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Preparation and characterization of spherical agglomerates of Ibuprofen by solvent change method

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ABSTRACT

Ibuprofen, 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 ibuprofen consisted of iso propyl alcohol(good solvent); water (poor solvent); iso propyl acetate (bridging liquid) in the ratio of 30:100:9, 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 commercial sample and recrystallized sample. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared with commercial sample.

Key Words: spherical agglomerates, Ibuprofen, 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].

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. Ibuprofen exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties[6]. Various methods were used to increase the flow properties of ibuprofen, e.g., Spheronisation , Direct compression, coating, granulation etc.

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from Micro labs, Bangalore, India. Iso propyl alcohol and isopropyl acetate was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of spherical crystals of Ibuprofen:
Ibuprofen (20.25 gm) was dissolved in 30 ml of isopropyl alcohol heated at 45^0C until a clear solution was obtained. The drug solution was poured quickly in to 100 ml of water maintained at 20^0C, under continuous stirring at 500 rpm with paddle device. When fine crystals of ibuprofen begin to precipitate (5min), 9 ml of isopropyl acetate was added. After 45 min stirring spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^0C for 12 hours.

Recrystallization of Ibuprofen
Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of spherical crystals were compared with commercial sample and recrystallized sample. Recrystallization of ibuprofen was carried out using same solvent composition as was used for spherical crystallization. Ibuprofen (20.25 gm) was dissolved in 30 ml of isopropyl alcohol heated at 45^0C and 9 ml of isopropyl acetate was added. The drug solution was poured quickly in to 100 ml of water maintained at 20^0C with occasional stirring. The crystals of ibuprofen were collected by filtration and were dried at 45^0C for 12 hours.

Drug content

Spherical agglomerates[7] (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 221 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 (2θ).

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

Mechanical Properties[8-10] like 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. 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.

Crushing strength

Crushing strength of agglomerates was determined using modified Jarosz and Parrot's mercury load cell method[14]. 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

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

Dissolution studies of agglomerates[7]

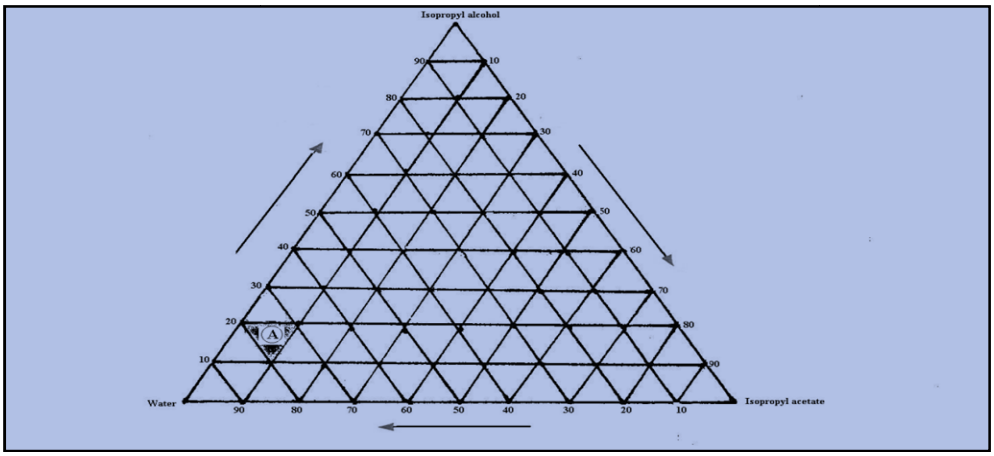
The dissolution of ketoprofen pure sample, spherical agglomerates and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.2 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 221 nm.

RESULT AND DISCUSSION

A typical spherical crystallization system involved a good solvent, a poor solvent for a drug and a bridging liquid. The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. Ibuprofen is freely soluble in acetone, chloroform, ethanol (95%) and more particularly in isopropyl alcohol (67.5%w/v at 45^0C).

To select the best solvent composition, a ternary diagram was envisaged. 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 crystallization, 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 crystallization is found in zone A (figure 1). These proportions of tetrahydro furan/water/isopropyl acetate (30:100:9) were then finally choosen for the study.

Figure .1 Ternary diagram of ibuprofen – Tetrahydrofuran solution/water / isopropyl acetate



To optimise Ibuprofen spherical crystallization by Isopropyl alcohol/ water / isopropyl acetate system, several parameters were considered; among these are temperature difference between drug solution in isopropyl alcohol and water, stirring time, stirring speed and amount of isopropyl acetate (Table 1).

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

Parameter	Variables	Observation
Conc. of bridging liquid (Iso propyl acetate)	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
	$20^0\pm1^0$	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

Bridging liquid used to cause the spherical agglomeration. It should be capable, not only of wetting the particle surface so as to form liquid bridges, but also of dissolving the sample particles. Hence bridging liquid exerts marked influence on the yield and rate of agglomeration

as well as on the strength of the resulting The rate determining step in the spherical crystallization is when the bridging liquid is squeezed out of the pores of the initial flocs, later transformed into small aggregates or spherical crystals. Hence the amount of bridging liquid used is one of the critical operating variables. The amounts of solvents selected from ternary diagram was further modified and studied for influence of bridging liquid on the process and product(Table 2).

Table 2 Amount of solvents selected from phase diagram used to prepare spherical crystals of ibuprofen

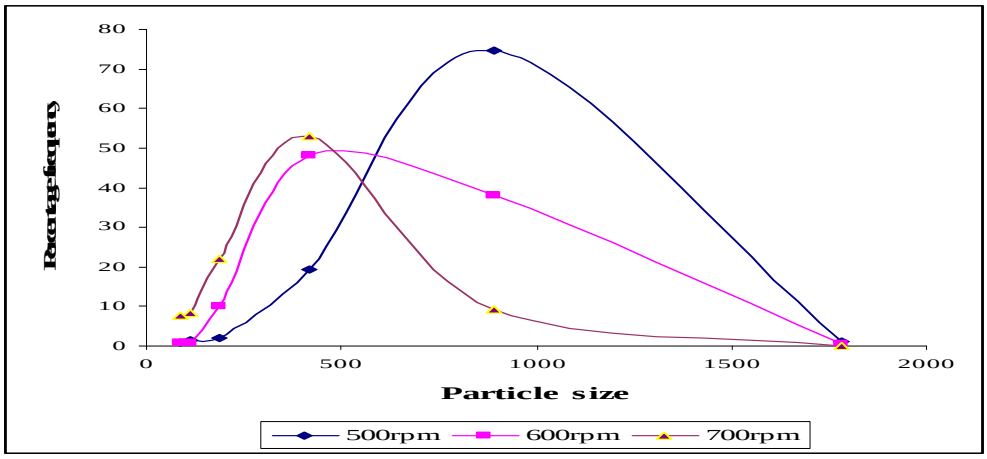
Amount(ml) of Isopropyl Alcohol used in ml (good solvent)	Amount (ml)of Isopropyl acetate used in ml (bridging liquid)	Amount (ml)of Water used in ml (poor solvent)	Percent of bridging liquid
30	09	100	6.4
30	10	99	7.2
30	11	98	7.9
30	12	97	8.6

Size distributions of particles at various degrees of agitation are given in the (Table 3 and Figure 2) below. It is evident from the table that the size of agglomerates is very much dependent on the degree of agitation. For a constant period of agglomeration, as the speed of agitation increases, the size of agglomerates obtained decreases. This may be due to the fact that as the speed of agitation increases the impact energy for collision of particle increases due to increased turbulence, resulting in agglomerates, which are more compact and dense.

Table .3 Effect of intensity agitation on size distribution of spherical crystals.

Particle diameter (μm)	Percentage frequency		
	500rpm	600rpm	700rpm
1785	1.045	0.5	0
890	74.53	38	9.2
420	19.47	48.25	53
187	2	10.25	22
115	1.5	1	8.25
89	1	1	7.8

Figure 2 Effect of intensity agitation on size distribution of spherical crystals.



Spherical crystals (50mg) were triturated and dissolved in 250ml of phosphate buffer pH7.2. The solution was filtered. After sufficient dilution with phosphate buffer pH7.2, solution was analyzed spectrophotometrically at 223nm (Shimadzu). Drug content was calculated from calibration curve of ibuprofen. The drug content was in the range of 95-98%.

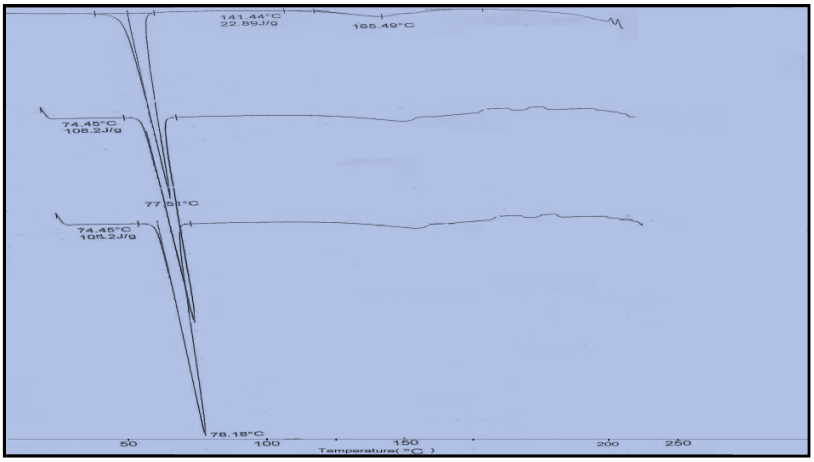
DSC studies were carried out for different crystals of Ibuprofen. The melting points of the crystals are in the range of 75-78^{0}C. The melting points of the crystals were estimated by open capillaries and found agree well with the DSC data. The melting endotherm for agglomerated ketoprofen was 77.51° with decreased enthalpy of (89.99 J/g) indicating decreased crystallinity (Table 4 and Figure 3). The DSC results indicate no significant between the mean values of the melting point onsets and melting points of the ibuprofen samples crystallized indicating that no polymorphic modifications occurred during crystallization process.

Table 4 - DSC data obtained for different Ibuprofen crystals

Ibuprofen Crystals	T_0	T_m	T_c	Melting range	Heat of fusion* J/gm
Commercial sample	74.45	78.18	85.25	10.8	108.25
Re-crystallized in solvents used in spherical crystallization	74.08	75.72	78.88	4.8	97.13
Spherical crystals	74.19	77.51	80.48	6.29	89.99

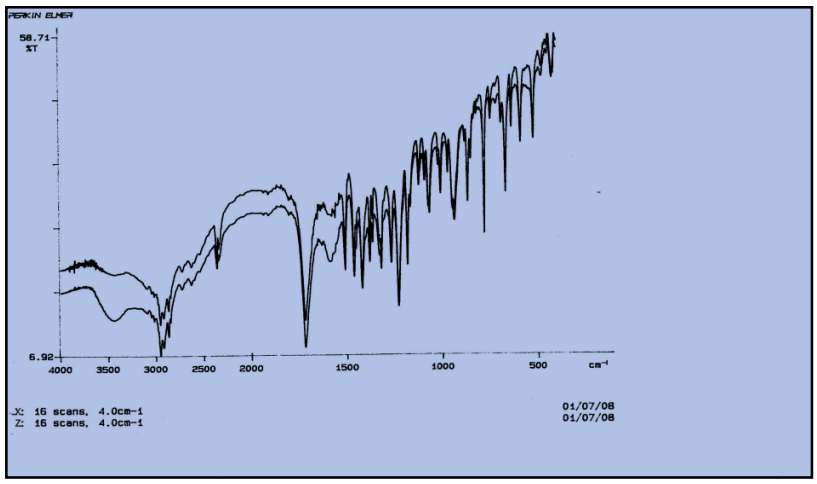
*T_0-Onset of melt T_m -Melting point Tc - Completion of the melt. Temperatures are reported in degrees Celsius. *- DSC data obtained in 10^{0}C/min*

Figure 3 DSC data obtained for different Ibuprofen crystals



Infrared spectra of ibuprofen, recrystallized ibuprofen and spherical crystals showed characteristic principal peaks at wave numbers 1721(C=O stretching vibrations of –COOH groups), 1268 (aromatic disubstitution), 1232, (-OH group bending vibrations), 1273, 1185 870 and 779 (Aromatic structure bending vibrations) and shown in (figure 4).

Figure 4. The FT-IR spectra of ibuprofen, recrystallized ibuprofen and spherical crystals



All the samples exhibited spectra with similar peak positions (2 theta values). Therefore the presence of different polymorphs of ibuprofen in these samples was ruled out. However relative intensities of X RD peaks were modified. This was attributed to the markedly different crystal habits of the samples. 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 this may be due to differences in crystal sizes(Figure 5 and Table 5).

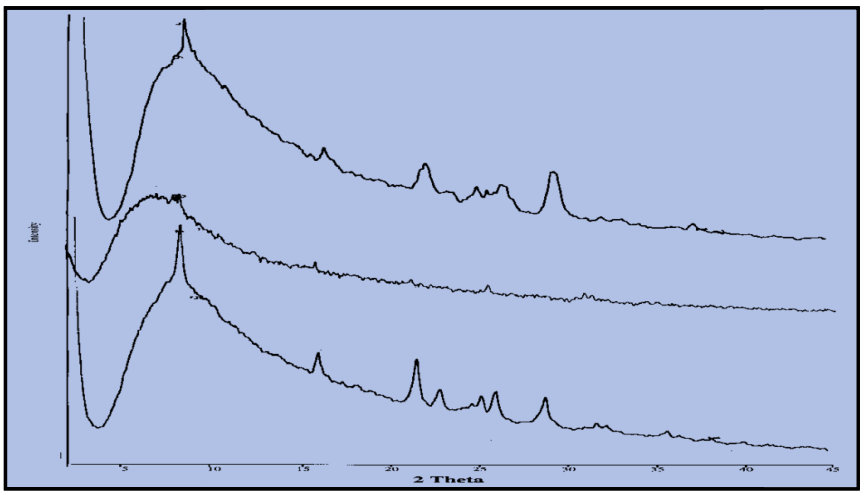
Table 5: different cell parameters obtained for ibuprofen crystals from XRD data.

	A	B	C	A	β	Γ	Unit cell volume
Pure sample	15.29	14.78	13.86	93.22	74.72	142.4	3132.17
Recrystallized Sample	15.27	13.86	13.04	94.25	82.40	54.97	938.73
Spherical crystals	13.86	11.09	7.17	92.84	64.53	81.38	11.02

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

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

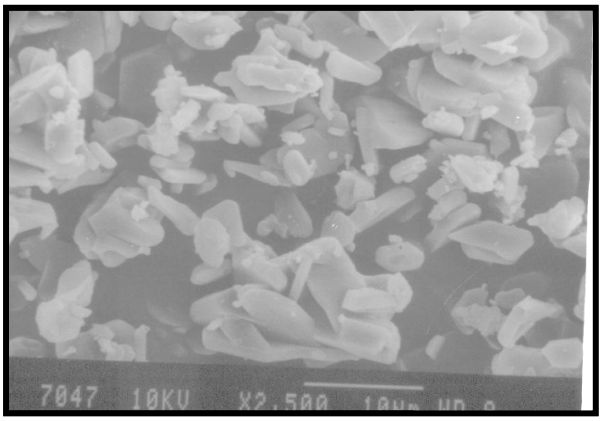
Figure 5 The XRD spectra of ibuprofen, recrystallized ibuprofen and spherical crystals

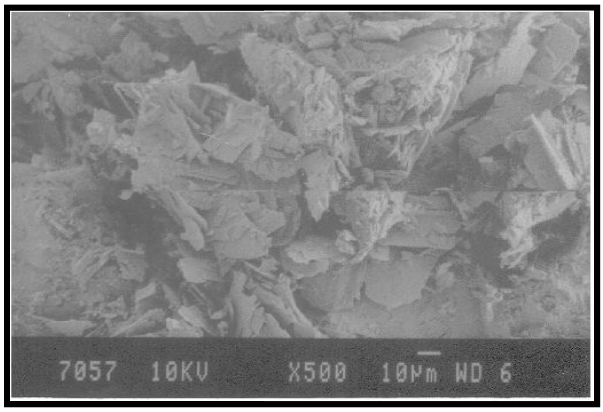


Crystals of pure sample are of the smallest size (1-3 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (3-15 µm). The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface (figure 6). Agglomerates obtained were spherical in shape with size 275-625 µm.

Figure 6 Scanning Electron Microscope photographs: A) Commercial Ibuprofen B) recrystallized sample of Ibuprofen C) Scanning Electron Microscope photographs:

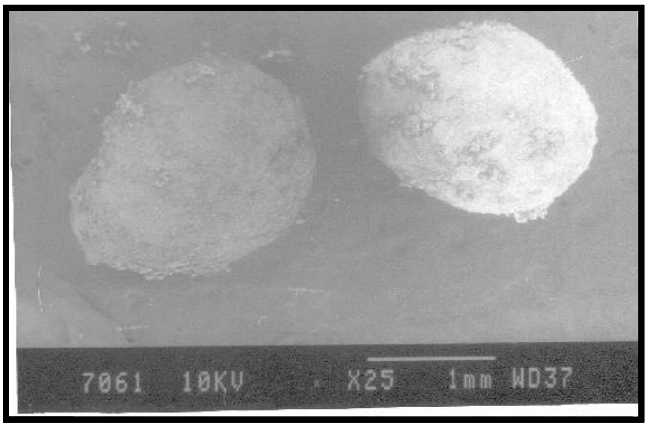
A





B

C



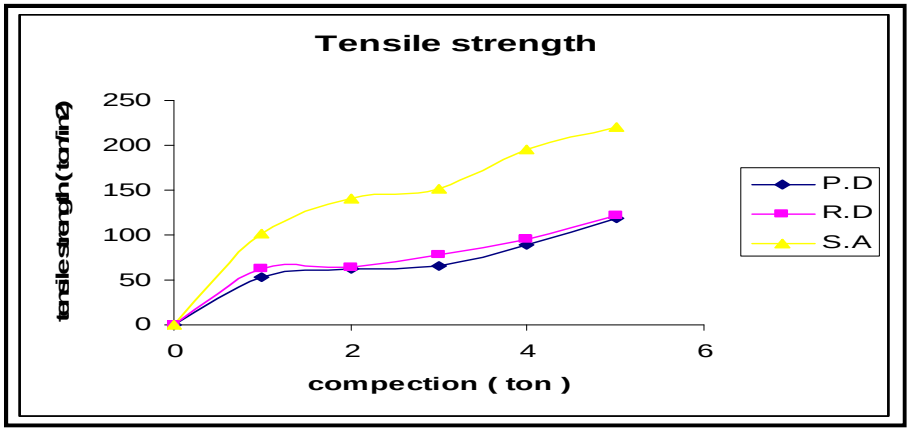
The different micromeritic properties of ibuprofen commercial, recrystallized and spherical crystals shown in (Table 6). The differences in the bulk densities may be related to their markedly different crystal habits, leading to different contact points, frictional and cohesive forces between the crystals. These factors affect the sliding of the particle against each other, leading to different packing geometry and thus different bulk densities. Flow rates are in agreement with morphology and bulk density data that spherical crystals with low bulk density exhibits better flow properties.

Table 6 Derived properties of Ibuprofen Commercial sample and spherical crystals obtained by solvent change method

Properties	Commercial sample	Re-crystallized Sample	Spherical crystals
Particle size	217µm	212µm	770µm
Flow rate	No flow	No flow	5.855gm/Sec
Angle of repose	32.88^0	31.156^0	29.88^0
Carr's index	2.697	2.582	2.2
Bulk density	0.6704 gm/ml	0.65 gm/ml	0.46284 gm/ml

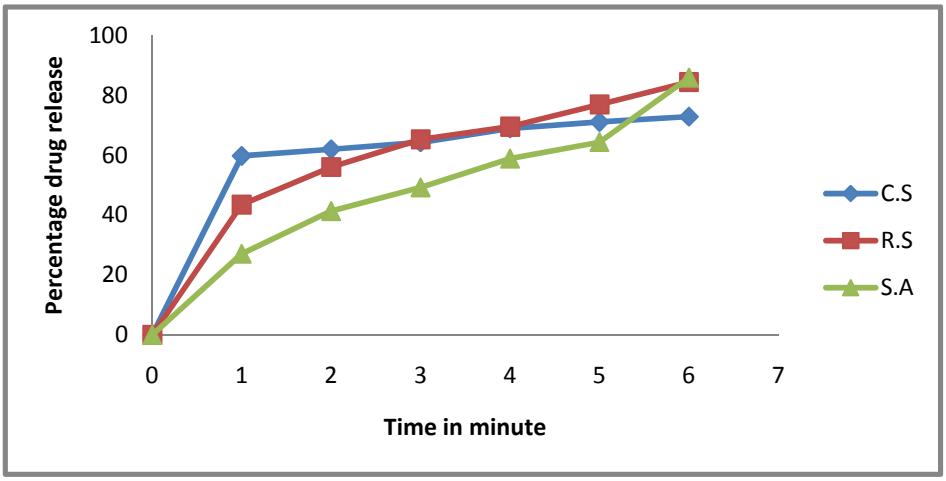
Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (figure 7). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter 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 90-101 g and was unaffected by the process variables.

Fig. 7: Tensile strength of spherical agglomerates Pure sample and Recrystallized Sample as a function of compaction pressure



The dissolution profiles of Ibuprofen (figure 8) 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.

Figure 8 Dissolution behavior of Ibuprofen crystals (commercial sample(C.S), Recrystallized sample(R.S),Spherical agglomeration (S.A))



CONCLUSION

Spherical crystals of Ibuprofen were prepared by solvent change method. 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 Ibuprofen 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 Ibuprofen by direct compression with directly compressible tablet excipients.

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