Controlled release colon targeted drug delivery systems of non-steroidal anti-inflammatory drug, indomethacin

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This study aimed to investigate the efficacy of both xanthan gum (XG) and guar gum (GG) controlling the release rate of the poorly water soluble drug, indomethacin (IDM) from colon target drug delivery systems. Binary mixtures of the drug and the hydrophilic carrier (XG) in the ratios of 1:1 and 1:2 and tertiary mixture in the ratio of 1:1:1 IDM: XG: GG were prepared using three different approaches namely, physical mixture, co-grinding and solid dispersion. The prepared binary and tertiary systems were compressed into core tablets. The core tablets were evaluated for their drug content, weight variation, hardness, friability and in-vitro dissolution rate study. The dissolution profiles in pH 6.8 buffer solutions revealed that increasing the gum content in the core tablet resulted in a decrease in the IDM release rate. The core tablets were then coated with two different type of coat (inner and outer). The inner coat consisted of guar gum solutions of different concentrations (0.2, 0.4, 0.6, 0.8% w/v) to prevent the drug release in pH 7.4. Tablets were then coated with an enteric coat by dipping in 5% Eudragit (ER L100) ethanolic solution to inhibit the drug release in pH 1.2. The coated tablets were then dried using hot air. The prepared coated tablets were subjected to release rate study which indicated that the release of the drug was inhibited in pH 1.2 whereas; a low percentage of the drug was released in pH 7.4. In pH 6.8, the release profiles showed a sustained release of the drug over 18 h. The coated tablets that showed the promising sustained release profiles were further evaluated in pH 6.8 buffer solution containing rat cecal content to study the effect of bacterial degradation on the polysaccharide gums.

Key words: Indomethacin, xanthan gum, guar gum, co-grinding, solid dispersion, dissolution rate, colon target drug delivery systems.

INTRODUCTION

The traditional non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (Cox-2) inhibitors potentially inhibited polyp development and tumour incidence (Gupta and DuBois, 2001). Cox-2 over expression is thought to play an important role in colon carcinogenesis, as it has been found to be elevated in 40% of colonic adenomas and up to 90% of sporadic CRC (Eberhart et al., 1994; Fujita et al., 1998). Its pharmacological inhibition by NSAIDs is the central event in the chemoprevention of colon cancer (Gupta, 2000;
El-Kamel et al., 2008; Asghar and Chandran 2008; Krishnaiah et al., 2002a). Indomethacin (IDM) is a non-steroidal anti-inflammatory agent with antipyretic and analgesic properties. It is a nonselective inhibitor of COX 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. It has been used in the symptomatic management of painful and inflammatory conditions. Therefore, many researches intended to formulate IDM as a colon drug delivery for the treatment of colorectal diseases as well as for the management of osteoarthritis (Ravi et al., 2008; Amrutkar and Gattani, 2009).

The aim of this study was to formulate controlled release colon drug delivery systems of IDM using hydrophilic carriers; namely xanthan and guar gums in different ratios. Binary mixtures of the drug and the hydrophilic carrier (XG) in the ratios of 1:1 and 1:2 and tertiary mixture in the ratio of 1:1:1 IDM: XG: GG were prepared using three different approaches namely, physical mixture, co-grinding and solid dispersion. The possible interaction between the drug and the gums in both the liquid and solid states was detected by the phase solubility study and the differential scanning calorimetry (DSC), respectively. The prepared binary and tertiary systems were further evaluated for their flow properties and dissolution rates. These mixtures were then compressed into core tablets to study the effect of the included gums being hydrogels upon IDM release from the compressed matrix tablets. Tablets for colon delivery were prepared by coating the core tablets with an inner coat consisting of guar gum solutions of different concentrations (0.2, 0.4, 0.6, 0.8% w/v) to prevent the drug release in pH 7.4 and with an enteric coat by dipping in 5% Eudragit (ER L100) ethanolic solution to inhibit the drug release in pH 1.2. IDM release studies from coated and uncoated tablets were performed in both pH 6,8 buffer solution with and without rat cecal content to show the effect of bacterial degradation on the drug release.

MATERIALS AND METHODS

Indomethacin (γ- polymorphic form) (IDM) was kindly supplied by Pharco Pharmaceuticals, Alexandria, Egypt. Guar gum, (Premcem gums Ltd, India); Xanthan gum (Ultrafine, India); microcrystallinecellulose (Avicol pH 102), (FMC Co., USA); Eudragit (ER L100); polyethylene glycol 400 (European Co. For Pharmaceutical Industries, Egypt); hydrochloric acid 10 N (Prolab, Adwic, Elnasr Pharmaceutical Chemicals Co., Egypt); sodium tribasic phosphate (Chemajet, Alexandria, Egypt). All other chemicals and buffers were of analytical reagent grades.

Preparation of binary and tertiary systems

IDM-XG binary systems were prepared using varying drug concentration of 50 and 33.33% w/w equivalent to drug: polymer ratios of 1:1and 1:2, respectively. The binary systems were prepared using different methods. Physical mixtures (PMs) of drug and polymer were obtained by simply blending with spatula, co-ground (CG) by co-grinding of drug and XG for 30 minutes in a ceramic mortar and solid dispersion (SD) by solvent evaporation technique were prepared. Xanthan gum or mixture of xanthan and guar gums was dispersed in a minimum amount of ethyl alcohol. Solution of IDM in minimum amount of ethyl alcohol was prepared and added to gum dispersion. The rota-vapor (IKA RV10, IKA, Germany) was used to evaporate the solvent and the solid powder was collected. The obtained powder was then sieved, and average particle size of 125 μm was used for further evaluation. The different systems were stored in desiccators till used.

Evaluation of the prepared powdered mixtures

Drug content

To estimate the drug content, an amount of the prepared powders equivalent to 10 mg of IDM were weighed accurately and transferred into 100 ml volumetric flask containing 25 ml ethanol. The flask was shaken vigorously and left to stand for about 6 h, then complete to volume with phosphate buffer (PB) pH 6.8 and left for 24 h. The concentration of IDM was assayed spectrophotometrically at 320 nm against ethanol-buffer mixture (1:3) as a blank.

Differential scanning calorimetry (DSC)

DSC thermograms of pure materials, PMs, CGs and SDs were recorded using Shimadzu differential scanning calorimeter (DSC-60, Shimadzu, Japan). The samples 2-5 mg of the pure drug or the above mentioned samples were weighed carefully and were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25 to 250°C. Thermograms of the samples were obtained using differential scanning calorimeter. Thermal analysis data were recorded using a TA 501 PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N2 was used as purging gas at the rate of 40 ml/min. The heat of fusion of crystallized drug in a LD was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was determined in a separate experiment. The ratio of these fusion energies was used to calculate the percent crystallinity of drug in the LDs and PMs using the following equation:

\[
\text{Percentage (\%) crystallinity} = \frac{\Delta H_s}{\Delta H_c} \times C \times 100
\]

Where, ΔHs and ΔHc are enthalpies of fusion of the sample and pure drug, respectively, and C is the weight fraction of drug in the mixture assuming that the pure drug was 100% crystalline (Rawlinson et al., 1997).

Scanning electron microscopy (SEM)

The surface morphology of IDM, XG, GG, PMs, CGs and SDs were examined under scanning electron microscope (Jeol, JSM-6360LV scanning microscope, Tokyo, Japan). Before microscopy, the dried samples were mounted at carbon tape and were sputter-coated using gold (Jeol, JFC-1100 fine coat ion sputter, Tokyo, Japan). The photomicrographies were taken at an acceleration voltage of 10 kV.

Flow properties

In order to ensure good flow properties of the binary and tertiary
systems, angle of repose measurements (fixed height cone method), Carr’s index and Hausner’s ratio were adopted (Luner et al., 2001). The procedure was done in triplicates and the average angle of repose was calculated for each powder. In the bulk density measurements, fixed weight of each of the powder formulae prepared were placed in graduated cylinder and the volume (V₀) occupied was measured and the initial bulk density (D₀) was calculated. The graduated cylinder was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement; the volume of the powder was then recorded as the final bulk volume (Vₐ), then the final bulk density (Dₐ) was calculated. Carr’s compressibility index was then calculated according to the following equation (Luner et al., 2001):

\[ \text{Carr's index} \% = \frac{D₀ - Dₐ}{D₀} \times 100 \]  

(2)

In addition, Hausner’s ratio was calculated from the following equation:

\[ \text{Hausner's ratio} = \frac{Dₐ}{D₀} \]  

(3)

The experiments were done in triplicate. Carr’s compressibility index and Hausner’s ratio with the corresponding standard deviations for each of the prepared formulae were then calculated.

**In-vitro dissolution study**

IDM dissolution study was evaluated using the USP XXIV dissolution rate apparatus II (Pharmatest, Germany) at a stirring rate of 100 ± 2 rpm. Powders samples containing 75 mg of pure drug or its equivalent amount of PM, CG and SD were placed in 900 ml 0.1 N HCl (pH 1.2) at 37 ± 0.5°C for 2 h then the medium was rendered alkaline to pH 6.8 by the addition of the calculated amount of sodium tribasic phosphate. At predetermined time intervals, 5 ml samples were withdrawn and immediately replaced with an equal volume of pre-heated (37 ± 0.5°C) dissolution medium. All samples were run in triplicate, filtered through 0.45 μm membrane filter and the amount of dissolved IDM was analyzed by spectrophotometer at 320 nm (guar gum did not interfere in the spectrophotometric reading of the drug at 320 nm). The percentage cumulative amount of the drug dissolved was plotted against time.

**Phase solubility studies**

In order to detect any possible interaction between IDM and XG in solution and explain the results of in-vitro dissolution studies, phase solubility experiments were performed. Aqueous solubility of IDM in the presence of xanthan gum was carried out according to the method described by Higuchi and Connors (1965). An excess amount of IDM was added to 10 ml of aqueous solutions containing an increasing concentration of XG (0, 2, 4, 6, 8 and 10 mM) in screw-capped vials. The suspensions were shaking in a thermostatically controlled water bath (type 1083, GFL GmbH, Burgwedel, German) at 37 ± 0.5°C for 48 h. After equilibrium had been attained (2 days), aliquots were withdrawn, filtered through 0.45 μm membrane filters, suitably diluted and analyzed for IDM using UV spectrophotometer at 320 nm (xanthan gum had no effect on the spectrophotometric reading at 320 nm). The apparent stability constant (Kₛ) of 1:1 complexes was calculated from the linear phase solubility diagram obtained by plotting the molar concentration of IDM in the solution vs. XG molar concentration according to the equation:

\[ Kₛ = \text{Slope}/S₀ (1\text{-slope}) \]

Where, S₀ is the intrinsic solubility of the drug in absence of XG. The solubilization efficiency of XG was calculated as the ratio of IDM aqueous solubility at the highest XG concentration used and IDM intrinsic solubility in pure water.

**Preparation of core tablets**

The drug binary and tertiary mixtures (125 μm) were prepared according to Table 1, and were compressed into core tablets using single punch tablet machine with punch of 9 mm in diameter to a tablet hardness of 7 Kg/cm².

**Drug content of core tablets**

To estimate the drug content, 10 tablets of each IDM formulation were weighed accurately, triturated and transferred into 500 ml volumetric flask containing 250 ml ethanol. The flask was shaken vigorously and left to stand for about 6 h, then complete to volume with phosphate buffer pH 6.8 and left for 24 h. The concentration of IDM was assayed spectrophotometrically at 320 nm against buffer as a blank.

**Preparation of coated tablets**

The prepared core tablets were coated with two different coats; a primary or an inner coat and an outer coat. The inner coat consisted of guar gum solutions of different concentrations (0.2, 0.4, 0.6, 0.8%) prepared by dissolving the appropriate weight of guar gum in a plasticized 2% cellulose acetate solution in acetone: methanol solvent system. PEG 400 was used as a plasticizer. The outer coat was an enteric coat using Eudragit ER L100 polymer. Tablets were coated by dipping in 5% ER L100 ethanolic solution and then dried using hot air (10 coats of each coating solution were applied which were equivalent to 10% increase in tablet weight).

**In-vitro release study of core tablets**

Dissolution rate study of IDM core tablets was carried out using the USP XXIV dissolution rate apparatus II (Pharmatest, Germany) at a stirring rate of 100 ± 2 rpm. Core tablets were placed in 900 ml 0.1 N HCl (pH 1.2) at 37 ± 0.5°C for 2 h then the medium was rendered alkaline to pH 6.8 by the addition of the calculated amount of sodium tribasic phosphate. At predetermined time intervals, 5 ml samples were withdrawn and immediately replaced with an equal volume of pre-heated dissolution medium at 37±0.5°C. All samples were run in triplicate, filtered through 0.45 μm membrane filter and the amount of dissolved IDM was analyzed by spectrophotometer at 320 nm. The percentage cumulative amount of the drug released was plotted against time.

**In-vitro dissolution of coated tablets**

The same procedure mentioned above was followed. Coated tablets were placed in 900 ml 0.1 N HCl (pH 1.2) at 37±0.5°C for 2 h then the medium was rendered alkaline to pH 7.4 by the addition of the calculated amount of sodium tribasic phosphate and the release study was continued for another 3 h. The tablets were then placed in pH 6.8 for 24 h. At predetermined time intervals, 5 ml samples were withdrawn and immediately replaced with an equal
volume of pre-heated dissolution medium. All samples were run in triplicate, filtered through 0.45 µm membrane filter and the amount of released IDM was analyzed by spectrophotometer at 320 nm. The percentage cumulative amount of drug released was plotted against time.

Preparation to mimic enzymatic media of the colon (rat cecal matter, RCM)

A group of 5 rats each weighing (150-200 g) and maintained on normal diet (soaked grain) were used to induce enzymes specifically acting on guar gum. The rats were treated with 1 ml of 2% w/v guar gum dispersion using oral needle for 7 days. The rats were then killed using CO₂ asphyxiation, 45 min before the study. The abdomen were opened, the ceca were traced, ligated at both the ends, dissected and immediately transferred into phosphate buffer of pH 6.8, previously bubbled with CO₂. The cecal bags were opened, their content individually weighed, pooled and then suspended in pH 6.8 to give 4% w/v dilution. As the cecum is naturally anaerobic, all operations were carried out under CO₂ ion, 45 min before the study. (Rama et al., 1998).

In vitro drug release in rat caecal matter

Drug release studies in the presence of rat caecal content were also carried out using USP dissolution test apparatus II, but with slight modification. After completing test in Ph 1.2 for 2 h and pH 7.4 for 3 h, baskets containing tablets were immersed in 250 ml beaker containing phosphate buffer solution (pH 6.8) and rat caecal content maintained in the jars of the dissolution apparatus for up to 24 h. Samples of 5ml each were withdrawn at different time intervals (6, 7, 8, 9, 24 h), filtered using filter paper and assayed spectrophotometrically for IDM at 320 nm. The same volume of fresh medium bubbled with CO₂ was added after each withdrawn sample (Krishnaiah et al., 2002b).

RESULTS AND DISCUSSION

Drug content of the prepared mixtures

The drug content of the prepared binary systems were found to be in the range of 97.23 ± 0.35 to 99.96 ± 0.29% indicating that the present methods for the preparation of solid systems can be applied with a high content uniformity.

Differential scanning calorimetry (DSC)

The DSC thermograms of IDM (Figure 1a) exhibited sharp endothermic peak at 161.17°C corresponding to its melting point, such sharp endothermic peaks signify that IDM used was in pure crystalline state (Mahmoud et al., 2009). XG and GG being amorphous anhydrous carriers did not show any characteristic peaks except broad band (Figure 1b). All the binary mixtures prepared by different methods revealed the presence of the drug peak with slight shift in the melting temperature of the drug along with significant decrease in the endothermic peak intensity (Figure 1 and Table 1). The intensity of the drug peak is reduced in the drug: XG ratio of 1:1 further increase in the gum content (1:2 drug: gum ratio) showed slight decrease in the intensity of the drug peak. No complete disappearance was noticed indicating partial loss of drug crystallinity. SD binary mixtures showed the highest reduction in the intensity of the IDM fusion peak. This modification of the DSC profile of the drug may be related to a chemical or physical interaction between the drug and XG or the possible formation of an amorphous system. In case of tertiary systems PM3, CG3 and SD3, the incorporation of GG potentiated the amorphization characteristic of XG. The order of reducing the intensity of the drug peak was as follow SD3 >CG3>PM3>IDM. The drug peak was still detectable in the SD3 system but with a significant reduction of drug crystallinity assuming a partial dispersion at a molecular level in the solid product, but did not seem to be indicative of a true complex formation. The enthalpy of drug fusion decreased sharply with the incorporation of the carrier indicating that the drug lost an appreciable percentage of its crystallinity (Table 1). For example, the heat of fusion of the pure IDM was significantly reduced from -380.81 to -194.83, -159. 61 and -148.03 in case of PM1, CG1 and

<table>
<thead>
<tr>
<th>Formula</th>
<th>Peak °C</th>
<th>Heat (mJ)</th>
<th>Crystallinity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDM</td>
<td>161.17</td>
<td>-380.81</td>
<td>100</td>
</tr>
<tr>
<td>IDM: X G (1:1)</td>
<td>159.63</td>
<td>-194.83</td>
<td>51.19</td>
</tr>
<tr>
<td>IDM: X G (1:2)</td>
<td>159.72</td>
<td>-184.42</td>
<td>48.43</td>
</tr>
<tr>
<td>IDM: XG: GG (1:1:1)</td>
<td>159.43</td>
<td>-145.67</td>
<td>38.25</td>
</tr>
<tr>
<td>IDM: X G (1:1)</td>
<td>159.32</td>
<td>-159.61</td>
<td>41.91</td>
</tr>
<tr>
<td>IDM: X G (1:2)</td>
<td>158.97</td>
<td>-138.36</td>
<td>36.33</td>
</tr>
<tr>
<td>IDM: XG: GG (1:1:1)</td>
<td>159.30</td>
<td>-133.13</td>
<td>34.96</td>
</tr>
<tr>
<td>IDM: XG (1:1)</td>
<td>159.20</td>
<td>-148.03</td>
<td>38.87</td>
</tr>
<tr>
<td>IDM: XG (1:2)</td>
<td>159.23</td>
<td>-88.76</td>
<td>23.31</td>
</tr>
<tr>
<td>IDM: XG (1:1:1)</td>
<td>159.78</td>
<td>-87.78</td>
<td>23.05</td>
</tr>
</tbody>
</table>

Table 1. Thermoanalysis data of IDM and its binary and tertiary systems.
Figure 1. A, DSC thermogram of indomethacin (IDM), xanthan gum (XG) and their physical and co-grinding mixtures in different ratios. A: IDM, B: XG, C: IDM: XG 1:1 physical mixtures (PM), D: IDM: XG 1:2 PM, E: IDM: XG 1:1 CG, F: IDM: XG 1:2 CG. B, DSC thermogram of indomethacin (IDM), xanthan gum (XG), guar gum and their physical mixtures (PM), co-grinding (CG) and solid dispersion (SD) in ratio, 1:1:1. A: IDM, B: XG, C: guar gum, D: PM, E: CG, F: SD. C, DSC thermogram of indomethacin (IDM), xanthan gum (XG) and their solid dispersion (SD) in different ratios. A: indomethacin, B: xanthan gum, C: 1:1 SD, D: 1:2 SD.
SD1, respectively.

**Scanning electron microscopy (SEM)**

Micrographs of Indomethacin powder are shown in (Figure 2a-g). IDM was formed of plate crystals with smooth borders, but irregularly shaped. Both XG and GG showed irregular shaped particles. PM of 1:2 IDM: XG micrograph demonstrated the plate crystals of IDM in combination with the irregular shaped XG particles. Co-ground mixture of 1:2 IDM: XG ratio showed large particles formed of aggregated small particles. Upon grinding, particle size reduction occurred which resulted in the formation of charged particles. These charged particles were aggregated through electrostatic attraction. The micrograph showed a conversion from the crystalline to the amorphous state. In case of 1:2 IDM: XG solid dispersion, the particle shape becomes completely different from the original shape of the drug particles.

**Flow properties**

Angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles. Its value will be high if the powder is cohesive and low if the powder is non-cohesive. Table 2 represents flowability parameters of IDM and prepared powdered mixtures using different techniques in terms of angle of repose, Carr index and Hausner’s ratio. PM3, CG2, CG3, SD1, SD2 and SD3 formulations demonstrated (θ) values in the range of 29.15 to 39.42 and Carr’s index up to 21, indicating that these formulations were systems with acceptable flowability. The prepared mixtures were found to have significantly lower angle of repose (P= 0.05) in comparison to the raw crystals of IDM, which could be due to the irregular shaped crystals of IDM, which hindered the uniform flow of crystals. The reason for the excellent flowability of prepared mixtures was due to significant reduction in interparticle friction because of their shape modification from crystal state to amorphous state or fragmented particles (Table 2). In addition, Hausner found that the ratio D1 /D0 was related to the inter particle friction, so, he showed that powders with low interparticle friction, had ratios of approximately 1.250 indicating good flow (Fahmy and Kassem, 2008). SD3 showed the lowest angle of repose, Carr’s index and Hausner’s ratio. Good flow properties were in the order of SD3 > SD2 > SD1 > CG3 > CG2 > PM3.

**In-vitro dissolution and phase solubility studies**

The effect of varying drug: gum ratios and method of preparation of drug: polymer mixtures on IDM dissolution rate in both pH 1.2 and 6.8 is shown in (Figures 3, 4 and 5). In 0.1 N HCl (pH 1.2), IDM exhibited a tendency to form large aggregates and floated on the surface of dissolution medium, due to its hydrophobic nature. The aggregation caused reduction in effective surface area of drug particles available for dissolution which resulted in 9.14% drug release after 2 h of dissolution test.

In general, XG is present predominantly in a unionized state at low pH, whereas XG is ionized under dilute acidic and alkaline conditions. This difference in the ionization state of xanthan gum in the dissolution media affected hydrogel formation and consequently, the retardation of drug release. When XG was present in a unionized state, an intramolecular hydrogelation was prevented due to the absence of ionic bonds, resulting in a considerable release of IDM in 0.1 N HCl (Ramanji et al., 2010).

It was observed that drug dissolution progressively improved with increasing the polymer proportion in the mixture and reached the highest values at the 1:2 drug: XG ratio. This result is evidenced by the phase solubility study. The phase solubility profiles for the IDM- XG systems are presented in Figure 6. The plot indicates a typical A∞-type (positively deviating isotherms) solubility curve as classified by Higuchi and Connors (1965). The diagram shows an increase in IDM solubility occurred as the amount of the complexing agent, XG increased. This is due to soluble complex formation which might be through hydrogen bonding between the hydroxyl (OH) groups XG and the carboxylic (COOH) group of IDM, thereby increasing the total amount of the IDM in the solution. Furthermore, A∞-type phase solubility diagram is formed when more than one molecule of the complexing agent is found in the complex (Luner et al., 2001). Positive deviation from linearity (A∞-type systems) are thought to indicate formation of complexes that are first order with respect to the drug but second or higher order with respect to the complexing agent (Karsten, 2009). The A∞-type phase solubility curve revealed the formation of a complex of IDM in 1:2 stoichiometric ratios with XG. The stability constants (K∞) for the complex at 37°C ± 0.5, assuming a 1:2 stoichiometric ratio, calculated from the slope of preliminary straight line portion of the phase solubility curve (333.733 mM⁻¹), demonstrated the relative affinity of the drug for the polymer and good complexation ability (Najib and Suleiman, 1989). This also suggests that there is an increase in the dissolution profile which would certainly increase bioavailability of IDM.

The slight increase in drug dissolution shown by simple physical mixtures could be due to a reduction of the interfacial tension between the hydrophobic drug particles and the dissolution medium, owing to the presence of the hydrophilic polymer, thus increased the wettability of the drug (Najib and Suleiman, 1989). It could also be due to the increased surface area available for dissolution being carried on by the hydrophilic amorphous XG. The high
Figure 2. Scanning electron micrographs. A, Indomethacin; B, xanthan gum; C, guar gum; D, 1:1 PM of IDM: XG; E, 1:2 PM of IDM: XG; F, 1:2 CG of IDM: XG; G, 1:2 SD of IDM: XG
rate of drug dissolution shown by the solid dispersion could be attributed to the intimate physical contact between IDM and hydrophilic carrier. It might also be due to the better dispersion of the drug on the surface of XG. Whereas in case of co-ground mixtures, the increase in drug dissolution rate could be due to particle size reduction brought about by the mechanical treatment and to a decrease in drug crystallinity during co-grinding with the amorphous carrier (Ramanji et al., 2010). These finding were in agreement with the results of the thermoanalysis studies, confirming that the best dissolution performance of SD products is mainly attributable to the almost higher degree of drug amorphization achieved in these systems (Figure 1). The incorporation of GG in the different formulations PM3, CG3 and SD3 increased the drug dissolution rate. The improvement of dissolution may be due to the swelling nature of the guar gum which resulted in increasing the
extensive surface of the gum during dissolution, and the dissolution rate of deposited drug was markedly enhanced. In addition, the hydrophilic and amorphous nature of the GG may be attributed to the increase in drug dissolution rate (Suchetha et al., 2011; Shah et al., 2010).

In phosphate buffer pH 6.8, it was expected that the drug dissolution rates from the various formulations could be reduced as a result of the intramolecular hydrogelation of XG being in the ionized state in alkaline medium (Ramanji et al., 2010). The drug dissolution rate increased as the acidic pH of medium was shifted to alkaline pH. This result can be attributed to the solubility of the acidic drug IDM in alkaline medium although the carrier in its ionized state.

The results of the dissolution rate studies revealed that the drug dissolution increased as the XG content increased in the different formulations. Physical mixture showed a slight increase in drug dissolution rate that might be due to the presence of the drug particle individually dispersed in the dissolution medium leading to an increase in its surface area. Consequently, this increase in IDM surface area increased its dissolution rate (Elkhodairy et al., 2011). Whereas, in the co-ground
Table 2. Flowability parameters of IDM and the different binary and tertiary mixtures.

<table>
<thead>
<tr>
<th>Formulae</th>
<th>Angle of repose (θ)˚</th>
<th>Carr’s Index</th>
<th>Hausner’s ratio</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
<td>49.32±0.004</td>
<td>40.32±0.001</td>
<td>1.99±0.011</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>32.45±0.006</td>
<td>20.00±0.003</td>
<td>1.37±0.012</td>
</tr>
<tr>
<td>PM1</td>
<td>43.98±0.010</td>
<td>29.14±0.004</td>
<td>1.62±0.021</td>
</tr>
<tr>
<td>PM2</td>
<td>40.62±0.021</td>
<td>28.32±0.002</td>
<td>1.60±0.012</td>
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<tr>
<td>PM3</td>
<td>39.42±0.031</td>
<td>21.32±0.003</td>
<td>1.23±0.031</td>
</tr>
<tr>
<td>CG1</td>
<td>42.08±0.024</td>
<td>27.98±0.012</td>
<td>1.67±0.014</td>
</tr>
<tr>
<td>CG2</td>
<td>36.94±0.030</td>
<td>18.32±0.024</td>
<td>1.15±0.012</td>
</tr>
<tr>
<td>CG3</td>
<td>36.33±0.006</td>
<td>18.67±0.012</td>
<td>1.15±0.025</td>
</tr>
<tr>
<td>SD1</td>
<td>34.61±0.016</td>
<td>16.73±0.021</td>
<td>1.11±0.015</td>
</tr>
<tr>
<td>SD2</td>
<td>32.31±0.023</td>
<td>15.69±0.026</td>
<td>1.12±0.013</td>
</tr>
<tr>
<td>SD3</td>
<td>32.15±0.024</td>
<td>15.32±0.014</td>
<td>1.11±0.012</td>
</tr>
</tbody>
</table>

Table 3. Composition of the different core tablets.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Ingredients in mg</th>
<th>IDM</th>
<th>XG</th>
<th>GG</th>
<th>Avicel pH 102</th>
<th>Mag. St.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Table (CT)</td>
<td></td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>300</td>
<td>5</td>
</tr>
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<td>1:1 PM (PM1)</td>
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<td>1:1:1 PM (PM3)</td>
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<td>1:2 PM (PMG)*</td>
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<td>1:1 CG (CG1)</td>
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<td>1:2 SD (SD2)</td>
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PMG*: 1:2 IDM: GG physical mixture. Total tablet weight: 380 mg.

mixture, the drug crystals were reduced in size during grinding leading to the increased dissolution rate compared to IDM original crystals. In case of SDs, in the dissolution medium, the drug particles were present in the form of amorphous powder of increased solubility and dissolution rate as compared to its original crystalline state. Formulations of SD showed an improved release behavior of IDM in comparison with the PM and CG mixtures. This could be explained by reducing the particle size and consequent increase in surface area, decreased crystallinity occurring during the formulation. Moreover, presence of the drug in a molecular dispersion in hydrophilic carrier matrix increased the wettability and the surface available to dissolution by reducing the interfacial tension between the hydrophobic drug and dissolution medium (Mortada, 2006).

The obtained results could be explained on the basis that in alkaline medium ionization of the acidic groups of both IDM and XG took place leading to the formation of anionic species. The absence of ionic interaction between the anionic species resulted in the presence of the drug in a free state in the dissolution medium. Thus, the high affinity of the anionic drug to the cationic medium resulting in liberation of the drug from the hydrogel formed, thus overcome the drug release retardation effect of the carrier. The replacement of half the amount of XG with GG reduced the hydrogel capacity of XG and the presence of GG which resulted in increasing the swelling capacity of the gum mixture over its hydrogelation power. This is the cause for the increased drug release in case of 1:1:1 IDM: XG: GG mixtures compared to 1:2 IDM: XG mixtures.

Evaluation of IDM tablets

Drug content of core tablets

The drug content of the prepared binary systems were found to be in the range of 95.73 ± 0.15 to 99.86 ± 0.19%.
**In-vitro release study of core tablets**

Figures 7 and 8 illustrate the effect of varying drug/gum ratios and method of preparation of drug powder on the amount of IDM released from tablets prepared from either PM, CG and SD mixtures by direct compression technique in 0.1N HCl for 2 h then in phosphate buffer (pH 6.8) for 24 h at 37°C ± 0.5. It is clear that the drug release rate from the control IDM tablet in pH 1.2 was very low because of the acidic nature of the drug. Increasing the pH of the medium from pH 1.2 to pH 6.8, the amount of drug released increased from 1.3 to 47 mg% (Table 4). The figures showed high retardation of IDM release from gum containing tablets compared to IDM control tablets. It is obvious that the release of IDM from tablets prepared of the SD was higher than that of tablets prepared by direct compression of the co-ground and physical mixtures. PM has higher retardant release rate than CG and SD, this was evident by the increase in $T_{25\%}$ of PM1 (3-4 h) compared to that of the correspond-
ing CG1 (2-3 h) and SD1 (1-2 h) (Table 4). This may be explained on the basis that tablets prepared by CG presented the drug particles in the reduced form and those prepared by SD showed higher wettability increasing front erosion and hence increased drug release. It was also observed that an inverse relationship was found between amount of gum and release rate of IDM. Increasing the gum concentration from 1:1 to 1:2 caused more retardation of drug release, as evidenced by lower dissolution efficiency (DE%) values and higher T25% values (Table 4). This result was not in agreement with that obtained in case of powder mixtures. The obtained results could be explained as the gum concentration increased, the thickness of the gel layer increased and the diffusion path length increased leading to delay in drug release. Hydration of individual xanthan gum particles causes swelling of each particle. The swollen particles coalesced together, resulting in a continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium (Yeole et al., 2006).

It was reported that Xanthan gum has the highest water uptake compared to HPMC and guar gum (Sinha et al., 2004). Based on this consideration, 3 mechanisms were suggested namely; swelling, erosion and then diffusion, which synchronized together forming gel layer of constant thickness. Accordingly, a zero-order release could be expected (Sinha et al., 2004). The higher water uptake but lower erosion of the tablets may describe the lower release rate of IDM (Lu et al., 1991). Incorporation of guar gum caused less retardation of drug release than pure xanthan gum. DE% values increased with decreasing T25% values as shown in Table 2. A combination of the anionic xanthan gum and the non ionic guar gum seems to produce a synergistic increase in viscosity. This may be attributed to the stronger hydrogen bonding between the carboxyl groups of the xanthan and the hydroxyl groups of guar gum, leading to stronger physical cross-linking between the polymers. Interaction between nonionic and ionic polymers has been reported to be greater than between molecules of the same species (Cerdeira et al., 1998).

**In-vitro drug release of coated tablets**

Core tablets that showed a promising results in sustaining the drug release namely PM 2 XG, PM 2 GG, PM 3, CG 2 and SD 2, were coated and subjected to dissolution rate studies. The obtained results are presented in Figures 9a and 9b. It was found that coated tablets prepared from the physical mixtures showed the highest retardation rate compared to those prepared from CG and SD mixtures. Therefore, tablets prepared from PM mixtures were selected for studying the release in the presence of rat cecal content, because bacteria accelerate the degradation of gums resulted in increase in drug release rate. Figure 10 shows coated tablets of PM2 and PM3 mixtures release profiles in pH 6.8 compared to that in the rat cecal content. It is obvious that the coating prevented the release in pH 1.2 and a slight release was observed in pH 7.4 then the presence of the rat cecal content (pH 6.8) increased the drug release rate to about three folds. The release profiles of IDM from the coated tablets indicated that these formulations could be used as extended colon targeted drug delivery systems.

**Conclusion**

It can be concluded that mixtures of xanthan and guar gum with different ratios could be used to modulate the
drug release rate from either powder mixtures or from compressed tablets. Xanthan gum showed higher drug release retardation from tablets compared to guar gum. Physical mixture approach demonstrated the slowest drug release compared to co-ground and solid dispersion techniques. Core tablets prepared from 1:2 drug: xanthan gum and 1:1:1 drug: xanthan gum: guar gum showed the highest drug release retardation among the other formulations under investigation. In addition, release profiles of IDM from coated tablets showed that tablets prepared from physical mixtures had the highest release retardation effect. Therefore, they are selected for formulating colon target drug delivery systems since the drug release in the colon will be increased in the presence of the rat cecal content. Tablets of PM2 and PM 3 could be used as once a day colon target drug delivery systems.

Figure 9. Release profiles of IDM from uncoated and coated tablets prepared from A, physical mixtures; B, CG and SD mixtures.
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ABBREVIATIONS

NSAIDs, Non-steroidal anti-inflammatory drugs; Cox, cyclooxygenase; IDM, indomethacin; XG, xanthan gum; GG, guar gum; DSC, differential scanning calorimetry; PMs, physical mixtures; CG, co-ground; SD, solid dispersion; SEM, scanning electron microscopy; DE%, dissolution efficiency.

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