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Influence of ethanol on aspirin release from hypromellose matrices

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Abstract

Release profiles of aspirin from hypromellose matrices in hydro-ethanolic media were studied. Percent aspirin released increased with increasing levels of ethanol in the dissolution media, correlating with the drug's solubility, however, dose dumping of aspirin did not occur. An initial rapid release was observed in media comprising 40% ethanol. Release in these conditions was considered to be both erosion and diffusion-mediated, in contrast to the release in 0, 10, 20 and 30% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling indicated a slower initial interaction between ethanol and hypromellose accounting for the initial rapid release. Cloud point studies suggested that ethanol retarded hydration of the polymer.

Keywords: Hypromellose; Hydro-ethanolic media; Controlled release; Aspirin; Matrices

1. Introduction

The potential impact of concomitant alcohol consumption on the *in vivo release* of drugs from modified release oral dosage forms is currently evincing interest. This is a consequence of the finding that co-consumption of significant quantities of alcoholic beverage can result in potentially serious dose dumping of the opioid analgesic hydromorphone from a controlled release capsule dosage form (FDA Alert, July 2005). As studies in human volunteers involving co-administration of drug and significant amounts of alcohol pose ethical and operational challenges it is appropriate to consider in vitro studies to provide insight on release mechanisms in hydro-alcoholic media, thereby guiding formulation programs assessing the potential for alcohol-related dose dumping.

The cellulose ether hypromellose, also known as hydroxypropylmethylcellulose or HPMC, is widely used to form swellable hydrophilic matrices that retard drug release to prolong therapeutic effect (Li et al., 2005). Release from such a matrix is mediated by a combination of polymer hydration, diffusion of drug through the gel layer, which forms as a result of polymer transition from a "glassy" to a "rubbery" state upon hydration, drug dissolution and polymer erosion (Nerukar et al., 2005).

The aim of this investigation was to assess the influence of alcohol on the rate and mechanisms of release of aspirin from hypromellose hydrophilic matrices.

2. Materials and methods

2.1. Materials

Hypromellose (Methocel® K4M, Dow Chemical Co., USA) was a gift from Colorcon Ltd., UK. Aspirin (acetyl salicylic acid, Sigma–Aldrich, UK), sodium acetate anhydrous (Fluka, UK) and glacial acetic acid (BDH Chemicals Ltd., UK) were all used as received. Absolute ethanol was standard reagent grade. Deionised water was produced with a reverse osmosis unit (Select analyst HP, Purite Ltd., UK).

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2.2. Formulation and tablet compaction

Tablets comprising 139.5 mg hypromellose, 139.5 mg aspirin and 1 mg magnesium stearate (hypromellose–aspirin matrices) or 279 mg hypromellose and 1 mg magnesium stearate (hypromellose tablets) were prepared by direct compression on a Manesty F3 single punch tablet press fitted with 8.95 mm diameter, flat punches. Tablets were produced to crushing strengths in the range of 5.5–6 kP (Dr. Schleuniger, 6D tablet tester).

2.3. Dissolution testing

Drug release was monitored using a British Pharmacopoeia (2005) Apparatus 1 (8ST, Caleva Ltd., UK) with rotation speed of 50 rpm, in 500 ml of medium at 37 °C. Media comprised acetate buffer (B.P.) with 0, 10, 20, 30 or 40% (v/v) ethanol. For each medium, six tablets were tested and drug release was monitored spectrophotometrically at 265 nm (Genesys 6, Thermo Electron Corporation, USA).

2.4. Data analysis

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

$$M = k(t - l)^n \quad (1)$$

where M is the percentage of drug release at time t, k a constant incorporating structural and geometric properties of the devices, l the lag time and n is the release exponent, indicative of the drug release mechanism.

2.5. Drug solubility

The solubility of the drug in the different hydro-ethanolic dissolution media was determined spectrophotometrically (265 nm) at ambient temperature, using a solution of known concentration of aspirin in the different media as a standard. To determine the solubility, a saturated solution was prepared by adding an excess of drug to 5 ml of media. This solution was then shaken for 2 h (preliminary tests indicated that 2 h was sufficient time to reach saturation) and a small amount (~1.5 ml) was centrifuged (Z160M, Hermle Laborthechnik, Germany) at 14,000 m^{-1} for 20 s. 0.5 ml of the supernatant was diluted until an absorbance value similar to that of the standard was obtained.

2.6. Compact swelling

The dynamics of the swelling process were investigated using a digital camera (Pixera 120es) and associated image analysis software (Image ProPlus®). Each compact (either hypromellose–aspirin matrix or hypromellose tablet) was placed vertically in a small plastic petri dish, and 10 ml of medium was added at ambient temperature. The petri dish was placed in a plane with a light source (tungsten lamp), and the camera, equipped with macro lens was placed above. The light beam direction was regulated to generate a high contrast image, with the tablet completely black in a bright background. The analysis was performed using the 0 and 40% ethanol media. Images were obtained at 0, 5, 10, 15, 20, 25, 35, 45, 60, 75, 90, 105 and 120 min. Each image was calibrated using a graduated ruler under the same conditions.

2.7. Viscosity

Viscosity measurements were performed on 2% (w/v) hypromellose gels in the different dissolution media. The gels were prepared with 150 ml of each dissolution media and 3 g of hypromellose. Initially, in a pre-weighed beaker, 80 ml of aqueous buffered solution (comprising sufficient buffer salts for 150 ml of media) was heated to 80 °C. Three grams of hypromellose was then added under stirring, until a uniform dispersion was obtained. At this point the heater was switched off, and the beaker was left stirring for 30 min. In this period a viscous gel was obtained and the additional liquid with the requisite amount of ethanol for each medium was added with continuous stirring. The dispersions were left to stir for 1 h and were then stored in a refrigerator (6 °C) for 48 h. Prior to testing, gels were allowed to stand for 1 h at ambient temperature. Additionally, the gels were weighed to determine whether losses due to ethanol evaporation had occurred. The effect of such evaporation resulted

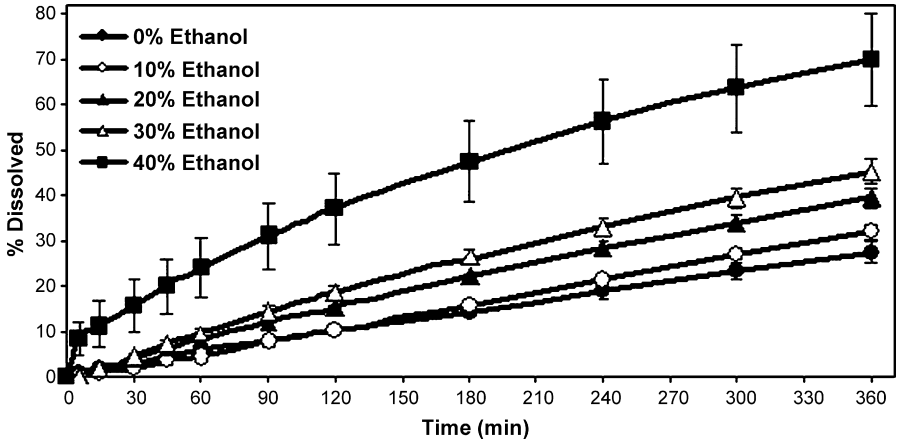

Fig. 1. The effect of ethanol concentration on the release of aspirin from hypromellose matrices in various hydro-ethanolic media ($n = 6 \pm$ S.D. for each data set).

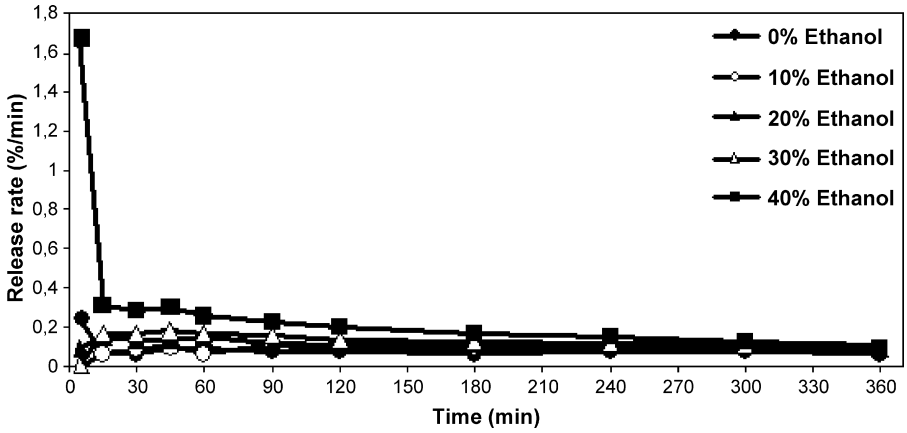

Fig. 2. The effect of time on the release rate (% min^{-1}) of aspirin from hypromellose matrices in various hydro-ethanolic dissolution media.

in hypromellose concentrations in the range of 1.9–2.1 % (w/v).

Gel viscosity was determined with a CSL^2_{500} Carri-Med rheometer (TA Instruments Ltd., USA) by plate–plate (steel plate, 4 cm diameter) geometry, 0.05 mm gap at 20 °C. Solutions were sheared at 2 Pa for 1 min. Shear rate was increased and decreased at constant acceleration from 0 to 1000 s^{-1} (up curve) and from 1000 to 0 s^{-1} (down curve) (Hino and Ford, 2001).

2.8. Cloud point

Cloud point is the temperature at which the light transmission of a gel is reduced by 50% of the initial value (Sarkar, 1979). Four samples of gel at different hypromellose concentrations (0.5, 1, 1.5, 2%) were prepared using both 0 and 40% ethanol media as reported in Section 2.7. After 48–64 h refrigeration, the samples were placed in a water bath (Clifton, Nickel-Electro Ltd., UK) and temperature was gradually increased. At 5 °C intervals (or 2 °C intervals when approaching the cloud point) sample transmittance was measured spectrophotometrically at 800 nm (Genesys 6, Thermo Electron Corporation) using an empty glass cuvette as a blank and a 0% hypromellose medium as control (Mitchell et al., 1990).

Table 1
The effect of ethanol concentration on the release exponent and regression coefficient from analysis of the release of aspirin from hypromellose matrices

	Ethanol				
	0%	10%	20%	30%	40%
n	0.9158	1.0880	0.9026	0.9051	0.5851
R^2	0.9996	0.9987	0.9990	0.9966	0.9983

Table 2
The effect of ethanol concentration on the solubility of aspirin in hydro-ethanolic dissolution media

	Ethanol				
	0%	10%	20%	30%	40%
Aspirin solubility (mg ml^{-1})	8.4	13.3	23.4	26.2	47.5

3. Results and discussion

3.1. Drug release

Release profiles of aspirin from hypromellose matrices are shown in Fig. 1. With the exception of the medium contain-

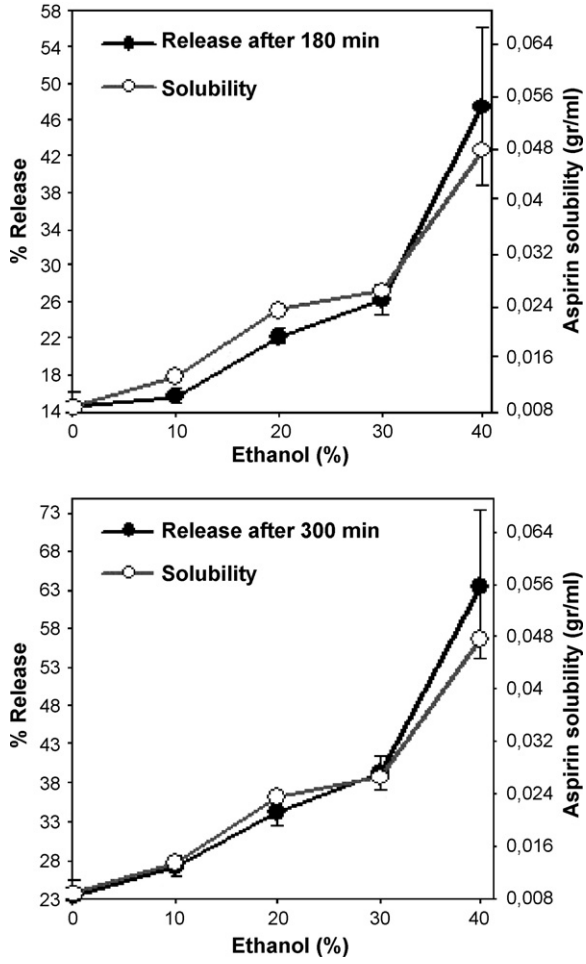

Fig. 3. The effect of ethanol concentration on the solubility of aspirin solubility and percent aspirin released (180 and 300 min data) from hypromellose matrices in various hydro-ethanolic media.

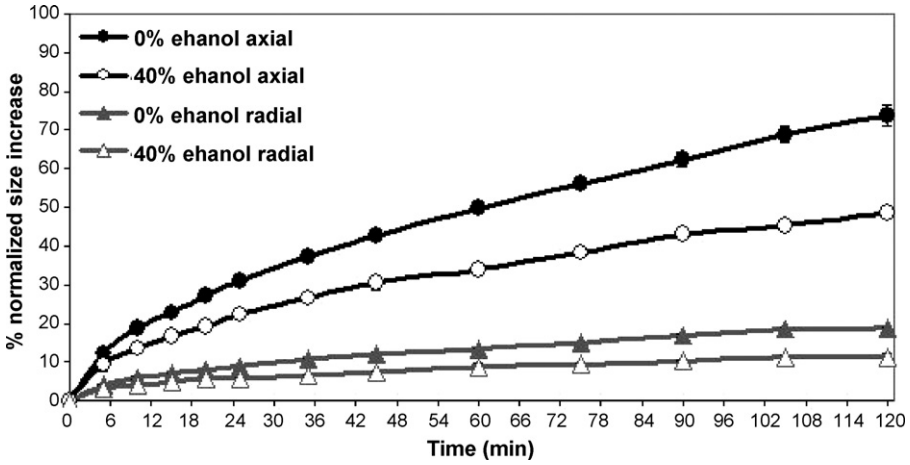

Fig. 4. The effect of ethanol concentration on the percent normalised size increase (radial and axial) for hypromellose–aspirin matrices in 0 and 40% ethanol media ($n = 2$).

ing 40% ethanol, profiles suggested near-zero order release. Release rates were proportional to the ethanol levels in the medium, although no dose dumping was evident. Release profiles in the 40% ethanol medium were characterised by an initial rapid release with rate progressively reducing over time, suggesting that a diffusion controlled release mechanism predominated. The high standard deviation for the 40% ethanol data could be indicative of non-uniform gel layer generation causing inconsistency in release.

Analysis of the release data using Eq. (1) is shown in Table 1. Data confirm the previous impression that release in 40% ethanol media was different from release in the other media. The release mechanism, denoted by the lower n value, appears to be dependent on both diffusion and erosion, while in all other media the higher n values indicate that an erosion mechanism is dominant (Ford et al., 1991).

The release rate in the various media (Fig. 2) was calculated from the average curves displayed in Fig. 1. Results indicate a similar trend for all media after 90 min, although the rates were different (particularly for the 40% ethanol medium). Marked differences occur during the first 30 min when the release in 40% ethanol medium was much higher, although this could not be equated to dose dumping.

3.2. Drug solubility

The solubility of aspirin measured in each of the five dissolution media are shown in Table 2. The most interesting aspect is the similarity between the solubility and the percentage of drug released, as shown in Fig. 3. The solubility of the drug in the media appears to account for the different release behaviours observed during the dissolution testing. However, this does not signify a diffusion controlled mechanism, since both diffusion and erosion are dependent on drug solubility (Bettini et al., 2001). Therefore, the initial rapid release observed in the 40% ethanol medium suggests that some other factor, together with the solubility, influences the release of aspirin from hypromellose matrices in the first 30 min.

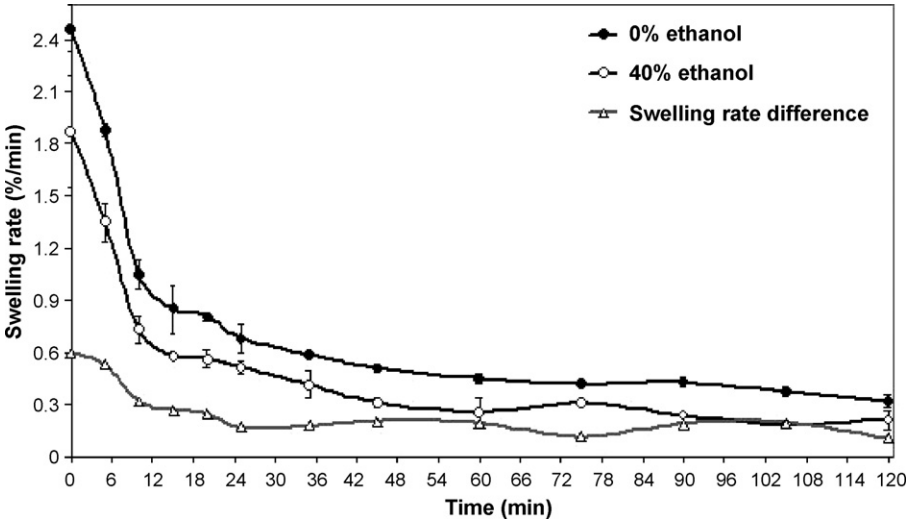

Fig. 5. The effect of time on the axial swelling rate (% min^{-1}) of hypromellose–aspirin matrices in 0 and 40% ethanol media ($n = 2$).

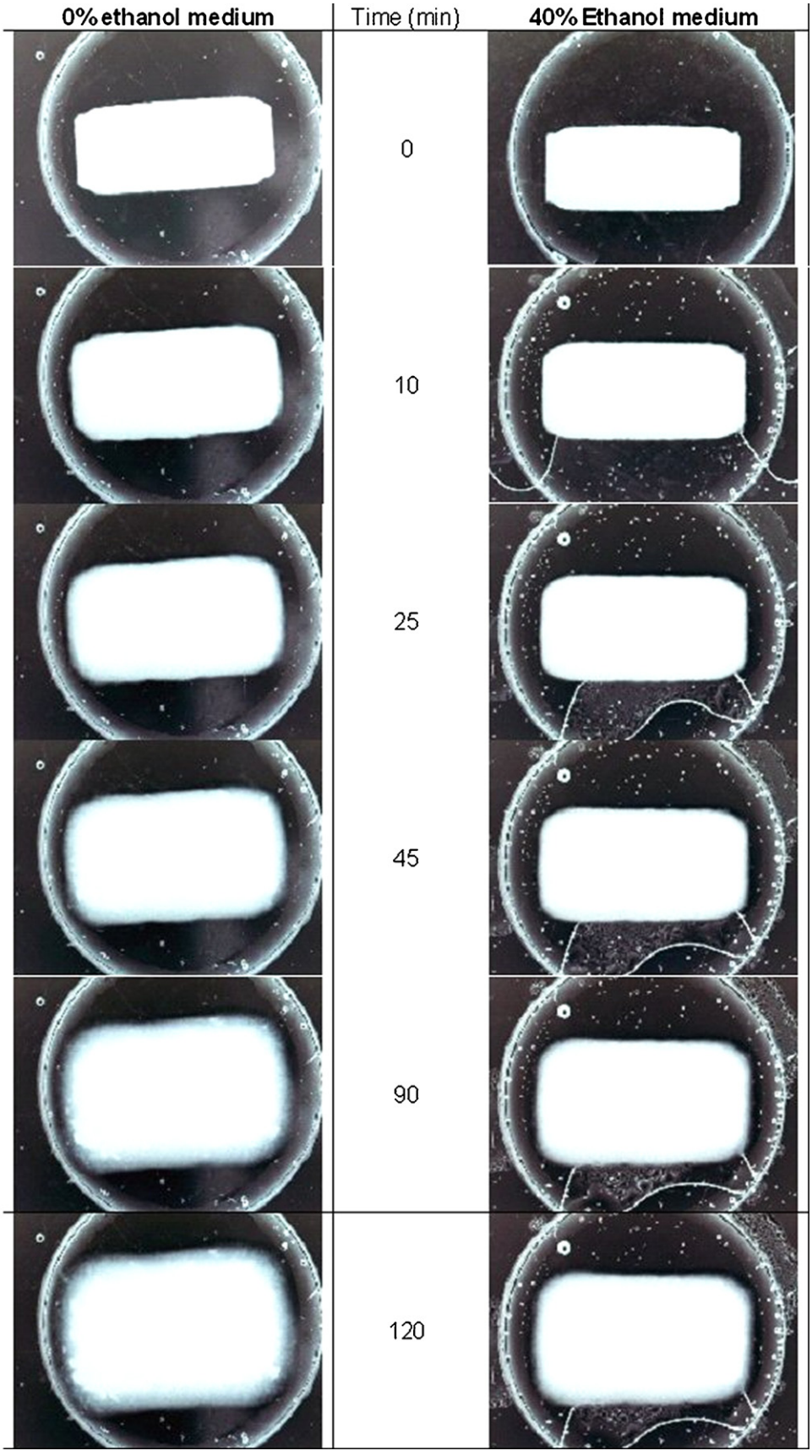

Fig. 6. The effect of time on the swelling of hypromellose–aspirin matrices at various time points in 0 and 40% ethanol media.

3.3. Compact swelling

Image analysis during hypromellose–aspirin matrix and hypromellose tablet swelling showed increases in both axial and radial dimensions. Percent normalised size increase was calculated as the axial or radial length increase with respect to the initial value (being the value measured at time 0 in the medium and not that determined prior to adding the medium to avoid errors generated by the "liquid lens" effect). Swelling rate was also calculated from the percent normalised size increase.

Results (Fig. 4.) show differences in swelling behaviour, with matrix swelling in 0% ethanol medium characterised by a greater size increase in both radial and axial directions. Consistent with other findings, axial swelling was greater than radial (Mitchell et al., 1990; Rajabi-Siahboomi et al., 1994; Colombo et al., 1990). From the swelling rates (Fig. 5) it is evident that the major distinction between the two media is during the first 20 min. These results indicate a variation in the interaction between media and tablets in the initial period of contact, which may be due to a different medium penetration speed. Such behaviour may depend on a slower initial interaction between the ethanol and hypromellose and could account for the initial rapid release observed during dissolution. After the initial period, the possible formation of a less porous and stronger gel layer, which limits the medium uptake, could increase the diffusion pathway and also decrease gel erosion. The images (presented as negatives) in Fig. 6 support this theory, where the different swelling behaviour is evident and it is possible to observe the border between medium and tablet. In the 40% ethanol medium this boundary became more difficult to differentiate after 75 min (picture not shown), whilst in the 0% ethanol medium, this occurred after 25 min. 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. This observation suggests that for the 0% ethanol medium, after 1 h in static conditions, the superficial gel layer has a low polymer concentration and low viscosity, probably with a high erosion rate, which concurs with the power law analysis of drug release.

The comparison of percent axial expansion for hypromellose–aspirin matrices and hypromellose tablets is shown in Fig. 7. Results show very small differences between the two sets of tablets. Only in the 40% ethanol medium there is a slight increase on the axial expansion. However, the radial expansion results (results not shown), exhibited results with the opposite trend (a similar curve for the 40% ethanol medium and slight differences for the 0% ethanol medium) confirming the triviality of the variation. As observed in the aspirin tablets, the axial swelling is also greater than radial for the100% hypromellose tablets. These results suggest that for hypromellose–aspirin matrices with hypromellose concentrations $\geq$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 hypromellose K4M concentrations above 30–40%. However, Vargas and Ghaly (1999) did not specify the reason for this observation. It is likely that the 30% hypromellose content represents the threshold over which swelling, and thus the release mechanism, depends only on the polymer.

3.4. Viscosity

The polymeric dispersion curves (not shown) were shear rate dependent and exhibited pseudoplastic behaviour, as previously reported (Dow commercial information, 2002). The viscosity curves were analysed (Rheology Advantage Data Analysis Software, TA Instruments Ltd.) using a power law model (Eq. (2)) suitable for pseudoplastic behaviour.

$$\sigma = a\gamma^m \tag{2}$$

In the power law equation (Bonacucina et al., 2004), σ is the shear stress, γ the shear rate, a the constant related to the

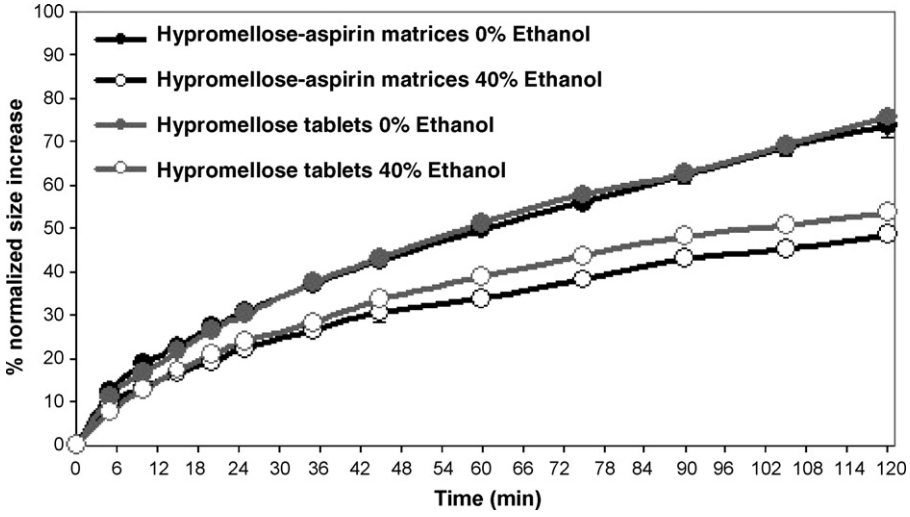

Fig. 7. The effect of time on the axial percent normalised size increase for hypromellose–aspirin matrices and hypromellose tablets in 0 and 40% ethanol media ($n = 2$).

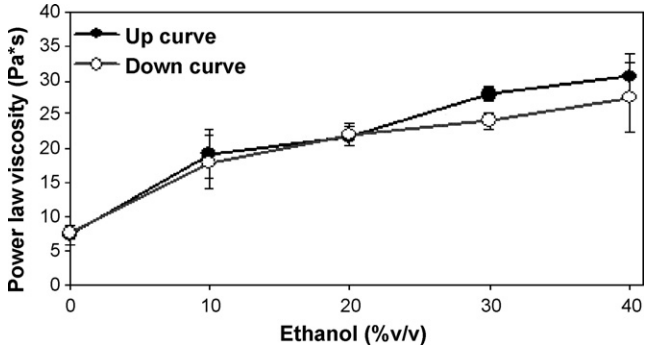

Fig. 8. The effect of ethanol concentration in media on hypromellose gel viscosity determined using the power law model ($n = 5 \pm$ S.D.).

viscosity and m is related to the flow patterns. m values >1, =1 and <1 denote dilatant, Newtonian and pseudoplastic behaviour, respectively. From these results the pseudoplastic behaviour of the dispersion was confirmed (highest m value, obtained for the 0% ethanol samples, was 0.519) and the trend of the viscosity, measured at low shear rate values, increased as the percent ethanol increased (Fig. 8). The viscosity data indicate that a stronger gel layer forms as a result of the increase in percent ethanol in the media.

3.5. Cloud point

Cloud point values for the 0% ethanol medium were calculated from linear regression of the last three points of the curve (Fig. 9), which displays a slight decrease in cloud point as the percent polymer increased (values of 75.1, 72.3, 71.7 and 71.2 °C for 0.5, 1, 1.5 and 2% hypromellose, respectively). The results agree with previous tests performed with Methocel K4M (Mitchell et al., 1993). The 40% ethanol sample did not display a cloud point (data not shown), with the cuvette remaining clear until the boiling point of the polymeric dispersion (∼78–80 °C) was reached. These results suggest a protective effect of the ethanol on the polymer hydration, similar to the salting in effect observed for other substances (e.g. aminophylline or propranolol hydrochloride, Mitchell et al., 1990). The interactions of the polymer solvated by ethanol are greater than the interactions of water and the polymer due to hydrogen bonding and van der Waals forces between the polymer and ethanol.

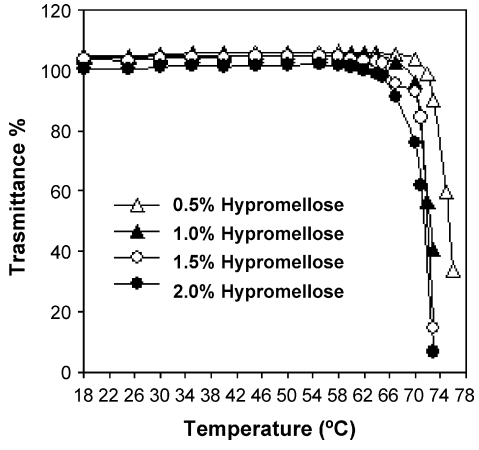

Fig. 9. The effect of the temperature on the percent transmittance of various hypromellose dispersions in the 0% ethanol medium. (No change in light transmission was observed for the 0% hypromellose sample—curve not shown).

4. Conclusions

These studies have shown that hydro-ethanolic media can affect the kinetics and mechanism of drug release from matrix-based controlled release formulations in a manner related to the ethanol content. In these studies release enhancement could have been caused by increased drug solubility in the dissolution medium but the initial rapid release observed in the first 30 min may be due to the polymer–alcohol interaction. Image analysis of the matrix swelling behaviour supported the theory that the ethanol interaction with hypromellose, 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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