



Enhancing Dissolution and Physicomechanical Properties of Indomethacin via Crystal Agglomeration Technique in Presence of Different Additives

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ABSTRACT

Spherical agglomeration using emulsion solvent diffusion method was employed to enhance the dissolution and physicomechanical properties of Indomethacin. Agglomerated crystals of Indomethacin were prepared by the means of three different solvents; methanol, dichloromethane and distilled water that act as a good, bridging and poor solvents respectively. Indomethacin crystals were also agglomerated in presence of different hydrophilic polymers: polyvinyl pyrrolidone K30 (PVP), polyvinyl alcohol (PVA), polyethylene glycol 400 (PEG400), polyethylene glycol 6000 (PEG 6000) and hydroxyl propyl methylcellulose E5 (HPMC-E5) to investigate the impact of these polymers on the properties of the drug crystals. The agglomerated crystals were characterized by fourier transforms infrared spectroscopy (FTIR), Powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). The results of these studies showed a decrease in crystallinity and alteration in the crystal habit of the drug. The solubility, dissolution rate and micromeritic properties of the agglomerated crystals were compared with those of the untreated drug. All prepared crystals showed significant improvement ($p < 0.05$) in the solubility, dissolution profile and physicomechanical properties especially in presence of polymers. The best results were obtained with samples agglomerated in presence of PVA and HPMC E5 (Indo-3 and Indo-6 respectively) and thus used to prepare tablets. The tablets were evaluated for weight variation, hardness, friability, drug content uniformity, disintegration and in-vitro dissolution study.

Keywords: Indomethacin agglomerated crystal, hydrophilic polymer, emulsion solvent diffusion method, solubility, and dissolution.

INTRODUCTION

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) used as analgesic for moderate and acute pain, and in the treatment of rheumatic diseases. It is usually supplied in different dosage forms such as capsules, suspension and suppositories.¹ Indomethacin is described as (Class II) drug Biopharmaceutical Classification Systems (BCS), that characterized by its low solubility and high permeability; therefore, the absorption of the drug is limited by its dissolution rate. Indomethacin is also known to have poor flowability.^{2, 3} Various techniques have been employed to enhance the solubility and dissolution rates of class II drugs, which in turn improve their oral bioavailability. For examples, particle size reduction by micronization, nanosuspension and sonocrystallization, cyclodextrins complexation, solubilization by surfactants, solid dispersion, and chemical modifications are extensively used for this class drugs. Dissolution rate of indomethacin was reported to be enhanced by various methods such as solid dispersion in polyvinyl pyrrolidone K30 and poloxamer 188, compaction the drug with polymers and by using lquisolid compacts.^{4, 5, 6}

On the other hand, crystal agglomeration was reported to enhance both the flowability and dissolution rate of many drugs. "Crystal agglomeration or spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for

improvement of flowability and compactability of crystalline drugs".⁷ These improvement are related to crystal habit modification of the drug i.e., modification in crystal size, shape, and the form of drug during crystallization; which consequently change the micromeritic properties (bulk density, flow property, compactability) of the drug. Crystal agglomeration was also reported as a technique that improves the physicochemical properties of the drug substances i.e., solubility, dissolution rate, bioavailability and stability. As this technique forms the spherically agglomerated crystal showing significant effect on the formulation and manufacturing of pharmaceutical dosage form.⁸

Several methods have been used to prepare agglomerated crystals; these are solvent change method, ammonia diffusion method, neutralization technique and emulsion solvent diffusion method. A technique used in this study was emulsion solvent diffusion method. This process involves pouring the saturated solution of the drug in good solvent and the bridging liquid into poor solvent. The bridging liquid is added in small amounts to promote the formation of agglomerates. Liquid bridges will form between the crystals of drug as their surfaces become wetted by the addition of bridging liquids. These bridges facilitate the association of the crystals and then to form spherical agglomerates.⁹ It was reported that the affinity between the drug and a good solvent is stronger than that of the drug and poor solvent and that the residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. Gradual diffusion



of the good solvent from emulsion droplets occurs due to the interfacial tensions between good and poor solvents.¹⁰

To study the impact of additives (polymers) on properties of indomethacin agglomerated crystals PVP, PVA, PEG 400, PEG 6000 and HPMC E5 were used as aqueous solution instead of poor solvent (water).

Manufacturing of powdered drug into tablets require numbers of processing such as formulation and granulation. These processes are used to increase the bulk of powdered drug and enhance its flow properties. Accordingly the powder mixture smoothly reaches the die of the tablet machine and compressed into tablets with uniform drug content. Introduction of new technologies in tablet manufacture assisted in reducing the number of the processes during tablet production and made the manufacturing of tablet easier. Direct compression is one of these technology that facilitate the production of tablet without the need of moisture and heat that usually are used during wet granulation and it also involves small number of processing steps.¹¹ In direct compression special diluents are necessary to be used in drug formulation to increase flowability and compressibility of the bulk powder in order to maintain a fixed supply of powder mixture to the tableting machine and add sufficient mechanical strength to 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. Therefore, in this study it was proposed to agglomerate indomethacin crystals by solvent diffusion method and compress the agglomerated crystals directly into tablets using directly compressible material.¹²

MATERIALS AND METHODS

Indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetic acid) was purchased from SDI, Iraq. HPMC E5 and PVA were purchased from Sinopharm Chemical Reagent Co., Ltd. China. PEG 400, PEG 6000, methanol and dichloromethane all from BDH Ind., China, PVP, avicel, magnesium stearate and croscarmellose sodium were obtained from SDI, Iraq. All other reagents and chemicals used were of analytical grade.

Preparation of Indomethacin Recrystallized Spherical Agglomerates by Emulsion Solvent Diffusion (ESD) technique.

In this technique agglomerated crystals was prepared by using three partially miscible solvents i.e. good solvent (methanol), bridging liquid (dichloromethane) and poor solvent (distilled water). The weighed quantity of indomethacin was dissolved in a ratio of 3:5 dichloromethane:methanol. This solution was then added to the 100mL purified water, which was agitated under 1500rpm.¹³ Under constant agitation, bridging liquid and good solvent form emulsion droplets into the dispersing medium and the drug particles in the solution recrystallize then are agglomerated by the linking action

of the bridging liquid. The agglomerates were precipitated then filtered by vacuum filtration and dried at room temperature to get final dried agglomerated crystals.

Water (poor solvent) was replaced by aqueous solution of hydrophilic polymers i.e., 5% solution of (PVP, HPMC-E5, PEG 400 and PEG 6000) and 1% solution of PVA which were used to study the effect of hydrophilic polymer on the dissolution and micrometric properties of agglomerated indomethacin.

Evaluation of the prepared indomethacin agglomerates.

Fourier Transform Infrared Spectroscopy (FTIR)

Samples of pure and recrystallized indomethacin (Indo1-Indo6) (about 5 mg) were ground and mixed with dry potassium bromide and pressed in the form of a disc. The disc was analyzed by FTIR spectroscopy (at 4000 to 400cm⁻¹).¹⁴

Powder X-Ray Diffraction (PXRD)

The extent of crystallinity was determined for pure and prepared indomethacin crystals (Indo1-Indo6) using X-ray powder diffraction system equipped with Cu-K α radiation ($\lambda=1.54 \text{ \AA}$) at a voltage of (40 Kv) and a current of (30 mA). The instrument was operated in the continuous scan mode and sample was analyzed in the range (5-50 $^\circ$) with a step size of (0.05 $^\circ$) at scanning speed of (5 $^\circ$ /min) and (2 θ) axis.¹⁵

Evaluation of the flow Properties of pure and agglomerated crystals

Angle of Repose

The angle of repose of each sample was determined by fixed funnel and petri dish method, where the sample powder poured into fixed funnel and allowed to flow gently over fixed diameter Petri dish. Equation (1) was used to calculate angle of repose of each sample.^{16, 17}

$$\tan \theta = h/r \dots \dots (1)$$

Where Tan θ is the tan of the angle of repose, h is the height of the resulted con after pouring, and r is the radius of the fixed Petri dish.

Compressibility Index (Carr's index) and (Hausner Ratio)

Carr's Index and Hausner ratio values for the powder were determined by measuring the initial volume (Vb) of a known weight (W) sample placed in a graduated measuring cylinder and then subjecting the cylinder to constant tapping (100 times) and measuring the final volume (Vt). From these volumes, the bulk density (W/Vb) and the tapped density (W/Vt) were calculated and substituted in equations (2) and (3).¹⁸

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \dots (2)$$

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \dots \dots (3)$$



Determination of Saturated Solubility

Saturation solubility of indomethacin was determined by adding an excess amount (about 50 mg) of the drug to 10ml phosphate buffer (pH6.8), which was stirred at 50 rpm on hot plate magnetic stirrer ($37 \pm 0.5^\circ\text{C}$) for 48 hours. The sample was then filtered through 0.45 μm membrane filter, suitably diluted, and analyzed by UV-visible spectrophotometer (Shimadzu, Japan) at 320 nm.¹⁷

In Vitro dissolution Study

In vitro dissolution study of pure and agglomerated crystals of indomethacin were performed using U.S. pharmacopeia type II dissolution apparatus, using 900 ml phosphate buffer pH 5.0 at 37°C and at a stirring speed of 50 rpm. An accurately weighed quantity (10 mg) of each sample was added to dissolution media and 5 ml samples were withdrawn at appropriate time intervals (5, 10, 15, 20, 30, 45, 60, 75, 90, and 120 minutes). To keep sink condition, the volume of the dissolution medium was kept constant throughout the study by replacing the withdrawal samples with an equivalent volume of fresh dissolution medium. The withdrawal samples were filtered through a 0.45 μm filter paper, suitably diluted and analyzed at 320 nm by UV-visible spectrophotometer (Shimadzu, Japan).¹³

Agglomerated samples that showed a remarkable improvement in the solubility and/ or dissolution rate (Ind-3 and Indo-6) were selected to prepare tablets and the release of drug from the prepared tablets was tested.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) is one of the thermal analysis techniques usually used for

characterization the thermal behavior of drug substance in pure state and in pharmaceutical mixture. Here, the melting point of indomethacin and the impact of different additives used during crystal agglomeration on the melting point of the drug were investigated.

The DSC analysis was carried on using DSC 60 (Shimadzu, Japan). The instrument was calibrated for temperature using lead and accurately weight (5mg) of pure drug (Indo-pure) and agglomerate samples (Indo-3 and Indo-6) were placed in crimped aluminum pans and scanned from 20 to 200°C at $10^\circ\text{C}/\text{min}$ under a nitrogen atmosphere.¹⁹

Scanning Electron Microscopy (SEM)

SEM was employed to gain further information about size, shape and surface morphology of pure and recrystallized samples. SEM provides a high resolution images that show details of a sample surface since a high energy beam of electrons typically from 0.5 kV to 40 kV is usually used to scan the surface of the sample.^{20,21}

Indomethacin tablets manufacturing

Tablets of pure and agglomerated indomethacin crystals (Indo-3 and Indo-6) were prepared by direct compression method. Accurately weighed amounts of drug, diluent and superdisintegrant shown in Table 1 are passed through sieve (0.36mm) and properly mixed together for 15 min then magnesium stearate were added, and blended with initial mixture. The powder blend was compressed into tablets using single punch tablet machine. The prepared tablets were evaluated for various parameters.⁶

Table 1: Composition of indomethacin tablets formulas

Ingredients (mg)	Active pharmaceutical ingredient (Indomethacin) mg	Diluent (Avicel PH 102) mg	Superdisintegrant (croscarmellose Na) mg	Lubricant (Mg stearate) mg	Total mg
Indo_tab	25	175	2	2	204
Indo3_tab	25	175	2	2	204
Indo6_tab	25	175	2	2	204

Evaluation of the Prepared Tablets

Weight Variation

The weight variation test was analyzed by selecting twenty tablets randomly and average weights were determined. Then individual tablet weighed and compared with the average. The requirement met the USP; if not more than two tablets differ from the average weight $\pm 5\%$ and no tablet differs in weight by double that percentage, the tablets will be accepted.^{18,22}

$$\text{Average weight of tablets} = \frac{\text{total weight of tablets}}{\text{number of tablets}} \dots \dots (4)$$

Tablet Hardness

The tablet requires a certain amount of strength, or hardness, to with stand mechanical shocks of handling during its manufacture, packaging and transport.³ The hardness of the tablets were determined using electrical Hardness tester. It is expressed in Kg/cm^2 . Five tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.²³

Tablet Friability

Friability test evaluate the tablet strength to withstand coating, packaging and shipping and other manufacturing



processes. According to BP specifications, the total weight loss should not exceed one percent and no tablet shows any type of breakage or crack. Ten tablets from each formula were selected randomly; de dusted and weighed (W_1) using analytical balance, then placed in the tumbling apparatus (Guoming Friabilator tester) that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed (W_2) and the percentage loss was determined.^{14,24}

$$\text{Percentage friability} = \frac{W_1 - W_2}{W_1} \times 100 \dots (5)$$

Tablet thickness

Tablet thickness was measured using digital micrometer caliper. Five tablets from each batch were used, and an average value was calculated. The limit specified was average thickness \pm standard deviation (SD)²⁵

Content Uniformity

Content uniformity done by weighing and powdering 20 tablets. Weigh accurately a quantity of the powder equivalent to 25 mg of indomethacin and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 minutes thereafter; the volume was made up to 100 ml with buffer. The resulted solution was filtered, and 1 ml of the filtrate was diluted and analyzed at 320 nm using UV-Visible spectrophotometer. The drug content of the each sample was estimated from their previously prepared standard curve.^{26,27}

In vitro Disintegration study

The disintegration time of prepared tablets was determined using 900 ml purified water at 37°C as disintegration medium. The disintegration time was measured using disintegration test apparatus (Copley, UK).¹⁹

In vitro Dissolution Study

The in vitro dissolution study was carried out by using USP type II (paddle type) dissolution test apparatus (Cosmo Lab. Equipment, India). Using 900 ml dissolution medium (phosphate buffer pH 6.8) at 37°C and rotation speed of 50 rpm. One tablet of each prepared formula was placed in dissolution vessel for 2 hours and at appropriate time intervals 5 ml samples were withdrawn and replenished with the same volume of fresh medium to keep the sink condition constant, samples then filtered, diluted and analyzed spectrophotometrically at 320 nm.²⁸

Statistical Analysis

The results of experiments were given as a mean of triplicate \pm standard deviation (SD) and were analyzed according to the one way analysis of variance (ANOVA single factor) at which the result consider significantly different when ($P < 0.05$) and non-significant when ($P > 0.05$).

RESULTS AND DISCUSSION

Evaluation properties of pure and agglomerated indomethacin crystals

FTIR spectra of indomethacin (Figure 1) showed characteristic absorption bands at 725 cm^{-1} , assigned as C-H out of plan deformation, 925 cm^{-1} represent carboxylic OH out of plan deformation, 1228 cm^{-1} assigned to C-O stretch plus OH deformation, 1450 cm^{-1} for O-CH₃ deformation, 1712 cm^{-1} assigned to C=O stretch and 1591 cm^{-1} assigned to aromatic C=C stretch.²⁹ Indomethacin is known to have two different polymorphs γ and α and presence of benzoyl C=O in FTIR spectrum of pure drug around 1698 cm^{-1} give an indication that the untreated drug is in γ form.

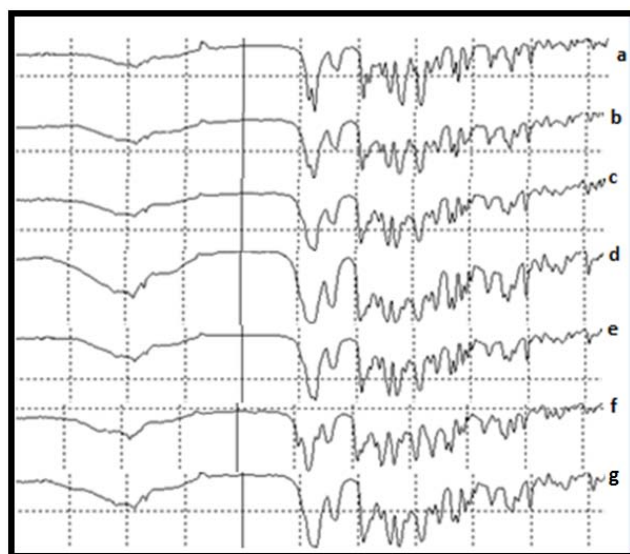


Figure 1: Fourier transform infrared spectroscopy (FTIR) of (a) pure indomethacin (b) Indo-1 (c) Indo-2 (d) Indo-3 (e) Indo-4 (f) Indo-5 (g) Indo-6

FTIR spectrum of Indo-1 showed all the characteristic peak of pure drug whereas the spectra of agglomerated crystals (Indo-2, Indo-3, Indo-5 and Indo-6), showed a slight shift in peaks position. On the other hand, in spectrum of Indo-4, which was prepared in presence of PEG400, showed a clear shift in absorption peak position of C=O stretching vibration from 1712 to 1734 cm^{-1} suggested to be resultant of hydrogen bond interaction between the drug and PEG400. Specific change concerning benzoyl C=O stretching vibration position was not very clear in IR spectra of all agglomerated samples. Therefore, a final conclusion about the conversion of γ form to α during crystal agglomeration cannot be obtained using FTIR spectroscopy.

X-ray diffractogram of indomethacin (result not seen here) showed several intense and moderate diffraction peaks indicating the crystallinity of the drug. However, in the diffractograms of agglomerated samples (Indo-2, Indo-3, Indo-5 and Indo-6), which are prepared in presence of PVP, PVA, PEG6000 and HPMC E5 respectively, the relative intensity of the peaks are

reduced markedly, indicating a reduction in the crystallinity of the drug in these samples. For Indo-4 which was prepared in presence of PEG 400, the reduction in the intensities of diffraction peaks are less than that in previous samples, therefore less reduction in the crystallinity obtained during the preparation of this agglomerated sample. A diffuse peaks and decrease in Crystallinity (results not shown here) observed in the diffractograms of agglomerated crystals prepared with polymers addition, may indicated interaction of the drug with the polymers.¹³ It was reported that recrystallised drug sample that shows different diffraction intensities of peaks compared to those of pure drug sample indicates habit modification of the drug, whereas presence of new peaks in the diffractogram refers to different polymorph formation.³⁰ Therefore, the results of x-ray diffractogram

study here give indication about habit modification of indomethacin during crystal agglomeration.

The micromeritic properties shown in Table 2 indicate that agglomerated crystals have better flow properties than pure drug. This improvement in flow properties suggested related to characteristic spherical shape that they have which also offer better packability and compressibility to agglomerated samples. Therefore these samples can be directly compressed into tablets.³¹ The improvement in the flow properties may also be attributed to their markedly different crystal habits, leading to different contact points, frictional and cohesive forces between the crystals.

Table 2: Micromeritic properties of pure and agglomerated crystals of indomethacin

Sample number	Angle of repose (degree)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr 's index	Hausner ratio	Type of flow
Indo-pure	44.78± 0.07	0.401 ± 0.05	0.601 ± 0.12	33.33333	1.5	poor
Indo-1	32.14± 0.02	0.218 ± 0.03	0.281 ± 0.05	23.07667	1.3	good
Indo-2	27.91± 0.05	0.301 ± 0.1	0.366 ± 0.03	17.89819	1.218	good
Indo-3	28.41± 0.07	0.256 ± 0.08	0.297 ± 0.08	13.94148	1.162	good
Indo-4	29.46± 0.05	0.241 ± 0.09	0.282 ± 0.1	14.74851	1.173	good
Indo-5	28.33± 0.08	0.281 ± 0.12	0.342 ± 0.05	18.03279	1.22	good
Indo-6	29.12± 0.04	0.242 ± 0.6	0.286 ± 0.07	15.39763	1.182	good

The result of saturated solubility of pure indomethacin in phosphate buffer (pH 6.8) showed that indomethacin is very slightly soluble drug, while those of agglomerated crystals showed significant increase (P<0.05) in the solubility (Figure 2).

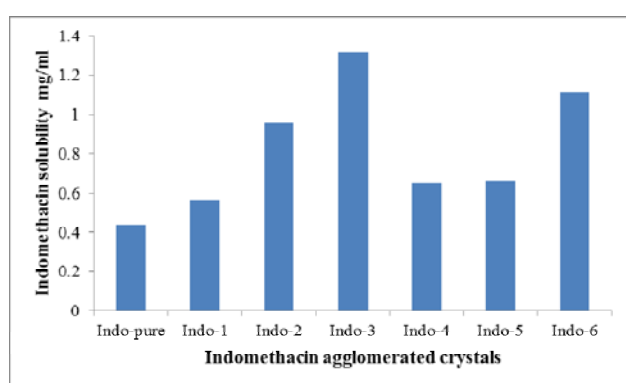


Figure 2: Saturated solubility of pure and agglomerated crystals of indomethacin in phosphate buffer (pH 6.8)

The improvement in the solubility may be due to change crystal form of the drug during spherical agglomeration by the addition of polymers. The recrystallization process may changes the crystal habit, structure, and surface properties of the drug. However, this requires further investigation using scanning electron microscope. Solvents that might remain within agglomerated crystals

and clathrates formation could contribute in increasing the solubility of indomethacin. It was reported that clathrates formation will change the surface properties and the reactivity of the drug particles as well as their internal energy.⁹ The results in this study also showed that type of hydrophilic polymers added during crystal agglomeration also has impact on the solubility of the drug.³² Indo-3 which was agglomerated with PVA showed the highest solubility (1.321 mg/ml), which is about 3 folds higher than of untreated indomethacin.

The dissolution study results of pure and agglomerated crystals of indomethacin (Figure 3) shows that crystal agglomerations significantly enhanced (p < 0.05) the dissolution of the drug. Amongst hydrophilic polymers used during crystal agglomeration, PVA and HPMC E5 showed the best results both on the solubility and dissolution rate of the drug. The increase in the dissolution rate of drug from agglomerates prepared with the addition of these hydrophilic polymers could be attributed to adsorption of specific polymer onto the surface of drug thus improving the wettability of the prepared samples. This improvement in wettability alongside a decrease in crystallinity of drug (as the results of X-ray diffraction study indicated) could be the reasons for enhancing drug dissolution from these samples. Hydrogen bond interaction between drug and added

polymer could be another factor for enhancing dissolution of drug from agglomerated crystals. *Tapas A.R. et al*³³ found that spherical agglomeration of felodipine in presence of PVP K-30, PEG 6000 and PVA enhanced the solubility, dissolution rate and micromeritics properties of the drug, which supports the results obtained in our study.

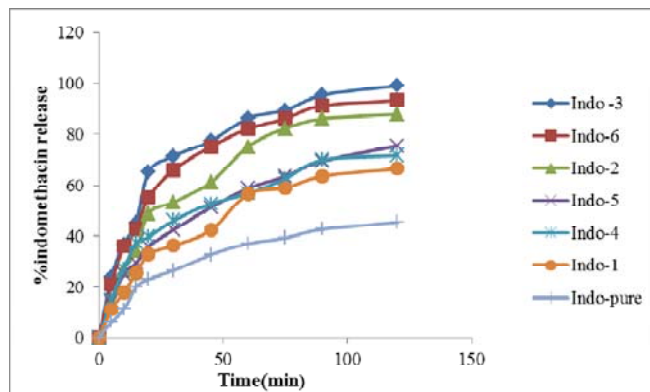


Figure 3: Percent drug release from pure and agglomerated crystals of indomethacin in phosphate buffer (pH 6.8). Values are mean \pm SD (n=3)

The results of DSC analysis study are shown in (Figure 4). The thermogram of pure drug (Figure 4-a) showed melting endothermic event at 158°C suggested to be related to the melting of γ form. Whereas, agglomerated crystals of indomethacin (Indo-3 and Indo-6) showed exothermic recrystallization event followed by endothermic event at lower temperature than that seen with pure drug (Figure 4 b and c).

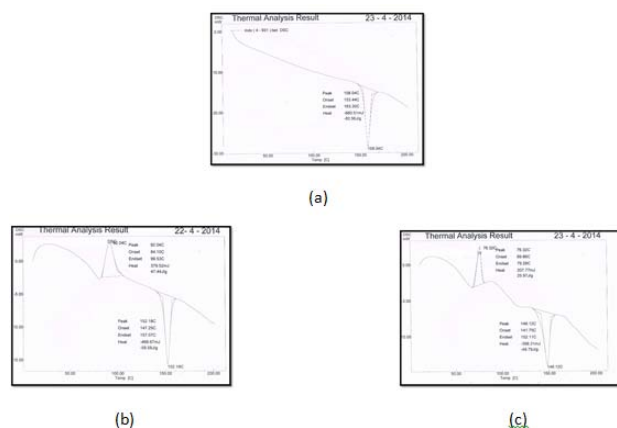


Figure 4: Differential scanning calorimetry: of (a) Indo-pure (b) Indo-3 and (c) Indo-6

It was reported that indomethacin in γ form melts at a range (158-162°C) whereas, in α form melts at lower range (150.8-155°C). Thus the results of DSC analysis of agglomerate samples give a clear indication about converting of drug from γ to α form. However, this conversion in drug form could either occur during crystal agglomeration process or DSC scan. Fast scanning thermal analysis (i.e. 100°C/ min or 200°C/ min) could be used to prevent changes in the polymorph that may occur during scanning and thus it will be possible to determine the form of drug in agglomerated sample precisely.

SEM photographs of pure and agglomerated indomethacin are shown in (Figure 5). These photos show that raw crystals were irregular and stone shaped. While prepared indomethacin agglomerated crystals are spherical in shape and composed of minute needle-like crystals indicating reduction in the crystal size and alteration in habit of drug crystal.³⁴ From the results of SEM and those obtained by FTIR spectroscopy it can be concluded that drug – polymer interaction through hydrogen bond may retard crystal formation or growth and consequently smaller size crystals with altered in the habit was obtained.

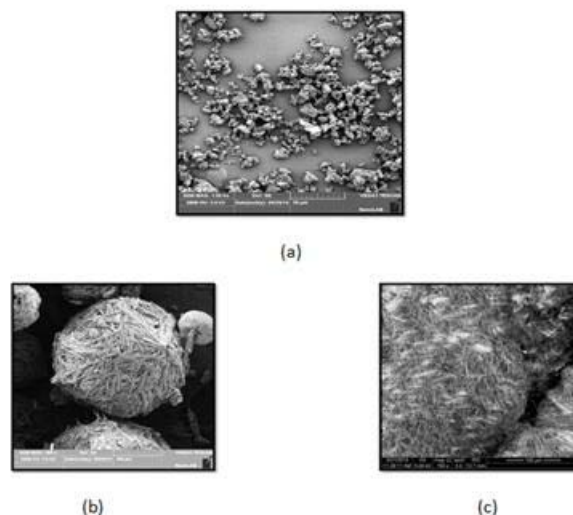


Figure 5: Scanning electron micrographs of (a) Indo-pure (b) Indo-3 and (c) Indo-6 under 1KX magnification

Evaluation of the Prepared Tablets

Post compression parameters of prepared tablets like the weight of tablets are found to be from (201 to 204mg) indicating the uniformity of dose in all formulas. The hardness of the tablets was in range of 6.5 kg/cm² to 7 kg/cm² which refer to the adequate strength property of the prepared tablets. All the prepared tablets also had acceptable friability; the weight loss was less than 1%. Thickness of prepared indomethacin tablets was in range (4.12 to 4.14 mm); this minor difference with constant tablet weight was due to good flow properties of the formula, uniform die fill, constant pressure used and balanced punch movement. The drug content percent was in range (98.32-100.2%) indomethacin in prepared tablets these result indicated that the prepared dosage form had uniform distribution and proper dose of the active ingredient.¹⁸

In vitro disintegration time for all prepared indomethacin tablets was found to be in the range (70-90 second). Disintegration of indomethacin agglomerated tablets into small particles within this short time will rapidly increase the surface area exposed to dissolution medium and accelerate the release of drug from tablets.

Figure (6) show the dissolution profiles of indomethacin tablets in phosphate buffer (pH 6.8). The release of

indomethacin from tablets prepared from agglomerated crystals (Indo3-tab and Indo6-tab) was significantly higher ($p < 0.05$) than those prepared from untreated indomethacin (Indo-tab). After 15 min 65.6% and 54.7% of indomethacin was released from Indo3-tablet and Indo6-tablet respectively, while only 25.4% was released from Indo-tablet. These findings might be attributed to increase in porosity and wettability of indomethacin agglomerates that facilitate the release of the drug from tablets.

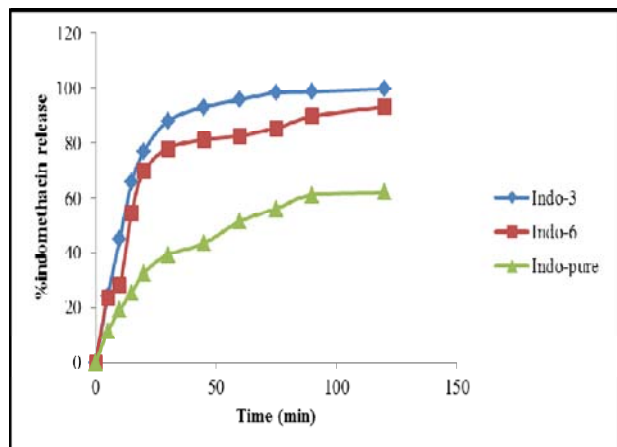


Figure 6: Percent of Indomethacin release from different formulas in phosphate buffer (pH 6.8). Values are mean \pm SD, n=3

CONCLUSION

All agglomerated crystals of indomethacin show a reduction in crystallinity and improvement in solubility, dissolution and micromeritic properties. Crystals that prepared in presence of PVA and HPMC E5 (Indo-3 and Indo-6) respectively give the best results than samples prepared using other additives (e.g. PVP, PEG400, PEG6000) The selected two samples as best formulas were prepared as tablets by direct compression method and show a significant improvement ($p < 0.05$) in dissolution in comparison with tablets prepared with pure drug.

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