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Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000

Mahmoud El-Badry ^{a,*}, Gihan Fetih ^b, Mohamed Fathy ^b

^a Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

^b Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

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Abstract The aim of this study was to prepare and characterize solid dispersions of water insoluble non-steroidal anti-inflammatory drug, indomethacin (IND), with polyethylene glycol 4000 (PEG4000) and Gelucire 50/13 (Gelu.) for enhancing the dissolution rate of the drug. The solid dispersions (SDs) were prepared by hot melting method at 1:1, 1:2 and 1:4 drug to polymer ratios. Scanning electron microscopy (SEM), X-ray powder diffractometry (XRD) 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 XRD showed that the drug was still detectable in its solid state in all SDs of IND–Gelu. and disappeared in case of higher ratio of IND–PEG4000. DSC thermograms showed the significant change in melting peak of the IND when prepared as SDs suggesting the change in crystallinity of IND. The highest ratio of the polymer (1:4) enhanced the drug solubility about 4-folds or 3.5-folds in case of SDs of IND–PEG or IND–Gelu., respectively. An increased dissolution rate of IND at pH 1.2 and 7.4 was observed when the drug was dispersed in these carriers in form of physical mixtures (PMs) or SDs. IND released faster from the SDs than from the pure crystalline drug or the PMs. The dissolution rate of IND from its PMs or SDs increased with an increasing amount of polymer.

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* Corresponding author.

E-mail address: elbadry@ksu.edu.sa (M. El-Badry).

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1. Introduction

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 (Sweetman, 2005). The drug is described as poorly soluble and highly permeable (Class II) drug (Lobenberg and Amidon, 2000). 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 (Hirasawa et al., 2003). The successful formulation of poorly water-soluble drugs is one of the major problems in pharmaceutical manufacturing. Indomethacin may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract. Additionally, this undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of a prolonged contact time with the mucosa (Alsaïdan et al., 1998).

Over the years, a variety of solubilization techniques have been studied to improve the dissolution rate of this widely used antirheumatic agent, to obtain more rapid and complete absorption such as; using adsorbants (Alsaïdan et al., 1998; Bogdanova et al., 2007), surfactant (Krasowska, 1980), hydrotropes and cosolvents (Etman and Nada, 1999), preparing coprecipitate (Habib et al., 1993), liquisolid compacts (Nokhodchi et al., 2005), fast releasing microparticles (Cavallari et al., 2007), interactive mixtures (Allahham and Stewart, 2007), solid dispersion (Valizadeh et al., 2004; Wang et al., 2007), compressing with buffers (Preechagoon et al., 2000) or complexation with cyclodextrins (Bandi et al., 2004; Jambhekar et al., 2004).

Solid dispersion technique was selected as it was utilized in a limited number of researches to increase the solubility of indomethacin. Solid dispersion (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 (Chiou and Riegelman, 1971; Ford and Rubinstein, 1978). It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs (El-Badry and Fathy, 2005, 2006; Douroumis et al., 2007; Thybo et al., 2007). In solid dispersions, the particle size of the drugs was reduced, the wettability and the dispersibility were enhanced; therefore, drug dissolution was improved markedly (Abdul-Fattah and Bhargava, 2002; Craig, 2002; Sethia and Squillante, 2004).

PEG and Gelucire are among the several carriers which have been employed in preparing solid dispersions (Leuner and Dressman, 2000) PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydrophilicity (Craig, 2002; Leuner and Dressman, 2000; Lin and Cham, 1996; Liu and Desai, 2005; Urbanetz and Lippold, 2005; Ahuja et al., 2007) Gelucire is a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These are available with a range of properties depending on their hydrophilic-lipophilic balance (HLB) and melting point range (33–65 °C) (Aïnaoui and Vergnaud, 1998; Sutananta et al., 1994). They have a wide variety of applications in pharmaceutical formulations as the preparation of fast release and sustained release formulations (Aïnaoui et al., 1997; Dennis et al., 1990; Cavallari et al., 2005).

The purpose of the current study is to characterize the solid-state properties of the solid dispersion system of indomethacin in PEG4000 and Gelucire 50/13 prepared at different ratios. The methods of characterization were achieved through using different tools as scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (XRD). Moreover, solubility and dissolution rate study were performed to qualify the solid dispersion comparing with the drug alone or as physical mixture (PM).

2. Experimental

2.1. Materials

Indomethacin (IND) was kindly supplied by Egyptian International Pharmaceutical Co.; (EIPICO 10th of Ramadan city, Egypt). PEG4000 was obtained from CLARIANT (Sulzbach, Germany). Gelucire 50/13 was provided by Gattefosse (Cedex, France) and has m.p. 50 °C and HLB 13. All other materials and reagents were of analytical grade of purity.

2.2. Methods

2.2.1. Preparation of physical mixture

Gelucire is a waxy pellet, so it is crushed to fine particles firstly to prepare the physical mixture. Physical mixtures (PMs) of IND with PEG4000 or Gelucire 50/13, at 1:1, 1:2 and 1:4 weight ratio of IND:drug, were prepared by blending them by trituration for 10 min followed by sieving (500 µm).

2.2.2. Preparation of solid dispersion

Solid dispersions (SDs) at various weight ratios were prepared by melting method. IND was added to the molten base comprising PEG4000 or Gelucire. The blend was heated 10 °C above the melting point of each carrier for 5 min with continuous stirring. The systems were placed in a freezer at –20 °C for 24 h. The mass was crushed, ground gently with a mortar and pestle and passed through 500-µm sieve. The samples were kept in a desiccator until the next experiments

2.2.3. Scanning electron microscopy (SEM)

The samples were coated with a thin gold layer by sputter coater unit (SPI, sputter, USA). Then, SEM photographs were taken by a scanning electron microscope (Joel JSM 5400LV SEM, Japan) operated at an acceleration voltage of 15 kV.

2.2.4. Differential scanning calorimetry (DSC)

The powdered sample (3–5 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min, over a temperature range of 25–200 °C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N₂ as purging gas at rate of 30 ml/min.

2.2.5. X-ray powder diffraction (XRD)

Samples were irradiated with monochromatized Cu K α radiation (1.542 Å) and analyzed between 2° and 40° (2 θ) 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/s.

2.2.6. Solubility determination

An excess amount of the sample was placed in contact with phosphate buffer 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 0.45 µm). 0.5 ml of the fil-

trate was immediately diluted and assayed spectrophotometrically at 320 nm. All experiments were conducted in duplicate.

2.2.7. Release rate studies

USP type II (paddle) method using Electrolab dissolution tester (TDT06 N, 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 or phosphate buffer (pH 7.4). The dissolution media were maintained at $37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$ and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through microfilter (0.45 μm), concentration of IND was determined spectrophotometrically (Jenway 6305 spectrophotometer, UK) at 320 nm. All experiments were carried out in duplicate.

3. Results and discussion

3.1. Scanning electron microscopy (SEM)

Figs. 1 and 2 display SEM photographs for IND, PEG4000, Gelu. 50/13, their corresponding PMs and SDs. The drug crystals seemed to be irregular in shape and size. IND crystals were much smaller than PEG or Gelucire particles. The physical mixture of the drug and carrier showed the presence of drug in the crystalline form. It was easy to recognize the polymer particles from that of drug despite the reduction in size of particles of polymers during mixing and its presence in high amount (1:4 ratio). In case of SDs, it was difficult to distinguish the presence of IND crystals. IND crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

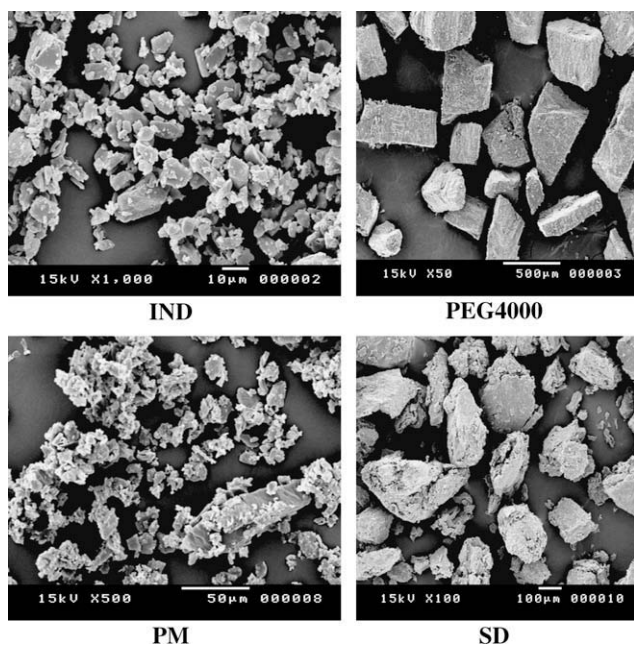


Figure 1 SEM micrographs for indomethacin–PEG systems: indomethacin (IND), polyethyleneglycol 4000 (PEG4000), physical mixture (PM) and solid dispersion (SD) at 1:4 ratio.

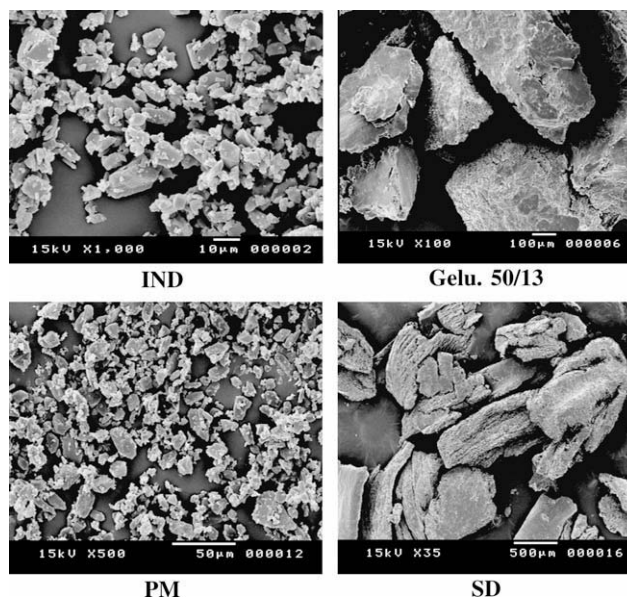


Figure 2 SEM micrographs for indomethacin–Gelucire systems: indomethacin (IND), Gelucire (Gelu. 50/13), physical mixture (PM) and solid dispersion (SD) at 1:4 ratio.

3.2. X-ray powder diffraction (XRD)

XRD patterns for different samples are displayed in Figs. 3 and 4 for IND–PEG4000 and IND–Gelu. 50/13 systems, respectively. The diffraction spectrum of pure IND showed that the drug is highly crystalline powder and possesses sharp peaks at 2θ equal to 11.6° , 16.4° , 19.6° , 21.7° , 26.89° and 29.3° . This corresponds to the γ -crystalline form polymorph of indomethacin (Pan et al., 2006). Characteristic peaks of PEG4000 (Fig. 3) appeared at 2θ equal to 13.68° , 19.24° , 23.32° and 27.37° . Gelucire showed two prominent peaks with the highest intensity at 2θ of 19.13° and 23.25° (Fig. 4).

All the principle peaks from PEG4000 (Fig. 3) and Gelucire 50/13 (Fig. 4) were present in their PMs but with lower intensity. In the case of the PMs, diffractograms were simply the sum of those of pure components and no interaction could be detected between them particularly at lower ratios (1:1 and 1:2). In case of PM of IND–PEG4000 system at 1:4 ratio (Fig. 3), there was a decrease in the intensity of IND but the major peaks remained at the same positions. The intensity of peaks reflected their mutual concentration. The decrease in the intensity of the diffractogram in case of the SD appeared at 1:2 ratio and the peaks of IND disappeared completely at 1:4 ratio. It could be attributed to the destruction of its crystal lattice, because of melting of drug into carrier. The peaks associated to the carriers are 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. This is common in mixtures of polymeric carriers with small amounts of low molecular weight drugs (Kreuter, 1999). In case of IND–Gelu. 50/13 (Fig. 4), diffractograms of physical mixtures are simply the sum of those of pure components in all cases while the intensity of the peaks of IND diminished with the increase in polymer ratio in case of SDs. Contrary to SD of PEG, the IND peaks remained

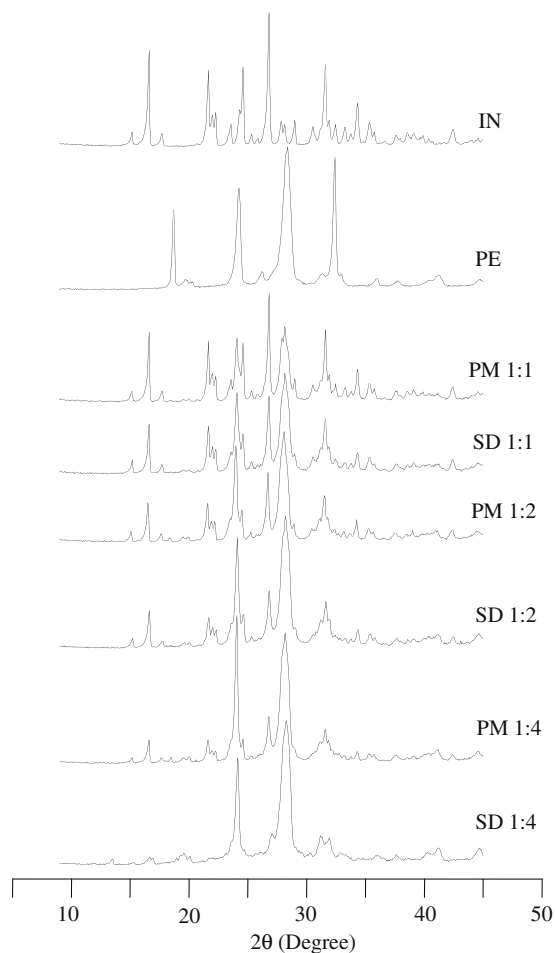


Figure 3 XRD diffractograms for: (IND) indomethacin; (PEG) polyethylene glycol 4000, and their different systems prepared at different ratios; (PM) physical mixture; (SD) solid dispersion.

viewed in higher ratio of polymer (1:4). From these results, it emerged that the amount of Gelu. is not sufficient to dissolve the IND completely so oversaturation occurred and pure drug crystals kept its structure inside the solid dispersion and appeared in the diffractogram (Fig. 4). Much decreased crystallinity of IND was suggested in the SDs of IND–Gelu., at 1:4 ratio, than the PM of same ratio (Fig. 4). The results indicated that both polymers affected the crystallinity of IND by different degrees. The change in crystallinity was dependent on the amount of polymer and solubility of drug in the polymer. At 1:4 ratio, the crystallinity of IND much decreased in case of Gelu., while it converted to amorphous state in case of PEG4000. No new peaks could be observed suggesting the absence of the chemical interaction between the drug and the carrier (Ahuja et al., 2007).

3.3. Differential scanning calorimetry (DSC)

Fig. 5 depicted thermograms of IND, PEG4000 their PMs and SDs. IND displayed endothermic peak at 161.26 °C corresponding to its melting point. PEG showed endothermic peak at 61.8 °C due to its melting point. Thermal traces for PM or SD at 1:1 ratios showed a very weak broad peak shifted to lower melting point. The peak appeared at 136.1 °C with heat of

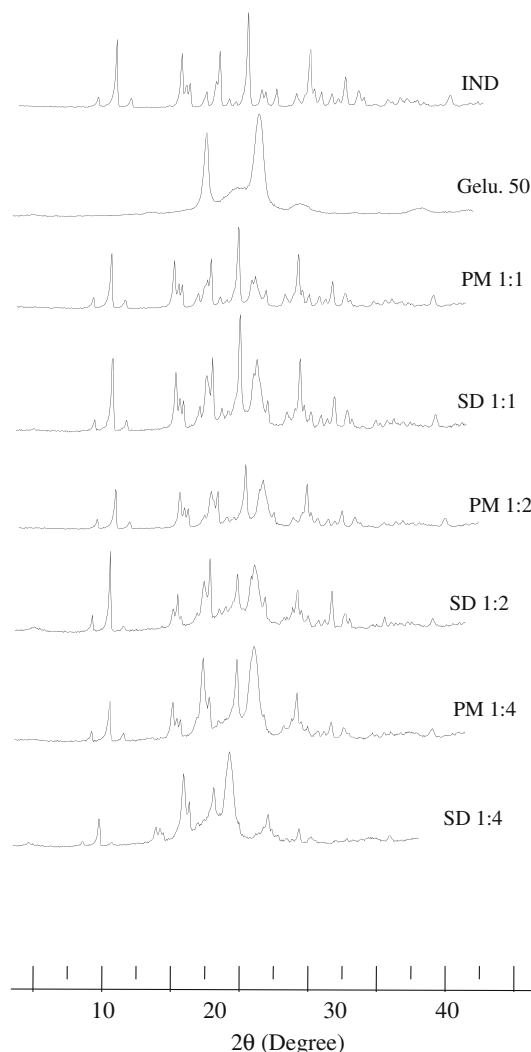


Figure 4 XRD diffractograms of for: (IND) indomethacin; (Gelu.) Gelucire 50/13, and their different systems prepared at different ratios; (PM) physical mixture; (SD) solid dispersion.

fusion about -5.2 J/g for PM and appeared at 115.52 °C with heat of fusion -7.2 J/g for SD (Table 1). At higher ratios (1:2 and 1:4), thermal profiles of both PMs and SDs exhibited a single endothermic peak corresponding to the fusion of the carrier. No peak was present representing the melting of the drug. The results were consistent with the previous data of XRD patterns (Fig. 3). In other study (Ford and Rubinstein, 1978) the indomethacin–PEG6000 produced only one-peak thermogram up to 40% w/w composition, while peaks related to the fusion of both polymorphs I and II appeared at 80% w/w indomethacin composition. Fini et al. (2005) reported that during the scanning of the temperature, the solid drug (diclofenac) dissolved into the molten PEG6000 starting from 60 °C and is no more present in its undissolved form inside the system. The results suggested that IND dissolved completely into polymer.

Fig. 6 demonstrates thermograms of IND, Gelucire 50/13, their PMs and SDs. The endotherm of Gelu. displayed broad peak appeared at 46.56 °C corresponding to its melting point with heat of fusion -160 J/g (Khan and Craig, 2003). This could be attributed to its composition, whereas, it is composed

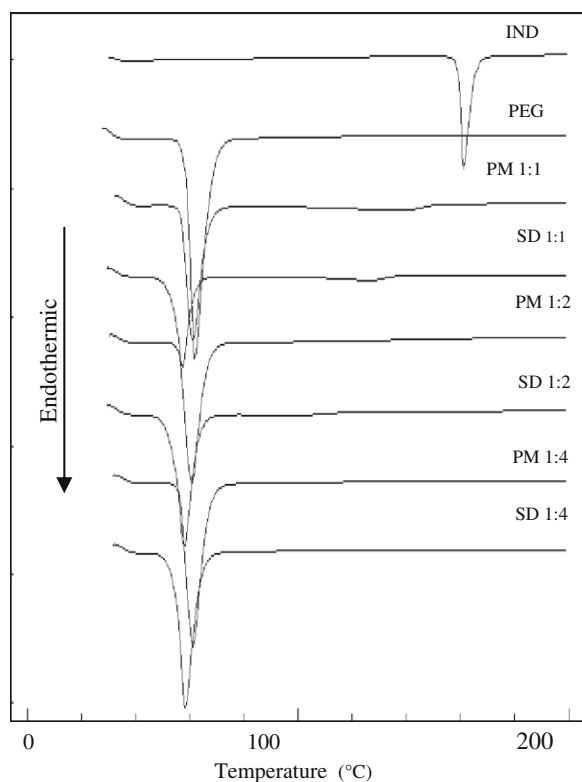


Figure 5 DSC thermograms for: (IND) indomethacin; (PEG) polyethylene glycol 4000, and their different systems prepared at different ratios; (PM) physical mixture; (SD) solid dispersion.

of a mixture of low melting component rather than a single one (Tantishaiyakul et al., 1999). The thermal behavior of both PMs and SDs of the drug was different. In case of PM (1:1), the peak of IND was weekend, broadened and appeared at 150.72 °C with heat of fusion – 50.4 while it became trace and shifted to 135.85 °C with heat of fusion – 15.6 J/g at 1:2 ratio and disappeared completely in case of 1:4 ratio. At 1:1 ratio of SD, the peak of IND appeared at 135.83 °C with heat of fusion – 22.8 J/g and disappeared completely at 1:2 and 1:4 ratios. The differences in the thermal behavior of IND in form of PMs and SDs suggested the drug crystallinity decreased when

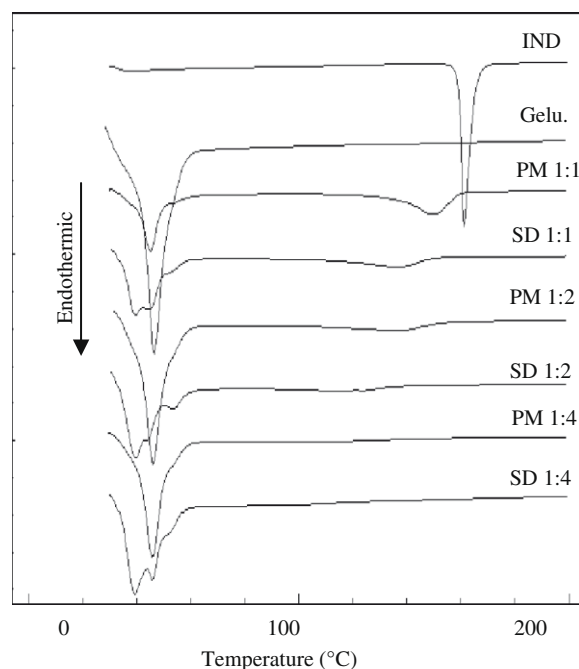


Figure 6 DSC thermograms for: (IND) indomethacin; (Gelu.) Gelucire 50/13, and their different systems prepared at different ratios; (PM) physical mixture; (SD) solid dispersion.

prepared as SD and that decrease was dependent on the ratio of the polymer. The low amount of crystals dissolved in the molten mass of Gelu. during DSC scanning and the peak of drug melting disappeared. In case of PM (1:1 and 1:2), the amount of molten polymer was not sufficient to dissolve the crystals of IND due to its presence in high amount. Increasing the amount of polymer (1:4 ratio), the molten mass became sufficient to dissolve the drug and consequently disappeared in the scan of PM. The difference between the effect of PEG and Gelu. on IND's crystallinity, probably, due to the lower crystalline nature of Gelucire with respect to PEG (Fini et al., 2005). The results from DSC and XRD indicated a decrease in crystallinity of IND in presence of higher amount of Gelucire.

Table 1 Solubility and thermal parameters of indomethacin (IND) alone and IND–polymer systems.

| System type | Ratio | IND–PEG4000 | | | | IND–Gelu. 50/13 | | | |
|-------------|-------|------------------------|-----------------------|----------------------|---------------------------------|------------------------|-----------------------|----------------------|--------------------|
| | | Thermal parameters | | | | Thermal parameters | | | |
| | | Onset temperature (°C) | Peak temperature (°C) | Heat of fusion (J/g) | Solubility ^a (mg/ml) | Onset temperature (°C) | Peak temperature (°C) | Heat of fusion (J/g) | Solubility (mg/ml) |
| IND | 1:0 | 151.24 | 161.26 | –50.7 | 0.223 | | | | |
| PEG | 0:1 | 56.43 | 61.82 | –160 | | | | | |
| Gelu. | 0:1 | | | | | 37.05 | 46.56 | –150 | – |
| PM | 1:1 | 128.92 | 136.61 | –5.2 | 0.297 | 137.19 | 150.72 | –50.4 | 0.280 |
| | 1:2 | – | – | – | 0.367 | 123.01 | 135.85 | –15.6 | 0.317 |
| | 1:4 | – | – | – | 0.401 | – | – | – | 0.354 |
| SD | 1:1 | 126.82 | 115.52 | –7.2 | 0.611 | 119.3 | 135.83 | –22.8 | 0.528 |
| | 1:2 | – | – | – | 0.764 | – | – | – | 0.617 |
| | 1:4 | – | – | – | 0.974 | – | – | – | 0.739 |

^a Solubility was determined in phosphate buffer (pH 7.4).

All PMs and SDs (Figs. 5 and 6) exhibited endothermic peaks due to the fusion of PEG4000 and Gelucire 50/13 around 62 °C and 45 °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 XRD pattern.

3.4. Solubility determination

The aqueous solubility of a drug is a prime determinant of its dissolution rate and compounds with aqueous solubility less than 0.1 mg/ml often present dissolution limitation to absorption. IND (pK_a 4.5) can be considered practically insoluble drug in simulated gastric fluid (pH 1.2) and slightly soluble in simulated intestinal fluid (pH 7.4) (Nokhodchi et al., 2005). The solubility of IND in phosphate buffer pH 7.4 was markedly increased in presence of PEG or Gelucire (Table 1). For instance, the solubility of IND at 37 °C increased 4-folds or 3.5-fold when IND formulated as SD at 1:4 ratio in PEG4000 or Gelucire 50/13, respectively. In general, the increase in solubility of IND was greater in SDs than in PMs (Table 1). It was shown that PEG4000 had solubilizing effect higher than Gelucire 50/13. The results confirmed that the extent of disruption of crystallinity of IND by PEG4000 was higher than that by Gelu.

3.5. Release rate studies

Drug release studies were carried out in 0.1 N HCl (Figs. 7 and 8) and phosphate buffer pH 7.4 (Figs. 9 and 10). Generally, the release of IND in phosphate buffer pH 7.4 was higher than that in 0.1 N HCl. The result was explained on the basis of the limited solubility of IND in acidic medium (Nokhodchi et al., 2005). Blending of IND with PEG4000 or Gelucire in form of PMs or SDs could enhance the release of IND. The faster dissolution rate of PMs compared to pure drug was observed for both of polymers and could be attributed to the

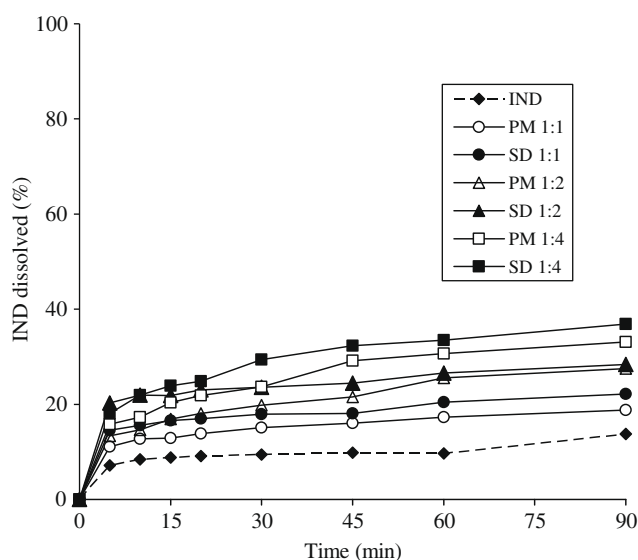


Figure 7 Dissolution profiles for IND-PEG4000 systems in 0.1 N HCl prepared at different ratios of IND:PEG4000. (IND) indomethacin alone; (PM) physical mixture; (SD) solid dispersion.

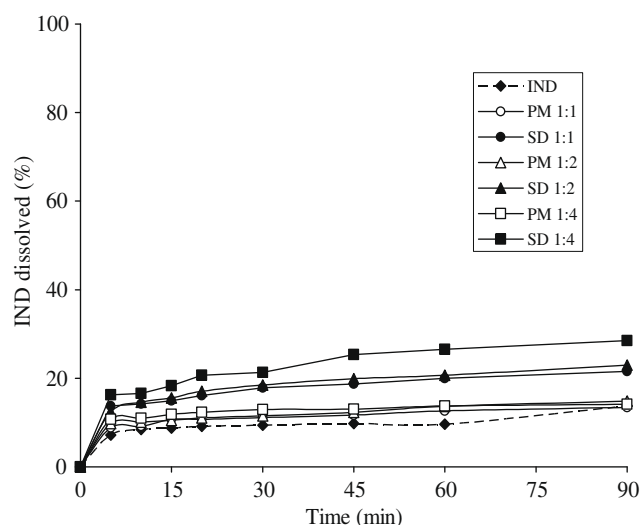


Figure 8 Dissolution profiles for IND-Gelucire 50/13 systems in 0.1 N HCl prepared at different ratios of IND:Gelu. (IND) indomethacin alone; (PM) physical mixture; (SD) solid dispersion.

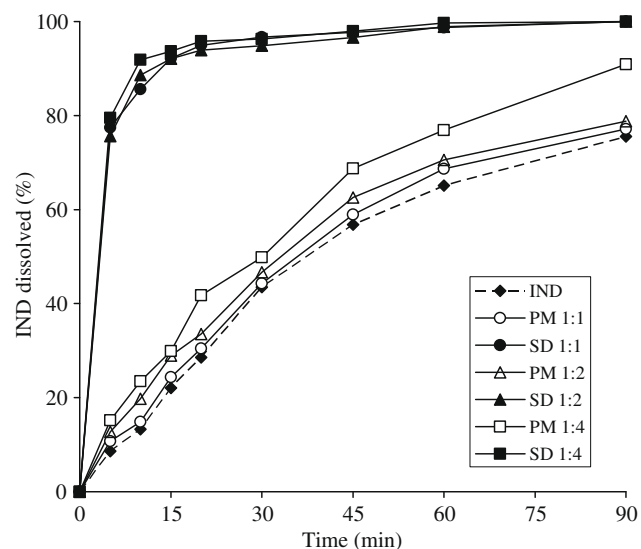


Figure 9 Dissolution profiles for IND-PEG4000 systems in phosphate buffer pH 7.4 prepared at different ratios of IND:PEG4000. (IND) indomethacin alone; (PM) physical mixture; (SD) solid dispersion.

improvement of wettability of IND particles due to the presence of highly hydrophilic polymers (Ahuja et al., 2007). Dissolution rates for SDs were greater than those for PMs and IND alone. The enhanced dissolution rates of SDs may be due to many factors such as decreased particle size of drug, specific form of drug in these SDs, in addition to the increase in drug wettability and preventing of drug aggregation by each polymer (Tantishaiyakul et al., 1999). Furthermore, both PEG and Gelucire affected the crystallinity of the drug could be considered as an important factor in enhancement the dissolution rate. It is known that amorphous drug represents the most ideal case for fast dissolution (Hancock and Zografi, 1997).

The percent of drug dissolved after 90 min (DP) and relative dissolution rate (RDR) after 30 min of IND, physical mix-

Table 2 The percent of drug dissolved after 90 min (DP) and relative dissolution rate (RDR) after 30 min of indomethacin, physical mixture and its solid dispersions in PEG4000 or Gelucire 50/13 prepared at different drug:polymer ratios.

| Dissolution medium | Polymer type | Ratio | PM | | SD | |
|--------------------|--------------|-------|------------------|-------------------|------------------|-------------------|
| | | | DP ₉₀ | RDR ₃₀ | DP ₉₀ | RDR ₃₀ |
| pH 1.2 | Drug | | 14.5 | 1.0 | 14.5 | 1.0 |
| | PEG4000 | 1:1 | 15.2 | 1.58 | 19.9 | 1.63 |
| | | 1:2 | 31.1 | 1.73 | 30.1 | 1.92 |
| | | 1:4 | 35.2 | 1.92 | 39.8 | 2.05 |
| | Gelucire | 1:1 | 14.5 | 1.09 | 20.2 | 1.57 |
| | | 1:2 | 14.9 | 1.12 | 21.4 | 1.61 |
| | | 1:4 | 15.2 | 1.22 | 30.0 | 1.92 |
| pH 7.4 | Drug | | 72.5 | 1.0 | 72.5 | 1.0 |
| | PEG4000 | 1:1 | 74.2 | 1.03 | 98.2 | 2.25 |
| | | 1:2 | 76.2 | 1.05 | 98.6 | 2.25 |
| | | 1:4 | 87.1 | 1.1 | 98.9 | 2.26 |
| | Gelucire | 1:1 | 80.1 | 1.46 | 82.5 | 1.53 |
| | | 1:2 | 90.2 | 1.69 | 91.4 | 1.90 |
| | | 1:4 | 98.1 | 1.94 | 99.2 | 2.05 |

DP: percent of drug dissolved after 90 min.

RDR: relative dissolution rate (ratio between the IND dissolved from PM, SD, and that dissolved from drug alone at 30 min).

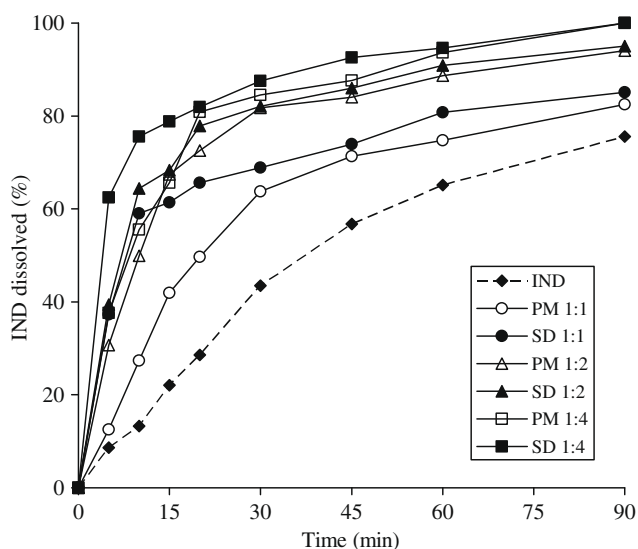


Figure 10 Dissolution profiles for IND–Gelucire 50/13 systems in phosphate buffer pH 7.4 prepared at different ratios of IND:Gelu. (IND) indomethacin alone; (PM) physical mixture; (SD) solid dispersion.

ture and its solid dispersions in PEG4000 or Gelucire 50/13 prepared at different drug:polymer ratios were illustrated in Table 2. It is shown that, the maximum percent amount of drug dissolved at pH 1.2 was 39.8% and the (RDR₃₀) values were in the range 1.09–1.92 for PM and 1.61–2.05 for SD of the used polymers. On the other hand, at the pH 7.4 the percent of drug dissolved after time period was different according to the polymer used and the (RDR₃₀) values were in the range 1.03–1.94 for PM and 1.53–2.27 for SD.

4. Conclusions

The study has demonstrated that dispersions of IND into water-soluble carriers like PEG4000 or Gelucire 50/13 changed

the crystallinity of IND according to type and amount of the polymer. The formation of IND–PEG solid dispersion destroyed almost completely the crystallinity of the drug and represents a suitable modification for improving its availability. The higher ratio of Gelu. (1:4) tested in this study was not sufficient for conversion of IND to amorphous form. However, it decreased the crystallinity of IND. Many factors contributed to faster release rate such as decrease in particle size, decrease in agglomeration of particles, increase wettability and decrease in crystallinity of the drug.

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تحسين ذوبانية ومعدل ذوبان الإندوميثاسين بواسطة البعثة الصلبة في الجليوسير 50/13 وبولي إيثيلين جليكول 4000

محمود البدري^{1*}، جيهان فتحي² و محمود فتحي²

ملخص البحث

تهدف هذه الدراسة إلى تحضير المبعثرات الصلبة والتحقق منها لدواء إندوميثاسين المضاد للالتهاب وغير الذائب في الماء مع بولي إيثيلين جليكول 4000 وجليوسير 50/13 لتحسين معدل ذوبان الدواء. وقد تم تحضير المبعثرات الصلبة بطريقة الإنصهار الحار عند نسبة 1:1، و 2:1، و 4:1 من الدواء إلى البوليمر. وتم استخدام الفحص المجهرى التفرسي، ومقياس الأشعة السينية لانعراج المسحوق، ومقياس الكالوري التفرسي التفرقي. وذلك لفحص الحالة الفيزيائية للدواء. وزيادة على ذلك، تم استكشاف ذوبانية ومعدل ذوبان الدواء في أنظمتها المختلفة. وأظهرت بيانات مقياس انعراج الأشعة السينية أن الدواء كان يمكن الكشف عليه في الحالة الصلبة في جميع المبعثرات الصلبة وفي إندوميثاسين جليوسير، واختفى في حالة النسبة العالية لدواء إندوميثاسين-بولي إيثيلين جليكول 4000. أما الصور الحرارية للمقياس الكالوري التفرسي التفرقي فقد أظهرت تغيراً معنوياً في ذروة الإنصهار لدواء إندوميثاسين عندما تم تحضيره كمبعثرات صلبة مما يوحى بالتغير في بللورية الدواء. وقد حسنت النسبة الأعلى للبوليمر (4:1) ذوبانية الدواء حوالي أربع مرات أو 3.5 مرة في حالة المبعثرات الصلبة مع بولي إيثيلين جليكول أو جليوسير، على التوالي. كما لوحظ زيادة معدل الذوبان لدواء إندوميثاسين عند درجة حموضة 1.2 و 7.4 عندما تمت بعثرة الدواء في هذه العوامل على شكل مخاليط فيزيائية أو مبعثرات صلبة. وكان إنطلاق دواء إندوميثاسين من المبعثرات الصلبة أسرع مما هو عليه من الدواء البللوري النقي أو من المخاليط الفيزيائية. وزاد معدل ذوبان الدواء من المخاليط الفيزيائية. أو المبعثرات الصلبة بزيادة كمية البوليمر.

1. قسم الصيدلانيات، كلية الصيدلة، جامعة الملك سعود، ص.ب 2457 الرياض 11451 المملكة العربية السعودية.
 2. قسم الصيدلانيات، كلية الصيدلة، جامعة أسيوط، أسيوط 71526، مصر.
- * المؤلف المراسل.