Influence of ethanol on swelling and release behaviors of carbomer-based tablets

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\textbf{Introduction}
Recently, there has been an increasing research attention regarding the impact of concomitant intake of ethanol on the release from oral controlled release (CR) dosage forms and the associated risk of dose dumping.

The aim of this study was to investigate the effect of ethanol on the \textit{in vitro} swelling and release behavior of carbomer-based tablets.

\textbf{Experimental methods}
\textbullet\ Materials
Carbopol\textsuperscript{®} (CP) 971P NF and 974P NF were obtained from Lubrizol, USA. Theophylline (THEO), caffeine (CAF) and metformin HCl (MH) were obtained from Sigma-Aldrich (USA), Fluka (USA) and JPM (Jordan), respectively.

\textbullet\ Hydro-ethanolic media
Six media comprising hydrochloric acid (0.1N, pH = 1.2) and phosphate buffer (pH = 6.8), each with 0, 20 and 40\% (v/v) ethanol were used in swelling and release studies.

\textbullet\ Determination of solubility of model drugs in the hydro-ethanolic media
The solubility test was performed by adding excess amounts of the model drugs to the hydro-ethanolic media (at 37 \textdegree C). The concentration of dissolved drug was determined spectrophotometrically.

\textbullet\ Preparation of CP drug-free compacts and matrix tablets
Drug-free CP compacts (200 mg, 13-mm diameter) were prepared by directly compressing (300 kg.cm\textsuperscript{-2}) powder from each grade. Matrix tablets (151.5 mg, 7-mm diameter) were prepared by direct compression (100 kg.cm\textsuperscript{-2}) of physical mixtures of CP with the model drug at a 1:4 polymer:drug ratio adding 1\% Mg stearate as a lubricant.

\textbullet\ \textit{In vitro} swelling studies
Swelling experiments were performed for drug-free CP tablets in a paddle dissolution system at 100 rpm using 500 ml of the hydro-ethanolic medium. Each tablet was fixed on a pin at the bottom of the dissolution vessel to avoid sticking to the vessel. At 1, 4 and 8 hours, tablets were gently withdrawn from the media and a filter paper was used to remove excess liquid from around the swollen tablets. The tablets were then weighed and dried at 105 \textdegree C to a constant weight. Medium uptake and mass loss were calculated according to Al-Zoubi et al. [1].

\textbullet\ \textit{In vitro} drug release testing
The release studies were performed in a basket dissolution system at 100 rpm using 900 ml of the hydro-ethanolic dissolution medium. Samples were analyzed by UV spectroscopy. The release data were fitted to Higuchi and Peppas models in order to characterize release rate and mechanism, respectively. Similarity factor (\textit{f}_2) was used to compare the release profiles of each model drug in media containing 20 and 40\% ethanol with the corresponding in medium with 0\% ethanol.

\textbf{Results and discussion}
\textbullet\ Solubility of model drugs
Fig. 1 shows that MH has the highest solubility and THEO has the lowest solubility in all of the tested media. Furthermore, by increasing the percentage of ethanol in both acidic and buffered media, the solubility of MH is decreased, due to suppression of salt dissociation, while the solubility of THEO and CAF is remarkably increased.

\textbullet\ \textit{In vitro} swelling behavior
Fig. 2 shows that increasing ethanol concentration in buffer causes a decrease in dissolution medium uptake and mass loss of CP drug-free compacts. On the other hand, the swelling and erosion of the compacts in acidic solution, were less clearly affected (for CP 971) or slightly increased (for CP 974P) by increasing ethanol concentration.
In vitro drug release

It can be seen from $K_{H}$ values in Table 1 that the effect of ethanol on release was different for model drugs according to their solubility change with ethanol concentration. No dose dumping was manifested. The release rate of MH was decreased with increasing ethanol concentration for both CP grades, probably due to the decrease of matrix erosion in buffer and of drug solubility, in acidic and buffered media, with increasing ethanol concentration.

For CAF and THEO, the release rate ($K_{H}$ results, Table1) in acidic and buffered media decreased by increasing ethanol concentration from 0 to 20%, while increased by increasing ethanol concentration from 20 to 40% (i.e. release was slowest at 20% ethanol concentration). This trend can be explained in buffered media by the contradicting effects of increasing ethanol concentration through decreased matrix erosion and increased drug solubility, which are expected to slow and hasten the release, respectively. However, in acid, the release rate was expected to increase persistently with increasing ethanol concentration because erosion results do not oppose the increase of drug solubility. Thus, the swelling and erosion results of drug-free polymer tablets were not in good consistence with the release results and this suggests that the effect of ethanol on swelling and erosion of both CP polymers might be different in the presence of model drugs.

Regarding release mechanism, the $n$ values in buffer were decreasing with increasing ethanol concentration for CAF and THEO because of increased drug solubility and decreased polymer swelling and erosion, but this trend is not found in the case of MH probably because of the contradicting effects of ethanol on release mechanism through decreasing both the solubility of MH and tablet swelling/erosion. For the three drugs in acid, the trend for the changing of release exponent ($n$) with ethanol concentration was less obvious. The results of similarity factor ($f_2$) are shown in Table 2. According to these results, ethanol led to different release profiles ($f_2 < 50$) in 7 of 8 cases for matrices containing MH and in 3 of 8 cases for matrices containing CAF and THEO.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CP grade</th>
<th>Ethanol Concentration (v/v%)</th>
<th>Eth. Acid Buffer</th>
<th>Acid Buffer</th>
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</thead>
<tbody>
<tr>
<td>MH</td>
<td>971P</td>
<td>0 0.41 70.02 0.46 66.41</td>
<td>971P 20 0.40 51.64 0.56 47.91</td>
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<td></td>
<td>971P 40  0.45 48.07 0.50 44.69</td>
<td>974P 0 0.40 71.90 0.44 50.25</td>
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<tr>
<td></td>
<td>974P 20  0.37 58.54 0.56 48.97</td>
<td>974P 40 0.53 48.63 0.53 42.71</td>
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<tr>
<td>CAF</td>
<td>971P 0   0.65 27.65 0.84 22.55</td>
<td>971P 20 0.70 26.08 0.75 22.43</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>971P 40  0.65 26.73 0.64 24.73</td>
<td>974P 0 0.80 32.55 1.10 35.28</td>
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<tr>
<td></td>
<td>974P 20  0.95 30.43 0.97 29.19</td>
<td>974P 40 0.85 36.26 0.84 33.04</td>
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<tr>
<td>THEO</td>
<td>971P 0   0.70 18.61 0.96 17.16</td>
<td>971P 20 0.71 17.02 0.74 12.57</td>
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<tr>
<td></td>
<td>971P 40  0.71 17.02 0.74 12.57</td>
<td>974P 0 0.92 23.93 1.15 31.47</td>
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<tr>
<td></td>
<td>974P 20  0.88 22.16 0.86 17.75</td>
<td>974P 40 0.83 23.76 0.78 21.58</td>
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<td></td>
</tr>
</tbody>
</table>

Conclusion

From this study, it was found that the presence of ethanol in dissolution media at concentrations relevant to alcoholic beverages affected the in vitro drug release from CP matrices, although no dose dumping was manifested and release was slowed in most cases. The influence of ethanol on release can be explained to a high extent by its combined effects on the solubility of model drugs and the swelling/erosion behavior of polymers.

References