Chem. Pharm. Bull. **43**(6) 994—999 (1995) Vol. 43, No. 6

A Study of the Hydrophilic Cellulose Matrix: Effect of Indomethacin and a Water-Soluble Additive on Release Mechanisms

Suwannee P. PANOMSUK, Tomomi HATANAKA, Tetsuya AIBA, Kazunori KATAYAMA, and Tamotsu KOIZUMI*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan. Received November 7, 1994; accepted January 26, 1995

The release profile of indomethacin (IM) from a direct compressible matrix containing three hydrophilic cellulose derivatives, methylcellulose (MC25 and MC50), hydroxypropylcellulose (HPC140), and hydroxypropylmethylcellulose (HPMC50) was studied. The drug release profile was affected by matrix size, polymer type, drug : polymer ratio and water soluble additive (lactose). An IM zero-order release matrix can be obtained by mixture and direct compression with MC50, HPMC50 and HPC140. The release rate from the MC50 and HPC140 matrix can be modified by replacing MC50 or HPC140 with MC25, and a zero-order release could be obtained even when the amount of replacement with MC25 is up to 35 and 45%, respectively. Lactose up to 10% slightly affected the release profile. IM released from this kind of matrix by a zero-order rate seems to be controlled by the swelling and relaxation of the polymer.

Key words hydrophilic cellulose matrix; indomethacin; release profile; water soluble additive; drug release mechanism

The hydrophilic matrix has attracted considerable attention in the development of sustained release systems in recent years. It can be achieved by using an appropriate type and concentration of matrix substances, followed by general manufacturing, which primarily includes granulation and compression. Of the hydrophilic matrix substances, cellulose polymer is a good candidate. Several papers have reported on the drug release from hydrophilic cellulose derivatives, various factors which affect the rate as well as the kinetics of drug release.[1-15] It is possible to modify the drug release rate from this kind of product by adding other excipients[2,4,5,10] which can be classified into two main types: soluble and non-soluble excipients. The study of drug release, including the modification of the release rate from hydroxypropylmethylcellulose (HPMC), has been widely investigated in recent years.[1,3-5,7-9,14,15] However, there are few reports which discuss drug release from methylcellulose (MC)[1,6,8,9] and hydroxypropylcellulose (HPC).[1,6,10-12] Moreover, only a limited study of the release of indomethacin (IM), a commonly used non-steroidal anti-inflammatory drug, from a hydrophilic matrix tablet,[9,16,17] especially from MC[9] and HPC,[6] has been reported. Therefore, study of the release of IM from MC, HPC and also HPMC could provide adequate data for construction of a hydrophilic cellulose matrix.

The aims of the present work are: i) to study the factors affecting the release and the release mechanisms of IM from hydrophilic cellulose matrices containing MC, HPC and HPMC, and ii) to study the effect of other excipients on the drug release. Since the release of a drug from a granulated product has greater entropic hindrance than that from a directly compressed tablet,[18] the release kinetics from a direct compressible matrix seems to project the real effect of a cellulose polymer on drug release. To make a compressed matrix with a dispersed active agent is also the simplest approach to modify the release formulation.[19] The experiment was designed to study the effect of matrix size, polymer type and the drug : polymer (D : P) ratio on the drug release profile. The release mechanism was investigated from the release data. Moreover, the effect of the second swellable component and lactose on the drug release rate and mechanisms was also observed.

Experimental

Materials IM powder was purchased from Nacalai Tesque, Inc. (Kyoto, 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, U.S.A.). All other materials were of analytical reagent grade.

Matrix Preparation A physical mixture of IM and polymer was prepared to obtain a D : P ratio of 1 : 2, 1 : 3 and 1 : 4. The mixture was directly compressed to a 400 mg, 12 mm-diameter matrix by a single punch tableting machine (Erweka Type EKO, Frankfurt, Germany). Only those tablets that were within ± 10 mg of the target weight were used in this study. Since the influence of compression pressure on the drug release rate from the hydrophilic matrices is reported to be

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	55	65	—	—	—	—	—	—
Lactose	—	—	—	—	—	—	—	—	—	1	3	5	7	10	15
Polymer[a]	75	70	60	50	40	37.5	30	20	10	74	72	70	68	65	60
Total							75								

a) MC50 and HPC140.

* To whom correspondence should be addressed.

negligible,[13,20] the effect of the pressure was not studied here. However, the matrix was controlled to 8—11 kg crushing strength. For a formulation containing a D : P ratio of 1 : 3, 300 and 400 mg matrices were made to study the effect of the matrix size on drug release pattern. The effect of the second swellable component (MC25) and water soluble component (lactose) on the release profile was also studied. The amount of MC25 and lactose used are listed in Table 1.

Disintegration Study Six matrices of each formulation were evaluated using the disintegration apparatus JPXII (Yazawa type HC-1, Tokyo, Japan). The disintegration study was carried out in water, the emersion fluid, at 37±2 °C for 30—40 min. Only the matrices that did not disintegrate within 30 min were selected for the drug release study.

Drug Release Studies The release of IM from matrices was obtained by the dissolution apparatus JPXII, a basket type, (Toyama NTR5S3, Tokyo, Japan) at 37±0.5 °C using a phosphate buffer (pH 6.2, 900 ml) as the release medium. Since the total gastro-intestinal transit time of nutrients and dosage forms on humans is approximately 8 h,[21] the drug release study was also performed for 8 h. The basket rotation speed was set at 100 rpm. At each sampling interval, a 10 ml sample was withdrawn and the same amount of medium was immediately added to keep the volume of the medium constant during the experiment. The amount of drug release was determined by UV-spectrophotometric method (Graphicord UV-240, Shimadzu, Kyoto, Japan) at 318 nm. Studies were performed in triplicate. The drug release profile was plotted between the cumulative percentage of drug release, calculated from the total amount of IM contained in the matrix, and time.

Data Analysis To analyze the mechanism of drug release from the matrix, the release data were fit with Eqs. 1 to 4 as follows:

$$\text{zero-order equation:} \quad Q_t = k_0 t + b \tag{1}$$

where Q_t = amount of drug release at time t, k_0 = drug release rate, b = constant;

$$\text{first-order equation:} \quad Q_t = Q_0(1 - e^{-k_1 t}) \tag{2}$$

where Q_0 = total amount of drug in the matrix, k_1 = first order rate constant;

$$\text{Higuchi's equation}^{22}\text{:} \quad Q_t = k_2 t^{1/2} + c \tag{3}$$

where k_2 = diffusion rate constant, c = constant;

$$\text{power law equation}^{23}\text{:} \quad Q_t/Q_\infty = k_3 t^n \tag{4}$$

where Q_∞ = total amount of drug, k_3 = kinetic constant, n = exponent characteristic of the release mechanism.

Results and Discussion

Effect of Polymer Type and D:P Ratio Figure 1 contains the release profiles of IM from various types of hydrophilic cellulose polymers. The matrix containing MC25 disintegrated and produced rapid, as well as in-constant, drug release. For the MC25 matrix, in which the D : P = 1 : 2, the release study was not performed since the disintegration time was less than 30 min. The release study of the HPC140 matrix, which contained a D : P ratio of 1 : 4, was also not performed because of its poor physical appearance. The surface of this matrix was not smooth since it stuck on the surface of the lower punch and was difficult to remove. The release from such a defected matrix would be varied. A sustained release effect was found to be maximum in the matrix containing HPC140 followed by MC50 and HPMC50 at each D : P ratio. Among the constant release preparations, HPC140 exhibited the highest ability to retard drug release.

The main structure of MC, HPC and HPMC is a 1,4-β-D-linked polyanhydroglucose unit with differences in two substituted groups which are: $-CH_3$ (2 groups) in MC, –H and $-CH_2CH(CH_3)OH$ in HPC, and $-CH_3$ and $-CH_2CH(CH_3)OH$ in HPMC. 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 is influenced by the hydroxyl group and size of the substituted group.[24] Actually, the hydration of the matrix was ranked as HPMC50 ≥ MC50 > HPC140 (data not shown).

Miyajima *et al.*[25] reported that the extent of hydration of a membrane may greatly influence the diffusion coefficients (D) of Ara-A. This dependence of D on the hydration of the membrane has been discussed based on the free-volume theory. In this theory, the relationship between D and the hydration can be expressed by the following equation:

$$\log D = \log D_0 - k[(1/H) - 1] \tag{5}$$

where D is the diffusion coefficient of a solute in the swollen membrane, D_0 is the diffusion coefficient of the solute in a saline solution, k is the proportional constant, and H is the hydration of the polymer.

In the present study, the relationship between the cumulative amount of drug release, ranked as HPMC50 > MC50 > HPC140, and the hydration, ranked as HPMC50 ≥ MC50 > HPC140, can also be discussed based on the free-volume theory.

The effect of the D : P ratio on the cumulative percentage of IM release in 8 h is shown in Fig. 2. For MC25, MC50 and HPMC50, the increase in polymer content caused a decrease in the cumulative percentage of drug release

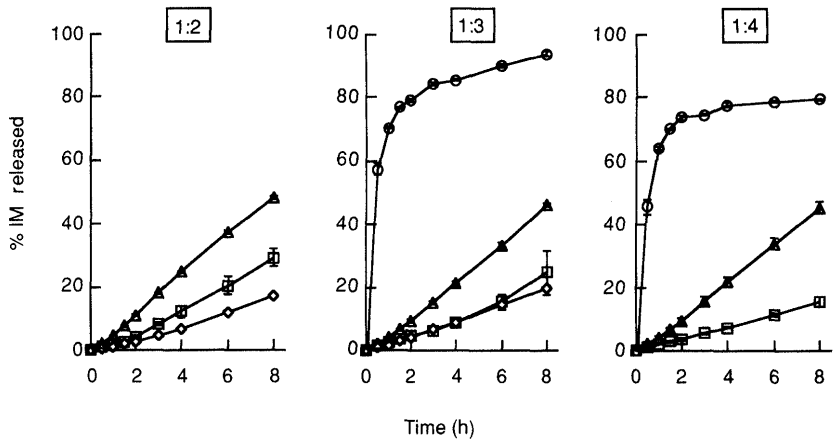

Fig. 1. Release Profile of IM from Various Types of Hydrophilic Cellulose Matrices (400 mg) Containing D : P = 1 : 2, 1 : 3 and 1 : 4 (○), MC25; (□), MC50; (△), HPMC50; (◇), HPC140. Each data represents the mean (n = 3) ± S.D.

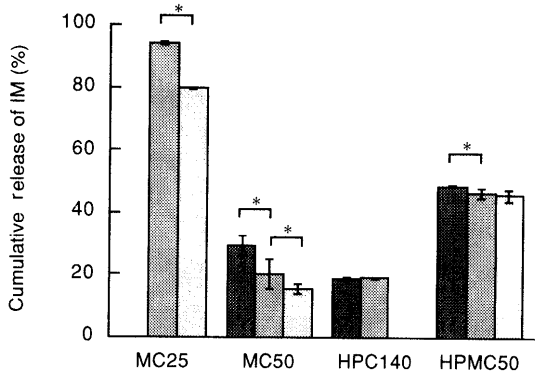

Fig. 2. Effect of D:P Ratio on the Cumulative Percentage Release in 8 h of IM from Matrices Containing Various Types of Hydrophilic Cellulose Polymer

Each value represents the mean ($n=3$) ± S.D. * Significant difference at $p<0.05$. ▩, 1:2; ▨, 1:3; □, 1:4.

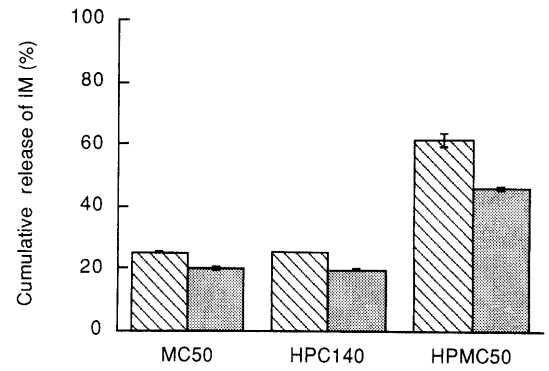

Fig. 3. Effect of Matrix Size on the Cumulative Percentage Release of IM from Matrices Containing Various Types of Hydrophilic Cellulose Polymer where D:P Ratio = 1:3

Each value represents the mean ($n=3$) ± S.D. ▨, 300 mg; ▩, 400 mg.

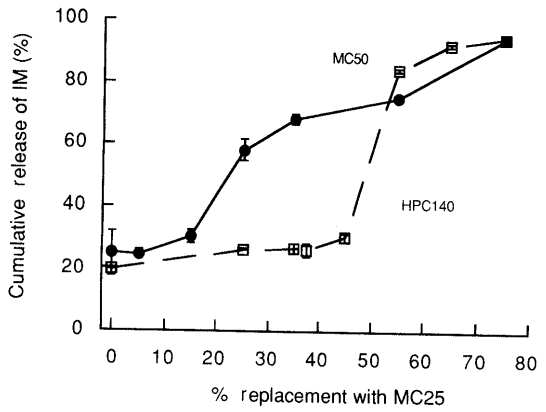

Fig. 4. Effect of the Replacing Amount of MC25 on Cumulative Percentage Release of IM from Matrices Containing D:P Ratio = 1:3

(●), MC50; (□), HPC140. Each value represents the mean ($n=3$) ± S.D.

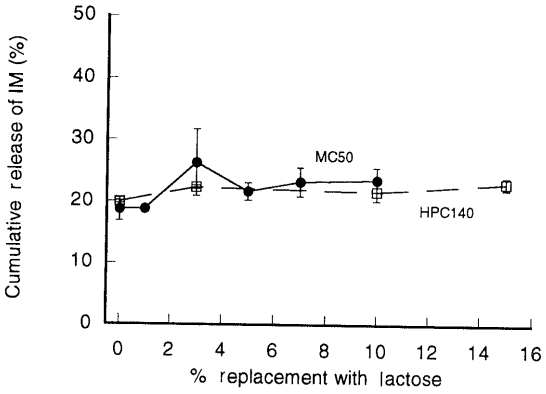

Fig. 5. Effect of the Replacing Amount of Lactose on Cumulative Percentage Release of IM from Matrices Containing D:P Ratio = 1:3

(●), MC50; (□), HPC140. Each value represents the mean ($n=3$) ± S.D.

($p<0.05$). This may be from the enhancement of the strength of the gel layer, which results in the reduction of drug diffusion and water uptake through the gel layer. The effect of polymer content in the matrix containing HPMC50 at D:P = 1:4 (when compared to D:P = 1:3) and in that containing HPC140 on the drug release was not clear.

Effect of Matrix Size As shown in Fig 3, the increase in matrix size caused a decrease in the cumulative percentage of IM release in 8 h from the MC50, HPC140 and HPMC50 matrices. Since the hardness of the matrix was controlled, as mentioned before, the increase in matrix weight from 300 to 400 mg causes the thicker matrix. This leads to a decrease in the surface area to volume ratio of the matrix that is exposed to the release medium, and thus a decrease in the cumulative percentage of drug release.[3]

Effect of MC25 Substituted for the MC50 or HPC140 in a Matrix Containing D:P = 1:3 Figure 4 shows that the replacement with MC25 increases the amount of IM released from both MC50 and HPC140 matrices. The increase in IM release was found when the replacing amount of MC25 was more than 15% in MC50 and 37.5% in HPC140 matrix. However, a marked increase in the cumulative percentage of IM release was observed in the HPC140 system when the replacing amount of MC25 is more than 45%.

A zero-order release tablet can be obtained by mixing and directly compressing a drug with an optimum amount of nonionic polymer such as HPC or MC and the ionic polymer CMC-Na.[26,27] Matsumura *et al.*[13] also found that the addition of MC to the micronized low-substituted HPC matrix tablet provides a controlled-release theophylline tablet with slow disintegration. In the present study, IM release could also be modified by replacing the highly retarding polymer (MC50 and HPC140) with MC25. The presence of MC25 may reduce the matrix integrity of MC50 and HPC140 by replacing the short chain molecule between the long chain and compact matrix of MC50 and HPC140, which causes a loosening of the matrix integrity.

Figure 4 also shows that besides the maximum sustained release effect, HPC140 has a high ability to maintain this effect even when the replacement amount of MC25 is up to 45%. The rapid increase in the drug release from 55% replacement with MC25 may be caused by the different structure between HPC140 and MC25, and this effect will occur when MC25 is the major component in the HPC140 and MC25 mixed system.

Effect of Lactose Substituted for the MC50 or HPC140 in a Matrix Containing D:P = 1:3 Figure 5 reveals that a partial replacement of MC50 or HPC140 with lactose slightly increases the cumulative percentage release of IM from the matrix. This result is the same as reported by

Van der Veen,[28] that although IM is a slightly water soluble drug, a slight increase in release rate was found when lactose was incorporated of up to 20% in theophylline monohydrate-containing amylodextrin tablets. This may be attributed to the faster water penetration into the tablets, caused by the hydrophilicity of the incorporated lactose.

Mechanism of Drug Release Table 2 shows the correlation coefficients of drug release data when fit with the zero-order equation (r_1^2), first-order equation (r_2^2), Higuchi's equation (r_3^2) and power law equation (r_4^2), from four polymer matrices at different D:P ratios. For MC50, HPMC50 and HPC140 matrices, the maximum r^2 was found when fitting the release data with the zero-order and power law equation. The r_1^2 of MC25 is very low when compared to the other three polymers, as is consistent with the disintegration, fast and inconstant drug release of the matrix mentioned above.

Table 2. Correlation Coefficient of IM Release Data from Matrices Containing MC25, MC50, HPMC50 and HPC140 at Various D:P Ratios when Fit with: Zero-Order (r_1^2), First-Order (r_2^2), Higuchi's (r_3^2) and Power Law (r_4^2) Equation

Polymer	D:P	r_1^2	r_2^2	r_3^2	r_4^2
MC25	1:3	0.2105	0.8368	0.7424	0.9435
	1:4	0.4095	0.5749	0.7024	0.7876
MC50	1:2	0.9864	0.9760	0.8371	0.9987
	1:3	0.9971	0.9932	0.8842	0.9974
	1:4	0.9872	0.9971	0.9021	0.9969
HPMC50	1:2	0.9993	0.9944	0.9086	0.9949
	1:3	0.9968	0.9837	0.8854	0.9999
	1:4	0.9982	0.9899	0.8947	0.9987
HPC140	1:2	0.9842	0.9778	0.8327	0.9987
	1:3	0.9970	0.9930	0.8771	0.9999

The effect of MC25 on the IM release mechanism was shown in Fig. 6. As the replacement amount of MC25 increased, followed by an increase of the drug release rate, the r_1^2 decreased. The replacement with MC25 may cause the weakening in the matrix integrity of both MC50 and HPC140, so that the drug is easily released from the matrix. The decrease in r_1^2, as the replacing amount of MC25 increases reveals that the release behavior tends to deviate from the zero-order release manner.

Figure 7 represents the effect of different replacing amounts of lactose on the release mechanism. The effect of lactose is the same as that of MC25. Lactose slightly increases the IM release rate from both the MC50 and HPC140 matrices. The release behavior tends to change from zero-order, as can be seen from the slight decrease in r_1^2.

Table 3 shows the parameters calculated by fitting the IM release data from matrices containing MC25, MC50, HPC140 and HPMC50 at different D:P ratios with Eq. 4. All the n values (except that of MC25) are more than

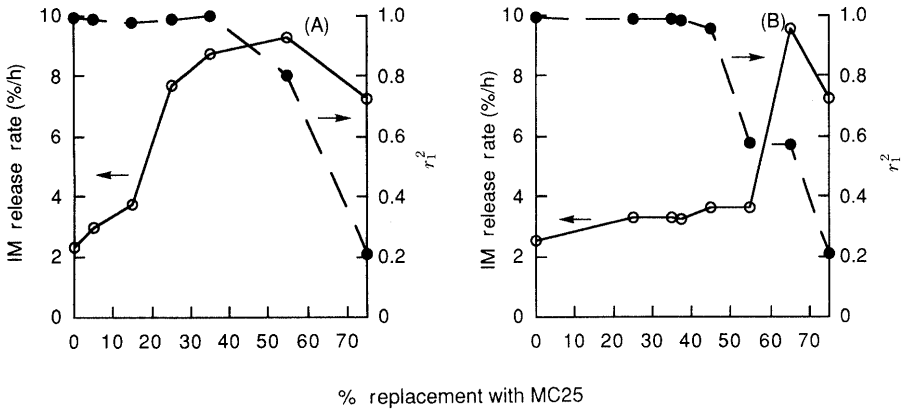

Fig. 6. Relationship between the IM Release Rate and the Correlation Coefficient of the Release Data when Fit with a Zero-Order Equation (r_1^2) at a Different Replacing Amount of the Second Polymer (MC25)

Matrices containing: (A), MC50; (B), HPC140 at D:P Ratio = 1:3; (○), IM release rate; (●), r_1^2.

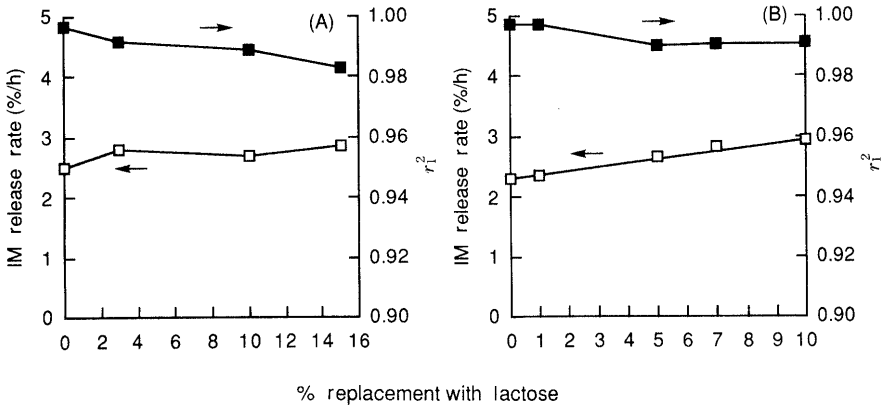

Fig. 7. Relationship between the IM Release Rate and the Correlation Coefficient of the Release Data when Fit with a Zero-Order Equation (r_1^2) at Different Replacing Amounts of Lactose

Matrices containing: (A), MC50; (B), HPC140 at D:P Ratio = 1:3; (□), IM release rate; (■), r_1^2.

0.89 ($r^2 > 0.99$) which reveals that the mechanism of IM release from a matrix is the non-Fickian and super case II type.[29] This kind of release corresponds to a more predictable type of swelling-controlled system in which the rate of solvent uptake into a polymer is largely determined by the rate of swelling and relaxation of the polymer chain. The kinetic constants (k) are in the same range for each polymer, which can be ranked from maximum as MC25 (*ca.* 0.6) followed by HPMC50 (0.04—0.05), MC50 (*ca.* 0.021) and HPC140 (*ca.* 0.018), respectively. The k-rank corresponds very well with the IM released data-rank mentioned before. This means that the k calculated from Eq. 4 can be used as a parameter reflecting the characteristics of the matrix and also the ability to retard the drug release.

The effect of different replacing amounts of MC25 and lactose on the parameters calculated from Eq. 4 of a matrix containing MC50 or HPC140 (D : P = 1 : 3) is presented in Table 4. Almost all n values are still more than 0.89 ($r^2 > 0.99$). The decrease of n to 0.166, where the replacing amount of MC25 is more than 45%, may be due to a change of matrix characteristics or matrix disintegration as described before. The k value increased when the percentage replacement of MC25 increased. Lactose up to 10 and 15% slightly affected the k value of both MC50 and HPC140, respectively.

In conclusion, MC50, HPC140 and HPMC50 can be used for the preparation of an IM sustained release matrix. A zero-order release matrix can be obtained by mixture and direct compression with MC50, HPMC50 and HPC140. The release rate can be modified by replacement with MC25. A zero-order release could be obtained when the replacing amount of MC25 is up to 35 and 45% in the matrices containing MC50 and HPC140, respectively. The replacement with lactose up to 10% slightly increased the IM release rate from both the MC50 and HPC140 matrix. IM is released from this kind of matrix by a zero-order release rate, which seems to be controlled by the swelling and relaxation of the polymer.

Table 3. Parameters Calculated from the Power Law Equation[a] of Release Data from Matrices Containing Various Types of Polymer at Different D : P Ratios

Polymer	D : P	k	n	r_4^2
MC25	1 : 3	0.6857	0.166	0.9435
	1 : 4	0.6015	0.174	0.7876
MC50	1 : 2	0.0208	1.242	0.9987
	1 : 3	0.0214	1.009	0.9974
	1 : 4	0.0207	0.937	0.9969
HPMC50	1 : 2	0.0472	1.168	0.9949
	1 : 3	0.0416	1.164	0.9999
	1 : 4	0.0427	1.155	0.9987
HPC140	1 : 2	0.0177	1.271	0.9987
	1 : 3	0.0189	1.126	0.9999

a) $Q_t/Q_\infty = kt^n$, r_4^2 = correlation coefficient.

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Table 4. Parameters Calculated from the Power Law Equation[a] of Release Data from Matrices Containing MC50 and HPC140 at D : P = 1 : 3 when Replacing the Polymer with Different Amounts of MC25 and Lactose

% replacement		MC50			HPC140		
		k	n	r_4^2	k	n	r_4^2
MC25	0	0.0214	1.009	0.9974	0.0189	1.126	0.9999
	5	0.0270	0.995	0.9854	—	—	—
	15	0.0238	1.153	0.9916	—	—	—
	25	0.0308	1.454	0.9876	0.0213	1.173	0.9981
	35	0.0628	1.211	0.9929	0.0259	1.067	0.9952
	37.5	—	—	—	0.0255	1.044	0.9899
	45	—	—	—	0.0840	0.619	0.9908
	55	0.2401	0.6868	0.8801	0.4274	0.460	0.7618
	65	—	—	—	0.4461	0.487	0.7385
	75	0.6857	0.166	0.9435	0.6857	0.166	0.9435
Lactose	0	0.0214	1.009	0.9974	0.0189	1.126	0.9999
	1	0.0177	1.134	0.9986	—	—	—
	3	0.0238	1.105	0.9952	0.0178	1.209	0.9998
	5	0.0246	0.988	0.9890	—	—	—
	7	0.0270	0.958	0.9872	—	—	—
	10	0.0231	1.069	0.9953	0.0192	1.112	0.9964
	15	—	—	—	0.0180	1.169	0.9956

a) $Q_t/Q_\infty = kt^n$, r_4^2 = correlation coefficient.

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