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A study of the hydrophilic cellulose matrix: effect of indomethacin and a water-soluble additive on swelling properties

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Abstract

A swelling measurement device was designed to observe the axial swelling direction of a matrix containing various types of hydrophilic cellulose derivatives (methylcellulose, hydroxypropylmethylcellulose and hydroxypropylcellulose). The effect of indomethacin and lactose on the swelling properties was also studied. The maximum swelling index and the apparent diffusion coefficient of water in the matrix, calculated from the swelling data, were used to describe the swelling properties of the matrix, reflecting the matrix integrity. The results showed that hydroxypropylcellulose produced a matrix with a high integrity. Indomethacin and lactose changed the swelling properties of the hydrophilic cellulose matrices in this study.

Keywords: Hydrophilic cellulose matrix; Indomethacin; Swelling properties; Mathematical model; Maximum swelling index; Apparent diffusion coefficient

1. Introduction

Cellulose polymer has received much attention as a hydrophilic matrix for sustained release formulations. The release of drug from this type of matrix is controlled by the rapid formation of the hydrogel layer around the matrix following exposure to aqueous fluid. Generally, it is found that the presence of the gel layer retards the process of drug liberation, and the rate of drug release is dependent on the rate and extent of tablet swelling and on the speed of drug diffusion (Alderman, 1984). In applied sciences, such as biochemical engineering and pharmaceutical technology, diffusion coefficients in gels have to be determined in order to predict diffusant transport, e.g. drug release rates. Pure scientists in the field of physical chemistry, on the other hand, often study diffusion in gels in order to extract information on, for example, polymer network structures (Westrin et al., 1994). Recently, the diffusion coefficient has been used in both pure and applied sciences. Several works have reported

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using the diffusion coefficient in studies of the transport properties of polymers (Foster et al., 1984), of solutes (Hastedt and Wright, 1990; Ek et al., 1994) and water (Brosio et al., 1994; Ek et al., 1994; García et al., 1994; Jerzewski and Lordi, 1994) to characterize the structure of the matrix system.

As it has been reported that the swelling behavior of the systems will be directly related to the drug release mechanism (Korsmeyer et al., 1983; Baveja et al., 1987; Rao and Devi, 1988; Colombo et al., 1992; Panomsuk et al., 1995) and the swelling characteristics of the polymer network are also influenced by the condition under which the network has been formed (Rathna et al., 1994), it is important to understand the swelling behavior to characterize both the release properties and matrix structure.

A greater swelling in the axial rather than the radial direction on exposure to water was observed in methylcellulose and hydroxypropylmethylcellulose (Mitchell et al., 1993; Papadimitriou et al., 1993), and the cylindrical polyvinyl alcohol matrix (Vandelli and Cameroni, 1993). This was reported to be probably the result of a uniaxial stress relaxation in the longitudinal direction in which the tablet was initially compressed (Bowtell et al., 1994). Additionally, it was found that the face-coating produces a significant change in the swelling dimensionality whilst the edge-coated sample behaved in a manner much more similar to the uncoated sample (Papadimitriou et al., 1993); thus the swelling in the axial direction can be used to represent the swelling pattern of the whole matrix.

In the present study, we observed the swelling profile of different hydrophilic cellulose derivatives matrices via the axial-swelling direction. The influence of indomethacin (IM) loading and the second polymer as well as the water-soluble component (lactose), in the matrix containing IM, on the matrix swelling properties was also investigated. Two parameters (the maximum swelling index and the apparent diffusion coefficient of water in the matrix), calculated from the obtained axial-swelling data via the equations proposed by Korsmeyer et al., 1986, were used to describe the swelling properties of the matrix.

2. Materials and methods

2.1. Materials

Indomethacin (IM) powder was purchased from Nacalai Tesque, Inc., Japan. Methylcellulose, 25 and 50 cp (MC25 and MC50), and hydroxypropylcellulose, 140 cp (HPC140), were purchased from Wako Pure Chemical Industries (Osaka, Japan). Hydroxypropylmethylcellulose, 50 cp (HPMC50), was purchased from Sigma Chemical Company (St. Louis, MO, USA). All other materials were of analytical reagent grade.

2.2. Matrix preparation

All substances were passed through a 42 mesh sieve before use. IM was dried at 60°C for 8 h before screening. The matrix containing only a polymer was weighed and directly compressed by a hydraulic press (Riken Power, Model No. P-16B, Japan) at 7.84 MNm^{-2} compressional pressure. A physical mixture of IM and polymer was prepared to obtain the drug/polymer (D/P) ratios of 1:2, 1:3 and 1:4. For the matrix containing D/P = 1:3, the effect of the second swellable component (MC25) and water soluble component (lactose) was also studied, and the amount of each component is listed in Table 1. The mixture was directly compressed by a tableting machine (Erweka Type EKO, Germany). All preparations were compressed to obtain the matrix with 0.78–1.08 MNm^{-2} crushing strength. The matrix was one flat-face, 400 mg weight and 12 mm diameter. Only those matrices that were within ± 10 mg were used in this study.

Table 1
The amount of the second swellable component (MC25) and the water soluble additive (lactose) in a matrix containing D/P = 1:3

	Amount in matrix (%)											
MC25	–	5	15	25	35	37.5	45	–	–	–	–	–
Lactose	–	–	–	–	–	–	–	1	3	5	7	10
Polymer[a]	75	70	60	50	40	37.5	30	74	72	70	68	65
Total						75						

[a]MC50 and HPC140.

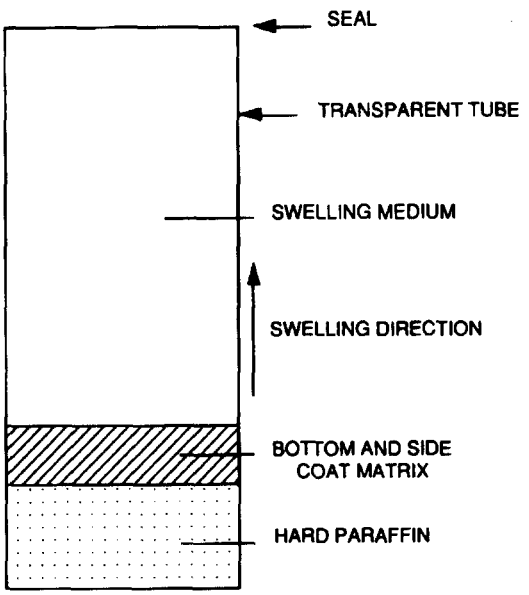

Fig. 1. The swelling experiment device.

2.3. Swelling experiment

The swelling was performed in a swelling experiment device (Fig. 1) to (1) observe the axial swelling, (2) make the penetration front occur only from the upper surface of the matrix, (3) determine the swelling without disturbing or destroying the system and (4) make the surface area per unit volume of the matrix exposed to the swelling medium equal, which will eliminate the convex-shaped hydrated layer caused by the greater extent of the surface area per unit volume at the edges of the tablet than in the center of tablet surface as reported by Rajabi-Siahboomi et al., 1994.

Fig. 1 represents the swelling experiment device, consisting of a transparent tube. By using hard paraffin, the bottom and edge of the matrix was coated. The coated-matrix was then fixed onto the flat-surface base made of hard paraffin which was colored by 0.5% w/w Sudan III to differentiate the border between the wax-base and the matrix. During the coating and fixing process, a matrix was held firmly by using a vacuum system. The swelling was performed at 37 ± 1°C by using a thermoregulated water bath. The experiment was started as soon as the medium (5 ml, 37 ± 1°C) touched the uncoated surface of the matrix. Phosphate buffer (pH 6.2), which was used as a medium in the drug release study (Panomsuk et al., 1995), was used as a swelling medium. The upper part of the unit was sealed to prevent the evaporation of the medium. At each time interval, the matrix thickness (H_t) was directly measured through the transparent tube. The swelling was observed for more than 8 h. Four replicate measurements were carried out for each preparation. The swelling profile was obtained by plotting the swelling ratio (H_t/H_0, where H_0 is the initial dry thickness of the matrix) versus time.

2.4. Data analysis

A mathematical model was developed to describe the diffusion of a penetrant and a solute in a swellable polymer slab (Korsmeyer et al., 1986). It was designed to incorporate the two most important features of diffusion in water-swellable polymers: water penetration by diffusion and volume changes due to swelling.

Water enters the matrix following Fick's law of diffusion:

$$\frac{\partial C}{\partial t} = \frac{D}{\tau_0}\frac{\partial^2 C}{\partial x^2} \tag{1}$$

where C is water concentration in the matrix relative to the equilibrium concentration, x is the space coordinate measured normal to the section, D is the diffusion constant of water in a fully swollen matrix and τ_0 is the tortuosity of the dry matrix. The boundary conditions are:

$$t = 0, \quad C = 0, \quad \text{at} \quad 0 \le x \le H_0$$
$$t > 0, \quad C = 1, \quad \text{at} \quad x = 0$$
$$\frac{\partial C}{\partial x} = 0, \quad \text{at} \quad x = H_0$$

Eq. (1) has a simple analytical solution:

$$C = 1 + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\cos(n\pi) - 1}{n}\sin\left(n\pi\frac{x}{2H_0}\right) \times \exp\left(-\frac{n^2\pi^2 D_w t}{4H_0^2}\right) \tag{2}$$

where D_w is the apparent diffusion coefficient of water in the matrix, D/τ_0.

The polymer swells depending on the water content, C, and increases the thickness of the polymer matrix, H_t.

$$H_t = \int_0^{H_0} \frac{dx}{1 - VC} \quad (3)$$

where V is a parameter governing the thickness of maximum swelling, $H\infty$.

$$V = 1 - \frac{H_0}{H_\infty} \quad (4)$$

We assume that the increase in the matrix thickness due to swelling is compensated by the decrease of tortuosity. The water path in the matrix or the effective thickness of the matrix remains constant and Eq. (2) still holds after the matrix has swollen.

C values corresponding to various x values are calculated by Eq. (2) for a given value of t. Using the sets of calculated C and x values, a value for H_t is obtained by Eq. (3). Integration of Eq. (3) is performed by Simpson's rule. In short, H_t is a function of t with two parameters, D_w and V, to be estimated. D_w and V were estimated by a least squares adaptation of Eqs. (2) and (3) to the observed data of swelling, using the algorithm proposed by Berman et al. (1962).

V, the relative value as represented in Eq. (4), indicated how much the matrix can swell or the ability of the polymer to control the matrix shape. Diffusion coefficient is one of the transport properties involving the friction factor which measures how strongly the system resists the motion of the diffusant (Hunter, 1993). Likewise, D_w can represent the friction of the polymer matrix network structure in which the transport of water molecule occurs. In this report, V and D_w were used as parameters reflecting the matrix integrity which is the swelling extent of the polymer matrix and the friction or the resistance of the matrix network structure against the movement of the molecule of water, respectively.

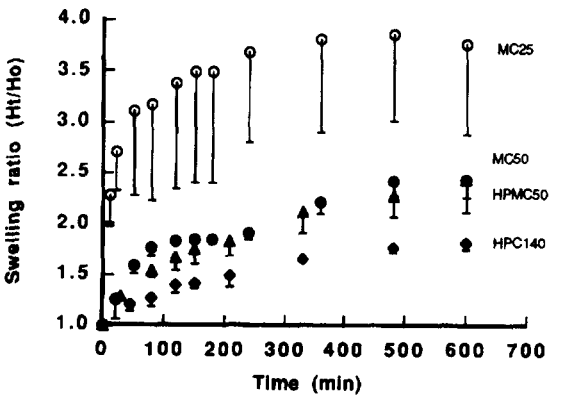

Fig. 2. Swelling profiles of hydrophilic cellulose matrices containing MC25, MC50, HPMC50, and HPC140. Each point represents the mean ± SD of four determinations.

3. Results and discussion

3.1. Effect of polymer type

Fig. 2 represents the swelling profiles of matrices containing only a polymer; the MC25 matrix showed the maximum swelling ratio followed by HPMC50 as well as MC50, and HPC140, respectively.

Parameters estimated from the data shown in Fig. 2 are represented in Table 2. From V values, the swelling extent of the matrix can be ranked as MC25 > MC50 ~ HPMC50 > HPC140. D_w shows that water molecules penetrated easily through the matrix containing MC25 followed by MC50 as well as HPMC50 and HPC140, respectively. D_w of MC50, HPMC50 and HPC140 range between 4.137 and 4.732 × 10^{-6} cm^2/s. These

Table 2
Estimated parameters: the maximum swelling index (V) and the apparent diffussion coeficient of water (D_w) of the matrices containing various types of polymer

Polymer	V	D_w ($\times 10^{-6}$ cm^2/s)
MC25	0.7136 ± 0.0072	37.870 ± 7.5560
MC50	0.5878 ± 0.0177	4.732 ± 0.7969
HPMC50	0.5916 ± 0.1007	4.407 ± 0.3873
HPC140	0.4715 ± 0.0104	4.137 ± 0.3595

Each value represents the mean ± S.D. of four determinations.

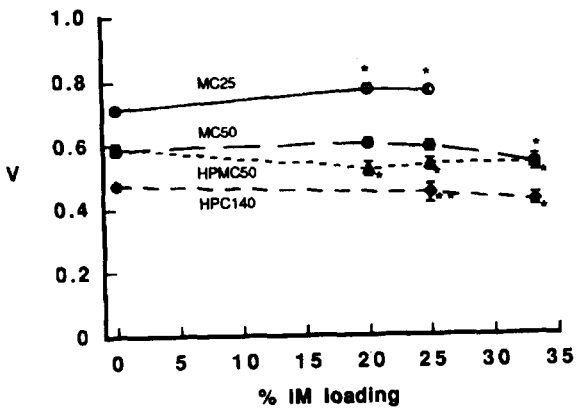

Fig. 3. Effect of indomethacin loading on the maximum swelling index (V) of matrices containing various types of hydrophilic cellulose. Significantly different from the unloaded matrix at: $^{*}P < 0.01$ and $^{**}P < 0.1$.

values are of the same order of magnitude as that obtained from the water front penetration data of the HPC matrix (4.15×10^{-6} cm^2/s) (Ashraf et al., 1994). The results in Table 2 show that HPC140 produced a matrix with high integrity, with both high ability to maintain the shape and high resistance of the network structure against the movement of water molecules.

3.2. Effect of indomethacin

Fig. 3 shows the effect of IM loading on V values of a polymer matrix. IM decreased V ($P < 0.01$) of MC50, HPMC50 and HPC140 but not of MC25. The decrease in the swelling extent of the matrix can be explained as the results of the decrease in the swellable part. At each percentage of IM loading, the MC25 matrix still showed the maximum V followed by MC50, HPMC50 and HPC140, respectively. The effect of IM loading on D_w is shown in Fig. 4; IM up to 33% did not effect D_w of the MC50, HPMC50 and HPC140 matrices but drastically decreased that of the MC25 matrix ($P < 0.01$), reflecting the great change in the structure of the MC25 matrix. Mitchell et al. (1991) also reported that drugs (propanolol hydrochloride, tetracycline hydrochloride and IM) play an important role in polymer swelling, and contribute to the matrix integrity.

The swelling of an unloaded matrix is due to water penetration, whereas the combination of water penetration and drug diffusion produces the changes of a loaded matrix (Vandelli and Cameroni, 1993). The decrease in V and constant D_w of the MC50, HPMC50 and HPC140 matrix indicate that, up to 33% IM loading, the matrix swelling occurs before the release of a drug. The increase in V ($P < 0.01$) and the rapid decrease in the apparent D_w of the IM loading of the MC25 matrix indicate the change in the matrix integrity, reported to be the matrix disintegration (Panomsuk et al., 1995).

3.3. Effect of the second swellable polymer (MC25) substituted for the MC50 or HPC140 in the matrix containing D/P = 1:3

Fig. 5a shows that V increases as the replacing amount of MC25 increases in both the MC50 and the HPC140 matrix ($P < 0.01$). The slow change of V in the HPC140 matrix also indicates that HPC140 has a high ability to maintain the matrix shape when compared with MC50. Moreover, V of the mix-polymer matrix is roughly dependent on the weight fraction and V of each polymer. In Fig. 5b, D_w of the MC50 and the HPC140 matrix decrease ($P < 0.01$) when the replacing amount of MC25 is up to around 30%. The first decrease

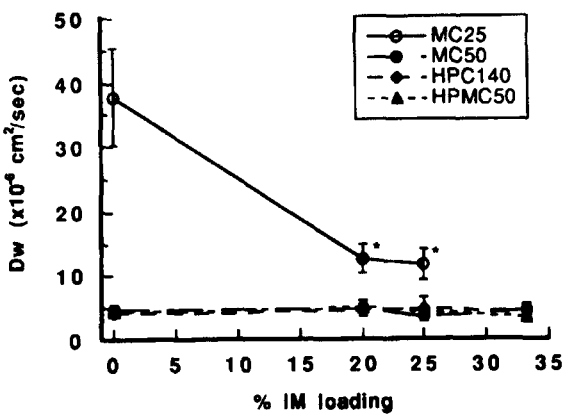

Fig. 4. Effect of indomethacin loading on the apparent diffusion coefficient of water (D_w) in the matrices containing various types of hydrophilic cellulose. Significantly different from the unloaded matrix at: $^{*}P < 0.01$.

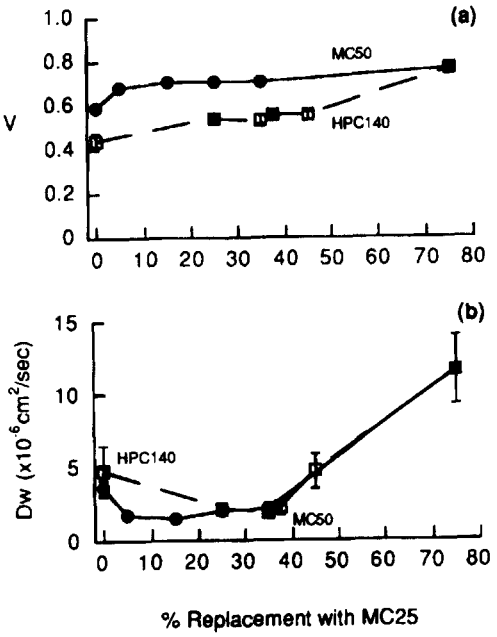

Fig. 5. Effect of the replacing amount of MC25 on: (a) the maximum swelling index (V) and (b) the apparent diffusion coefficient of water (D_w) of MC50 and HPC140 matrices containing a drug/polymer ratio of 1:3.

of D_w indicates the more dense matrix network structure formed by filling of the short chain of MC25 in the polymer network of the MC50 and HPC140 matrices. The rapid increase in D_w ($P < 0.01$) occurred when the replacing amount of MC25 was more than 30%. D_w seems to be proportional to the amount of MC25 when MC25 is the major component in the matrix.

3.4. Effect of the water soluble component (lactose) substituted for the MC50 or HPC140 in the matrix containing D/P = *1:3*

The effect of lactose on V and D_w of the MC50 and HPC140 matrix is shown in Fig. 6. Fig. 6a shows that lactose increased V in both the MC50 and HPC140 matrix ($P < 0.01$). A non-swellable water soluble particle such as lactose will not inhibit the swelling process of the polymer but may interfere with the interchain bonding of the polymer network, and thus a decrease in the ability to keep the matrix shape. In Fig. 6b, lactose decreased D_w in both the MC50 ($P < 0.01$) and HPC140 ($P < 0.05$) matrices. The existence of solid particles in the polymer network may increase the friction of the network structure because of their high density. Fig. 6 shows that lactose influences the swelling properties of the hydrophilic cellulose derivatives matrix.

4. Conclusion

The swelling profile of a matrix, together with the parameters V and D_w, can be used to describe the swelling properties as well as the integrity of a hydrophilic cellulose matrix which are the capability to maintain the matrix shape and the friction or the resistance of the polymer network structure. The results reveal that HPC140 produced a matrix with high integrity in the presence and absence of IM. The replacement of the hydrophilic cellulose polymer with the second

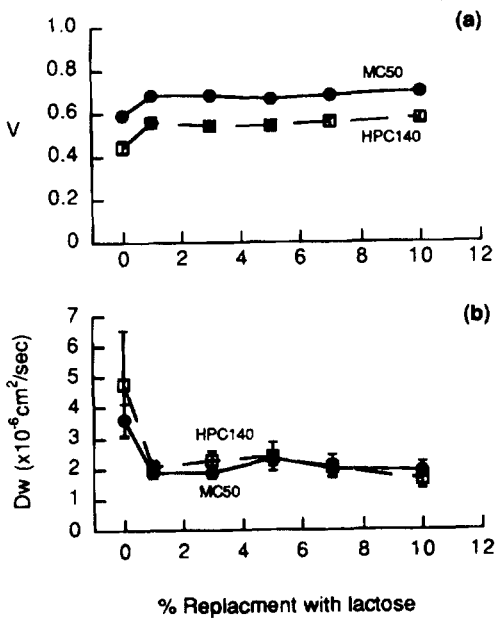

Fig. 6. Effect of the replacing amount of lactose on: (a) the maximum swelling index (V), and (b) the apparent diffusion coefficient of water (D_w) of MC50 and HPC140 matrices containing a drug/polymer ratio of 1:3.

swellable polymer or lactose changed the swelling properties of the matrix. In addition, the drug release study also showed that HPC140 produced the maximum sustained release effect and a high ability to maintain this effect even when replacing with MC25 (Panomsuk et al., 1995).

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