Investigation of the Effects of Hydro-Alcoholic Media on Rheological and Textural Properties of Various Grades of Hypromellose (HPMC)

INTRODUCTION

Hydrophilic matrices are widely used in formulation of extended release dosage forms, with hypromellose (hydroxypropyl methylcellulose, HPMC), being the most popular rate-controlling polymer. In 2005, the FDA issued an alert regarding the potential negative influence that alcoholic beverages may have on extended release formulations.[1&2] The integrity and performance of an HPMC matrix formulation depends on rapid hydration and gel formation upon ingestion. The objective of this study was a fundamental investigation of the effect of hydro-alcoholic solutions, having various ethanol contents (0 - 40% v/v), on textural and rheological properties of different viscosity grades of hypromellose compacts or solutions.

METHODOLOGY

Materials

Different viscosity grades of hypromellose (METHOCEL™, premium cellulose ethers, i.e., K100LV, K4M CR and K100M CR, International Flavors and Fragrances Inc., USA) were used in this study. Textural and rheological analyses were conducted in hydro-alcoholic media with varying ethanol contents, 0, 5, 20, and 40% v/v, representing the alcohol content present in beer and spirit beverages.

Textural Analysis

Textural analyses were performed on METHOCEL™ compacts (10mm round flat-faced) manufactured on an instrumented 10-station rotary tablet press (Piccola, Argentina), at the compression force of 20 kN (Table 1).

Table 1. Composition of METHOCEL™ Compacts

Ingredients	Supplier	mg/tablet
Hypromellose (METHOCEL™ Premium CR	International Flavors and Fragrances Inc., USA	297.0
Fumed Silica (Aerosil 200)	Degussa, France	1.5
Magnesium Stearate	Peter Greven, UK	1.5
Total		300.0

Compacts were allowed to hydrate inside sinkers in 500 ml of the media, maintained at 37°C in a USP compliant dissolution bath using apparatus II at 100 rpm (Sotax Corporation, USA). The compacts were exposed to the hydro-alcoholic media for the first 2 hours and were then transferred to deionized water. The compacts were removed at pre-determined intervals (0, 2, 4, and 6 hours), patted lightly with a paper towel to remove extra moisture and subjected to textural analysis using a texture analyzer (TA.XT Plus, Texture

Technologies Inc., USA). The force – distance profiles associated with the penetration of a 2-mm round-tipped stainless steel probe into the swollen matrices were monitored. The probe advanced into the sample at a speed of 0.5 mm/s until the maximum force of 45 N was achieved.[3] All measurements were carried out in triplicate.

Rheological Analysis

METHOCEL™ samples were prepared by hydrating different grades of METHOCEL™ in the hydroalcoholic media to achieve a 2% w/v concentration. Prior to analysis the hydrated METHOCEL™ samples were allowed to deaerate. Rheological behavior of various METHOCEL™ grades in the hydro-alcoholic media 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 METHOCEL™ samples.

RESULTS AND DISCUSSIONS

Figure 1 shows the typical textural profiles for METHOCELTM compacts. These profiles are used to determine the textural properties of the compacts.

Figure 1. Typical Textural Profiles of Tablets (data shown below are for K4M PREM CR compacts in DI water).

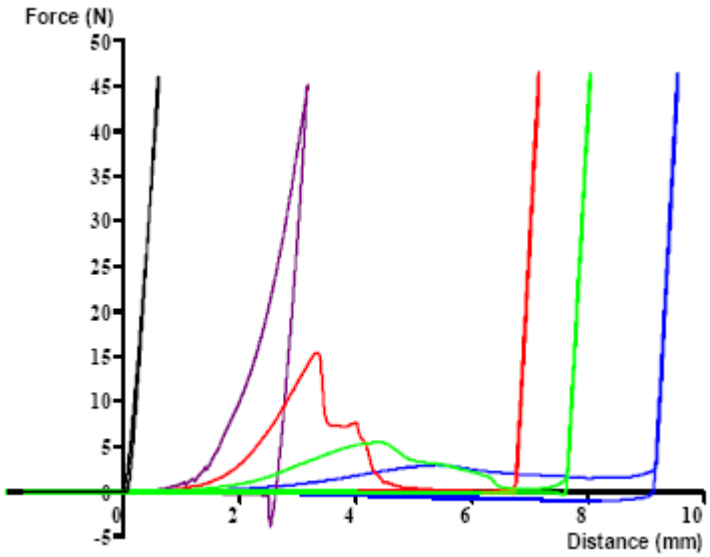


Table 2 shows the values for the work of penetration done by the probe on the compacts, which is equivalent to the area under the force-distance profile. This value was calculated from the point that the probe reaches the compact to the distance of 2.1 mm within the compact and is a measure of the textural strength of the compacts.

Table 3 compares the gradient values for each compact in different media. This value represents textural resilience and is obtained from the slope of each textural profile between 1 and 2 mm of probe displacement within the hydrated compact. The results for work of penetration and gradient revealed greater values at earlier time points for the compacts subjected to the media with higher ethanol contents (20% and 40% v/v).

This effect could be due to a difference in hydration of the compacts in the presence of ethanol, which may delay the formation of a coherent gel layer. This difference in hydration becomes more significant as the molecular weight of the polymer is increasing. As hydration proceeds, the difference between the values is decreasing, which may indicate that over a longer period of time textural behavior of the compact should not be affected by initial exposure to different hydro-alcoholic media.

Table 2. Comparison of Work of Penetration J* 10-3 for METHOCEL™ Compacts in Different Media at Probe Displacement of 0.0 to 2.1 mm on the Textural Profile

K100LV PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
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 PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
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 PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
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

Table 3. Comparison of Gradient Values (N/m * 103) for METHOCEL™ Compacts in Different Media at Probe Displacement of 1.0 to 2.0 mm on the Textural Profile

(1 and 2 hour samples are in hydro-alcoholic media; 4 and 6 hour samples are in hydro-alcoholic media for the first 2 hours, followed by DI water)

K100LV PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
1	20.54 ± 4.14	18.55 ± 4.92	27.54 ± 2.65	22.63 ± 1.87
2	4.79 ± 0.65	9.22 ± 0.53	11.56 ± 1.12	9.75 ± 1.55
4	1.76 ± 0.63	2.10 ± 0.41	2.72 ± 0.42	2.51 ± 0.11
6	0.91 ± 0.22	0.59 ± 0.14	0.76 ± 0.33	1.04 ± 0.01

K4M PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
1	8.80 ± 0.17	10.90 ± 0.91	14.50 ± 0.76	14.32 ± 1.08
2	2.30 ± 0.24	2.04 ± 0.30	5.65 ± 0.13	5.30 ± 0.94
4	0.69 ± 0.04	0.66 ± 0.10	0.73 ± 0.13	0.66 ± 0.10
6	0.28 ± 0.05	0.38 ± 0.07	0.38 ± 0.03	0.28 ± 0.03

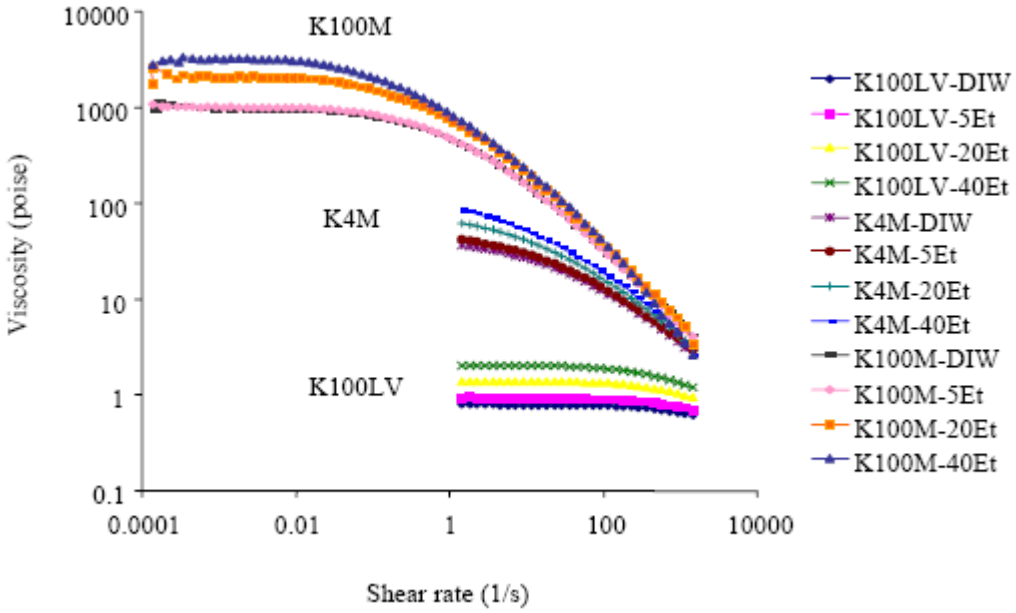
K100M PREM CR

Time (h)	DI Water	5% Ethanol	20% Ethanol	40% Ethanol
1	7.53 ± 0.47	6.04 ± 0.03	15.78 ± 1.64	16.38 ± 1.07
2	1.72 ± 0.04	2.12 ± 0.57	3.71 ± 1.33	4.99 ± 0.41
4	0.38 ± 0.02	0.44 ± 0.03	0.53 ± 0.10	0.39 ± 0.02
6	0.30 ± 0.03	0.26 ± 0.04	0.27 ± 0.02	0.30 ± 0.03

Rheological data demonstrated that, regardless of the media, all METHOCEL™ grades exhibited a shear-thinning behavior. The higher ethanol contents of the media led to an increase in the viscosity of all samples (Figure 2). This effect might be due to the reduced volume of water in the hydroalcoholic mixture or dielectric constant of the hydroalcoholic media, leading to the formation of new bonds/structures.[4]

Figure 2. Rheological Behavior of Different METHOCELTM Grades in Various Media

(K100M samples were tested over a broader range of shear rates to demonstrate the Newtonian behavior at lower shear rate values; media has a negligible effect on the results).



CONCLUSIONS

The rheological profiles of METHOCEL™ samples demonstrated that an increase in ethanol content of the media resulted in higher viscosity for METHOCEL™ samples, regardless of the viscosity grade. The results of textural analyses showed that at earlier time points, the higher ethanol content of the media may affect the hydration and gel formation of the hypromellose HPMC compacts. This is shown through the greater values for the work of penetration and gradient for METHOCEL™ compacts. However, over a longer period of hydration the overall textural properties and thus matrix integrity are not significantly affected by the presence of ethanol up to 40% v/v.

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