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The Influence of Hydro-Alcoholic Media on Hypromellose Matrix Systems

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Hydrophilic matrices are widely used for extended release drug delivery, with hypromellose (HPMC) being a popular rate-controlling carrier. The FDA has recently issued an alert regarding the potential negative influence of alcohol on extended release dosage forms.

The aim of this study was to investigate the hydroalcoholic solution effect on hydration, gel formation and drug release from HPMC matrices. None of the investigated matrix formulations (felodipine, gliclazide, and metformin hydrochloride) resulted in dose-dumping when exposed to ethanol solutions.

HPMC compacts made of three different viscosity grades of Methocel showed consistent swelling and gel formation when exposed to hydroalcoholic media.

Keywords hydroalcoholic; hypromellose; extended release; felodipine; gliclazide; metformin HCl; HPMC

INTRODUCTION

Hydrophilic matrix systems are a popular and widely used approach to achieve extended drug release. Hypromellose [hydroxypropyl methylcellulose (HPMC)] is typically the polymer of choice for the rate-controlling carrier in these systems because of its safety, availability, global compliance, and physicochemical/mechanical characteristics (Colombo et al., 2000; IMS data, 2002; Li et al., 2005; Longer & Robinson, 1990; Rajabi-Siahboomi & Jordan, 2000).

HPMC in the matrix hydrates rapidly on contact with the aqueous media to form a gelatinous layer on the surface of the tablet. Soluble drugs are released primarily by diffusion through the gel layer, whereas drugs with low solubility are released primarily by gel erosion. Typically, however, drug release occurs by a combination of these two mechanisms (Siepmann & Peppas, 2001; Velasco et al., 1999). Rapid polymer hydration and uniform gel formation are critical to the integrity and subsequent performance of hypromellose matrix systems.

Drug release rate from HPMC extended release (ER) tablets is dependent upon factors such as polymer type and level; drug solubility and dose; polymer/drug ratio; filler type and level; polymer/filler ratio; particle size of drug and polymer; porosity and shape of the matrix (Bettini et al., 1994; Campos-Aldrete & Villafuerte-Robles, 1997; Ford et al., 1985, 1987; Lapidus & Lordi, 1968; Li et al., 2005; Rodriguez et al., 2000). Drug release rate may also be significantly affected by the medium to which the matrix is exposed to upon ingestion, i.e. pH, electrolytes, surfactants, enzymes (Alderman, 1984; Doherty et al., 1991; Johnson et al., 1993; Mitchell et al., 1990; Pagay, 1988; Rajabi-Siahboomi et al., 1994; Sheu et al., 1992; Wilder et al., 1991). The influence of hydro-alcoholic media on hypromellose matrices, for cases when the dosage may be taken with, shortly before or after an alcoholic drink has not been fully investigated.

In July 2005 the FDA issued an alert for healthcare professionals regarding an alcohol-Palladone™ interaction. When ingested with alcohol the peak plasma concentration of hydromorphone increased to potentially lethal levels due to breakdown of the ER formulation. Since this alert, there have been some reports of the influence of hydro-alcoholic media on the performance of solid oral modified release systems. Koziara et al. (2006) claimed an increased permeability, elasticity and swelling of cellulose acetate semi-permeable membranes used for osmotic drug delivery in 0–60% ethanol solutions. Although, a slight increase in drug release from OROS® systems was recorded, no dose-dumping effect was observed. Roberts et al. (2006) studied the influence of alcohol on the release of aspirin from HPMC matrix tablets. They found that ethanol affects kinetics and mechanism of aspirin release, but does not result in a dose-dumping effect.

The objective of this study was to investigate the influence of hydro-alcoholic solutions on the hydration, swelling and gel formation of HPMC compacts and drug release from their matrices.

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MATERIALS AND METHODS

Formulation and Preparation of HPMC Matrix Tablets

The influence of hydro-alcoholic media on hypromellose matrix formulations of three different candidate drugs: felodipine, gliclazide and metformin hydrochloride (HCl) was investigated. Table 1 shows the solubility of these drugs in water and alcohol.

Hypromellose matrix (12-h release) formulations were developed as suggested by the HyperStart® (Levina et al., 2006) formulation service, and are shown in Tables 2–4.

All formulations, batch size 500 g, were prepared using a three-dimensional shaker-mixer (Turbula, Model 2T, Bachoffen).

Felodipine, one-half of the lactose, and the fumed silica were blended for 5 min. This blend was then screened through a 500 μm (35 mesh) sieve, returned to the mixer with the HPMC and the remaining lactose, and blended for an additional 5 min.

TABLE 1
Drug Solubility in Water and Alcohol (Martindale, 1999)

Active	Solubility in Water	Solubility in Alcohol
Felodipine	Practically insoluble	"freely soluble in absolute alcohol, in methyl alcohol"
Gliclazide	Practically insoluble	"slightly soluble in alcohol"
Metformin HCl	Freely soluble	"slightly soluble in alcohol"

TABLE 2
Felodipine 5 mg HPMC ER Formulation Suggested by HyperStart

Material	Supplier	% w/w	mg/tablet
Felodipine	Spodefell, UK	2.5	5
HPMC (Methocel® K100LV CR)	Colorcon Ltd, UK	37.0	74
Lactose (Fast Flo®)	Foremost Farms, USA	59.5	119
Fumed silica (Aerosil® 200)	Degussa, France	0.5	1
Magnesium stearate	Peter Greven, UK	0.5	1
Total		100.0	200

TABLE 3
Gliclazide 30 mg HPMC ER Formulation Suggested by HyperStart

Material	Supplier	% w/w	mg/tablet
Gliclazide	Synergy Enterprises, India	15.0	30
HPMC (Methocel® K100LV CR)	Colorcon Ltd, UK	35.0	70
Microcrystalline cellulose (Avicel® PH102)	FMC, Ireland	49.0	98
Fumed silica (Aerosil® 200)	Degussa, France	0.5	1
Magnesium stearate	Peter Greven, UK	0.5	1
Total		100.0	200

TABLE 4
Metformin HCl 500 mg HPMC ER Formulation Suggested by HyperStart

Material	Supplier	% w/w	mg/tablet
Metformin HCl	Ferico Labs, India	50.0	500
HPMC (Methocel® K100M CR)	Colorcon Ltd, UK	30.0	300
Microcrystalline cellulose (Avicel® PH102)	FMC, Ireland	19.0	190
Fumed silica (Aerosil® 200)	Degussa, France	0.5	5
Magnesium stearate	Peter Greven, UK	0.5	5
Total		100.0	1000

For gliclazide and metformin HCl blends, microcrystalline cellulose (MCC) and fumed silica were screened through a 500 μm sieve. All ingredients (except for the magnesium stearate) were then blended for 5 min.

For all three blends, magnesium stearate was added last and the formulations were mixed for a further 1 min.

Tablets were manufactured using an instrumented 10 station rotary tablet press (Piccola, Riva, Argentina) running at 20 rpm.

Felodipine tablets were compressed at 20 kN using 7 mm normal concave tooling to a breaking force of 31.4 ± 0.4 kp. Gliclazide matrices (9.2 ± 1.0 kp) were produced using 7 mm normal concave tooling at 10 kN compression force. Metformin HCl tablets (10.3 ± 0.7 kp) were manufactured using 7×18 mm caplet tooling at 20 kN compression force.

Dissolution Studies

Dissolution testing was performed in a USP compliant dissolution bath (Sotax) using Apparatus II (paddle method), small (8×23 mm) sinkers (Sotax); at 100 rpm and 37.0 ± 0.5°C. A dual beam spectrophotometer (Perkin Elmer) fitted with 10 mm (for felodipine), 5 mm (for gliclazide), and 0.01 mm (for metformin HCl) glass cells was used for the UV drug detection. Testing was performed over a 12 h time period using an automated sampling device.

For felodipine, the dissolution medium was 500 ml of pH 6.5, 0.1M phosphate buffer and 1% w/v sodium lauryl sulphate (SLS), according to the USP methodology <724>. The amount of felodipine released in the media was measured at a UV wavelength of 362 nm.

For gliclazide, the dissolution medium was 900 ml of purified water. The absorbance readings were taken at 226 and 290 nm. The absorbance value at 290 nm was then subtracted from the value at 226 nm.

For metformin HCl, the dissolution medium was 1000 ml of purified water. The amount of drug present was measured at a wavelength of 233 nm.

For all three formulations, additional dissolution testing was performed in 5% or 40% v/v ethanol (USP/BP, Hayman Ltd) solutions for either 1 or 12 h using paddles at 100 rpm and sinkers (Table 5).

Tablets tested for only 1 h in alcohol were transferred together with sinkers to the relevant non-alcoholic medium and dissolution testing continued for an additional 11 h as described above.

The dissolution results were compared to the drug release in non-hydro-alcoholic media using the f_2 factor (Federal Register, 1995; Moore & Flanner, 1996). An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.

To investigate the mechanism of drug release in various media, the release data of the drugs between 5 and 60% were fitted to Eq. (1):

$$Q = kt^n \quad (1)$$

where Q is the percentage drug released at time t, k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the release exponent indicative of the drug release mechanism.

Values of n approximating 0.5 indicate predominantly diffusion control and values approximating 1.0 correspond to zero-order release.

Preparation and Testing of HPMC Compacts

Discs of 10 mm diameter (300 mg) HPMC compacts were prepared from Methocel® K100LV CR, K4M CR, and K100M CR using a typical hydraulic IR hand press (Thermo Spectronic).

The influence of media composition on the swelling and erosion properties of the above Methocel compacts was determined using a modified version of the method described by Tahara et al. (1995) and Kavanagh & Corrigan (2004). In this method the wet weights of the hydrated HPMC compacts were measured. Testing was conducted in a USP-compliant dissolution bath (Erweka) using Apparatus II (paddle method) in 900 ml of dissolution media at 100 rpm with sinkers. The media were ethanol (dehydrated ethanol USP/EP, Ineos Enterprises) and purified water mixtures in the following ratios: 0:100, 25:75, and 50:50 v/v at 37.0 ± 0.5°C.

The HPMC compacts were exposed to the dissolution media for 15, 30, 60, and 120 min, and then each compact was removed into a pre-weighed plastic container. The excess media was drained and blotted from around the disc without touching it. The compact and the container were weighed and then the wet weight of each compact was established. Each determination at each time point was performed in triplicate, and average and standard deviation values were calculated.

The relative swelling of the compacts, calculated, as the ratio of the wet weight to the initial weight was determined, as an indication of the extent of matrix swelling.

$$\text{Relative swelling} = W_w / W_i \quad (2)$$

TABLE 5
Summary of the Dissolution Tests Performed

	Felodipine	Gliclazide	Metformin HCl
No exposure to alcoholic media	Phosphate buffer with 1% w/v SLS	Purified water	Purified water
Long (12 h) exposure to hydro-alcoholic media	5% or 40% v/v solution of ethanol in phosphate buffer with 1% w/v SLS	5% or 40% v/v aqueous solutions of ethanol	5% or 40% v/v aqueous solutions of ethanol
Short (1 h) exposure to hydro-alcoholic media	1 h in 5% or 40% v/v aqueous solutions of ethanol; then 11 h in phosphate buffer with 1% w/v SLS	1 h in 5% or 40% v/v aqueous solutions of ethanol; then 11 h in purified water	1 h in 5% or 40% v/v aqueous solutions of ethanol; then 11 h in purified water

where W_w is the wet weight of the compact at time t and W_i the initial weight of the compact.

Saturated Solubility Measurement for the Candidate Drugs

The saturated solubility of each drug was determined by dispersing an excess amount of the drug in a beaker of purified water, 5 or 40% v/v ethanol at 37°C. The dispersions were stirred at 300 rpm and samples of the supernatant were withdrawn at 12 and 24 h for analysis. Drug concentrations were measured by UV absorbance, as described above, and the mean values of triplicate samples were calculated.

RESULTS AND DISCUSSION

The Effect of Hydro-Alcoholic Media on Drug Release from HPMC ER Matrices

Dissolution profiles of drug formulations in the presence of 0, 5 or 40% v/v of ethanol are shown in Figures 1–3. For all three-drug formulations, even extreme exposure to the hydro-alcoholic media for up to 12 h did not result in a failure of the HPMC matrices. The differences observed in drug release profiles in different media may be due to changes in drug solubility in the respective media (Tables 1 and 6).

Drug release from felodipine ER formulation in 5 and 40% v/v ethanol showed higher variability compared to water medium as indicated by an increase in standard deviation values from less than 2.50 in both volume ratios to up to 6.75 and 6.87, respectively (Figure 1). Although the solubility of felodipine increased up to 5-fold in 40% v/v ethanol, drug release profiles remained similar with f_2 values greater than 50 (Table 7).

Similar to felodipine formulation, gliclazide ER dissolution data also indicated some increase in standard deviation values from up to 4.36 (in water) to a maximum of 6.12 (in 5% v/v ethanol) and to a maximum of 7.14 (in 40% v/v ethanol) (Figure 2). However, despite increased solubility of gliclazide in hydro-alcoholic media (11-fold in 40% v/v ethanol, Table 6), drug release profiles remained similar to that in water with f_2 values greater than 50 (Table 7).

Metformin HCl solubility decreased from 450 g/L in water to 379 g/L in 5% v/v ethanol and to 295 g/L in 40% v/v ethanol solution. This progressive reduction in solubility of the drug in the presence of 5 or 40% v/v ethanol in the media is clearly observed in the release profiles shown in Figure 3.

Although there is a slight change in dissolution of metformin HCl ER formulation in 5% v/v ethanol compared to the water medium, the f_2 metrics value (Table 7) of 68 showed similarity of release profiles. On the other hand an f_2 value of 44 for the drug release in 40% v/v ethanol and water confirmed that these profiles are not similar.

Alcohol is rapidly absorbed from the gastro-intestinal tract (GIT) and is distributed throughout the body fluids (Martindale, 1999). The rate of absorption of alcohol from the GIT may be modified by factors such as presence of food, concentration of alcohol, and period of time during which it is ingested. It is unlikely, however, for any tablet taken with alcohol (or shortly before or after an alcoholic drink) to have a prolonged exposure, i.e., 12 h to the alcoholic solution in the GIT.

Therefore, in order to assess the behaviour of HPMC matrices under GIT relevant conditions, the HPMC ER formulations were exposed to the ethanol solutions only for 1 h before they were transferred to non-alcoholic media as outlined in Table 5. Figures 4 and 5 show drug release profiles from felodipine and gliclazide ER formulations, respectively when exposed to 5% or 40% v/v ethanol followed by non-alcoholic media.

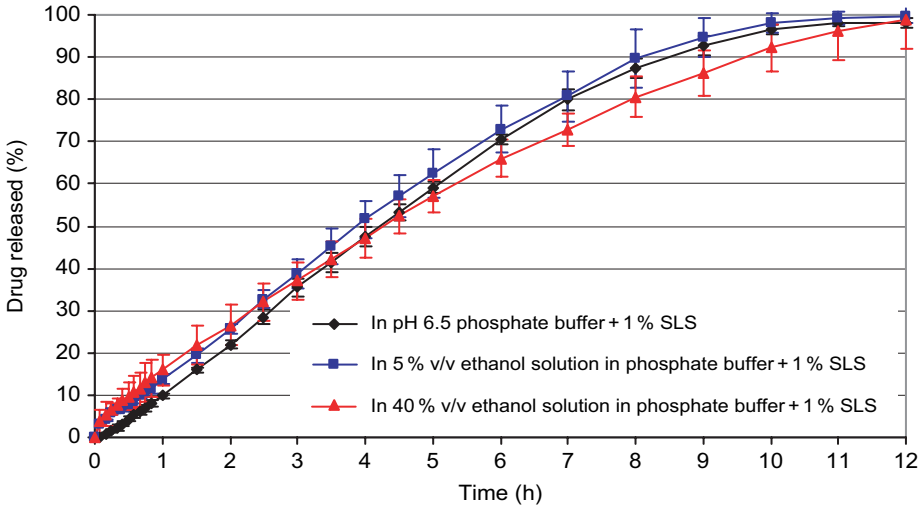

FIGURE 1. Felodipine 5 mg release profiles from HPMC ER matrices in the media containing 0, 5 or 40% v/v ethanol (n=3).

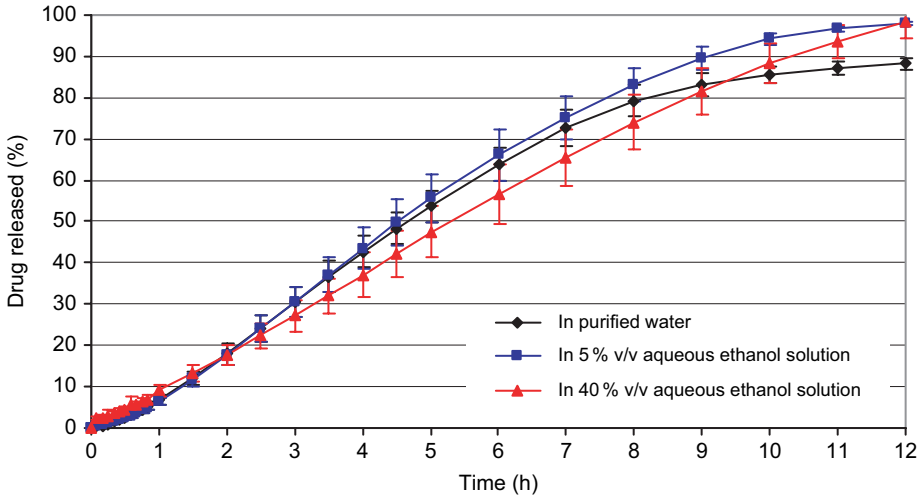

FIGURE 2. Gliclazide 30 mg release profiles from HPMC ER matrices in the media containing 0, 5 or 40% v/v ethanol (n = 3).

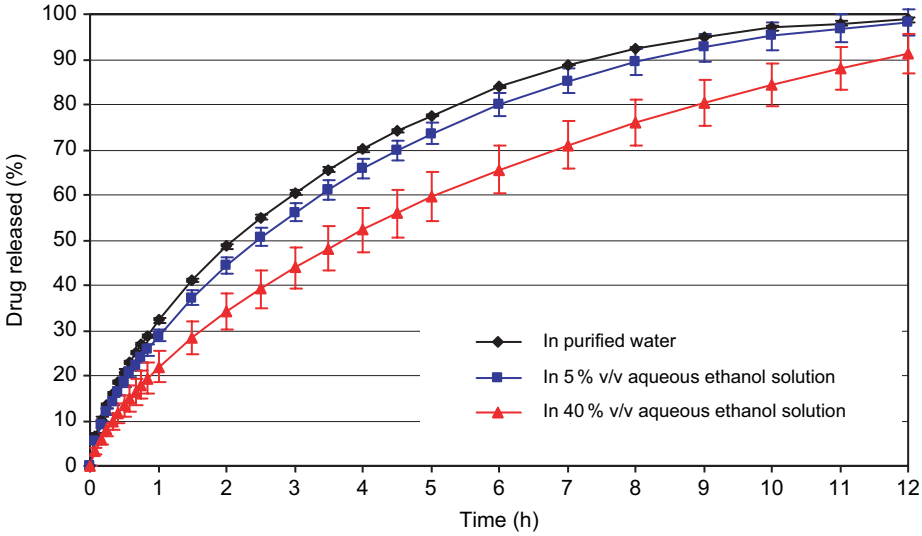

FIGURE 3. Metformin HCl 500 mg release profiles from HPMC ER matrices in the media containing 0, 5 or 40% v/v ethanol (n = 3).

TABLE 6
Saturated Solubility of the Candidate Drugs in Various Media (g/L)

	Felodipine	Gliclazide	Metformin HCl
Water	0.002	0.045	450.413
5% v/v ethanol in water	0.005	0.054	378.647
40% v/v ethanol in water	2.490	0.503	295.466
pH 6.5 phosphate buffer+1% SLS	0.811	–	–
5% v/v ethanol in phosphate buffer+1% SLS	0.721	–	–
40% v/v ethanol in phosphate buffer+1% SLS	4.374	–	–

TABLE 7
f_2 Values for Drug Release Profiles from HPMC Matrices in Hydro-alcoholic Media Compared to When They were not Exposed to Ethanol Solutions

	5% v/v Ethanol		40% v/v Ethanol	
Duration of Exposure to Alcohol Containing Media	12 h	1 h	12 h	1 h
Felodipine formulation	71	76	63	63
Gliclazide formulation	80	65	79	55
Metformin HCl formulation	68	86	44	54

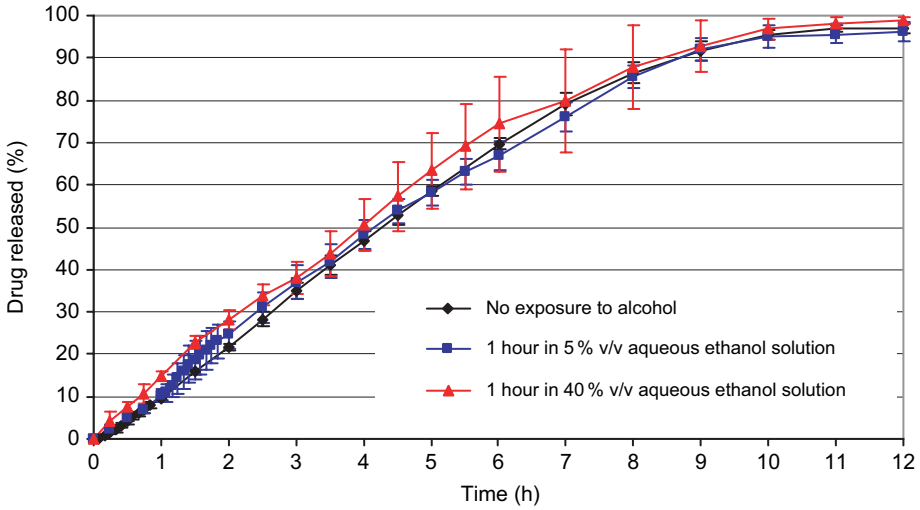

FIGURE 4. The effect of 1 h exposure of HPMC ER matrices to the media containing 0, 5 or 40% v/v ethanol on felodipine 5 mg release profiles (n = 3).

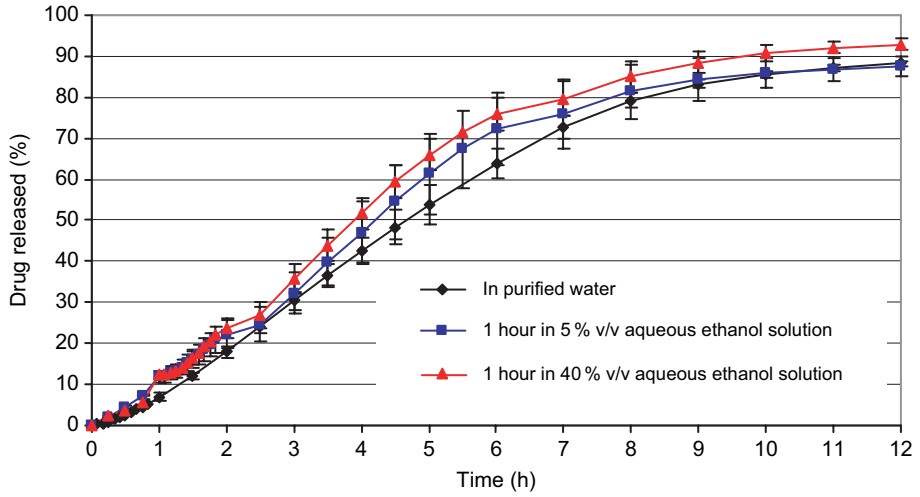

FIGURE 5. The effect of 1 h exposure of HPMC ER matrices to the media containing 0, 5 or 40% v/v ethanol on gliclazide 30 mg release profiles (n = 3).

The solubility of felodipine is markedly dependent on the dissolution media used (Table 6). Saturated solubility of the drug in pH 6.5 phosphate buffer containing 1% w/v SLS is 0.811 g/L and 2.49 g/L in 40% v/v ethanol solution, respectively. The f_2 values for felodipine release profiles from tablets exposed for 1 h to 5 and 40% v/v ethanol solutions, as compared to the release in non-alcoholic medium, were found to be 76 and 63, respectively (Table 7). These indicate similarity.

It was also found that there is an increase in drug release variability for tablets exposed to the hydro-alcoholic media. Standard deviation increased from up to 2.6% (no exposure to alcohol) to 4.7% (exposure to 5% v/v alcohol) and to 12.0% (exposure to 40% v/v alcohol), respectively.

The solubility of gliclazide is also dependent on the dissolution media used (Table 6). For gliclazide ER matrices, when subjected to hydro-alcoholic media for 1 h, a slight change in the drug release can be attributed to the change in drug solubility from practically insoluble in water to slightly soluble in alcohol. The f_2 values for gliclazide release profiles from tablets exposed for 1 h to 5% and 40% v/v ethanol solutions, as compared to the release in water, were found to be 65 and 55, respectively (Table 7) indicating similarity.

The effect of 1 h exposure to hydro-alcoholic media on metformin HCl ER matrices is presented in Figure 6. The f_2 values for the drug release profiles from the tablets exposed for 1 h to 5 and 40% v/v ethanol solutions, as compared to the release in

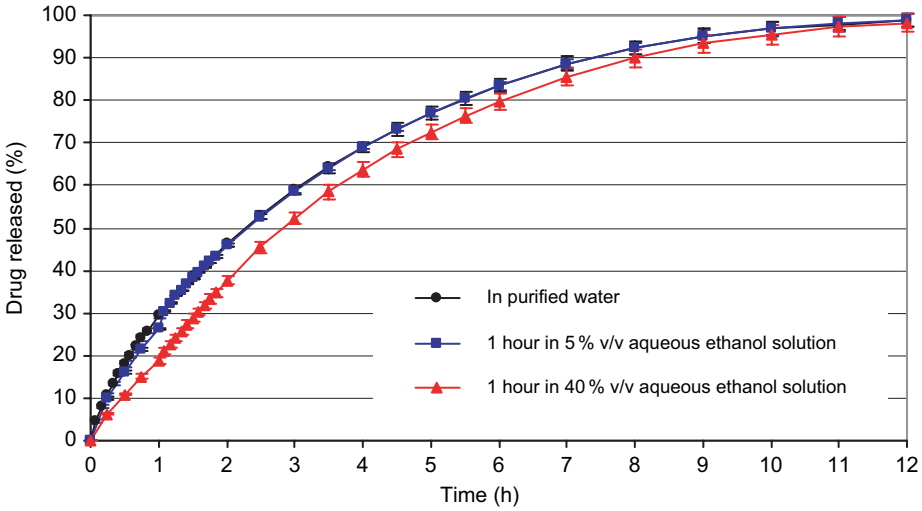

FIGURE 6. The influence of 1 h exposure of HPMC ER matrices to the media containing 0, 5 or 40% v/v ethanol on metformin HCl 500 mg release profiles (n = 3).

water, were found to be 86 and 54, respectively (Table 7). These data indicate similarity of the release profiles in water and hydro-alcoholic media despite the reduced solubility of metformin HCl in ethanol solutions (Table 6).

The values of the kinetic constant (k), the release exponent (n), and correlation coefficient (R^2) determined from the drug release data are presented in Table 8.

For matrix tablets, an n value of near 0.5 indicates a diffusion control and an n value of near 1.0 indicates an erosion or relaxation control mechanism of drug release (Espinoza et al., 2000; Ford et al., 1991). Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.

The values of n and k are inversely related, i.e., it can be expected that with a decrease in n value, k value is expected to increase (Ebube et al., 1997). A very high k value may suggest a burst drug release from the matrix.

TABLE 8
Values of the Kinetic Constant (k), Diffusional Exponent (n) Derived from Eq. (1) and Correlation Coefficients (R^2), for HPMC Matrices in Various Media

Drug	Dissolution Testing Conditions	k	n	R^2
Felodipine	No exposure to alcohol	9.68	1.14	0.999
	1 h in 5% v/v ethanol	11.05	1.09	0.985
	1 h in 40% v/v ethanol	14.59	0.90	0.998
Gliclazide	No exposure to alcohol	8.41	1.30	0.989
	1 h in 5% v/v ethanol	10.66	1.05	0.991
	1 h in 40% v/v ethanol	10.26	1.17	0.976
Metformin HCl	No exposure to alcohol	28.76	0.69	0.999
	1 h in 5% v/v ethanol	27.66	0.74	0.994
	1 h in 40% v/v ethanol	20.08	0.87	0.998

Felodipine is practically insoluble in water; therefore its release in non-alcoholic medium is predominantly controlled by erosion with n value equal to 1.14. Value of n decreases only slightly after 1 h exposure to 5% v/v (n = 1.09) and 40% v/v (n = 0.90) ethanol solutions. An increase in k value from 9.68 (in non-alcoholic medium) to 14.59 (in 40% v/v ethanol) indicates an initial increase in drug release from the matrix.

Gliclazide is practically insoluble in water and slightly soluble in alcohol. For these matrices drug is predominantly released by erosion under all three testing conditions. This is confirmed by n values of near 1.0. Gliclazide matrix tablets produced slightly lower n and higher k values in hydro-alcoholic media compared to the values obtained in water. This indicates that the rate of drug release is slightly faster in ethanol solutions compared to the water medium.

For metformin HCl ER tablets, n values between 0.69 and 0.87 suggest that diffusion and erosion contribute to the overall drug release mechanism. Metformin HCl solubility changes from freely soluble in water to slightly soluble in alcohol resulting in a greater erosion contribution to the drug release from the tested matrices. This is reflected in n values increase from 0.69 in water to 0.74 and 0.87 from the tablets exposed to 5 and 40% v/v ethanol solutions, respectively.

With the values of n and k being inversely related, k values change slightly from 28.76 in water to 27.66 and 20.08 from the tablets exposed to 5 and 40% v/v ethanol solutions, respectively. This implies that the rate of drug release from the metformin HCl formulation is slightly slower in 40% ethanol solution compared to the dissolution in water.

When evaluating the effect of hydro-alcoholic solutions on the drug release from HPMC matrices, it is important to take into account other than the drug solubility change factors, i.e., differences in the solubility of matrix ingredients in various media.

The most commonly used fillers in hypromellose matrices are microcrystalline cellulose (MCC), lactose, pregelatinized starch (PGS), and dibasic calcium phosphate dihydrate (DCPD). Table 9 summarises solubility data for these materials in various media. The effect of hydro-alcoholic media exposure on tablets with different fillers will probably increase in the following order: MCC or DCPD - > PGS - > lactose.

The Effect of Hydro-Alcoholic Media on Swelling of HPMC Compacts

It was observed that in water and hydro-alcoholic solutions all compacts underwent swelling and gelation without any disruption to the matrix integrity.

The change in wet weight with time for compacts made of polymers with three different viscosity grades is summarized in Figure 7 and Table 10. The study shows a similar progressive weight gain by compacts in water and hydro-alcoholic media with time.

Relative swelling of the compacts in various media is shown in Table 11. It was found that the extent of swelling increased with increasing viscosity grade of HPMC from 100 to 4000 cps. However, no significant difference in compact relative swelling was observed for Methocel K4M CR and K100M CR.

CONCLUSIONS

Extended release HPMC tablets of felodipine 5 mg, gliclazide 30 mg, and metformin HCl 500 mg retained their hydrated structural integrity when exposed to 5 and 40% v/v ethanol solutions for up to 12 h without any failure of the matrices resulting in dose-dumping. Drug release profiles from these ER tablets were different when exposed to 0, 5, and 40% v/v ethanol solutions, respectively, for 12 h that were explained by changes in drug solubility in the various media. However, when the matrices were exposed to hydro-alcoholic media for only 1 h the change in drug release profiles was not significant.

During testing of HPMC compacts made from polymers of three different viscosity grades (Methocel K100LV CR, K4M CR, and K100M CR), it was shown that in water and hydro-alcoholic solutions, all compacts underwent swelling and

TABLE 9
Solubility of Tableting Fillers in Various Media (*Handbook of Pharmaceutical Excipients*, 2003)

Filler	Solubility in Water	Solubility in Alcohol
MCC	Practically insoluble	Practically insoluble in most organic solvents
Lactose	1 in 4.63	Practically insoluble in ethanol
PGS	Slightly soluble to soluble	Practically insoluble in organic solvents
DCPD	Practically insoluble	Practically insoluble in ethanol

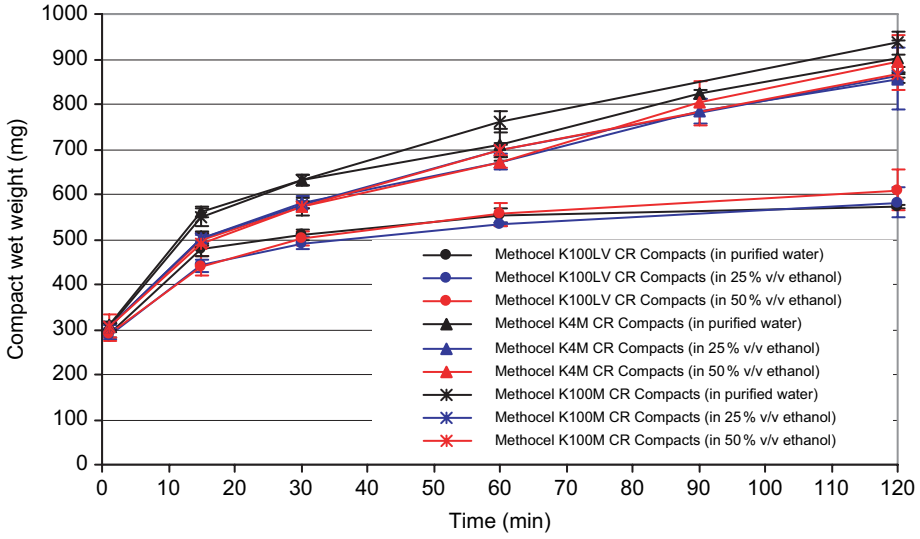

FIGURE 7. Effect of hydro-alcoholic media containing 0, 5 or 40% v/v ethanol on wet weight of Methocel (K100LV CR, K4M CR and K100M CR) compacts (n = 3).

TABLE 10
Effect of Hydro-alcoholic Media on Wet Weight of Methocel Compacts (n = 3)

	Methocel K100LV CR			Methocel K4M CR			Methocel K100M CR		
	Water	25% v/v Ethanol	50% v/v Ethanol	Water	25% v/v Ethanol	50% v/v Ethanol	Water	25% v/v Ethanol	50% v/v Ethanol
Wg t_0	291 ± 11	288 ± 10	292 ± 8	310 ± 10	306 ± 2	305 ± 50	305 ± 7	304 ± 8	306 ± 9
Wg t_{15}	477 ± 15	443 ± 13	440 ± 22	560 ± 13	501 ± 8	499 ± 17	548 ± 20	503 ± 15	489 ± 25
Wg t_{30}	509 ± 13	491 ± 14	503 ± 15	631 ± 13	581 ± 14	574 ± 6	631 ± 12	576 ± 9	572 ± 19
Wg t_{60}	552 ± 16	533 ± 5	555 ± 26	708 ± 35	672 ± 17	672 ± 15	760 ± 23	699 ± 15	697 ± 13
Wg t_{120}	573 ± 5	582 ± 34	610 ± 46	903 ± 37	857 ± 69	894 ± 61	936 ± 26	863 ± 17	865 ± 6

TABLE 11
Effect of Hydro-alcoholic Media on Relative Swelling of Methocel Compacts

	Methocel K100LV CR			Methocel K4M CR			Methocel K100M CR		
Time (min)	Water	25% v/v Ethanol	50% v/v Ethanol	Water	25% v/v Ethanol	50% v/v Ethanol	Water	25% v/v Ethanol	50% v/v Ethanol
15	1.64	1.54	1.51	1.81	1.64	1.64	1.80	1.65	1.60
30	1.75	1.70	1.72	2.04	1.90	1.88	2.07	1.89	1.87
60	1.90	1.85	1.90	2.28	2.20	2.20	2.49	2.30	2.28
120	1.97	2.02	2.09	2.91	2.80	2.93	3.07	2.84	2.83

gelation without any disruption to the matrix integrity. The compact wet weight appeared to be similar in water and aqueous ethanol solutions for the Methocel grades studied. The extent of their relative swelling was found to increase with increasing viscosity of HPMC from 100 to 4000 cps. No significant difference in compact swelling was observed for Methocel K4M CR and K100M CR.

REFERENCES

Alderman, D. A. (1984). A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int. J. Pharm. Tech. Prod. Mfr*., *5*, 1–9.

Bettini, R., Colombo, P., Massimo, G., Gatellani, P. L., & Vitali, T. (1994). Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. *Eur. J. Pharm. Sci*, *2*, 213–219.

Campos-Aldrete, M. E., & Vallafuerte-Robles, L. (1997). Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. *Eur. J. Pharm. Biopharm*., *43*, 173–178.

Colombo, P., Bettini, R., Santi, P., & Peppas N. A. (2000). Swelling matrices for controlled drug delivery: behaviour, mechanisms and optimal performance. *Pharm. Sci. Tech. Today*, *3*(6), 198–204.

Doherty, C., & York, P. (1989) Microenvironmental pH control of drug dissolution. *Int. J. Pharm*., *50*, 223–232.

Espinoza, R., Hong, E., & Villafuerte, L. (2000). Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets. *Int J Pharm*., *201*, 165–173.

Fadda, H., ALBasarah, Y., & Basit, A. (2006). Impairment of modified release formulations by alcohol in dissolution media and influence on drug release. *AAPS Annual Meeting and Exposition, San Antonio, TX, USA.*

Federal Register. (1995). Food and Drug Administration, Volume 60, No. 230, p. 61642.

FDA. (2005, July). *FDA alert for healthcare professionals*. Hydromorphone hydrochloride extended-release capsules (marketed as Palladone™), Alcohol-Palladone™ interaction.

Ford, J. L., Mitchell, K., Rowe, P., Armstrong, D. J., Elliott, P. N. C., Rostron, C., & Hogan, J. E. (1991). Mathematical modelling of drug release from hydroxypropylmethylcellulose matrices: Effect of temperature. *Int J Pharm*., *71*, 95–104.

Ford, J. L., Rubinstein, M. H., & Hogan, J. E. (1985). Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulose matrices. *Int. J. Pharm*., *24*, 327–338.

Ford, J. L., Rubinstein, M. H., McCaul, F., Hogan, J. E., & Edgar, P. J. (1987). Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropyl methylcellulose matrix tablets, *Int. J. Pharm*., *40*, 223–234.

IMS data. 2002.

Johnson, J. L., Holinej, J., & Williams, M. D. (1993). Influence of ionic strength on matrix integrity and drug release from hydroxypropylcellulose compacts. *Int. J. Pharm*., *90*, 151–159.

Kavanagh, N., & Corrigan, O. I. (2004). Swelling and erosion properties of hydroxypropylmethylcellulose (hypromellose) matrices—Influence of agitation rate and dissolution medium composition. *Int. J. Pharm., 279*, 141–152.

Koziara, J., So, J., & Agarwal, N. (2006). The effect of ethanol on semipermeable cellulose acetate-based membranes. *AAPS Annual Meeting and Exposition, San Antonio, TX, USA.*

Lapidus, H., & Lordi, N. G. (1968). Drug release from compressed hydrophilic matrices. *J. Pharm. Sci*., *57*(8), 1292–1301.

Levina, M., Gothoskar, A., & Rajabi-Siahboomi, A. R. (2006). Application of a modeling system in the formulation of extended release hydrophilic matrices. *Pharm. Tech. Eur*., *18*(7), 20–26.

Li, C. L., Martini, L. G., Ford, J. L., & Roberts, M. (2005). The use of hypromellose in oral drug delivery. *J. Pharm. Pharmacol*., *57*(5), 533–546.

Longer, M. A., & Robinson, J. R. (1990). Sustained-release drug delivery systems. In A.R. Gennaro (Ed.) *Remington's pharmaceutical sciences* (pp. 1676–1693). PA, USA: Mack Publishing.

Martindale (1999). K. Parfitt (Ed.) London, UK: Pharmaceutical Press, pp. 320, 330, 867, 1100.

Mitchell, K., Ford, J. L., Armstrong, D. J., Elliott, P. N. C., Rostron, C., & Hogan, J.E. (1990). The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrices. *Int. J. Pharm*., *66*, 233–242.

Moore, J. W., & Flanner, H. H. (1996). Mathematical Comparison of Dissolution Profile. *Pharm. Tech*., *20*(6), 64–74.

Pagay S. N. (1988). Use of buffers in matrix capsule formulations. *Drug Dev. Ind. Phar*., *14*, 875–894.

Rajabi-Siahboomi, A. R., Adler, J., Davies, M. C., & Melia, C. D. (1994). Particle swelling and the mechanism of failure of HPMC matrices. *Proc. 3rd Assoc. UK APS Conf*., 21.

Rajabi-Siahboomi, A. R., & Jordan, M. P. (2000). Slow release HPMC matrix systems. *Eur Pharm. Rev*., *5*(4), 21–23.

Roberts, M., Cespi, M., Ford, J. L., Dyas, A. M., Martini, G. L., & Crowley, P. J. (2006). The influence of ethanol on aspirin release from hypromellose matrix tablets. *The British Pharmaceutical Conference & Exhibition, Manchester, UK.*

Rodrigues, C. F., Bruneua, N., Barra, J., Alfonso, D., & Doelker, E. (2000). Hydrophilic cellulose derivatives as drug delivery carriers: Influence of substitution type on the properties of compressed matrix tablets. In D. L. Wise (Ed.), *Handbook of pharmaceutical controlled release technology* (pp. 1–30). New York: Marcel Dekker, Inc.

Rowe, R. C., Sheskey, P. J., & Weller, P. J. (Ed.) (2003). *Handbook of pharmaceutical excipients* (pp. 73, 109, 330, 610). London, UK: Pharmaceutical Press.

Sheu, M.-T., Chou, H. L., Kao, C.-C., Liu, C.-H., & Sokoloski, T.D. (1992). Dissolution of diclofenac sodium from matrix tablets. *Int. J Pharm*., *85*, 57–63.

Tahara, K., Yamamoto, K., & Nishihata, T. (1995). Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose. *J. Contr. Rel*, *2910*, *35*, 59–66.

The United States Pharmacopeia (2004). Rockville, MD: The United States Pharmacopeial Convention, Inc., pp. 969, 778.

Velasco, M. V., Ford, J. L., Rowe, P., & Rajabi-Siahboomi, A. R. (1999). Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *J. Contr. Rel*., *57*(1), 75–85.

Vuong, H., Levina, M., & Rajabi-Siahboomi, A. R. (2006). The influence of hydro-alcoholic media on hypromellose matrix systems. *AAPS Annual Meeting and Exposition, San Antonio, TX, USA.*

Wan, L. S. C., Heng, P. W. S., & Wong, L. F. (1995). Matrix swelling: a simple model describing extent of swelling of HPMC matrices. *Int. J. Pharm*., *116*, 159–168.

Wilder, P. V., Detaevernier, M. R., & Michotte, Y. (1991). In vitro dissolution of two oral controlled release preparations of diclofenac sodium. *Drug Dev. Ind. Pharm*., *17*, 141–148.