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Improving Dissolution of Indomethacin Using Jet Milling and Solid Dispersion Techniques

Zaky A.A.[1]*, El-bakry A.M.[2], Abu-Elyazid S.K.[1], Ramadan A.A.[2], Samy.A.M.[1]

[1]Department of Pharmaceutics and industrial Pharmacy, Faculty of pharmacy, Al-Azhar University, Nasr City, Cairo. Egypt.
[2]Department of Pharmaceutics and industrial Pharmacy, Faculty of pharmacy, Al-Azhar University, Nasr City, Cairo. Egypt (Girls).

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***Corresponding author:**

E-mail: azaky69@yahoo.com
Phone: 00202 0141568824

ABSTRACT

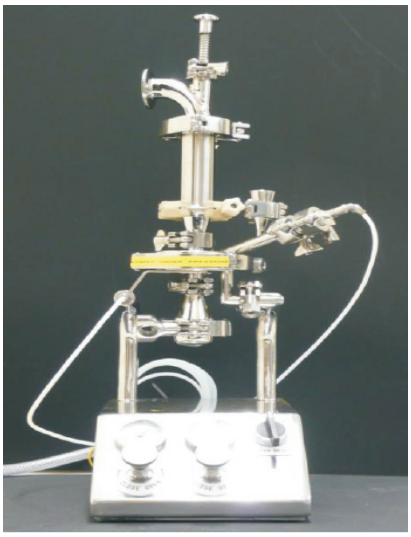
Several techniques were compared for improving the dissolution of indomethacin (IND), a poorly soluble non-steroidal anti-inflammatory drug. The aim of this study was to prepare, characterize and differentiate the different techniques used as physical mixture (PM), jet milling (JM) and solid dispersion (SD). The PM, JM, and SD techniques were prepared at 1:4 drug to polymer ratio with both polyethylene glycol (PEG) 6000 and 10000. Scanning electron microscope (SEM), X-ray powder diffractometry (X-ray) and differential scanning calorimetry (DSC) were used to examine the physical state of the drug. Furthermore, the solubility and the dissolution rate of the drug in its different systems were explored. The data from the X-ray showed that the crystallinity of the drug was still detectable (slightly disappeared) in its solid state in the physical mixture, jet milling of IND-PEG, whereas it disappeared in SD of IND-PEG. DSC thermograms showed the significant change in melting peak of the IND when prepared as SD and milling particles suggesting the change in crystallinity of IND. However, the specific surface area of the IND-PEG particles increased and the crystallinity decreased (i.e., the amorphization level increased) as the JM progressed. The drug solubility enhancement increased with PM, JM and SD of IND-PEG 6000 (PEG-6) and 10000 (PEG-10). An increased dissolution rate of IND at pH 7.4 was observed when the drug was dispersed in these carriers in form of SD, JM and PM. IND released faster from the SD and JM than from the pure crystalline drug and PM. It was concluded that, the dissolution rate of IND from jet milling increased with increasing the specific surface area and decreasing the crystallinity that leads to increase the wettability of IND-PEG particles.

INTRODUCTION

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more therapy that is reliable. Indomethacin is a member of the non-steroidal anti-inflammatory drugs (NSAIDs). It is used to reduce pain/swelling involved in osteoarthritis, rheumatoid arthritis, bursitis, tendinitis, gout, ankylosing spondylitis, and headaches [1]. The drug described as poorly soluble and highly permeable (Class II) drug [2]. Because water-insoluble drugs often show low absorption and weak bioavailability, improvement in dissolution rate and/or solubility are important for development of drug preparations [3]. The successful formulation of poorly-water soluble drugs is one of the major problems in pharmaceutical manufacturing. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [4, 5]. The increase in bioavailability after micronization of drugs, by jet or ball milling, has been well documented e.g., danazol [6], progesterone [7], digoxin [8] mefenamic acid [9] and fenofibrate [10]. Also, the jet milling can be used for enhancement of absorbation of water soluble drugs with special application e.g., Insulin [11], calcitonin [12] Horseradish peroxidase [13]. Micronization by jet milling is the most common method to produce particles in the lower micrometer range. In brief, the raw material with a maximum size of about 1 to 2 mm is introduced into the milling chamber via a gas stream. Within the milling chamber a circular gas stream accelerates the particles which are micronized by collision with each other or with the wall of the chamber. The ground particles are removed from the milling chamber by the gas stream. Solid dispersion technique select as it was utilized to increase the solubility of indomethacin. SD is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-

fusion methods [14, 15]. It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs [16-19]. Therefore, drug dissolution was improved markedly [20–22]. PEG is among the several carriers which have been employed in preparing solid dispersions [23]. PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydropholicity [21, 23-27].

The current paper compares the production of indomethacin preparations by several techniques including jet milling, solid dispersion and physical mixture with PEG 6000 and 10000. These preparations were evaluated with respect to their X-ray diffraction (X-ray), Differential Scanning Calorimetry (DSC), Scanning electron microscopy (SEM), solubility and dissolution behavior. Moreover, solubility and dissolution rate studies were performed to qualify the jet milling compared with the solid dispersion, physical mixture and drug alone.



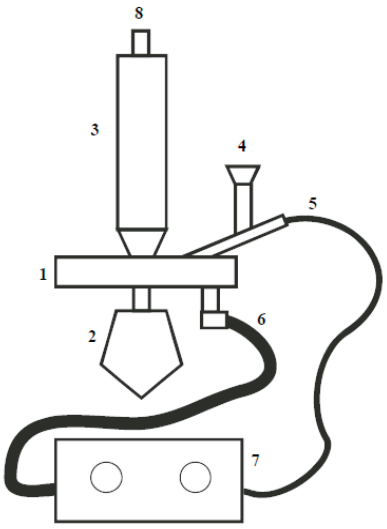


Fig. 1: schematic diagram of the used jet mill: (1) milling chamber, (2) product collection container with cyclone separator, (3) exhaust gas filtration unit, (4) product feed by venturi injector, (5) gas feed for venturi injector, (6) gas feed for milling chamber, (7) control device for applied pressure on milling chamber and venturi

MATERIALS AND METHODS

Indomethacin (IND) was kindly supplied by Egyptian International Pharmaceutical Co.; (EIPICO) 10th of Ramadan city, Egypt. PEG 6000 and 10000 was obtained from Sigma-Aldrich Chemical Company (Steinheim, Germany). Phosphate buffer saline (PBS) was obtained from Gibco (Gibco, Karlsruhe, Germany). All other materials and solvent were of analytical grade of purity.

Incorporation of indmethacin in polymer using different techniques

Preparation of Solid Dispersion formulation

Solid Dispersion at 1:4 drug to polymer ratio was prepared by melting method. IND was added to the molten base comprising PEG-6 or PEG-10. The blend was heated at 10 ºC above the melting point of each carrier for 5 minutes with continuous stirring. The systems were placed in a freezer at -20 ºC for 24 h. The mass was crushed, ground gently with a mortar and pestle and passed through 250 µm sieves. The samples were kept in a desiccator until the next experiments

Preparation of micronized drug-polymer mixtures by jet milling

Micronized indomethacin-PEGs was prepared by JM (Fig. 1) the drug by itself or as a physical mixture with various polymers (PEG-6 or PEG-10) in an Alpine 50 AS jet mill (Hosokawa Alpine AG, Germany) operating at 10 bar air pressure and a feed rate of 0.5–1.0 g/min. The milled powder was then manually filled into (Coni-Snap Supro) a hard gelatin capsules, after blending with PEG to obtain a concentration of the active substance of 1:4 drug to polymer ratio. Homogeneity of the IND-PEGs mixtures micronizing was confirmed by quantitative assay spectrophotometrically at 320 nm for determination of the drug content after accurate weighting of an aliquot of powder (n = 3). The samples were stored in a desiccator until further use.

Preparation of physical mixture.

Physical mixture of IND with PEG-6 or PEG-10 at 1:4 drug to polymer ratio were prepared by blending them by triturating for 10 min followed by sieving (250 µm). The samples were stored in a desiccator until next use.

Particle size measurement

Particle size was determined by laser light diffraction. The equipment consisted of a Malvern Mastersizer 2000 (Malvern Instruments, Germany) including a Scirocco 2000 module for dry measurement purposes operating at 3.0 bar air pressure. For dispersion, it had been established that a sufficient dispersion of particles but no milling occurs at this level of air pressure with evaluation of data by Malvern software version 4.0 using the Fraunhofer approximation as the evaluation algorithm. Particle size of mean diameter between d (0.10), d (0.50) and d (0.90), are reported based on volume [28].

Determination of drug content

The drug content was determined by certain weight of PM, JM and SD dissolving the samples formulation in dimethylformamide (DMF), extracting the IND and diluted with phosphate buffer saline (PBS) pH 7.4 and analyzed spectrophotometrically at 320 nm. To this end weighed amounts

of PM, JM and SD (approx 50 mg±0.5 mg, which equivalent to 10 mg IND) were suspended in DMF and intermittently vortexed until completely dissolved. The IND content was calculated from standard curves obtained from known concentrations of IND in DMF with diluted PBS buffer. Measurements were corrected for the reading obtained for pure polymer without drug. The experiments were conducted in triplicates (n=3).

Solubility determination

An excess amount of the samples was placed in contact with PBS pH 7.4. The samples were shaken for 48 h at 37 °C in a horizontal shaker. The supernatant was filtered through a Millipore filter (pore size 0.22 µm). 0.5 ml of the filtrate was immediately diluted and assayed spectrophotometrically at 320 nm. Results from solubility determinations (n = 3) are presented as mean values with standard deviations.

Scanning electron microscope (SEM)

The samples particle morphologies were investigated by SEM. The particles were mounted on aluminum stubs using conductive carbon tape (LeitTabs; Plannet GmbH, Germany) and coated with gold by sputtering three times for 20 seconds (SEM Autocoating unit E2500; Polaron equipment LTD, UK).

X-ray powder diffraction

Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 and 40° (2θ) employing a Philips FW 1700 X-ray diffractometer (Philips, Netherlands). The voltage and current used were 40 kV and 30 mA, respectively. The chart speed was 10 mm/sec.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to determine the crystal structure of IND and polymers. Samples of 3.5 mg±0.05 mg of the IND, PEGs and IND-PEGs formulations were sealed into AutoDSC aluminum sample pans (TA Instruments, Alzenau, Germany) and DSC thermograms were recorded using a 2920 differential scanning calorimeter (TA Instruments, Alzenau, Germany) with an empty pan as reference. Scans were recorded between 20 ^{0}C and 200 ^{0}C with a rate of 10 K/min. The obtained data were evaluated with the DSC-software Universal Analysis 2000 for Windows 98/NT, version 2.5 H (TA instruments, Alzenau, Germany).

Release rate studies

Release from the capsules of different formulations was determined by USP type II (paddle) method using Electrolab dissolution tester (TDT-06N, India) was adopted. Amount of samples equivalent to 50 mg of drug were dispersed into the dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2) or phosphate buffer (pH 7.4). The dissolution media were maintained at 37°C ± 0.5°C and stirred at 75 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through microfilter (0.22 µm), concentration of IND was determined spectrophotometrically (Jenway 6305 spectrophotometer, UK) at 320 nm. All experiments were carried out in triplicate. Results from dissolution studies (n = 3) are presented as mean values with standard deviations.

RESULTS AND DISCUSSION

Drug content

The drug content of the prepared formulations with different techniques (PM, JM and SD) was found to be in the range of 97.9-100.5 % indicating the applications of the present method for the preparation of different formulations with high content uniformity (Table 1).

Solubility studies

The solubility of pure IND in PBS buffer was found to be 0.232±0.05 mg/ml at 37°C. A linear relationship with respect to increase in solubility of IND with PEG-6 and PEG-10 of three different techniques were determined for PM, JM and SD (0.368, 0.820 and 0.965 mg/ml) and (0.388, 0.872 and 1.049 mg/ml) respectively (table 1). The increase in solubility of micronized drug in the presence of PEG was slightly lower than SD, which could be attributed to increase the wettability of IND due to a decrease in the particle size and interfacial tension between the drug and aqueous solution. It is hypothesis that the wettability of the small lipophilic characters of indomethacin particles was further improved by the presence of the hydrophilic polymer (PEG).

Particle size distribution of IND-PEGs formulations

Particle size distributions of IND-PEGs were prepared by PM, JM and SD is shown in table 1. IND-PEG-6 particles obtained by

Table No.1: Particle size distribution, solubility and drug content of IND-PEG-6 and IND-PEG-10 particles prepared by physical mixture, jet milling and solid dispersion

	System type	Drug content [%]	Solubility [mg/ml]	Particle size distribution [µm]			
				d[0.50]	d[0.90]	Mean D [µm]	span
PEG 6000	Physical mixture	99.8 ± 1.7	0.368 ± 0.05	65 ± 2.8	215 ± 3.8	125 ± 2.8	2.8 ± 0.06
	Jet milling	97.9 ± 3.8	0.820 ± 0.07	4.5 ± 1.7	10.5 ± 1.6	6.2 ± 1.5	1.8 ± 0.05
	SD technique	99.5 ± 1.6	0.965 ± 0.08	85 ± 1.6	230 ± 2.7	139 ± 4.8	2.4 ± 0.07
PEG 10000	Physical mixture	100.5 ± 3.2	0.388 ± 0.06	74 ± 2.9	225 ± 4.2	135 ± 3.9	3.1 ± 0.02
	Jet milling	98.8 ± 4.3	0.872 ± 0.05	3.5 ± 1.2	9.70 ± 0.2	5.3 ± 1.3	1.9 ± 0.04
	SD technique	99.9 ± 3.2	1.049 ± 0.12	92 ± 1.6	248 ± 1.4	158 ± 3.7	3.3 ± 0.03

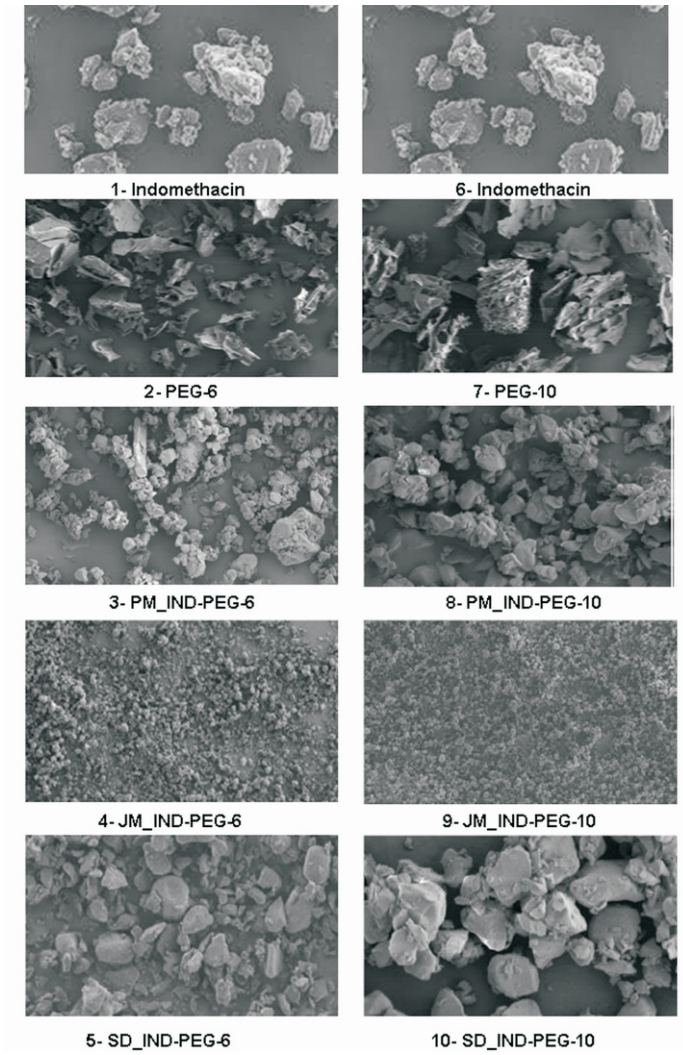


Fig. 2: SEM pictures of IND-PEGs systems: **1.** IND, **2.** PEG-6, **3.** PM_IND-PEG-6, **4.** JM_IND-PEG-6, **5.** SD_IND-PEG-6 and **6.** IND, **7.** PEG-10, **8.** PM_IND-PEG-10, **9.** JM_IND-PEG-10 and **10**. SD_IND-PEG-10 at 1:4 ratio was showed (scale bar = 100).

PM, JM and SD had mean diameters of 125.0, 6.2 and 139.0 µm and span 2.8, 1.8 and 2.4 respectively. On the other hand, the mean particle size diameter of IND-PEG-10 particles prepared by PM, JM and SD were 135.0, 5.3 and 158.0 µm, also the span values was 3.1, 1.9 and 3.3 respectively. The span value gives an indication about the particle size distribution, when the value is not more than two; this is an indication for good particle size distribution (narrow distribution). From the results, the particle size and span values of the particles prepared by JM were smaller than the PM and SD particles.

Scanning electron microscope

Alterations in morphology during the manufacture process were assessed by SEM. Figure 2 displayed SEM photographs for IND, PEG-6, PEG-10 and their corresponding PM, JM and SD. The drug crystals seemed to be irregular in shape and size. IND crystals were much smaller than PEGs particles. The physical mixture of the drug and carrier showed the presence of drug in the crystalline form. However, the micronization of IND-PEGs by JM reduced the particle size with spherical shape of formulation. Moreover, the presence of PEG in high amount ratio (1:4) was decreased the crystallinity of drug via surrounding by PEG, this could be attributed to dispersion of the drug in the molten mass of the polymer. In case of SD, it was difficult to distinguish the presence of IND crystals. In addition, the produced particles of IND-PEG-6 and IND-PEG-10 had large variation in size and shape.

X-ray powder diffraction

Figure 3, showed the powder X-ray diffraction patterns of the IND-PEG system. The diffraction spectrum of pure IND showed that the drug is highly crystalline powder and possesses sharp peaks at 2θ equal to 15.4°, 20.6°, 22.5°, 25.2° and 30.5°. This corresponds to the γ-crystalline form polymorph of indomethacin [29]. Characteristic peaks of PEG-6 appeared at 2θ equal to 14.36°, 21.64°, 24.72° and 28.87°. All the principles peaks from PEG-6 was present in their PM and JM (modified PM) but with lower intensity. In the case of the PM, diffractograms were simply the sum of those of pure components and no interaction could be detected between them. Whereas, in case of JM of IND-PEG formulations there was a decrease in the intensity of IND but the major peaks remained at the same positions. The amorphization of the IND particles progressed as they were micronized and the crystallinity decreased slightly after the grinding limit was attained. A remarkable decrease of the diffraction peaks was observed at the diffraction angles corresponding to both the diffraction planes formed by symmetric molecules.

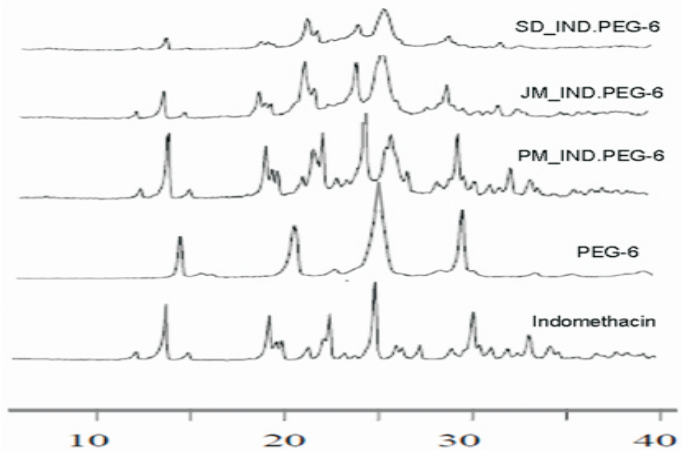


Fig. 3: X-ray diffractograms of indomethacin; PEG-6 and their different system prepared by physical mixing, jet milling and solid dispersion.

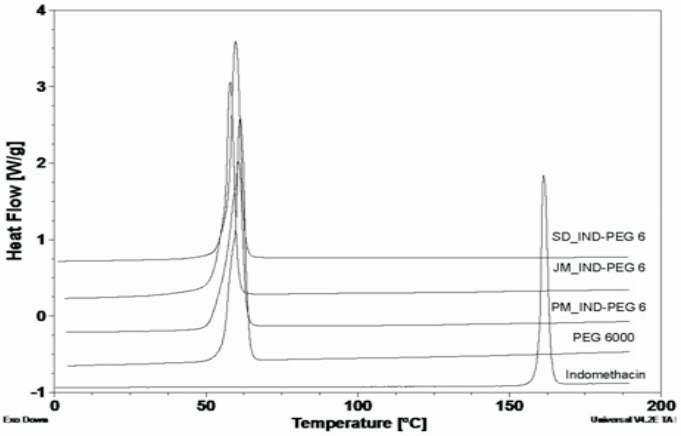


Fig. 4: DSC thermograms of indomethacin; PEG-6 and their different system prepared by physical mixture, jet milling and solid dispersion.

The intensity of the diffractogram IND prepared by SD system was completely disappeared. It could be attributed to the destruction of its crystal lattice, because the melting of drug into carrier. The peaks associated to the carriers not shifted with respect to the physical mixture. This suggested the formation of an insertion-type solid where drug molecules found place inside the structure of the carrier without or with a limited deformation of the original crystal lattice [30]. No new peaks could be observed suggesting the absence of the chemical interaction between the drug and the carriers [27]. PEG-10 formulation showed the same x-ray results of PEG-6 (data not shown).

Differential scanning calorimetry

Figure 4, depicted thermograms of IND, PEG-6 and their PM, JM and SD. Thermograms of IND, PEG-10 prepared by different techniques PM, JM and SD showed in Fig. 5. IND displayed endothermic peak at 161.25 °C corresponding to its melting point. PEG-6 and PEG-10 showed endothermic peak at 61.21 °C and 63.44 °C due to its melting point. Thermal traces for PM, JM or SD showed a weak broad peak shifted to a lower melting point with both polymers (PEG-6 and PEG-10) which exhibited a single endothermic peak corresponding to the fusion of the carriers. No peak appeared representing the melting of the drug. The results suggested that IND dissolved completely in the polymer. Accordingly, the grinding mechanism of IND-PEG particles prepared by jet milling could be summarized as follows; the size reduction and amorphization of IND particles progressed simultaneously with grinding.

Moreover, the amorphization gradually progressed and hydrogen bonds between the carboxyl groups were broken after the micronization was attained. Thermal profiles of PM, JM and SD were confirmed with the previous data of X-ray patterns (Fig. 3). The results of DSC and X-ray indicated a decrease in crystallinity of IND in presence of higher amount of PEGs. All PM, JM and SD (Fig. 4 & 5) exhibited endothermic peaks due to the fusion of PEG-6 and PEG-10 around 61.2°C and 63.1°C respectively. This revealed the existence of both polymers in the crystalline state that was consistent with the appearance of diffraction peaks in the corresponding X-ray pattern.

Dissolution studies

The in vitro release study of IND and IND-PEGs prepared by PM, JM and SD were carried out in 0.1 N HCl (Fig. 6a & 7a) and phosphate buffer pH 7.4 (Figure 6b & 7b). Generally, the release of IND in phosphate buffer pH 7.4 was higher than that in 0.1 N HCl. The results that obtained based on the limited solubility of IND in acidic medium [31]. Blending of IND with PEG-6 or PEG-10 in form of PM, JM and SD could enhance the release of IND. The increase in the dissolution rate of PM compared with pure drug was observed for both polymers and could be attributed to the improvement of wettability of IND particles due to the presence of highly hydrophilic polymers [27]. The enhancement of dissolution rate of different IND formulations differ according to the technique used, IND-PEGs prepared by JM showed higher dissolution rate than those prepared by PM and slightly lower rate than SD formulation. Dissolution rate enhancements of drug prepared by jet milling (modified physical mixture) with surfactants or hydrophilic polymers (PEG) are often caused by generation of amorphous drug [32, 33]. Indeed, the mechanical stress associated with milling may cause partial amorphous states, this leads to fast release of IND prepared by JM. However, the dissolution rate was significantly improved by the grinding jet milling. The initial dissolution rate before the grinding limit

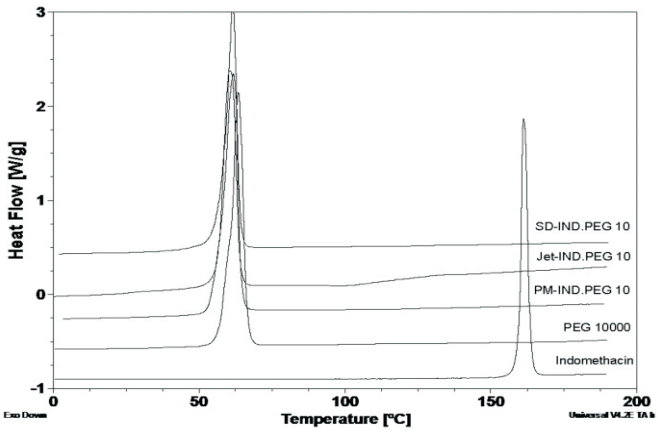


Fig. 5: DSC thermograms of indomethacin; PEG-10 and their different system prepared by physical mixtue, jet milling and solid dispersion.

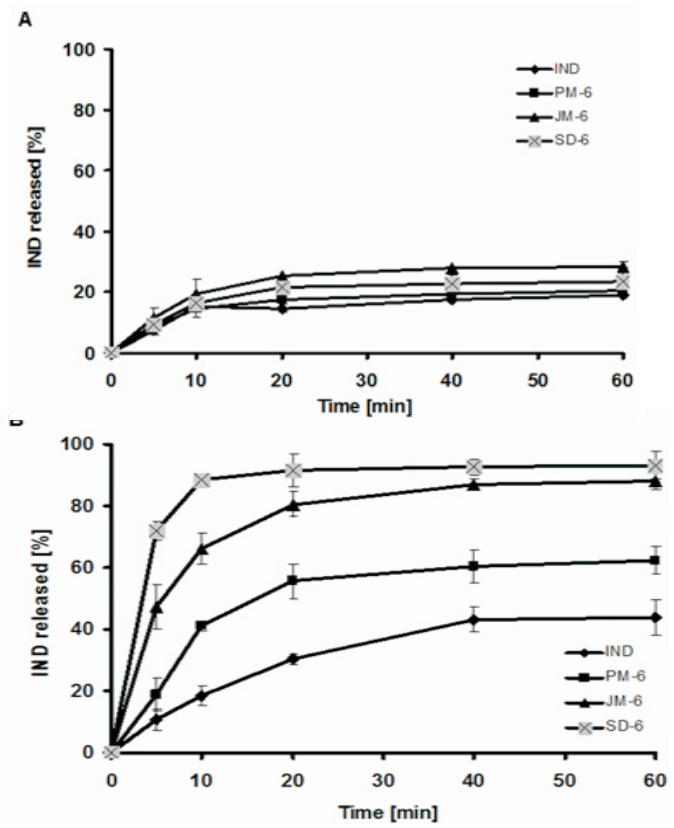


Figure 6: **(A)** Release profiles of indomethacin and IND-PEG-6 at 1:4 drug polymer ratio prepared by physical mixture,jet milling, and (**X**) solid dispersion technique in 0.1 N HCl pH 1.2. **(B)** with phosphate buffer saline pH 7.4.

increased due to both increasing specific surface area and decreasing crystallinity. After the grinding limit was attained, hydrogen bonds between the carboxyl groups were broken gradually with milling, and the IND molecules were rapidly hydrated and diffused into the aqueous solution, resulting in further enhancement of the dissolution rate. In addition, Polymers, including PEGs, are known to be able to surrounding fine drug crystals after the grinding by JM, resulting in an effective improvement of the dissolution rate. Furthermore, the results prove that the dissolution rate of the IND can be controlled

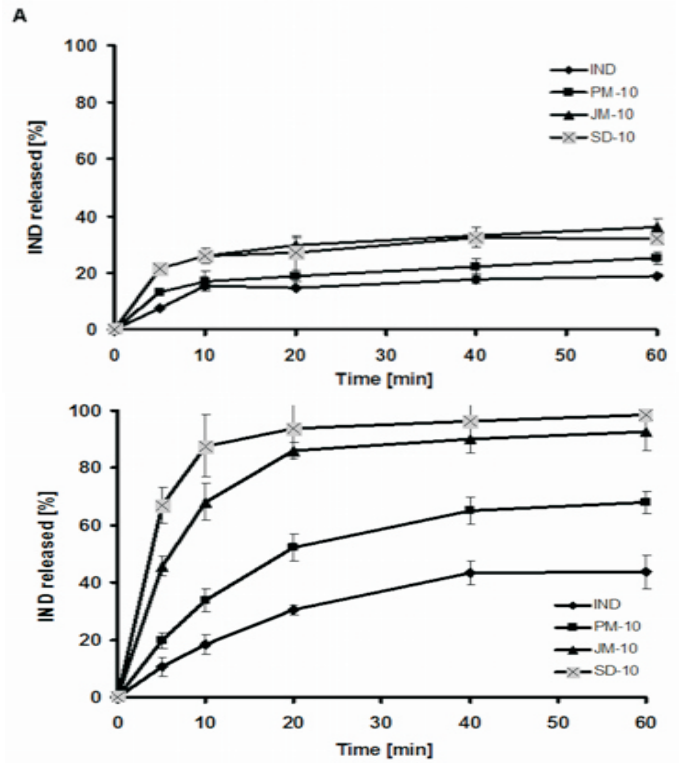


Fig. 7: (A) Release profiles of indomethacin and IND-PEG-10 at 1:4 drug polymer ratio prepared by physical mixture, jet milling, and (**X**) solid dispersion technique in 0.1 N HCl pH 1.2. **(B)** with phosphate buffer saline pH 7.4.

by utilizing the change of both the particle size and the crystalline structure. The enhancement dissolution rates of SD may be due to increasing in drug wettability and preventing of drug aggregation by each polymer [34]. Furthermore, both PEG-6 and PEG-10 affected the crystallinity of the drug could be considered as an important factor in enhancement of the dissolution rate. It is known that amorphous drug represents the most ideal case for fast dissolution [35]. Finally, the dissolution rate of IND-PEG-10 was greater than the rate of IND-PEG-6 prepared by different techniques (PM, JM and SD). This could be attributed to the long chain length of PEG-10.

CONCLUSION

Our results revealed that dispersions of IND into water-soluble carriers like PEG-6 or PEG-10 changed the crystallinity of IND according to different techniques and polymers used. The IND-PEG particles were prepared by jet milling in a dry process in order to enhance the water dissolution rate. The grinding progressed during jet milling process increased the specific surface area of the IND particles incorporated into the polymer, which leads to decreasing in the crystallinity of indomethacin. Furthermore, the hydrogen bonds, which had formed between the carboxyl groups of IND molecules, were broken, resulting in an effective improvement of the dissolution rate. The formulation of IND-PEG prepared by solid dispersion did not show any kind of crystallinity of the drug, and represents a suitable modification for improving its availability. It is recommend that, the comparison between binary and ternary system of drug milling in the presence of hydrophilic polymer with or without surfactant prepared by jet milling for enhancing the solubility and dissolution rate will be studied. Finally, jet milling is a promising technique for improvement the solubility of poorly soluble drug in industrial scale.

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