

The Influence of Anionic Polymers on Hydrochlorothiazide Extended Release Hypromellose Matrices

INTRODUCTION

Hydrophilic matrices are the most commonly used oral extended release (ER) systems because of broad regulatory acceptance of the polymers, as well as their ability to provide desired release profiles for a wide range of drugs, a robust formulation, and a cost effective manufacturing process.^{1&2} To date, hypromellose (hydroxypropyl methylcellulose, HPMC) has been well characterized, and remains the polymer of choice as the rate-controlling carrier in pharmaceutical ER matrix applications.

HPMC matrices offer a platform for blending other polymers to provide flexibility to the formulator for achieving a desired release profile. Ionic, non ionic and insoluble polymers have been used in HPMC matrices to modulate the release profile of various drugs.³⁻⁵

The objective of this study was to investigate the effect of blending anionic polymers (carbomer and polyvinyl acetate phthalate [PVAP, Phthalavin]) with HPMC, on extending the release of hydrochlorothiazide, a very slightly soluble drug (~1.0 mg/ml). The effects of varying the polymer blend ratio and excipient choice were studied in terms of drug release profile and textural properties of the hydrated matrix tablets.

METHODOLOGY

Tablet Formulations

Hydrochlorothiazide was formulated with various blends of anionic polymers and HPMC (Table 1). Polymer blend, drug and filler were used at 33% w/w each; glidant and lubricant were used at 0.5% w/w each. Lactose (Fast Flo, Foremost Farms, USA), dicalcium phosphate (Di-Tab, Rhodia, France), partially pre-gelatinized starch (Starch 1500®, partially pregelatinized maize starch, Colorcon, USA) or microcrystalline cellulose (Emcocel 50M, JRS, Germany) were used as fillers. All ingredients (except lubricant) were mixed in a twin-shell mixer (Patterson-Kelley, USA) for 10 minutes. Magnesium stearate was then added and blended for an additional 3 minutes. The blend was compressed into tablets using standard concave tooling (3/8" round) on an instrumented 10 station rotary press (Piccola, Riva, Argentina). The compression force for each batch was adjusted such that the resulting tablets possessed similar breaking forces in a target range of 11-15 kp. A total of 12 different tablet compositions were produced. Tablet weights, breaking force and thickness were measured with an automated tablet tester (Multicheck, Erweka, Germany). Tablet friability was measured according to USP <1216> with a friabilitor (Model 45-2000, VanKel, USA).

Drug release profiles were measured using USP Apparatus I at 100 RPM. The dissolution medium was 900 ml of deionized water or phosphate buffer, pH 6.8 at 37°C ± 0.5°C. Drug release was measured spectrophotometrically at a wavelength of 278 nm. Textural profiles were used to study the dynamics of

hydrated matrix, and swelling.⁶ Tablets were allowed to hydrate inside sinkers in 900 ml of media (water of phosphate buffer, pH 6.8), maintained at 37°C in a USP compliant dissolution bath using apparatus II at 100 rpm. The tablets were removed at pre-determined time intervals (0-7 hours) and subjected to textural analysis using a texture analyzer (TA.XT Plus with probe TA-52R, Stable Micro Systems Ltd., UK). The force-displacement profiles were used to compare the textural properties of the hydrated matrix tablets.

Data Analysis

Release exponent (n) and release rate constant (k) were calculated by fitting the dissolution data to the Power Law equation:

$$Q = k t^n \text{ Equation 1}$$

Where Q is the fractional amount released at time t, k is the kinetic constant and n is the release exponent.

To provide a measure of the gel strength by textural analysis, the total work of penetration (WT) was calculated at each interval as the area under the force/distance curve (Figure 1):

$$W_T = F \cdot d \text{ Equation 2}$$

Where WT is the work required to penetrate the probe from the outer tablet boundary through the gel layer to the dry region of the core; F = force acting on the probe; d = distance travelled into the tablet from the gel boundary.

The percent swelling of the hydrated tablets was calculated at each testing interval as follows

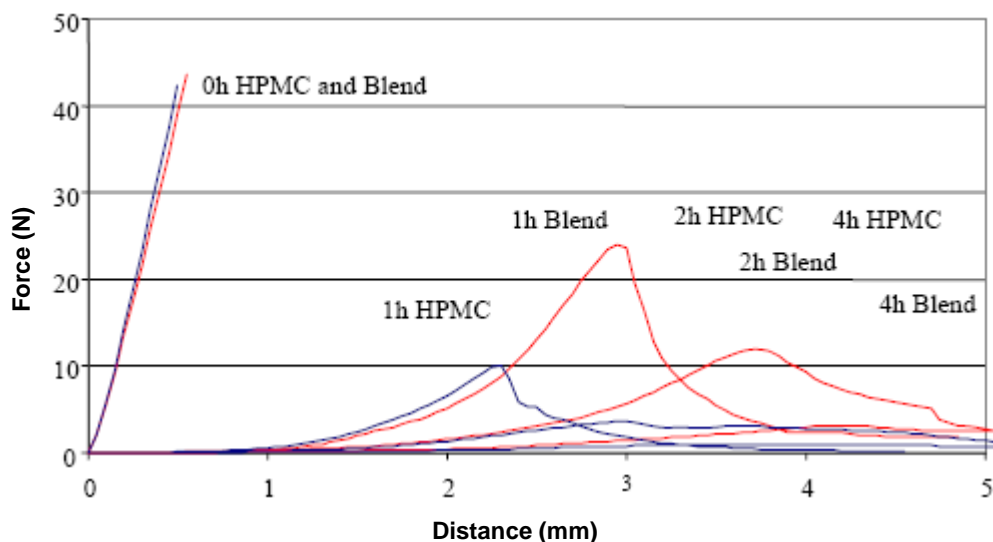
$$\text{Percent swelling} = 100 \cdot [(\text{thickness}_{\text{initial}} - \text{thickness}_{\text{time } t}) / \text{thickness}_{\text{initial}}] \text{ Equation 3}$$

Table 1: Hydrochlorothiazide ER Matrix Formulations

| No | Ingredient | Functionality | % w/w | mg/tablet |
|----|--|--|--------|-----------|
| 1 | Hydrochlorothiazide (Hu Zhou Synthetic, China) | API | 33.00 | 115.50 |
| 2 | HPMC (METHOCEL™ K4M, International Flavors and Fragrances Inc.) | Release Controlling Agent (Matrix Blend) | 33.00 | 115.50 |
| 3 | PVAP (Phthalavin, Colorcon) | | | |
| 4 | Carbomer (Carbopol 974 PNF, Lubrizol) | | | |
| 5 | Filler ^a | Filler Excipient | 33.00 | 115.50 |
| 6 | Colloidal Silicon Dioxide CAB-O-SIL M-5P, Cabot) | Glidant | 0.50 | 1.75 |
| 7 | Magnesium Stearate (Mallinckrodt) | Lubricant | 0.50 | 1.75 |
| | | Total | 100.00 | 350.00 |

^aLactose (Fast Flo, Foremost Farms), dicalcium phosphate (Di-Tab, Rhodia), partially pre-gelatinized starch (Starch 1500, Colorcon) or microcrystalline cellulose (Emcocel 50M, JRS) were used as fillers.

Figure 1. Typical Force vs. Distance Profiles for Hydrating Matrix Tablets: HPMC versus Polymer Blends



RESULTS AND DISCUSSIONS

All formulations yielded tablets with acceptable pharmacotechnical properties. Tablet weight variation ranged from 0.4-2.4%, tablet breaking forces ranged from 11-15 kp and friability for all batches was less than 1%.

All formulations provided extended release of hydrochlorothiazide. Blending of anionic polymers (carbomer and PVAP) with HPMC resulted in further reductions in release rates compared to HPMC-only control formulations (See Table 2). Modulation in the drug release profiles of hydrochlorothiazide was possible by altering the ratio of carbomer and PVAP in the matrix blend. Further, the use of the matrix blend resulted in slower release in phosphate buffer, pH 6.8 than in water.

Table 2. Dissolution Data for Hydrochlorothiazide ER Matrix Formulations in Water and Phosphate Buffer, pH 6.8

| No | Batch No | Water | | | | | Phosphate Buffer, pH 6.8 | | | | |
|----|----------|-------|------|------|------|------|--------------------------|------|------|------|-------|
| | | n | k | T15% | T30% | T65% | n | k | T15% | T30% | T65% |
| 1 | L1 | 0.96 | 0.08 | 3.9 | 8.0 | 19.0 | 0.67 | 0.39 | 3.5 | 10.5 | 34.4 |
| 2 | L2 | 0.87 | 0.08 | 7.0 | 15.9 | 42.1 | 0.83 | 0.10 | 6.9 | 15.9 | 35.7 |
| 3 | L3 | 0.79 | 0.22 | 3.7 | 8.1 | 28.5 | 0.80 | 0.12 | 7.6 | 16.6 | 38.8 |
| 4 | M1 | 0.95 | 0.09 | 3.5 | 7.5 | 18.9 | 0.78 | 0.16 | 5.8 | 12.5 | 29.8 |
| 5 | M2 | 0.82 | 0.09 | 8.6 | 19.2 | 47.3 | 0.82 | 0.10 | 7.5 | 15.9 | 35.7 |
| 6 | M3 | 0.74 | 0.21 | 5.3 | 12.9 | 33.1 | 0.87 | 0.07 | 7.4 | 17.7 | 45.6 |
| 7 | S1 | 1.00 | 0.06 | 4.1 | 8.3 | 18.9 | 0.80 | 0.11 | 7.3 | 23.0 | 94.0 |
| 8 | S2 | 0.78 | 0.10 | 10.7 | 24.0 | 59.0 | 0.91 | 0.05 | 8.7 | 18.9 | 45.0 |
| 9 | S3 | 0.90 | 0.11 | 4.1 | 9.0 | 23.6 | 0.87 | 0.06 | 10.0 | 20.1 | 43.3 |
| 10 | D1 | 1.04 | 0.05 | 4.1 | 8.3 | 18.9 | 0.78 | 0.12 | 7.4 | 52.5 | 781.7 |
| 11 | D2 | 0.96 | 0.05 | 6.3 | 13.2 | 30.2 | 0.85 | 0.08 | 8.7 | 18.9 | 45.0 |
| 12 | D3 | 0.79 | 0.12 | 7.4 | 16.0 | 38.1 | 0.94 | 0.04 | 8.5 | 16.8 | 36.0 |

L, M, S and D are formulations with lactose (L), microcrystalline cellulose (M), Starch 1500 (S) or dicalcium phosphate (D) as filler, respectively. Batch prefixes 1, 2 and 3 indicate matrix blend formulations with 100% HPMC and matrix blends with extremes of PVAP and carbomer, respectively. T15%, T30% and T65% is the time (hr) for 15, 30 and 65% drug release, respectively.

Blending of PVAP and carbomer with HPMC also influenced the release exponent (n) indicating a possible shift in the mechanism of drug release.

The results of textural analysis indicated that the total work of penetration (WT) was higher for matrix blend tablets compared to HPMC-only formulations in water and phosphate buffer, pH 6.8 (Figures 2 and 3). The total work of penetration is a measure of matrix stiffness or rigidity, indicating that both matrix blends exhibited higher matrix gel strength compared to HPMC-only formulations. The higher gel strength in polymer blend matrix could be attributed to differences in hydration of HPMC in presence of anionic polymers or to the interaction between the polymers.

The results of swelling studies indicated that matrix blend with higher carbomer level resulted in higher swelling than other formulations in water and phosphate buffer (Figures 4 and 5).

Figure 2. Total Work of Penetration (WT) for Hydrochlorothiazide- MCC Matrix Tablets in De-ionized (DI) Water. Similar Trends were Observed for Other Excipients

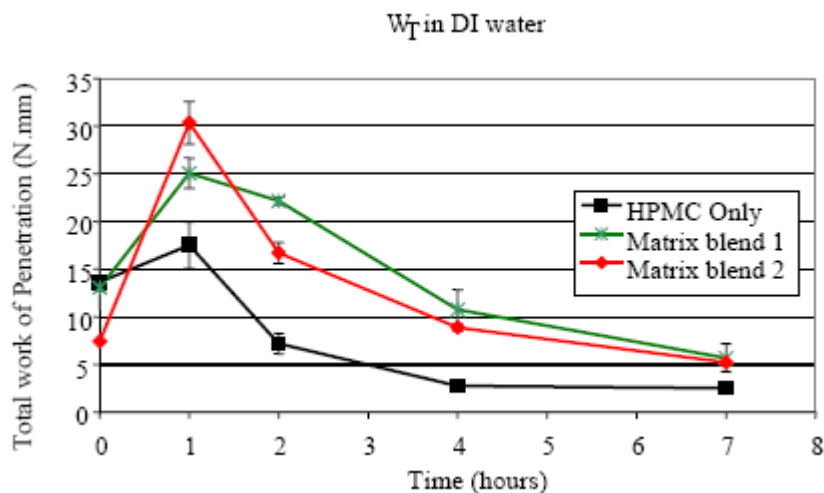


Figure 3. Total Work of Penetration (WT) for Hydrochlorothiazide-MCC Matrix Tablets in Phosphate Buffer, pH 6.8 Similar Trends were Observed for Other Excipients

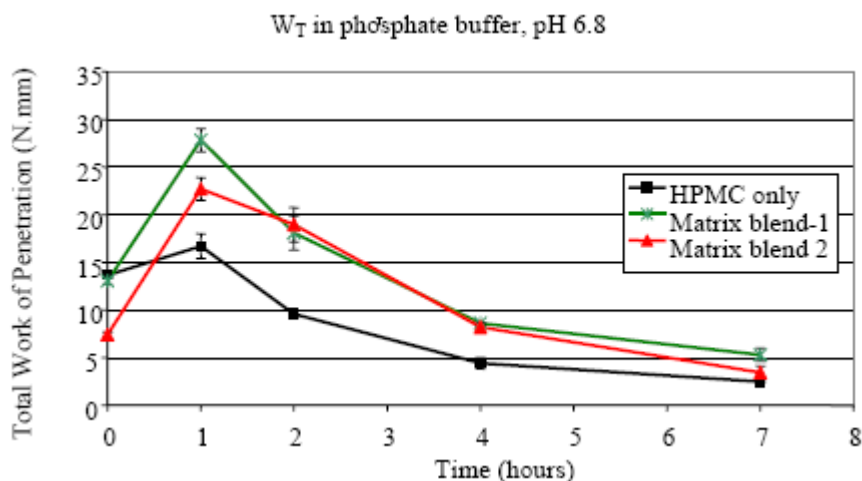


Figure 4. Percent Swelling of Hydrochlorothiazide- MCC Matrix Tablets in De-ionized (DI) Water. Similar Trends were Observed for Other Excipients

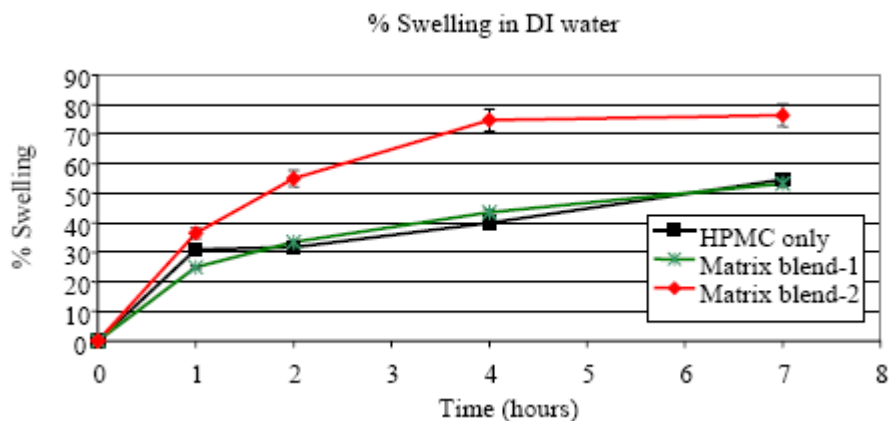
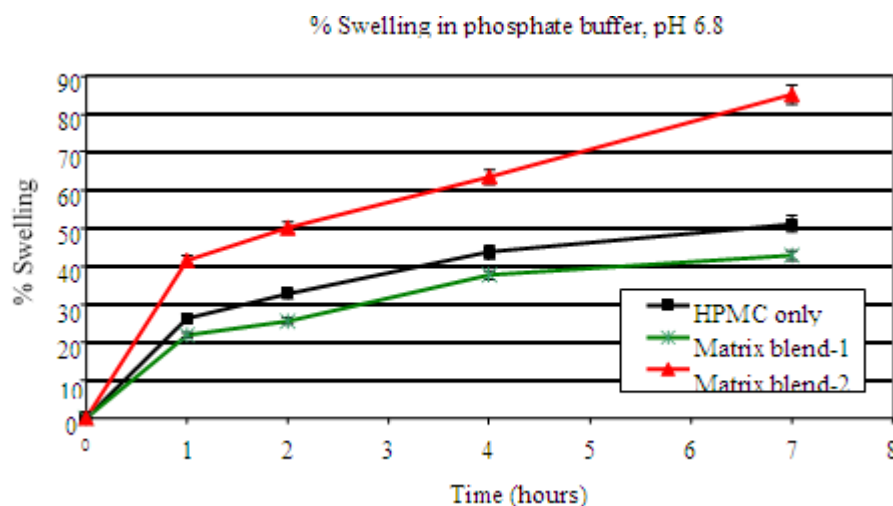


Figure 5. Percent Swelling of Hydrochlorothiazide-MCC Matrix Tablets in Phosphate Buffer, pH 6.8 Similar Trends were Observed for Other Excipients



CONCLUSION

The results of this study indicate that blends of HPMC and anionic polymers can be used to modulate drug release of poorly water soluble drugs like hydrochlorothiazide in ER matrices. Synergistic behavior of the polymer blends resulted in a range of release profiles in various dissolution media. Blending of these polymers strongly influenced the gel strength and rate of hydration of the matrix tablets, which in turn affected the rate and mechanism of drug release in various media.

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