DISSOLUTION AND COMPATIBILITY STUDY OF BINARY AND TERNARY INTERACTIVE MIXTURES OF INDOMETHACIN: COMPARISON WITH COMMERCIAL AVAILABLE CAPSULES

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Abstract: The main objective of this work was to use Weibull distribution function and Baker-Lonsdale models to study the dissolution kinetics of prepared binary and ternary interactive mixtures containing indomethacin in comparison with three commercially available capsules of indomethacin, namely, Rothacin®, Indomin® and Indylon®. Differential scanning calorimetry (DSC) in conjunction with cloud point method was used to study the compatibility of indomethacin with polyvinylpyrrolidone (PVP) and lactose and to provide an explanation(s) for the insignificant increase in dissolution rate observed in the ternary interactive mixture as well as for the reduction in the dissolution rate observed from the binary system in our previous study. Results showed that the Weibull distribution function equation was the best fit to the dissolution data for all formulations used in this study. DSC curves showed that the decrease in dissolution rate from the binary and ternary interactive mixtures was due to incompatibility of indomethacin with PVP. Also DSC curves showed that lactose was compatible with indomethacin and that lactose was used as excipient in two commercial products (Rothacin® and Indylon®). Results from the cloud point method showed that the addition of indomethacin to 1% PVP solution containing ammonium sulfate (with cloud point at 76°C) reduces the cloud point of PVP indicating that there is an interaction between indomethacin and PVP, while the cloud point of 1% PVP containing ammonium sulfate was not affected by the addition of lactose.

Keywords: indomethacin, ternary interactive mixture, compatibility, polyvinylpyrrolidone, lactose, DSC

Indomethacin, a commonly used non-steroidal anti-inflammatory drug (NSAID), shows slow dissolution and high permeability through stomach. It is used to reduce pain/swelling involved in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, gout, bursitis and headaches. According to the Biopharmaceutics Classification System, indomethacin is classified as class II drug in which the dissolution is rate limiting step in the process of drug absorption. Because water-insoluble drugs often show weak bioavailability, improvement in solubility and/or dissolution rate is a very important consideration for drug development process (1-3).

Micronization, solid dispersion, solubilization by surfactants and use of complexing agents are some of the methods which have been used to enhance dissolution of water insoluble drugs. Previous studies have found that interactive mixtures prepared from finally divided poorly water soluble drug particles with coarse carrier increased the dissolution rate, compared with the micrionized particles alone, but agglomeration was not totally eliminated (4-7). Research in this area suggested that the use of micronized excipient as a ternary additive might enhance the dissolution of agglomerated micronized drugs (7-10). There is evidence from the literature that addition of fine lactose to the interactive mixture containing indomethacin resulted in an increase in the in vitro dissolution of drug from interactive mixture (11, 12). However, in our previous study, we showed that the release of indomethacin was reduced from binary system containing 10% PVP as additive and the release was increased after the addition of 10% fine lactose to the binary system to prepare the ternary interactive mixture. In the same study, results showed that the release of indomethacin from commercially available capsules was higher (12). It is well known that the decrease in the dissolution rate occurs due to many factors such as particle size of drug, type and amount of excipients used, particle strength, drug morphology, drug - excipient incompatibility, drug-
fine lactose ratio and many other factors (12-19). A number of experimental techniques (i.e., DSC, X-ray powder diffraction, optical and electron microscopy, FT-IR spectroscopy, cloud point method, equilibrium dialysis and solubility measurement etc.) have been used to investigate the interaction between drug and excipients (20-24). DSC is a quick technique to investigate excipient - drug incompatibility derived from the appearance, disappearance or shifts of peaks and/or variation in the corresponding ΔH (enthalpy of transition). The cloud point method is a simple and good reproducible method used to study the interaction between low molecular weight compounds and other water soluble macromolecules (25, 26).

The aim of this work was to study the dissolution kinetics of all formulations (binary system, ternary interactive mixture and three commercially available capsules) by using Weibull distribution function and Baker-Lonsdale models. DSC was used to study the possibility of drug – excipient interaction and to give an explanation(s) for the release reduction observed in the binary and ternary interactive mixtures containing indomethacin. In addition, DSC curves obtained for the

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weibull equation</th>
<th>Baker-Lonsdale model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>Time scale (a)</td>
</tr>
<tr>
<td>Indomin</td>
<td>0.97</td>
<td>1.44</td>
</tr>
<tr>
<td>Indylon</td>
<td>0.95</td>
<td>1.97</td>
</tr>
<tr>
<td>Rothacin</td>
<td>0.95</td>
<td>2.10</td>
</tr>
<tr>
<td>Binary system</td>
<td>0.85</td>
<td>2.52</td>
</tr>
<tr>
<td>Ternary mixture</td>
<td>0.98</td>
<td>2.50</td>
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</table>

Figure 1. A linear plot of dissolution data in accordance with the Weibull distribution function model: Indomin (○), Indylon (●), ternary interactive mixture (x), binary mixture (x) and Rothacin (x)
Table 2: Data for melting onset, melting point, endset of melting and enthalpy of fusion obtained from DSC curves for micronized indomethacin mixtures and commercially available capsules.

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin melting onset $T_m/°C$</th>
<th>Indomethacin peak of melting $H_m/°C$</th>
<th>Indomethacin endset of melting $T_m/°C$</th>
<th>Indomethacin enthalpy of fusion $J/g$</th>
<th>Lactose onset $T_m/°C$</th>
<th>Lactose peak $H_m/°C$</th>
<th>Lactose endset $T_m/°C$</th>
<th>Lactose enthalpy $J/g$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin (micronized)</td>
<td>159.64</td>
<td>162.27</td>
<td>166.16</td>
<td>93.86</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indomethacin + PVP (90 : 10)</td>
<td>156.8</td>
<td>160.13</td>
<td>163.37</td>
<td>101.09</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indomethacin + 50% PVP (50 : 50)</td>
<td>133.82</td>
<td>144.88</td>
<td>160.97</td>
<td>49.44</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indomethacin + Lactose (90 : 10)</td>
<td>159.27</td>
<td>161.78</td>
<td>164.75</td>
<td>65.06</td>
<td>*Deh. 145.51</td>
<td>148.16</td>
<td>151.31</td>
<td>2.6</td>
</tr>
<tr>
<td>Indomethacin + Lactose (50 : 50)</td>
<td>159.01</td>
<td>161.67</td>
<td>166.0</td>
<td>61.52</td>
<td>*Deh. 144.63</td>
<td>148.26</td>
<td>152.74</td>
<td>128.49</td>
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<tr>
<td>Binary system</td>
<td>-</td>
<td>155.88</td>
<td>-</td>
<td>-</td>
<td>*Deh. 140.16</td>
<td>145.92</td>
<td>153.2</td>
<td>91.62</td>
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<tr>
<td>Ternary system</td>
<td>166.90</td>
<td>171.85</td>
<td>176.62</td>
<td>3.38</td>
<td>*Deh. 155.23</td>
<td>158.06</td>
<td>160.30</td>
<td>2.75</td>
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<tr>
<td>Rothacin</td>
<td>-</td>
<td>157.0</td>
<td>-</td>
<td>-</td>
<td>*Deh. 144.42</td>
<td>147.99</td>
<td>152.59</td>
<td>58.59</td>
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<tr>
<td>Indomin</td>
<td>148.73</td>
<td>154.89</td>
<td>157.67</td>
<td>6.44</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Indylon</td>
<td>-</td>
<td>157.95</td>
<td>-</td>
<td>-</td>
<td>*Deh. 144.25</td>
<td>149.08</td>
<td>155.06</td>
<td>70.09</td>
</tr>
<tr>
<td>Lactose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>*Deh. 143.17</td>
<td>148.74</td>
<td>154.23</td>
<td>31.46</td>
</tr>
</tbody>
</table>

*Dehydration, **Decomposition
commercially available capsules of indomethacin (Rothacin®, Indomin® and Indylon®) were compared with the binary and ternary interactive mixtures prepared in this study. Finally, the cloud point method was used to support results obtained from DSC concerning drug – excipient interaction.

EXPERIMENTAL

Materials

Commercial indomethacin capsules (Rothacin®, Indomin® and Indylon®) were purchased from the Saudi market. Lactose monohydrate and povidone (PVP) were obtained from Sigma, USA. Indomethacin was donated by Deef (Deef, Qassim, Kingdom of Saudi Arabia) and originally manufactured by Albemarle (USA). Fine lactose was prepared by manually grinding lactose monohydrate using a mortar and pestle and then sieving it using a standard stainless steel sieve (45 µm).

Preparation of binary and ternary interactive mixtures

Lactose-povidone granules and ternary interactive mixture were prepared as described by Allahham and Maswadeh (12). In brief, the lactose-povidone granules were prepared from lactose and povidone in a 9 : 1 ratio by wet granulation using a 10% (w/w) povidone solution. The wet granules were tray-dried and dry granules were lightly comminuted using a mortar and pestle and then sieved to obtain the required size fraction (125–250 µm). The binary interactive mixtures were prepared by weighing the required amount of micronized indomethacin (with volume mean diameter of 12.20 µm) and placing it between two equal layers of the coarse carrier in a glass vial, making the total weight up to 2.5 g with carrier and then shaken vigorously for 5 min by hand. Ternary interactive mixtures were prepared by weighing the required amounts of drug and the ternary additive (fine lactose with volume mean diameter of 22.93 µm) and placing them between two equal layers of coarse carrier in a glass vial, making the total weight up to 2.5 g with carrier. The glass vial was then turned over and shaken in the same way as described for the binary interactive mixture.

In vitro dissolution study

In vitro dissolution for all indomethacin capsules (formulated and commercial) was evaluated as described in Allahham and Maswadeh (12).

Differential scanning calorimetry (DSC)

DSC runs of all materials and mixtures used for the preparation of binary and ternary interactive mixture as well as commercially available capsules were performed by using DSC-60 (Shimadzu, Japan). The thermal profiles of these materials were measured by DSC using 4 mg of sample in crimped aluminum pans and a heating rate of 10°C/min.

Cloud point study

The cloud point method was used to study the interaction between indomethacin and PVP.
Reduction of cloud point for 1% PVP solution was performed by the addition of ammonium sulfate. The cloud point temperatures (CPT) were obtained by placing the test tubes each containing 10 mL of 1% PVP solution containing ammonium sulfate with 2, 4, 6 and 8 mg indomethacin into a temperature-controlled bath. The sample solutions were heated to a temperature where cloudy appearance was visualized. Typically, it was observed that the solution turns completely turbid within one degree. The temperature at the first sign of the turbidity was taken as the CPT.

RESULTS AND DISCUSSION

The Weibull distribution function and Baker-Lonsdale equations were used to study the mechanism of drug release from the binary system, ternary interactive mixture and three commercially available capsules of indomethacin namely, Rothacin®, Indylon® and Indomin®.

The Weibull distribution function is a general empirical equation that can be successfully applied to almost all kinds of dissolution curves and is commonly used in these studies (27-31). The linear form of Weibull equation is expressed as (32):

\[
\log[-\ln (1 - m)] = b \log (t - T) - \log a
\]  

(1)

In this equation, the scale parameter, \(a\), defines the time scale of the process. The shape parameter, \(b\), characterizes the curve as either exponential (\(b = 1\)) (case 1), sigmoid (\(b > 1\)) (case 2), or parabolic, with a higher initial slope and after that consistent with the exponential (\(b < 1\)) (case 3).

The shape parameter (\(b\)) is obtained from the slope of the line and the scale parameter - \(a\), is estimated from the intercept. The parameter, \(a\), can be replaced by the dissolution time, \(T_d\), that is defined by \(T_d = (a)^{1/b}\) and is equivalent to \(m = 0.632\), \(T_d\) represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form (32).

The dissolution data of all formulations were plotted in accordance with the linear form of Weibull distribution function (Fig. 1). Results show that Weibull distribution function equation fit to the dissolution data for all formulations with a linear regression coefficient of determination \(r^2\) values between 0.85 and 0.98 (Table 1). The curve of dissolution for all formulations was parabolic, with a

![Figure 3. DCS curves for (a) micronized indomethacin, (b) mixture of indomethacin : PVP (90 : 10), (c) mixture of indomethacin : PVP (50 : 50), (d) pure PVP](image)

![Figure 4. DCS curves for (a) micronized indomethacin, (b) micronized lactose, (c) mixture of indomethacin : lactose (90 : 10), (d) mixture of indomethacin : lactose (50 : 50)](image)
higher initial slope and after that consistent with the exponential \((b < 1)\) as shown in Table 1. The dissolution time \((T_d)\) was 3.3, 5.0, 5.8, 7.3 and 12.4 min for Indomin®, Indylon®, Rothacin®, ternary and binary interactive mixtures, respectively (Table 1). Dissolution time \((T_d)\) indicates that the release rate of indomethacin was faster from commercially available capsules in compression with the ternary and binary interactive mixtures.

Baker-Lonsdale model was developed by Baker and Lonsdale (1974) from the Higuchi model and describes the drug controlled release from a spherical matrix, microcapsules or microspheres, being represented by the following linear expression (32-35):

\[
\frac{3}{2} \left[ 1 - \left( 1 - \frac{M_t}{M_\infty} \right)^{2/3} \right] - \frac{M_t}{M_\infty} = Kt
\]  

where the release constant \((K)\) corresponds to the slope. \(M_t\) is the drug released amount at time \(t\) and \(M_\infty\) is the amount of drug released at an infinite time.

The dissolution data for all formulations were plotted in accordance with the Baker-Lonsdale equation (Fig. 2). Results show that Baker-Lonsdale equation fits to the dissolution data with a linear regression coefficient of determination \(r^2\) values between 0.67 to 0.96 indicating that Weibull distribution function model is best described by the dissolution data for all formulations with higher \(r^2\) values (Table 1).

To study the possibility of drug - excipient interaction, DSC curves for all formulations and a mixtures of micronized indomethacin – PVP/or lactose (90 : 10% w/w and 50 : 50 w/w) were obtained by using DSC-60 (Shimadzu, Japan).

Table 2 and Figure 3 show that pure micronized indomethacin has a melting peak at 162.7°C with enthalpy of fusion equal to 93.86 J/g. Results indicate that PVP was interacted with micronized indomethacin in all concentrations used (Table 2 and Fig. 3). More specifically, the addition of 10% PVP produces a decrease in melting peak of micronized indomethacin by 2.14°C and at higher concentration of PVP (50%) the enthalpy of fusion was dramatically decreased and a decrease in the

![Figure 5. DCS curves for (a) indomethacin, (b) binary mixture and (c) ternary interactive mixture](image)
melting peak of micronized indomethacin by 17.39°C was observed. This finding appears to be in agreement with previous studies, where it was found that PVP was incompatible with a wide range of active pharmaceutical ingredients such as oxprenolol, atenolol, ibuprofen, indomethacin, ranitidine and raloxifene hydrochloride (36-38). It has been reported that PVP mainly interacts with drug molecules by electrostatic bonds (ion to ion, ion to dipole, dipole to dipole) along with Van der Waals forces and H-bonds. Drug-excipient interaction through H-bond interaction of indomethacin-PVP may produce drug-excipient interaction (39-43).

Mixtures of micronized indomethacin-micronized lactose (90 : 10% w/w and 50 : 50 w/w) were used to study the indomethacin-lactose interaction. Table 1 and Figure 4 show that the addition of 10% fine lactose to micronized indomethacin decrease the melting peak of indomethacin by 0.49°C and the addition of 50% fine lactose to the micronized indomethacin produces a decrease in the melting peak of indomethacin by 0.6°C. Micronized indomethacin-fine lactose interaction was not found and the decrease in the melting point was insignificant.

In case of binary system (Fig. 5b) composed from 20% micronized indomethacin and 80% fine lactose-PVP (9 : 1) used in this study, a decrease of 7.1°C of the melting peak of micronized indomethacin was observed and the peak was very close to the melting peak of lactose indicating a very strong interaction of indomethacin with the mixture lactose – PVP (9 : 1 w/w).
The effect of the addition of fine lactose 20% to the binary system was also investigated. Table 1 and Figure 5c show that the addition of 20% fine lactose to the binary system has a different type of indomethacin - excipient interaction by increasing the melting peak of indomethacin from 162.2 to 171.8°C.

Commercially available capsules of indomethacin (Rothacin®, Indomin® and Indylon®) were used to compare the melting point for micronized with non-micronized indomethacin and to study the type of excipient(s) used in the three commercially available formulations. Table 1 shows that the melting peak of Rothacin® and Indylon® was similar with insignificant differences. This similarity was supported by the DSC curves obtained for Rothacin® and Indylon showing that lactose was used as excipient in both formulations (Fig. 6a and 6c). In case of Indomin® a small peak at 109.7°C and a broad peak between 30-70°C were observed and represent some additives (excipient) in the formulation, but lactose was not found. However, it is important to note that the initial release rate from Indomin® was faster than the release rate from Rothacin® and Indylon as well as from the binary and ternary interactive mixtures prepared in this study. The enhancement in the dis-

![Figure 7](image7.png)

**Figure 7. Reduction of cloud point of 1% PVP by the addition of ammonium sulfate**

![Figure 8](image8.png)

**Figure 8. The effect of indomethacin in the cloud point of 1% PVP containing ammonium sulfate**

\[
y = -11.579x + 202.88
\]

\[
R^2 = 0.9881
\]
solution rate observed from Indomin®, Rothacin® and Indylon® in comparison with the binary and ternary interactive mixtures may be due to some additives in their formulations, such as non-ionic surfactant that enhance dissolution. This additive was observed in the DSC curves, by a small peak at 110°C for Indomin®, Rothacin® and Indylon® (Fig. 6).

The cloud point method is a simple and good reproducible method used to study the interaction between low molecular weight compounds and other macromolecules (44, 45). It was reported that the cloud point of PVP is > 100°C and can appeared by addition of the least amount of ammonium sulfate and that the cloud point of PVP aqueous solutions lowered linearly with increasing concentration of ammonium sulfate. The amount of ammonium sulfate needed to coacervate the solution of 1% PVP is shown in Figure 7. Results show that the addition of indomethacin to 1% PVP solution containing ammonium sulfate (with cloud point at 76°C) reduces the cloud point of PVP indicating that there is an interaction between indomethacin and PVP (Figs. 8, 9). A second cloud point was observed after cooling due to salting out of indomethacin and appeared at 35°C and 40°C after the addition of 4 mg and 6 mg of indomethacin, respectively (Figs. 8, 9). The cloud point of 1% PVP containing ammonium sulfate was not affected by the addition of lactose.

CONCLUSIONS

It can be concluded that the reduction in the dissolution rate from the binary and ternary interactive mixtures of indomethacin in our previous study was due to the drug – PVP interaction. This interaction was also confirmed by the cloud point method that showed that the cloud point of 1% PVP containing ammonium sulfate was reduced after indomethacin addition. Therefore, PVP must be avoided in the preparation of binary and ternary interactive mixtures of indomethacin to prevent drug - excipient interaction. Also it can be concluded that indomethacin was compatible with lactose and that lactose was used as excipient in Rothacin® and Indylon®, while PVP was not detected.

REFERENCES


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