Relationship Between Polymer Viscosity and Drug Release from a Matrix System

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INTRODUCTION

The use of hydroxypropylmethylcellulose (HPMC) to modify the release of drug from solid dosage forms has been studied (1–3). HPMC, a water-soluble hydrophilic polymer, can affect the dissolution behavior and transport properties of drug molecules by an increase in solution viscosity. There has been considerable interest in the relationship between bulk solution viscosity and the rate of dissolution of a wide range of materials (4,5). A number of empirical equations have been proposed (6,7) to describe the relationship of dissolution rate as a function of the viscosity of the dissolution medium raised to a power where the exponent ranged from -0.25 to -0.8. This study was undertaken to explore the relationship of polymer viscosity and drug release from a matrix system.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride (USP grade) was used as supplied. HPMC 2208 USP of five viscosity grades were used, Metolose K4, K15, K30, K50, and K100 (Shin-Etsu Chemical, Japan). The apparent viscosities of 2% (w/v) aqueous solutions of these HPMC grades were 4380, 18,200, 35,800, 44,400, and 100,000 cps, respectively (USP method).

Preparation of Matrices

The drug and HPMC were thoroughly mixed in a mixing bag for 10 min. A weighed amount of the mixture was fed manually into the die of a single-punch tabletting machine (Manesty-E2, England) to produce a matrix of 300 mg and porosity of 0.15 ± 0.01 using flat-surface punches 9.5 mm in diameter. Matrices were prepared using the various viscosity grades of HPMC and with different concentrations of the drug. All matrices were compacted for approximately 2 sec and kept at 25 ± 0.5°C for a week prior to dissolution testing.

Viscosity Measurements

A U-tube viscometer (size A) was used to determine the viscosity of the HPMC solutions at 37°C. Accurately weighed amounts of the five HPMC viscosity grades, K4 to K100, were dissolved in 100 ml of distilled water to produce HPMC solutions of varying concentrations. These HPMC solutions were allowed to hydrate for at least 72 hr prior to viscosity measurement. The period of hydration required was determined from preliminary investigations. The mean of not fewer than three replicates was taken to represent the viscosity.

Dissolution Studies

The dissolution test was carried out in 1000 ml distilled water at 37 ± 0.5°C using the rotating-basket apparatus (Hanson Research, Model 72RL, USA). The operating speed of the dissolution basket was 100 rpm. Progress of the dissolution was monitored by withdrawing filtered samples at predetermined intervals using an automated sampler (Hanson Research, Dissoette 27-6a-1-2) and assayed spectrophotometrically (Hewlett Packard, Model 8452A) using the area under the curve for absorbance over the range of 278 to 298 nm. Three replicates for each formulation were tested and their mean percentages release calculated.

RESULTS AND DISCUSSION

When the hydrophilic HPMC polymer comes into contact with water, it absorbs water and swells to form a gel. This gel serves as a barrier to drug diffusion. The process of drug release from a HPMC–drug matrix involves water penetration into the dry matrix, hydration and gelation of the polymer, dissolution of drug, and diffusion of the dissolved drug through the resultant gel layer. Since movement of the drug solute through the matrix system is diffusion-controlled, it may be expected from the Stokes–Einstein equation that the process will be slower in the more viscous medium (5–9).

Viscosity of the HPMC Gelatinous Layer

It is realized that the capillary viscometer is a single-point viscometer and that the HPMC solution, being non-Newtonian, would be affected by different shear rates. Nevertheless, it can be used for comparative purposes, as all the solutions were measured with the same viscometer throughout the study. It is also noted that the USP recommends the use of capillary viscometer.

Due to the high viscosity of the gel layer present in the matrix system, its viscosity could be measured only in diluted conditions. An assumption was thus made that the bulk viscosities of the diluted polymer solutions are indicative of the diffusive resistance experienced by the solute. The degree of entanglement of a polymer solution can be estimated from the Huggins constant obtained from dilute polymer solutions (10). Further, nonNewtonian flow, which is commonly attributed to chain entanglement, has been observed at molecular weights significantly lower than the recognized value of critical molecular weight for entanglement. Al-

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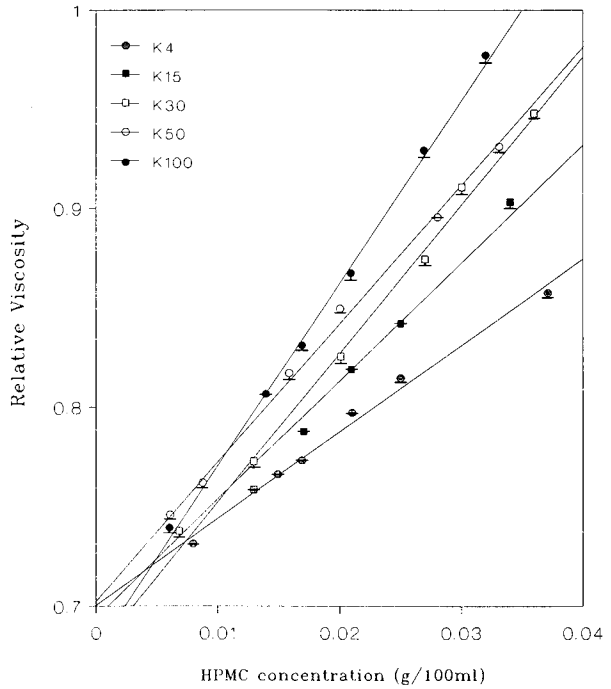

Fig. 1. Influence of HPMC viscosity grade and concentration on the relative viscosities of HPMC of viscosity grade K4 to K100 at 37°C.

though simple geometrical calculations indicate that in the concentrated polymer solution and in the melt, the degree of entanglement must be larger than in dilute solution or the molecules contract considerably, it has been suggested that such contraction would occur even in dilute solution due to "nonideal part of the osmotic pressure" (11).

The relative viscosities of the HPMC solutions (K4 to K100) at various concentrations are presented in Fig. 1. The viscosities of the respective HPMC solutions increased with concentration. From these linear plots, the relative viscosities of the five HPMC viscosity grades were obtained for the actual HPMC concentration used in the matrix systems. These values are used for comparing the effect of various viscosity grade on drug release.

The polymer molecules of HPMC are giant macromolecules compared to drug and water molecules. They are made up of hundreds of chain segments in random coils held tightly by hydrogen bonding. HPMC, being hydrophilic, has a great affinity for water. When a polymer chain comes into contact with water, polymer–water interaction replaces polymer–polymer attraction. Polymer molecules adopt more extended configuration depending on their viscosity grade. Their hydrodynamic volumes also increase. High-viscosity grade HPMCs are made up of larger macromolecules (12,13). These HPMCs therefore produced highly viscous mucilage.

HPMC and Water Uptake

The water penetration into plain HPMC compacts has been discussed in detail in a previous paper (10). The rate of water penetration into hydrophilic matrices is determined by the balance of forces promoting water entry and the viscous force opposing it. As the matrix swells, the relative polymer concentration decreases due to hydration and dilution. This

Table I. The Percentage of Drug Released for Matrices Containing Various Concentrations of HPMC Using a Viscosity Grade of K4 to K100

Percentage HPMC	Sampling time (min)	Percentage of drug released				
		K4[a]	K15[a]	K30[a]	K50[a]	K100[a]
0	30	98.64	98.64	98.64	98.64	98.64
	60	99.31	99.31	99.31	99.31	99.31
	120	99.45	99.45	99.45	99.45	99.45
	240	99.53	99.53	99.53	99.53	99.53
5	30	89.03	67.34	69.78	68.51	60.39
	60	97.20	96.71	90.02	93.25	83.24
	120	98.15	99.26	97.94	95.81	98.42
	240	98.63	99.57	98.91	96.49	99.57
10	30	44.25	32.74	30.14	31.65	27.81
	60	73.49	53.97	46.93	51.61	40.32
	120	97.15	84.46	75.00	75.51	62.98
	240	99.02	99.39	98.36	99.30	98.69
25	30	17.90	15.38	15.44	15.59	14.19
	60	28.04	26.31	25.47	25.40	23.42
	120	45.33	42.15	40.96	40.11	38.01
	240	77.80	66.97	65.47	62.80	61.07
50	30	13.74	13.08	13.10	13.05	13.13
	60	21.92	20.02	20.43	20.10	20.66
	120	31.24	31.06	31.28	31.57	31.65
	240	48.55	47.81	49.31	48.92	48.90
75	30	12.44	11.83	12.07	10.93	9.20
	60	19.05	18.35	18.72	16.85	15.26
	120	27.90	28.47	28.77	25.77	23.77
	240	43.95	43.83	43.92	39.72	42.00

[a] HPMC viscosity grade.

Table II. Effect of the HPMC Content on $W_r/\sqrt{t}$, Dissolution $T_{50\%}$, and Relative Solution Viscosity of the Polymer for Various HPMC Viscosity Grades

HPMC grade	% HPMC	$T_{50\%}$ (min)	$W_r/\sqrt{t}$ (%/$\sqrt{\text{min}}$)	r^2 value	Relative viscosity
K4	0	4.90	—	—	—
	5	9.60	16.59	0.9991	0.7064
	10	36.00	9.60	0.9920	0.7129
	25	135.40	5.58	0.9905	0.7322
	50	253.10	3.46	0.9988	0.7646
	75	295.20	3.20	0.9950	0.7969
K15	0	4.90	—	—	—
	5	18.49	13.50	0.9999	0.7035
	10	53.29	8.55	0.9952	0.7122
	25	153.76	5.09	0.9948	0.7383
	50	262.44	3.43	0.9824	0.7818
	75	299.29	3.16	0.9980	0.8253
K30	0	4.90	—	—	—
	5	18.00	14.00	0.9997	0.6871
	10	66.00	7.94	0.9976	0.6982
	25	161.29	4.87	0.9955	0.7318
	50	245.00	3.55	0.9972	0.7876
	75	301.50	3.13	0.9984	0.8435
K50	0	4.90	—	—	—
	5	14.60	11.26	0.9994	0.7085
	10	56.90	7.58	0.9951	0.7190
	25	166.60	4.60	0.9972	0.7504
	50	250.20	3.50	0.9971	0.8027
	75	350.70	3.86	0.9959	0.8550
K100	0	4.90	—	—	—
	5	16.70	8.91	0.9966	0.6954
	10	84.30	5.64	0.9890	0.7088
	25	181.00	4.52	0.9956	0.7489
	50	250.20	3.55	0.9968	0.8158
	75	354.10	3.08	0.9885	0.8828

decreases the viscosity, thereby reducing the viscous force opposing liquid uptake.

The presence of HPMC in the matrices improved wetting and enhanced water uptake into the matrices. A large volume of liquid uptake was obtained with a greater amount of HPMC used. The action of HPMC on water uptake can be divided into two groups, namely, high molecular weight HPMC, containing K30 to K100, and low molecular weight HPMC, of K4 and K15. An increase in viscosity in the former promotes water entry, whereas the reverse is seen in the latter. In all cases, the kinetics of water uptake changed from capillary rise to slow diffusion with time when the swollen gel blocked the interparticulate voids (12).

HPMC and Drug Release

Matrices containing 5, 10, 25, 50, and 75% (w/w) of HPMC were prepared. Their release profiles are presented in Table I. Matrices formed using 5% (w/w) of HPMC retarded the drug release only marginally (Table I). More than 60% of drug was released within 30 min and 80% was released in 1 hr. When the amount of HPMC present in the matrices was doubled, 10% (w/w), the percentage drug release after 30 min was halved (Table I). Complete drug release was obtained within 4 hr.

Attempts to prolong the drug release were made possible by increasing the HPMC content to 25% (w/w). Only 15% of drug was released in the first 30 min compared to more than 60% in formulations containing 5 or 10% (w/w) HPMC. The amount of drug released in the next few hours was also reduced, less than 30% in the first hour, 40% by the next hour, and only 60% in 4 hr. Formulations containing 50 and 75% (w/w) yielded less than 50% release in 4 hr. The remainder of the drug was not released even after 7 hr as the core of the swollen matrix remained dry.

Relationship Between Dissolution and Viscosity

The release of drug from HPMC matrices (Table II) follows Higuchi $t_{1/2}$ equation:

$$\frac{W_r}{\sqrt{t}} = S\left[DC\left(2\frac{W_o}{v} - C\right)\right]^{1/2}$$

where W_r is the amount of drug released in time t, S is the effective diffusive area, W_o is the initial amount of drug present in the matrix, v is the effective volume of the hydrated matrix, D is the diffusion coefficient, and C is the solubility of the drug in the matrix.

These findings suggest that the diffusion layer model is operative (1–3,13). The effect of HPMC on drug release can be divided into two parts: concentration effect and viscosity effect.

Concentration Effect. A complete diffusion barrier is

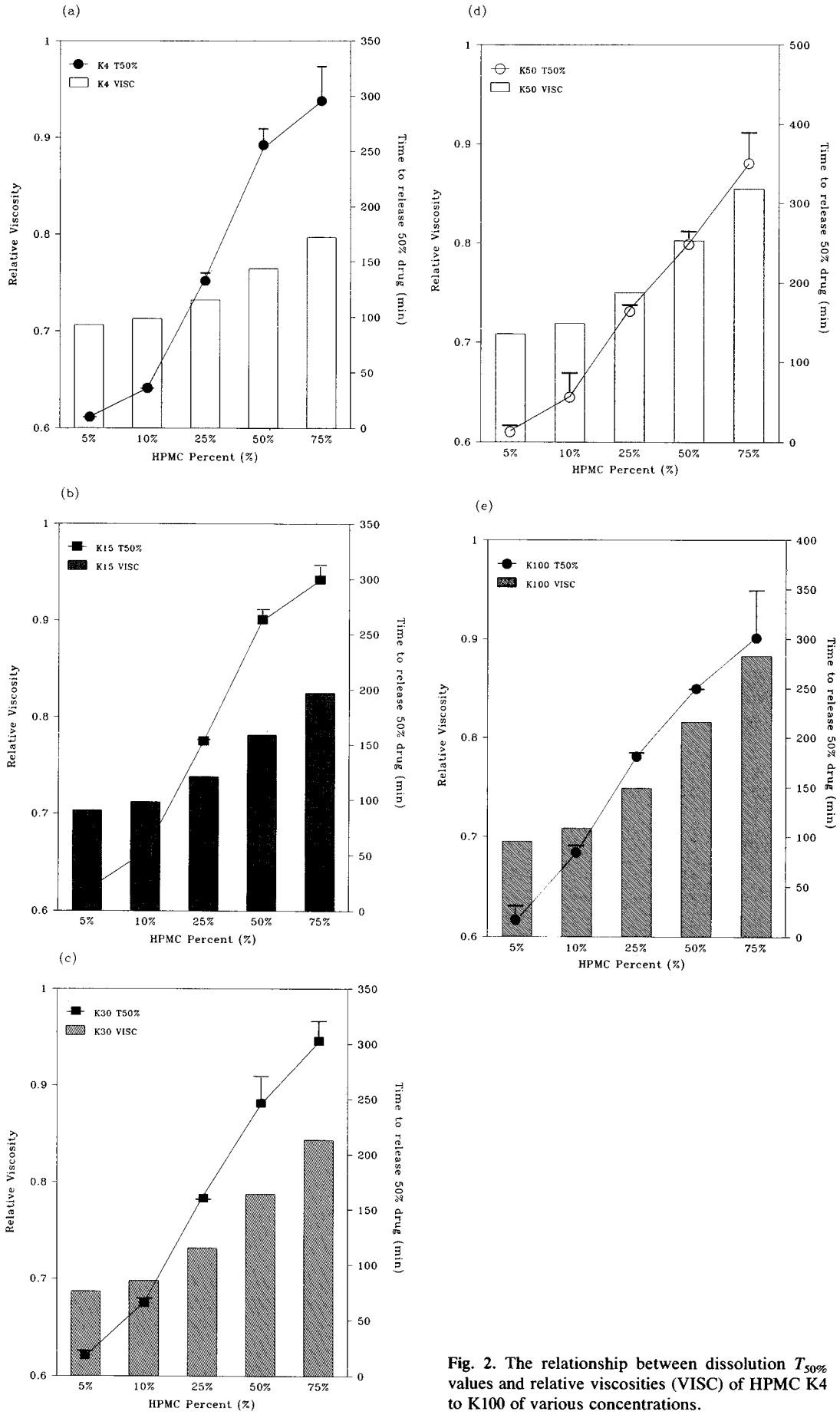

Fig. 2. The relationship between dissolution $T_{50\%}$ values and relative viscosities (VISC) of HPMC K4 to K100 of various concentrations.

essential to retard drug release (Tables I and II). Retardation of drug release was minimal at 5% (w/w) HPMC content. At 5% (w/w), the amount of HPMC present is insufficient to form a continuous gel layer and the incomplete gel layer acts as a poor diffusion barrier (Table II). A higher HPMC content (>10%) promotes water uptake into matrices. This can improve wetting and drug dissolution. However, the thickness of HPMC gel is also increased, forming a more complete gel barrier which retards drug release.

Viscosity Effect. The solution viscosity and gel thickness vary directly with the viscosity grade of HPMC used (Figs. 2a–e). The effect of HPMC viscosity grade is observed only in the optimal concentration range. At a low concentration (5%), an effective gel barrier is not formed. At a higher HPMC content, 50–75% (w/w), the viscosity effect is not shown clearly, as it is masked by the concentration effect. The viscosity effect is best seen in the formulation prepared with 25% (w/w) HPMC (Table II). The gradual increase in the dissolution $T_{50\%}$ values indicates the predominant effect of viscosity in controlling drug release.

The order of effectiveness in reducing the dissolution rate is in accordance with that in the viscosity of HPMC in the dilute HPMC solution (Table II). The influence of viscosity on the dissolution rate (R) from a diffusion-controlled system can be expressed (8) as follows:

$$R = \frac{DC}{h}$$

where h is the effective film thickness. The diffusivity of a substance in a particular medium depends on the degree of interaction between the solute and the diffusion medium. In general, there is an inverse relationship of diffusion coefficient and viscosity (9).

Many empirical diffusion coefficient equations applicable to dilute solutions have been developed and can be generalized (9) as follows:

$$D = a\eta^{-b}$$

where a and b are empirical coefficients dependent on the system. Chang and Parrott (9) proposed that

$$R = m\eta^{-n}c$$

where R is dissolution rate and m and n are coefficients, depending on the molecular weight and configuration of the polymer in solution.

From the results obtained in this study, it is found that the coefficient n takes the value of 0.5 in all systems evaluated and a constant is required to be inserted into the above equation. In this investigation, $T_{50\%}$ was used in place of dissolution rate as it is independent of the lag time involved in the dissolution study. The square of dissolution $T_{50\%}$ varied proportionately with the solution viscosity and can be represented by the following equation:

$$T^2 = mv' + k$$

where T is dissolution $T_{50\%}$, m is the gradient, v' is the solution viscosity, and k is a constant. The values of the coefficient of correlation (r^2 values) evaluated from the experimental dissolution $T_{50\%}$ values and viscosities are given in Table III.

Table III. The Relationship Between Polymer Viscosity and Dissolution $T_{50\%}$[a]

HPMC viscosity grade	m (× 1 million)	k (× 1 million)	r^2 value
K4	1.0305	−0.7213	0.9833
K15	0.7823	−0.5436	0.9824
K30	0.5896	−0.3986	0.9990
K50	0.8258	−0.5766	0.9824
K100	0.6628	−0.4522	0.9738

[a] m is the gradient, k is a constant, and r^2 is the correlation coefficient.

It appears that for a viscosity-enhancing polymer such as HPMC, a relationship may be expressed between the solution viscosity of the polymer and the dissolution behavior of a drug. The square of dissolution $T_{50\%}$ varies proportionately with the solution viscosity of the polymer. This viscosity can be varied with the thickness of HPMC forming the gel layer as well as the viscosity grade. The larger the amount or the higher the viscosity grade of the HPMC present in the matrix, the greater the solution viscosity of the gel layer and the more resistant the gel layer is to diffusion. Drug release from matrices with a diffusion-controlled release mechanism is therefore retarded.

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