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RELATIONSHIP BETWEEN SWELLING AND DRUG RELEASE IN A HYDROPHILIC MATRIX

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ABSTRACT

Hydroxypropylmethylcellulose (HPMC) is widely used for controlled-release preparations. The process of drug release is controlled by matrix swelling and polymer dissolution. This study examines the mechanism of behaviour of HPMC in a polymer-drug directly-compressed matrix. The results obtained show that the swelling of HPMC which can be described by first-order kinetics is affected by concentration and viscosity grade of the polymer. This swelling action of HPMC in turn is controlled by the rate of water uptake into the matrices. An inverse relationship exists between the drug release rate and matrix swelling rate. This implies that HPMC swelling is one of the factors affecting drug release. The swelling behaviour of HPMC is therefore useful in predicting drug release.

INTRODUCTION

Hydrophilic matrices are becoming popular in the formulation of controlled-release solid dosage forms. Various types of polymers are used as the gel forming agent in matrices, such as methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) and sodium carboxymethylcellulose (Na CMC)

The literature on the prolonged release of drug from compressed HPMC matrices was extensively reviewed recently by Alderman (1). The mechanism of drug release from drug-loaded HPMC matrices is controlled by two factors: matrix swelling and polymer

dissolution (2-3). Evidence of these factors affecting drug release is however limited in the literature.

Preliminary studies had been carried out to show the influence of the matrix swelling and polymer dissolution on drug release (4). In contact with an aqueous environment, the HPMC matrix hydrates, a viscous gel layer forms and this controls drug release via two mechanisms: diffusion through the gel and erosion of the gel barrier.

Drug release data from HPMC matrices follows the classical Higuchi dissolution equation relating drug release with square root of time (4-8). The process of drug release from a HPMC-drug matrix involves water penetration into the dry matrix, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix and erosion of the gel layer. A conventional dissolution test provides the resultant of these many separate processes. Investigations on the hydration and gelation of HPMC may give an insight into the various stages of the release process. The aim of this study is to examine the manner by which HPMC exerts its effect on the swelling process and the correlation of HPMC swelling behaviour with the drug release profile of these matrices.

MATERIALS AND METHODS

Materials

Ibuprofen (Pharmaceutical grade, Italy) was chosen as the model drug. HPMC 2208 USP of four viscosity grades were used, K4, K15, K30 and K50 (Metolose, Shin-Etsu Chemical Co., Japan). The apparent viscosities of 2%(w/v) aqueous solution of these HPMC grades were 4380, 18200, 35800 and 44400 cps respectively.

Preparation of matrices

The drug and HPMC were thoroughly blended in a mixing bag for 10 minutes. A weighed amount of the mixture was fed manually into the die of a single punch tabletting machine (Manesty F3, England) to produce a matrix of 600 mg and porosity of 0.10±0.01 using flat-surface punches of diameter 14 mm. Matrices were prepared using the various viscosity grades of HPMC and with different concentrations of the drug.

Matrix Swelling Measurement

The dimensions of each matrix were measured using a micrometer screw gauge prior to swelling determination. The method used was modified from that described by Westman and

Lindstrom (9). Essentially it involves mounting the matrix between two filter papers (Whatman No.54). The linear increase in the matrix thickness with time was monitored with a dial indicator (Mitutoyo, Model 2118-50, Japan). The results from at least three matrices were averaged.

Dissolution Studies

The dissolution test was carried out in 900 mL phosphate buffer pH 7.2 (USP XXII) at 37±0.5°C using the rotating basket apparatus (Hanson Research, Model 27RL, USA). The operating speed of the dissolution basket was 50 rpm. Progress of the dissolution was monitored by withdrawing filtered samples at pre-determined intervals using an automated sampler (Hanson Research, Dissoette Model 27, USA) and assayed spectrophotometrically (Hewlett Packard, Model 8452A, USA) using the area under the curve for absorbance over the range of 266 to 268 nm. Three replicates for each formulation were tested and their mean percent release calculated.

RESULTS AND DISCUSSION

Swelling behaviour of HPMC matrices

Taking a as the original thickness of the dry matrix, s as the thickness of the swollen matrix, the normalized increase in matrix thickness, d, can be used as an index where :

$$d=\frac{s-a}{a} \qquad \text{Equation 1}$$

When a HPMC-drug matrix is immersed in a dissolution medium, wetting of matrix surface occurs. Liquid then penetrates into the matrix. The surface polymer swells to form a gel and the matrix increases in size. Slowly this hydrated gel dissolves and erodes away. A new gel layer is then exposed. This continues until the core of the matrix is completely wetted and erosion of the gel is not replenished with a new HPMC gel formation. A slow diminution of the HPMC gel thickness then occurs until finally the whole matrix is completely dissolved.

The plots of percent increase in matrix thickness, δ, where δ is the value of d expressed as a percentage, against square root of time ($\sqrt{t}$) for HPMC of different viscosity grade are linear with the exception of matrices containing 5% HPMC (Table 1). These matrices contain insufficient HPMC for significant measurable swelling of matrices to occur. Also, they

TABLE 1

Table showing the curve fitting of matrix swelling and Equation 1

HPMC Viscosity Grade	HPMC content (%)	Swelling Rate ϕ (% / $\sqrt{s}$)	constant c_1	r^2-values
K4	5	0.0019	0.1313	0.5720
	10	0.0412	0.3971	0.9877
	20	0.2008	0.3397	0.9941
	30	0.2446	0.3802	0.9963
	40	0.3341	-0.1058	0.9987
	50	0.4152	-0.2628	0.9985
	100	0.4378	-1.5158	0.9831
K15	5	0.0004	0.0219	0.6678
	10	0.0375	0.2324	0.9862
	20	0.2272	0.2905	0.9974
	30	0.2768	0.2554	0.9985
	40	0.3513	0.0964	0.9992
	50	0.3736	-0.3264	0.9982
	100	0.4193	-1.4963	0.9842
K30	5	0.0098	0.1817	0.9683
	10	0.0455	0.0761	0.9778
	20	0.2292	-0.0328	0.9983
	30	0.2854	0.2003	0.9976
	40	0.4036	0.1977	0.9998
	50	0.4064	0.0307	0.9996
	100	0.4854	-1.6390	0.9887
K50	5	0.0236	0.0477	0.9235
	10	0.0543	0.0709	0.9977
	20	0.2291	0.4172	0.9989
	30	0.2839	0.6634	0.9987
	40	0.3832	0.3433	0.9989
	50	0.4312	-0.2392	0.9936
	100	0.5345	-2.2615	0.9749

are observed to undergo slow surface erosion which is believed to be the cause for such deviation. In all cases, the percent increase in matrix swelling increases with the HPMC content in the matrix. The linear relationship of δ with $\sqrt{t}$ suggests that swelling process is dependent on the surface area exposed to the aqueous medium. The kinetics of HPMC swelling could be described by the following equation:

$$\delta = \phi\sqrt{t} + c_1 \qquad \text{Equation 2}$$

where δ is the percent increase in swelling from time $(t-1)$ to time t, ϕ is the swelling rate constant ($\%/\sqrt{s}$) and c_1 is a constant. Table 1 shows the results of this curve-fitting process.

Previous work has shown that the water uptake into HPMC matrices follow Washburn's equation (10). The above relationship of ϕ and $\sqrt{t}$ implies that the swelling of matrix depends very much on the rate of water entry into the matrix. When the water uptake into matrices is enhanced with a greater amount of HPMC, the swelling of the polymer is increased. This swelling action of the polymer in turn affects the subsequent water uptake rate.

Studies on the capacity of the plain HPMC matrix to swell in the aqueous medium show that HPMC of higher viscosity grade swell to greater extent (Table 1). This is in accordance with the finding that a higher viscosity grade HPMC has greater intrinsic water uptake property than that of a lower viscosity grade (10).

The rate of swelling of HPMC, ϕ, increases with an increase in the concentration and the viscosity grade of the polymer. A sigmoidal curve is obtained when ϕ is plotted against the logarithm of HPMC content, W, with a linear portion between 10% and 50% HPMC content which can be described by the first-order kinetics (Fig. 1 and Table 2) equation :

$$\phi = mW + c_2 \qquad \text{Equation 3}$$

where m is the slope and c_2 is a constant.

Deviation at 5% HPMC may be due to insufficient polymer for significant swelling to take place. On the other hand, the swelling process tends towards a saturation state at high polymer content, beyond 50%. This is because as the HPMC becomes hydrated and forms a swollen gel, dissolution and surface erosion of this water-logged gel occurs simultaneously.

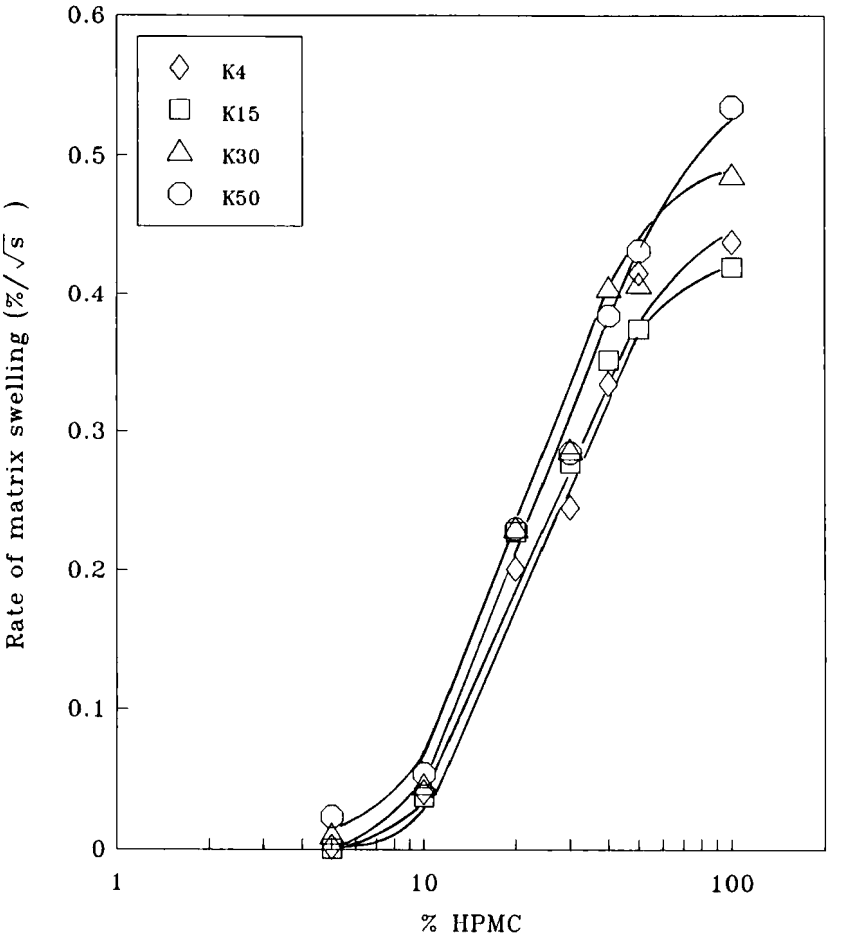

FIGURE 1
The effect of HPMC content on the rate of matrix swelling.

TABLE 2

Statistical data showing regression analysis results of Equation 3

HPMC Viscosity Grade	Slope m $(1/\sqrt{s})$	Intercept c_2 (%/√s)	Regression Coefficient r^2
K4	0.2203	-0.4712	0.9758
K15	0.2088	-0.4275	0.9798
K30	0.2316	-0.4809	0.9771
K50	0.2309	-0.4764	0.9897

The water uptake rate also slows down in very high polymer concentration as the polymer swelling can in turn affect the water uptake rate.

Drug Release

The release of a drug incorporated into the matrix is altered by the polymer content and viscosity grade (Table 3). Matrices containing more than 10%(w/w) of HPMC conformed to the Higuchi dissolution equation relating matrix release with the square root of time (4). The matrices containing only 5% HPMC did not appear to follow Higuchi dissolution equation. These matrices followed zero-order release kinetics.

As the amount of polymer in the matrix increases from 10% to 20%, the rate of ibuprofen released is reduced. Further increase in the HPMC content beyond 20% appears to have marginal influence in retarding the drug release rate. A maximum retardation is reached around 30-50% for K4, 20-50% for K15, K30 and K50.

The process of drug release from a HPMC-drug matrix is a complex one. The overall drug release is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. Water uptake rate into matrix is enhanced in the presence of HPMC due to the its high hydrophilicity. However, like all swellable polymers, HPMC swells as it absorbs water. The thickness of gel layer formed varies with the polymer content. High polymer content results in a greater amount of HPMC gel being formed and vice versa. This gel increases the diffusional path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result, a reduction in drug release rate is obtained.

However, when 10% of high viscosity grade HPMC is used in the matrix, the release rate is in fact increased compared to the other formulations. This is because the matrix containing higher viscosity grade HPMC swells faster. A thick and viscous swollen gel is formed. However, this gel is not continuous as isolation of HPMC particle aggregates due to its limited amount present in the system results in localised pockets of polymer. In this respect, HPMC behaves very much like a strongly swelling disintegrant. Consequently, on wetting, localised particulate swelling of HPMC helps to break up the matrix.

Swelling and Drug release

An inverse relationship is found between the swelling rate and the Higuchi drug release rate constant (Fig. 2). The correlation (r^2-values) between these two parameters is relatively good (Table 3). The deviation in 5% HPMC K50 is due to the disintegration of

TABLE 3

The relationship of HPMC content, viscosity grade and swelling on the drug release from ibuprofen : HPMC matrices.

HPMC Viscosity Grade	HPMC content (%)	Release rate (% / √min)	1/Swelling rate (√s / %)	r^2-values
K4	5	3.09	527.00	0.91
	10	2.39	24.30	
	20	1.46	4.98	
	30	.0.92	4.09	
	40	0.89	2.99	
	50	0.84	2.41	
K15	5	2.82	2377.00	0.95
	10	1.77	26.70	
	20	0.99	4.40	
	30	0.80	3.61	
	40	0.68	2.85	
	50	0.86	2.68	
K30	5	2.75	102.50	0.98
	10	2.19	21.97	
	20	0.88	4.36	
	30	0.74	3.50	
	40	0.82	2.48	
	50	0.89	2.46	
K50	5	2.19	42.34	0.99
	10	4.17	18.43	
	20	1.15	4.37	
	30	0.81	3.52	
	40	0.72	2.61	
	50	0.86	2.32	

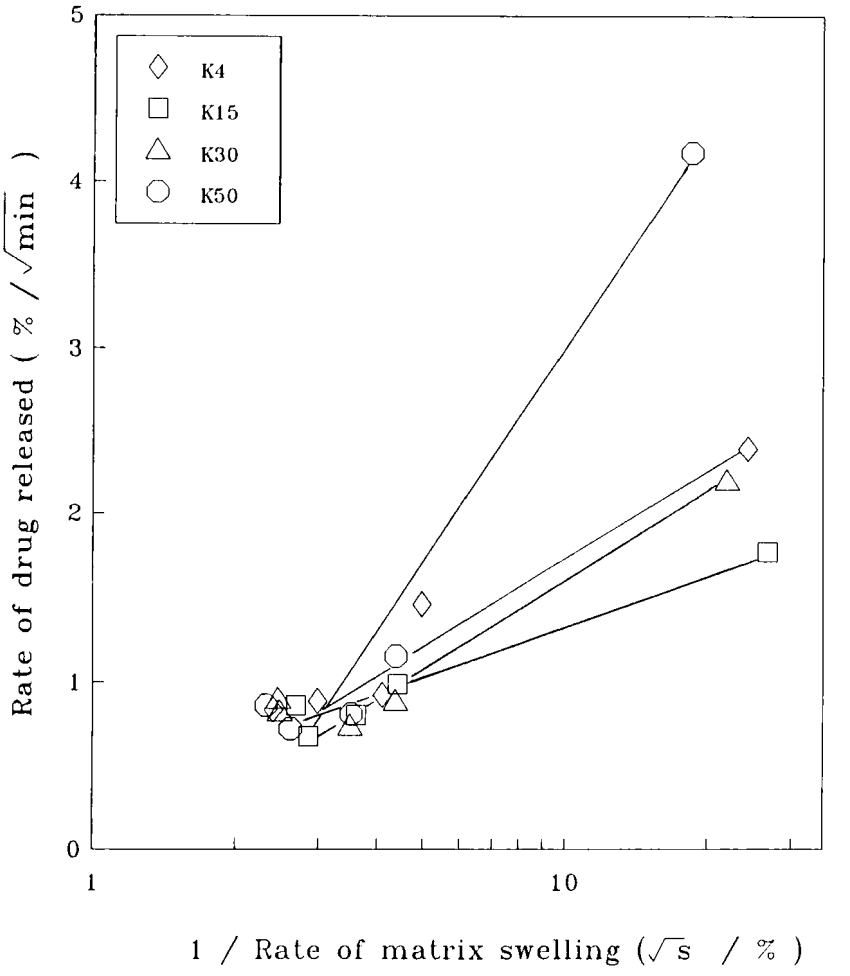

FIGURE 2
The relationship of rate of drug release with rate of matrix swelling in ibuprofen : HPMC matrices.

matrix during dissolution. This inverse relationship implies that the rate of drug release is affected by the swelling of HPMC. When the amount of HPMC in the matrix is high, wetting improves and water uptake into matrices is enhanced. The higher amount of HPMC causes a greater degree of swelling. This in turn reduces the drug release, as the diffusional path length of drug is now longer. Conversely, reduction in the amount of HPMC reduces the degree of swelling and the thickness of gel layer. This enables faster drug release rates.

In conclusion, an inverse relationship between HPMC swelling rate constant and Higuchi dissolution rate constant is obtained. This implies that HPMC swelling may be one of the controlling factors affecting drug release. Hence the swelling behaviour of HPMC matrices is a useful parameter for predicting drug release.

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