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Research Article

Investigation of the Effects of Hydroalcoholic Solutions on Textural and Rheological Properties of Various Controlled Release Grades of Hypromellose

Shahrzad Missaghi,[1,2] Kurt A. Fegely,[1] and Ali R. Rajabi-Siahboomi[1]

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Abstract. Hypromellose (hydroxypropyl methylcellulose, HPMC) matrices are widely used in the formulation of sustained release dosage forms. The integrity and performance of an HPMC matrix formulation depends on rapid hydration and gel formation upon ingestion. Due to the recent alert issued by the Food and Drug Administration regarding the potential negative influence of alcoholic beverages on extended release (ER) formulations, several researchers have evaluated the potential influence of hydroalcoholic media on drug release from ER dosage forms. It has been reported that HPMC matrix formulations do not show "dose dumping" in hydroalcoholic media. The purpose of this study was a fundamental investigation on the effect of hydroalcoholic solutions (0–40% *v*/*v* ethanol) on textural and rheological properties of different viscosity grades of neat HPMC, as the functional ingredient within a hydrophilic matrix. In general, hydroalcoholic solutions had little effect on gel formation and mechanical properties of hydrated compacts, while the rheological behavior of HPMC showed dependency on the ethanol content of such solutions.

KEY WORDS: alcohol; extended release; HPMC; hydrophilic matrix; hypromellose; rheological analysis; texture analysis.

INTRODUCTION

Hydrophilic matrix systems are a popular approach in the formulation of extended release (ER) oral drug delivery systems. High viscosity grades of hypromellose (hydroxypropyl methylcellulose, HPMC) are widely used as the rate-controlling polymer in these systems. This popularity of HPMC matrices is due to their proven safety, wide availability, global regulatory compliance, and physicochemical characteristics (1–4).

In July 2005, the Food and Drug Administration (FDA) issued an alert regarding the potential interaction between an ER dosage form when ingested with alcoholic beverages (5). FDA concern was that an ER dosage form could be compromised in the presence of alcohol, potentially leading to accelerated drug release or "dose dumping" and thereby increasing the risk of drug toxicity. Since this alert, there has been a greater interest in studying the influence of hydroalcoholic solutions on the performance of solid oral modified release systems (6). Roberts *et al.* (7) and Levina *et al.* (8) studied the influence of ethanol on the release of drug from HPMC matrices and showed that although ethanol affected the kinetics and mechanism of the drug release, dose dumping did not occur.

Upon contact with aqueous media, HPMC within the matrix tablet hydrates rapidly and forms a gelatinous layer on the surface of the tablet. Rapid polymer hydration and uniform gel formation are critical to the integrity of HPMC matrices and subsequent drug release from matrix tablets (8). In general, gel strength is an important factor in controlling water transport, drug diffusion, matrix erosion, and subsequent drug release. Drug diffusivity through a hydrated matrix increases as gel strength decreases since the diffusion coefficient is inversely proportional to the viscosity of the diffusion medium (hydrated gel; 9). The potential exists that gel formation and hence matrix integrity be influenced in the presence of hydroalcoholic solutions. Given that HPMC is commonly used as an integral part of a hydrophilic matrix system, understanding the textural and rheological properties of this polymer in hydroalcoholic solutions is critical in predicting matrix integrity and, consequently, its potential propensity to dose dumping. The objective of this study therefore was to investigate the effect of hydroalcoholic solutions on the mechanical properties of the hydrated compacts of plain HPMC, using textural analysis. In addition, the effect of hydroalcoholic solutions on the rheological properties of neat HPMC solutions/dispersions was also evaluated.

MATERIALS AND METHODS

Materials

Different viscosity grades of HPMC (METHOCEL™ Premium CR, specifically K100 LV CR, K4M CR and K100M CR, the Dow Chemical Company, USA) were used in this

[1] Colorcon, 415 Moyer Boulevard, West Point, PA 19486, USA.
[2] To whom correspondence should be addressed. (e-mail: SMissaghi@colorcon.com)

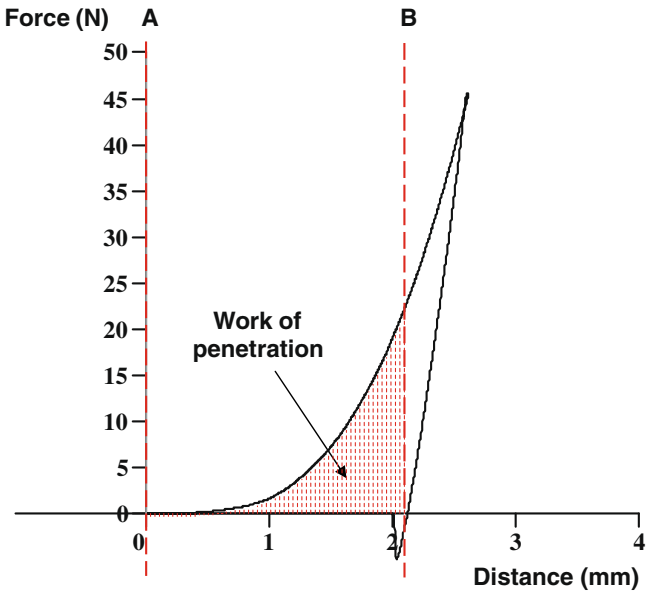

Fig. 1. A typical textural profile of HPMC compact at 1 h of hydration demonstrating the textural properties. "Work of penetration" is the work done by the probe on the compact and is obtained from the area under the force–distance profile between 0.0 and 2.1 mm of probe penetration within the compact. The value for "work of penetration" is an indication of the textural strength of the compact with higher values indicating greater strength and has the unit of Newton × meter or Joules. "Gradient" is obtained from the slope of the ascending portion of the profile between 0.0 and 2.1 mm. This part of the profile was linearized using force *versus* distance to the exponent of 3 (F *vs.* D^3). "Gradient" is another indication of textural strength, with higher values representing greater strength. This value is reported in Newton per meter. Note: The probe displacement of 0.0 to 2.1, represented by anchors *A* and *B*, was selected as a standardized distance for a meaningful comparison of all textural profiles

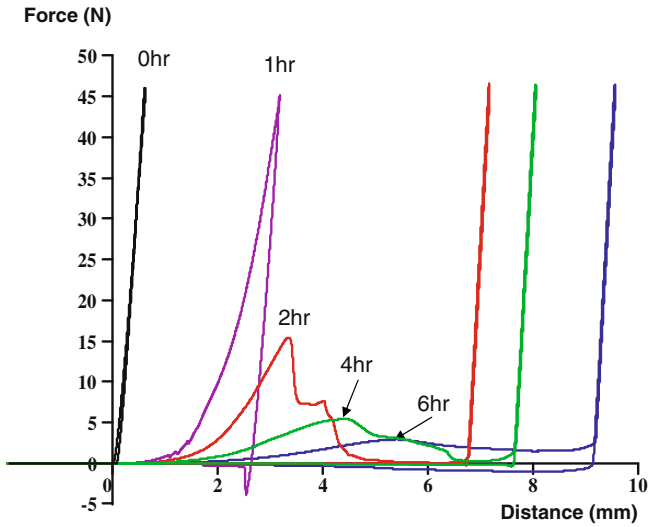

Fig. 2. Typical textural profiles of compacts (data shown are for METHOCEL K4M PREM CR compacts in deionized water). The end peaks indicate the point where the maximum force of 45 N was achieved. After 2 h of hydration, the compacts become softer and the probe travels the entire thickness of the compact and reaches the stainless steel platform where the sample is positioned

study. The nominal viscosities for these grades are 100, 4,000, and 100,000 mPa•s or cP, respectively. The viscosity is determined at 2% concentration in water at 20°C (12).

Fumed silica (Aerosil® 200) and magnesium stearate were obtained from Evonik (France) and Peter Greven (UK), respectively. Textural and rheological analyses were conducted in hydroalcoholic solutions with varying ethanol contents (0%, 5%, 20%, and 40% *v/v*), representing the range of alcohol content present in beer and spirit beverages. The ethanol used in this study was dehydrated alcohol, 200 proof, USP (Spectrum Chemical, USA), and the medium without alcohol was deionized water.

Table I. Comparison of Physical Properties for HPMC Compacts Compressed at 20 kN (Values Are Reported as Mean and Standard Deviation; $n=10$)

METHOCEL compact	Weight (mg)	Thickness (mm)	Hardness (kp)
K100 LV CR	305.7±2.8	3.4±0.0	28.5±1.4
K4M CR	297.7±4.3	3.4±0.0	17.2±1.0
K100M CR	299.7±2.3	3.4±0.0	21.2±1.1

Methods

Textural Analysis

To prepare neat HPMC compacts, each METHOCEL grade was blended with fumed silica for 5 min, followed by lubrication with magnesium stearate for 2 min. The blends

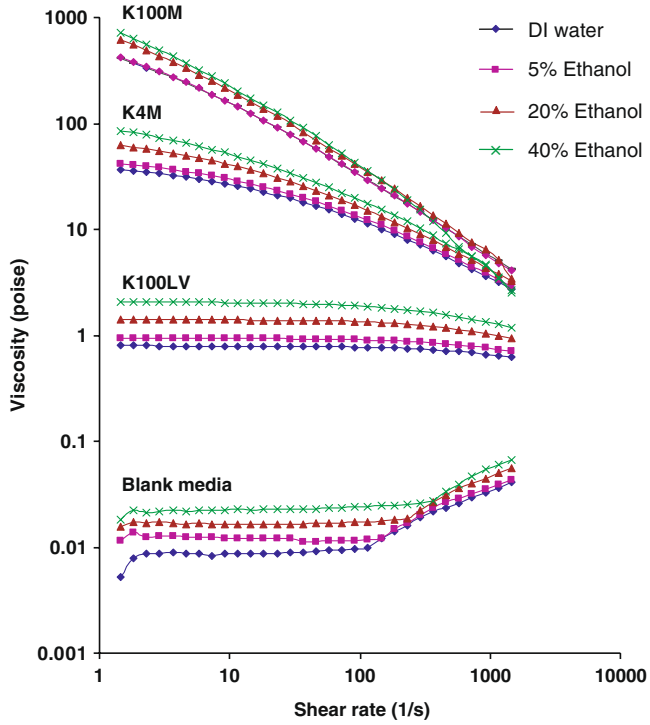

Fig. 3. Rheological behavior of the blank hydroalcoholic solutions and of different METHOCEL grades in various solutions (both viscosity and shear rate are presented in log scale)

Table II. Comparison of "Work of Penetration" ($J \times 10^{-3}$) for HPMC Compacts in Different Solutions at Probe Displacement of 0.0 to 2.1 mm on the Textural Profile

	Hydration time (h)	DI water	5% Ethanol	20% Ethanol	40% Ethanol
K100 LV CR	1	13.03±2.82	11.97±3.56	20.56±3.04	16.28±1.41
	2	3.04±0.47	5.64±0.45	8.22±0.90	7.32±1.08
	4	1.33±0.53	1.74±0.39	2.06±0.14	1.59±0.14
	6	0.80±0.16	0.52±0.12	0.64±0.30	0.87±0.12
K4M CR	1	4.96±0.35	6.52±0.55	10.30±0.51	10.94±0.70
	2	1.59±0.11	1.46±0.16	3.79±0.19	3.97±0.66
	4	0.63±0.02	0.62±0.10	0.65±0.09	0.59±0.11
	6	0.30±0.08	0.38±0.10	0.38±0.05	0.25±0.04
K100M CR	1	4.34±0.48	3.54±0.08	9.93±1.23	10.92±0.94
	2	1.17±0.02	1.49±0.30	2.60±0.61	3.42±0.18
	4	0.45±0.06	0.48±0.02	0.54±0.08	0.46±0.03
	6	0.36±0.03	0.32±0.05	0.34±0.04	0.36±0.02

were compressed on an instrumented ten-station rotary tablet press (Piccola, Argentina), at the compaction force of 20 kN, using 10-mm round flat-faced tooling. Each compact (300 mg) contained 297 mg HPMC and 1.5 mg of each of fumed silica and magnesium stearate. The physical properties of the tablets were determined using a MultiCheck system (Erweka GmbH, Germany).

Compacts were allowed to hydrate inside sinkers in 500 ml of varying types of solutions, maintained at 37°C in a USP-compliant dissolution bath using apparatus II at 100 rpm (AT7 Smart, Sotax Corporation, USA). The compacts were exposed to the hydroalcoholic solutions for the first 2 h and were then transferred to deionized water. The compacts were removed at predetermined intervals (1, 2, 4, and 6 h), patted lightly with a paper towel to remove extra moisture, and subjected to analysis using a texture analyzer (TA.XT Plus, Texture Technologies Inc., USA), equipped with a 5-kg load cell and Texture Exponent software. The force–distance profiles associated with the penetration of a 2-mm round-tipped stainless steel probe into the swollen compacts were monitored. The probe speed was set at 1.0 mm/s. Once a trigger force of 0.005 N was detected (at the contact point of the probe with the compact), the probe was advanced into the sample at a speed of 0.5 mm/s until the maximum force of 45 N was achieved (10). The resulting profiles were analyzed and used to compare the textural properties of different compacts in various solutions. For this purpose, the "work of penetration" and "gradient" values for each textural profile were calculated and used for comparison (Fig. 1). All measurements were carried out in triplicates.

Rheological Analysis

Samples of METHOCEL solutions/dispersions were prepared by hydrating different grades of METHOCEL in the hydroalcoholic solutions to achieve a 2.0% *w/v* concentration. Prior to analysis and depending on the viscosity grade, the hydrated HPMC samples were allowed to deaerate for 2, 24, and 48 h for K100 LV CR, K4M CR, and K100M CR, respectively. Rheological behavior of various solutions/dispersions was characterized using an AR-G2 Rheometer (TA Instruments, USA), equipped with a rotational concentric cylinder. The viscosity was measured at a controlled temperature of 25°C. Viscosity–shear rate profiles were used for comparing the rheological characteristics of the samples.

Table III. Comparison of "Gradient" Values ($N/m \times 10^3$) for HPMC Compacts in Different Solutions at Probe Displacement of 0.0 to 2.1 mm on the Textural Profile

	Hydration time (h)	DI water	5% Ethanol	20% Ethanol	40% Ethanol
K100 LV CR	1	2.78±0.59	2.52±0.73	4.20±0.58	3.37±0.28
	2	0.64±0.10	1.19±0.10	1.71±0.19	1.49±0.22
	4	0.26±0.10	0.34±0.07	0.41±0.04	0.33±0.03
	6	0.15±0.03	0.10±0.02	0.12±0.06	0.17±0.02
K4M CR	1	1.07±0.06	1.42±0.12	2.13±0.11	2.18±0.14
	2	0.32±0.03	0.29±0.04	0.78±0.04	0.79±0.13
	4	0.12±0.00	0.11±0.02	0.12±0.02	0.11±0.02
	6	0.05±0.01	0.06±0.01	0.06±0.01	0.04±0.00
K100M CR	1	0.95±0.10	0.78±0.01	2.13±0.25	2.28±0.19
	2	0.23±0.00	0.30±0.07	0.51±0.15	0.69±0.04
	4	0.06±0.01	0.07±0.00	0.08±0.01	0.07±0.00
	6	0.05±0.00	0.04±0.01	0.05±0.00	0.05±0.00

RESULTS AND DISCUSSION

Textural Analysis

Physical properties of HPMC compacts were evaluated for ten samples, with results summarized in Table I. The compaction force of 20 kN produced hard tablets with hardness values in the range of 17.2–28.5 kp.

All HPMC compacts, when placed in the solutions, hydrated and formed a protective gel layer. The hydrated matrices retained their integrity up to 6 h of testing, regardless of ethanol concentration in the solutions. Figure 2 demonstrates typical textural profiles for HPMC compacts. These profiles are used to determine and compare the textural properties of the compacts.

The textural strength of the compacts was also investigated. The "work of penetration" done by the probe on the compact, which is equivalent to the area under the force–distance profile, was evaluated with results displayed in Table II. This value was calculated from the point that the probe reaches the compact to the distance of 2.1 mm within the compact. Table III compares the "gradient" values for each compact in different solutions. "Gradient" is another indication of textural strength and is obtained from the slope of the ascending portion of each textural profile between 0.0 and 2.1 mm of probe displacement within the hydrated compact (Fig. 1). The results for "work of penetration" and "gradient" revealed greater values at earlier time points for the compacts subjected to the solutions with higher ethanol contents (20% and 40% *v*/*v*). This effect could be due to a difference in hydration behavior of the compacts in the presence of ethanol. This difference in hydration becomes more significant as the molecular weight of the polymer is increased:

As hydration proceeds, the difference between the values is decreasing. Statistical analysis of the data for each HPMC grade showed a significant difference ($p<0.05$) among the "work of penetration" and "gradient" values at 1 and 2 h of hydration. For 4 and 6 h of hydration, the statistical difference becomes insignificant ($p>0.05$). This may indicate that, over a longer period of time, textural behavior of the HPMC compact should not be affected by the initial exposure to the hydroalcoholic solutions.

These results are in agreement with the findings of Levina *et al.* (8), where the authors examined the swelling behavior and gel formation of HPMC compacts in both aqueous and hydroalcoholic solutions and found that the level of media uptake was similar in all media without any disruption to the matrix integrity. In addition, these results confirm the findings of Roberts *et al.* (7) that the exposure of HPMC matrices to the hydroalcoholic media did not cause dose-dumping effect.

Rheological Analysis

The rheological behavior of HPMC samples in various hydroalcoholic solutions as well as the control "blank media" was evaluated. As seen in Fig. 3, the viscosity of the blank solutions is low indicating that the media contribution to the overall rheological behavior of HPMC samples is negligible.

As previously reported, aqueous solutions of HPMC demonstrate pseudoplastic behavior (11). The rheological data of this study showed that regardless of the hydroalcoholic solution, all HPMC grades exhibited a shear-thinning behavior. The higher ethanol contents of the solutions led to an increase in the viscosity of all samples, independent of the viscosity grade of the polymer (Fig. 3). This effect might be due to the reduced volume of water in the hydroalcoholic mixture and dielectric constant of the hydroalcoholic solutions, leading to the formation of new bonds/structures between the polymer molecules and the solvating media (12).

CONCLUSIONS

Based on the results of this study, it is speculated that HPMC should not cause dose dumping in the presence of alcoholic beverages, even though the textural and rheological properties of the hydrated HPMC may be influenced in the presence of ethanol up to 40% *v*/*v*. It should be noted that the performance of a hypromellose matrix system, as a whole, in hydroalcoholic solutions depends on the overall performance of each of the formulation component in such solutions.

REFERENCES

1. M. A. Longer, and J. R. Robinson. Sustained-release drug delivery systems. In A. R. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, Mack, Pennsylvania, 1990, pp. 1676–1693.
2. P. Colombo, R. Bettini, P. Santi, and N. A. Peppas. Swellable matrices for controlled drug delivery: Gel-layer behaviour, mechanisms and optimal performance. *Pharm. Sci. Tech. Today.* **3**(6):198–204 (2000).
3. A. R. Rajabi-Siahboomi, and M. P. Jordan. Slow release HPMC matrix systems. *Eur. Pharm. Rev.* **5**(4):21–23 (2000).
4. C. L. Li, L. G. Martini, J. L. Ford, and M. Roberts. The use of hypromellose in oral drug delivery. *J. Pharm. Pharmacol.* **57** (5):533–546 (2005).
5. FDA Alert for Healthcare Professionals (2005). Hydromorphone hydrochloride extended-release capsules (marketed as Palladone™), alcohol–palladone™ interaction, http://www.fda.gov/cder/drug/infopage/palladone/default.htm.
6. J. Koziara, J. So, and N. Agarwal. The effect of ethanol on semi-permeable cellulose acetate-based membranes. AAPS Annual Meeting and Exposition, San Antonio, TX, USA (2006).
7. M. Roberts, M. Cespi, J. L. Ford, A. M. Dyas, G. L. Martini, and P. J. Crowley. Influence of ethanol on aspirin release from hypromellose matrices. *Int. J. Pharm.* **332**:31–37 (2007).
8. M. Levina, H. Vuong, and A. R. Rajabi-Siahboomi. The influence of hydro-alcoholic media on hypromellose matrix systems. *Drug Dev. Ind. Pharm.* **33**(10):1125–1134 (2007).
9. S. Jamzad, and R. Fassihi. Development of a controlled release low dose class II drug-Glipizide. *Int. J. Pharm.* **312**:24–32 (2006).
10. S. Missaghi, and R. Fassihi. Analysis of matrix geometry and front movements for hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and polyethylene oxide (PEO), AAPS Annual Meeting and Exposition, Nashville, TN, USA (2005).
11. Dow, Using METHOCEL cellulose ethers for controlled release of drugs in hydrophilic matrix systems. The Dow Chemical Company, USA, 2006, p.11, www.dowexcipients.com.
12. D. S. Jones, G. P. Andrews, C. P. McCoy, and A. D. Woolfson. Physical characterisation of hydro-alcoholic cellulose ether gels. AAPS Annual Meeting and Exposition, Toronto, ON, Canada (2002).