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RESEARCH PAPER

Influence of Hydroxypropyl Methylcellulose Mixture, Apparent Viscosity, and Tablet Hardness on Drug Release Using a 2^3 Full Factorial Design

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ABSTRACT

This study investigates the effects of three factors: (1) use of a mixture of two different grades of hydroxypropyl methylcellulose (HPMC), (2) apparent viscosity, and (3) tablet hardness on drug release profiles of extended-release matrix tablets. The lot-to-lot apparent viscosity difference of HPMC K15M on in vitro dissolution was also investigated. Four test formulations were made, each containing 10% of a very water-soluble active pharmaceutical ingredient (API), 32% HPMC K15M, or a mixture of HPMC K100LV and HPMC K100M, 56% diluents, and 2% lubricants. Each formulation was made at two hardness levels. A 2^3 full factorial design was used to study various combinations of the three factors using eight experiments conducted in a randomized order. Dissolution studies were performed in USP apparatus I. The values of $t_{50\%}$ (time in which 50% drug is released) and t_{lag} (lag time, the time taken by the matrix tablet edges to get hydrated and achieve a state of quasi-equilibrium before erosion and the advance of solvent front through the matrix occur) were calculated from each dissolution profile. The similarity factor (f_2) was also calculated for each dissolution profile against the target dissolution profile. A simple Higuchi-type equation was used to analyze the drug release profiles. Statistical analysis using analysis of variance (ANOVA) and similarity factor (f_2) values

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calculated from the data indicated no significant difference among the $t_{50\%}$ values and dissolution profiles respectively for all formulations. Within the 3.3–6 kp hardness range investigated, dissolution rates were found to be independent of tablet hardness for all the formulations. Although significantly shorter lag times were observed for the tablets formulated with low- and high-viscosity HPMC mixtures in comparison to those containing a single grade of HPMC, this change had no significant impact on the overall dissolution profiles indicated by the similarity factor f_2 values. From this study it can be concluded that lot-to-lot variability in apparent viscosity of HPMC should not be a concern in achieving similar dissolution profiles. Also, results indicated that within the viscosity range studied (12,000–19,500 cps) an HPMC mixture of two viscosity grades can be substituted for another HPMC grade if the apparent viscosity is comparable. Also, the drug release is diffusion-controlled and depends mostly on the viscosity of the gel layer formed.

Key Words: *Apparent viscosity; HPMC; Factorial design; Polymer mixture; Hardness effects on drug release*

INTRODUCTION

Use of a hydrophilic polymer matrix is one of the most popular approaches in formulating an extended-release dosage form (1–3). This is due to the fact that these formulations are relatively flexible and a well-designed system usually gives reproducible release profiles. Among the various swellable polymers used to prolong drug release, hydroxypropyl methylcellulose (HPMC) has been widely used due to its rapid hydration, good compression and gelling characteristics, along with its ease of use, availability, and very low toxicity.

There have been many studies demonstrating that the drug release profile from a hydrophilic matrix tablet is influenced by the viscosity of the gel layer formed due to its polymer hydration (1,4,5). Also, it has been shown to depend on various other factors like water-solubility and particle size of the drug, particle size and type of the polymer, type of diluents used, and temperature of the release media (6–11). However, little work has been done to study the influence of lot-to-lot apparent viscosity difference on in vitro dissolution. Also, not much has been done to compare the effect of using a single grade of HPMC vs. a mixture of two different grades of HPMC on drug release (12). The current apparent viscosity range specification for HPMC K15M given by the manufacturer is 11,250–21,000 cps (13). Frequently, due to lot-to-lot variability, two lots of this polymer may differ widely from each other in terms of apparent viscosity. In the present study, it was intended to study whether this difference in apparent viscosity due to lot-to-lot variability affects the drug release rate from matrix tablets of this polymer. Another objective was to prepare mixtures of HPMC K100LV and HPMC K100M mixed uniformly in such a proportion as to give similar apparent viscosities to those of the HPMC K15M lots, and to study their effect on drug release profiles. It was also intended to study the influence of tablet hardness on drug release characteristics from the swollen matrix.

For this, factorial experiments were employed to make test formulations from various combinations of the three factors studied. Each formulation was then tested for Higuchi-type release rate (K_H), $t_{50\%}$, and lag time. Statistical analysis of the data was carried out using analysis of variance (ANOVA), and the similarity factor f_2 was determined to compare the dissolution profiles.

MATERIALS AND METHODS

The active pharmaceutical ingredient (API) and magnesium stearate NF were provided by Mallinckrodt, Inc., St. Louis, MO. Hydroxypropyl methylcellulose 2208 USP (Methocel®, viscosity grades K15M, K100LV, K100M) was kindly provided by Dow Chemicals, Midland, MI. Spray-dried lactose monohydrate NF (lactose 315) and Fast-Flo® lactose monohydrate NF (lactose 316) were

obtained from Foremost Farms USA, Rothschild, WI. Colloidal silicon dioxide NF (Syloid® 244FP) was purchased from W.R. Grace and Co., Columbia, MD.

Tablet Formulation

Four formulations were made, each consisting of:

API	10%
HPMC or HPMC mixture	32%
Spray-dried lactose	20%
Fast-Flo® lactose	36%
Colloidal silicon dioxide	0.5%
Magnesium stearate	1.5%

The API used in this study was a salt form of a weakly alkaline drug which has low molecular weight and high water solubility. The particle size of the API was less than 150 μm. The HPMC viscosity grades used in each formulation were as follows: formulation A, HPMC K15M (Lot No. OD 17012N01) having a nominal apparent viscosity 12,140 cps; formulation B, HPMC K15M (Lot No. OE 04012N02) having a nominal apparent viscosity of 19,580 cps; formulation C, mixture of 37% HPMC K100LV and 63% HPMC K100M having a combined apparent viscosity of ~12140 cps; formulation D, mixture of 28.6% HPMC K100LV and 71.4% HPMC K100M having a combined apparent viscosity of ~19,580 cps.

Experimental Design

A 2^3 full factorial design was used to determine the effect of the three factors: tablet hardness, polymer apparent viscosity, and polymer composition on drug release from the matrix tablet. Each factor was tested at two levels designated as −1 and +1. Hardness: 3.3 kp (−1) and 6.0 kp (+1). Polymer viscosity: ~12,140 cps (−1) and ~19,580 cps (+1). Polymer composition: use of single polymer HPMC K15M (−1) and use of polymer mixture HPMC K100LV:HPMC K100M (+1). The factorial design studied the effects of the three factors in eight runs as given in Table 1. Here F1–F8 represent the eight types of tablets prepared from the formulations A–D, each formulation being used for making tablets at two hardness levels. For each formulation, responses studied were K_H (the Higuchi-type release rate), t_{lag} (lag time, i.e., the time taken by the matrix tablet to get hydrated and achieve the state of quasi-equilibrium before erosion and the advance of solvent front through the matrix occur), and $t_{50\%}$ (time in which 50% drug is released).

Table 1

Randomized Study Design

Tablet	Tablet Hardness (kp)	Apparent Viscosity (cps)	HPMC Composition
F1	−1	−1	−1
F4	+1	+1	−1
F7	−1	+1	+1
F2	+1	−1	−1
F3	−1	+1	−1
F8	+1	+1	+1
F6	+1	−1	+1
F5	−1	−1	+1

Preparation of HPMC Mixture

The two viscosity grades of HPMC (HPMC K100LV and HPMC K100M) were mixed thoroughly in a mixing bag for 5 min. The proportions of the two grades to be mixed to achieve the required viscosities were obtained by using the empirical equation provided by Dow Chemical Company (13):

$$\eta^{1/8} = X_1\eta_1^{1/8} + X_2\eta_2^{1/8} \quad (1)$$

where η is the desired combined apparent viscosity; X_1 and X_2 are the percentages of HPMC K100LV and HPMC K100M, respectively; η_1, is the apparent viscosity of HPMC K100LV (Lot No. OI 19012N21) = 88 cps; and η_2, is the apparent viscosity of HPMC K100M (Lot No. OB 06012N12) = 82,238 cps.

Tableting

For each formulation, all the ingredients were blended together uniformly by shaking for 5 min. in a glass bottle. Then tablets were prepared from each formulation by direct compression on a Korsch PH 106 tablet press using a 7.14 mm (9/32 inch) deep-cup concave tooling to the targeted hardness levels of 3.3 and 6 kp and targeted weight of 150 mg. Tablets F1 and F2, F3 and F4, F5 and F6, F7 and F8 listed in Table 1 were made from

formulations A, B, C, and D, respectively. The weight and hardness of the tablets were measured using standard techniques.

Dissolution Studies

Drug release profiles were determined using the USP I (basket) apparatus at 50 rpm and with 900 mL distilled water as media maintained at 37°C (±0.5°C). Three to six tablets were used for each test. Ten-milliliter samples were collected at 1, 2, 4, and 8 hr without replacement with fresh media. Samples were analyzed by high-performance liquid chromatography (HPLC) and the average percentage drug dissolved at each sampling time was calculated after correction for the cumulative amount removed in previous samples.

Release Profile Analysis

The Higuchi square-root equation (14) gives the drug release from a planar surface of an insoluble, heterogeneous matrix by diffusion through the intergranular openings created by the porosity of the matrix:

$$Q = [D\epsilon C_s t(2A - \epsilon C_s)\tau]^{1/2} \quad (2)$$

where Q is the cumulative amount of drug released per unit area at time t; D is the diffusion coefficient of the drug in the dissolution medium; ϵ is the porosity of the matrix; C_s is the solubility of the drug in the dissolution medium; τ is the tortuosity of the matrix; A is the drug concentration in the tablet. The equation predicts a straight-line relationship if Q is plotted vs. $t^{1/2}$. In the present work, release data was subjected to a simple Higuchi-type equation:

$$Q = (K_H \times t^{1/2}) + c \quad (3)$$

where Q is the percentage cumulative drug released in time t; K_H is the Higuchi-type release rate; c is the y-intercept.

Statistical Analysis

Data obtained from the eight experiments was analyzed by ANOVA and by calculating the similarity factor f_2. StatGraphics Plus, Version 3 (Manugistics, Inc., Rockville, MD, USA) was used to generate the study design and to perform ANOVA. The ANOVA table partitions the variability in the responses ($t_{50\%}$, t_{lag}, and K_H) into separate pieces for each of the factors (apparent viscosity, tablet hardness, and polymer composition) studied and then tests the statistical significance of each factor by comparing the mean square against an estimate of the experimental error. The p-values at 0.05 level of significance obtained for each of the responses studied are given later in Table 3. The similarity factor, f_2, was calculated to compare the various dissolution profiles (values reported later in Table 4):

$$f_2 = 50 \log \left\{ \left[1 + 1/n \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (4)$$

where log = logarithm to base 10; n = number of sampling time points; $\sum$ = summation over all time points; R_t = dissolution at time point t of the reference product; T_t = dissolution at time point t of the test product. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar (15). Tablet F4 from Table 1 was selected as the reference product due to its closeness to the predetermined target dissolution profile, and f_2 values were calculated for dissolution profiles of all other formulations in comparison with the dissolution profile of F4.

RESULTS AND DISCUSSION

The dissolution results of all the eight types of tablets and the calculated values for t_{lag}, K_H, and $t_{50\%}$ are listed in Table 2. Drug release profiles obtained for each formulation at 3.3 and 6 kp hardness levels are shown in Figs. 1–4. The drug used in this study has a high aqueous solubility. Hence both diffusion and attrition should contribute to its release rate from HPMC matrix tablets. On plotting percentage cumulative drug release vs. the square root of time, it was observed that a straight line was obtained for the data only up to 4 hr of release for all the tablets. After 4 hr, the release profile showed negative deviation from linearity. This is consistent with the findings of Lapidus and Lordi (7) who found that the Higuchi model for diffusional release from inert matrices was applicable to whole tablets only during a relatively short initial stage after which the tablets underwent attrition or erosion, which caused deviation from the initial pattern. But unlike Lapidus and Lordi

Table 2

Dissolution Characteristics of the Eight Types of Tablets

Tablet	Slope K_H (%/hr$^{1/2}$)	y-Intercept c (%)	r^2 (Regression Coefficient)	t_{lag} (min)	$t_{50\%}$ (hr)
F1	39.41	−6.62	0.999	10.08	2.06
F2	42.67	−7.71	0.999	10.84	1.83
F3	43.11	−7.65	0.997	10.65	1.79
F4	42.48	−7.73	0.999	10.92	1.85
F5	40.57	−3.47	0.998	5.14	1.74
F6	40.37	−4.08	0.999	6.06	1.79
F7	39.12	−3.56	0.999	5.46	1.87
F8	39.97	−3.76	0.999	5.65	1.81

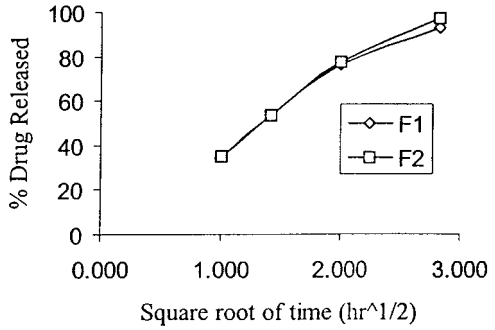

Figure 1. Effect of hardness on drug release from tablets containing HPMC K15M (12,140 cps).

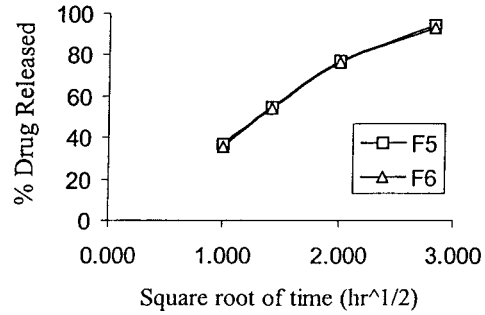

Figure 3. Effect of hardness on drug release from tablets containing HPMC mixture (~12,140 cps).

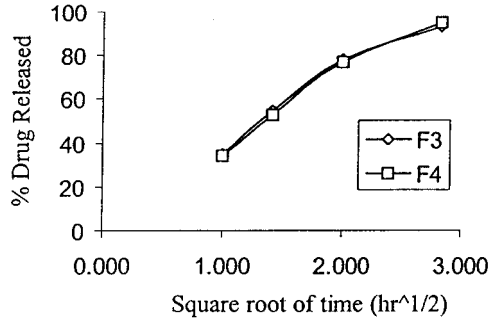

Figure 2. Effect of hardness on drug release from tablets containing HPMC K15M (19,580 cps).

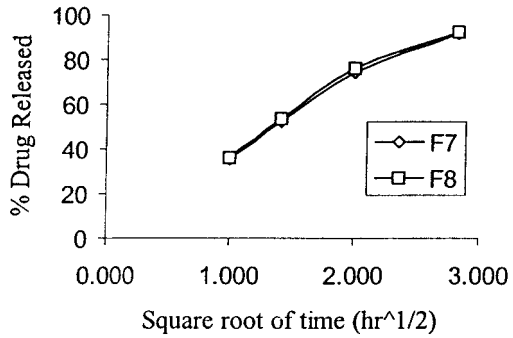

Figure 4. Effect of hardness on drug release from tablets containing HPMC mixture (~19,580 cps).

who found a positive deviation from linearity, in the present study all curves displayed negative deviations from linearity after approximately 75% of drug release. This slow-down in release rate can be due to depletion of the drug in the matrix. Consequently, the dissolution rates or the Higuchi-type release rates were determined only from the linear portions of the curves. This is in accordance with the observations of Ford et al. (8,9).

Statistical analysis of the data using ANOVA shows that hardness, viscosity, and polymer composition (whether single or mixture) did not have a significant effect on the Higuchi-type release rate or the $t_{50\%}$ values (p-value > .05) for all formulations.

But it was found that the use of a polymer mixture significantly decreased the t_{lag} (p-value $< .05$). Also, tablet hardness does seem to contribute to the difference in t_{lag} between the simple and mixed polymer formulations, although it is not statistically significant. Results are given in Table 3. The f_2 values (Table 4) indicated similar dissolution profiles for all formulations ($50 < f_2 \leq 100$) compared with the reference dissolution profile, F4.

These findings are in agreement with those of Ford et al. (8,9) and Huber and Christenson (16) who reported that varying the compaction pressure for tableting did not significantly affect the release rate. Also, they found that using various viscosity grades (K4M, K15M, K100M) of HPMC for a given fixed drug:HPMC ratio did not alter the Higuchi-type release rate significantly (except for HPMC K100LV for which faster release rates were observed by Ford et al.). They have therefore concluded that the viscosities of the hydrated higher-molecular-weight HPMC matrices may be identical despite the apparent differences in their viscosity grades. In the present study, a mixture of HPMC K100LV and HPMC K100M was used that had similar apparent viscosity to that of HPMC K15M. But tablets made from either HPMC K15M or from a mixture of HPMC K100LV and HPMC K100M both gave similar dissolution profiles. This implies that the viscosities of the gel layers formed from both the mixture and single HPMC grade matrices must be similar. Thus, the drug release from these tablets should depend mostly on the viscosity of the gel layer formed from the hydrated matrix. Since the observed data gives a good fit to the Higuchi-type equation (up to about 75% drug release), it indicates a diffusion-dominated drug release pattern. But other mechanisms such as erosion and dissolution of the polymer may also contribute to the overall mechanism.

Table 3

ANOVA Test Results

Factors[a]	p-Value for $t_{50\%}$	p-Value for t_{lag}	p-Value for K_H
A	0.8440	0.2578	0.8015
B	0.7308	0.0711	0.6119
C	0.5704	0.0076	0.3633
AB	0.7308	0.1237	0.6525
AC	0.5000	0.1997	0.4617
BC	0.7578	0.7952	0.7641

[a]A: Viscosity. B: Hardness. C: Polymer composition.

Table 4

Similarity Factor f_2 *Values*

Tablet	f_2 Value
F1	69.3
F2	91.5
F3	89.9
F4[a]	100.0
F5	86.9
F6	87.7
F7	80.9
F8	85.4

[a]F4 is used as the reference product.

All release rate curves displayed negative y-intercepts indicating a lag time. This initial lag time can be explained as the time taken by the matrix edges to get hydrated until a state of quasi-equilibrium is achieved (17). It was calculated from the respective linear regression equations as $-c/K_H$. Values obtained are given in Table 2. Earlier work by Salomen et al. (18) indicates that the viscosity grade does have an impact on $t_{lag.}$ In the present study, statistical analysis (Table 3) shows that the given range of viscosity does not affect t_{lag} significantly (p-value $> .05$) but polymer composition, i.e., the use of polymer mixture, does show a significant decrease in t_{lag} (p-value $< .05$). The shorter lag time observed for tablets containing the polymer mixture may be related to the HPMC K100LV which has a shorter polymer chain length. It can be proposed that this shorter-chain-length polymer gets eroded from the surface of the tablet on contact with dissolution medium, and thus allows for faster water penetration and subsequent gelling of the matrix. This difference in the initial lag periods, however, had no significant impact on the overall dissolution profiles for tablets made with either HPMC K15M or with HPMC K100LV: HPMC K100M mixture.

For all the tablets made in this study, a dry blend and direct compression approach was used. This manufacturing process cannot be applied in real production due to poor flowability of the dry blend. A wet granulation or a dry blend

approach with roller compaction is commonly used in preparing this kind of matrix tablets. Whether a change in the manufacturing process like this will yield similar results is currently under investigation.

CONCLUSIONS

The study shows that lower and higher viscosity grades of HPMC can be mixed uniformly in definite proportions to get the desired apparent viscosity, and within the viscosity range studied (~12,000 to ~19,500 cps), such a mixture of two viscosity grades can be substituted for another HPMC grade if the apparent viscosity is comparable. Incorporating a low viscosity grade of HPMC K100LV in the formulation would lead to a significantly shorter t_{lag}, however, it imposes minimal impact on the overall dissolution profile. The lot-to-lot difference in apparent viscosity did not have any significant impact on in vitro dissolution characteristics. Also, it can be concluded that the drug release from an HPMC matrix tablet prepared by dry blend and direct compression approach is independent of tablet hardness, is diffusion-controlled, and depends mostly on the viscosity of the gel layer formed. Whether or not this holds true for HPMC matrix tablets prepared by wet granulation or dry blend with roller compaction methods is currently under investigation.

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