Influence of Various Polymers on the Improvement of Etodolac Solubility and Dissolution Rate via. Solid Dispersion Technique

Ahmed Abdelbary1, Omaima N El-Gazayerly1, Rania H Fahmy1*, Lamis H Salem2

Abstract: According to the Biopharmaceutical Classification System (BCS), Etodolac belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. Aiming at achieving this goal, five water soluble polymers were assessed as solid dispersion (SD) carriers to enhance the solubility and dissolution profile of Etodolac, each in three ratios. PEG 4000 and 6000 were used to produce 2nd generation solid dispersions, while carriers possessing surface activity or self-emulsifying properties such as Pluronic F-127 and Gelucire 44/14 or 50/13 were used for production of 3rd generation SDs. Saturate solubility studies revealed higher Etodolac solubility in alkaline rather than acidic environments due to its acidic nature, also, amphiphilic polymers (Gelucries and Pluronic F127) showed higher solubility of Etodolac in both media. XRD and DSC studies revealed that the enhanced dissolution might be due to either amorphization of the drug or due to the increased surface area of the drug crystallites after formation of the solid dispersions leading to better wettability and higher dissolution. Etodolac dissolution profiles showed two distinct phases of drug dissolution. SDs exhibited faster dissolution rates than the intact drug and the corresponding PMs, and, increasing the ratio of the solubilizing carrier to drug, resulted in corresponding enhancement in the drug dissolution rate. Accordingly, solid dispersion technique can be assertively considered as a promising procedure for preparing Etodolac in an enhanced solubility and dissolution form.

INTRODUCTION

It is a well established fact for poorly water-soluble drugs that the rate-limiting step in their absorption process is the dissolution rate in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall; therefore, by improving the release profiles of such drugs, it is possible to enhance their bioavailability and reduce their side effects. [1-4] According to the Biopharmaceutical Classification System (BCS), Etodolac (1, 8-diethyl-1, 3, 4, 9-tetrahydropyrano [3, 4- 6] in dol-1-yl) acetic acid) belongs to class II drugs; a drug that is characterized by low solubility and high permeability, [5, 6] therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. Etodolac is a selective COX-2 inhibitor; with 10-fold COX-2 selectivity over COX-1, therefore, it can be prescribed safely for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis at an oral dose of 200 mg twice daily without causing gastric irritation, ulceration, or bleeding. [7]

Among the various ways used for enhancing drug dissolution, solid dispersion (SD) of drug in a water-soluble polymer is one of the promising techniques [8, 9] that can provide enhancement in dissolution rate that sometimes can reach as high as 400-fold relative to intact drug. Such enhanced dissolution rate provided by solid dispersions can be attributed to either: a) reduction of Particle size: the molecular dispersions, as solid dispersions, represent final systems. These systems are either second generation SDs using polymeric carriers such as polyethylene glycol (PEG), or third generation SDs using carriers possessing surface activity or self-emulsifying properties such as Pluronic F-127 and Gelucire in two different grades. Moreover, each of the carriers was used in different ratios to ensure achieving the objective of the highest Etodolac solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Etodolac (kindly gifted from Pharco Pharmaceuticals, Alexandria, Egypt). Polyethylene glycol 4000 (PEG 4000) and Polyethylene glycol 6000 (PEG 6000) were purchased from Fluka BioChemika (Switzerland). Gelucire 44/14 and Gelucire 50/13 powder solid were purchased from

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Gattefossé Corporation (Saint-Priest-Cedex, France). Pluronic F127 was purchased from Sigma-Aldrich Co. (St. Louis, USA). Buffer Reagents: Disodium hydrogen phosphate and potassium dihydrogen phosphate (Riedel-de Haën, Sigma-Aldrich Laborchemikalen, GmbH, Germany). All other reagents and chemicals were of analytical grade.

Preparation of Etodolac Solid Dispersion Systems (SDs)
Solid dispersions of Etodolac using the five different carriers were prepared each in three ratios. The selected drug:carrier ratios were 1:1, 1:2 and 1:4 drug to carrier ratio for PEG 4000 and PEG 6000, while higher ratios of 1:2, 1:4 and 1:8 were used for Gelucire 44/14, Gelucire 50/13 and pluronic F127 as lower ratios showed poor dissolution profiles in preliminary studies. The detailed composition of each of the formulations is presented in Table 1. The solid dispersion systems (SDs) were prepared using the fusion method;[14-16] the calculated amounts of each of the carriers were left to melt over a thermostatically controlled magnetic stirrer, each at its respective melting point. After their complete melting, the calculated amounts of Etodolac were suspended in their corresponding molten polymers, then the blend was heated at a temperature 10°C above the melting points of the polymer with continuous stirring for 10 min. The molten mixtures were then immediately put in a freezer for 24 hours. Afterwards, the resulting frozen masses were crushed, milled and sieved through a 200 μm sieve and stored in closed containers away from the light and humidity until use.

Table 1: Composition of the ETD Solid Dispersions Formulations, Their Drug Content, and the Corresponding Saturated Solubility (mg/ml) of ETD, SDs, and PMs with PEG 4000, 6000, Gelucire 44/14, 55/13, and Pluronic F 127 at various Weight Ratios in SGF (pH 1.2) and SSF (pH 6.8)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Carrier Used</th>
<th>Drug : Carrier Ratio</th>
<th>Drug Content of SDs (% w/w ± S.D.*)</th>
<th>Saturated Solubility (mg/ml)</th>
<th>pH 1.2</th>
<th>pH 6.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etodolac</td>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>PM</td>
</tr>
<tr>
<td>F1a</td>
<td>PEG 4000</td>
<td>1:1</td>
<td>104.2 ± 1.2</td>
<td>0.11</td>
<td>2.17</td>
<td>0.275</td>
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<tr>
<td>F1b</td>
<td>PEG 4000</td>
<td>1:2</td>
<td>104.6 ± 2.1</td>
<td>0.278</td>
<td>2.15</td>
<td>0.283</td>
</tr>
<tr>
<td>F1c</td>
<td>PEG 4000</td>
<td>1:4</td>
<td>100.6 ± 2.3</td>
<td>0.283</td>
<td>2.75</td>
<td>0.283</td>
</tr>
<tr>
<td>F1a</td>
<td>PEG 6000</td>
<td>1:1</td>
<td>102.6 ± 1.9</td>
<td>17.4</td>
<td>2.25</td>
<td>0.237</td>
</tr>
<tr>
<td>F2b</td>
<td>PEG 6000</td>
<td>1:2</td>
<td>100 ± 2.1</td>
<td>17.2</td>
<td>2.87</td>
<td>0.283</td>
</tr>
<tr>
<td>F2c</td>
<td>PEG 6000</td>
<td>1:4</td>
<td>98.7 ± 2.2</td>
<td>17.1</td>
<td>2.87</td>
<td>0.283</td>
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<tr>
<td>F3a</td>
<td>Gelucire 44/14</td>
<td>1:1</td>
<td>105.1 ± 0.8</td>
<td>2.2</td>
<td>2.29</td>
<td>2.65</td>
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<tr>
<td>F3b</td>
<td>Gelucire 44/14</td>
<td>1:2</td>
<td>101 ± 2.1</td>
<td>2.6</td>
<td>2.46</td>
<td>2.61</td>
</tr>
<tr>
<td>F3d</td>
<td>Gelucire 44/14</td>
<td>1:4</td>
<td>97.5 ± 2.2</td>
<td>2.7</td>
<td>2.74</td>
<td>2.76</td>
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<tr>
<td>F4b</td>
<td>Gelucire 50/13</td>
<td>1:1</td>
<td>99.8 ± 2.4</td>
<td>2.1</td>
<td>2.35</td>
<td>2.11</td>
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<tr>
<td>F4c</td>
<td>Gelucire 50/13</td>
<td>1:2</td>
<td>98 ± 2.3</td>
<td>2.5</td>
<td>2.39</td>
<td>2.55</td>
</tr>
<tr>
<td>F4d</td>
<td>Gelucire 50/13</td>
<td>1:4</td>
<td>99 ± 1.9</td>
<td>2.5</td>
<td>2.68</td>
<td>2.59</td>
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<tr>
<td>F5b</td>
<td>Pluronic F127</td>
<td>1:1</td>
<td>102.1 ± 2.1</td>
<td>2.7</td>
<td>2.45</td>
<td>2.79</td>
</tr>
<tr>
<td>F5d</td>
<td>Pluronic F127</td>
<td>1:2</td>
<td>104.3 ± 1.9</td>
<td>2.7</td>
<td>4.25</td>
<td>2.79</td>
</tr>
</tbody>
</table>

S.D.: standard deviation from the mean, SD: solid dispersion system, PM: physical mixture system.

Table 2: Percentage Etodolac Dissolved after 10 Minutes Q_{10} (%) from its Solid Dispersions in SGF (pH 1.2) and SSF (pH 6.8)

<table>
<thead>
<tr>
<th>Solid Dispersion System</th>
<th>SGF (pH 1.2)</th>
<th>SSF (pH 6.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain Drug</td>
<td>4.78</td>
<td>15.26</td>
</tr>
<tr>
<td>PEG 4000</td>
<td>18.42</td>
<td>54.05</td>
</tr>
<tr>
<td>PEG 6000</td>
<td>23.2</td>
<td>62.74</td>
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<tr>
<td>Gelucire 44/14</td>
<td>34.04</td>
<td>70.44</td>
</tr>
<tr>
<td>Gelucire 50/13</td>
<td>21.51</td>
<td>57.16</td>
</tr>
<tr>
<td>Gelucire 50/13</td>
<td>30.17</td>
<td>72.68</td>
</tr>
<tr>
<td>Gelucire 50/13</td>
<td>40.03</td>
<td>77.33</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>22.69</td>
<td>38.79</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>36.09</td>
<td>41.36</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>38.02</td>
<td>50.11</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>25.25</td>
<td>60.99</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>26.75</td>
<td>63.06</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>49.42</td>
<td>65.11</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>42.36</td>
<td>62.75</td>
</tr>
<tr>
<td>Pluronic F127</td>
<td>47.8</td>
<td>70.82</td>
</tr>
</tbody>
</table>

*Q_{10}: Etodolac dissolved after 10 minutes (%)*
In the present study, physical mixtures (PM) of Etodolac with each of the carriers in the same ratios were prepared by gentle blending of the accurately weighed amounts of Etodolac and the corresponding carrier in a mortar for 5 minutes. The mixture is then sieved and the fraction of the powder that passed through a 200 μm sieve was collected and stored in a closed container away from the light and humidity for further investigations. \[1, 15, 17\]

**Determination of Saturated Solubility of Etodolac in Different PM and SD Systems**

The saturated solubility of Etodolac was determined experimentally to verify the pH dependency of solubility for the intact drug, each of the solid dispersion and physical mixture systems. An excess amount of the sample to be tested (either intact drug, SDs, or PMs) was added to 10 ml of either enzyme-free simulated gastric fluid (SGF, pH 1.2) or enzyme-free simulated saliva fluid (SSF, pH 6.8) in 30 ml screw capped vials. The vials were well closed and left to be shaken for 48 hours in a thermostatically controlled shaker at 25±1°C. The suspensions were then filtered through 0.45 μm Millipore filters (Versapor, German Sciences, Germany), diluted and assayed spectrophotometrically (Shimadzu, model UV-1601 PC, Kyoto, Japan) for their Etodolac content at $\lambda_{max}$ 279 nm. All experiments were run in duplicate. \[18, 19\]

**Determination of Content Uniformity**

Equal amounts of each of the SDs (equivalent to 100 mg of Etodolac), were accurately weighed, dissolved in 100 ml volumetric flask containing SSF (pH 6.8), then 1 ml of the solution was withdrawn and diluted to 100 ml with SSF, and the absorbance was measured spectrophotometrically at the predetermined $\lambda_{max}$ of Etodolac 279 nm. The mean value of duplicate estimates was used in calculating the required amounts for dissolution experiments. \[20\]

**Solid State Characterization of Etodolac SDS and PMS**

**X-ray Diffraction (XRD)**

Figure 1: X-ray diffraction patterns of: (a) pure Etodolac, PEG 4000, PEG 6000, and their corresponding physical mixtures (PM) and solid dispersions (SDs), all in 1:2 ratios. (b) pure Etodolac, Gelucire 44/14, Gelucire 50/13, Pluronic F127, and their corresponding physical mixtures (PM) and solid dispersions (SDs), all in 1:2 ratio. The curves have been displaced vertically for better visualization.
In order to determine the powders’ crystalline state, X-ray powder diffraction was performed using X-ray diffractometer (Scintag XGEN-4000, Advanced Diffraction systems, Scintag Inc., USA). The X-ray diffraction (XRD) patterns were determined for Etodolac, all polymeric SDs and PMs in the ratio 1:2. The samples were exposed to nickel-filtered Cu-Kα radiation at a scan rate of 8°/min over the 2θ range of 4° and 50° (voltage of 45 kV and a current of 40 mA) and the results were then obtained as peak height (intensity) versus 2θ.

**Thermal Analysis**

To examine any interaction between Etodolac and different carriers used, the thermotropic properties and phase transition behavior of Etodolac, all polymeric SDs and PMs in the ratio 1:2 were evaluated using Differential Scanning Calorimeter, DSC-50 (Shimadzu DSC TA-50 ESI, Kyoto, Japan). Samples of about 5 mg were sealed in a 50 μl aluminium pans at a heating rate of 10°C/min throughout the analysis. The results were then obtained as peak height (intensity) versus 2θ.

**Evaluation of the Dissolution Behavior of Etodolac from Different Systems**

The pharmaceutical dissolution behavior of the intact drug alone, and the dissolution behavior from various PMs and SDs prepared using the different ratios of the selected polymers were evaluated using in vitro dissolution studies and compared to that of intact Etodolac. Our goal was to illustrate the enhanced dissolution profile observed from various solid dispersion systems over pure drug and physical mixtures. Dissolution experiments were conducted in duplicate using 900 ml either enzyme-free SGF (pH 1.2) or enzyme-free SSF (pH 6.8) using a USP II dissolution test apparatus (rotating paddle) (Pharma Test, Germany). Sieved samples (100 mg of Etodolac or Etodolac-equivalent SDs or PMs) were dispersed on the surface of the dissolution medium at the beginning of the study. The paddle was rotated at 50 rpm and the temperature of the dissolution medium maintained at 37±0.5°C. Three milliliters aliquot samples were withdrawn, filtered using 0.45 μm Millipore filters and replaced with an equal volume of dissolution medium at 10, 20, 30, 45, 60, 75, and 90 minutes. The samples were
RESULTS AND DISCUSSION

Selection of suitable carriers suitable carriers for the preparation of Etodolac solid dispersion systems using fusion method were selected by testing the solubility and miscibility of five of the easily-available water- soluble inert excipients; namely PEG 4000 and 6000, gelucire 44/14 and 55/13, and pluronic F127. All of the selected carriers have lower melting point than that of Etodolac (150.02°C), [7] therefore, it is suitable to avoid drug decomposition during the excessive heating during solid dispersions preparation using the fusion technique.

In general, polyethylene glycol polymers are characterized by low melting point (M.P. of PEG 4000 ≈ 50-58°C and that of PEG 6000 ≈ 56-63°C) that can be used to formulate 2nd generation solid dispersions. In addition, both PEGs have rapid solidification rate, favorable solution properties, low toxicity and low cost. [25-27]

On the other hand, both Gelucires and pluronic F127 belong to the amphiphilic carriers possessing surface activity or self-emulsifying properties that are used to prepare 3rd generation solid dispersions. [5, 28, 29] Gelucires belong to a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids with a melting point range (33-65°C). [28] Also, poloxamers (Pluronic F127) consists of hydrophilic polyoxyethylene chain, and hydrophobic core (polypropylene) arranged in a tri block structure to give an amphiphilic structure, therefore, a hydrophobic drug can be solubilized within the core of micelle or conjugated to the micelle forming polymer to increase dissolution of poorly water-soluble drugs [29]. Preliminary studies established that, for PEGs, drug to carrier ratios of 1:1, 1:2 and 1:4 gave good solubilization results, but for Gelucires and Pluronic F127, higher carrier ratios were found to give better solubilization and dissolution results over the lower ratios, therefore, ratios: 1:2, 1:4, and 1:8 were used.
Saturated Solubility of Different Etodolac Systems

The saturated solubility of plain Etodolac, its SDs and PMs with the five carriers in the different selected ratios at 25°C in either SGF (pH 1.2) or SSF (pH 6.8) are presented in Table 1. The solubility of plain Etodolac was found to be 0.11 mg/ml and 6.19 mg/ml in SGF and SSF, respectively. The higher solubility of Etodolac in the basic media of intestine compared to the gastric acidic environment might be due to the acidic nature of Etodolac (indole acetic acid derivative), leading to its presence in its ionized form in the basic medium, and hence increasing its solubility. [30]

Similarly, for each formulation, the solubility of the drug from either the SDs or PMs was found to be higher in SSF (pH 6.8) when compared to its solubility in SGF (pH 1.2). Additionally, it was observed that, for each of the carriers used, the increase in the carrier ratio was accompanied by an increase in Etodolac solubility; Serajuddin justified that by the increase in the solubilizing effect of the carrier with increasing its concentration. [31] Also, the Etodolac solid dispersions exhibited higher drug solubility all over the tested ratios than those prepared as physical mixtures.

The highest drug solubilities were reached with Etodolac solid dispersions using PEG 6000 at the ratio 1:4 and Pluronic F127 at the ratio 1:8 in both media used. In SGF, they produced 38-fold increments in the solubility of the drug, whereas in SSF, they increased the solubility by four-folds. On the other hand, Gelucire 44/14 at the ratio 1:8 increased the solubility 25-fold compared to that of pure Etodolac in SGF, and four-fold increase in SSF. These results suggest the formation of soluble complex in solution between water-soluble polymeric carriers (PEG 4000 and 6000) and poorly soluble drug. [32, 33] While the improvement of drug solubility by using the amphiphilic excipients, as in the case of Gelucires and Pluronic has been explained by two possible mechanisms: improvement of wetting characteristics and micellar solubilization of the drug. [5, 34, 35] In addition, Craig [8] has previously found that Gelucire 50/13 is able to exist in several different crystalline forms and that there is a potential for these structural states to influence the dissolution behavior. While for Gelucire 44/14 has not been reported to behave in the same manner; however, when in contact with an aqueous medium, this material appears to self-emulsify, while all the other Gelucires remain essentially intact which makes the Gelucire 44/14 of great importance in the field of dissolution improvement [8]. Because wetting is hindered by the drug hydrophobic surface, the enhancement of Etodolac solubility in the physical mixtures may be attributed to the wetting improvement resulting from mixing the hydrophobic drug surface with hydrophilic excipients, as previously reported by several authors working with different hydrophobic substances. [35]

Determination of Content Uniformity

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The mean values of Etodolac content (%) in the five carrier systems in different ratios are presented in Table 1. The drug content of the prepared SDs was found to be in the range of 97.5 and 105.1 % and standard deviation from the mean ranging from 1.2 to 2.4 % indicating the applicability of the carriers and method used for the preparation of solid dispersions with acceptable content uniformity.

Solid State Characterization of Etodolac SDs and PMs

X-Ray Diffraction (XRD)

Powder X-ray scans of Etodolac, Etodolac-PMs, and Etodolac-SD systems using the five carriers in 1:2 ratios were made to determine if there is a loss or modification of the pure drug’s crystal structure after it is formed into a solid dispersion, and to determine if any new crystalline phases may have formed. The X-ray diffraction pattern of each system in comparison with plain Etodolac are presented in Figure 1 (a & b). The X-ray diffractogram of plain Etodolac in Figure (1-a) showed that the drug was highly crystalline as indicated by the numerous sharp peaks, the most characteristic of which were allocated at 20°.
diffraction angles of 9.49°, 14.61°, 16.75°, 18.87°, 20.59°, 22.59°, 23.11°, and 27.85°. Regarding the polyethylene glycols, PEG 4000 showed single distinct characteristic peak at 23.27° and three sharp but less intense peaks at 14.63°, 19.15°, and 36.29°, while PEG 6000 showed three characteristics sharp peaks at 19.21°, 23.01°, and 23.51°.

As for the PM diffractograms in Figure (1-a), the characteristic peaks of both Etodolac and PEGs were clearly observed at the same 20 values but with lower intensity which might be due to the dilution by the carrier. The presence of the same peaks indicate that the crystallinity of Etodolac was not changed in the physical mixture, however, in the Etodolac-PEG 4000 or Etodolac-PEG 6000 SDs at weight ratios 1:2, showed significant decrease in intensity of some of the drug peaks: 9.49°, 14.61°, 16.75°, and 27.85° which indicates reduced Etodolac crystallinity during the solid dispersion formulation. [36, 37] Also, no new peaks could be observed suggesting the absence of the chemical interaction between the drug and the carriers used. [28]

Also, as presented by Figure (1-b), for Etodolac - Gelucire 44/14, Etodolac - Gelucire 50/13, as well as Etodolac - Pluronic solid dispersions, none of the peaks disappeared, only significant reduction of the intensity of the peaks at 20 values of 9.49°, 14.61°, 16.75°, and 27.85°. This suggests that both the amount of the carrier might not be sufficient to dissolve the Etodolac completely and the pure drug crystals kept their structure inside the solid dispersion and appeared in the diffractogram. Or indicate that at this polymer ratio, the pure drug is not completely converted into the amorphous form which can be achieved by using higher amounts of carriers or that the drug has kept its crystallinity and that the enhanced solubility and dissolution observed practically was due to the increased surface area of the drug crystallites after formation of the solid dispersions and not due to a change from a crystalline to an amorphous state. Similar results were obtained by Hussain et al. [22]

Thermal Analysis (DSC)

In the solid dispersion area, DSC is a powerful tool in evaluating the drug-carrier interactions, determining the solubility of a drug in a polymeric carrier, detecting polymorphic modifications and examining age-induced changes. When new peaks emerge, when there is gross polymorphic modifications and examining age-induced changes. When new peaks emerge, when there is gross broadening or elongation of an exothermic or endothermic peak, or when second order transitions produce changes in the baseline; some chemical interaction have occurred or eutectic or solid-solution type melts have been produced. [38] Therefore, the DSC was used in this study to determine the possible physicochemical interactions between the drug entity and the carriers used in its formulations.

DSC thermograms of pure Etodolac, pure carriers used, PMs and SDs, both in 1:2 ratio, are presented in Figure 2 (a & b). The thermogram of Etodolac demonstrated a sharp characteristic endothermic peak at 150.02°C corresponding to its melting temperature \( (T_m) \), such sharp peak signifies that Etodolac used was in pure crystalline state. [7] The thermogram of PEG 4000 showed single endothermic peak at 54.32°C and that of PEG 6000 also exhibited a single peak at 62°C corresponding to their melting points. Also, Gelucire 44/14 and Gelucire 50/13, and pluronic F127 showed sharp endothermic peaks corresponding to their melting points at 41.63°C, 47.07°C, and 54.87°C, respectively. [5, 14, 26]

The DSC thermograms of the prepared PM and SD systems in Figure 2 (a & b) confirmed that there were no apparent differences between the DSC thermograms of PMs and solid dispersions for each carrier system; they all verified complete disappearance of Etodolac characteristic peak and showed a single characteristic peak corresponding to the carrier melting in a temperature matching to its melting temperature. Usually, the complete disappearance of the drug melting peak in the SD thermograms indicate homogenous dispersion of the drug into carriers and complete drug amorphization, however, the disappearance from the PM thermograms as well indicate that drug amorphization was not the sole reason. Moreover, when the results of both DSC and XRD are combined, it could be deduced that a portion of Etodolac is still in crystalline state as indicated by XRD diffractions (Figure 1). Consequently, the disappearance of Etodolac peak in the PM and SDs thermograms (Figure 2) might be explained that during the DSC scanning, the solid drug dissolves in the molten carrier before reaching its fusion temperature and there is no more drug in its undissolved form at its melting point. [37, 39] Similar results were previously observed with meloxicam [15] nifidipine [1] and ofloxacine. [9]

Evaluation of the Dissolution Behavior of Etodolac from Different Systems

When a solid dosage form is orally administered, the drug substance has to be dissolved first so that it can be absorbed, a drug with low solubility-high permeability will be present in the GIT for a longer time and its absorption will occur over an extended period of time. [5, 6] The dissolution behavior of Etodolac from physical mixtures and solid dispersions prepared using various carriers, in both SGF and SSF, in comparison with the intact drug was examined by plotting the percentage of drug released against time as shown in Figures 3 – 5 for PEG 6000, Gelucire 50/13, and Pluronic F127 SDs only (for PEG 4000 and Gelucire 44/13, data not presented). Plain Etodolac exhibited the slowest dissolution behavior at both pH 1.2 and pH 6.8; this is because its hydrophobic nature caused the powder to float on the surface of the dissolution medium and preventing its surface contacting the medium and its wetting by the solvent medium. [40]

For all the solid dispersion formulations prepared, it was clear that all Etodolac dissolution profiles showed two distinct phases of drug dissolution: an initial rapid phase in the first 15–30 min followed by a slower almost plateau phase. Similar results were obtained by Aboelwafa and Fahmy. [15] Moreover, the results in fig 3-5 indicated that, for all the carriers used, and in all ratios, the amount of the drug released in SSF (pH 6.8) was greater than that released in SGF (pH 1.2), this result could be explained on.
the basis of the limited solubility of Etodolac in acidic medium due to its acidic nature which leads to its ionization in the basic medium, and hence increasing its solubility. [30] Such results were in good agreement with those of the solubility studies.

A higher release of the PMs compared to that of pure Etodolac was also observed and could be attributed to the improvement of wettability of ETD particles or to the formation of soluble complexes with the highly hydrophilic polymers, (PEG 4000 and PEG 6000), as well as the solubilizing effect of the amphiphilic polymers (Gelucire 44/14, Gelucire 50/13 and Pluronic F127) that lower the surface tension resulting in wetting the hydrophobic drug. [8, 14, 28]

Moreover, in all cases, solid dispersions exhibited faster dissolution rates than the intact drug and the corresponding physical mixtures. This might be due to either the reduction of particle size caused by the formation of a solid solution of the drug in the carrier in which the drug was molecularly dispersed in almost solubilized form within the solid dispersion matrix, [8] or due to the fact that the carriers used affected the crystallinity of the drug, and converted a great portion of its crystals to the amorphous form which represents the a more solubilized form of the drug as presented by the DSC and XRD results. [26, 41] Another explanation is that the enhanced dissolution might correspond to the increased surface area of the drug crystallites after formation of the solid dispersions and not due to a change from a crystalline to an amorphous state. [22]

Additionally, with all the carriers used, increasing the ratio of the solubilizing carrier to drug, resulted in an corresponding enhancement in the drug dissolution rate. It was noticed that the percentage of drug dissolved from its solid dispersions was proportional to the concentration of carrier used. As we see the highest ratio from each carrier gave the best dissolution results.

In order to further investigate the enhancement of the dissolution rate from different solid dispersion systems, Table (2) presents the dissolution of Etodolac after 10 minutes (%) from each formula at pH 6.8, and pH 1.2 (Q10). The results of Q10 augmented the previous findings regarding the faster dissolution observed for Etodolac from the solid dispersion systems in the first 10 minutes than that of pure drug. Etodolac- Gelucire 50/13 SDs and Etodolac- pluronic, both in 1:8 ratio, showed 10 - fold increment in etodolac dissolution rate in SGF (pH1.2) and 4.2 and 5.3- folds increment in SSF (pH 6.8), respectively.

Also, PEG 6000 showed 8- fold increase and 5-fold increase, in the percentage of Etodolac dissolved in the first 10 minutes as compared to Etodolac alone, in SGF and SSF, respectively. The results revealed that the dissolution profiles of Etodolac SD systems in SSF can be ordered from the highest to the lowest percentage of Etodolac dissolved after 10 minutes as follows: ETD : Pluronic F127 at 1:8 < ETD : PEG 6000 at 1:4 < ETD : Pluronic F127 at 1:4 < ETD : PEG 6000 at 1:2. However, for further comparison, the similarity factor (f2) calculation between these four formulae, was calculated. [42] The similarity factor (f2) is a logarithmic reciprocal square root transformation of the similarity in the percent (%) dissolution between the two curves.

\[ F_2 = 50 \log \left( \left[ 1 + \frac{1}{n} \sum \frac{t}{(R_t - T_t)^2} \right]^{0.5} \right) \]

For curves to be considered similar, f2 values should be greater than 50 (50-100) to ensure sameness or equivalence of the two curves. The results revealed that, when the dissolution rates of the four highest dissolution rate SD formulations, the first three formulae showed similar dissolution profiles; namely, Pluronic F127 (1:8), PEG 6000 (1:4), Pluronic F127 (1:4) were similar. However, F2b (Etodolac: PEG 6000 in the ratio 1:2) was not similar to F5d (Etodolac : Pluronic in the ratio 1:8). Form this, it can be concluded that the formulae Etodolac: Pluronic F127 (1:8), Etodolac: PEG 6000 (1:4), Etodolac: Pluronic F127 (1:4) can be used interchangeably as a tool for etodolac dissolution enhancement.

REFERENCES AND NOTES


