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A theoretical approach to evaluate the release rate of acetaminophen from erosive wax matrix dosage forms

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ABSTRACT

To predict drug dissolution and understand the mechanisms of drug release from wax matrix dosage forms containing glyceryl monostearate (GM; a wax base), aminoalkyl methacrylate copolymer E (AMCE; a pH-dependent functional polymer), and acetaminophen (APAP; a model drug), we tried to derive a novel mathematical model with respect to erosion and diffusion theory. Our model exhibited good agreement with the whole set of experimentally obtained values pertaining to APAP release at pH 4.0 and pH 6.5. In addition, this model revealed that the eroding speed of wax matrices was strongly influenced by the loading content of AMCE, but not that of APAP, and that the diffusion coefficient increased as APAP loading decreased and AMCE loading increased, thus directly defining the physicochemical properties of erosion and diffusion. Therefore, this model might prove a useful equation for the precise prediction of dissolution and for understanding the mechanisms of drug release from wax matrix dosage forms.

Recently, mathematical modeling for predicting drug dissolution, as well as for understanding the mechanisms of drug release, has attracted attention in pharmaceutical research (Siepmann and Siepmann, 2008). In this study, we aimed to derive a mathematical model of drug release kinetics for wax matrix dosage forms because these formulations have a number of advantages: organic solvent-free preparation, non-toxicity and cost effectiveness (Shiino et al., 2010).

Generally, drug diffusion within a matrix has been considered to be the rate-controlling step of drug release from a wax matrix, and many studies have investigated drug release kinetics from wax matrices on the basis of Fick's second law of diffusion (Crowley et al., 2004; Cheboyina and Wyandt, 2008). However, Yajima et al. reported that when aminoalkyl methacrylate copolymer E (AMCE, a pH-dependent functional polymer) was included in wax matrix formulations with glyceryl monostearate (GM, a wax base), isokinetic erosion derived from the polymer characteristics was the rate-controlling step of drug release (Yajima et al., 1996). Further, they derived a mathematical model similar to the cube-root law (Hixson and Crowell, 1931). However, the applicability of Yajima's model is limited to a narrow set of conditions, such as the initial stages of dissolutions; for long dissolution times, diffusion becomes the dominant step controlling drug release. Therefore, development of a new mathematical model that accounts for both erosion and diffusion is warranted.

If we restrict ourselves to cases where the diffusion is radial, the diffusion equation for a sphere takes the form (Crank, 1975)

$$\frac{\partial c}{\partial t} = \frac{1}{r^2}\left\{\frac{\partial}{\partial r}\left(Dr^2\frac{\partial c}{\partial r}\right)\right\}. \quad (1)$$

Here, c denotes the concentration of drug as a function of time t and radius r within a spherical wax matrix particle. D is the diffusion coefficient of drug. By setting the initial and boundary conditions as

$$C|_{t=0} = C_0, \quad (2)$$

$$\left.\frac{\partial c}{\partial r}\right|_{r=0} = 0, \quad (3)$$

and

$$C|_{r=a(t)} = 0. \quad (4)$$

Eq. (1) can be solved exactly to give

$$c(r,t) = \frac{-2c_0a_0(a(t))^2}{\pi r}\sum_{n=1}^{\infty}\frac{(-1)^n}{n}\exp\left(-\frac{n^2\pi^2}{(a(t))^2}Dt\right)\sin\frac{n\pi}{a(t)}r. \quad (5)$$

Here, c_0 represents the initial drug concentration within a spherical wax matrix particle; $a(t)$ and a_0 represent the distance of the eroding front from the center of the wax matrix particle at time t and the initial time, respectively. According to Yajima et al., the eroding front progresses at a constant speed given by

$$a(t) = a_0 - kt, \quad (6)$$

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Table 1
Selected variables and levels for preparation of wax matrix particles.

Level	Factor x_1: APAP loading (%)	Factor x_2: AMCE loading (%)	Factor x_3: Particle radius (μm)
−1	10	0	125
0	20	5	180
1	30	10	235

where k is the erosion rate coefficient. Hence, the amount of drug within a wax matrix particle is found by integrating Eq. (5):

$$M(t) = \frac{8c_0a_0(a(t))^2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n^2}\ \exp\left(-\frac{n^2\pi^2}{(a(t))^2}Dt\right). \quad (7)$$

For m wax matrix particles having equal diameter, the total amount of drug within the particles is given by

$$M_{total} = mM, \quad (8)$$

and the initial total amount of drug is

$$M_{total|t=0} = \frac{4}{3}m\pi a_0^3c_0. \quad (9)$$

Therefore, the drug release ratio at time t is given by

$$R(t) = 1 - \frac{6(a(t))^2}{\pi^2a_0^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\ \exp\left(-\frac{n^2\pi^2}{(a(t))^2}Dt\right). \quad (10)$$

Hereinafter, Eq. (10) is referred to as the hybrid model, which we compare with the conventional pure diffusion model devised by Crank (1975):

$$R_d(t) = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\ \exp\left(-\frac{n^2\pi^2}{a_0^2}Dt\right). \quad (11)$$

Eqs. (10) and (11) were fitted to the set of experimentally obtained values by the nonlinear least-squares method. The Levenberg–Marquardt algorithm was used in the numerical calculations.

Wax matrix particles were prepared by a spray congealing technique. Acetaminophen (APAP), a model drug, was dried for 12 h at 60 °C and milled in a vibrating sample mill (TI-300, Heiko Seisakusho, Japan); the milled APAP was immediately sieved (100 mesh). GM was melted at 115 ± 5 °C, and AMCE was added into the molten GM. After AMCE was completely dissolved, sieved APAP was added into the GM solution. The mixture was then agitated until APAP was sufficiently dispersed. The APAP dispersion was dropped onto a metal disk rotating at about 1700 rpm. Then, the APAP dispersion was sprayed and solidified into spherical particles. The prepared particles were incubated for 24 h at 40 ± 0.5 °C, and were stored more than 1 week at room temperature thereafter. After incubation, APAP-loaded wax matrix particles were sieved. Formulations of wax matrix particles were prepared according to a three-factor, three-level Box–Behnken design. The correlations between levels and each independent factor are listed in Table 1. Each preparation was adjusted with GM to 100%. Table 2 lists the experimentally determined particle radius and circularity for each batch. From Table 2, the particle circularity for every batch was found to be ~1; thus, all the prepared particles were deemed to be sufficiently spherical for analysis with our hybrid model.

The release of APAP from the particle was examined in accordance with the paddle method listed in the JP (15th edition). The test solution was either 900 mL pH 4.0 acetate buffer solution or pH 6.5 phosphate buffer solution, and was maintained at 37.0 ± 0.5 °C throughout the experiment. Figs. 1 and 2 show the experimentally obtained drug release behavior from wax matrix particles at pH 6.5 and pH 4.0. Here, the solid and dashed curves represent the results

Table 2
Box–Behnken experimental design and results of physicochemical properties such as particle radius and circularity.

Batch	Factor			Particle radius (μm)	Circularity
	x_1	x_2	x_3		
1	−1	−1	0	171.2 ± 14.0	0.963 ± 0.003
2	−1	0	−1	123.5 ± 12.2	0.944 ± 0.049
3	−1	0	1	232.2 ± 10.1	0.954 ± 0.007
4	−1	1	0	173.0 ± 20.2	0.948 ± 0.013
5	0	−1	1	234.1 ± 6.9	0.961 ± 0.004
6	0	−1	−1	127.8 ± 11.0	0.961 ± 0.006
7	0	1	1	240.0 ± 11.0	0.959 ± 0.010
8	0	1	−1	130.3 ± 9.6	0.964 ± 0.008
9	1	−1	0	177.8 ± 19.3	0.956 ± 0.004
10	1	0	−1	124.6 ± 10.1	0.960 ± 0.006
11	1	0	1	233.9 ± 9.5	0.940 ± 0.014
12	1	1	0	179.5 ± 20.6	0.966 ± 0.003
13–15	0	0	0	186.6 ± 18.2	0.963 ± 0.008

of fittings using Eqs. (10) and (11), respectively. In every case, agreement with the experimental values was better for the hybrid model (Eq. (10)) than the pure diffusion model (Eq. (11)). In order to quantitatively compare the goodness of fit, the residual sum of squares (RSS) values were calculated in each case, and the results are listed in Table 3. Here, all RSS values for the hybrid model are smaller than those for the pure diffusion model at each pH examined, suggesting that a better fitting was observed for the hybrid model. These results indicate that drug release kinetics was not controlled by

Table 3
Estimated residual sum of squares (RSS) values of the hybrid model and conventional pure diffusion model for each batch at pH 6.5 and pH 4.0.

Batch	pH 6.5		pH 4.0	
	Hybrid	Conventional	Hybrid	Conventional
1	9.69×10^{-4}	1.49×10^{-1}	1.11×10^{-3}	8.32×10^{-3}
2	4.15×10^{-2}	5.13×10^{-2}	1.16×10^{-2}	2.44×10^{-2}
3	1.36×10^{-2}	1.03×10^{-1}	7.73×10^{-3}	3.18×10^{-2}
4	3.28×10^{-2}	1.71×10^{-1}	3.24×10^{-3}	3.00×10^{-2}
5	4.34×10^{-6}	6.28×10^{-3}	2.42×10^{-5}	4.48×10^{-3}
6	4.90×10^{-4}	9.46×10^{-3}	3.29×10^{-4}	6.91×10^{-3}
7	4.88×10^{-3}	1.85×10^{-2}	2.31×10^{-3}	1.06×10^{-2}
8	6.67×10^{-3}	4.88×10^{-2}	1.29×10^{-3}	2.28×10^{-2}
9	4.54×10^{-5}	1.78×10^{-2}	8.88×10^{-5}	1.40×10^{-2}
10	1.40×10^{-2}	7.26×10^{-2}	1.98×10^{-2}	1.05×10^{-1}
11	8.80×10^{-3}	2.91×10^{-1}	7.02×10^{-3}	8.34×10^{-2}
12	3.00×10^{-3}	1.82×10^{-2}	5.22×10^{-3}	2.71×10^{-2}
13	7.89×10^{-3}	1.56×10^{-1}	1.94×10^{-2}	1.18×10^{-1}
14	9.39×10^{-3}	1.41×10^{-1}	2.84×10^{-2}	1.13×10^{-1}
15	6.09×10^{-3}	1.43×10^{-1}	2.27×10^{-2}	9.57×10^{-2}

Table 4
Estimated values of erosion rate coefficient k and diffusion coefficient D for each batch at pH 6.5 and pH 4.0.

Batch	k (μm/min)		D (μm²/min)	
	pH 6.5	pH 4.0	pH 6.5	pH 4.0
1	6.58×10^{-2}	4.12×10^{-2}	6.31×10^{-1}	8.97×10^{-1}
2	9.20×10^{-2}	1.01	1.09×10	6.48×10
3	1.05×10^{-1}	8.08×10^{-1}	6.20	5.57×10
4	3.94×10^{-1}	5.34	7.24	3.84×10
5	6.37×10^{-2}	5.43×10^{-2}	8.07×10^{-2}	1.16×10^{-1}
6	3.71×10^{-2}	2.97×10^{-2}	1.64×10^{-1}	1.70×10^{-1}
7	6.00×10^{-1}	2.98	9.86	2.15×10^{2}
8	1.52	1.08×10	1.86	9.74×10
9	1.10×10^{-1}	8.45×10^{-2}	4.81×10^{-2}	9.05×10^{-2}
10	1.44×10^{-1}	2.70	4.07	8.48
11	1.55×10^{-1}	1.06	1.57	1.96×10
12	5.09×10^{-1}	3.19	2.00	3.19×10
13	1.70×10^{-1}	9.11×10^{-1}	3.38	4.23×10
14	1.56×10^{-1}	9.69×10^{-1}	3.78	4.11×10
15	1.59×10^{-1}	7.98×10^{-1}	3.63	4.88×10

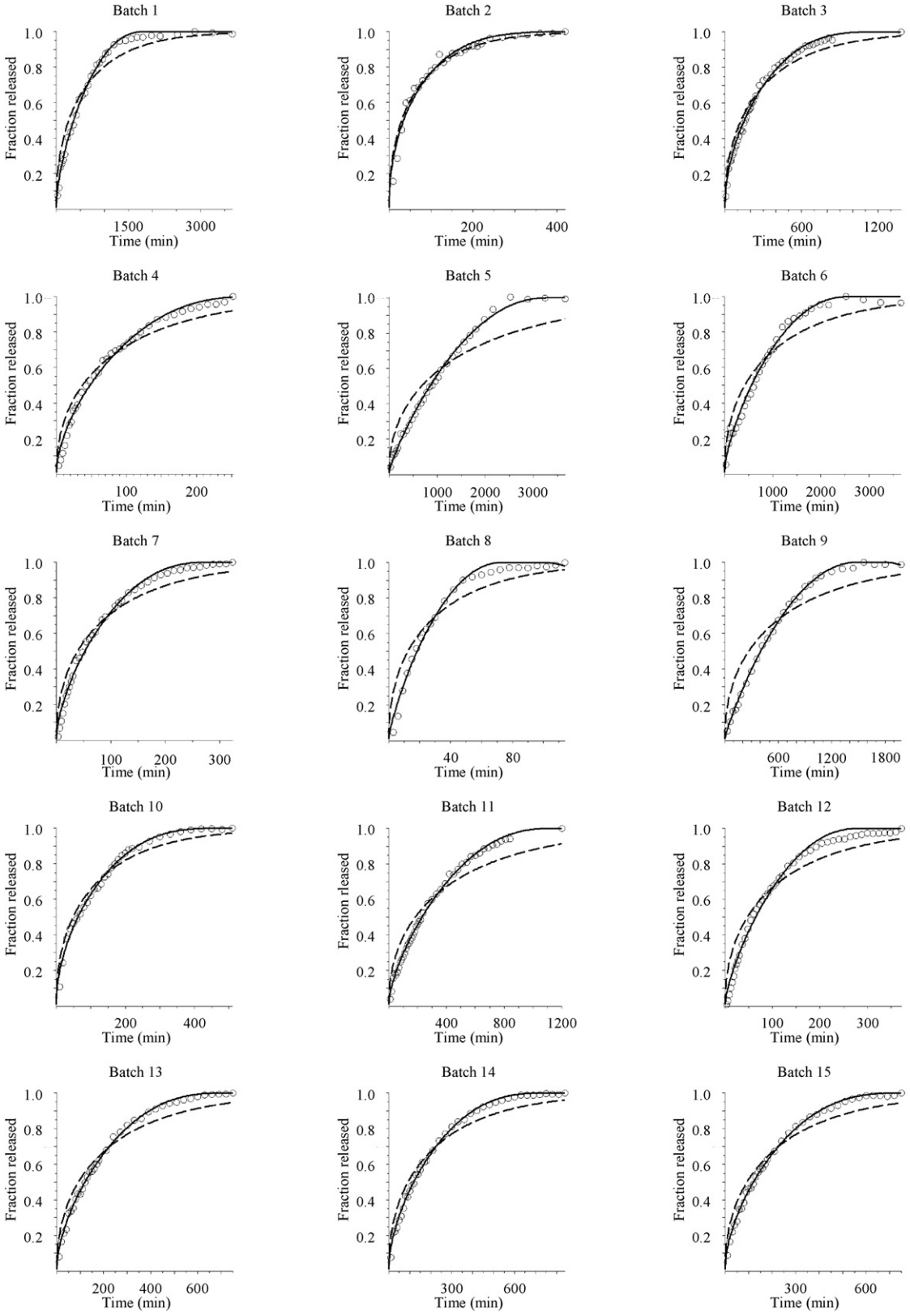

Fig. 1. Release behavior of APAP from wax matrix particles at pH 6.5. Symbols represent experimental values, solid curves represent results of fitting using Eq. (10), and dashed curves represent results of fitting using Eq. (11).

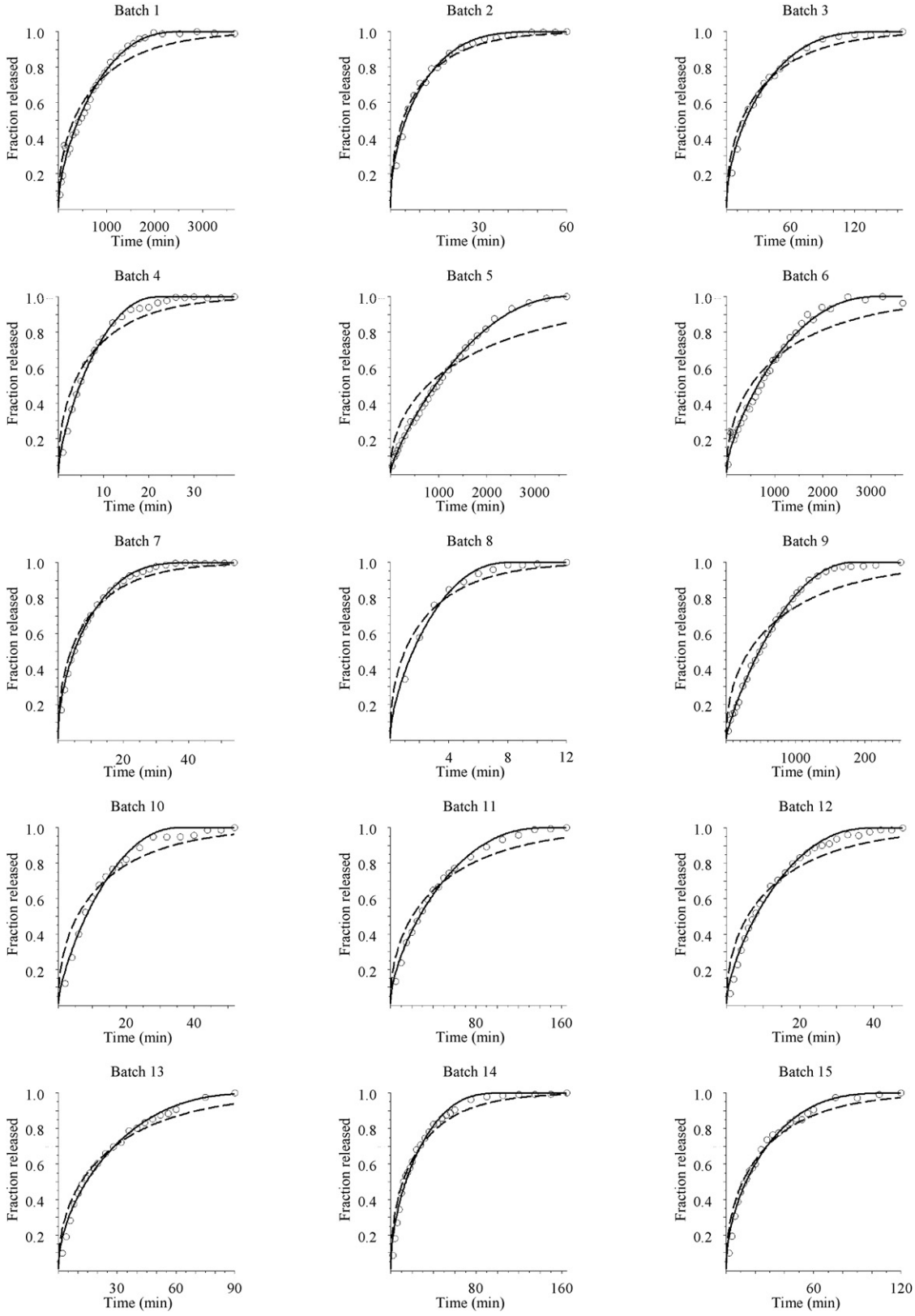

Fig. 2. Release behavior of APAP from wax matrix particles at pH 4.0. Symbol represents experimental values, solid curve represents the result of fitting using Eq. (10), and dashed curve represents the result of fitting using Eq. (11).

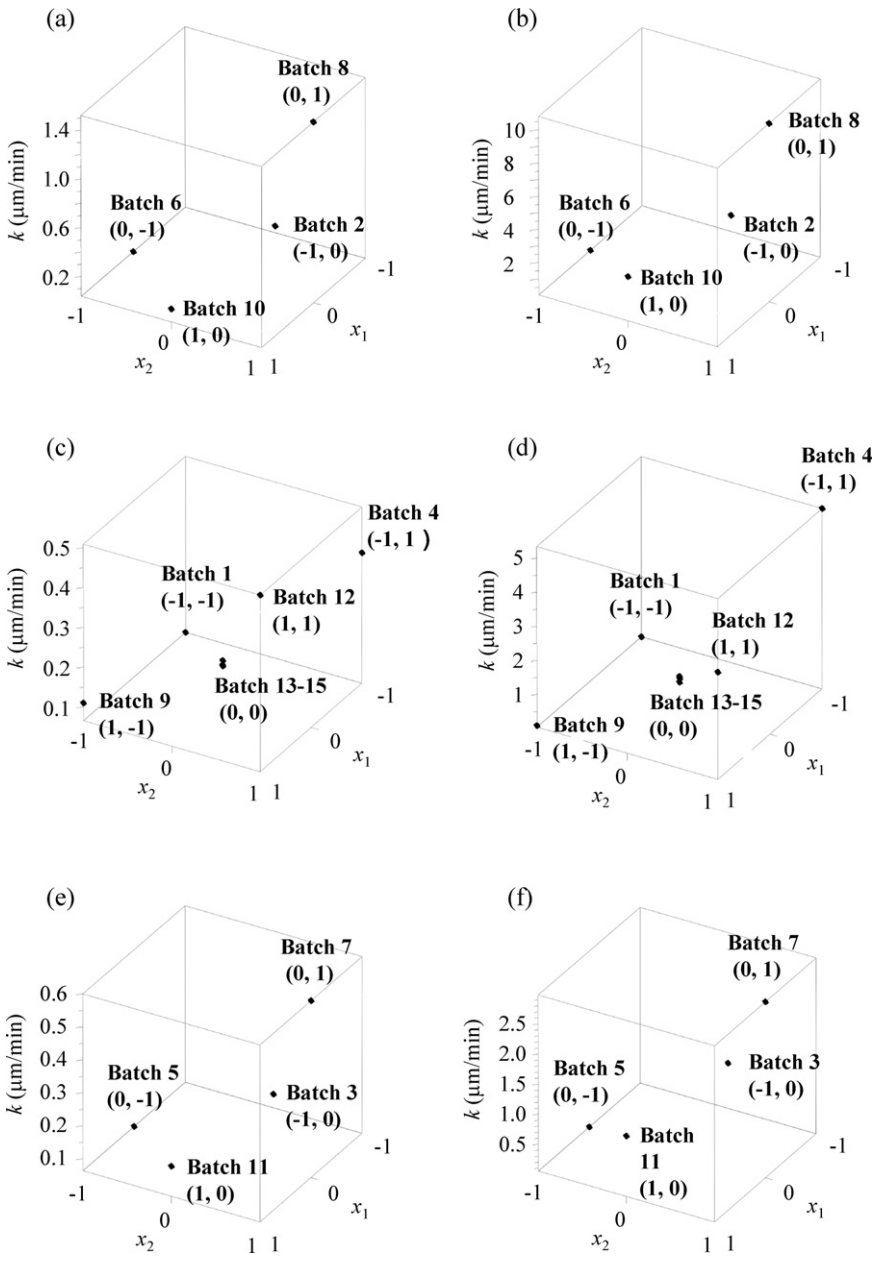

Fig. 3. Plots of estimated values of erosion rate coefficient k versus x_1 and x_2 for each batch. (a) $x_3 = -1$ and pH 6.5, (b) $x_3 = -1$ and pH 4.0, (c) $x_3 = 0$ and pH 6.5, (d) $x_3 = 0$ and pH 4.0, (e) $x_3 = 1$ and pH 6.5, and (f) $x_3 = 1$ and pH 4.0.

pure diffusion and that the hybrid model considering diffusion and erosion may be a superior.

Table 4 shows the erosion rate coefficient and diffusion coefficient obtained by fitting the hybrid model (Eq. (10)) to the experimentally obtained data. Fig. 3 shows plots of the erosion coefficient. Fig. 3(a) shows the estimated erosion coefficient values for batches 2, 6, 8, and 10, where the levels of particle radius (x_3) are -1 (125 μm). From the estimated erosion coefficients for batches 2 and 10, it can be seen that the erosion coefficient was not affected by the loading content of APAP (x_1); furthermore, from batches 6 and 8, the erosion coefficient can be seen to increase drastically with increasing loading content of AMCE (x_2). This can be explained by the physicochemical properties of AMCE. Because AMCE is more soluble in water than is GM, erosion of the matrix progressed as the proportion of AMCE was increased. This tendency can be seen in other cases (Fig. 3(b)–(f)). Fig. 4 shows the plots of the diffusion coefficient. Fig. 4(a) shows the estimated diffusion coefficient values for batches 2, 6, 8 and 10, where the levels of particle radius (x_3) are -1 (125 μm). For batches 2 and 10 (Fig. 4(a)), an increase in APAP loading (x_1) resulted in a decrease in the value of the diffusion coefficient. This might be explained by the relatively low dissolution rate of APAP. This low dissolution rate of APAP allows the structure of the wax matrix to be tight. Furthermore, an increase in AMCE (x_2) contributed to an increase in the diffusion coefficient. This might also be attributable to the solubility of AMCE in water. Dissolution and subsequent release of AMCE led to expansion of the water-filled network and increased the free volume available for drug diffusion. Then, drug diffuses readily within matrix. This tendency can be also seen in other cases (Fig. 4(b)–(f)).

In conclusion, the proposed hybrid model agreed well with experimental data and provided two parameters having physi-

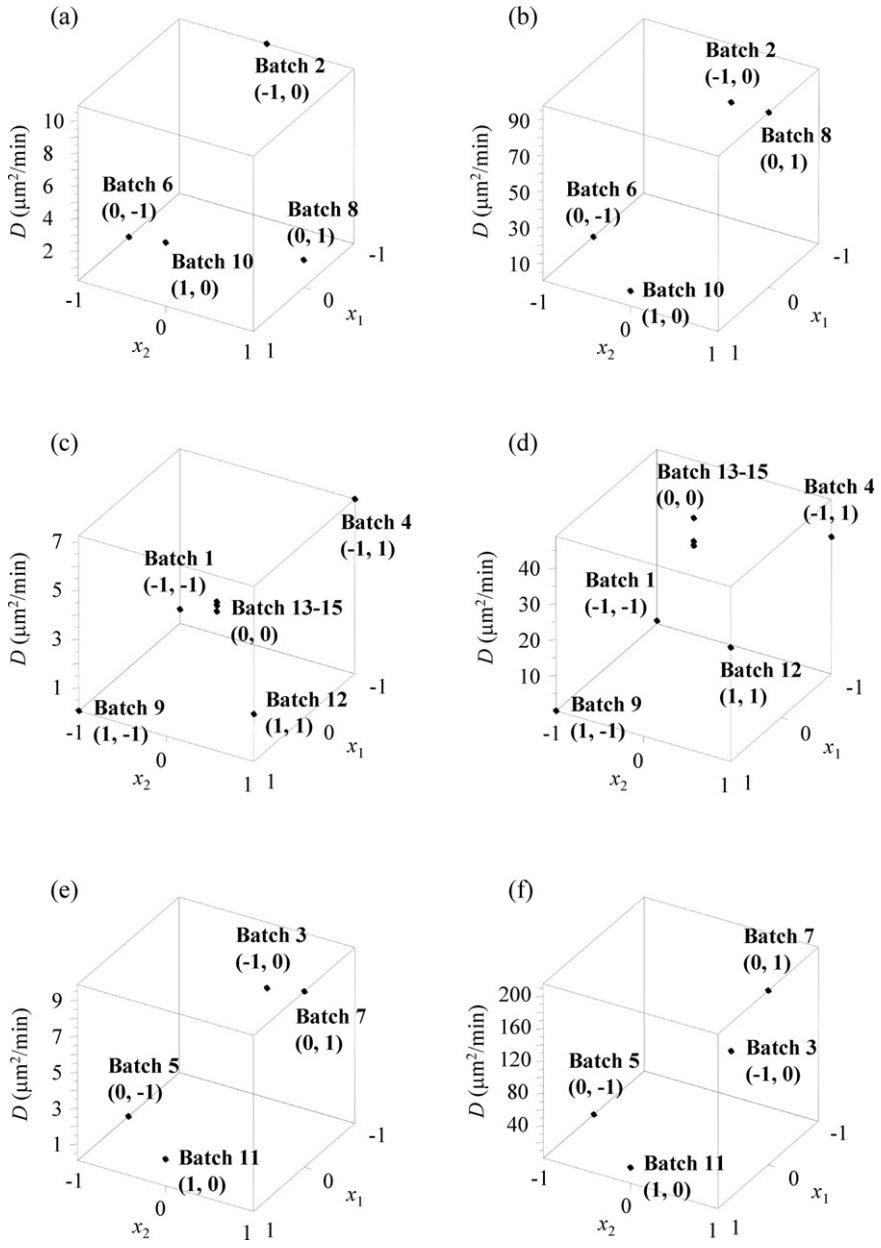

Fig. 4. Plots of estimated values of diffusion coefficient D versus x_1 and x_2 for each batch. (a) $x_3 = -1$ and pH 6.5, (b) $x_3 = -1$ and pH 4.0, (c) $x_3 = 0$ and pH 6.5, (d) $x_3 = 0$ and pH 4.0, (e) $x_3 = 1$ and pH 6.5, and (f) $x_3 = 1$ and pH 4.0.

cal meaning. Hence, the hybrid model should be beneficial for designing formulations of wax matrix dosage forms. In the present study, although GM was used as a wax base to adjust each preparation to 100%, it was considered that GM might affect *in vivo* release of drug due to the presence of gastric or intestinal juice. Therefore, further release studies using an acidic medium like 0.1 M HCl, not just pH 4.0 and pH 6.5, would also be required to accurately evaluate the usefulness of this hybrid model. In future work, we plan to develop formulations of wax matrix particles that give desirable drug release patterns by applying this hybrid model.

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