A Study of the Hydrophilic Cellulose Matrix: Effect of Drugs on Swelling Properties

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The swelling properties of hydrophilic cellulose matrices were studied using three drugs having different water solubility: indomethacin, theophylline, and mannitol. Two swelling parameters: maximum swelling index (V) and the apparent diffusion coefficient of water in the matrix (D_w), were calculated from the swelling data and were used to describe structures and properties of the swollen matrices. The V value indicates the swelling extent as well as the capacity of maintaining the matrix shape, whereas D_w represents the swelling rate that also reflects the structural resistance of the polymer network against the movement of water molecules. The results show that both polymers and incorporated drugs influence the swelling properties of the matrices. Polymers that contain more hydroxypropoxyl group produce matrices with high integrity, even in the presence of drugs. V values indicated that the capacity of the matrices to maintain their shape depends on polymer (*i.e.*, the swelling part). The effect of drug solubility can be seen from D_w values. For a highly water-soluble drug, the structural resistance of the swollen matrices is mainly governed by the drug. In contrast, this is primarily influenced by the polymer in the case of drugs that are slightly or poorly water soluble.

Key words hydrophilic cellulose matrix; swelling property; maximum swelling index; apparent diffusion coefficient

The swelling behavior of a drug delivery system, especially polymeric matrices, has been reported to be directly related to the drug release mechanism^{1–4)} and also by the conditions under which the network of that system has been formed.⁵⁾ The optimum design or selection of polymer for controlled release systems requires an understanding of the factors related to the structure and morphology of the polymer, and properties related to its interaction with the environment.

A number of methods have been used to study the effects of a drug on the swelling as well as the swollen polymer network structure.^{6–11)} In our previous work,¹²⁾ the swelling profiles of the hydrophilic cellulose matrices were observed *via* the axial-swelling direction. The maximum swelling index (V) and the apparent diffusion coefficient of water (D_w), calculated from the swelling data, 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 molecules of water, respectively.

In the present study the axial-swelling profiles and the swelling parameters (V and D_w) of the hydrophilic cellulose matrices were used to determine the influence of a drug, the amount of drug-loading and polymer types on the swelling properties as well as the matrix network structure. Indomethacin, theophylline and mannitol were used as model drugs representing various solubilities.

Experimental

Materials Indomethacin (IM): M.W. 357.81, water solubility (25°C) 4.0 mg ml⁻¹¹³⁾; theophylline (TP): M.W. 180.17, water solubility (25°C) 8.3 mg ml⁻¹; and mannitol (MT): M.W. 182.17, water solubility (25°C) 180 mg ml⁻¹, were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Methylcellulose (MC): 4000 cP (SM), and hydroxypropyl methylcellulose (HPMC): 4000 cP (65SH and 90SH), were obtained from Shin-Etsu Chemical Co., Ltd. (Niigata, Japan). The properties of polymers used are represented in Table I. All other materials were of analytical reagent grade.

Matrix Preparation A physical mixture of drug and polymer was

prepared to obtain the 0, 10, 25, 40 and 50% of drug-loading and was directly compressed by a hydraulic press (Riken Power, Model No. P-16B, Japan) at 80 kg cm⁻² compressional pressure. The matrix was one flat-face, 400 mg-weight and 12 mm-diameter.

Swelling Experiment The swelling was performed by fixing each matrix in a swelling experiment device as described previously.¹²⁾ The swelling was studied at 37 ± 0.5°C using a thermoregulated water bath. Deionized water was used as a swelling medium. At each time interval the matrix thickness (H_t) was directly measured through a transparent tube. The swelling was observed for more than 8 h and three measurements were carried out for each preparation. The swelling profile was obtained by plotting the swelling ratio (H_t/H_0 , H_0 =initial dry thickness of the matrix) *versus* time.

Data Analysis According to our previous report,¹⁴⁾ swelling parameters defined by Eqs. 1 and 3 were established:

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

$$V = 1 - \frac{H_0}{H_\infty} \quad (2)$$

$$C = 1 + \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{\cos(n\pi) - 1}{n} \sin\left(n\pi \frac{x}{2H_0}\right) \exp\left(-\frac{n^2\pi^2 D_w t}{4H_0^2}\right) \quad (3)$$

where H_t is the thickness of the matrix at time t , H_0 is the initial dry thickness of the matrix, V is the maximum swelling index as shown in Eq. 2 where H_∞ is the fully swollen thickness of the matrix. C is the water concentration in the matrix relative to the equilibrium concentration, and D_w is the apparent diffusion coefficient of water in the matrix. C values corresponding to various x values at any time t are calculated by Eq. 3. Using the sets of calculated C and x values, a value of H_t is obtained by Eq. 1. Integration of Eq. 1 is performed by Simpson's rule. In short, H_t is a function of t with two parameters to be estimated, D_w and V . The parameters were estimated by a least squares adaptation

Table I. Properties of the Hydrophilic Cellulose Polymers

Type	Viscosity (cP)	% Methoxyl group	% Hydroxypropoxyl group
SM (MC)	4000	1.8	—
65SH (HPMC)	4000	1.8	0.15
90SH (HPMC)	4000	1.4	0.20

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of Eqs. 1 and 3 to the observed data of swelling, using the algorithm proposed by Berman *et al.*¹⁵⁾ Both V and D_w were estimated from swelling data observed for 8 h.

The effect of polymer type and the incorporated drug on the swelling of the hydrophilic cellulose matrices was evaluated by the two parameters, V and D_w .

Results and Discussion

Swelling Property of the Polymer Matrix The swelling profiles of the matrices containing only hydrophilic cellulose polymer are shown in Fig. 1. Dotted lines represent the calculation data from Eqs. 1—3. The SM matrix showed the maximum swelling profiles followed by 65SH and 90SH matrix, respectively. Time required for matrices to swell more than twice of their initial thickness was only 15 min for SM while that of 65SH or 90SH was about 2 h. Within 8 h the maximum swelling ratio of SM, 65SH and 90SH matrices was 5.79 ± 0.550 , 2.45 ± 0.135 and 2.40 ± 0.080 , respectively.

V , the relative value as represented in Eq. 2, indicated how much the matrix can swell or the capacity 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.¹⁶⁾ Likewise, D_w can represent

Fig. 1. Swelling Profiles of Hydrophilic Cellulose Matrices Containing SM, 65SH and 90SH

Each value represents the mean ($n=3$) $\pm$ S.D. Dotted lines represent the fit according to Eqs. 1—3.

the friction of the polymer matrix network structure in which the transport of water molecules 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 molecules of water, respectively.

The swelling parameters estimated from the swelling data of the hydrophilic cellulose matrix are shown in Table 2. 65SH and 90SH matrices show nearly the same V and D_w values ($p < 0.01$). As shown in Fig. 1, the dotted line did not fit the swelling profile of the SM matrix, thus, satisfactory parameters were not obtained from the profiles of this matrix. The explanation, from Eq. 3,¹⁴⁾ is that in addition to the diffusion, water may enter the SM matrix by another fast penetration process caused by breaking of the hydrogen bonds and widening of the pores during the penetration. SM is methylcellulose which has no hydroxypropoxyl group in its structure as shown in Table 1. On swelling in water, the hydrated polymer chains may not be able to form a strong network structure against the rapid penetration of water because of their weak hydrogen bonding.

Effect of Drug on the Swelling of MC Matrix The swelling profiles of SM matrices loaded with 10 and 40% of various drugs are shown in Fig. 2. TP increased the swelling while MT decreased that of the SM matrix. However, the effect of IM was seen only in the first 100 min of swelling. IM increased the slope of the swelling profile but did not affect the maximum swelling ratio of the SM matrix.

In the presence of TP the polymer would be more soluble in water, thus increasing the amount of water associated

Table 2. Estimated Parameters: the Maximum Swelling Index (V) and the Apparent Diffusion Coefficient of Water (D_w) of the Matrices Containing Only Polymer

Polymer	V	D_w ($\times 10^{-6} \text{ cm}^2/\text{s}$)
65SH	0.596 ± 0.008	6.675 ± 0.503
90SH	0.582 ± 0.012	6.192 ± 0.632

Each value represents the means $\pm$ S.D. of three determinations.

Fig. 2. Swelling Profiles of SM Matrices Loading with 10 and 40% of Various Kinds of Drugs Compared with Unloaded Matrix

Each value represents the mean ($n=3$) $\pm$ S.D.

Fig. 3. Effect of Drug Loading on the Maximum Swelling Index (V) of 65SH and 90SH Matrices

Each value represents the mean ($n=3$) $\pm$ S.D. *, ** Significant difference from the unloaded matrix at $p < 0.05$ and 0.01 , respectively.

Fig. 4. Effect of Drug Loading on the Apparent Diffusion Coefficient of Water (D_w) in 65SH and 90SH Matrices

Each value represents the mean ($n=3$) $\pm$ S.D. *, ** Significant difference from the unloaded matrix at $p < 0.05$ and 0.01 , respectively.

with MC and being able to gel rapidly. Increase in the amount of MT loading, however, caused a decrease in the extent of swelling. The osmotic property of MT itself would increase the water influx into the matrix. It might be from MT molecule which dissolved from the swollen layer, leaving an increased surface area and thereby accelerating the dissolution of the gel.¹⁷⁾ IM, a practically water insoluble drug, may exist in between the polymer chains allowing each chain to hydrate freely without the effect of intramolecular hydrogen bonding.

Effect of Drug on the Swelling of HPMC Matrix The effect of percentage loading of various drugs on V and D_w of 65SH and 90SH matrices is shown in Figs. 3 and 4, respectively. Figure 3 shows that three drugs decreased V of both polymer matrices. For each polymer type, V values obtained from matrices containing various drugs at the same amount of loading are nearly the same. This suggested that the swelling extent of the hydrophilic matrix is proportional to the amount, not to the solubility, of the incorporated drug. The effect of drug solubility can be seen in Fig. 4. Among the three drugs, MT most markedly influenced D_w of both polymer matrices whereas this seemed to be unaffected in the case of IM or TP.

Although a significant increase in D_w of both polymer matrices was observed only in some loading concentrations, the D_w values of these matrices containing various drugs could be ranked $\text{MT} > \text{IM} \geq \text{TP}$. This indicated that the structural resistance of the swollen matrices was influenced by a high water-soluble drug.

The hydration, which occurs when the molecules of water penetrate along the polymer chain, depends on the cohesion force or the integrity of the polymer network which, in turn, is influenced by the hydroxyl group and size of the substituted group.¹⁸⁾ The greater the number and strength of the hydrogen bonding, the slower is the diffusion of the molecules in the hydrated matrix.¹⁹⁾

The penetration of molecules of water into the MT-loaded matrices is the summation effect from the solubility and osmotic properties of the drug. Being highly soluble, more MT leached out of the swollen mass than TP and IM. It left behind a highly porous and weak matrix structure as shown by the increase in D_w values. Moreover, water penetration was also promoted by the osmotic pressure generated by dissolved MT inside the matrix. TP had little effect on D_w values in HPMC matrices as shown in Fig. 4. One explanation could be that the

diffusion of water into the matrices is not greatly facilitated by the water uptake of TP but, rather, by the water uptake of the hydrophilic polymer; the same effect of TP was also reported in poly(ethylene oxide) tablets.²⁰⁾ Being a slightly water soluble drug, TP might be present between the hydrated polymer chains as a hydrophilic part without affecting the strength of the intramolecular hydrogen bonding. Since the D_w value represents the matrix network structure, the results suggested that a slightly water soluble drug such as TP had little effect on the network structure of HPMC matrix. The cloud point study of the HPMC also indicated that TP did not disturb the hydration process of this polymer.²¹⁾ The effect of IM in allowing each chain to hydrate freely may result in weak hydrogen bonding areas around the IM molecules. These areas may decrease the strength of the swollen layer followed by a small increase in the amount of the penetrated water.

According to the osmotic and highly water-soluble properties of MT, matrices containing this drug produced a transparent swollen matrix, and a partial dissolution occurred at the surface. It is difficult to differentiate the border between swollen matrices and the swelling medium which causes a large S.D. as well as a fluctuation in the V values. The fluctuation of D_w in 65SH matrices containing MT may be from the effect of the drug, as described above, and from the polymer itself which has little capability to maintain the matrix shape.

Effect of Polymer Type There is no difference in V and D_w values of the unloaded 65SH or 90SH matrix ($p < 0.01$). However, as the drug loading increases, a marked change in the parameters, especially D_w , is easily observed. This reveals that in the presence of drug, a non-swellaible excipient, 90SH polymer produces a matrix with high capable of maintaining the shape and high structural resistance.

65SH and 90SH are HPMC with differences in the amount of substituted groups (Table 1); the presence of more hydroxypropoxyl group in 90SH thus produces a swollen matrix of higher integrity. High network integrity, however, could be clearly seen from the change in D_w values when the polymer was partially replaced with drugs as described above. Furthermore, without any hydroxypropoxyl group, the SM matrices swell quickly (Fig. 1) but are not able to form such a strong network as 65SH matrices which have the same amount of methoxyl group. Methocel A4M, the same polymer matrix type as SM, also showed rapid expansion and collapsed within 2 h.⁶⁾

The effect of high drug loading (50%) on V and D_w values is, however, different from that of other drug loadings. As the amount of drug increases, the property of the matrix is gradually governed by the property of the incorporated drug in turn to the influence of the polymer.

The percent drug loading at which the property of the matrix tends to deviate can be called the "critical" drug loading amount. From Figs. 3 and 4, the critical drug loading amount of both 65SH and 90SH matrices is between 40 to 50 %.

In conclusion, the parameters can describe the swelling properties of the hydrophilic cellulose matrices. The swelling of matrices is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules plays an important role in the matrix integrity of the swollen hydrophilic cellulose matrices. The swelling extent of the HPMC matrix depends on polymers, regardless of the drug solubility. The network structure of the swollen matrices is influenced by the amount and the properties of an incorporated drug. Marked change in the matrix integrity was observed when matrices were loaded with a highly water soluble drug. The results suggest that drugs play an important role in polymer swelling and contribute to the matrix integrity; a drug which is highly water soluble is the primary influence on matrix integrity, whereas the main influence is the polymer when the drug is slightly or poorly water soluble.

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