In recent years, there has been a growing concern regarding the impact of concomitant intake of ethanol on the release from oral controlled release (CR) dosage forms. This concern was a consequence of the FDA alert on the potentially-fatal plasma concentrations of the opioid analgesic hydromorphone as a result of interaction between alcohol and Palladone®.[1] Since then, an increased research attention on this issue has been observed. Some researchers investigated the effect of ethanol on the release behavior of some release controlling agents such as hypromellose as a matrix former[2,3] and ethyl cellulose-hydroxypropyl cellulose blend as a membrane former.[4] Others investigated the effect of ethanol on several marketed CR formulations.[5–10] However, there is still limited information in this field, and the effect of ethanol on many release controlling agents and systems remains uninvestigated.

Hydrophilic swellable matrices represent a simple and flexible approach to controlled drug delivery because of their cost-effectiveness, simple manufacturing process and limited risk of dose dumping. In recent years, carboxomers (acrylic acid polymers, carboxyvinyl polymers, Carbopol®) are being widely used in developing oral CR hydrophilic matrix tablets.[11] Three commercially-available grades of Carbopol® (974P, 971P and 71G) are suitable for use in oral CR tablets. Carbopol® 974P is highly crosslinked, whereas Carbopol® 971P is lightly crosslinked. Carbopol® 71G is a dry-granulated grade of Carbopol® 971P with improved flow properties, making it suitable for direct compression.

The main aim of this study is to investigate the effect of ethanol on the in vitro release behavior of Carbopol® matrix tablets. To our knowledge, there is no published information on this issue. Two grades, Carbopol® 971P and 974P, were studied. Three model drugs (metformin HCl, caffeine and theophylline) were used in the study. The swelling behavior of drug-free compacts and the release of model drugs from matrix tablets were evaluated in acidic and buffered media with 0, 20 and 40% (v/v) ethanol. Release data were analyzed by fitting to Higuchi and Peppas models and calculation of similarity factor ($f_2$). ANOVA tests were performed to determine significant factors on swelling and release. It was found that ethanol affects swelling and erosion of drug-free Carbopol® compacts, and the effect was highly dependent on medium pH. For matrix tablets, no dose dumping due to ethanol was manifested. The release rate and mechanism, however, were significantly affected by ethanol concentration as indicated by ANOVA applied to the constant, $K_w$, from Higuchi model and the exponent, $n$, from Peppas model, respectively. The effect of ethanol on release was further confirmed by similarity factor results, which indicated that ethanol led to different release profiles ($f_2 < 50$) in seven of eight cases for matrices containing metformin HCl and in three of eight cases for matrices containing caffeine and theophylline.

**Keywords:** Controlled-release, matrix, erosion, metformin HCl, caffeine, theophylline

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**Introduction**

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HCl, caffeine and theophylline) were used in the release studies and were selected, based on preliminary solubility studies, to represent different degrees of aqueous solubility (from freely to slightly soluble) and different effects of ethanol addition to aqueous media on drug solubility. Swelling of drug-free polymer compacts was also investigated for further understanding of ethanol effect.

Materials and methods

Materials

Carbopol® 971P NF and Carbopol® 974P NF were obtained from Lubrizol, Wickliffe, OH, USA. Theophylline, caffeine (both in anhydrous form) and metformin HCl were used as model drugs and were obtained from Sigma-Aldrich (MO, USA), Fluka (USA) and JPM (Amman, Jordan), respectively. The powder size fraction <180 µm, obtained by sieving, was used. Magnesium stearate from Harcros Chemical Group (Durham, UK) was used as a lubricant. Absolute ethanol of analytical grade was obtained from Medical, Scientific and Chemical Corporation, Amman, Jordan.

Hydro-ethanolic media for swelling and release studies

Six media comprising hydrochloric acid (0.1 N, 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. The 40% ethanol concentration, equivalent to the concentrations found in most undiluted spirits, was used to represent the worst-case scenario and the 20% was selected as an intermediate concentration equivalent to those found in a strong mixed drink.\(^9\)

Determination of the 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 acidic and buffered media. The suspensions were left in a shaking water bath adjusted at 37 ± 0.5°C for 24 h. Samples were then taken, filtered and the concentration of dissolved drug was determined spectrophotometrically after appropriate dilution at wavelength corresponding to maximum absorbance (233, 271 and 272 nm for metformin HCl, theophylline and caffeine, respectively).

Preparation of drug-free Carbopol® tablets for swelling experiments

Drug-free Carbopol® tablets (compacts) were prepared by compressing 200 mg of powder from each grade at a pressure of 322 MPa for 30 s in a 13-mm diameter round flat-faced punch and die set using manually-operated hydraulic press (Riken Seiki, Japan).

In vitro swelling experiments

Swelling experiments for drug-free Carbopol® tablets were performed in a USP Apparatus II (paddle) dissolution system (Pharma Test PTW 2, Hainburg, Germany) at 100 rpm using 500 mL of the hydro-ethanolic medium at a temperature of 37 ± 0.5°C. Each tablet was fixed on a pin at the bottom of the dissolution vessel to avoid sticking to the glass dissolution vessels commonly observed with hydrophilic matrix forming materials.\(^12\) At certain time intervals (1, 4 and 8 h), tablets were gently withdrawn from the media. A filter paper was used to remove excess liquid from around the swollen tablets carefully to avoid touching and deforming the jelly layer. The tablets were then weighed and dried at 105°C to a constant weight. Three tablets were used for each time point and swelling parameters were determined according to the following equations:

\[
\text{Dissolution medium uptake} = \frac{(W_w - W_d)}{W_d} \quad (1)
\]

\[
\text{Mass loss (\%)} = \frac{W_i - W_d \times 100}{W_i} \quad (2)
\]

where \(W_w\) is the initial tablet weight, \(W_d\) is the weight of wet tablet after immersion into the dissolution medium and \(W_d\) = weight of dried tablet after immersion into the dissolution medium and drying to constant weight.

Morphological examination of the swollen tablets was also carried out after immersion in the different media for 4 h. The tablets were taken out from the media and were imaged using a digital camera (EasyShare Z1285, KODAK, USA).

Preparation of matrix tablets for in vitro drug release experiments

For preparation of matrix tablets, Carbopol® (971P or 974P) was mixed with the model drug (metformin HCl, caffeine or theophylline) at 1:4 polymer:drug ratio for 15 min using a spatula. Thereafter, 1% magnesium stearate was added as a lubricant and additionally mixed for 5 min. Weighed samples (151.5 mg) of the powder mixture were then compressed in a 7-mm diameter round flat-faced punch and die set using manually-operated hydraulic press (Riken Seiki, Japan) at a pressure of 370 MPa for 30 s. The relatively high pressure and long dwell time were used to ensure uniform powder consolidation and minimum achievable porosity of tablets. The blend uniformity of mixtures was checked prior to compression (coefficient of variation, CV, of the drug mass fraction in eight samples ≤6%). Small batches (40 tablets) were prepared, and the quality of tablets was controlled regarding 1) uniformity of mass (CV ≤ 1%, \(n = 20\)) and 2) mechanical strength of tablets (mean tensile strength ≥ 1 MPa, CV ≤ 20%, \(n = 10\)).

In vitro drug release experiments

The release experiments were performed in a USP Apparatus 1 (basket) dissolution system (Pharma Test PTW 2, Hainburg, Germany) at 100 rpm using 900 mL of the hydro-ethanolic dissolution medium at a temperature of 37 ± 0.5°C. At predetermined time intervals, samples were withdrawn, filtered and the concentration
of dissolved drug was determined, after suitable dilution, by UV spectroscopy. Three tablets were used for each release experiment and from the mean concentration, the drug released (%) was determined.

Release data modeling and analysis
In order to characterize the release mechanism, the power law model of Peppas was fitted to the first 60% release data:

$$M_t / M_\infty = K_p \times t^n$$  \hspace{1cm} (3)

where $M_t / M_\infty$ represents the fractional release of drug at time $t$, $K_p$ is the release rate constant and $n$ is the release exponent. For cylindrical tablet, a value of $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ indicates non-Fickian (anomalous) diffusion, $n = 0.89$ indicates Case-II transport (erosion control and zero-order kinetics) and $n > 0.89$ indicates Super Case-II transport.[14]

In order to evaluate and compare the release rate for profiles with different release mechanisms ($n$ values), the square root model of Higuchi was fitted to the release data:

$$M_t = K_{H} \times t^{0.5}$$  \hspace{1cm} (4)

where $M_t$ is the amount of drug released at time $t$ and $K_{H}$ is the Higuchi release rate constant.

For further assessment of the effect of adding ethanol to the dissolution media on the release of model drugs from Carbopol® matrix tablets, the release profiles of each model drug in media with 20 and 40% ethanol were compared with the corresponding profile in medium with 0% ethanol. The similarity factor ($f_2$) was used for comparison and was calculated according to the following equation:[15]:

$$f_2 = 50 \log \left[ 1 + \frac{n}{2} \sum_{i=1}^{n} \left( \frac{R_i - T_i}{R_i + T_i} \right)^2 \times 100 \right]$$  \hspace{1cm} (5)

Where $n$ is the number of dissolution time points and $R_i$ and $T_i$ are the reference and test dissolution values at time $t$, respectively. The similarity factor ($f_2$) can estimate the overall difference between two release profiles attributed to concurrent differences in rate and mechanism. Generally, to ensure sameness between the profiles $f_2$ should be in the range of 50–100.[16]

Statistical analysis
Analysis of variance (ANOVA) tests were applied to evaluate the statistical significance of the main effects and two-factor interactions for: (i) ethanol concentration, Carbopol® grade, medium pH and time, on the swelling parameters (dissolution medium uptake and mass loss) and (ii) ethanol concentration, Carbopol® grade, medium pH and drug type on the release rate and mechanism (expressed by the constant, $K_{H}$, from Higuchi model and the exponent, $n$, from the power law model, respectively). For ANOVA, the program SPSS 14.0 (Chicago, IL, USA) was used.

Results and discussion
Solubility of model drugs
The solubility results for model drugs (metformin HCl, caffeine and theophylline) in hydro-ethanolic acidic and buffered media are shown in Figure 1. The difference in solubility between the three model drugs is obvious, where it can be seen that metformin HCl has the highest solubility and theophylline has the lowest solubility in all of the tested media. The pH of medium does not remarkably affect the solubility results of model drugs, indicating minor effect on their degree of ionization.

Furthermore, it can be seen that the solubility of theophylline and caffeine is increased by increasing ethanol concentration in acidic as well as in buffered media and that the increase in solubility is higher by increasing ethanol percentage from 20 to 40% than from 0 to 20%. On the other hand, the solubility of metformin HCl is decreased by increasing the concentration of ethanol in both acidic and buffered media, probably due to suppression of salt dissociation.

Swelling behavior
Swelling study was performed to help in explaining the effect of ethanol on drug release. Drug-free polymer tablets (compacts) were used in the study in order to investigate the intrinsic behavior of Carbopol® polymers (i.e. to avoid affecting swelling and erosion results by the presence of model drugs).

The results of swelling parameters (dissolution medium uptake and mass loss) at three time intervals (1, 4 and 8 h) for Carbopol® tablets in hydro-ethanolic acidic and buffered media are shown in Figure 2. The corresponding results of ANOVA showing the significance of time, Carbopol® grade, medium pH, ethanol concentration and their two-factor interactions on swelling parameters are presented in Table 1.
From Figure 2 it can be seen that, as expected, tablets of both Carbopol® grades (971P and 974P) showed increasing of medium uptake and mass loss with time in all of the tested media. However, the increase with time of both swelling parameters was generally sharper for Carbopol® 974P than for Carbopol® 971P and sharper in buffered than in acidic media. The effect of medium pH and Carbopol® grade, accordingly, was clearer at 4 and 8 than at 1 h.

Thus, by comparing the values at 4 and 8 h of immersion in Figure 2A, it can be seen that both Carbopol® grades showed generally higher dissolution medium uptake values in buffered than in acidic media, which is explained by the pH-dependent swelling of Carbopol® polymers.[17]

Regarding the effect of Carbopol® grade, Carbopol® 974P showed higher medium uptake (at 4 and 8 h of immersion) and mass loss (at all time intervals) than Carbopol® 971P. Complete erosion of Carbopol® 974P tablets was observed at 8 h in 0 and 20% ethanol/buffer media.

The effect of medium pH on compact erosion was dependent on Carbopol® grade indicating interaction between the two factors. More specifically, Carbopol® 971P showed slightly higher mass loss in acidic than in buffered media except for one case corresponding to 8 h and 0% ethanol concentration, whereas Carbopol® 974P showed higher mass loss in buffered than in acidic media except for one case corresponding to 1 h and 40% ethanol concentration (Figure 2B).

Regarding the effect of ethanol, Figure 2 shows that increasing ethanol concentration in buffer from 0 to 40% caused a decrease in dissolution medium uptake and mass loss for Carbopol® tablets. The decrease was relatively small for mass loss of Carbopol® 971P tablets, while

Table 1. ANOVA results for the effect of time (t), Carbopol® grade (CG), medium pH (MpH), ethanol concentration (EC) and two-way interactions on swelling parameters.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Dissolution medium uptake*</th>
<th>Mass loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td>t</td>
<td>20.447</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CG</td>
<td>7.161</td>
<td>0.018</td>
</tr>
<tr>
<td>MpH</td>
<td>15.400</td>
<td>0.002</td>
</tr>
<tr>
<td>EC</td>
<td>3.016</td>
<td>0.081</td>
</tr>
<tr>
<td>t × CG</td>
<td>1.968</td>
<td>0.177</td>
</tr>
<tr>
<td>t × MpH</td>
<td>3.766</td>
<td>0.049</td>
</tr>
<tr>
<td>t × EC</td>
<td>0.700</td>
<td>0.605</td>
</tr>
<tr>
<td>CG × MpH</td>
<td>2.471</td>
<td>0.138</td>
</tr>
<tr>
<td>CG × EC</td>
<td>0.349</td>
<td>0.711</td>
</tr>
<tr>
<td>MpH × EC</td>
<td>3.949</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*Missing values were excluded.
remarkable for mass loss of Carbopol® 974P tablets and for medium uptake by tablets from both grades.

On the other hand, the effect of ethanol on dissolution medium uptake and mass loss in acid was different from and generally less remarkable than the corresponding effect in buffer. Specifically, increasing ethanol concentration in the case of Carbopol® 974P tablets caused a relatively small increase in mass loss at all time intervals and in medium uptake at 8 h (i.e. opposite to its effects in buffer). In the case of Carbopol® 971P tablets, ethanol caused a negligible change of medium uptake and a small decrease of mass loss at 1 and 4 h.

The results of ANOVA, Table 1, show that for both medium uptake and mass loss the main effects of Carbopol® grade, medium pH and time were significant ($P = 0.018, 0.002$ and $< 0.001$, respectively, for medium uptake and $P < 0.001$ for mass loss). The main effect of ethanol concentration was non-significant ($P = 0.081$ and $0.230$ for medium uptake and mass loss, respectively). However, the interaction term between ethanol concentration and medium pH was significant ($P = 0.044$ and $0.029$ for medium uptake and mass loss, respectively). Also significant were the interactions, noticed from Figure 2 and mentioned earlier, of time with medium pH ($P = 0.049$ and $0.032$ for medium uptake and mass loss, respectively) and, for mass loss, of Carbopol® grade with each of time and medium pH ($P < 0.001$).

Pictures of swollen drug-free Carbopol® tablets after 4 h of immersion in hydro-ethanolic acidic and buffered media are shown in Figure 3. By comparing pictures of swollen Carbopol® 971P and 974P tablets, dissimilarity in the gelling behavior is obvious. Whereas surface (heterogeneous) erosion was demonstrated in the case of Carbopol® 971P by the appearance of a transparent gel layer around the tablets, bulk (homogenous) erosion was observed with Carbopol® 974P tablets.$[18]$ This might be explained by the faster and easier penetration of the dissolution media into the tablets of Carbopol® 974P through the less viscous channels between the highly cross-linked “fuzzball” gel structures.$[19]$ Furthermore, for swollen Carbopol® 971P tablets, the thickness of formed gel layer and the diameter of the tablet were larger in buffered than in acidic media, in agreement with the results of dissolution medium uptake observed in Figure 2A. The gel layer was relatively clear for tablets in 0 and 20% ethanol/buffer and slightly turbid for the other tablets probably due to decreased solubility of polymer caused by the acidic pH and the high concentration of ethanol.$[20,21]$ Regarding Carbopol® 974P, by comparing the tablets immersed in buffered media, the tablet corresponding to 0% ethanol concentration had a texture that was more jelly and highly penetrated by dissolution medium, in comparison with the tablets corresponding to 20 and 40%. On the other hand, pictures of Carbopol® 974P tablets in acidic media did not show high difference in dissolution medium penetration into the tablets. Thus, similarly to Carbopol® 971P, the swelling photographs for Carbopol® 974P tablets were in agreement with Figure 2 and with the significant interaction between medium pH and ethanol concentration indicated by ANOVA results in Table 1.

**In vitro drug release**

The profiles of release of metformin HCl, caffeine and theophylline from Carbopol® matrix tablets in hydro-ethanolic media are shown in Figures 4–6, respectively, where it can be seen that some profiles representing
different ethanol concentrations intersected and were close to each other. Therefore, modeling of release was performed to enable quantitative evaluation of release rate and mechanism for easier elucidation of ethanol effect.

The results of fitting to power law model of Peppas and the square root model of Higuchi are presented in Table 2. The corresponding results of ANOVA showing the significance of drug type, Carbopol® grade, medium pH, ethanol concentration and two-way interactions on the Higuchi release rate constant (K_H) and release exponent (n) of Peppas model are given in Table 3.

**Release rate**

It can be seen from K_H values in Table 2 and from Figures 4–6 that the release rate of model drugs from Carbopol® matrix tablets was consistent with their solubility order, where release was fastest for metformin HCl tablets and slowest for theophylline tablets.

The release was generally slower, due to formation of stronger gel layer, from Carbopol® 971P than from Carbopol® 974P matrices, consistent with previously reported results.[17,22,23] An exceptional slower release from Carbopol® 974P than from Carbopol® 971P matrix tablets was seen in the cases corresponding to metformin HCl in 0 and 40% ethanol/buffer, Table 2. This might be explained based on ionic interaction between the anionic carboxylic acid groups of the polymer and the cationic drug, which may be more extensive in the case of Carbopol® 974P due to more complete and uniform hydration of the matrix.

Furthermore, the release from Carbopol® 971P matrix tablets was slower in buffered than in acidic media due to formation of thicker and more viscous gel layer around the tablets, consistent with previous studies.[24–27] In contrast, the release from Carbopol® 974P matrix tablets is known to be faster in buffered than in acidic media.[28] However, only two cases corresponding to caffeine and theophylline in media with 0% ethanol concentration were consistent with the reported results and for the other cases the release was slower in buffered than in acidic media, Table 2. This might be explained by the increased and decreased erosion of Carbopol® 974P with increasing ethanol concentration in acidic and buffered media,

![Figure 4. Release profiles of metformin HCl from Carbopol® 971P and 974P matrix tablets in hydro-ethanolic acidic (A and C, respectively) and buffered media (B and D, respectively). Error bars represent standard deviation (n = 3).](image-url)
respectively, as mentioned earlier and shown in Figure 2, in addition to increased drug-polymer ionic interaction in buffered media, in the case of metformin HCl.

The effect of ethanol on release was found different for model drugs according to their solubility change with ethanol concentration. More specifically, the release rate of metformin HCl was decreased with increasing ethanol concentration for both Carbopol® grades, probably due to the decrease of matrix erosion in buffer, and of drug solubility in acidic and buffered media.

For caffeine and theophylline, the effect of ethanol concentration on release was most obvious in the case of Carbopol® 974P in buffer (Figures 5D and 6D) and minimal in the case of Carbopol® 971P in acid (Figures 5A and 6A), in agreement with the swelling and erosion results (Figure 2). It can be seen from Figures 5 and 6, and more clearly from Kₜ results (Table 2) that the release rate for both model drugs, 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 on release rate by decreasing matrix erosion and increasing drug solubility, which are expected to slow and hasten the release, respectively.

In acid, however, the solubility for both drugs increases and the erosion of drug-free polymer tablets was either negligibly affected (for Carbopol® 971P) or slightly increased (for Carbopol® 974P) by increasing ethanol concentration and therefore, the release rate was expected to increase persistently with increasing ethanol concentration. Thus, regarding the effect of ethanol, the swelling and erosion results of drug-free polymer tablets in acidic media were not very consistent with the corresponding release results, and this suggests that the effect of ethanol on swelling and erosion of both Carbopol® polymers might be different in the presence of model drugs.

From ANOVA results (Table 3) it can be seen that the main effects of medium pH, Carbopol® grade, ethanol concentration and drug type on release rate were significant ($P = 0.016, 0.006, 0.001$ and $< 0.001$, respectively).
Also were significant the interactions, mentioned above, between drug type and each of Carbopol® grade and ethanol concentration ($P = 0.031$ and 0.003, respectively).

Hence, the ANOVA results show that the main effect of ethanol concentration was significant on the release rate from Carbopol® matrix tablets, although on swelling and erosion of drug-free Carbopol® tablets the only significant effect for ethanol concentration was the interaction term with medium pH. This provides indication that ethanol effect on release is partially attributed to its effect on solubility of model drugs, which was similar in acidic and buffered media, in addition to its effect on polymer swelling and erosion, which was highly pH-dependent.

In the literature, previous studies have reported good correlation between drug release rate and swelling parameters for various hydrophilic matrix systems.27,29,30 Other studies have investigated the relationship between release rate and drug solubility.31–33

For estimation of the extent of contribution of drug solubility to the release rate and to check the extent to which swelling and erosion results of drug-free polymer tablets are related with the drug release from matrix tablets, we sought in the present work to correlate the release rate constant ($K_r$) with drug solubility and swelling parameters (medium uptake and mass loss at 1, 4 and 8 h). The correlation analysis was performed for the whole data corresponding to the three model drugs together and for the data corresponding to each model drug individually.

The results of Pearson’s correlation coefficient (Table 4) show that for the whole data, only the drug solubility was in good and significant correlation with the release rate. Similar result was found when correlation analysis was performed for the data corresponding to the freely soluble metformin HCl. On the other hand, for the less soluble drugs, caffeine and theophylline, the correlation of release rate with drug solubility was poor. Instead, release rate was in good and significant correlation with mass loss, for both drugs, and with medium uptake at 4 h for theophylline. These results are in agreement with previous literature regarding the effect of drug solubility on the release mechanism from Carbopol® matrices, where it is reported
Table 2. Results of fitting of release data to power law and Higuchi square root models for Carbopol® matrix-tablets in hydro-ethanolic media.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Carbopol® grade</th>
<th>Ethanol concentration (v/v %)</th>
<th>Acid</th>
<th>Higuchi model</th>
<th>Buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Power law model</td>
<td>Higuchi model</td>
<td>Power law model</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(K_p(h^{-n}))</td>
<td>(R)</td>
<td>(K_p(h^{-0.5}))</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>971P</td>
<td>0</td>
<td>0.709</td>
<td>0.413</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td>971P</td>
<td>20</td>
<td>0.522</td>
<td>0.397</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>971P</td>
<td>40</td>
<td>0.490</td>
<td>0.447</td>
<td>0.993</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>0</td>
<td>0.737</td>
<td>0.398</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>20</td>
<td>0.544</td>
<td>0.372</td>
<td>0.995</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>40</td>
<td>0.468</td>
<td>0.526</td>
<td>0.997</td>
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<tr>
<td>Caffeine</td>
<td>971P</td>
<td>0</td>
<td>0.243</td>
<td>0.648</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td>971P</td>
<td>20</td>
<td>0.203</td>
<td>0.696</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>971P</td>
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<td>0.213</td>
<td>0.654</td>
<td>1.000</td>
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<tr>
<td></td>
<td>974P</td>
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<td>0.298</td>
<td>0.798</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>20</td>
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<td>0.951</td>
<td>0.994</td>
</tr>
<tr>
<td></td>
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<td>40</td>
<td>0.219</td>
<td>0.846</td>
<td>0.991</td>
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<td>Theophylline</td>
<td>971P</td>
<td>0</td>
<td>0.132</td>
<td>0.700</td>
<td>0.988</td>
</tr>
<tr>
<td></td>
<td>971P</td>
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<td>0.117</td>
<td>0.712</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>971P</td>
<td>40</td>
<td>0.132</td>
<td>0.681</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>0</td>
<td>0.152</td>
<td>0.922</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>20</td>
<td>0.119</td>
<td>0.885</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>40</td>
<td>0.129</td>
<td>0.834</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Table 3. ANOVA results for the effect of drug type (DT), Carbopol® grade (CG), medium pH (MpH), Ethanol concentration (EC) and two-way interactions on the release rate and mechanism (expressed by the Higuchi rate constant, \(K_p\) from square root model and the exponent, \(n\), from power law model).

<table>
<thead>
<tr>
<th>Effect</th>
<th>Higuchi rate constant ((K_p))</th>
<th>Release exponent ((n))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(F)</td>
<td>(P)</td>
</tr>
<tr>
<td>DT</td>
<td>221.980</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CG</td>
<td>10.257</td>
<td>0.006</td>
</tr>
<tr>
<td>MpH</td>
<td>7.279</td>
<td>0.016</td>
</tr>
<tr>
<td>EC</td>
<td>11.267</td>
<td>0.001</td>
</tr>
<tr>
<td>DT × CG</td>
<td>4.346</td>
<td>0.031</td>
</tr>
<tr>
<td>DT × MpH</td>
<td>2.493</td>
<td>0.114</td>
</tr>
<tr>
<td>DT × EC</td>
<td>6.336</td>
<td>0.003</td>
</tr>
<tr>
<td>CG × MpH</td>
<td>0.143</td>
<td>0.710</td>
</tr>
<tr>
<td>CG × EC</td>
<td>0.051</td>
<td>0.950</td>
</tr>
<tr>
<td>MpH × EC</td>
<td>0.104</td>
<td>0.902</td>
</tr>
</tbody>
</table>

Specifically, the release exponent (\(n\)) values in Table 2 range between 0.372 and 1.147 corresponding to release mechanism ranging between Fickian diffusion and Super Case-II. The \(n\) values for the freely soluble drug in the media, metformin HCl, were lowest (between 0.372 and 0.565 indicating that the release mechanism was either pure or close to pure Fickian diffusion). For the less soluble drugs, caffeine and theophylline, the release mechanism was ranging between anomalous diffusion and Super Case-II (\(n\) values are between 0.638 and 1.100 for caffeine, and between 0.645 and 1.147 for theophylline).

The \(n\) values were higher in buffered than in acidic media, indicating shift towards polymer relaxation as expected for Carbopol® polymers, except for four cases corresponding to 40% ethanol concentration and matrices of both Carbopol® grades containing caffeine and theophylline, and one case corresponding to 20% ethanol concentration and matrix of Carbopol® 974P containing theophylline. These exceptions are probably attributed to the pH-dependent effect of ethanol concentration on swelling and erosion of Carbopol® tablets mentioned earlier, i.e. with increasing ethanol concentration swelling and erosion of Carbopol® tablets decrease in buffer for both grades, shifting the release towards Fickian diffusion, while increase in acid in the case of Carbopol® 974P (Figure 2).

Furthermore, the \(n\) values were higher for Carbopol® 974P matrices than for the corresponding Carbopol® 971P matrices, except for cases corresponding to metformin HCl in acidic and buffered media with 0 and 20% ethanol. This interaction suggests that the presence of drug and its properties may affect the difference in swelling between the two Carbopol® grades. Similar interaction between

that the release for highly soluble drugs occurs mainly by diffusion of dissolved drug through viscous gel layer, while for poorly soluble drugs occurs mainly through swelling and erosion of matrix followed by drug dissolution.[17]

Release mechanism

The release mechanism for Carbopol® matrices is reported to shift from Fickian diffusion towards polymer relaxation (Case-II) by decreasing drug solubility, as mentioned above, and by increasing medium pH.[17] In the present work, the effects of drug solubility and medium pH on release mechanism results were generally consistent with the reported results with some exceptions probably attributed to the complications related to presence of ethanol.

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drug and polymer type has been reported previously for cellulose derivatives in matrix tablets.[32]

Regarding the effect of ethanol on release mechanism, the n values in buffer were decreasing with increasing ethanol concentration for caffeine and theophylline because of increased drug solubility and decreased polymer swelling and erosion. However, this trend is not found in the case of metformin HCl where n values were highest at 20% ethanol concentration, probably because of the contradicting effects of ethanol on release mechanism by decreasing both the drug solubility and tablet swelling/erosion.

For the three drugs in acid, no clear trend was found for the changing of release exponent (n) with ethanol concentration. This might be partially attributed to the less obvious effect of ethanol on matrix swelling in acid and increasing swelling and erosion in some cases (observed mainly for Carbopol® 974P tablets, Figure 2), which has an opposing effect to the increase in solubility, in the cases of caffeine and theophylline, on release mechanism.

From Table 3, it can be seen that the main effects of drug type, Carbopol® grade, medium pH and ethanol concentration on the release mechanism were significant (P = 0.005 for ethanol concentration and < 0.001 for the other factors). Also significant were the two-factor interaction terms of ethanol concentration with drug type and medium pH (P = 0.001) and of drug type with Carbopol® grade (P < 0.001).

Release similarity
The results of similarity factor (f<sub>i</sub>) used to assess if the noticed changes in release rate and mechanism due to ethanol addition to the media led to an overall difference in release profiles are shown in Table 5. According to these results, ethanol led to different release profiles (f<sub>i</sub> < 50) in seven of eight cases for matrices containing metformin HCl and in three of eight cases for matrices containing caffeine and theophylline.

More specifically, the release of metformin HCl was different from the test (0% ethanol) for all cases except for Carbopol® 974P in 20% ethanol/buffer. For caffeine and theophylline, the release similarity results are consistent with the minimal and maximal changes due to ethanol observed in Figures 5 and 6 as follows: the release profiles for both drugs from Carbopol® 971P matrices in acidic media with 20 and 40% ethanol were all similar (f<sub>i</sub> > 50) to the reference profile (0% ethanol). On the other hand, the profiles for Carbopol® 974P matrices in hydro-ethanolic buffered media were different from the reference profile (0% ethanol) except for the profile of caffeine in 40% ethanol/buffer, which was similar although close to the decision cut point (f<sub>i</sub> = 51.1).

Moreover, as seen in Table 5, the release profiles in hydro-ethanolic acidic media were similar to the reference for Carbopol® 974P matrices containing theophylline but different for those containing caffeine. In addition, the release profiles for Carbopol® 971P matrices in hydro-ethanolic buffered media were similar to the reference except for the case of theophylline and 20% ethanol.

Accordingly, these results confirm that the effect of ethanol on release from Carbopol® matrices is highly dependent on drug type.

General discussion
In the present work, the release experiments on Carbopol® matrix tablets were performed separately in acidic and buffered hydro-ethanolic media. It was found that ethanol concentration and medium pH, in addition to drug type and Carbopol® grade, affect significantly the release rate and mechanism, although no dose dumping was manifested and in most cases, the release was slowed in presence of ethanol.

However, for orally administered matrix tablets, the in vivo scenario regarding their potential interaction with coingested ethanol generally involves the exposure of tablets to acidic gastric medium followed by neutral intestinal media. The ethanol concentration for each

<table>
<thead>
<tr>
<th>Drug</th>
<th>Carbopol® Grade</th>
<th>20% ethanol</th>
<th>40% ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acid Buffer</td>
<td>Acid Buffer</td>
<td>Acid Buffer</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>971P</td>
<td>43.4</td>
<td>41.0</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>46.2</td>
<td>60.3</td>
</tr>
<tr>
<td>Caffeine</td>
<td>971P</td>
<td>68.5</td>
<td>65.3</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>42.7</td>
<td>34.5</td>
</tr>
<tr>
<td>Theophylline</td>
<td>971P</td>
<td>70.7</td>
<td>48.1</td>
</tr>
<tr>
<td></td>
<td>974P</td>
<td>62.0</td>
<td>28.1</td>
</tr>
</tbody>
</table>

Table 4. Correlation of Higuchi rate constant (K<sub>H</sub>) for release from matrix tablets with drug solubility and swelling parameters (medium uptake and mass loss at 1, 4 and 8 h) for drug-free polymer tablets.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
<th>Medium uptake</th>
<th>Mass loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
<td>4 h</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>0.597*</td>
<td>0.237</td>
<td>-0.134</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.157</td>
<td>-0.090</td>
<td>0.388</td>
</tr>
<tr>
<td>Theophylline</td>
<td>-0.047</td>
<td>0.208</td>
<td>0.686*</td>
</tr>
<tr>
<td>MCT†</td>
<td>0.918*</td>
<td>0.060</td>
<td>0.076</td>
</tr>
</tbody>
</table>

*The whole data for the three model drugs (metformin HCl, caffeine and theophylline) was used in the correlation analysis.
*Correlation is significant at the 0.05 level (two-tailed).
stage will be highly dependent on the drinking habit (the rate of ingestion and the concentration of ethanol in alcoholic beverage) and on the rates of ethanol absorption and gastric emptying. Taking into consideration the variability in drinking habit and that there are many factors which affect ethanol absorption and gastric emptying such as presence and composition of coingested food, cigarette smoking, some disease and surgery cases and co ingestion of some medicines, it can be concluded that the in vivo outcome can not be perfectly and definitely predicted from the in vitro results.

Nevertheless, based on in vitro results and taking into consideration that subjecting the matrix tablets to high and intermediate ethanol concentrations (40 and 20% v/v, respectively) for a relatively long period (≥4h) did not result in dose dumping for Carbopol® matrix tablets, it is not expected that dose dumping will occur under in vivo conditions. However, the changes in release (either slowing or hastening) due to ethanol presence might be significant on the in vivo pharmacokinetic profile and efficacy of drug therapy particularly for drugs of narrow therapeutic window.

Conclusions
From the present study, it may be concluded that the presence of ethanol in dissolution media at concentrations relevant to alcoholic beverages does not result in dose dumping from Carbopol® matrices. However, it may significantly affect rate and mechanism of drug release from them. The influence of ethanol on release was explainable to a high extent by its combined effects on the solubility of model drugs and the swelling/erosion behavior of polymers. The release rate was decreased in most cases by presence of ethanol and it was increased in 40% (compared to 20%) hydro-ethanolic solutions in cases of theophylline and caffeine, probably due to remarkable increase in their solubility. Since, both overmedication and undermedication associated with the increase and decrease of drug release rate, respectively, may present a health risk, we suggest further investigation of the effect of ethanol on the release from carbomer-based marketed CR dosage forms for assurance of safety of their concomitant intake with ethanol.

Declaration of interest
The authors report no conflicts of interest.

References
25. Xiaoniang X, Minjie S, Feng Z, Yiqiao H. Floating matrix dosage form for phenoprolamine hydrochloride based on gas forming


