Hydro-Alcoholic Media: An Emerging in vitro Tool for Predicting Dose Dumping from Controlled Release Matrices

M.O. Emje, P.I. Nwabunike, C.Y. Isimi, O.O. Kunle and S.I. Ofoefule

1Department of Pharmaceutical Technology and Raw Material Development, National Institute for Pharmaceutical Research and Development Idu, P.M.B. 21, Garki-Abuja, Nigeria
2Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka, Enugu State, Nigeria

Abstract: In present study, the release profiles of hydrochlorothiazide from polyacrylic acid polymer (carbopol 71G) matrices in hydro-ethanolic media were done. Percent drug released increased with increasing levels of ethanol in the dissolution media, but there was no direct correlation with the drug's solubility in the media. Although, the result showed that an initial rapid release was observed in the media containing 30% ethanol, this could not be regarded as dose dumping of hydrochlorothiazide. Release in this medium was considered to be both erosion and diffusion-mediated, in contrast to the release in 0, 10, 20, 40 and 50% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling and swelling kinetics suggests a complex interaction between ethanol, hydrochlorothiazide and Carbopol 71 G accounting for the suppressed drug release in the ethanolic-media.

Key words: Carbopol 71 G, hydro-ethanolic media, sustained release, hydrochlorothiazide, matrices

INTRODUCTION

The report of US FDA in July 2005 that a potentially serious dose dumping of an opioid analgesic, hydromorphone from a controlled release capsule was possible if consumed with significant quantity of alcoholic beverage is generating interest among scientists (Roberts et al., 2007). However, studies in human volunteers involving co-administration of a drug and alcohol poses very serious ethical challenges, it is therefore appropriate to consider in vitro studies to provide insight on the release mechanism in hydro-alcoholic media, thereby guiding formulators in assessing the potential for alcohol-related dose dumping (Roberts et al., 2007).

For many reasons, oral drug delivery continues to be the preferred route of drug administration and the use of hydrophilic matrices in achieving this is increasingly becoming important especially in controlling the release rate of drugs from solid dosage forms (Vazquez et al., 1992; Varshosaz et al., 2006; Suja-areevath et al., 1996; Emje et al., 2006a, b). These systems are attractive approaches from economic as well as process development view point (Juarez et al., 2001; Emje and Kunle, 2004; Conti et al., 2007). A sustained release matrix tablet consists of a compressed compact containing a mixture of one or more bioactive agent (s) with one or more matrix former (s), which retards drug release (Conti et al., 2007). Hydrophilic swellable polymers have widely been used to control the release of drugs from matrix tablet formulations in the last three decades (Suja-areevath et al., 1996; Emje et al., 2005; Emje et al., 2006) and the increasing need for suitable polymers to achieve the desired drug release profile makes pharmaceutical research to widely screen a large variety of both synthetic and natural polymers which show drug release retarding ability.
Historically, carbopol polyacrylic acid polymers have demonstrated many useful performance properties in tablet applications (Aditya et al., 2004; Grabovac et al., 2005; Ganesh et al., 2006). They are useful at low levels (1-3%) as binders and at higher levels (5-30%), they achieve modified or even zero order controlled release of bioactives. Carbopol 71G is one member of the carbopol family of polymers that is suitable for use in oral dosage forms since it was polymerized in ethyl acetate, a relatively non toxic solvent. It is a water-swellable high molecular weight polyacrylic acid cross linked with allyl ethers of pentaerythritol (Anonymous, 2006). Due to their extremely efficient thickening and gelling characteristics, carbopol resins have been widely used in various pharmaceutical applications, including beads, gels and ointments (Ganesh et al., 2006). Information available to us from the manufacturer indicate that carbopol 71G is the latest polyacrylic acid derivative and literature survey reveal that very few reports exist on it (Varshosaz et al., 2006). In the present study, we assess the influence of alcohol on the rate and mechanisms of release of hydrochlorothiazide from carbopol 71G hydrophilic matrices.

MATERIALS AND METHODS

Materials

Carbopol 71G was a gift from Noveon, USA, Hydrochlorothiazide was a gift from Evans Nig. Plc. Absolute ethanol was standard reagent grade.

Preparation of Compacts

Tablets comprising 99.0 mg C71, 99.0 mg HCTZ and 2 mg magnesium stearate (carbopol)-HCTZ matrices or 198 mg C71 and 2 mg magnesium stearate (carbopol tablet) were prepared by direct compression on a manesty single punch tablet press (THP, Shangai, China) fitted with 8.5 mm diameter, flat punches. Tablets were produced to crushing strengths in the range of 20.0-22.5 kN.

Dissolution Studies

Drug release was monitored using the British Pharmacopoeia (2004) Apparatus 1 (Erweka, GmbH, Germany) with rotation speed of 50 rpm, in 500 mL of medium at 37±0.5°C. Media comprised acetate buffer (BP) with 0, 10, 20, 30, 40 or 50% (v/v) absolute ethanol. For each medium, 6 tablets were tested and drug release was monitored spectrophotometrically at 299 nm (Shimadzu, Japan).

Data Analysis

Drug release data were analyzed using a modified power law equation (Eq. 1) proposed by Ford et al. (1991).

\[ Q = k (t - I)^n \]

Where,
- \( Q \) = Percentage of drug release at time \( t \),
- \( k \) = Constant incorporating structural and geometric property of the devices,
- \( I \) = Lag time and \( n \) is the release exponent, indicative of the drug release mechanism.

Drug Solubility

The solubility of the drug in the different hydro-alcoholic dissolution media was determined spectrophotometrically (299 nm) at ambient temperature, using a solution of known concentration of HCTZ in the different media as a standard. To determine the solubility, the method of
Roberts et al. (2007) was slightly modified; a saturated solution was prepared by adding excess of drug to 10 mL of media. This solution was then shaken for 4 h and 5 mL was centrifuged (Beckman, London) at 3500 rpm for 5 min. The concentration of HCTZ in the clear supernatant was spectrophotometrically determined.

**Swelling Studies**

The dynamics of the swelling process were investigated by placing each compact (either carbopol-HCTZ matrix or carbopel tablet alone) in a small plastic Petri dish and adding 10 mL of medium at ambient temperature. The study was performed using the 0 and 50% ethanol media. Images of the compacts were captured (using a digital camera Fuji film, 7.5 mp) at varying time intervals; 0, 5, 10, 15, 20, 25, 35, 45, 60, 75, 90, 105 and 120 min.

**Compact Swelling**

Image analysis during C71G-HCTZ matrix and C71G tablet swelling showed increases in both axial and radial dimensions (Table 1, Fig. 1). Percent normalized size increase was calculated as the radial length increase with respect to the initial value to avoid error due to lens effect. Swelling rate was also calculated from the percent normalized size increase.

The differences in swelling rates significantly noticed within the first 30 min indicate a variation in the interaction between media and tablets in the initial period of contact, which maybe due to a different speed of medium penetration (Fig. 2). Such behavior may depend on a slower initial interaction between the ethanol and C71G and could equally account for the initial rapid release observed during dissolution. After the initial period, the formation of a less porous and stronger gel layer, which limits fluid uptake, could increase the diffusion pathway and also decrease gel erosion. The images in Fig. 1 are evidence of this theory, as it is possible to observe the polymer-drug and polymer-ethanol interactions as evidenced by the differences in tablet hydration. In the absence of drug (B2 and EB2), the presence of ethanol (EB2) resulted in faster hydration and spread of the polymer (increase in size). The presence of drug in the polymer (B1 and EB1) shows evidence of interactions between drug, polymer and ethanol, as the images show that the presence of ethanol prevented the rapid spread of the polymer earlier noticed with carbopel tablets alone. The border between medium and tablet was clearly visible in the 0% ethanolic medium (B1 and B2) and ethanolic medium with drug (EB1) until about 75 min when these boundary disappeared. However, the same boundary became less visible in the carbopel tablets without drug (EB2) from about 15 min in the medium. After 25 min in this medium, the tablets were characterized by slower swelling rate.

**Drug Release**

Generally, the presence of ethanol in the dissolution medium suppressed drug release. With the exception of 30% ethanol, retardation of drug release was proportional to the ethanol levels in the medium (Fig. 3). There was a clear evidence of no dose dumping. Release profiles in all the media were

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>B1 (cm)</th>
<th>B2 (cm)</th>
<th>EB1 (cm)</th>
<th>EB2 (cm)</th>
</tr>
</thead>
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<tr>
<td>5</td>
<td>1.3±0.00</td>
<td>1.2±0.00</td>
<td>1.1±0.00</td>
<td>1.2±0.00</td>
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<td>10</td>
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<td>1.2±0.05</td>
<td>1.1±0.05</td>
<td>1.2±0.05</td>
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<td>15</td>
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<td>1.1±0.02</td>
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</tr>
<tr>
<td>20</td>
<td>1.5±0.10</td>
<td>1.0±0.00</td>
<td>1.3±0.00</td>
<td>1.2±0.00</td>
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<tr>
<td>25</td>
<td>1.5±0.10</td>
<td>1.0±0.00</td>
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<td>1.3±0.00</td>
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<tr>
<td>35</td>
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<td>1.1±0.05</td>
<td>1.2±0.00</td>
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</tr>
<tr>
<td>45</td>
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<td>1.0±0.00</td>
<td>1.2±0.00</td>
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</tr>
<tr>
<td>60</td>
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<td>0.9±0.00</td>
<td>1.2±0.00</td>
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<td>75</td>
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<td>1.8±0.00</td>
<td>1.5±0.00</td>
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<tr>
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<td>1.8±0.20</td>
<td>1.6±0.05</td>
<td>1.6±0.05</td>
</tr>
<tr>
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<td>1.6±0.00</td>
<td>1.9±0.00</td>
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<td>1.8±0.05</td>
<td>1.7±0.02</td>
<td>1.9±0.05</td>
</tr>
</tbody>
</table>

(n = 3±standard deviation)
Fig. 1: Continued
Fig. 1: Swelling behaviour difference with matrix swelling at 0% ethanol
characterized by an initial rapid release with rate progressively reducing over time, suggesting that diffusion controlled release mechanism predominated. The 50% ethanol data had the lowest correlation, this maybe indicative of non-uniform gel generation causing inconsistency in drug release.

Analysis of release data using equation 1 shows that with the exception of 30% ethanol medium which has the lowest n value indicative of diffusion and erosion mechanism, release mechanism in the other media appears to be predominated by diffusion and erosion (Ford et al., 1991). The release rates in the various media indicate a similar trend for all media after 30 min, although rates were different particularly for the 30% ethanol medium. Significant differences occurred during the first 30 min when the release in 30% ethanol medium was much higher, although this could not be equated to dose dumping especially as the batch with 0% ethanol medium had the highest drug release (Cmax) at end of dissolution. After 1 h in the 0% ethanol medium, it became difficult to accurately measure the tablet size due to the visual absence of a well defined tablet-medium boundary. For 0% ethanol medium, after 1 h in static conditions, the superficial gel layer has a low polymer concentration and low viscosity, probably with a higher erosion rate, which agrees with the power law analysis of drug release. This observation is consistent with that of Roberts et al. (2007).

In general, the result suggests that for C71G-HCTZ matrices with C71G concentrations > 50%, swelling properties are controlled by the polymer and the dissolution medium. These results are consistent with those by Vargas and Ghaly (1999), where the authors reported the release profile of theophylline to be independent of the diluent type for HPMC K4M concentrations above 30-40%.
**Drug Solubility**

The solubility of HCTZ measured in each of the six dissolution media are presented in Fig. 4. The result shows that there was no direct correlation between the solubility and the percent drug released, as shown in Fig. 5. The solubility of the drug in the media appears not be able to account for the different release behaviors observed during the dissolution studies. This observation is contrary to that of Roberts et al. (2007), where the authors reported a direct correlation between the solubility and dissolution of aspirin in different hydro-ethanolic media, thereby adding aspirin’s release to its increased solubility in the ethanolic media. Therefore, different release behaviors observed in the different dissolution media and the rapid release observed in the 30% ethanol medium suggests that some other factors, such as polymer-drug and/or polymer-alcohol interactions rather than solubility, influence the release of HCTZ from carbopol 71G matrices.

**CONCLUSIONS**

Present study have shown that hydro-alcoholic media can affect the kinetics and mechanism of drug release from matrix-based controlled release formulations in a manner related to the ethanol
content. Release retardation could have been caused by polymer-drug, or polymer-alcohol interactions rather than the drug solubility in the dissolution medium. Polymer-alcohol interaction maybe responsible for the initial rapid release observed in the first 30 min. In these studies, 30% ethanol appeared to be the threshold for polymer-alcohol interaction. Image analysis of the matrix swelling behavior supports the theory that the ethanol interaction with carbopol, particularly in the initial period of contact, was crucial in drug release, but did not result in a dose dumping effect.

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REFERENCES