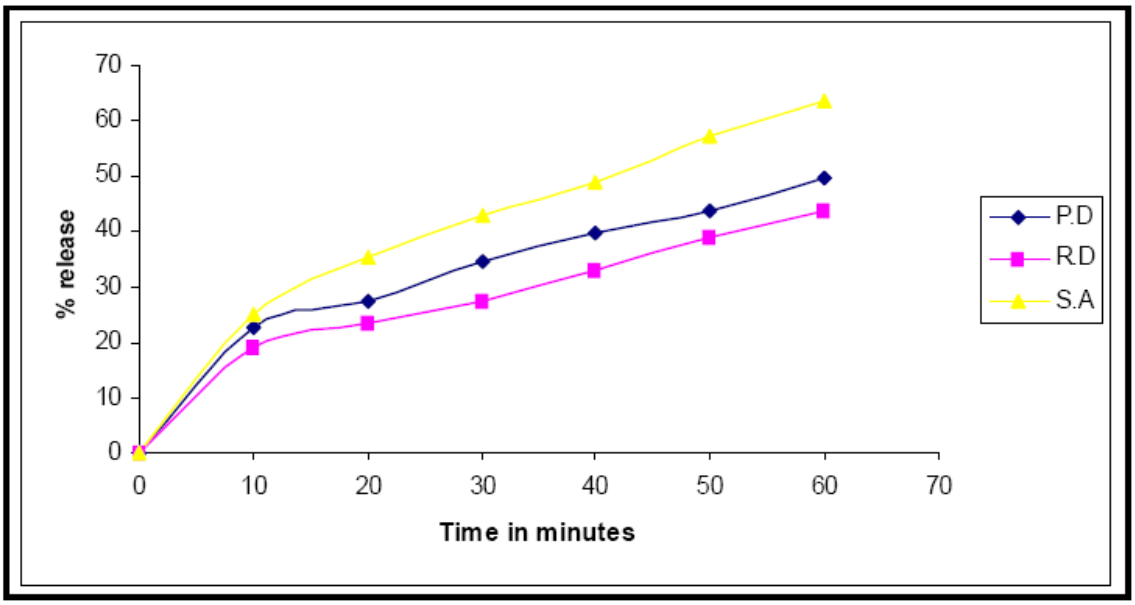


Figure 10: Dissolution profile of Ketoprofen crystals.



Crystals of pure sample are of the smallest size (5-11 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (9-15 µm). The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface (fig's. 5-8). Agglomerates obtained were spherical in shape with size 350-830 µm.

The differences in the bulk densities may be related to their markedly different crystal habits, leading to different contact points, frictional and cohesive forces between the crystals Spherical agglomerates exhibited higher packing ability than pure sample. It is due to lower surface area and wider particle size distribution of spherical agglomerates. The smaller crystals might have settled in voids between larger particles. Three measures of flowability were utilized to analyze the flow of particles. Flow rate measurement allowed quick estimation of flow properties. Angle of repose is able to provide gross measurements of the flowability of crystals. Pure sample exhibited higher angle of repose than spherical agglomerates, due to irregular shape and smaller crystal size. The higher flowability of spherical agglomerates was due to perfect sphericity and larger size of the crystals. The compressibility index is a simple and fast method for estimating flow of powder. Powders with compressibility above 40% had poor flow. Flow rates are in agreement with morphology and bulk density, spherical agglomerates with low bulk density exhibits better flow properties (Table 3).

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (fig. 9). 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 dissolution profiles of ketoprofen (fig. 10) 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.

CONCLUSION

Spherical crystals of Ketoprofen were prepared by simple 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. Sivakumar, Principal, J.S.S.College of Pharmacy, Mysorefor providing facilities to carry out 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 2004; 41(6): 319-329.
2. P.K.Kulkarni and B.G.Nagavi. Spherical crystallization: Indian J Pharm Edu 2002; 36:66-73.
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 DevInd Pharm 1999; 25(10): 1073-1081.
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 1987; 76(Jun): 471-474.
5. Sano A, Kuriki T, Kawashima Y, Takeuchi H, NiwaT.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 Bull1990; 40(11):3030-3035.
6. Janos Bajdik, KlaraPintye-Hodi, Odon Planinsek, ZsofiaTuske, LjiljanaTasic, GezaRegdon Jr., StaneSrcic, Istavan Eros. Surface treatment of indomethacin agglomerates with eudragit. Drug DevInd Pharm 2004; 30(4):381-388.
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 DevInd Pharm2002; 28(10):1213-1220.
9. Chourasia MK, Vijaya R, Jain N, Jain SK, Jain S. and Jain NK. Preparation and characterization of Spherical crystal agglomerates for direct tabletting by spherical crystallization technique**.** Indian Drugs. 2004; 41(4):214-220.
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 1990; 38(3):733-739.
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 2000; 197(1-2):95-106.
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 2004; 90(10):1620-1627.
13. YousefJavadzadeh, 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 PharmSci2005;8(1):18-25.
14. Paradkar AR, Pawar AP, Chordiya JK, Patil VB and Ketkar AR. Spherical crystallization of celecoxib. Drug DevInd Pharm2002; 28(10):1213-1220.

****