

Influence of Physicochemical Properties on Drug Release Rate from Hydroxypropylmethylcellulose Matrix Tablets

Hiroshi KURAHASHI,^a Hiroshi KAMI,^a and Hisakazu SUNADA^b

Research and Development Laboratories, Schering-Plough Kabushiki Kaisha,^a 1–4 Sasagaoka, Minakuchi-cho, Koka-gun, Shiga 528, Japan and Faculty of Pharmacy, Meijo University,^b 150 Yagotoyama, Tempaku-ku, Nagoya 468, Japan. Received October 16, 1995; accepted December 25, 1995

An examination was made of the release of isoniazid, anhydrous caffeine, theophylline, salicylic acid and indomethacin from hydroxypropylmethylcellulose (HPMC) matrices, and the results were usually found to follow first order kinetics. The release rate of the drug was influenced by the solubility of the drug, and by the viscosity and the content of HPMC. As the drug solubility increased, the drug release rate also increased, and conversely, as the viscosity and/or the content of HPMC increased, the drug release rate decreased. A multiple regression analysis was used to determine the relationship between response (release rate) and factors (drug solubility, HPMC viscosity and HPMC content), and a statistically significant model was obtained. This model allows not only predictions of the drug release rate from HPMC matrices, but also establishment of the formulation of the target drug without experimental determination.

Key words hydroxypropylmethylcellulose; sustained release; multiple regression analysis

A hydrophilic cellulose derivative, hydroxypropylmethylcellulose (HPMC), has been widely used to control drug release from solid doses, such as from sustained release or controlled release systems, and there have been many reports about factors affecting drug release from the HPMC matrix. It is already known that the drug release rate from an HPMC matrix is affected by the physical properties of a polymer such as viscosity grade^{1–3)} and particle size,⁴⁾ by drug/polymer ratio,^{2,3,5)} and by the physicochemical properties of a drug such as solubility⁶⁾ and particle size,^{2,3)} as well as by the kind of diluents used,^{5,7)} etc.

In order to quantitatively analyze the influence of those factors, a simple regression analysis has been carried out concerning the relationship between drug release rate and drug/polymer ratio using promethazine hydrochloride,²⁾ aminophylline and propranolol hydrochloride³⁾ as the model drugs by Ford *et al.* Xu *et al.*⁵⁾ quantitatively analyzed the relationship between the release rate of indomethacin and the content of HPMC and diluent, using a multiple regression analysis.

However, few reports have systematically explained the influence of the various factors on drug release rate, and few could be generalized for any drug. In this paper, the drug solubility, HPMC viscosity and HPMC content were targeted as factors affecting the drug release rate. HPMC matrices with varied factors were prepared, dissolution tests were carried out and the influence of those factors was analyzed by a multiple regression model.

Experimental

Materials Metolose 90SH-100SR, 4000SR, 15000SR and 100000SR (HPMC) (Shin-Etsu Chemical Co., Japan) were used as hydrophilic polymers. Isoniazid (Yukigosei Kogyo Co., Japan), anhydrous caffeine (Shiratori Seiyaku Co., Japan), theophylline (Shiratori Seiyaku Co., Japan), salicylic acid (Wako Pure Chemical Industries, Ltd., Japan), indomethacin (Sumitomo Pharmaceuticals Co., Japan) and aspirin (Katayama Chemical Co., Japan) were used as model drugs. Lactose was served as a diluent. The solubility of the drugs at 37°C and the viscosity of 2% HPMC solution are shown in Table 1.

Preparation of Matrix Tablet Flat-faced tablets 8.5 mm in diameter

were prepared by directly compressing a sample powder at 1000 kg/cm² for 30 s under a hydraulic press (O. J. Shop, press model 10, Osaka Jack MFG. Co., Japan).

Formulations used for this study are shown in Table 2. To determine the effect of the solubility of drugs and the viscosity of HPMC, model drugs (see Materials), except for aspirin, and each viscosity grade of HPMC were used as drug and HPMC in formulation, respectively.

Dissolution Studies Dissolution was measured by a dissolution tester (Toyama Sangyo Co., Japan). A tablet was put in a small basket identified here as JP XII, and the paddle method was used. 900 ml of purified water (except for indomethacin tablet; pH 7.2 buffer) maintained at 37°C was used as the dissolution medium. The stirring rate was 100 rpm. The drug concentration was monitored with a spectrophotometer (UV-160, Shimadzu Co., Japan), at 290 nm for isoniazid, at 278 nm for anhydrous caffeine, at 271 nm for theophylline, at 297 nm for salicylic acid, at 318 nm for indomethacin and at 240 nm for aspirin.

Table 1. The Properties of the Materials

Materials	Properties
Model drugs	Solubility at 37°C (mg/ml)
Isoniazid	195
Anhydrous caffeine	37
Theophylline	11
Salicylic acid	3.3
Indomethacin	0.9 ^{a)}
HPMC	Apparent viscosity (cP)
Metolose 90SH-100SR	104
Metolose 90SH-4000SR	4830
Metolose 90SH-15000SR	15300
Metolose 90SH-100000SR	105000
Diluent	
Lactose	

a) Phosphate buffer pH 7.2.

Table 2. Formulations of Various HPMC Matrices

Ingredient	Content (mg/tablet)			
Drug substance	25	25	25	25
HPMC	50	65	90	125
Lactose	75	60	35	0
Total	150	150	150	150

* To whom correspondence should be addressed.

Comparison of Release Rate In order to compare the drug release rate from each HPMC matrix, first-order kinetics (Eq. 1)⁸⁾ was used. The equation is as follows:

$$\ln(100 - W) = \ln 100 - Kt \quad (1)$$

where W is the percent drug release at time t , and K is the release rate constant.

Results and Discussion

Typical drug release profiles are shown in Fig. 1, and we confirmed linearity by a first-order plot (Fig. 2).

Influence of HPMC Viscosity In each matrix, with an increase in HPMC viscosity, the drug release rate had a

tendency to decrease; however, in spite of a great difference in release rates between the low viscosity grade (100 cP) HPMC and higher, little difference was observed in the higher grade (more than 4000 cP) matrices (Fig. 3). This result is supported by Ford *et al.*^{2,3)}

When low viscosity grade HPMC was used in low amounts, disintegration of the tablets including salicylic acid or indomethacin was observed in a few minutes. By Tuitou *et al.*⁹⁾ and Mitchell *et al.*,¹⁰⁾ it was indicated that the gelation temperature of cellulose derivatives is increased by large ions, therefore, HPMC matrices

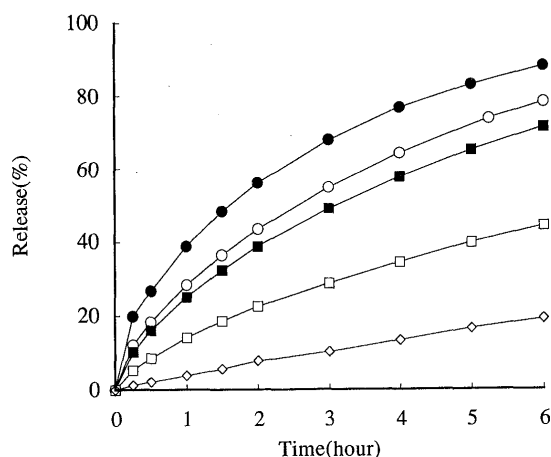


Fig. 1. Typical Drug Release Profiles from the Matrices Containing 125 mg of HPMC15000

—●—, isoniazid; —○—, anhydrous caffeine; —■—, theophylline; —□—, salicylic acid; —◇—, indomethacin.

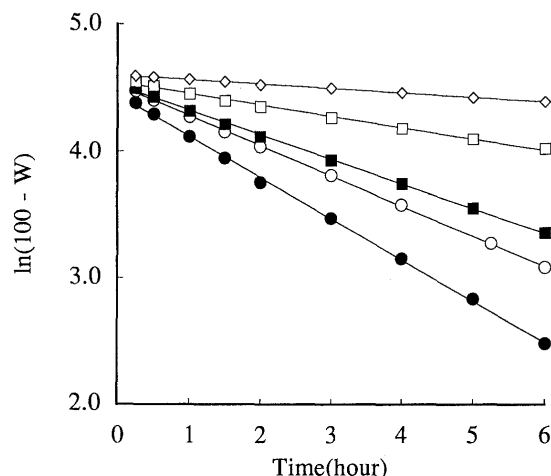


Fig. 2. The First Order Plots of the Data from the Matrices Containing 125 mg of HPMC15000

—●—, isoniazid; —○—, anhydrous caffeine; —■—, theophylline; —□—, salicylic acid; —◇—, indomethacin.

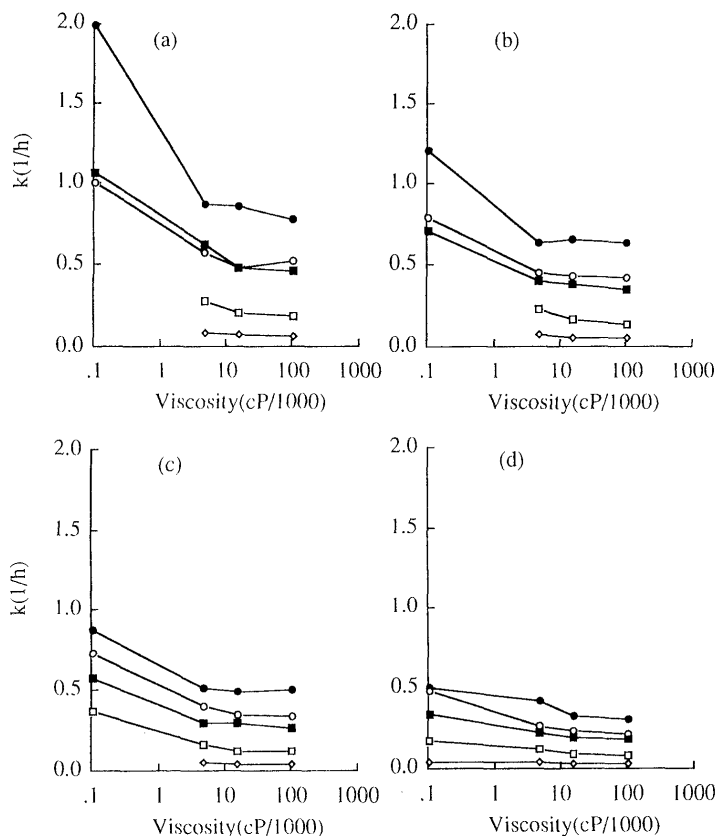


Fig. 3. Relationship between the Release Rate and the Viscosity of HPMC

HPMC content: (a) 33.3%, (b) 43.3%, (c) 60.0%, (d) 83.3%. —●—, isoniazid; —○—, anhydrous caffeine; —■—, theophylline; —□—, salicylic acid; —◇—, indomethacin.

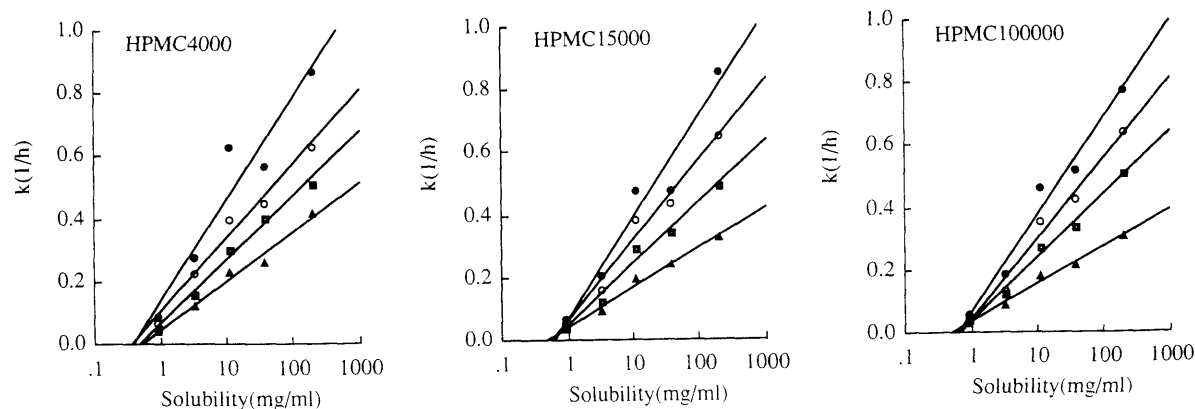


Fig. 4. Relationship between the Release Rate and the Solubility of the Drug

HPMC content: ●, 33.3%; ○, 43.3%; ■, 60.0%; ▲, 83.3%.

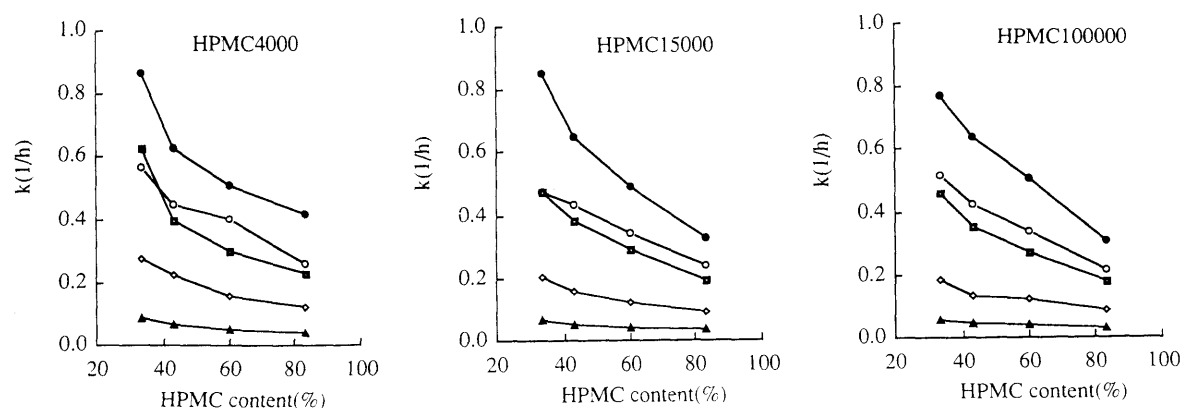


Fig. 5. Relationship between the Release Rate and the Content of HPMC

—●—, isoniazid; —○—, anhydrous caffeine; —■—, theophylline; —◇—, salicylic acid; —▲—, indomethacin.

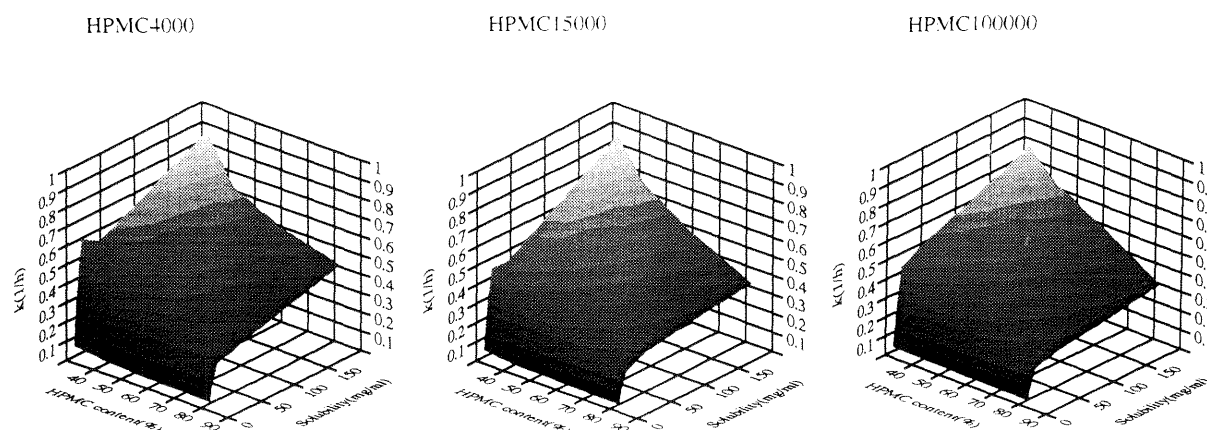


Fig. 6. The Effect of the Solubility of the Drug, the Viscosity and the Content of HPMC on Drug Release Rate

including an organic acid such as salicylic acid or indomethacin were not gelled during a dissolution test, and they disintegrated rapidly. The test results using a low HPMC (100 cP) were excluded from the following analysis.

Influence of Drug Solubility With an increase in drug solubility, the drug release rate also increased in each of the matrices, and the release rate indicated a linear relation for the logarithm of solubility (Fig. 4). In the mechanism of the drug release from an HPMC matrix, water dissolves the drug at the surface first, then penetrates the matrix *via* pores, bringing about a gelling of the polymer. Dissolved

drug was released by diffusion through the gel, and finally the drug release rate began to fall when the water reached the center of the matrix and drug concentration decreased to less than its solubility.¹¹⁾ The drug release rate at these steps depends on the drug dissolution rate; therefore it depends on drug solubility.

Influence of HPMC Content With an increase in HPMC content, the drug release rate decreased in each matrix (Fig. 5). In the case of low HPMC content, dissolution of drug and/or lactose would leave a matrix of HPMC of high porosity and low tortuosity which would

Table 3. Predicted and Experimental Release Rate from HPMC Matrices of Aspirin

Formula No.	Content (mg/tablet)				K (1/h)	
	Aspirin	HPMC4000	HPMC100000	Lactose	Predicted value	Experimental value
1	25	80	—	45	0.277	0.250
2	25	—	125	—	0.128	0.139

presumably possess a low gel strength and rapid diffusion of the drug, and it would be subject to rapid erosion.²⁾

Multiple Regression Analysis In a three-dimensional graph, the drug release rate could be expressed as a surface depending on the solubility of the drug and the content of HPMC for each HPMC viscosity grade (Fig. 6). The effects of the factors as controlled variables on the drug release rate as a response variable were determined by multiple regression analysis, and a model was obtained as follows:

$$K = 1.025 \cdot \log S - 0.021 \cdot \log V \cdot \log C - 0.467 \log S \cdot \log C + 0.220 \quad (2)$$

$$N = 60 \quad R^2 = 0.9589 \quad T(56) < 0.05 \quad F(3, 56) = 483.8$$

where K is a first order release rate constant, S is the solubility (mg/ml) of the drug at 37°C, V is the viscosity (cP) of a 2% solution of HPMC, and C is the content (%) of HPMC. And, where N is number of formulations, R^2 is the coefficient of determination, T is the significance level from the Student's t -test, and F is a value obtained by the F -test.

To confirm the propriety of Eq. 2, HPMC matrices containing aspirin, which was not used for this model, were prepared and tested. As a result, experimental K

values approximate to calculated values were obtained (Table 3), and matched Eq. 2. It was suggested that Eq. 2 allows predictions of the release rate from an HPMC matrix and would be equally beneficial in deciding the formulation for a target drug with an expected release rate not experimentally determined.

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