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Preparation and characterization of spherical agglomerates of mefenamic acid by neutralization method

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Abstract

Mefenamic acid, 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 Mefenamic acid consisted of 1 M Sodium hydroxide; 0.7 M hydrochloric acid; iso propyl acetate (bridging liquid) in the ratio of 20:280:15, 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, Mefenamic Acid, 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].

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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.

Material and methods

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

Preparation of spherical crystals of Mefenamic acid by Neutralization Method

4gm of Mefenamic acid was dissolved in 20 ml of 1N sodium hydroxide at 40^0C. This solution was poured in to 0.07N hydrochloric acid (280ml) maintained at 20^0C solution was agitated at 500rpm for 20minutes. During the process fine crystals of Mefenamic acid were produced by neutralization of sodium hydroxide. The precipitated crystals were simultaneously agglomerated by adding 15ml of isopropyl acetate. Spherical crystals formed were separated from the solution by filtration. Spherical crystals were dried at 40^0C 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 286 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

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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

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

Solubility studies[12]

The solubility of Mefenamic acid 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 286 nm.

Dissolution studies of agglomerates[7]

The dissolution of Mefenamic acid 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 286 nm.

Results and Conclusion

1 M Sodium Hydroxide is miscible in any proportion with water and iso propyl acetate. The 0.7 N hydrochloric acid was added to neutralize the 1 M Sodium hydroxide of Mefenamic acid.The proportions of 1 M Sodium hydroxide; 0.25 M hydrochloric acid; iso propyl acetate (bridging liquid) in the ratio of 20:280:15 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).

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 Mefenamic acid crystals. This one step melt might be due to only one crystal form (Triclinic) of the Mefenamic acid formed during the crystallization process, thus indicating that Mefenamic acid did not under go any crystal modification. The temperature range of the endothermic peak of all the Mefenamic acid crystals lies in the range of 224.17^0 to 235.02^0. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated Mefenamic acid was 242.06° with decreased enthalpy of (74.21 J/g) indicating decreased crystallinity Infrared spectra of mefenamic acid commercial, recrystallized and spherical crystals showed characteristic peaks at 1255 cm^{-1} (-OH group bending and vibrations of COOH), 1647 cm^{-1} (N-H stretching vibration), 1572 cm^{-1} (C=O stretching), 1504 cm^{-1} (Aromatic C-H plane deformation), 1163 cm^{-1} (Aromatic-O-CH_3) and 757(Aromatic C-C vibration for ortho substitution). Spectrum of recrystallized mefenamic acid was slightly different from commercial sample in the region of wave number between 3350 and 3300 cm^{-1}. This suggests that the recrystallized mefenamic acid from the mixture of water isopropyl acetate and THF has a different crystalline form than its crystalline form in commercial sample and in spherical agglomerates (Figure-2).

The X-ray powder diffraction measurements show no difference between commercial sample and spherical crystals. The d values and relative intensities were comparable. However, the intensity and position of peaks for recrystallized MA were different, suggesting the change in the crystalline form. In general, for two forms of crystals, when the patterns (i.e. peak positions) are identical they have the same internal structure, whereas if the pattern are different then the crystal have different internal structure and are polymorphs. Here the Commercial MA and

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spherical exhibited spectra with similar peak position (2 theta values). Therefore, the presence of different polymorphs of Mefenamic acid was ruled out. However, relative intensities of X-rd peaks were modified in case of commercial MA and spherical crystals of MA, attributed to the relative abundance of the planes exposed to the x-ray source. The 2θ data were processed using multidimension minimization programme. The programme helps to calculate 2θ values and cell parameters a, b, c, α, β, and γ which fits observed reflections to less than 5% of the mean values. Commercial MA and Spherical crystals of MA exhibited space group OrthorhombicP222 while the recrystallized sample showed space group triclinic p1.Result showed in figure 3 and table 2.

Crystals of pure sample are of the smallest size (5-14 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (10-18 µm). The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface (fig's. 4). Agglomerates obtained were spherical in shape with size 325-850 µm.

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

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (fig. 5). 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 96-103 g and was unaffected by the process variables. The dissolution profiles of Mefenamic acid (fig. 6) 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.

Spherical crystals of Mefenamic acid 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 Mefenamic acid 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 Mefenamic acid by direct compression with directly compressible tablet excipients.

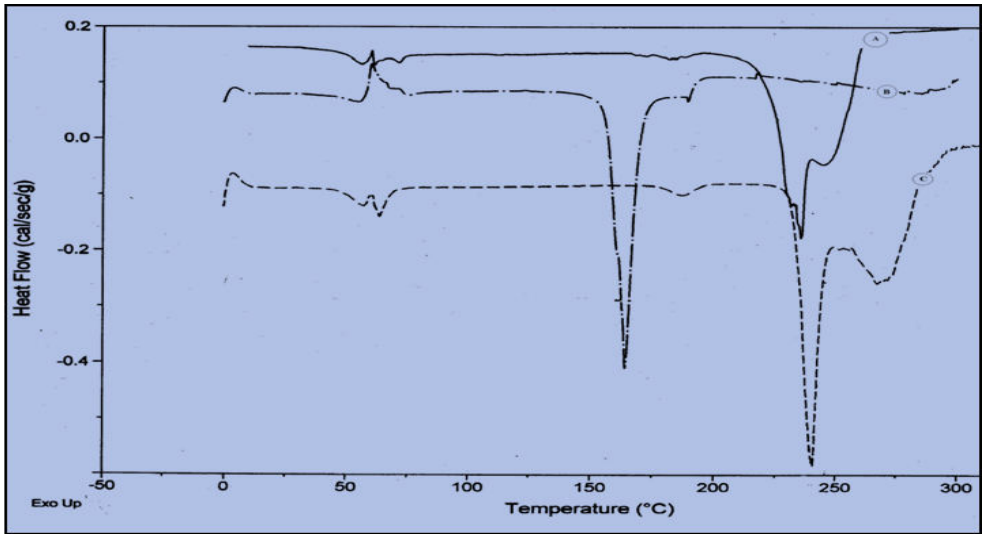

Fig.1: DSC curves of different crystals of mefenamic acid :A) Commercial sample, B) recrystallized MA, C) spherical crystals of MA.

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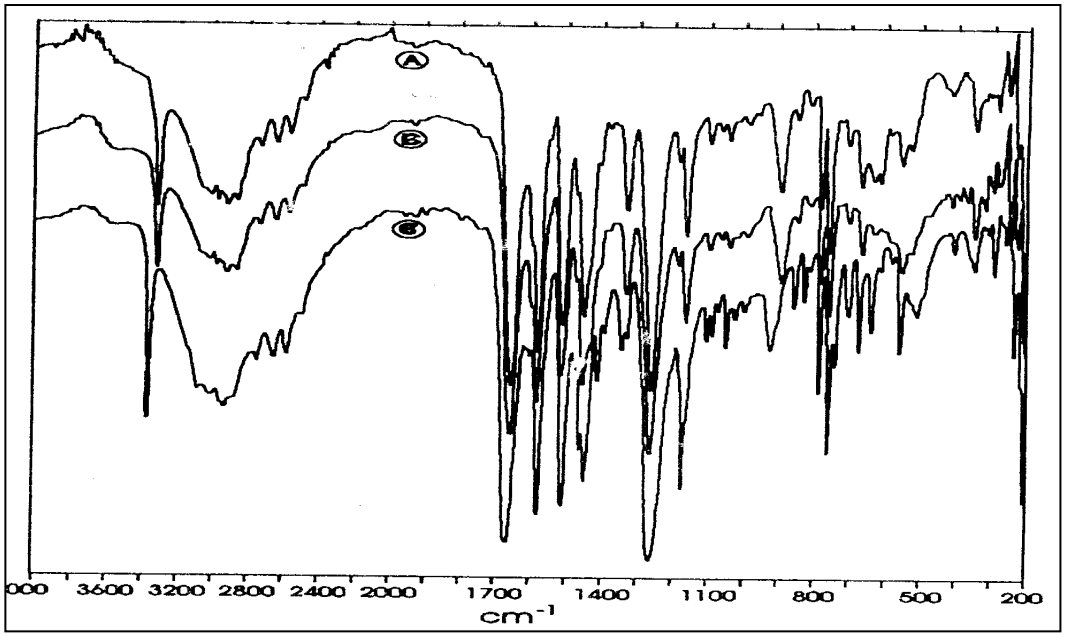

Fig. 2: IR spectra of mefenamic acid A) Mefenamic acid B) Recrystallized mefenamic acid C) spherical crystals of mefenamic acid

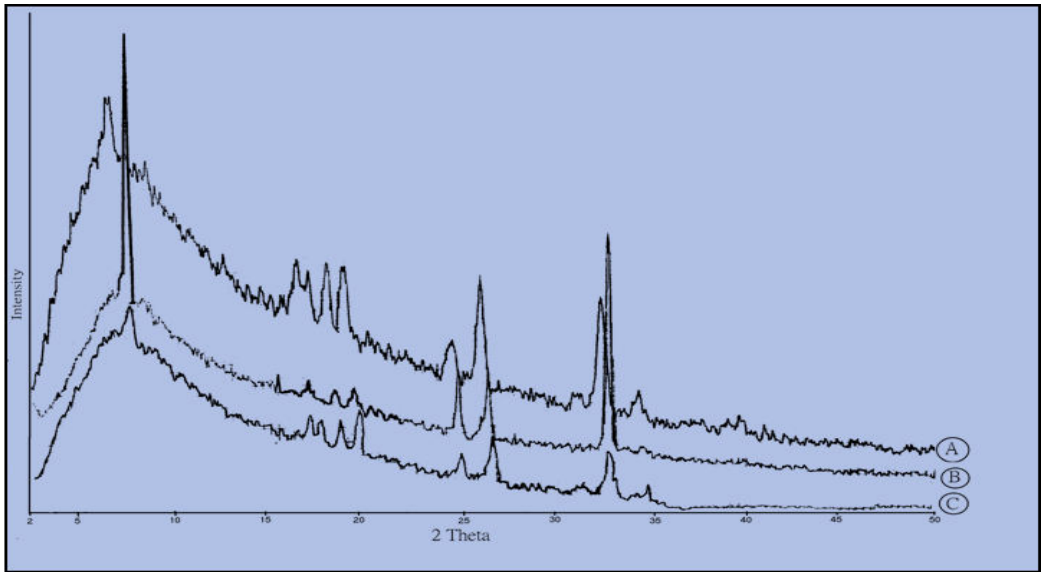

Fig. 3: X-ray diffraction patterns of A) commercial sample B) Recrystallized sample and C) Spherical crystals of mefenamic acid

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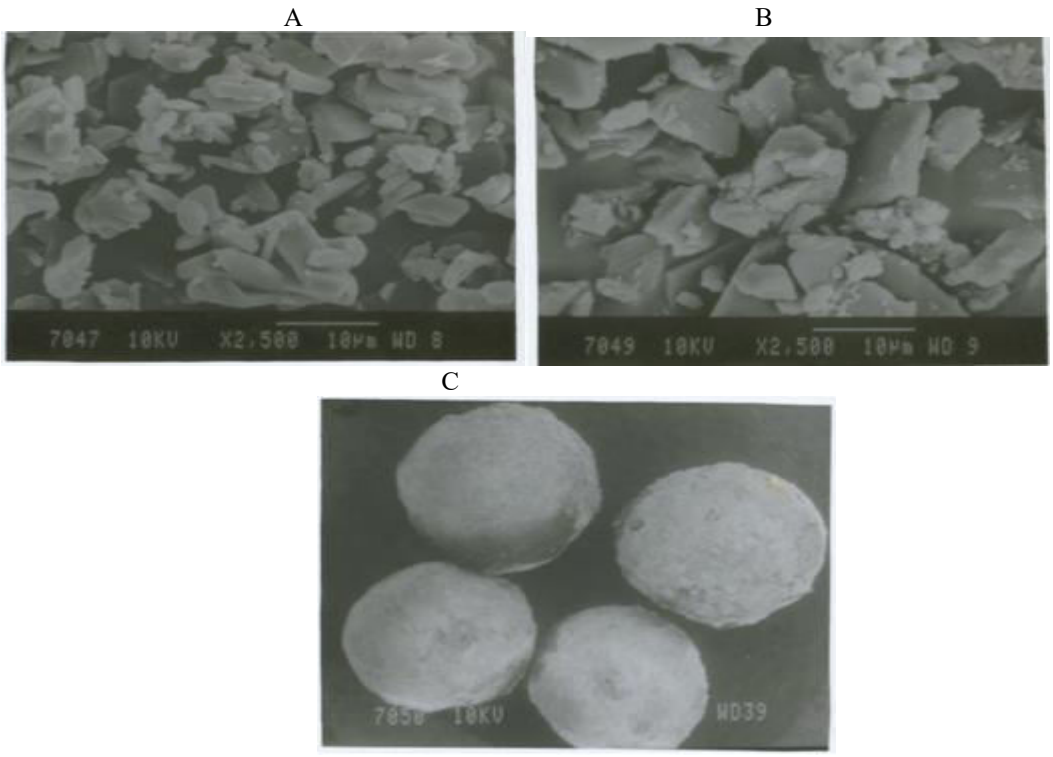

Fig. 4: (A) SEM of Ketoprofen pure sample, (B)SEM of ketoprofen-recrystallized sample in mixture of 1M Sodium Hydroxide: chloroform 0.7 Hydrochloric acid.(C) SEM of spherical agglomerate at 50X

Fig. 5: Tensile strength of spherical agglomerates Pure sample and Recrystallized Sample as a function of compaction pressure(pure drug: Recrystaillized : spherical agglomeration)

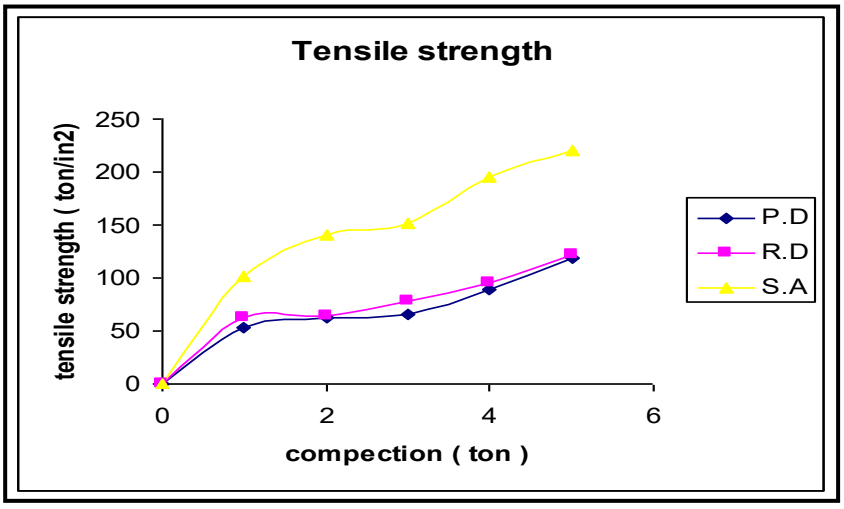

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Fig. 6: Dissolution of Mefenamic acid in Phosphate buffer pH7.2 for commercial sample, recrystallized sample, and spherical crystals.

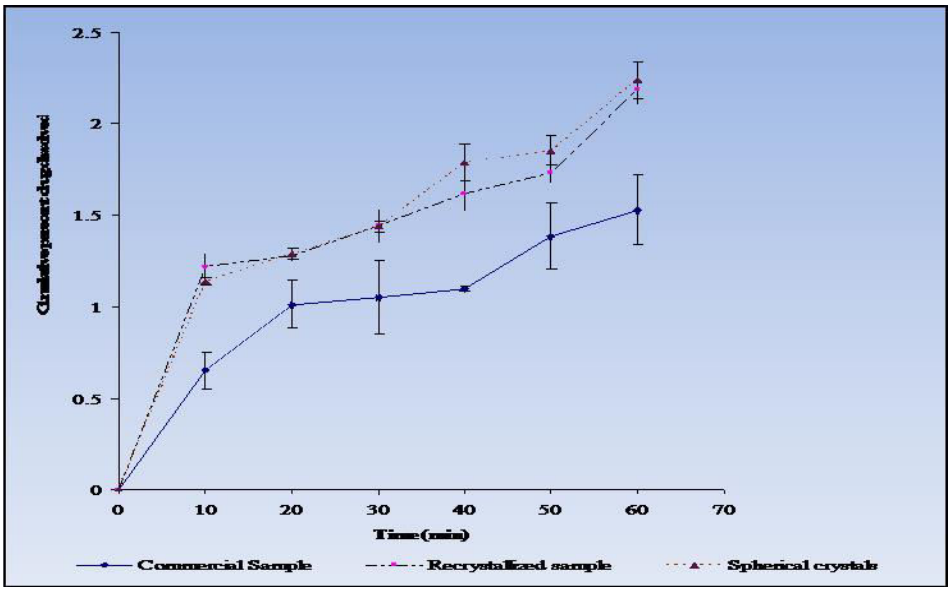

Table 1: Effect of variables on formulation of spherical agglomerates of Mefenamic acid

Parameter	Variables	Observation
Conc. of bridging liquid (Iso propyl acetate)	2% 8% 15%	No agglomeration No agglomeration Agglomeration
Agitation speed	300±25 400±25 500±25 600±25	Clumps Spherical & large Spherical Spherical & small
Agitation time	10 min 20 min	Incomplete agglomerates Spherical agglomerates
Temperature	5 ± 1^0 $20^0\pm1^0$ 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

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Table 2: X-ray diffraction patterns of A) commercial sample B) Recrystallized sample and C) Spherical crystals of mefenamic acid

	A	B	C	A	B	Γ	Unit cell volume
Pure sample	14.78	13.64	11.9	90	90	90.1	2441.37
Recrystallized Sample	14.78	6.99	6.35	89.3	89.5	87.4	2410.09
Spherical crystals	13.86	6.35	6.18	82.88	64.57	81.94	543.91

Table 3: Micromeritic properties of mefenamic acid pure sample and spherical agglomerates obtained by solvent change method.

Properties	Commercial sample	Re-crystallized Sample	Spherical crystals
Particle size(μm)(±SD)	5-14	10-18	325-850
Angle of repose(^{0}±SD)	32.88(1.28)	31.16(2.1)	19.76 (2.42)
Friability (%)(±SD)	--	--	0.48(0.80)
Apparent density (gm/ml ±SD)	0.308(0.16)	0.340(0.08)	0.33(0.10)
Tapped density(gm/ml±SD)	0.401(0.80)	0.506(0.08)	0.35(0.12)
Carr's compressibility (%)	23.2	32.80	5.714

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