Indomethacin-Polyethylene Glycol Tablet Fabricated with Mold Technique

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Abstract

The purpose of this study is to improve solubility of indomethacin using different molecular weight and ratio of polyethylene glycol (PEG) as carrier for the solid dispersion system prepared by melting method and fabricated into tablet with mold technique. Effect of ratio, type and amount of carrier, and drug loading on physical properties of solid dispersion tablet was investigated. The 70:30 PEG 4000:PEG 400 system was the suitable carrier for tablet prepared with this technique. Higher amount solid PEG 4000 increased the tablet hardness. This inert carrier system could effectively enhance the drug solubility whereas an addition of xanthan gum could sustain the drug release. The drug release form tablets containing 150-mg and 300-mg indomethacin were slightly lower than that from indomethacin capsule. While the drug release from tablet containing 25-mg, 50-mg, 75-mg and 100-mg indomethacin were higher than indomethacin capsule, respectively. Differential scanning calorimetry (DSC) study indicated the amorphous state of drug in PEG carrier. Photomicrograph from SEM study indicated the drug diffusion outward through the porous network of this developed matrix tablet into the dissolution fluid. Least square fitting the experimental dissolution data to the mathematical expressions (power law, first order, Higuchi’s and zero order) was carried out to study the drug release mechanism. The drug release from the developed system was mostly occurred by diffusion with best described by the Fickian diffusion and the high drug loaded matrix tablets exhibited the best fitted to zero order model.

Key words: Solubility, Indomethacin, Polyethylene glycol, Mold technique

Introduction

Bioavailability of drug notably depends on drug solubility; therefore many efforts were performed to increase dissolution of the aqueous insoluble drugs such as salt formation, micronization, and addition of solvent or surface-active agent. Solid dispersion (SD) is one of these methods, and involved a dispersion of medicaments in an inert carrier in the solid state prepared by melting, dissolution in a solvent, or melting solvent method.(3) The interest in utilization of surface-active agents for poorly water soluble drugs has been increased in recent years. (17) Gelucire 44/14, vitamin E and polysorbate 80 were examples of such carriers which could improve the dissolution rate and enhance the bioavailability a poorly water-soluble drug. (3) To improve such poor solubility issues, solid dispersion techniques were widely applied to increase the apparent solubility or enhance the bioavailability of poorly water-soluble compounds.(7)

Polyethylene glycol (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. (23) Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. For solid dosage formulations, higher M.W. PEG can act as the effective binder. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds. (24) PEG grades 200-600 are liquids; grades 1000 are above are solid at ambient temperatures. Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and bitter, slightly burning taste. Grades of PEG 6000 and above are solid at ambient temperatures. Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and bitter, slightly burning taste. Grades of PEG 6000 and above are available as free-flowing milled powders that can used as excipient for tabletting. All grade of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycol. Polyethylene glycols do not support microbial growth and they do not become rancid. (4)

Indomethacin is non-steroidal anti-inflammatory agent with anti-pyretic and analgesic...
properties. It has been used in the symptomatic management of painful and inflammatory conditions. It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gouty arthritis. In usual initial dose by mouth in musculoskeletal and joint disorder is 25 mg two or three times daily with food. To alleviate night pain and morning stiffness, 100 mg may be administered by mouth, or rectally as a suppository. In acute gouty arthritis a suggested dose is 50 mg three times daily and in dysmenorrheal up to 75 mg daily has been suggested. Indomethacin is practically insoluble in water, soluble 1 in 50 of ethanol, 1 in 30 of chloroform, and 1 in 40 to 45 of ether, and soluble in acetone.\(^{(13)}\)

Hydrophilic matrix has become extremely popular in controlling the release rate of drugs from solid dosage forms. When a matrix containing a swellable glassy polymer comes into contact with a solvent, a progressive alteration from the glassy to the rubbery state leads to a swelling process. For matrix system, drug is often released by diffusion, because a sort of receding drug boundary comes to exist within the system.\(^{(2)}\) Xanthan gum has been widely used in oral and topical formulations, cosmetics and food as thickening agent.\(^{(20)}\) Xanthan gum has been used as an effective excipient for sustained release dosage forms since it can retard the drug release and sometimes provide the time-dependent release kinetics.\(^{(8,6)}\)

In the present study, the indomethacin solid dispersion tablets were prepared from different carriers such as PEG 20000, PEG 4000 mixed with plasticizers such as PEG 400, propylene glycol (PG) and glycerin. Effect of drug loading on the physical properties and the release of indomethacin from the prepared solid dispersion tablet containing 5% xanthan gum and thermal property were assessed.

**Material and Experimental Procedures**

**Materials**

Indomethacin (Batch No. 050814) was purchased from China National Chemical Imp. & Exp., China. PEG 4000 (lot. 504907), PEG 20000 (lot. 190922), PEG 400 (lot. PO76049), propylene glycol (PG) (lot. 313423) and glycerin (lot. 203708) were purchased from PC Drug, Thailand. Xanthan gum (xantural 75) lot. 01-100 was supplied from Monsanto Singapore Co., Singapore. Di-sodium hydrogen orthophosphate (lot no. 405300, Ajax Finechem, Australia) and potassium dihydrogen orthophosphate (lot no. E23W60, Ajax Finechem, Australia) were used for dissolution medium preparation.

**Preparation of Solid Dispersion Tablet**

Solid dispersion tablet was prepared by melting PEG 4000 or PEG 20000 on the water bath and mixed with plasticizer i.e. PEG 400, PG or glycerin and then the mixtures was poured into the stainless steel mold with diameter of 12 mm (Figure 1). Tablets with various ratios of carrier: plasticizer (Table 1) were prepared. Chosen systems containing PEG4000:PEG400 and 75-mg indomethacin were fabricated with various ratio of these two polymers as shown in Table 2. Furthermore, the tablets containing different amount of indomethacin (Table 3) were also prepared. The ratio of carrier, PEG 4000 : PEG 400, was kept constant at 70:30 by weight and the amount of xanthan gum was kept constant at 5% (w/w).
Table 1. Tablet composition containing different ratio of PEG and plasticizer

<table>
<thead>
<tr>
<th>Substance Ratio</th>
<th>9.5:5</th>
<th>9:1</th>
<th>8.5:1.5</th>
<th>8:2</th>
<th>7.5:2.5</th>
<th>7:3</th>
<th>6.5:3.5</th>
<th>6:4</th>
<th>5.5:4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG4000</td>
<td>86.8</td>
<td>82.2</td>
<td>77.7</td>
<td>73.1</td>
<td>68.5</td>
<td>63.9</td>
<td>59.4</td>
<td>54.8</td>
<td>50.3</td>
</tr>
<tr>
<td>PEG400</td>
<td>4.59</td>
<td>9.14</td>
<td>13.7</td>
<td>18.3</td>
<td>22.8</td>
<td>27.4</td>
<td>31.9</td>
<td>36.5</td>
<td>41.1</td>
</tr>
</tbody>
</table>

Table 2. Tablet composition containing 75-mg of indomethacin and different ratio of PEG4000 and PEG400

<table>
<thead>
<tr>
<th>Substance</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>25 50 75 100 150 300</td>
</tr>
<tr>
<td>PEG4000</td>
<td>561 543.6 526 508.6 473.6 368.6</td>
</tr>
<tr>
<td>PEG400</td>
<td>240.5 232.9 225.5 217.9 202.9 157.9</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>43.5 43.5 43.5 43.5 43.5 43.5</td>
</tr>
</tbody>
</table>

Table 3. Tablet composition containing different amount of indomethacin

<table>
<thead>
<tr>
<th>Substance</th>
<th>Substance Ratio</th>
<th>9.5:5</th>
<th>9:1</th>
<th>8.5:1.5</th>
<th>8:2</th>
<th>7.5:2.5</th>
<th>7:3</th>
<th>6.5:3.5</th>
<th>6:4</th>
<th>5.5:4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG4000</td>
<td>86.8</td>
<td>82.2</td>
<td>77.7</td>
<td>73.1</td>
<td>68.5</td>
<td>63.9</td>
<td>59.4</td>
<td>54.8</td>
<td>50.3</td>
<td></td>
</tr>
<tr>
<td>PEG400</td>
<td>4.59</td>
<td>9.14</td>
<td>13.7</td>
<td>18.3</td>
<td>22.8</td>
<td>27.4</td>
<td>31.9</td>
<td>36.5</td>
<td>41.1</td>
<td></td>
</tr>
</tbody>
</table>

Dissolution Profile Fitting

Least square fitting the experimental dissolution data (cumulative drug release >5% and up to 80%) to the mathematical equations (power law, first order, Higuchi’s and zero order) was carried out using a nonlinear computer programme, Scout for Windows, version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination ($r^2$) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (msc),

$$msc = \ln\left(1 + \sum_{i=1}^{n} w_i \left(\frac{Y_{obs_i} - \bar{Y}_{obs}}{Y_{cal_i}}\right)^2\right) - \frac{2p}{n}$$

$Y_{obs_i}$ and $Y_{cal_i}$ are observed and calculated values of the $i$-th point, respectively, and $w_i$ is the weight that applies to the $i$-th point, $n$ is number of points and $p$ is number of parameters.

Determination of Surface Topography of Tablets

The surface and cross-sectional topography of the prepared matrix tablet were determined using scanning electron microscope (SEM) (Maxim 200 Camscan Cambridge, England). Sample was determined after dissolution testing as described above. Tablets were withdrawn from the dissolution vessels at different time intervals (5, 30, 240 and 480 minutes). Then they were freeze dried for 24 hrs to avoid the collapse of porous structures. The samples were stuck on a metal stub using carbon double adhesive and sputter-coated with gold before test. Micrographs were taken with
a scanning electron microscope at an accelerating voltage of 15 kV.

**Differential Scanning Calorimetry (DSC)**

DSC study was performed using a differential scanning calorimeter (Perkin Elmer, Japan). A heating rate of 10 °C/min was employed over a temperature range of 25-300 °C with nitrogen purging (20 ml/min). The sample, approximately 5 mg, was weighed into aluminum pan and analyzed in a sealed aluminum pan. Moreover, analysis by heating the samples to 80°C and then reverse run to -30°C was also performed.

**Results and Discussion**

Phase separation was occurred in the systems containing PEG20000-glycerin and PEG4000- glycerin. Consequently, the mixture of PEG4000 with PG and PEG4000 with PEG400 were attempted but the hardness of the mixture of PEG4000 with PG was very low (data not shown). Therefore the mixtures of PEG 4000 with PEG 400 was selected as carrier of solid dispersion system. The physical properties of these systems are shown in Table 4. Hardness of tablet was increased as the amount of PEG4000 was increased because the amount of solid polyethylene glycol like a PEG 4000 was higher in the system. System comprising 70:30 PEG4000:PEG400 was chosen as carrier for tablet prepared with mold technique since it could be easily removed from the mold and the desired hardness could be obtained. Difficult removal of tablet from the mold was found as the higher amount of PEG 4000 was included. An addition of 5% xanthan gum and 75-mg indomethacin slightly increased the tablet hardness (Table 5). This might be the properties of xanthan gum to enhance the viscosity of SD system and promoted the tablet hardness. The remarkable property of xanthan gum was its capability of producing a large increased viscosity with a very small quantity of gum. The molecule of xanthan gum consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. Xanthan solutions are highly viscous even at low polymer concentrations. These properties are useful in many industrial applications, especially in the food industry where xanthan is used as a thickener, and to stabilize suspensions and emulsions. It has been reported by many authors that xanthan gum

### Table 4. Physical properties of solid dispersion tablet containing different ratio of PEG4000 and PEG400.

<table>
<thead>
<tr>
<th>Ratio of PEG4000:400</th>
<th>Physical Properties</th>
<th>Weight (g) (n=20)</th>
<th>Thickness (mm) (n=10)</th>
<th>Diameter mm (n=10)</th>
<th>Hardness (Newton) (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.5:0.5</td>
<td>Very hard and difficult to remove form mold</td>
<td>0.8531± 0.0252</td>
<td>6.58± 0.09</td>
<td>11.89± 0.02</td>
<td>55.87± 7.15</td>
</tr>
<tr>
<td>9:1</td>
<td>Very hard and difficult to remove form mold</td>
<td>0.8733± 0.0194</td>
<td>6.58± 0.10</td>
<td>12.01± 0.01</td>
<td>47.46± 7.41</td>
</tr>
<tr>
<td>8.5:1.5</td>
<td>Very hard and difficult remove form mold</td>
<td>0.8809± 0.0140</td>
<td>6.57± 0.02</td>
<td>12.02± 0.02</td>
<td>34.36± 4.79</td>
</tr>
<tr>
<td>8:2</td>
<td>Hard and difficult to remove form mold</td>
<td>0.8912± 0.0225</td>
<td>6.66± 0.09</td>
<td>11.97± 0.01</td>
<td>28.41± 2.55</td>
</tr>
<tr>
<td>7.5:2.5</td>
<td>Hard and difficult to remove form mold</td>
<td>0.8853± 0.0108</td>
<td>6.55± 0.02</td>
<td>12.02± 0.01</td>
<td>16.45± 1.66</td>
</tr>
<tr>
<td>7:1</td>
<td>Easy to remove form mold</td>
<td>0.8932± 0.0146</td>
<td>6.53± 0.02</td>
<td>12.01± 0.01</td>
<td>14.33± 0.79</td>
</tr>
<tr>
<td>6.5:3.5</td>
<td>Easy to remove form mold</td>
<td>0.8789± 0.0375</td>
<td>6.56± 0.08</td>
<td>12.01± 0.01</td>
<td>13.76± 1.47</td>
</tr>
<tr>
<td>6:4</td>
<td>Easy to remove form mold</td>
<td>0.9123± 0.0275</td>
<td>6.65± 0.09</td>
<td>11.99± 0.02</td>
<td>13.76± 1.17</td>
</tr>
<tr>
<td>5.5:4.5</td>
<td>Easy to remove form mold</td>
<td>0.8298± 0.0193</td>
<td>6.60± 0.04</td>
<td>11.97± 0.01</td>
<td>12.25± 2.76</td>
</tr>
</tbody>
</table>

*Presented as mean±S.D.*
can be used as an effective excipient for sustained-release formula. The physical properties of tablet containing various amounts of indomethacin and 5% xanthan gum are shown in Table 5. The hardness of prepared tablet was increased as the amount of indomethacin was increased. Higher content of solid drug in hydrophilic waxy matrix promoted the greater rigid structure; therefore the hardness was apparently increased.

Table 5. Physical properties of solid dispersion tablet containing 5% xanthan and different amount of indomethacin.

<table>
<thead>
<tr>
<th>Amount of indomethacin (mg)</th>
<th>Appearance</th>
<th>Weight (g) (n=20)</th>
<th>Thickness (mm) (n=10)</th>
<th>Diameter (mm) (n=10)</th>
<th>Hardness (Newton) (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Easy to remove form mold</td>
<td>0.8954± 0.0252</td>
<td>6.58± 0.09</td>
<td>11.89± 0.02</td>
<td>14.33± 0.79</td>
</tr>
<tr>
<td>50</td>
<td>Easy to remove form mold</td>
<td>0.8707± 0.0194</td>
<td>6.58± 0.10</td>
<td>12.01± 0.01</td>
<td>14.49± 1.66</td>
</tr>
<tr>
<td>75</td>
<td>Easy to remove form mold</td>
<td>0.8833± 0.0140</td>
<td>6.57± 0.02</td>
<td>12.02± 0.02</td>
<td>16.46± 1.41</td>
</tr>
<tr>
<td>100</td>
<td>Hard and difficult to remove form mold</td>
<td>0.8949± 0.0225</td>
<td>6.66± 0.09</td>
<td>11.97± 0.01</td>
<td>18.41± 1.55</td>
</tr>
<tr>
<td>150</td>
<td>Hard and difficult to remove form mold</td>
<td>0.8819± 0.0108</td>
<td>6.55± 0.02</td>
<td>12.02± 0.01</td>
<td>29.36± 1.79</td>
</tr>
<tr>
<td>300</td>
<td>Very hard and difficult to remove form mold</td>
<td>0.8912± 0.0146</td>
<td>6.53± 0.02</td>
<td>12.01± 0.01</td>
<td>40.87± 1.15</td>
</tr>
</tbody>
</table>

* Presented as mean±S.D.

To evaluate an influence of hydrophilic polymer on drug release, drug dissolution from systems without or containing 5% w/w xanthan gum were investigated. The drug release of tablet containing 5% w/w xanthan gum was apparently slower than that of tablet without an addition of this polymer. Drug release from capsule was apparently lower than that of tablet without or containing 5% w/w xanthan gum because indomethacin powder from capsule is a poorly soluble drug (5 μg/mL).225) Additionally, PEG system could promote the drug solubility. The result indicated that xanthan gum could retard the release longer than 8 hrs. Release of indomethacin was decreased as the amount of indomethacin was enhanced because the amount of carrier was decreased under amount to promote drug solubility. The drug release form tablets containing 150-mg and 300-mg indomethacin were slightly lower than that from indomethacin capsule. While the drug release from tablet containing 25-mg, 50-mg, 75-mg and 100-mg indomethacin were higher than indomethacin capsule, respectively. The drug release from capsule was only about 20% drug release at 8 hours. Therefore, this solid dispersion system could enhance the release of indomethacin at amount lower than 150-mg when compared with that from 75-mg indomethacin capsule. Xanthan gum played the important role by rapid hydration after contact to dissolution fluid and subsequently to form gel around the tablet and the dissolved drug molecules gradually diffused from the tablet through the developed gel layer into the dissolution fluid. Therefore the dissolved drug molecules inducing with carrier could prolong release by an addition of xanthan gum in the matrix system.

From visual observation, tablet containing 5% xanthan gum showed a core tablet in which the totally hydrated matrix core was evident after 2 hrs of dissolution test. This behaviour suggested that swelling and erosion rates were comparable and that the two mechanisms were both effective in the control of drug release process as described by Maggi, et al. (2002). The external part had a consistence similar to a gel and the inner core was not solid but completely wetted. Initial tablet swelling demonstrated a high hydration of all tablets containing xanthan gum. When a matrix containing a swellable glassy polymer such as xanthan gum contacted with a solvent, a progressive change from the glassy to the rubbery state led to a swelling process as also described by Siepmann, et al. (2002).

The kinetic of indomethacin release from the developed matrices was analyzed using the power law expression. This equation (an empirical equation) gained popularity for analysis of release.
The $n$ value from power law is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms are classified based on the value that $n$ assumes. For a cylinder, the mechanism of drug transport is described by Fickian diffusion when $n = 0.45$. When $0.45 < n < 0.89$, it indicates anomalous (non-Fickian) transport and for values of $n = 0.89$, Case II or zero order release kinetics is indicated.\(^{(14)}\) Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms; the coupling of drug diffusion and polymer relaxation.\(^{(15, 11)}\) The large value of coefficient of determination ($r^2$) or model selection criteria (msc) indicated a superiority of the dissolution profile fitting to mathematical equations. The $r^2$ and msc from curve fitting to power law, first order, Higuchi’s and zero order equations are shown in Table 6. The estimated parameters from curve fitting to power law equation are presented in Table 7. Fitting experimental drug dissolution profiles to power law equation provided high $r^2$ (a range of 0.9913 - 0.9986) and high msc (a range of 4.16 – 5.95), indicating a superiority of this model.

The $n$ value of almost formula was close to 0.45, indicating the Fickian diffusion or nearly tended to Fickian diffusion ($n=0.45$). Release mechanism of formula containing different amount of indomethacin were close to Fickian transport and nearly trend to time-independent. Drug diffusion occurred at the core–gel interface then through this gel.\(^{(13)}\) The erosion of the swollen layer and the dissolution of the matrix itself were also observed. Typically, the diffusion, swelling and erosion were the three most important rate controlling mechanisms for the controlled or sustained release formulations. The drug release from the polymeric system was mostly occurred by diffusion and was best described by the Fickian diffusion. In vitro release data of tablet containing 150-mg and 300-mg indomethacin exhibited the

### Table 6. Comparison of degree of goodness-of-fit from curve fitting of drug dissolution profiles in phosphate buffer pH 6.2 to different release models.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Power law</th>
<th>First order</th>
<th>Higuchi’s</th>
<th>Zero order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>msc</td>
<td>$r^2$</td>
<td>msc</td>
</tr>
<tr>
<td>Capsule</td>
<td>0.9913</td>
<td>4.16</td>
<td>0.9955</td>
<td>2.98</td>
</tr>
<tr>
<td>5 % xanthan gum</td>
<td>0.9985</td>
<td>5.95</td>
<td>0.8996</td>
<td>1.90</td>
</tr>
<tr>
<td>25-mg indomethacin</td>
<td>0.9915</td>
<td>5.03</td>
<td>0.9567</td>
<td>2.34</td>
</tr>
<tr>
<td>50-mg indomethacin</td>
<td>0.9915</td>
<td>5.03</td>
<td>0.9427</td>
<td>2.06</td>
</tr>
<tr>
<td>75-mg indomethacin</td>
<td>0.9985</td>
<td>5.72</td>
<td>0.8995</td>
<td>1.90</td>
</tr>
<tr>
<td>100-mg indomethacin</td>
<td>0.9978</td>
<td>5.55</td>
<td>0.9794</td>
<td>3.52</td>
</tr>
<tr>
<td>150-mg indomethacin</td>
<td>0.9966</td>
<td>5.07</td>
<td>0.9921</td>
<td>4.45</td>
</tr>
<tr>
<td>300-mg indomethacin</td>
<td>0.9986</td>
<td>5.73</td>
<td>0.9986</td>
<td>6.03</td>
</tr>
</tbody>
</table>

### Table 7. Estimate parameter from curve fitting of drug dissolution in phosphate buffer pH 6.2 to power law expression.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$k \pm sd \times 10^{-1}$</th>
<th>$t_l \pm sd \text{ (min)}$</th>
<th>$n \pm sd$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule</td>
<td>0.1232 ± 0.0208</td>
<td>3.12 ± 1.03</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td>5 % xanthan gum</td>
<td>0.0098 ± 0.0011</td>
<td>64.39 ± 4.23</td>
<td>0.51 ± 0.02</td>
</tr>
<tr>
<td>25-mg indomethacin</td>
<td>0.0084 ± 0.009</td>
<td>5.13 ± 0.25</td>
<td>0.56 ± 0.02</td>
</tr>
<tr>
<td>50-mg indomethacin</td>
<td>0.0084 ± 0.009</td>
<td>5.13 ± 0.25</td>
<td>0.56 ± 0.02</td>
</tr>
<tr>
<td>75-mg indomethacin</td>
<td>0.0098 ± 0.0011</td>
<td>64.39 ± 4.23</td>
<td>0.51 ± 0.02</td>
</tr>
<tr>
<td>100-mg indomethacin</td>
<td>0.0680 ± 0.0043</td>
<td>13.62 ± 0.55</td>
<td>0.43 ± 0.01</td>
</tr>
<tr>
<td>150-mg indomethacin</td>
<td>0.0003 ± 0.0003</td>
<td>-63.87 ± 43.60</td>
<td>1.13 ± 0.15</td>
</tr>
<tr>
<td>300-mg indomethacin</td>
<td>0.0005 ± 0.0004</td>
<td>40.03 ± 32.47</td>
<td>0.96 ± 0.12</td>
</tr>
</tbody>
</table>
Indomethacin-Polyethylene Glycol Tablet Fabricated with Mold Technique

best fitted to zero order model with n value > 0.84 hence exhibited Case-II transport. This suggested that more than one mechanism may be involved, i.e., combination of matrix erosion and diffusion of the drug in the hydrated xanthan gum matrices, but approached Case II transport. These results were in agreement with some research works that established a correlation among the swelling, erosion and drug release in hydrophilic matrices elaborated from natural gums as xanthan, karaia and locust bean gum.

Micrographs of indomethacin powder are shown in Figure 2. Indomethacin was formed by plate crystals with smooth borders, but irregularly shaped and this morphology was retained also at small size. The scanning electron micrographs of cross-section of indomethacin tablet containing 75-mg indomethacin and 5% xanthan gum before and after dissolution test are presented in Figure 3. Although some particles were observed in the solid dispersion, most drug should be molecular dispersed in the PEG4000:PEG400 matrix. The tablet containing 5% xanthan gum exhibited the less porosity. Surface of tablet containing 300-mg indomethacin after dissolution test at 5 and 30 min were smooth and homogeneous. Some pore and tablet crack were evident after dissolution test at 240 min and 480 min. These indicated drug diffusion within the porous network. As the drug loading was increased, the interaction of drug crystals with the dissolution medium was decreased since the surface to volume ratio of the drug was decreased and the occlusion of the pores by the drug crystals led to a lower release rate.

![Figure 2. SEM micrographs of indomethacin powder at different magnifications.](image)

![Figure 3. SEM micrographs of tablet containing 75-mg indomethacin and 5% xanthan gum after dissolution test in phosphate buffer pH 6.2 at different time intervals with different magnifications.](image)
Differential scanning calorimetry (DSC) is frequently the thermal analysis technique which can effectively provide the detailed information about both the physical and energetic properties of a substance. The temperature endothermal peak and enthalpy of the prepared system are presented in Table 8. The endothermic peak of pure indomethacin showed apparent at 161.4°C with enthalpy of fusion ($\Delta H$) 106 mJ/g. Similarly, the melting peak of PEG 20000, PEG 4000 and PEG 400 was observed at 58.8, 58.9 and 58.2°C, respectively. Melting peak of all mixtures of PEG 4000:PEG400 were observed in rank of 28.4-42.8°C. Thermogram of 75-mg and 300-mg indomethacin solid dispersion tablet exhibited the endothermic fusion peak at 46.2°C and 50.7°C with an associated fusion enthalpy at 158 mJ/mg and 121 mJ/mg, respectively (Figure 5). The thermograms of the solid dispersion showed the characteristic peak of the carrier matrix, without drug peak indicating that the drug was completely dissolved in the carrier. This alteration of drug in PEG-based SD system has been reported previously by. Thermograms of the PEG-based system showed the characteristic peak of the carrier matrix around 50°C, but without the drug endothermic melting peak, indicating that the drug was changed into amorphous structure. Reverse DSC run was carried out for 75-mg and 300-mg indomethacin SD tablets. The recrystallized exothermal peak of 75-mg indomethacin SD tablet was exhibited but not found in 300-mg indomethacin SD tablet. The exothermic peak of tablets containing 75-mg indomethacin exhibited at 24.7°C after reverse run to -30°C. Because system containing 75-mg indomethacin contained a high ratio of carrier, the carrier was recrystallized which the exothermic peak was occurred. The exothermic peak in system containing 300-mg indomethacin could be not detected. Because the carrier improved solubility of high amount indomethacin, the carrier not remained for recrystallization of indomethacin.
Indomethacin-Polyethylene Glycol Tablet Fabricated with Mold Technique

Table 8. Temperature peak and enthalpy of different systems evaluated by differential scanning calorimetry.

<table>
<thead>
<tr>
<th>No.</th>
<th>Component</th>
<th>Onset (°C)</th>
<th>Peak (°C)</th>
<th>Enthalpy (mJ/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Indomethacin</td>
<td>158.6</td>
<td>161.4</td>
<td>106</td>
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<tr>
<td>2</td>
<td>PEG 20000</td>
<td>58.8</td>
<td>64.2</td>
<td>136</td>
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<tr>
<td>3</td>
<td>PEG 4000</td>
<td>58.9</td>
<td>62.2</td>
<td>172</td>
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<td>4</td>
<td>PEG 400</td>
<td>58.2</td>
<td>59.3</td>
<td>123</td>
</tr>
<tr>
<td>5</td>
<td>Xanthan gum</td>
<td>30.0</td>
<td>58.1</td>
<td>258</td>
</tr>
<tr>
<td>6</td>
<td>PEG 4000:PEG 400 (95:5)</td>
<td>38.5</td>
<td>52.3</td>
<td>108</td>
</tr>
<tr>
<td>7</td>
<td>PEG 4000:PEG 400 (90:10)</td>
<td>38.2</td>
<td>51.4</td>
<td>106</td>
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<tr>
<td>8</td>
<td>PEG 4000:PEG 400 (85:15)</td>
<td>32.7</td>
<td>48.4</td>
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<tr>
<td>9</td>
<td>PEG 4000:PEG 400 (80:20)</td>
<td>30.5</td>
<td>47.1</td>
<td>88.5</td>
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<tr>
<td>10</td>
<td>PEG 4000:PEG 400 (75:25)</td>
<td>28.4</td>
<td>46.8</td>
<td>94.2</td>
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<td>11</td>
<td>PEG 4000:PEG 400 (70:30)</td>
<td>35.7</td>
<td>52.5</td>
<td>142</td>
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<tr>
<td>12</td>
<td>PEG 4000:PEG 400 (65:35)</td>
<td>42.8</td>
<td>51.0</td>
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<td>13</td>
<td>PEG 4000:PEG 400 (60:40)</td>
<td>40.2</td>
<td>50.6</td>
<td>106</td>
</tr>
<tr>
<td>14</td>
<td>PEG 4000:PEG 400 (55:45)</td>
<td>39.1</td>
<td>50.2</td>
<td>108</td>
</tr>
</tbody>
</table>

Indomethacin was presented as an amorphous state in the solid dispersion according to the results of DSC.

Acknowledgment

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References


