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Research Article

PREPARATION AND CHARACTERIZATION OF SPHERICAL AGGLOMERATES OF IBUPROFEN BY NEUTRALIZATION METHOD

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ABSTRACT
Ibuprofen, 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 Ibuprofen consisted of 1N sodium hydroxide; 0.07M HCl, isopropyl acetate (bridging liquid) in the ratio of 20:66.5:13.5 ml, respectively. Spherical agglomerates were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. Micromeritic and mechanical property 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, Ibuprofen, 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]. 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. All chemicals and buffers used were of analytical grade.

Preparation of spherical crystals of Ibuprofen by Neutralization Method

This process involved the formation of fine crystals and their agglomeration. The crystallization is generally achieved by neutralization method. Sano et al have reported spherical crystallization by this technique. 3.29 gm of ibuprofen was dissolved in 20 ml of 1N sodium hydroxide maintained at 40^0C. Alkaline solution of drug was quickly poured into 66.5 ml of 0.07M HCl maintained at 20^0C under continuous stirring at 500 rpm. When fine crystals of ibuprofen begin to form, 13.5 ml of isopropyl acetate was added. After 30 min stirring spherical crystals were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^0C for 12 hours[2, 3].

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 (3.29 gm) was dissolved in 20 ml of 1N sodium hydroxide at 40^0C and 13.5 ml of isopropyl acetate was added. The drug solution was poured quickly in to 66.5 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[2].

Characterization of spherical crystals

Drug content

Spherical crystals (50mg) were triturated and dissolved in 250ml of phosphate buffer pH7.2. The solution was filtered. After suitable dilution with phosphate buffer pH7.2, solution was analyzed spectrophotometrically (Shimadzu). Drug contents were calculated from calibration curves.

Differential Scanning Calorimetry (DSC)

Thermograms were obtained using a DSC DuPont 9900, with thermal analyzer. Accurately weighed samples were in an aluminum crucible Calorimetric measurements were made with empty cell (High purity alumina discs) as the reference.

Fourier Transform Infrared spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA).

X-ray powder diffraction

Crystal X-ray scattering measurements were performed using Fe K_α radiation (α=1.934A^0) and a scan speed of 4^0 per minute. The data recorded over a range of 2^0 to 50^0. Chart speed was 5mm/2^0.

Scanning electron microscopy

The Scanning electron microscopic photographs were obtained to identify and to confirm spherical nature, morphological characteristics of the crystals. Scanning electron microscopic studies were carried out using SEM Model Joel- LV-5600, USA, with magnification of 250X.

Micromeritic properties

Particle size of recrystallized sample, pure samples and spherical agglomerates were determined by microscopic method using calibrated ocular micrometer. Apparent particle densities of agglomerates 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 agglomerates and commercial crystals was measured by fixed funnel method.

Mechanical Properties

Crushing strengths of agglomerates were determined by using mercury lad cell method. It was carried out using 10ml glass hypodermic syringe. Tip of syringe and top end of the plunger are removed. The barrel was used as hallow 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 of platen. The plunger acted as movable platen. It was set directly on the agglomerates, positioned on the lower platen. Mercury is

added to the plunger at a predetermined rate from burette from a fixed height. The total weight of mercury plus weight of plunger required to break the agglomerates was the crushing strength.

Tensile strength of spherical crystals was determined by compressing 500 mg of crystals using a IR press at 0.5 tons 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 of compacts was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (Kg/cm^2) was calculated using following equation[8].

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

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

Dissolution studies of agglomerates

The dissolution of ibuprofen 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.

RESULTS

Drug content

The drug content was found to be in the range of 95-98%.

Differential scanning calorimetry (DSC)

DSC studies were carried out for different crystals of Ibuprofen. The DSC thermograms of ibuprofen crystals are presented in Figure 1 and table 2. For commercial sample re-crystallized sample and spherical crystals respectively. The data obtained from the DSC scans for the crystals are given in the Table 1in terms of onset of melt (T_0), melting point (T_m) and completion of melt (T_c). 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. In the DSC melt temperature range about 25^{0}C is normally considered as narrow, indicating a high degree of purity with respect to crystallinity.

FT-IR Spectroscopy

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). That showed there is not much significant difference in all spectra's of ibuprofen.

X-ray analysis

The X-ray diffraction patterns were obtained for the crystals of ibuprofen commercial sample, recrystallized sample and spherical crystals. The patterns are reported in Figures 3. The observed 2θ were processed using multi-dimension minimization program. The program helps to calculate 2θ values and cell parameters a, b, c, α, β and γ which will fit the observed reflections to less than 5% of the mean values.

The photomicrograph of different crystals forms of ibuprofen under different crystalline conditions are shown in the figure 4. Method of preparation of crystals affected the crystal form and size and shape of the drug. Crystals of commercial sample are of the smallest size (less than 3μm) and they have irregular, prismatic and needle like (acicular) crystal shapes. Recrystallization produced crystals with inter mediate size (3-15μm) which had flattened plates and rod like shapes.

Micromeritic properties

Table 3. Shows the different micromeritic properties of ibuprofen commercial, recrystallized and spherical crystals. 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.

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (figure 5).

Dissolution behavior of crystals

The dissolution profiles of ibuprofen (fig. 6) exhibited improved dissolution behaviour for spherical agglomerates than pure sample.

DISCUSSION

Ibuprofen offers free carboxylic group to neutralize with alkali hydroxides like potassium or sodium hydroxide. Ibuprofen was dissolved (3.29gms) in excessive of sodium hydroxide (20 ml of 1N) than was required to neutralize the ibuprofen. Crystallization of ibuprofen was induced by neutralizing the sodium hydroxide by adding large excess of hydrochloric acid (66.5ml of 0.07N). 13.5 ml of isopropyl acetate was added and stirred till the spherical crystals of ibuprofen were obtained. Amount of bridging liquid required to cause the spherical crystallization was much higher than the solvent change method. This might be due to formation of very fine crystals offering the large surface area, requiring larger amounts of bridging liquid to cause spherical crystallization.

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

In DSC study, during the course of heating, DSC thermograms (Figure 1) of ibuprofen, crystals have not exhibited the presence of polymorphic modifications, i.e., transitional changes due to conversion of one to the other. In other words, all the crystals are highly stable. Thermograms show sharp endothermic transitions corresponding to the melting point (75 to 78^0C). 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.

The FT-IR spectra of ibuprofen, recrystallized ibuprofen and spherical crystals are presented in Figure 2. All the crystals have exhibited general characteristic peaks. 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.

In XRD study, 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.

SEM figure reveal that the surfaces of some of the spherical crystals composed of stacks of crystals with roughly the same shape as the unmodified compound, while in some spherical crystals the surface is continuous and smooth depending on the crystallization conditions. The outlines of the crystals were distinct. Edges of recrystallized compound were curved around the corners. The cores of the spherical crystals were dense and almost all fused together, but the surface was rough and porous suggesting that the surface particle did not dissolve entirely but partially dissolved and fused with adjacent ones during interfacial recrystallization. Possible explanation could be, part of the particles must have dissolved in the bridging liquid, and these dissolving particles then acted as the nucleus for initial agglomeration. The remaining undissolved particles were then collected through collision and partially dissolved and recrystallized so as to fuse with initial agglomerates. It could be observed later, the process can be enhanced to certain extent by increasing the agitation.

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals. 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 92-98 g and was unaffected by the process variables.

The dissolution profiles of ibuprofen (fig. 6) exhibited improved dissolution behavior 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 ibuprofen were prepared by neutralization 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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Table 1: Effect of variables on formulation of spherica agglomerates of ibuprofen samples

Parameter	Variables	Observation
Conc. of bridging liquid (isopropyl acetate)	2% 8% 13.5%	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 30 min	Incomplete agglomerates Spherical agglomerates
Temperature	5 ± 1^0 $20^0\pm1^0$ 45 ± 1^0	Loose Spherical agglomerates Agglomeration Very large agglomerates
Mode of addition of bridging liquid	Whole at a time Drop wise	Crystals of irregular geometry Spherical agglomerates

Table 2: DSC data obtained for different Ibuprofen crystals

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 10^0C/min

Table 3: Derived properties of spherical agglomeartion of Ibuprofen obtained by neutralization method

Properties	Commercial sample	Re-crystallized Sample	Spherical crystals
Particle size	2-3µm	3-15µm	340-770µm
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

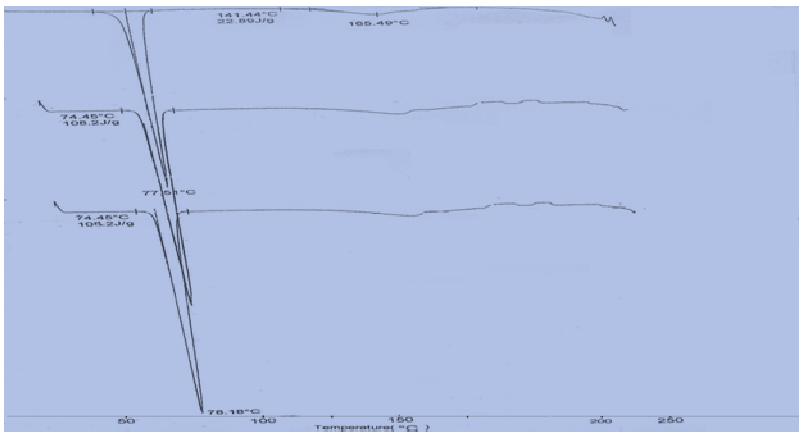

Figure 1 DSC data obtained for different Ibuprofen crystals

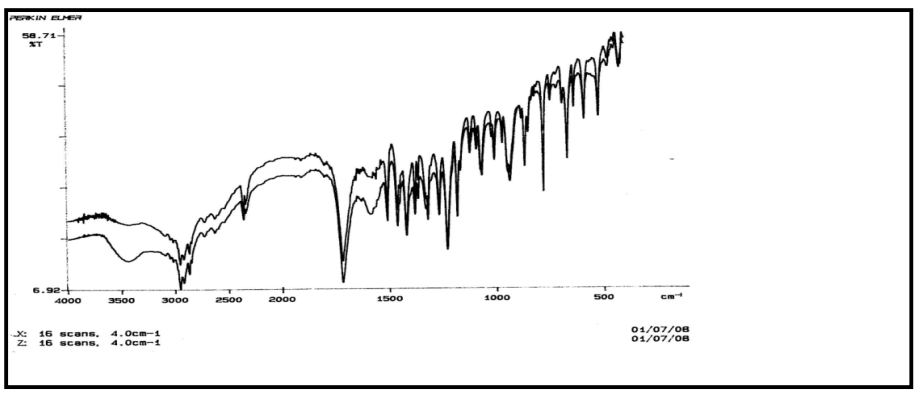

Figure 2 The FT-IR spectra of pure ibuprofen and spherical crystals

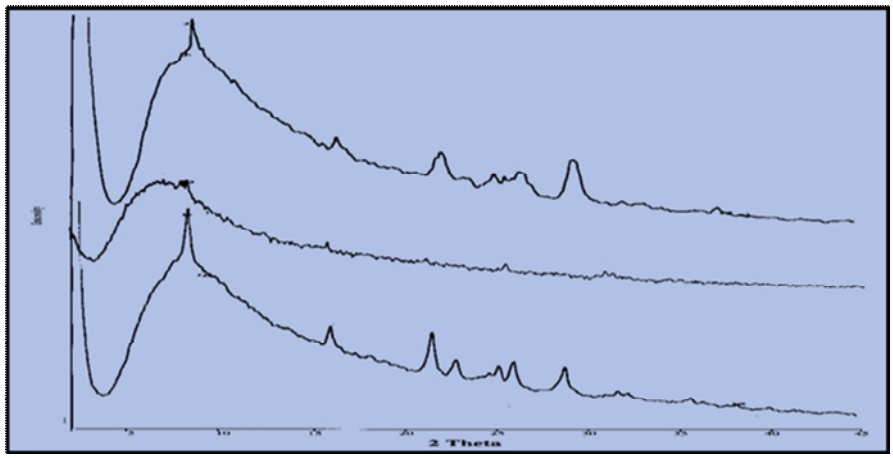

Figure 3: The XRD spectra of pure ibuprofen, recrystallized ibuprofen and spherical crystals.

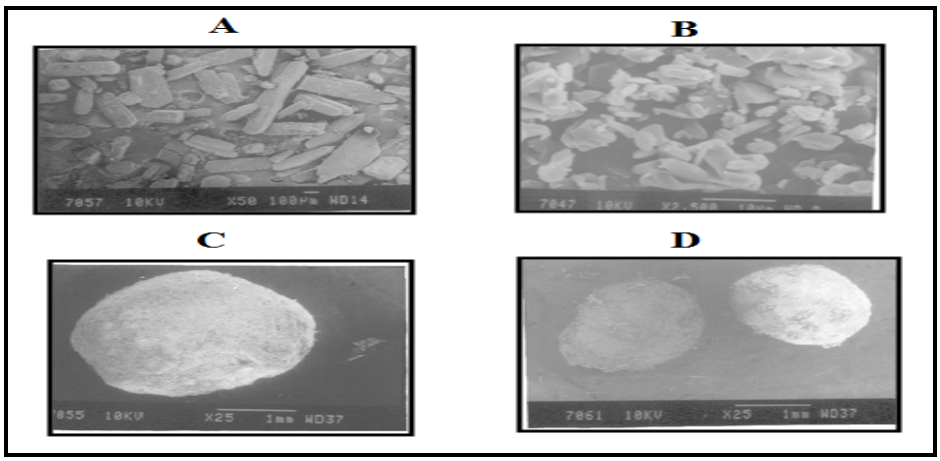

Figure 4: Scanning Electron Microscope photographs: A) Commercial Ibuprofen B) recrystallized sample of Ibuprofen C & D) Spherical agglomeration:

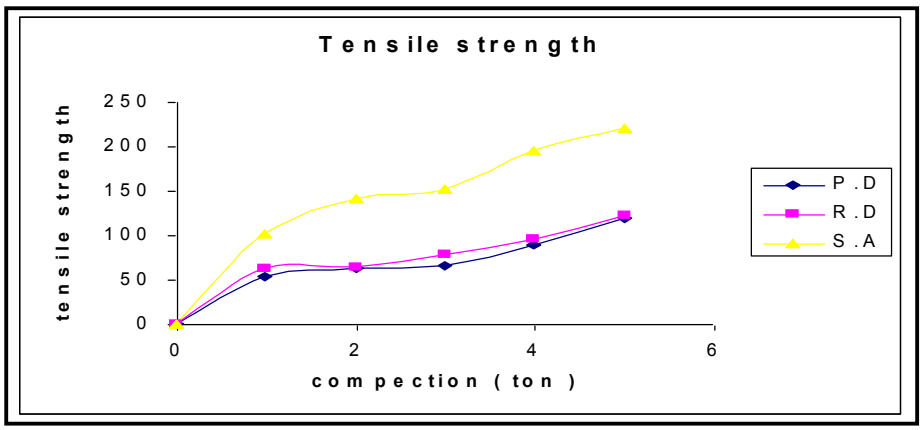

Fig. 5: Tensile strength of Pure sample and Recrystallized Sample,spherical agglomeration.

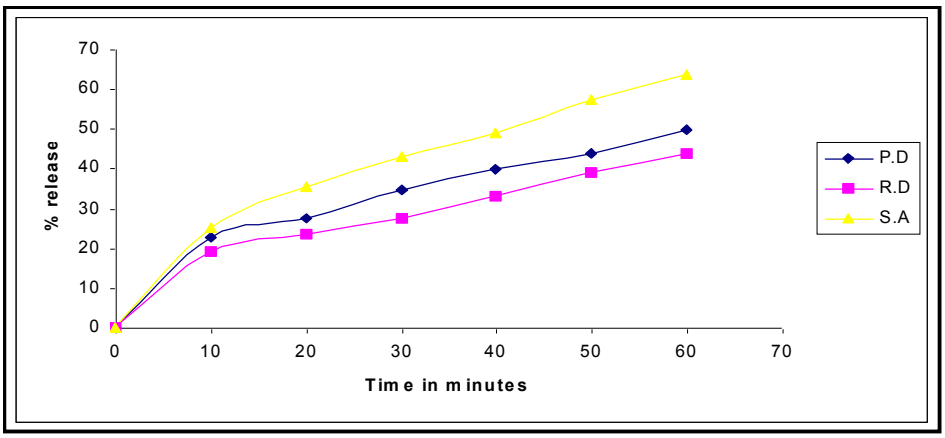

Figure 6: Dissolution profile of ibuprofen crystals.
P.D-Pure drug, R.D- Recrystallized drug- S.A- Spherical agglomerates

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