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The effect of hydroxypropylmethylcellulose on water penetration into a matrix system

L.S.C. Wan, P.W.S. Heng and L.F. Wong

Department of Pharmacy, National University of Singapore (Singapore)

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Summary

The action of hydroxypropylmethylcellulose (HPMC) on aqueous penetration into matrices containing HPMC of varying viscosity and concentration was studied. The incorporation of HPMC into ibuprofen matrices improved wetting and enhanced water uptake into the matrices. A large volume of water uptake was obtained with a greater amount of HPMC used. A higher molecular weight HPMC has greater intrinsic water uptake property than that of a lower molecular weight. The action of HPMC on aqueous uptake depends on the molecular weight of HPMC. HPMC can be divided into two groups according to its molecular weight. Depending on which group is used in the matrix, increasing the viscosity of HPMC within each group can either increase or decrease the water uptake into the matrices.

Introduction

Hydroxypropylmethylcellulose (HPMC) is a hydrophilic cellulose ether widely used as an excipient in controlled-release preparations. The release of drug from compressed HPMC matrices was extensively reviewed by Alderman (1984). Although much research has been directed on the effect of HPMC on the drug release properties, there has been little investigation on the effect of water penetration into such matrices as liquid uptake can control the degree of polymer swelling (Korsmeyer et al., 1983; Ford et al., 1985a,b, 1987; Braveja and Ranga Rao, 1986, 1988).

One mechanism proposed for drug release from HPMC matrices involves water penetration into the dry matrix, hydration and swelling of HPMC, diffusion of dissolved drug and erosion of polymer gel layer (Alderman, 1984; Wan et al., 1990). Earlier investigations were focused on the action of different viscosity grade HPMC on the matrix swelling behaviour and dissolution properties of HPMC matrices (Wan et al., 1990).

The purpose of this study is to examine the effect of HPMC of various viscosity grade on water uptake into HPMC matrices.

Correspondence: L.S.C. Wan, Dept of Pharmacy, National University of Singapore, Singapore.

Materials and Methods

Materials

Ibuprofen (Pharmaceutical grade, Italy) was used as supplied. HPMC 2208 USP of four viscosity grades was used: Metolose K4, K15, K30 and K50 (Shin-Etsu Chemical Co., Japan). The apparent viscosities of 2% aqueous solutions of these HPMC were 4380, 18200, 35800 and 44400 cps, respectively (USP method).

Preparation of matrices

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

Liquid penetration studies

The method adopted was that described previously (Wan and Choong, 1986). Essentially, it consists of a sintered glass filter connected to a horizontal graduated capillary containing phosphate buffer pH 7.2. The uptake of the buffer solution at $37 \pm 0.5\,^{\circ}C$ into the matrix placed centrally on the filter paper in the sintered glass filter is measured by the change in the volume of the buffer solution in the capillary tube with time. The mean of not less than three determinations was taken to represent the uptake volume.

Results and Discussion

When a matrix comes into contact with an aqueous solution, wetting occurs, first at the surface and then progresses by way of microscopic pore spaces into the matrix. The excipient in the matrix also absorbs water, hydrates and swells to block up existing pores, dissolves the content to create a more porous structure, gels to form a viscous solution giving rise to positive pressure opposing liquid entry or causes disintegration of the matrix.

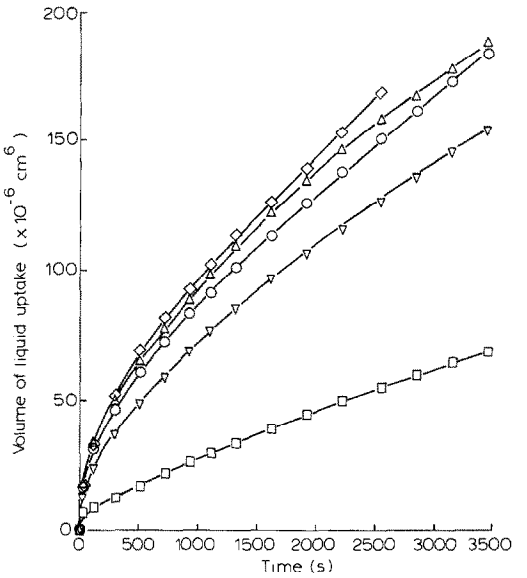

Fig. 1. Uptake of liquid into compacts compressed from ibuprofen and hydroxypropylmethylcellulose of varying viscosity: K4 (▽), K15 (○), K30 (△), K50 (◇) and plain ibuprofen (□).

The relationship between liquid uptake into matrices and matrix properties has been studied (Charmers and Elworthy, 1976). Before a liquid can enter a matrix, there must exist a driving force which is derived from the pressure difference. The rate of liquid penetration into the matrix is determined by the balance of this force promoting fluid entry towards the interior and the viscous force opposing it, which soon develops as the soluble excipients in the matrix dissolve or swell.

The liquid penetration profile into plain ibuprofen compact, i.e., without HPMC, was examined. It was found that the uptake was slow and the volume taken up was low (Fig. 1). In order to examine the effect of HPMC on the liquid uptake, different amounts of HPMC of varying viscosity grades were added to the formulation.

Fig. 1 shows the liquid penetration profile into plain HPMC compacts, i.e., without ibuprofen. HPMC compacts have higher liquid uptake rates compared to plain ibuprofen matrix (Fig. 1). Compacts containing HPMC of higher molecular weights show greater capacity for liquid uptake.

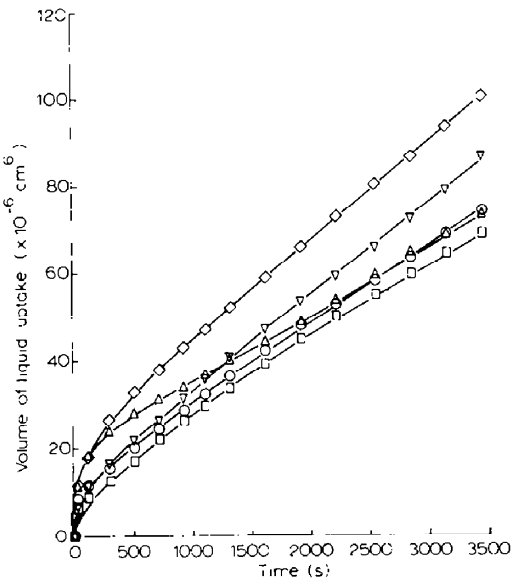

Fig. 2. Uptake of liquid by ibuprofen matrices containing 5% of HPMC of various viscosity: K4 (▽), K15 (○), K30 (△), K50 (◇) and plain ibuprofen (□).

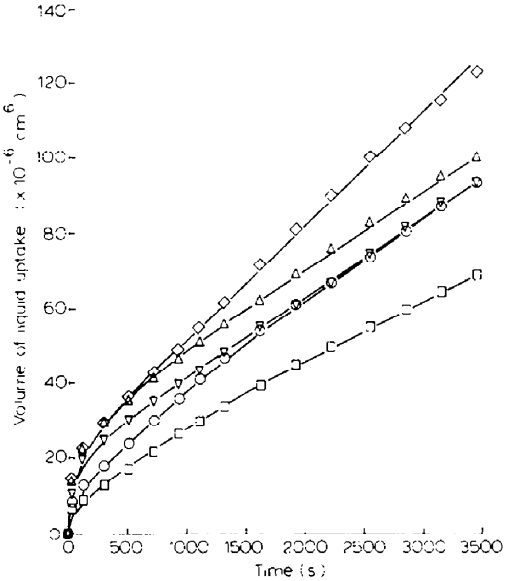

Fig. 3. Uptake of liquid into ibuprofen matrices containing 10% of HPMC of various viscosity: K4 (▽), K15 (○), K30 (△), K50 (◇) and plain ibuprofen (□).

Studies on varying the amount of these HPMCs with liquid penetration in the presence of a second component were carried out.

HPMCs of various viscosity grades were incorporated into ibuprofen matrices in three concentrations: 5, 10 and 50% w/w. The liquid uptake profiles of these matrices are presented in Figs 2–4.

Fig. 2 shows the liquid penetration profiles of matrices containing 5% HPMC of viscosity grades K4, K15, K30 and K50. The volume of liquid uptake is low – comparable to plain ibuprofen matrices. The addition of 5% HPMC improved the wetting of matrices to different extents depending on the viscosity grade of the HPMC used.

The entry of liquid into matrices containing 10% and 50% HPMC was rapid, the rate being influenced by the viscosity grade of the HPMC (Figs 3 and 4). The action of the HPMC in improving aqueous uptake can be divided into two groups, namely, high molecular weight HPMC consisting of K30 and K50 (MH) and low molecular weight HPMC of K4 and K15 (ML). As the viscosity of MH increases, the amount of aqueous uptake is greater while the reverse holds true for ML.

This apparently inconsistent behaviour of HPMC action on aqueous uptake into matrices

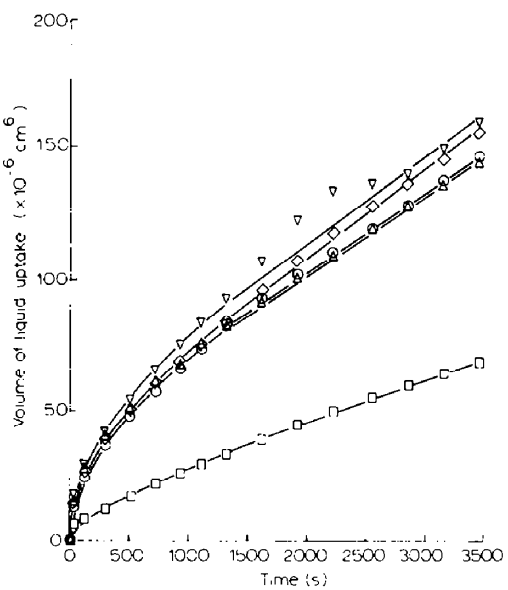

Fig. 4. Uptake of liquid into ibuprofen matrices containing 50% of HPMC of various viscosity: K4 (▽), K15 (○), K30 (△), K50 (◇) and plain ibuprofen (□).

can be explained as follows. Polymer molecules are giant molecules compared to those of water. They are made up of hundreds of chain segments. These long-chain molecules are not in the form of extended straight chains but are tightly folded random coils. Individual polymer coils are not discrete and separate, but interlocked and entangled with each other. They also have varying degrees of cohesive and attractive forces between different segments of the same molecular coils as well as neighbouring coils. Forces such as dispersion, induction, dipole-dipole interaction and hydrogen bonding (both intramolecular and intermolecular) hold the molecular coils and their segments tightly.

When a polymer comes into contact with water, forces of attraction, chiefly hydrogen bonding, start acting between them. HPMC, being a hydrophilic polymer, has a great affinity for water. The polymer-water interaction is likely to be preferred over polymer-polymer attraction. Thus, the forces holding the polymer segments together are much reduced. Water molecules force their way between the segments, breaking the polymer-polymer contacts, surrounding individual polymer coils and establish contact with them. As liquid molecules penetrate into the interstices of the polymer, the water molecule entrapment in the polymer causes the polymer to hydrate, the polymer starts to swell and increases in size. The polymer chains slowly begin to unfold and gradually become solvated. However, they do not assume the shape of an extended straight chain. The coiled nature of the polymer is still retained but with a very much expanded coil volume. Voids created as the polymer unfolds are occupied by the water molecules. The apparent volume occupied by these expanded coils is referred to as the hydrodynamic volume.

At the molecular level, the viscosity of a polymer solution is a direct measure of the hydrodynamic volume of the polymer molecules in the same solvent. In the ML group, the hydrodynamic volume of the polymer molecule increases with viscosity. Molecular mobility within the swollen polymer gel is restricted. Intermolecular friction increases. There is an increase in gel viscosity when HPMC K4 was replaced with K15. Although there is an increase in the pressure difference due to volume expansion as the polymer swells, the viscous force is also increased. This viscous drag is sufficient to oppose the driving pressure force. Thus, liquid uptake drops as the viscosity of HPMC increases.

On the other hand, the MH group is composed of longer chain molecules coiled tightly together. As liquid penetrates the interstices of the polymer coils, HPMC unfolds and swells. The hydrodynamic volume of the expanded uncoiled HPMC molecule increases with time. However, the viscosity difference in this case is lower than that in the ML group. This effect is perhaps less marked when compared to the negative pressure so created within the expanded volume. Hence, a resultant increase in liquid entry is obtained. When there is sufficient HPMC (50%) present in the matrix (Fig. 4), the liquid uptake in K4 HPMC actually exceeds that in K50 even though the trend of uptake in MH and ML groups still persists. This suggests that the viscosity of the MH group, in particular K50, slows down the liquid uptake into the matrix.

Figs 5–8 show the liquid penetration profiles containing varying amounts of K4, K15, K30 and

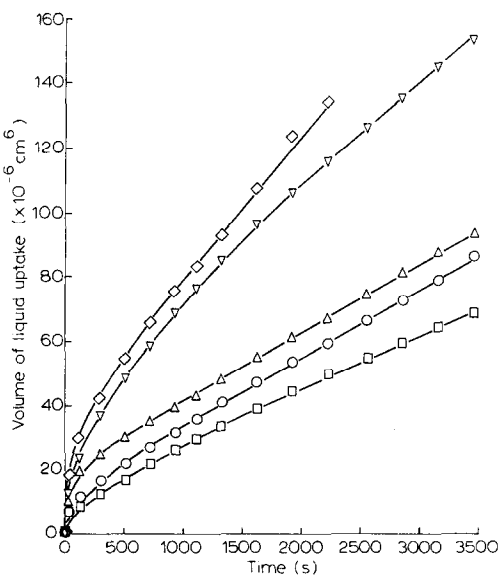

Fig. 5. Liquid penetration profiles of ibuprofen matrices with different amounts of K4 HPMC: 0% (□), 5% (○), 10% (△), 50% (◇) and 100% (▽).

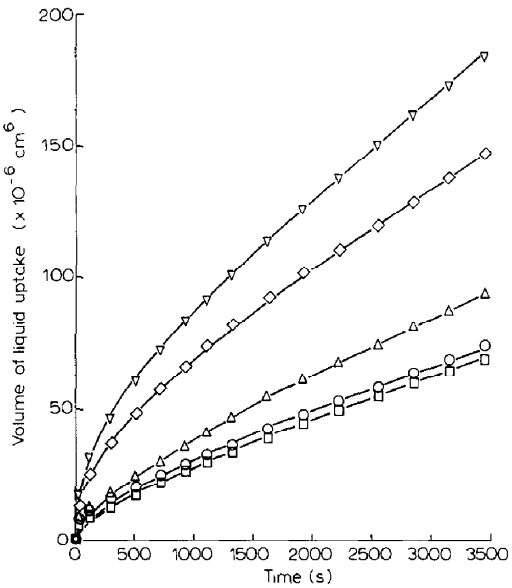

Fig. 6. Liquid penetration profiles of ibuprofen matrices with different amounts of K15 HPMC: 0% (□), 5% (○), 10% (△), 50% (◇) and 100% (▽).

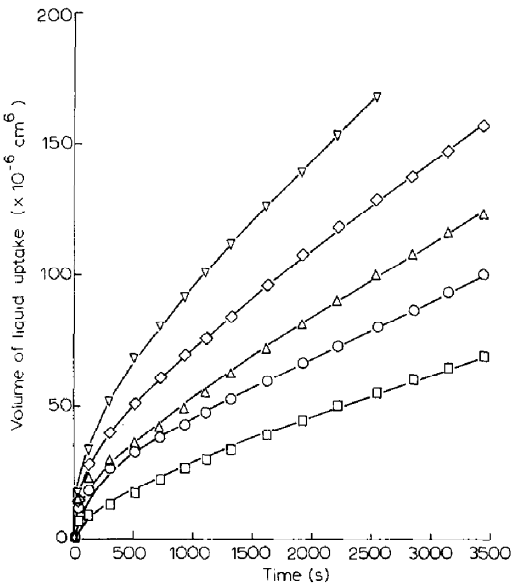

Fig. 8. Liquid penetration into ibuprofen matrices containing various amounts of K50 HPMC: 0% (□), 5% (○), 10% (△), 50% (◇) and 100% (▽).

K50. Generally, the volume taken up increases with concentration.

Two distinct gradients can be derived from the double-logarithmic plots of these results based on the following equation:

$$\ln V = k \ln t$$

where V denotes the volume of liquid uptake, k is the gradient and t represents time.

The first gradient, k_1 is always smaller than the second gradient, k_2 (Table 1). The values of k_1 for ML tend to be close to 0.5. This indicates that the liquid uptake follows the equation of Washburn (1921) and liquid uptake is by the capillary mechanism. On the other hand, the values of k_2 for this group are greater than 0.5. In the case of the MH group, the values for k_1 are always less than 0.5 while for k_2s they cluster around 0.5.

In all cases, the kinetics of liquid uptake change from capillary rise to slow diffusion with time. HPMC absorbs water, hydrates and swells. Breakage of hydrogen bonds as HPMC fibres relax and uncoil leaves behind large interstitial pores facilitating liquid entry. Interparticular wicking of the liquid due to the fibrous nature of HPMC also assists the liquid entry. As time proceeds, these voids are blocked by the swollen

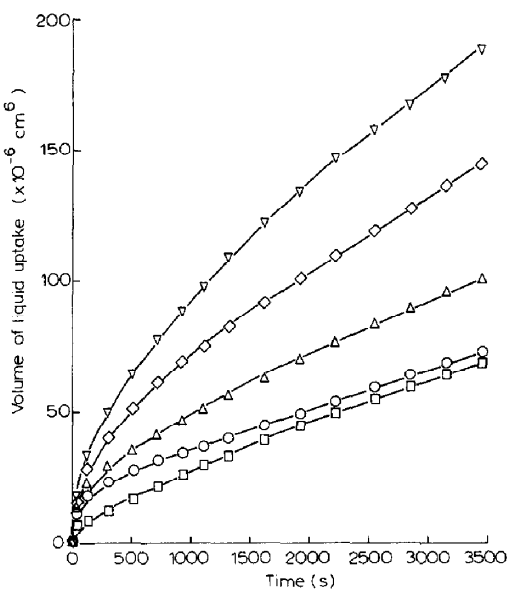

Fig. 7. Liquid penetration profiles of ibuprofen matrices containing various amounts of K30 HPMC: 0% (□), 5% (○), 10% (△), 50% (◇) and 100% (▽).

TABLE 1

k_1 and k_2 for ibuprofen matrices containing various viscosity grades and varying amounts of HPMC

Viscosity grade	% HPMC	k_1	k_2
K4	5	0.5697	0.7719
	10	0.3492	0.6827
	50	0.4681	0.6240
	100	0.4940	0.6069
K15	5	0.4356	0.7076
	10	0.4993	0.7230
	50	0.4515	0.5936
	100	0.4331	0.5873
K30	5	0.2946	0.6129
	10	0.3827	0.6016
	50	0.4135	0.5612
	100	0.5720	0.5866
K50	5	0.4034	0.6149
	10	0.2749	0.6343
	50	0.3852	0.5740
	100	0.4021	0.6002

HPMC leaving them to become inaccessible pores. Liquid in this case is taken up mainly by slow diffusion and imbibition.

As the molecular weight of the HPMC increases, liquid uptake rates slow down. This may be due to the increase in viscous drag which is dependent on the molecular weight of HPMC used. HPMC of high molecular weight tends to swell faster and this may block up the pores prematurely, impeding further liquid entry. The values of k_1 for this MH group are often less than those predicted with Washburn's equation (Table 1).

Thus, from these studies, it can be concluded that incorporation of HPMC into ibuprofen matrices improves wetting and water uptake into the matrices. A larger amount of HPMC leads to a higher volume of water taken up. The action of HPMC on liquid uptake depends on the molecular weight. Although HPMC of a higher molecular weight has a greater liquid uptake capacity, this phenomenon can be altered in the presence of an additive. The liquid uptake into such matrices will depend on the resultant balance between the viscous drag and increased swollen volume of the HPMC.

References

Alderman, D.A., A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int. J. Pharm. Technol. Prod. Mfr.*, 5 (1984) 1–9.

Braveja, S.K. and Ranga Rao, K.V., Sustained release tablet formulation of centperazine. *Int. J. Pharm.*, 31 (1986) 169–174.

Braveja, S.K., Ranga Rao, K.V. and Padmalatha, D.K., Release characteristics of some bronchodilators from compressed hydrophilic polymeric matrices and their correlation with molecular geometry. *Int. J. Pharm.*, 41 (1988) 55–62.

Charmers, A.A. and Elworthy, P.H., Oxytetracycline tablet formulations: effect of variations in binder concentration and volume on granule and tablet properties. *J. Pharm. Sci.*, 28 (1976) 228–233.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Formulation of sustained-release promethazine hydrochloride tablet using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 24 (1985a) 327–338.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.*, 24 (1985b) 339–350.

Ford, J.L., Rubinstein, M.H., Hogan, J.E. and Edgar, P.J., Importance of drug type, tablet shape, added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J. Pharm.*, 40 (1987) 223–234.

Korsmeyer, R.W., Doelker, G.E., Buri, P. and Peppas, N.A., Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15 (1983) 25–35.

Wan, L.S.C., Heng, P.W.S. and Wong, L.F., Effect of hydroxypropylmethylcellulose on drug release from a matrix system. *Japan Society for the Promotion of Science-National University of Singapore Conference-Proceeding, Chiba, Japan* (25-26 October 1990) pp. 35–56.

Wan, L.S.C. and Choong, Y.L., The effect of excipients on the penetration of liquid into tablets. *Pharm. Acta Helv.*, 61 (1986) 150–156.

Washburn, E.W., The dynamics of capillary flow. *Phys. Rev.*, 17 (1921) 273–283.