The Influence of Hydro-Alcoholic Media on Hypromellose Matrix Systems

OBJECTIVES

The hydrophilic matrices (HM) continue to be a popular and widely used strategy for oral extended release (ER) drug delivery. In addition, hypromellose (HPMC) remains the polymer of choice as the rate-controlling carrier.

The FDA (2005) has recently issued an alert for healthcare professionals regarding dissolution media effects on drug release from an ER dosage form, i.e. alcohol-Palladone interaction. When ingested with alcohol the peak plasma concentration of the drug hydromorphone increased to potentially lethal levels due to breakdown of the ER formulation.

The aim of this study therefore was to investigate the effect of hydro-alcoholic solutions on the performance of hypromellose matrices. The hydro-alcoholic media effect on HPMC of different viscosity grades and an ER matrix formulation of metformin HCl were investigated. Hydration properties of the polymer and drug release from their matrices in different hydro-alcoholic media were studied.

METHODOLOGY

Preparation and Testing of HPMC Compacts

HPMC compacts were made using METHOCEL™, premium cellulose ethers, K100LV CR, K4M CR and K100M CR. Discs of 13 mm diameter with a target weight of 300 mg were manufactured using a hydraulic IR hand press (Thermo Spectronic, UK).

The effect of dissolution medium composition on the swelling and erosion properties of these hypromellose 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 weight of the hydrated HPMC compacts was 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. Dissolution media were ethanol: purified water mixtures in the following ratios: 0:100, 25:75 and 50:50 at 37.0 ± 0.5ºC.

The experiment consisted of allowing the HPMC compacts to dissolve in the medium for certain time periods (15, 30, 60, 120 minutes) before they were removed into a pre-weighted plastic container. The excess dissolution medium was drained and blotted from around the disc without touching it. The compact and the container were weighted and then the wet weight of the 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 (Ww) to the initial weight (Wi) was determined, as an indication of the extent of matrix swelling using a similar index to Panomsuk et al. (1996).

Relative swelling = *Ww / Wi*

Formulation and Preparation of HPMC Matrix Tablets

ER formulation of metformin HCl was developed using the HyperStart®, oral solid dose formulation service, (Levina et al, 2006) and shown in Table 1.

Table 1. Metformin HCl HPMC Formulation

Material	% w/w	Mg/tablet
Metformin HCl (Ferico Labs)	50.0	500
HPMC (METHOCEL™ K100M CR, IFF)	30.0	300
MCC (Avicel PH102, FMC)	19.0	190
Fumed Silica (Aerosil 200, Degussa)	0.5	1
Magnesium Stearate (Peter Greven)	0.5	1
Total	100.0	1000

MCC and fumed silica were screened through a 500µm (35 mesh) sieve. All ingredients except for the lubricant were then blended in a Turbula mixer for 5 minutes. Magnesium stearate was added last and the formulation was blended for a further 1 minute.

Tablets were manufactured on an instrumented 10 station rotary tablet press (Piccola, Riva, Argentina) using 7x18 mm caplet tooling at 20 rpm and 20 kN compression force.

Dissolution testing was performed in a Sotax bath using USP Apparatus II (paddles) at 100 rpm and small (8 mm diameter, 23 mm length) sinkers (Sotax). The dissolution medium was 1000 mL of purified water at 37.0 ± 0.5ºC. The amount of drug was measured at a wavelength of 233 nm.

Additional testing was performed in 5% or 40% v/v ethanol aqueous solutions for 1 hour using paddles at 100 rpm and sinkers. After 1 hour tablets together with sinkers were transferred to water medium and dissolution testing continued for an additional 11 hours as described above. The results were compared to the drug release in water only using the *f2* factor (FDA, 1995; Moore & Flanner, 1996). An *f2* 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 active between 5 and 60% were fitted to an equation proposed by Siepmann & Peppas (2001): $Q = kt^n$

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

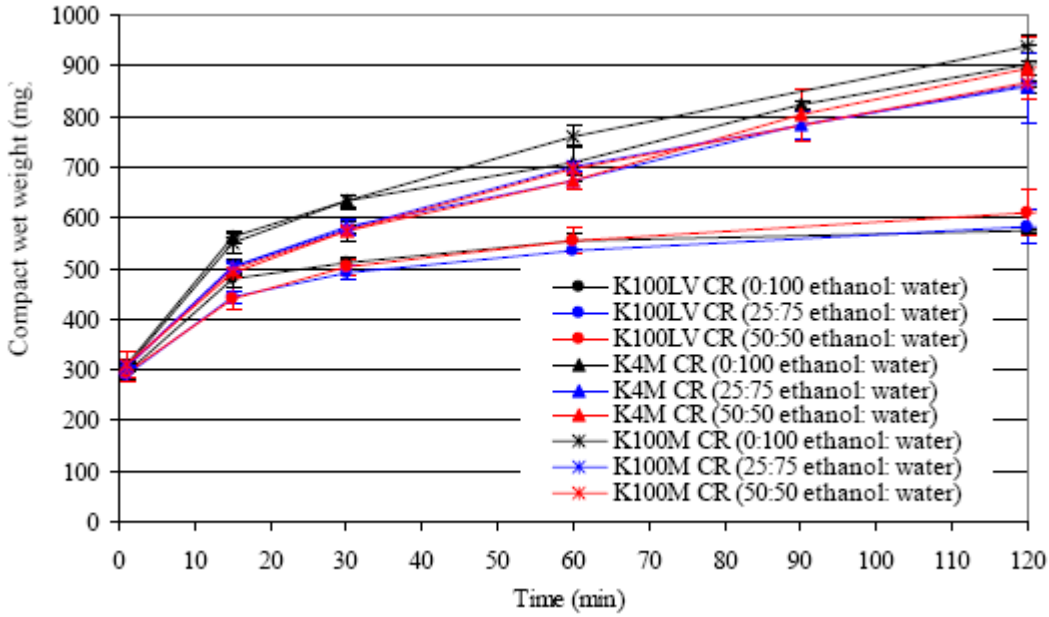
RESULTS

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 viscosities is summarized in Figure 1. For all three grades of HPMC, it appeared that compact wet weight was similar in water and hydro-alcoholic media.

It was found that the extent of relative swelling increased with increasing viscosity of HPMC from 100 to 4000 cps (Table 2). No significant difference in compact swelling was observed for METHOCEL™ K4M CR and K100M CR.

Figure 1. Wet Weight of METHOCEL™ Compacts



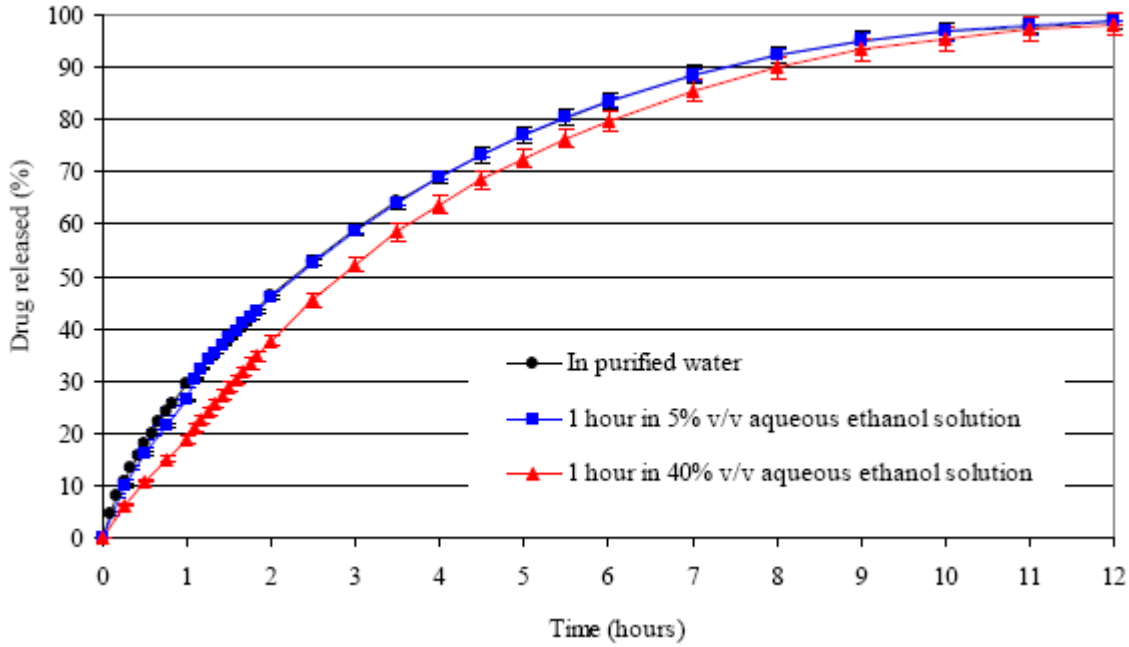
The effect of 1 hour exposure to hydro-alcoholic media on HPMC matrices containing metformin HCl is presented in Figure 2. Any differences in drug release profiles can be explained by a decrease in the saturated drug solubility from 450 g/L (in water) to 379 (in 5% v/v ethanol) and to 295 g/L (in 40% v/v ethanol).

The *f2* values for drug release profiles from the tablets exposed for 1 hour to 5 and 40% v/v ethanol solutions, as compared to the release in water, were found to be 86 and 54 respectively. This indicates similarity between the profiles.

Table 2. Effect of Hydro-Alcoholic Media on Relative Swelling of METHOCEL™ Compacts

Time (min)	METHOCEL™ K100LV CR			METHOCEL™ K4M CR			METHOCEL™ K100M CR		
	In Water	In 25% Ethanol	In 50% Ethanol	In Water	In 25% Ethanol	In 50% Ethanol	In Water	In 25% Ethanol	In 50% 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

Figure 2. Metformin HCl Dissolution



The values of the kinetic constant (*k*), the release exponent (*n*) and correlation coefficient (*R2*) determined from the drug release data are presented in Table 3. For matrix tablets, an *n* value of near 0.5 indicates diffusion control and an *n* value of near 1.0 indicates erosion. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.

Table 3. k, n and R^2 Values for the Metformin HCl HPMC Matrices in Various Media

Dissolution Testing Conditions	k	n	R2
No Exposure to Alcohol	28.757	0.6944	0.9985
1 Hour in 5% v/v Ethanol	27.664	0.7410	0.9942
1 Hour in 40% v/v Ethanol	20.078	0.8712	0.9979

Values of *n* between 0.6944 and 0.8712 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 change from 0.6944 in water to 0.741 and 0.8712 from the tablets exposed to 5 and 40% ethanol solution respectively.

CONCLUSIONS

For all three grades of HPMC, it appeared that compact relative swelling was similar in water and in hydro-alcoholic media of up to 50% v/v ethanol.

For metformin HCl HPMC tablets, there was no significant effect of one hour exposure to 5 and 40% v/v ethanol aqueous solutions on drug release. Any differences in the dissolution profiles could possibly be explained by a decrease in drug solubility in hydro-alcoholic media compared to water.

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