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Application of model-independent and model analysis for the investigation of effect of drug solubility on its release rate from hydroxypropyl methylcellulose sustained release tablets

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Abstract

The effect of drug solubility on the dissolution from the sustained release (SR) matrix tablet prepared with hydroxypropyl methylcellulose (HPMC) 2910 4000 cps was investigated using model-independent moment analysis and Higuchi-type model analysis. In this study, seven model drugs which have various solubilities in the dissolution medium were used for preparation of tablets and dissolution studies were then performed. To determine the mechanisms behind the sustained release, the infiltration rate of the medium into the matrix tablet and the erosion rate of the matrix tablet were also investigated. The model-independent moment parameters i.e. mean dissolution time (MDT), mean medium infiltration time (MIT), mean tablet erosion time (MET), mean swelling time (MSWT) and mean diffusion time (MDFT) as well as Higuchi-type model analysis which, based on release mechanisms, were demonstrated for optimization of HPMC matrix tablets. Both in the model-independent and model analyses, the relationships obtained between drug solubility and release characteristics were similar. Regarding the poorly soluble drug, U-78875, the observed dissolution rate is slower than the erosion rate of the matrix tablet, which indicates that the main rate limiting factor for the dissolution is erosion of the matrix tablet. In the case of drugs whose solubilities are between 0.5 mg/ml and 5 mg/ml (methyl-paraben, ethyl-paraben and propyl-paraben), dissolution rates are observed between the erosion rate of the matrix tablet and the infiltration rate of medium into the matrix tablet, and. the dissolution rate increases with increasing drug solubility. Regarding highly soluble drugs, whose solubilities are more than 5 mg/ml (procaine hydrochloride, acetaminophen, and theophylline), the dissolution rates are not influenced so much by drug solubility but show a similar rate of medium infiltration into matrix. In the latter two cases, the primary rate limiting factor of dissolution is infiltration of medium into the matrix tablet. The reported MDT and MDFT values were within the range 3.16–8.75 h and 1.11–6.70 h, respectively, except for U-78875. Also, MIT, MET and MSWT values as device matrix characteristics were 2.05, 12.05 and 10.00 h, respectively. The model-independent moment parameters, MDT, MIT, MET, MSWT and MDFT are directly comparable to each other. Further, these parameters would be applicable in comparing the device and dissolution characteristics of different types of formulation. These model-independent analytical approaches allow us to optimize the SR matrix formulation at the development stage.

Keywords: Matrix tablet; Sustained release; Dissolution; Hydroxypropyl methylcellulose; Solubility; Moment analysis

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1. Introduction

Several reviews on the use of cellulose ether for controlled release dosage forms had been reported (Alderman, 1984; Langer and Peppas, 1987; Ranga Rao et al., 1988; Hogan, 1989). Hydroxypropyl methylcellulose (HPMC) is often used to prepare the matrix type sustained release tablets (Shah et al., 1989; Skoug et al., 1991; Tahara et al., 1993). The importance of drug type, tablet shape and added diluents on drug release kinetics from HPMC matrix tablets has also been reported (Ford et al., 1985a,b,c, 1987; Ranga Rao et al., 1990). The relationship between drug solubility and release kinetics using promethazine hydrochloride (Ford et al., 1985a), aminophylline, propranolol hydrochloride (Ford et al., 1985b), indomethacin (Ford et al., 1985c), tetracycline hydrochloride, theophylline hydrochloride and diazepam (Ford et al., 1987) as model drugs has been thoroughly discussed. Regarding analytical methods and mathematical modelling of drug release and swelling kinetics of matrix based on mechanisms, numerous papers have been published (Lapidus and Lordi, 1966, 1968; Korsmeyer et al., 1983; Peppas, 1985; Peppas and Ritgar, 1987a,b; Lee and Peppas, 1987; Harland et al., 1988; Peppas and Sahlin, 1989; Colombo et al., 1990, 1992; Ford et al., 1991; Wan et al., 1991; Papadimitriou et al., 1993). In a previous paper (Tahara et al., 1995), we have proposed that the dissolution of highly water soluble drug from the matrix type tablet prepared with HPMC 2910 4000 cps occurs predominantly according to the square root law (Higuchi, 1962, 1963); i.e. the drug is released after dissolution by the infiltrated medium in the matrix tablet. On the other hand, poorly water soluble drugs seem to be released in particle state mainly by the erosion of matrix type tablet which occurs according to the Hixson–Crowell cube root law before dissolution of the drug (Hixson and Crowell, 1931). Thus, the dissolution of the poorly water soluble drugs from the sustained release matrix type tablets occurs predominantly after the release of drug particles into the medium.

To determine a widely applicable matrix type sustained release formulation prepared with HPMC for drugs with various physico-chemical characteristics, it is important to obtain the intrinsic relationships between the drug characteristics and device characteristics such as medium infiltration rate into the matrix tablet and erosion rate of the tablet. In this study, we demonstrate the application of model-independent moment analysis as well as Higuchi-type model analysis for the investigation of the effect of drug solubility on its release rate from the sustained release matrix tablets prepared with HPMC 2910 4000 cps to assist in the development and optimization of formulation.

2. Materials and method

2.1. Materials

To prepare the sustained release matrix tablets of drugs with various solubilities, seven model drugs were employed as follows: procaine hydrochloride anhydrous (PRC; Sigma, St. Louis, MO); acetaminophen JP (AAP; Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan); theophylline JP (THP; Shiratori Pharmaceutical Co., Ltd., Chiba, Japan); methyl *p*-hydroxybenzoate (methyl-paraben, METP; Wako Pure Chemical Ind., Ltd., Osaka, Japan); ethyl *p*-hydroxybenzoate (ethyl-paraben, ETHP; Wako Pure Chemical Ind., Ltd., Osaka, Japan); propyl *p*-hydroxybenzoate (propyl-paraben, PROP; Wako Pure Chemical Ind., Ltd., Osaka, Japan); and U-78875 (The Upjohn Company, Kalamazoo, MI). The material properties such as molecular weight, melting point, solubility (described in Section 2.2) and UV wavelength used for detection of these model drugs are listed in Table 1.

Hydroxypropyl methylcellulose (HPMC) 2910 4000 cps, USP (Methocel E4M) was supplied by Dow Chemical Company (Midland, MI). All other reagents used were JP, USP or analytical grade.

2.2. Measurement of drug solubility in the medium

The measurements of solubility of seven model

Table 1
List of model drugs used for preparation of sustained release (SR) matrix tablet

Drug code[a]	Molecular weight	Melting point, °C	Solubility, mg/ml[b]	UV for detection, nm
PRC	272.80	153–156	453 ± 3.17	290
AAP	151.16	169–172	18.9 ± 0.33	242
THP	180.17	271–275	10.6 ± 0.27	271
METP	152.14	125–128	3.11 ± 0.01	255
ETHP	166.18	115–118	1.27 ± 0.01	255
PROP	180.20	96–97	0.53 ± 0.00	255
U-78875	335.37	171	0.07 ± 0.00	316

[a]PRC, procaine hydrochloride anhydrous; AAP, acetaminophen; THP, theophylline; METP, methyl-paraben; ETHP, ethyl-paraben; PROP, propyl-paraben.
[b] Solubility was determined in the JP second disintegration medium (pH 6.8); each value of solubility represents the mean ± S.D. (n = 3).

drugs in JP second disintegration medium (pH 6.8) were performed. Briefly, the measurement procedure was as follows; 1.0 g of each model drug was added to 10 ml of JP second disintegration medium at pH 6.8 in a beaker, which was maintained at 37°C and stirred with a magnetic stirrer for 48 h. Then, 5 ml of sample was collected in a test tube, and centrifuged at 3000 rev./min for 10 min. The supernatant was collected through a Millipore filter with 0.22-μm pore size and assayed for each model drug concentration by UV spectrophotometer. The detection of each model drug was performed at 290 nm for PRC, 242 nm for AAP, 271 nm for THP, 255 nm for METP, ETHP, and PROP, and 316 nm for U-78875 (Table 1).

2.3. Preparation of sustained release matrix tablets

Tablets were formulated with HPMC 2910 4000 cps and lactose (2.1:1) as drug release controlling agents, and contained 15 mg of PRC, AAP, THP, ETHP, METHP, PROP or U-78875; the total tablet weight was 200 mg. To maintain matrix integrity as device formulation, the content of model drug was kept somewhat low (7.5 w/w% per tablet) for each formulation. To remove the different particle size effects of the bulk model drug, tablets were prepared by granulating the model drug with corn starch using a wet granulation technique and all granules were sieved with 150-μm mesh, then blending the granulated material with the HPMC and lactose. The blended materials were compressed into tablets with flat-faced round (8 mm diameter) tooling.

Seven types of sustained release matrix tablets including 15 mg of each model drug were obtained with the following formulation codes; PRCSR including procaine hydrochloride anhydrous; AAPSR including acetaminophen; THPSR including theophylline; METPSR including methyl-paraben; ETHPSR including ethyl-paraben; PROPSR including propyl-paraben; and U-78875SR including U-78875.

2.4. Estimation of medium infiltration into matrix tablet

To determine the medium infiltration into the matrix tablet, the core (dry portion) weight of tablet after immersing in the medium was measured as illustrated in Scheme 1A, which is a modified method from a previous report (Tahara et al., 1995). In this part of the study, placebo tablets without the model drug and keeping the same content ratio of other ingredients and tablet weight, were employed along with the tested sample tablet. Measurement procedures and data analysis were carried out as follows. A tablet (initial weight, W_i) was placed in a basket equipped with a dissolution tester (described in Section 2.6 which was immersed in the dissolution

medium (JP second disintegration medium, pH 6.8). The tablet was lifted from the medium at designated time intervals, and the swollen HPMC gel layer at the swelling front in the matrix manually removed. The core (dry portion) weight (W_{co}) of tablet was determined by semimicro electric balance (Mettler AE240, Greifnsee, Switzerland). One tablet was used for each testing run, and three tablets for each formulation were examined.

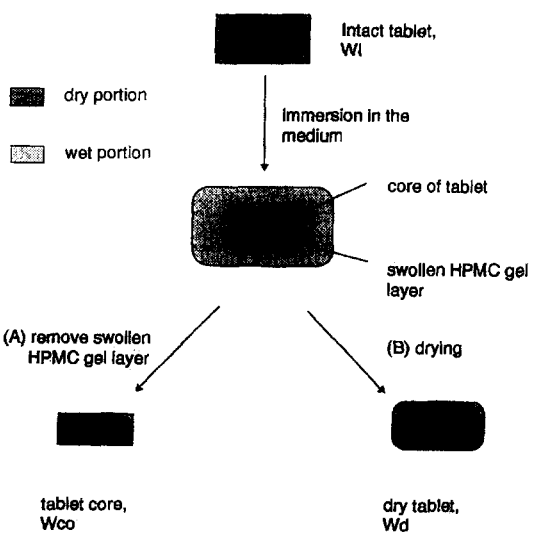
To estimate the degree of medium infiltration (Mi, %), Eq. (1) was employed for data analysis:

$$Mi = (W_i - W_{co})/W_i \times 100 \quad (1)$$

where W_i is the initial weight of the matrix tablet; and W_{co} is the core (dry portion) weight of tablet after immersing in the medium.

2.5. Estimation of erosion of matrix tablet

To estimate the overall erosion of the matrix tablet, the dry weight of tablet after immersing in the medium was measured as illustrated in Scheme 1B, which is described in a previous report (Tahara et al., 1995). In this part of the study, placebo tablets without model drug were also employed. The testing apparatus and testing conditions used were the same as that in Section 2.4. The tablet was lifted from the medium at designated time intervals, and the dry weight (W_d) of tablet was determined using an infrared moisture meter (Electric Moisture Balance; Model FD-220, Kett-Kagaku, Tokyo, Japan). For the drying of the tablet, a temperature of 120 ± 0.5°C was adopted, and the end of drying was defined when the ratio of decreasing weight of tablet was < 0.5% for 5 min. One tablet was used for each testing run, and three tablets were examined for each formulation.



Scheme 1. Illustration of the measurement procedures of medium infiltration into matrix tablet (A), and erosion of matrix tablet (B).

To estimate the overall erosion of matrix tablet, the degree of erosion (Er, %) was calculated with Eq. (2):

$$Er = (W_i - W_d)/W_i \times 100 \quad (2)$$

where W_i is the initial weight of matrix type tablet and W_d is the dry weight of tablet after immersing in the medium.

2.6. In vitro dissolution study

The in vitro dissolution study was conducted according to the JP rotary basket method using the following apparatus and conditions. The dissolution tester equipped with an autosampler (Toyama Sangyo Co., Ltd., Tokyo, Japan) was connected to a UV-spectrophotometer (Shimadzu Seisakusyo, Kyoto, Japan). A 900-ml aliquot of JP second disintegration medium was used, pH 6.8 and at 37°C and the rotation speed was adjusted to 100 rev./min. The wavelength used for the detection of each dissolved model drug is listed in Table 1. One tablet from each formulation was used for each drug release testing run, and three tablets were examined from each formulation. The dissolution profile of each model drug was expressed as the mean ± S.D. of the percentage of drug dissolved as a function of time.

3. Results and discussion

3.1. Model-independent analysis of medium infiltration, tablet erosion and dissolution profiles

Seven model drugs with different solubilities

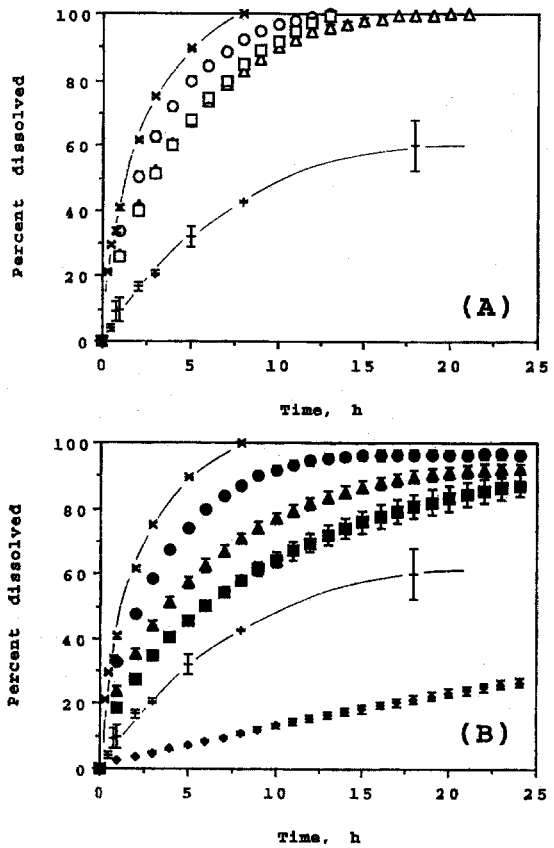


Fig. 1. Profiles of medium infiltration into the matrix tablets (×) from Eq. (1), erosion of matrix tablets (+) from Eq. (2), and dissolution of model drugs from matrix type tablets with formulation code PRCSR (○), AAPSR (△), and THPSR (□) in (A); METPSR (●), ETHPSR (▲), PROPSR (■) and U-78875SR (◆) in (B). Each value represents the mean ± S.D. (n = 3).

(Table 1) were used in this study. The dissolution profiles of model drug, estimated medium infiltration profile into matrix tablet, and the estimated overall erosion profile of the matrix tablet are shown in Fig. 1A,B. The drug dissolution profiles, except for that of U-78875SR, were observed between the medium infiltration profile and the erosion profile of matrix tablet.

To analyze the relationship between the solubility of model drugs and the apparent overall dissolution rate, in vitro mean dissolution times (MDT) which are the model-independent characteristics based on moment analysis, were calculated with Eq. (3) (Tanigawara et al., 1982a,b):

$$MDT = \int_0^\infty t(dm/dt)dt \Big/ \int_0^\infty (dm/dt)dt \quad (3)$$

where m is the mass of the model drug dissolved in the solution at time t.

Further, to investigate the relationship between the apparent overall dissolution rate (MDT) of the model drug, the medium infiltration rate into the matrix and the erosion rate of the matrix tablet, we expanded the above model-independent moment analysis to include the latter two parameters; i.e. mean medium infiltration time (MIT) and mean tablet erosion time (MET) defined by Eqs. (4) and (5), respectively:

$$MIT = \int_0^\infty t(dMi/dt)dt \Big/ \int_0^\infty (dMi/dt)dt \quad (4)$$

where Mi is the degree of medium infiltration at time t calculated from Eq. (1) and

$$MET = \int_0^\infty t(dEr/dt)dt \Big/ \int_0^\infty (dEr/dt)dt \quad (5)$$

where Er is the degree of tablet erosion at time t calculated from Eq. (2).

The MDT values for each model drug obtained by calculation are summarised with the time required for model drug dissolution of 25%, 50% and 75% ($T_{25\%}$, $T_{50\%}$ and $T_{75\%}$) in Table 2, and the MIT and MET values obtained by calculation are summarised with the time required for medium infiltration of 25%, 50% and 75% ($I_{25\%}$, $I_{50\%}$ and $I_{75\%}$) and the time required for tablet erosion of 25%, 50% and 75% ($E_{25\%}$, $E_{50\%}$ and $E_{75\%}$) in Table 3. The MDT is the value which indicates the overall behavior of numerous drug molecules, and which has its own dissolution probability. The MIT and MET are also the values which indicate the overall behavior of the medium infiltration into the matrix tablet and the erosion of matrix tablet as matrix device characteristics. Unfortunately, we could not calculate the $T_{25\%}$, $T_{50\%}$ and MDT values for U-78875, because only 25% was dissolved after 24 h. As shown in Tables 2 and 3, the MDT value of each model drug except for U-78875, and the MIT value are larger than $T_{50\%}$ or $I_{50\%}$ (MDT > $T_{50\%}$ or MIT > $I_{50\%}$), respectively. These results indicate that the dissolution or medium infiltration require longer times at later stages in comparison to the initial phase,

because the diffusion distance becomes longer with time. Conversely, the MET value was slightly lower than $E_{50\%}$ (MET < $E_{50\%}$), which indicates a faster erosion rate at later stages. Since, in the present formulation, erosion occurred only from the surface of the swollen layer, this phenomenon might be caused by an increase in surface area to volume ratio of the matrix tablet at the late stage.

When the mean swelling time (MSWT) is defined by Eq. (6):

$$MSWT = MET - MIT \quad (6)$$

this MSWT value indicates the overall mean time to maintain the integrity of the swollen gel layer, i.e. the reciprocal value of MSWT (1/MSWT) might parallel the swollen gel layer thickness. The calculated MSWT of the tested formulation was 10.00 h.

Further, when the mean diffusion time (MDFT) of the model drug is defined by Eq. (7):

$$MDFT = MDT - MIT \quad (7)$$

this MDFT value indicates the overall mean time required for diffusion in the swollen gel layer, i.e. MDFT can be explained as the apparent overall mean retention time of the model drug in the swollen gel matrix. The MDFT values obtained were 1.11 h for PRC, 2.18 h for AAP, 2.39 h for THP, 1.16 h for METP, 3.32 h for ETHP and 6.70 h for PROP, respectively.

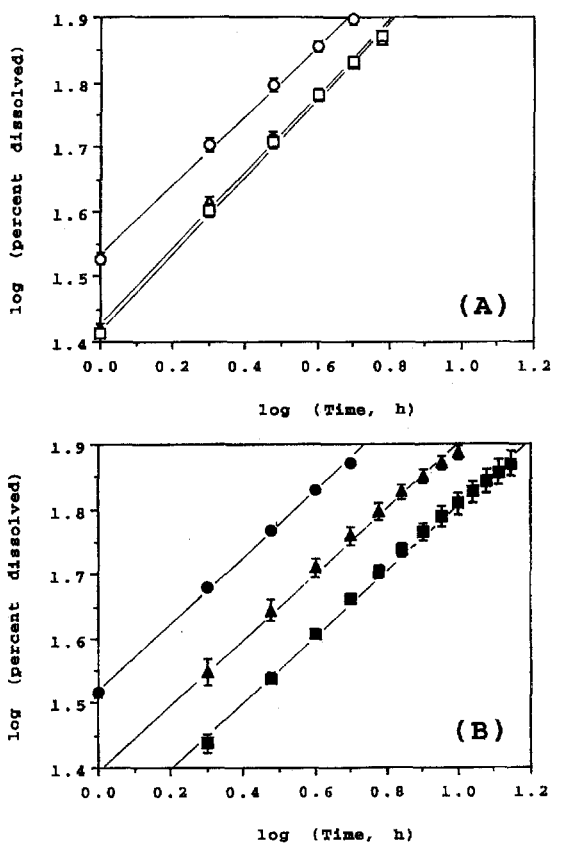


Fig. 2. Plots of log value of percent of model drug dissolved from matrix type tablets with formulation code PRCSR (○), AAPSR (△) and THPSR (□) in (A); METPSR (●), ETHPSR (▲) and PROPSR (■) in (B) against log value of time calculated with Eq. (9). Each value represents the mean ± S.D. (n = 3).

3.2. Model analysis of dissolution profiles

To clarify the release exponent for each model drug, the log value of the percentage drug dissolved was plotted against the log of time for each drug according to Eq. (9) which is derived from Eq. (8) (Peppas, 1985):

$$Mt/Min = kt^n \quad (8)$$

$$\log(Mt/Min) = \log k + n \log t \quad (9)$$

where Mt/Min is the percent of model drug dissolved; k is the constant in the incorporating structure as well as geometric characteristics of the release device (HPMC matrix); and n is the release exponent that indicates the release mechanism. As shown in Fig. 2A,B, straight lines were observed for each model drug (graph for U-78875SR was not shown). As listed in Table 4, since the slope of straight lines in Fig. 2 (n value) was about 0.5 except for the U-78875SR which was 0.79, the apparent dissolution of those six drugs from the matrix tablets seems to occur according to Higuchi's square root law described in Eqs. (10) and (11) (Higuchi, 1963):

$$Qd = Sq[\tfrac{DV_I}{\tau}(2A - V_I Cs)Cst]^{1/2} \quad (10)$$

$$= k_1 t^{1/2} \quad (11)$$

where Qd is the amount of drug released after time t; D is the diffusitivity of the drug in the infiltrated medium in the matrix; τ is the tortuosity factor of the diffusion system in the swollen matrix; A is the total amount of drug present in

Table 2
Model-independent release parameters of model drug from sustained release (SR) matrix tablet

Formulation code	Dissolution time, h			MDT, h
	$T_{25\%}$	$T_{50\%}$	$T_{75\%}$	
PRCSR	0.62 ± 0.02	1.98 ± 0.09	4.42 ± 0.19	3.16 ± 0.11
AAPSR	0.93 ± 0.02	2.80 ± 0.08	6.28 ± 0.28	4.23 ± 0.25
THPSR	0.96 ± 0.02	2.90 ± 0.12	6.11 ± 0.23	4.44 ± 0.20
METPSR	0.64 ± 0.02	2.19 ± 0.03	5.13 ± 0.07	3.21 ± 0.06
ETHPSR	1.09 ± 0.12	3.81 ± 0.24	9.26 ± 0.59	5.37 ± 0.09
PROPSR	1.70 ± 0.09	5.92 ± 0.26	14.74 ± 1.63	8.75 ± 0.59
U-78875SR	21.83 ± 1.53	—	—	—

MDT, mean dissolution time of model drug from Eq. (3); each value represents the mean ± S.D. (n = 3).

the matrix; Cs is the solubility of the drug in the infiltrated medium; V_I is the porosity (interspace) volume of the matrix; Sq is the total exposed area; and k_1 is the apparent dissolution rate constant of the model drug. These results indicate the diffusion controlled release mechanisms for these six drugs. When the percentage of drug dissolved was plotted against the square root of time according to Eq. (11) (Fig. 3A,B), a good straight line was obtained for each model drug except for U-78875 and the slope represents the k_1 value. Because the apparent dissolution of the six drugs occurred according to Higuchi's equation, the mechanism behind the release of these drugs can be explained by the following process: (1) infiltration of medium into the matrix tablet; (2) hydration and swelling of the matrix; (3) dissolution of drug in the matrix, and (4) diffusion of the solubilized drug through interstitial channels. Thus, drugs are released from the matrix in the soluble condition rather than the particulate condition. The apparent release is dependent on the solubility of the drug in the medium as described in Eq. (11). The k_1 value of each drug is summarized in Table 4.

3.3. Formulation optimization of the HPMC matrix sustained release tablet

Regarding poorly water soluble drugs such as U-78875, the dissolution of the drug occurs mainly from drug particles which are released from the tablet by erosion as proposed previously (Tahara et al., 1995). The dissolution of the poorly soluble drug is delayed in comparison to the erosion of matrix tablet. After the drug particles are released, dissolution occurs according to the Hixson–Crowell cube root law, and the dissolution from the drug particles is dependent on the initial characteristics of the drug particle itself with crystal condition (Hixson and Crowell, 1931). Thus, the erosion rate of the matrix tablet could control the total dissolution rate of poorly soluble drugs such as U-78875 from the matrix tablets.

When $T_{25\%}$, $T_{50\%}$ and $T_{75\%}$ values are plotted against the log value of solubility of each model drug except for U-78875 (Fig. 4), T values decrease according to the increase in solubility of the model drug. In the case $T_{75\%}$ in particular, it was greatly influenced by the solubility of the model drug. Furthermore, when the MDT values are plotted against the log value of solubility of each model drug (Fig. 5), the same phenomenon was observed, i.e. the MDT value decreases according to the increase in solubility of the model drug between the time range of MIT and MET values.

In the formulation used in this study, the $T_{25\%}$, $T_{50\%}$, $T_{75\%}$ and MDT values of those model drugs such as METP, ETHP and PROP, whose solubility is between 0.5 mg/ml and 5 mg/ml, decreased according to the increase in solubility. However, when the solubility of the model drug is >5 mg/ml (PRC, AAP and THP), the $T_{25\%}$, $T_{50\%}$, $T_{75\%}$, and MDT values are not influenced so much by their solubility. These values indicated

Table 3
Model-independent medium infiltration and tablet erosion parameters

	Medium infiltration time, h			MIT, h
	$I_{25\%}$	$I_{50\%}$	$I_{75\%}$	
Mi	0.36 ± 0.01	1.44 ± 0.01	3.01 ± 0.07	2.05 ± 0.00
	Tablet erosion time, h			MET, h
	$E_{25\%}$	$E_{50\%}$	$E_{75\%}$	
Er	3.80 ± 0.37	13.09 ± 2.28	- -	12.05 ± 2.32

MIT, mean medium infiltration time from Eq. (4); MET, mean tablet erosion time from Eq. (5); each value represents the mean ± S.D. (n = 3).

the similar values of $I_{25\%}$, $I_{50\%}$, $I_{75\%}$ and MIT (Tables 2 and 3). These highly soluble drugs dissolve immediately in the infiltrated medium in the matrix, and then quickly diffuse out from the matrix tablet. Because the content ratio of model drug in the matrix tablet used in this study is somewhat low (7.5 w/w%) PRC, AAP, and THP did not reach the solubility of each drug in the infiltrated medium. Thus, when the content ratio of the model drug increases, the dissolution rate might drop depending on the drug solubility.

When the values of the apparent dissolution rate constant (k_1 from Eq. (11)) of the model drug, the slope of straight lines in Fig. 3, are plotted against the log value of solubility (Fig. 6), k_1 values increase according to the increase in solubility of the model drugs whose solubilities are between 0.5 mg/ml and 5 mg/ml, and become constant value when solubility is > 5 mg/ml.

The relationships between drug solubility and drug release characteristics from the tested formulations obtained from both model-independent moment analysis and Higuchi-type model analysis are similar. These results on the effect of drug solubility are consistent with previously reported results (Ford et al., 1985a,b,c, 1987). The relationships between solubility of drug (Cs), the total amount of drug present in a tablet (A) and the porosity (interspace) volume of the matrix (V_I) described in Eq. (10) are as follows: in case (1), $Cs \ll A/V_I$ (U-78875), in case (2), $Cs \leq A/V_I$ (METP, ETHP and PROP), and in case (3), $Cs \geq A/V_I$ (PRC, AAP and THP). To control the dissolution rate of drug from the matrix tablet, the most effective approach is to control the erosion rate of the matrix in case (1), and to control the medium infiltration into the matrix in cases (2) and (3). In case (2) in particular, the amount of infiltrated medium might be the dominant factor on the dissolution rate, while in case (3), the infiltration rate of medium is the dominant factor. Furthermore, from the turning point ($Cs = A/V_I$) in Figs. 4 and 5, and Fig. 6, (Cs = 5 mg/ml) and the total amount of drug present in the matrix (A = 15 mg), the apparent overall effective porosity (interspace) volume (V_I) of the tested formulation could be estimated at about 3 ml.

4. Conclusion

The model-independent moment parameters, MDT, MIT, MET, MSWT and MDFT were calculated for the investigation of the effect of drug solubility on its release rate from HPMC matrix SR tablets. These model-independent parameters were directly comparable, and applicable to compare the device characteristics, such as medium infiltration rate or erosion rate of matrix and drug release characteristics. Further, the moment parameters from different types of formulation could also be compared. These model-independent moment analytical approaches allow us to optimize SR matrix formulations in the development stage.

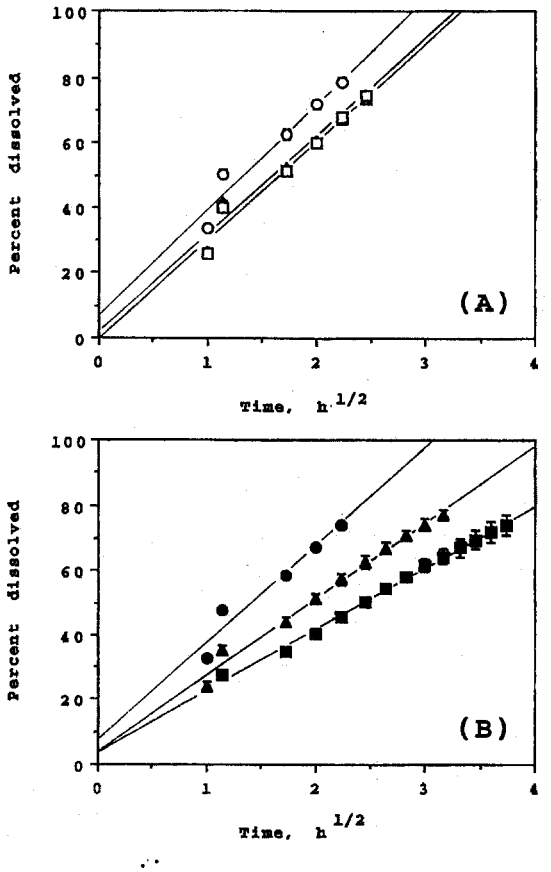


Fig. 3. Plots of percent of model drug dissolved from matrix tablet with formulation code PRCSR (○), AAPSR (△) and THPSR (□) in (A); METPSR (●), ETHPSR (▲) and PROPSR (■) in (B) against square root of time calculated with Eq. (11). Each value represents the mean ± S.D. (n = 3).

Table 4
Model parameters for the dissolution of model drug from sustained release (SR) matrix tablet

Formulation code	n	k_1
PRCSR	0.53 ± 0.01	36.76 ± 0.58
AAPSR	0.57 ± 0.00	32.58 ± 0.67
THPSR	0.59 ± 0.00	33.66 ± 0.90
METPSR	0.51 ± 0.01	33.74 ± 0.49
ETHPSR	0.51 ± 0.02	24.83 ± 0.52
PROPSR	0.51 ± 0.01	20.10 ± 1.29
U-78875SR	0.79 ± 0.02	—

n, release exponent from Eq. (9), slope of straight line in Fig. 2; k_1, apparent dissolution rate constant of model drug from Eq. (11), slope of straight line in Fig. 3; each value represents the mean ± S.D. (n = 3).

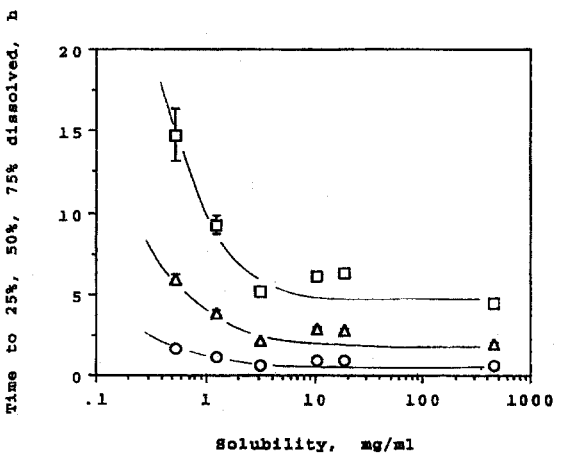


Fig. 4. Plots of values of $T_{25\%}$ (○), $T_{50\%}$ (△) and $T_{75\%}$ (□) against log value of solubility of model drug. Each value represents the mean ± S.D. (n = 3).

In conclusion, if the physico-chemical properties of drugs such as solubility and device characteristics are clarified, the dissolution rate of the drug and its controlling method can be predicted using model-independent moment analysis as well as model analysis. These approaches might provide us with useful parameters in the development and optimization stage of SR formulations.

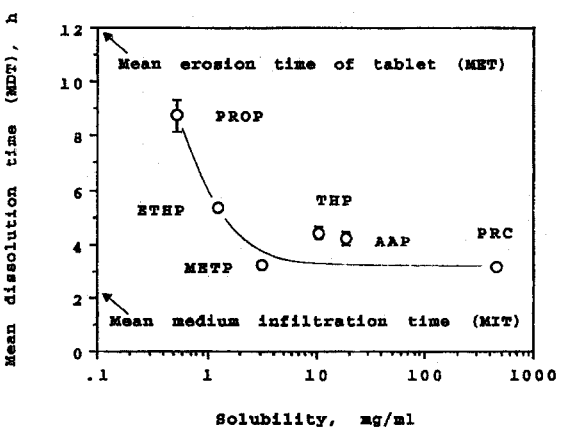


Fig. 5. Plots of MDT values calculated with Eq. (3) against log value of solubility of model drug. MIT and MET values were calculated with Eqs. (4) and (5), respectively. Each value represents the mean ± S.D. (n = 3).

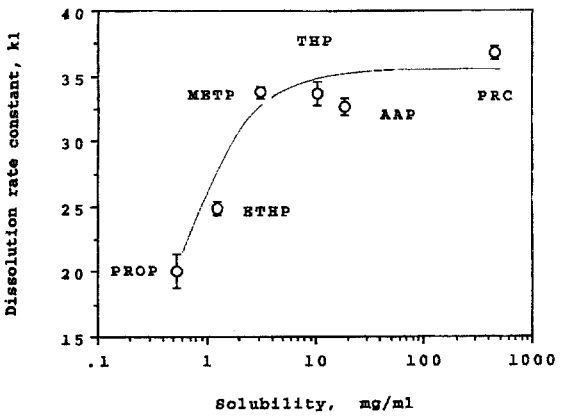


Fig. 6. Plots of apparent dissolution rate constant of model drug (k_1) calculated with Eq. (11) against log value of solubility of model drug. Each value represents the mean ± S.D. (n = 3).

References

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

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangalli, M.E., Peppas, N.A. and La Manna, A., Drug release modulation by physical restriction of matrix swelling. *Int. J. Pharm.*, 63 (1990) 43–48.

Colombo, P., Catellani, P.L., Peppas, N.A., Maggi, L. and Conte, U., Swelling characteristics of hydrophilic matrices for controlled release. New dimensionless number to describe the swelling and release behavior. *Int. J. Pharm.*, 88 (1992) 99–109.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Formulation of sustained release promethazine hydrochloride tablets 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. and Hogan, J.E., Dissolution of a poorly water soluble drug, indomethacin, from hydroxypropylmethylcellulose controlled release tablets. *J. Pharm. Pharmacol.*, 37 (1985c) 33P.

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

Ford, J.L., Mitchell, K., Rowe, P., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Mathematical modelling of drug release from hydroxypropylmethylcellulose: effect of temperature. *Int. J. Pharm.*, 71 (1991) 95–104.

Harland, R.S., Gazzaniga, A., Sangalli, M.E., Colombo, P.C. and Peppas, N.A., Drug/polymer matrix swelling and dissolution. *Pharm. Res.*, 5 (1988) 488–494.

Higuchi, T., Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Higuchi, W.I., Analysis of data on the medicament release from ointments. *J. Pharm. Sci.*, 52 (1962) 802–804.

Hixson, A.W. and Crowell, J.H., *Ind. Eng. Chem.*, 23 (1931) 923.

Hogan, J.E., Hydroxypropylmethylcellulose sustained release technology. *Drug Dev. Ind. Pharm.*, 15 (1989) 975–1000.

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

Langer, R.S. and Peppas, N.A., Present and future applications of biomaterials in controlled drug delivery. *Biomaterials*, 2 (1987) 201–214.

Lapidus, H. and Lordi, N.G., Some factors affecting the release of water-soluble drug from a compressed hydrophilic matrix. *J. Pharm. Sci.*, 55 (1966) 840–843.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.*, 57 (1968) 1292–1301.

Lee, P.I. and Peppas, N.A., Prediction of polymer dissolution in swellable controlled-release systems. *J. Control. Release*, 6 (1987) 207–215.

Papadimitriou, E., Buckton, G. and Efentakis, M., Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 98 (1993) 57–62.

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta. Helv.*, 60 (1985) 110–111.

Peppas, N.A. and Ritgar, P.L., A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release*, 5 (1987a) 23–36.

Peppas, N.A. and Ritgar, P.L., A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J. Control. Release*, 5 (1987b) 37–42.

Peppas, N.A. and Sahlin, J.J., A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int. J. Pharm.*, 57 (1989) 169–172.

Ranga Rao, K.V. and Padmalatha Devi, K., Swelling controlled-release systems: recent developments and applications. *Int. J. Pharm.*, 48 (1988) 1–13.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P., Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. *J. Control. Release*, 12 (1990) 133–141.

Shah, A.C., Britten, N.J., Olanoff, L.S. and Basalamenti, N.J., Gel-matrix systems exhibiting bimodal controlled release for oral drug delivery. *J. Control. Release*, 9 (1989) 169–174.

Skoug, J.W., Borin, M.T., Fleishaker, J.C. and Cooper, A.M., In vitro and in vivo evaluation of whole and half tablets of sustained release adinazolam mesylate. *Pharm. Res.*, 8 (1991) 1482–1488.

Tahara, K., Mikawa, M., Yokohama, S. and Nishihata, T., Characteristics of intestinal absorption of adinazolam and in vivo evaluation of oral sustained release tablets of adinazolam in beagle dogs. *Int. J. Pharm.*, 99 (1993) 311–320.

Tahara, K., Yamamoto, K. and Nishihata, T., Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. *J. Control. Release*, 35 (1995) 59–66.

Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno, T., New method for the evaluation of in-vitro dissolution time and disintegration time. *Chem. Pharm. Bull.*, 30 (1982a) 1088–1090.

Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno, T., Moment analysis for the separation of mean in vivo disintegration dissolution, absorption and disposition time of ampicillin products. *J. Pharm. Sci.*, 71 (1982b) 1129–1133.

Wan, L.S.C., Heng, P.W.S. and Wong, L.F., The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. *Int. J. Pharm.*, 73 (1991) 111–116.