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Research Article

Influence of various bridging liquids on spherical agglomeration of indomethacin

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ABSTRACT

For poorly soluble, highly permeable (Class II) drugs, such as Indomethacin, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Therefore together with the permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. Indomethacin is an anti-inflammatory drug that is characterized by poor water solubility and flow properties. The main objective of the present study is to prepare spherical agglomerates of Indomethacin by using various bridging liquids and to study the effect of bridging liquids on micromeritic properties and dissolution behavior. Spherical agglomerates were prepared by using solvent change method. Solvent composition for spherical agglomeration was determined by constructing ternary diagram. Crystallization medium used for spherical agglomerates of Indomethacin were DMF (good solvent); water (poor solvent); chloroform/isopropyl acetate/dichloromethane (bridging liquids) in the ratio of 25:62.5:12.5 respectively. Spherical agglomerates were characterized by differential scanning calorimetry, IR spectroscopy, XRD and Scanning electron microscopy. Gas phase chromatography was carried to estimate the residual DMF, chloroform, isopropyl acetate and dichloromethane. Micromeritic and dissolution behavior studies were carried out. Process variables such as amount of bridging liquid were optimized. Dissolution profile of the spherical agglomerates was compared with commercial 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 profiles of Indomethacin tablets prepared using spherical agglomerates exhibit greater dissolution behaviour than tablets prepared by powder raw material. Hence this technique can be used for formulation of tablets of Indomethacin by direct compression with directly compressible tablet excipients.

Keywords: Spherical agglomeration; Indomethacin; bridging liquid; ternary diagram; tensile Strength; agglomeration; micromeritic properties; direct compression.

INTRODUCTION

The technique of spherical agglomeration was first developed by Kawashima et al., (1982). The 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. (Kawashima Y et al. 1995) In the Spherical agglomeration method, saturated solution of the drug, in a solvent in which it is very soluble, is poured into a poor solvent of the drug. Provided that the good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, crystals precipitate immediately. (Piera Di Martino et al. 2000) A suitable amount of a third solvent, which is not miscible with the poor solvent and which preferentially wets the precipitated crystals, is added to the system while stirring. This third solvent, which is called a 'bridging liquid', can collect the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid. (Piera Di Martino et al. 2000) By using this technique, the physicochemical properties of pharmaceutical crystals were dramatically improved for pharmaceutical processes, e.g., mixing, filling and tabletting, because of their excellent flowabilities and packabilities. Apart from particle enlargement, it has also been applied for various purposes such as taste masking, e.g., Enoxacin (Kawashima Y et al. 1990), Crystallinity and crystal form changes, e.g., Tolbutamide (Sano A et al. 1989) and Tranilast anhydrate (Kawashima Y et al. 1991), increase in solubility, dissolution rate of poorly soluble drugs

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e.g., Fenbufen (Piera Di Martino et al. 1999), Tolbutamide (Sano A et al. 1987), Celecoxib (Paradkar AR et al. 2002), Norfloxacin (Peuchagut HG et al. 1998).

Chloroform was used as a bridging liquid in the preparation of salicylic acid (Kawashima Y et al. 1984), Aspirin (Deshpande MC et al. 1991), Roxithromycin (Chourasia M K et al. 2004), Trimethoprim (Deshpande MC et al. 1991), Tranilast anhydrate (Kawashima Y et al. 1991)and Tranilast monohydrate (Kawashima Y et al. 1991) spherical crystals. In the preparation of Propyphenazone (Piera Di Martino et al. 2000), Acebutolol hydrochloride (Kawashima Y et al. 1995), Tolbutamide (Sano A et al. 1989, 1990, 1992), Fenbufen (Piera Di Martino et al. 1999) and Phenytoin (Kawashima Y et al. 1986) spherical crystals isopropyl acetate was used as a bridging liquid.

Paradkar AR. et al., prepared Celecoxib spherical crystals by using dichloromethane as a bridging liquid. For poorly soluble, highly permeable (Class II) drugs, such as Indomethacin, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Therefore together with the permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. (Yousef Javadzadeh et al. 2005) Various methods are applied to increase the solubility of Indomethacin, e.g., Complexation (Fini A et al. 2001), self emulsifying system (Kimi Y A et al., 2000) etc. And also Indomethacin exhibits poor flow and a high tendency of adhesion. (Janos Bajdik et al. 2004) Various methods are applied to increase the flow properties of Indomethacin (Janos Bajdik et al. 2004), e.g., coating, granulation etc.

MATERIALS AND METHODS

Materials

Indomethacin was a gift sample of Micro labs, Bangalore, India. N, N dimethylformamide, isopropyl acetate, dichloromethane and chloroform were procured from Merck, Mumbai, India. All chemicals and buffers used were analytical grade.

Preparation of spherical agglomerates of Indomethacin

For spherical agglomeration of Indomethacin N, N-dimethylformamide was found to be suitable good solvent because of its excellent solubility and miscibility with dispersing phase water (poor solvent). Chloroform, isopropyl acetate and dichloromethane were chosen as bridging liquids because of their good wettability with the drug. Indomethacin 5 gm was dissolved in 25 ml of N, N-dimethylformamide heated at 45^0C until a clear solution was obtained. The drug solution was poured quickly in to 62.5 ml of water maintained at 20^0C, under continuous stirring at 500 rpm with a propeller type agitator. When fine crystals of Indomethacin begin to precipitate (5 min), 10 ml of chloroform/ isopropyl acetate/dichloromethane was added. After 10 min 2.5 ml of chloroform was added again. After 30 min stirring spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^0C for 12 hours. The agglomerates prepared by using chloroform, isopropyl acetate and dichloromethane bridging liquids were denoted by IM-A, IM-B and IM-C respectively.

Characterization of spherical agglomerates

Drug content

Spherical agglomerates (50mg) were triturated with 10 ml of water. Allowed to stand for 10 minutes with occasional swirling and methanol was added to produce 100ml. 5 ml of this solution was mixed with equal volumes of methanol and phosphate buffer 7.2 to produce 100ml.Absorbance of the resulting solution was measured at 320 nm. Drug content was determined from standard plot.

Fourier Transform Infrared spectroscopy

The FT IR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 mg of the pure drug, recrystallized and spherical agglomerates were used separately. Pure drug, spherical agglomerates and recrystallized samples were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm^2 pressure. FT-IR spectra were obtained by powder diffuse reflectance on FT-IR spectrophotometer.

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. All accurately weighed samples (about 1 mg of Indomethacin or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10^0C min^{-1}, from 25^0 to 250^0C. An empty aluminum pan was used as reference.

X-ray analysis

X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. 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 40mA, 45 kV. The samples were analyzed in the 2θ angle range of 3-50 and the process parameters used were set as scan step size of 0.0170 (2θ), scan step time of 51.0362 sec and time of acquisition of 1h. 2θ values were processed using multidimensional minimization programme to calculate cell volume, cell parameters and space grouping.

Scanning electron microscopy

The Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250X.) photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

Surface topography (Peuchagut H G et al., 1998)

Tracings of spherical agglomerates were taken using Camera Lucida fixed to optical microscope (magnification 45X) and were used to calculate circulatory factor (S) as

$$S=P^2/(12.56XA)$$

Where A is area (cm^2) and P is perimeter (cm).

Micromeritic properties

Particle size of recrystallized sample and commercial 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, India). The angle of repose of agglomerated and commercial crystals was measured by fixed funnel method.

Determination of contact angle (Lerck C R 1976)

A drop of saturated solution of Indomethacin commercial sample and spherical agglomerates in water was placed on the tablet surface and height of the drop was measured. The contact angle was determined using following equation

$$Cos\theta = 1- Bh^2/\{3(1-\varepsilon)(1- Bh^2/2)\}^{1/2}$$

Where $B = \rho g/2\gamma$ (γ =surface tension of saturated solution of Indomethacin commercial sample/spherical agglomerates in water dyne/cm),ε = porosity of the tablet, h = height of liquid drop in cm.

Mechanical Properties

Tensile strength (Peuchagut H G et al., 1998)

Tensile strength of spherical agglomerates was determined by compressing 500 mg of crystals using hydraulic press at different kg/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 of compacts was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (kg/cm^2) was calculated using following equation.

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

Where F, D and t are hardness (kg/cm^2), compact diameter (cm) and thickness (cm) respectively.

Crushing strength (Peuchagut H G et al., 1998)

Crushing strength of agglomerates was determined using modified Jarosz and Parrot's mercury load cell method. 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 platen. The plunger acted as a movable platen. It was set directly on the agglomerate, positioned on the lower platen. Mercury was added to the plunger at a rate of 10 g/sec 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 (gm).

Mechanical strength (Friability) (Takeo Kuriki et al., 1990)

Two grams (W/o) 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 two minutes. After passing this through a sieve having a mesh size 125µm, the weight (W) of the material which did not pass through the sieve was determined, and friability (X) was calculated using equation

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

Determination of residual solvents concentration (Piera Di Martino et al., 2000)

Residual water in spherical agglomerates was determined using Karl Fischer (Polmon, Hyderabad, India) titrater, calibrated with sodium tartrate.

Gas chromatography (Shimadzu GC-14B chromatograph, Japan) was used to estimate residual DMF, chloroform, isopropyl acetate and dichloromethane in spherical agglomerates.

Experimental Conditions

Column: DB – 624 (6% cyanopropyl phenyl and 94% dimethyl polysiloxane)

Length – 30 m, internal diameter – 0.53 mm, Film thickness – 5 µm

Detector: FID Carrier gas: Helium Pure gas: Nitrogen

Flow: Hydrogen - 60 kpa equivalent to 50 ml/min, Zero air- 50 kpa equivalent to

500 ml/min, Nitrogen - 100 kpa equivalent to 40 ml/min

Column flow: 30 kpa equivalent to 4.29 ml/min

Temperature: Detector- 260°C, Capillary injector- 220°C.

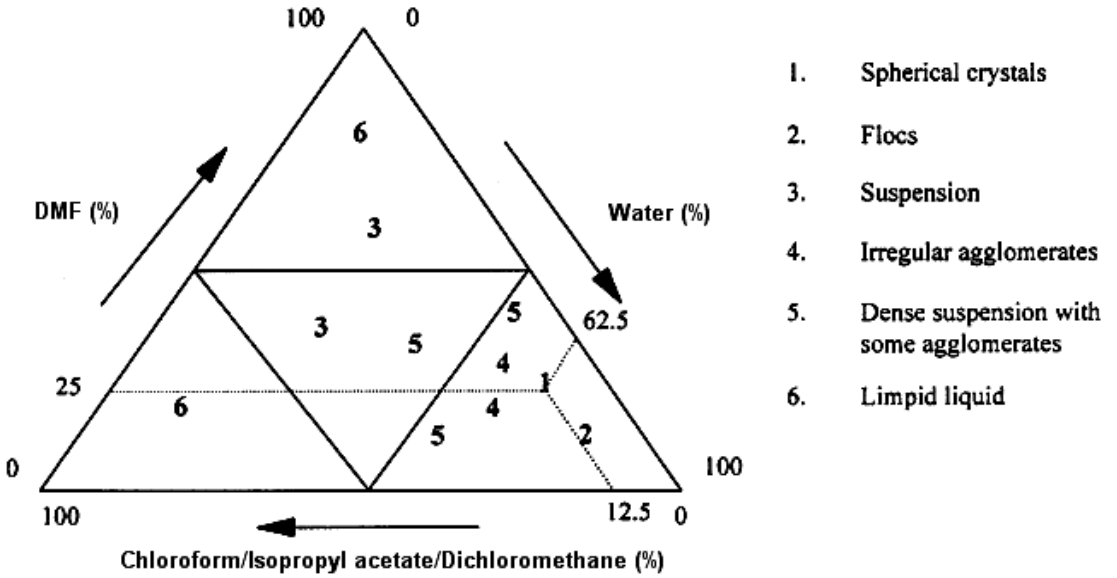

Figure 1: Ternary diagram showing the results of different studies and the area for agglomerate obtention are indicated

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

Parameter	*Variables*	*Observation*
Conc. of bridging liquid	2% 8% 12.5%	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° C 20°C 45±1° C	No agglomeration Spherical agglomerates Very large agglomerates
Mode of addition of bridging liquid	Whole at a time Drop wise	Crystals of irregular geometry Spherical agglomerates

Column oven temperature

Column temperature was maintained 120°C for 8 minutes; temperature was gradually raised to 220°C at the rate of 30°C per minute.

Solubility studies (Nocent M et al., 2001)

The solubility of Indomethacin spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates was added to screw- capped 50 ml glass vials. The vials were shaken for two hours on mechanical shaker. The solution was filtered through whatmann filter paper no.1. The drug concentration was determined spectrophotometrically at 320 nm.

Preparation of tablets (Yousef Javadzadeh et al., 2005)

Indomethacin conventional tablets were prepared by mixing the commercial sample and spherical agglomerates with microcrystalline cellulose-silica (20:1) 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 10-mm punch and die using a tableting machine (Rimek, Mumbai, India) equipped with strain gauge (10-400 kg/cm2). Sufficient compression load between 80-100 kg/cm^2 was applied in order to produce tablets hardness of 6-7 kg/cm^2. The formulation prepared with commercial sample and spherical agglomerates (IM-A, IM-B and IM-C) was denoted as F, F1, F2 and F3 respectively and each tablet contains 25 mg Indomethacin, 100 mg of coarse granular microcrystalline cellulose, 5 mg of nm-sized silica, 5 mg sodium starch glycolate and 65 mg lactose.

Dissolution studies of tablets

The dissolution of Indomethacin tablets was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai, India.). 750 ml of dissolution medium consisted of (one part of 7.2 Phosphate buffer and four parts of water). 10 ml of dissolution medium were withdrawn every 10 min for 60 min. The amount

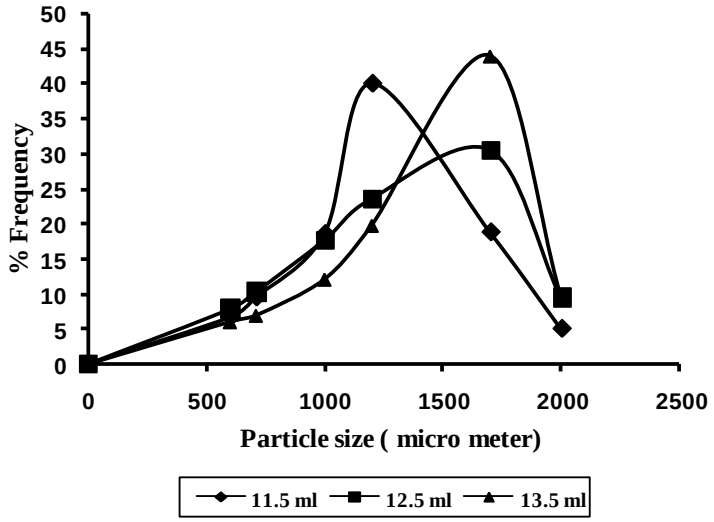

Figure 2: Effect of amount of chloroform on size distribution of Spherical agglomerates (IM-A)

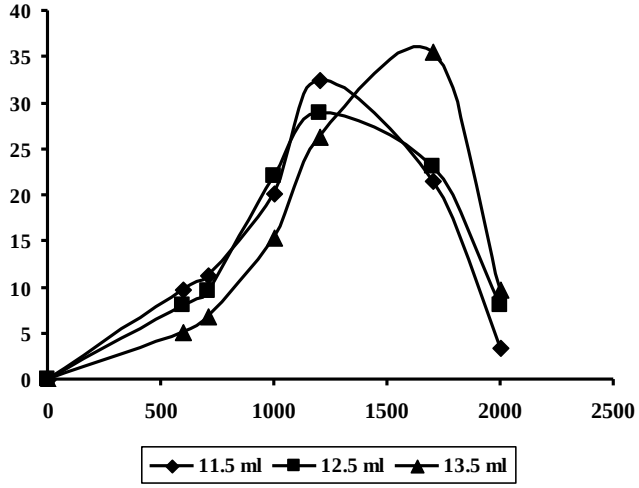

Figure 3: Effect of amount of isopropyl acetate on size distribution of Spherical agglomerates (IM-B)

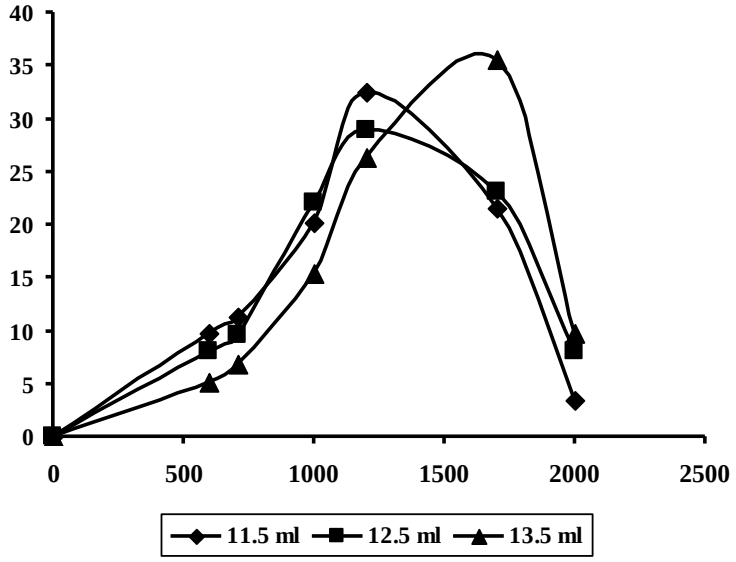

Figure 4: Effect of amount of dichloromethane on size distribution of Spherical agglomerates (IM-C)

of dissolved drug was determined using UV Spectrophotometer method (UV 1601 A, Shimadzu, Japan) at 320 nm.

Results and discussion

DMF is miscible in any proportion with water, chloroform, isopropyl acetate and dichloromethane. If the ternary diagram is envisaged, to select the solvent composition. Chloroform/ isopropyl acetate / dichloromethane and water are like an emulsion in a large of area of this diagram (Figure 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 (Figure 1). These proportions of DMF-water-chloroform/isopropyl acetate/dichloromethane were finally chosen for the study.

To optimize Indomethacin spherical agglomeration by DMF-water-chloroform/isopropyl acetate/ dichloromethane system, other process parameters were considered; like amount and mode of addition of bridging liquid, stirring speed and time and temperature (Table 1).

The average diameter of agglomerated crystals was found to increase with increasing amount of bridging liquid in the crystallization medium due to enhanced agglomeration of crystals. Agglomerates have excessive bridging liquid on the surface of for coalescence. Size distributions of particles at different concentrations of different bridging liquids are shown in the Figs.2, 3, 4.

The movement of droplets within the medium induces circulation inside the droplets. The intensity of this internal circulation depends on the speed. Higher speed (>600 rpm) induces crystal agglomerate destruction. A lower stirring rate (<400 rpm) reduces the possibility of obtaining spherical agglomerates. It is evident that the size of agglomerates is very much

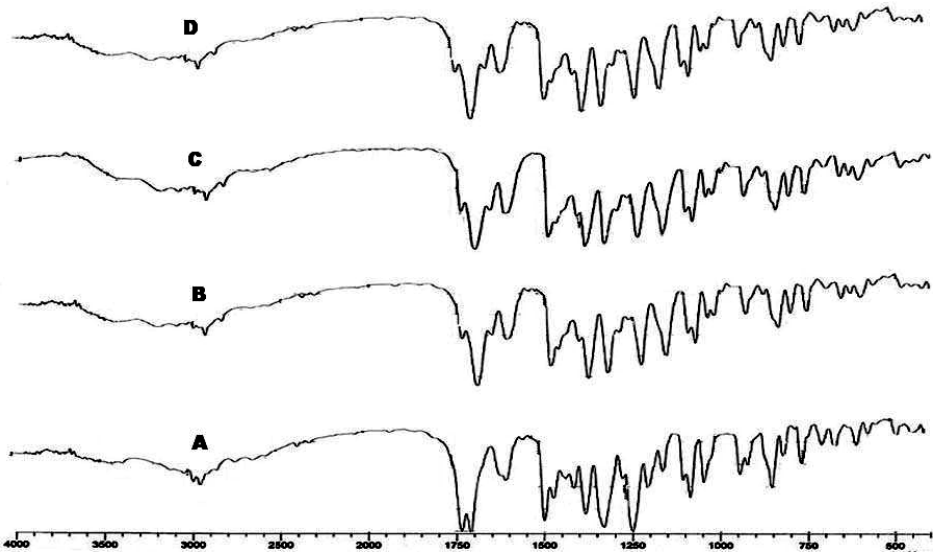

Figure 5: FT-IR spectra of Indomethacin A: Commercial sample, B: IM-A, C: IM-B, D: IM-C

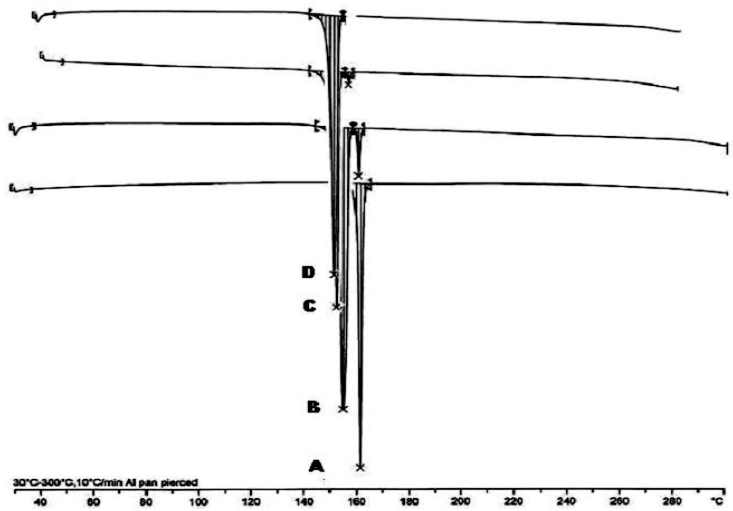

Figure 6: DSC thermograms of Indomethacin. A: Commercial sample, B: IM-A, C: IM-B, D: IM-C

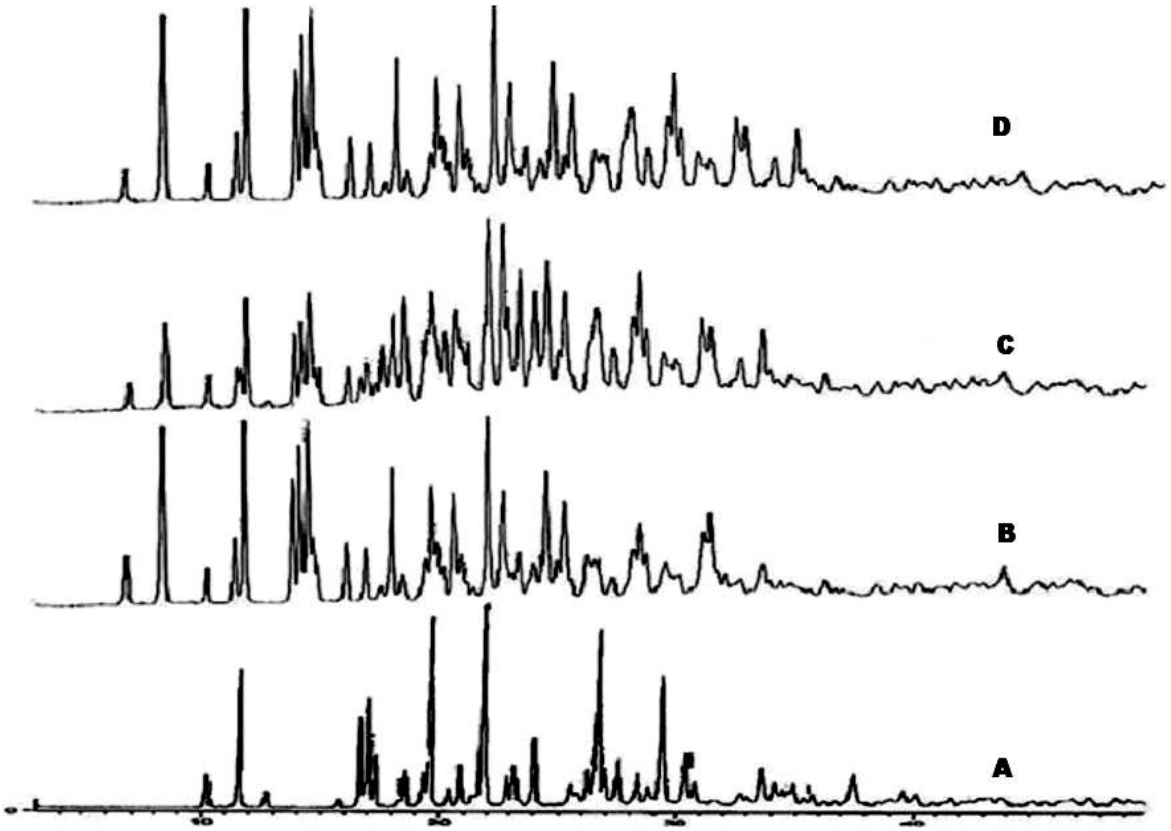

Figure 7: X-ray diffraction spectra of Indomethacin. A: Commercial sample, B: IM-A, C: IM-B, D: IM-C

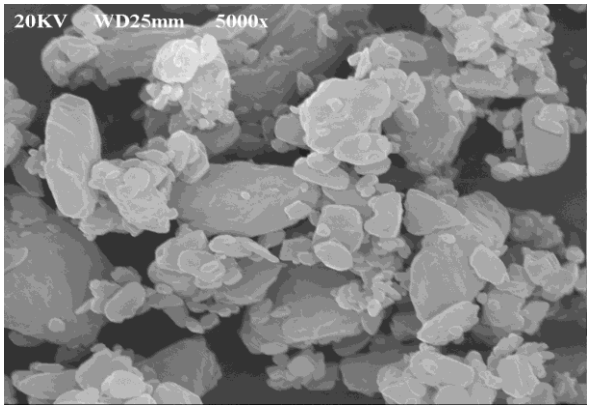

Figure 8: SEM of Indomethacin commercial sample

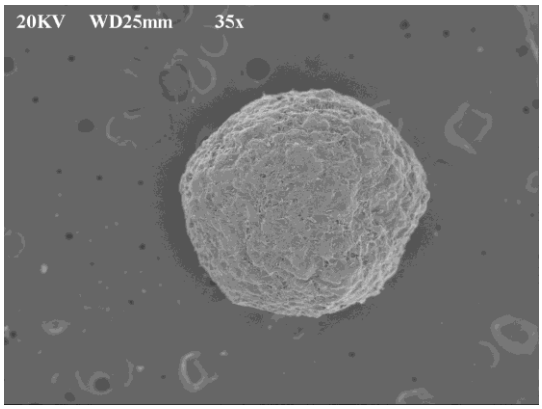

Figure 9: SEM of Indomethacin spherical agglomerate (IM-A)

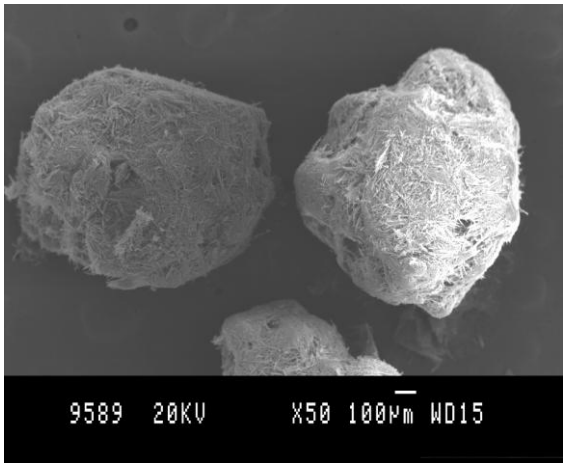

Figure 10: SEM of Indomethacin spherical agglomerate (IM-B)

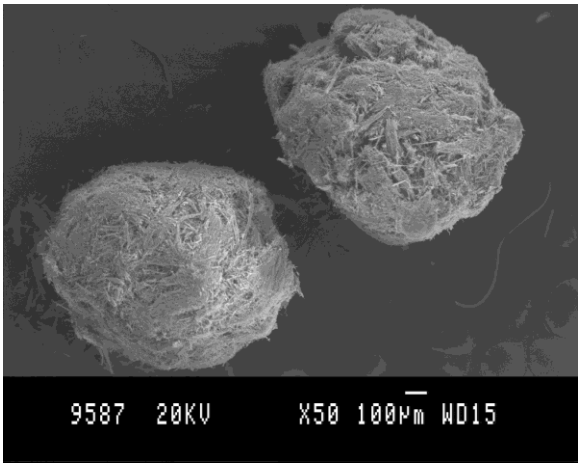

Figure 11: SEM of Indomethacin spherical agglomerates (IM-C)

Table 2: Micromeritic properties of Indomethacin commercial sample and spherical agglomerates obtained by solvent change method

Properties	*Commercial sample*	*IM-A*	*IM-B*	*IM-C*
Particle size(μm)	5-10	830	759	954
Flow rate (gm/Sec)	No flow	7.75	8.83	8.05
Angle of repose (θ)	38.88	28.72	28.98	29.45
Tapped density(gm/ml)	0.9259±0.009	0.1937±0.04	0.1582±1.36	0.1402±1.04
Bulk density(gm/ml)	0.6664±0.0084	0.1857±0.006	0.1426±0.84	0.1552±0.64
Carr's index	27.57	7.41	9.67	9.66
Mechanical strength (%)	-	0.8974±0.65	0.7842±1.24	0.9461±1.86
Contact angle	54.8°±1.65	88.6°±2.46	83.32°±1.94	79.72°±2.1

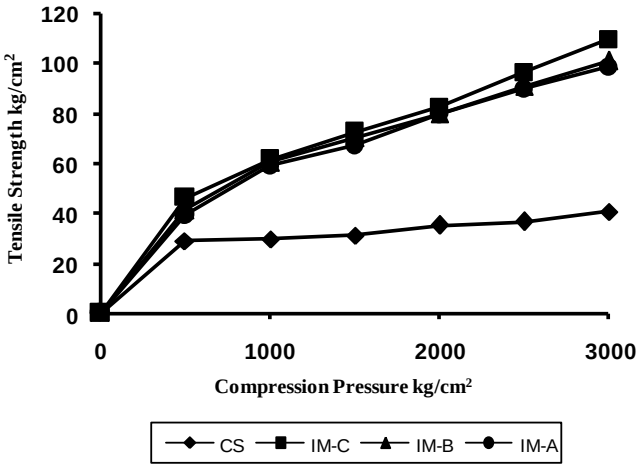

Figure 12: Tensile strength of spherical agglomerates and commercial Sample as a function of compaction pressure CS-Commercial sample

Table 3: Residual solvent contents in Indomethacin agglomerates

Residual solvent	*Concentration(ppm)*	*Concentration limit (ppm) (According to ICH guide lines)*
DMF	4.2036	880
Chloroform	2.3095	60
Isopropyl acetate	31.2452	-
Dichloromethane	9.6512	600

Table 4: Solubility of Indomethacin in water

Formulations	*(% W/V)*
Commercial sample	0.00586± 1.031
IM-A	0.00795± 0.93
IM-B	0.00775± 1.53
IM-C	0.00687± 1.95

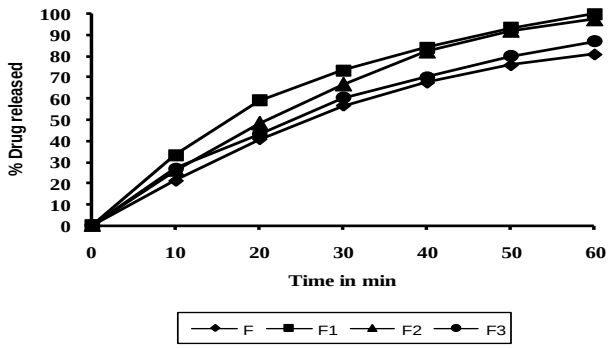

Figure 13: Dissolution profile of Indomethacin from tablets

dependent on the degree of agitation. For a constant period of agglomeration, as the speed of agitation is increased, the size of agglomerates obtained was decreased. 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.

The temperature of agglomerating solvents was found to have pronounced effect on the process of spherical agglomeration. Agglomeration and hence formation of crystal agglomerates could not occur when the process was carried out at 5±1^{o}C. It could be due to reduced solubility of drug in agglomerating solvent. This did not effect efficient wetting of drug particles and hence reduced agglomeration. When the temperature of the process was increased to 45±1^{o}C very large agglomerates were produced and the amount of the recovery of the drug was reduced. It could be due to increased solubility of the drug at higher temperature. Optimum agglomeration was achieved at 20±1^{o}C.

Uniform distribution of bridging liquid was achieved when it was added dropwise with continuous stirring of agitator; this process resulted in the formation of spherical agglomerates due to efficient agglomeration. Addition of bridging liquid in agglomerating vessel at a time produced spherical agglomerates of irregular geometry, due to localization of bridging liquid and hence its unavailability for efficient agglomeration.

The yield obtained was in the range of 96.58±1.54%, with the drug content of 99.12± 1.32%.

All the crystals have exhibited general characteristic peaks at 3400-2500 cm^{-1} (Aromatic C-H stretch carboxylic acid O-H stretch), 1715 -1695 cm^{-1} (C=O stretch), 1600 cm^{-1} (Aromatic C=C stretch), 1450 cm^{-1} (O-CH $_3$ deformation), 1230 cm^{-1} ((C-O) stretch plus O-H deformation), 925 cm^{-1} (Carboxylic O-H out of plane deformation), 900-600 cm^{-1} (C-H out of plane deformation for substituted aromatic) (Figure 5).

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. The DSC thermograms of Indomethacin and agglomerates show a sharp endothermic peak (Figure 6).

This one step melt might be due to only one crystal form (Triclinic) of the Indomethacin formed during the crystallization process. Thus indicating that Indomethacin did not undergo any crystal modification. The temperature range of the endothermic peak of all the Indomethacin crystals lies in the range of 155^{0}C to 165^{0}C. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherms for agglomerates IM-A, IM-B and IM-C were 155.09°C, 154.49°C and 154.43°C with decreased enthalpy of (95.83 J/g, 78.55J/g and 80.06J/g respectively) indicating decreased crystallinity. All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of Indomethacin was ruled out. However relative intensities of XRD peaks were modified (Figure 7).

This could be 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 may be due to differences in crystal sizes. Indicating that decrease in crystallinity.

Crystals of commercial sample are of the smallest size (5-10 µm) and they have irregular shapes. The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface covered with numerous rod shaped crystals. (Figures 8, 9, 10, 11) Agglomerates obtained were spherical in shape with circularity factor ranging between 1 and 1.001.

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 commercial 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. Commercial sample exhibited higher angle of repose than spherical agglomerates (Table 2), 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.

The contact angle of water to the compressed crystals was determined in order to quantify the wettability of the crystals. Spherical agglomerates exhibited higher wettability than commercial sample (Table 2), which is reflected from the lower values of contact angle of spherical agglomerates than commercial sample. This could be due to the lower crystallinity of agglomerated crystals in comparison to the commercial sample.

Spherical agglomerates exhibited superior compressibility characteristics compared to conventional drug crystals (Figure 12) and in the order IM-C> IM-B> IM-A. 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 86-102 gm and in the order IM-C> IM-B> IM-A.

Residual solvent concentration of DMF, chloroform, isopropyl acetate and dichloromethane are largely below the tolerated limits (Table 3).

Spherical agglomerates showed increased solubility than the commercial sample in water (Table 4).

The dissolution of Indomethacin tablets containing (Figure 13.) spherical agglomerates exhibited improved dissolution behaviour than tablets prepared by powder raw material. Complete dissolution of drug from the tablets of (F1) occurred within 45–60 min. During dissolution studies it was observed that tablets disintegrated in with in 10 min. The slower drug release from F3 may be attributed to the higher crushing strength of the agglomerates released after disintegration of the tablets. Significant increase in Indomethacin release in F2 compared with F. The drug release from the tablets was in the order F1>F2>F3>F. The reason for this faster dissolution could be linked to the better wettability of the spherical agglomerates.

CONCLUSION

Spherical agglomerates of Indomethacin were prepared by simple spherical crystallization technique. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. Type of bridging liquid, amount of bridging liquid, speed of agitation and duration of agitation affect the mechanical and micromeritic properties of spherical agglomerates. DSC and XRD study results showed that there is no change in the crystal structure of Indomethacin during the crystallization process i.e. polymorphism. The dissolution profiles of Indomethacin tablets prepared using spherical agglomerates exhibit greater dissolution behaviour than tablets prepared by powder raw material. Hence this technique can be used for formulation of tablets of Indomethacin by direct compression with directly compressible tablet excipients.

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