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Kinetic Approach to Determine the Generation Rate of Available Surface Area during the Dissolution Process[1)]

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The initial rate of increase (K_h) of available surface area ($S(t)$) of flufenamic acid (FFA) in tablets during the disintegration and deaggregation (dispersion) processes, as well as the rate of decrease (K_d) of $S(t)$ during the subsequent dissolution process, was determined by using two approaches. One was based on the assumption that the increase and decrease are dependent in a first-order manner on $S(t)$ generated at time t. The other was based on the assumption that the initial rate of increase of $S(t)$ is independent of $S(t)$, whereas the subsequent rate of decrease is dependent on the $S(t)$ at time t. By using the $S(t)$ equations developed from these two approaches, the ratio of the $S(t)$ generated by time t to the total $S(t)$ generated during the dissolution process ($F(t)$) could be expressed as a function of time, which included K_h and K_d as the constants. Furthermore, from the non-linear regression of $F(t)$ data, which it is possible to obtain from a dissolution study, to these $F(t)$ functions, well-matching K_h and K_d values for the FFA (200 mg) tablets could be obtained. The influence of the level of disintegrant and the compression pressure on K_h and K_d, as well as the results of simulation of the $S(t)$-generation patterns of FFA (200 mg) tablets are also discussed.

Keywords——dissolution profile; available surface area; kinetic-dependent; time-dependent; Laplace transform; non-linear regression; computer simulation; flufenamic acid

In general, the dissolution of solid dosage forms consists of disintegration and deaggregation (dispersion of disintegrated granules and powders) processes, and since the mechanism is very complex, there have been few reports giving precise consideration to this phenomenon. In our previous studies, time-course equations for available surface area ($S(t)$) generated in the dissolution process were derived by using probability distributions, and the influences of the manufacturing process,[2)] compression pressure and formulation[1a)] on the dissolution process of flufenamic acid (FFA) in tablet form, and the wetting factors affecting the dissolution behavior of powdered particles of FFA[3)] were evaluated. However, since the patterns of $S(t)$ generated were expressed by using probability distributions in these studies, the exact rates of increase and decrease of $S(t)$ generated during the dissolution process could not be obtained.

In the present study, a new method was developed to elucidate the kinetics of $S(t)$ patterns during the dissolution process by two approaches, and the rate constants of increase (K_h) and decrease (K_d) of $S(t)$ were determined for FFA (200 mg) tablets having various levels of disintegrant content and prepared at various compression pressures.

Theoretical

New Approaches to Derivation of the $S(t)$ Rate Equation

When a solid dosage form dissolves, it first disintegrates into aggregates and subsequently deaggregates (disperses) into small particles. Throughout these processes, disso-

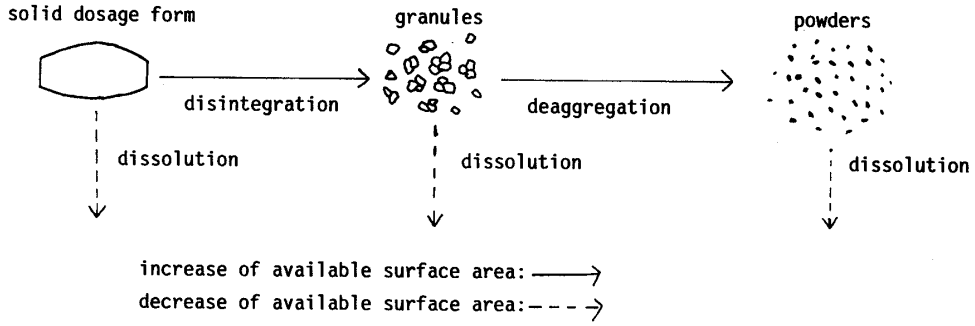
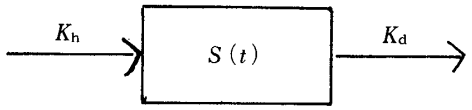


Chart 1. The Scheme for a Solid Dosage Form in the Dissolution Medium



K_h: rate of increase of $S(t)$
K_d: rate of decrease of $S(t)$

Chart 2. The Simplified Model for $S(t)$ in the Dissolution Medium

lution of the drug occurs. It can be assumed from the surface area point of view that $S(t)$ increases during disintegration and deaggregation and decreases during dissolution. Accordingly, Wagner's scheme[4] for drug dissolution from a solid dosage form can be modified as shown in Chart 1, where the full line represents the process of increase of $S(t)$ and the broken line the process of decrease of $S(t)$. Furthermore, if the constants for the rates of increase and decrease of $S(t)$ are determined, Chart 1 can be simplified to the situation shown in Chart 2, where K_h and K_d are the constants for the rates of increase and decrease of $S(t)$, respectively. In general, the disintegration of a solid dosage form results from the swelling of aggregates and the release of particles from the solid surface. From the surface area point of view, if the former has more effect on the disintegration, $S(t)$ will increase exponentially with first-order kinetics. On the other hand, if the latter has more effect, the rate of increase of $S(t)$ will be independent of $S(t)$. Based on these assumptions, two approaches were investigated to obtain the time-course equations for $S(t)$, which include K_h and K_d as constants.

(1) Approach I——If the increase and decrease of $S(t)$ are both first-order processes, the following differential equations can be written:

$$dA(t)/dt = -K_h \cdot A(t) \tag{1}$$

$$dS(t)/dt = K_h \cdot A(t) - K_d \cdot S(t) \tag{2}$$

where $A(t)$ represents the surface area of the powdered drug remaining at time t. The Laplace transforms of Eqs. 1 and 2 are:

$$\overline{sA(s)} = -K_h \cdot (S_o - \overline{A(s)}) \tag{3}$$

$$\overline{sS(s)} = K_h \cdot \overline{A(s)} - K_d \cdot \overline{S(s)} \tag{4}$$

where the bars above the function and the s represent the Laplace transform of the function and S_o is the initial surface area of the powdered drug in the solid dosage form. Substituting Eq. 3, in Eq. 4 gives:

$$\overline{S(s)} = S_o \cdot K_h / \{(s+K_h) \cdot (s+K_d)\} \tag{5}$$

TABLE I. Dissolution Rate of FFA (200 mg) Tablets (Experimental Data)

CMC-Ca amount (mg/tab.)	Compression pressure (t)	% dissolved Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	11.1	21.4	28.8	42.6	63.1	82.0	89.3	96.7	95.7
	0.2	0.6	1.0	2.4	12.4	37.9	59.9	71.7	85.6	94.0
	0.5	—	—	—	1.4	1.4	2.0	2.4	5.0	8.6
	0.8	—	—	—	1.1	1.8	2.6	3.1	4.3	6.0
	1.5	—	—	—	—	1.3	2.3	2.2	2.9	4.2
5	0	9.9	20.7	27.1	38.1	60.3	77.8	89.4	97.2	99.6
	0.2	7.6	17.2	27.2	39.3	64.0	79.6	87.3	93.6	98.5
	0.5	2.0	5.6	10.4	37.2	54.9	75.4	78.7	91.7	95.8
	0.8	0.3	0.7	2.4	2.6	3.8	6.7	11.4	25.3	47.5
	1.5	—	—	—	1.3	2.0	3.1	3.5	6.0	8.2
10	0	21.1	34.3	44.6	59.2	79.9	91.0	96.9	98.7	99.3
	0.2	12.6	32.1	41.7	51.1	81.0	94.0	96.6	99.2	99.7
	0.5	7.8	21.5	33.7	51.4	74.7	88.4	93.7	98.0	97.6
	0.8	2.4	5.3	13.4	28.3	54.1	68.8	88.8	97.0	99.0
	1.5	0.5	1.0	1.7	3.1	13.5	28.1	48.3	75.5	91.8
15	0	29.8	43.2	53.4	66.0	83.8	91.9	95.4	98.2	95.1
	0.2	17.4	34.3	47.1	63.5	83.0	97.6	97.2	100.5	99.8
	0.5	10.5	23.0	36.7	54.3	77.1	86.8	93.7	98.1	102.8
	0.8	5.6	12.3	21.5	41.4	70.4	84.1	95.9	98.2	97.5
	1.5	0.6	1.4	3.3	7.8	22.5	40.6	60.6	84.3	95.6
25	0	29.1	51.2	66.4	77.5	91.5	96.5	99.5	99.1	101.3
	0.2	16.4	37.8	51.9	68.0	85.4	90.5	95.5	100.0	98.7
	0.5	12.3	32.6	48.1	64.2	84.7	95.6	96.4	100.0	101.6
	0.8	4.2	14.4	28.5	50.6	71.3	85.8	91.6	97.6	100.0
	1.5	1.6	4.7	10.2	23.4	57.4	77.6	88.1	95.6	99.2

Rearranging with the use of Laplace transform tables[5] yields:

$$S(t)=S_o\cdot K_h/(K_h-K_d)\cdot\{\exp(-K_d\cdot t)-\exp(-K_h\cdot t)\} \quad (6)$$

which is the $S(t)$ equation when the increase of $S(t)$ is a first-order process.

(2) Approach II——If the increase of $S(t)$ is independent of $S(t)$ and the decrease of $S(t)$ is a first-order process, the following differential equations can be written:

$$dA(t)/dt=-S_o\cdot K_h\cdot t \quad (7)$$

$$dS(t)/dt=S_o\cdot K_h\cdot t-K_d\cdot S(t) \quad (8)$$

Eq. 7 may be integrated to give:

$$A(t)=S_o\{1-(K_h/2)\cdot t^2\} \quad (9)$$

which indicates that the process of increase of $S(t)$ is complete at $t=\sqrt{2/K_h}$. Then, Eq. 8 can be applied only for $t\leqq\sqrt{2/K_h}$. The Laplace transforms of Eq. 8 yield:

$$\overline{S(s)}=S_o\cdot K_h/\{(s+K_d)\cdot s^2\} \quad (10)$$

Rearranging with the use of Laplace transform tables yields:

$$S(t)=S_o/K_d\cdot[K_h\cdot t-(K_h/K_d)\cdot\{1-\exp(-K_d\cdot t)\}] \quad (11)$$

TABLE II. The K_h and K_d Values in Relation to $S(t)$ of FFA (200 mg) Tablets

CMC-Ca amount (mg/tab.)	Compression pressure (t)	Approach I			Approach II		
		K_h (min^{-1})	K_d (min^{-1})	AIC	K_h (min^{-2})	K_d (min^{-1})	AIC
0	0	2.58×10^{3}	1.01×10^{-1}	−72.7	2.97×10^{2}	1.02×10^{-1}	−72.7
	0.2	1.94×10^{-1}	8.40×10^{-2}	−83.8	7.36×10^{-2}	7.10×10^{-2}	−104.8
	0.5	(3.69×10^{-1})[a]	(1.87×10^{-3})	−109.9	(9.88×10^{-5})	(9.77×10^{2})	−75.1
	0.8	(1.15×10^{3})	(1.38×10^{-3})	−128.9	(7.68×10^{-5})	(1.41×10^{3})	−72.3
	1.5	(6.71×10^{4})	(9.84×10^{-4})	−138.4	(5.20×10^{-5})	(2.60×10^{2})	−57.0
5	0	9.99×10^{2}	9.38×10^{-2}	−74.6	9.21×10^{2}	9.50×10^{-2}	−74.7
	0.2	3.93	9.81×10^{-2}	−71.0	12.4	9.87×10^{-2}	−72.2
	0.5	7.79×10^{-1}	8.70×10^{-2}	−52.6	5.14×10^{-1}	7.47×10^{-2}	−54.1
	0.8	3.34×10^{-2}	3.34×10^{-2}	−69.8	2.13×10^{-3}	3.14×10^{-2}	−86.6
	1.5	(1.88×10^{-3})	(1.64)	−74.2	(1.03×10^{-4})	(1.06×10^{3})	−63.3
10	0	5.01×10^{4}	1.67×10^{-1}	−52.1	6.70×10^{2}	1.69×10^{-1}	−51.3
	0.2	1.38×10^{4}	1.79×10^{-1}	−38.4[b]	3.73×10^{2}	1.55×10^{-1}	−31.5[b]
	0.5	2.47	1.38×10^{-1}	−75.0	1.49×10^{2}	1.29×10^{-1}	−69.8
	0.8	3.55×10^{-1}	1.09×10^{-1}	−60.1	2.95×10^{-1}	9.52×10^{-2}	−57.8
	1.5	7.86×10^{-2}	7.90×10^{-2}	−46.2	7.79×10^{-3}	7.26×10^{-2}	−66.4
15	0	1.96×10^{4}	2.17×10^{-1}	−39.2	1.33×10^{3}	2.22×10^{-1}	−38.6
	0.2	2.12×10^{4}	1.85×10^{-1}	−60.4	5.56×10^{2}	1.86×10^{-1}	−60.7
	0.5	4.31	1.42×10^{-1}	−64.7	1.27×10^{2}	1.37×10^{-1}	−71.0
	0.8	7.78×10^{-1}	1.30×10^{-1}	−68.0	7.60×10^{-1}	1.24×10^{-1}	−64.5
	1.5	9.57×10^{-2}	9.57×10^{-2}	−58.0	1.58×10^{-2}	7.43×10^{-2}	−58.8
25	0	1.30×10^{4}	3.08×10^{-1}	−43.8	1.20×10^{3}	3.13×10^{-1}	−43.5
	0.2	1.66×10^{2}	2.02×10^{-1}	−45.2	8.81×10^{2}	2.03×10^{-1}	−45.3
	0.5	3.70	1.99×10^{-1}	−59.8	6.70×10^{2}	1.85×10^{-1}	−56.5
	0.8	1.35	1.31×10^{-1}	−67.0	1.69	1.31×10^{-1}	−69.0
	1.5	2.07×10^{-1}	1.55×10^{-1}	−50.6	1.31×10^{-1}	1.16×10^{-1}	−49.5

a) Since the dissolved amounts were very small, well-defined K_h and K_d could not be determined. b) $n=1$; the other values were obtained from the regression of dissolution data from 2 trials.

which is the $S(t)$ equation for $t\leqq 2/K_h$ when the increase of $S(t)$ is independent of $S(t)$.

On the other hand, in the case of $t>\sqrt{2/K_h}$, the $S(t)$ merely decreases with first-order kinetics. In such circumstances, the following equation can be written:

$$S(t)=S(\sqrt{2/K_h})\cdot\exp\{-K_d\cdot(t-\sqrt{2/K_h})\}$$

$$=S_o/K_d[\sqrt{2K_h}-(K_h/K_d)\cdot\{1-\exp(-K_d\cdot\sqrt{2/K_h})\}]\cdot\exp\{-K_d\cdot(t-\sqrt{2/K_h})\} \quad (12)$$

which is the $S(t)$ equation for $t>\sqrt{2/K_h}$ when the increase of $S(t)$ is independent of $S(t)$.

Determination of Best-Fitting Values for K_h and K_d

In our previous paper,[2] we reported that the ratio of $S(t)$ generated by time t to the total $S(t)$ generated by infinite time ($F(t)$) can be obtained from both a function of t and the experimental data obtained in dissolution studies, as shown in Eqs. 13 and 14,

$$F(t)=\int_0^t S(t)dt \Big/ \int_0^\infty S(t)dt \quad (13)$$

$$F(t)=\ln\{C_s/(C_s-C)\}/\ln\{C_s/(C_s-W_o/V)\} \quad (14)$$

where C_s, C, W_o and V in Eq. 14 represent the solubility, the solute concentration, the initial

TABLE III. The Time-Course of $S(t)$ during the Dissolution Process of FFA (200 mg) Tablets Obtained from Approach I

CMC-Ca amount (mg/tab.)	Compression pressure (t)	Available surface area (cm^2/200 mg FFA) Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	158.1	142.9	129.2	105.6	63.7	38.4	23.2	8.5	3.1
	0.2	24.6	42.8	56.0	71.3	73.9	58.8	42.5	19.9	8.8
	0.5	1.0	1.7	2.2	2.7	3.1	3.2	3.1	3.1	3.0
	0.8	2.4	2.4	2.4	2.4	2.4	2.3	2.3	2.3	2.3
	1.5	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.6
5	0	148.0	134.8	122.7	101.7	63.6	39.8	24.9	9.7	3.8
	0.2	154.5	143.1	129.8	106.7	65.3	40.0	24.5	9.2	3.4
	0.5	77.6	106.8	114.3	106.3	71.0	46.0	29.8	12.5	5.2
	0.8	1.9	3.6	5.3	8.1	13.8	17.6	19.8	21.3	20.3
	1.5	2.6	3.1	3.2	3.2	3.2	3.2	3.1	3.1	3.0
10	0	244.7	207.1	175.2	125.5	54.4	23.6	10.2	1.9	0.4
	0.2	259.2	216.7	181.2	126.7	51.8	21.1	8.6	1.4	0.2
	0.5	199.1	190.3	167.2	127.0	63.7	31.9	16.0	4.0	1.0
	0.8	53.3	85.1	102.5	111.8	83.8	51.8	30.6	10.3	3.5
	1.5	9.9	18.4	25.5	36.3	48.9	49.5	44.5	30.3	18.4
15	0	302.5	243.5	196.0	127.0	42.9	14.5	4.9	0.5	0.1
	0.2	266.3	221.3	183.9	127.0	50.4	20.0	7.9	1.2	0.2
	0.5	217.2	191.4	166.1	125.0	61.5	30.2	14.9	3.6	0.9
	0.8	113.2	151.4	156.8	135.6	73.5	38.5	20.1	5.5	1.5
	1.5	14.4	26.2	35.7	49.1	60.9	56.6	46.8	27.0	13.8
25	0	392.0	288.1	211.7	114.3	24.5	5.3	1.1	0.5	—
	0.2	286.2	233.8	191.1	127.6	46.5	16.9	6.2	0.8	0.1
	0.5	289.5	244.4	200.5	134.7	50.0	18.4	6.8	0.9	0.1
	0.8	155.3	176.4	165.2	130.2	67.8	35.2	18.3	4.9	1.3
	1.5	46.4	77.4	96.9	112.7	92.0	56.6	31.1	8.1	1.9

amount of drug in the solid dosage form and the solvent volume, respectively. By substituting Eq. 6 into Eq. 13, $F(t)$ obtained from approach I can be written as:

$$F(t)=[K_h\{1-\exp(-K_d\cdot t)\}-K_d\{1-\exp(-K_h\cdot t)\}]/(K_h-K_d) \tag{15}$$

By substituting Eqs. 11 and 12 in Eq. 13, $F(t)$ obtained from approach II can be written as:

$$F(t)=K_h\cdot t^2/2-(K_h/K_d^2)\cdot\{K_d\cdot t+\exp(-K_d\cdot t)-1\} \quad \text{for} \quad t\leqq\sqrt{2/K_h} \tag{16}$$

$$F(t)=[\sqrt{2K_h}-(K_h/K_d)\cdot\{1-\exp(-K_d\cdot\sqrt{2/K_h})\}] \times[1-\exp\{-K_d\cdot(t-\sqrt{2/K_h})\}]+F(\sqrt{2/K_h}) \quad \text{for} \quad t>\sqrt{2/K_h} \tag{17}$$

Then, best-fitting values of K_h and K_d can be determined by non-linear regression of the experimental data in Eq. 14 to Eq. 15 or Eqs. 16 and 17. Furthermore, if K_h and K_d are determined, it is possible to simulate the time-course equations for $S(t)$ generated in the dissolution process and also the dissolution rate in relation to $S(t)$ using Eqs. 18 and 19, respectively.

$$S(t)=V/k\cdot\ln\{C_s/(C_s-W_o/V)\}\cdot dF(t)/dt \tag{18}$$

TABLE IV. The Time-Course of $S(t)$ during the Dissolution Process of FFA (200 mg) Tablets Obtained from Approach II

CMC-Ca amount (mg/tab.)	Compression pressure (t)	Available surface area (cm^2/200 mg FFA) Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	160.7	145.1	131.0	106.8	64.2	38.5	23.1	8.3	3.0
	0.2	4.4	17.3	38.0	100.8	77.7	54.5	38.2	18.8	9.2
	0.5	0.2	0.3	0.5	0.9	1.7	2.6	3.4	5.1	6.8
	0.8	0.1	0.3	0.4	0.7	1.3	2.0	2.7	4.0	5.3
	1.5	0.1	0.2	0.3	0.5	0.9	1.4	1.8	2.7	3.6
5	0	151.0	137.3	124.9	103.3	64.2	39.9	24.8	9.6	3.7
	0.2	159.0	144.1	130.5	107.2	65.4	39.9	24.4	9.1	3.4
	0.5	32.4	123.0	114.1	98.3	67.7	46.6	32.1	15.2	7.2
	0.8	0.1	0.3	0.5	1.4	5.2	11.2	19.0	39.0	30.1
	1.5	0.2	0.4	0.5	0.9	1.8	2.7	3.6	5.4	7.1
10	0	248.9	210.2	177.5	126.6	54.4	23.4	10.0	1.9	0.3
	0.2	231.7	198.4	169.9	124.6	57.4	26.5	12.2	2.6	0.5
	0.5	198.3	174.3	153.2	118.4	62.1	32.6	17.1	4.7	1.3
	0.8	23.6	91.4	146.4	121.0	75.2	46.7	29.0	11.2	4.3
	1.5	0.4	1.8	4.1	10.9	39.0	79.1	66.2	32.0	15.5
15	0	310.0	248.3	198.9	127.6	42.0	13.9	4.6	0.5	0.1
	0.2	269.7	223.9	185.9	128.1	50.6	19.9	7.9	1.2	0.2
	0.5	209.3	182.5	159.1	121.0	61.0	30.7	15.5	3.9	1.0
	0.8	78.3	191.8	169.5	132.2	71.1	38.3	20.6	6.0	1.7
	1.5	1.0	3.9	8.5	22.5	80.5	75.1	51.8	24.6	11.7
25	0	399.8	292.4	213.8	114.3	23.9	5.0	1.0	—	—
	0.2	289.0	235.9	192.6	128.3	46.5	16.9	6.1	0.8	0.1
	0.5	268.3	223.0	185.3	128.0	50.8	20.1	8.0	1.3	0.2
	0.8	183.6	192.1	168.5	129.7	67.3	35.0	18.2	4.9	1.3
	1.5	12.0	46.4	100.9	147.1	84.9	49.0	28.3	9.4	3.1

$$C = C_s[1 - \exp[-[\ln\{C_s/(C_s - W_o/V)\} \cdot F(t)]]] \quad (19)$$

Experimental

Materials——FFA was of commercial grade and the specific surface area measured by an air permeation method was 580 cm^2/200 mg. Lactose (LA), carboxymethylcellulose calcium (CMC-Ca), hydroxypropylcellulose (HPC-L), magnesium stearate (St. Mg) and polysorbate 80 were all of JP X grade. All other chemicals were of reagent grade.

Preparation of FFA (200 mg) Tablets——The manufacturing process and formula for samples, which contained 200 mg of FFA and various levels (from 0 to 25 mg/tab.) of CMC-Ca, were described in our previous paper.[1b]

Dissolution Studies——The dissolution of FFA from the preparations was tested in a USP dissolution test apparatus using method II (Paddle method) in pH 6.8 phosphate buffer containing 10^{-2}% (w/v) of polysorbate 80, with agitation at 100 rpm at 37 °C. The dissolution rate constant per unit area (k) was determined by the rotating disk method and the result was $k = 0.127$ cm/min. The solubility of FFA was determined by incubating the powder in the dissolution medium at 37 °C and the result was $C_s = 1025$ mg/ml. Details of these studies have already been presented in our previous paper.[1b]

Results and Discussion

Determination of K_h and K_d for FFA (200 mg) Tablets

The dissolution data for FFA (200 mg) tablets containing various levels of CMC-Ca and

TABLE V. The Theoretical Dissolution Rate in Relation to $S(t)$ Obtained from Approach I

CMC-Ca amount (mg/tab.)	Compression pressure (t)	% dissolved Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	10.7	20.2	28.5	42.6	66.4	80.1	88.1	95.7	98.4
	0.2	0.8	3.1	6.3	14.5	37.6	57.2	71.3	87.5	94.6
	0.5	—	0.1	0.2	0.6	1.5	2.6	3.6	5.6	7.5
	0.8	0.2	0.3	0.5	0.8	1.5	2.3	3.1	4.5	6.0
	1.5	0.1	0.2	0.3	0.6	1.1	1.6	2.2	3.3	4.3
5	0	9.9	18.8	26.8	40.3	63.7	77.7	86.2	94.7	97.9
	0.2	7.9	17.4	25.8	40.1	64.4	78.6	87.0	95.2	98.2
	0.5	2.9	9.0	16.1	29.9	55.9	72.0	82.1	92.6	96.9
	0.8	0.1	0.2	0.5	1.4	5.0	10.1	16.0	28.9	41.5
	1.5	0.1	0.3	0.5	0.9	2.0	3.0	4.0	6.0	8.0
10	0	17.0	30.9	42.3	59.6	83.0	92.7	96.9	99.4	99.9
	0.2	18.1	32.7	44.5	62.1	85.0	93.9	97.5	99.6	99.9
	0.5	9.2	21.6	32.6	49.9	75.7	88.0	94.0	98.5	99.6
	0.8	1.9	6.4	12.5	26.1	55.8	74.5	85.3	95.1	98.4
	1.5	0.3	1.2	2.7	6.7	20.6	35.8	49.8	71.0	84.0
15	0	21.5	38.0	50.9	68.9	89.8	96.6	98.8	99.9	100.0
	0.2	18.6	33.6	45.6	63.2	85.8	94.5	97.8	99.7	99.9
	0.5	11.5	24.3	35.2	52.2	77.2	89.0	94.6	98.7	99.7
	0.8	4.3	13.0	22.7	40.6	69.9	84.6	92.0	97.8	99.4
	1.5	0.5	1.8	3.8	9.4	27.2	45.0	60.0	80.1	90.6
25	0	28.9	49.0	63.2	80.6	95.9	99.1	99.8	100.0	100.0
	0.2	20.1	35.9	48.4	66.3	88.1	95.7	98.4	99.8	100.0
	0.5	15.0	31.6	44.8	63.8	87.0	95.3	98.3	99.8	100.0
	0.8	6.3	17.1	27.8	45.5	72.6	86.0	92.8	98.1	99.5
	1.5	1.6	5.7	11.3	24.7	56.2	76.7	88.2	97.2	99.4

compressed with various pressures are shown in Table I. By substituting the data in Table I into Eq. 14, the experimental values of $F(t)$ could be calculated. Furthermore, the best-fit values of K_h and K_d were determined by non-linear regression (simplex method)[6] of $F(t)$ to Eq. 15 or Eqs. 16 and 17. The K_h and K_d values determined are shown in Table II, where the fit of the experimental data was estimated in terms of Akaike's information criterion (AIC).[7] Since each AIC in Table II has a large negative value, the $F(t)$ values of FFA (200 mg) tablets were estimated to be well-regressed to Eq. 15 and Eqs. 16 and 17. Furthermore, K_h obtained from both approaches increased as the compression pressure decreased, as well as when the level of CMC-Ca increased. On the other hand, K_d was not so affected by compression pressure and the level of CMC-Ca, as compared with K_h, and there was little difference between the K_d values determined by the two different approaches.

Time-Course of $S(t)$ in the Dissolution Process of FFA (200 mg) Tablets

By substituting the K_h and K_d listed in Table II into Eq. 15 or Eqs. 16 and 17, $F(t)$ could be calculated as a function of time (t). The time-course of $S(t)$ during the dissolution process could then be calculated by using Eq. 18. The results are shown in Tables III and IV for the cases where the increase of $S(t)$ is a first-order process (approach I) and is independent of $S(t)$ (approach II), respectively. There was little difference between the $S(t)$ values determined by the two approaches, except for cases where the compression pressure was high and the level of

TABLE VI. The Theoretical Dissolution Rate in Relation to $S(t)$ Obtained from Approach II

CMC-Ca amount (mg/tab.)	Compression pressure (t)	% dissolved Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	9.9	19.5	28.0	42.3	66.3	80.1	88.1	95.7	98.3
	0.2	0.1	0.8	2.5	11.1	39.7	58.7	71.5	86.3	93.3
	0.5	—	—	0.1	0.1	0.6	1.3	2.2	5.0	8.8
	0.8	—	—	—	0.1	0.4	1.0	1.7	3.9	6.9
	1.5	—	—	—	0.1	0.3	0.7	1.2	2.6	4.7
5	0	9.2	18.3	26.4	40.1	63.9	78.0	86.5	94.8	98.0
	0.2	7.8	17.4	25.9	40.2	64.6	78.8	87.2	95.3	98.3
	0.5	0.7	5.5	13.1	26.3	50.7	66.8	77.4	89.5	95.1
	0.8	—	—	—	0.2	1.2	3.8	8.6	26.4	47.6
	1.5	—	—	0.1	0.1	0.6	1.3	2.3	5.2	9.2
10	0	16.5	30.6	42.2	59.7	83.2	92.8	96.9	99.4	99.9
	0.2	15.3	28.6	39.6	56.7	80.7	91.3	96.0	99.2	99.9
	0.5	12.5	24.1	34.1	50.1	74.6	86.9	93.2	98.2	99.5
	0.8	0.5	4.0	12.4	29.0	57.4	74.1	84.1	94.0	97.7
	1.5	—	0.1	0.3	1.2	8.9	27.1	50.4	76.8	88.9
15	0	21.4	38.3	51.4	69.6	90.3	96.9	99.0	100.0	100.0
	0.2	18.1	33.2	45.4	63.2	86.0	94.6	97.9	99.7	100.0
	0.5	13.1	25.3	35.6	52.0	76.6	88.4	94.2	98.5	99.6
	0.8	1.7	11.9	23.2	41.3	69.5	83.9	91.4	97.5	99.3
	1.5	—	0.2	0.6	2.5	18.1	44.6	62.7	82.7	91.9
25	0	28.7	49.1	63.5	80.9	96.1	99.2	99.8	100.0	100.0
	0.2	19.7	35.7	48.4	66.4	88.2	95.8	98.6	99.9	100.0
	0.5	18.1	33.1	45.3	63.0	85.8	94.5	97.9	99.7	100.0
	0.8	4.0	17.0	28.1	45.9	72.8	86.1	92.9	98.1	99.5
	1.5	0.3	2.0	6.7	25.0	58.4	76.6	86.7	95.6	98.5

CMC-Ca was low. Furthermore, the peak time was delayed, and the maximum value decreased, as the compression pressure became higher, as well as when the level of CMC-Ca became lower. Specifically, the $S(t)$ values of tablets containing less than 5 mg of CMC-Ca and compressed at a force of 1.5 t were not more than one-hundredth of the specific surface area of FFA in the tablets (580 cm^2/200 mg) throughout the dissolution process.

The theoretical dissolution rates in relation to $S(t)$, calculated from Eq. 19, are shown in Tables V and VI for the cases where the increase of $S(t)$ is a first-order process (approach I) and is independent of $S(t)$ (approach II), respectively. There was little difference between the experimental data in Table I and the regression data obtained from the two approaches. Therefore the $S(t)$ values in Tables III and IV were assumed to be reasonable.

Typical dissolution patterns are shown in Fig. 1 and the $S(t)$ patterns are shown in Fig. 2, where the full lines and the broken lines represent the regression curves obtained by approach I and approach II, respectively. At the sigmoid region of the dissolution patterns at the initial time, the pattern obtained from approach II (broken line) fitted better with the experimental data so that the broken lines of the $S(t)$ patterns in Fig. 2 were considered to be more reliable.

In conclusion, methods for determining the rate of increase of $S(t)$ during the disintegration and deaggregation processes and the rate of decrease of $S(t)$ during the dissolution process were developed. By applying these methods to FFA (200 mg) tablets with various dissolution patterns, the approach was confirmed to be useful for analyzing the kinetics of $S(t)$ patterns, which cannot be determined by experimental measurements.

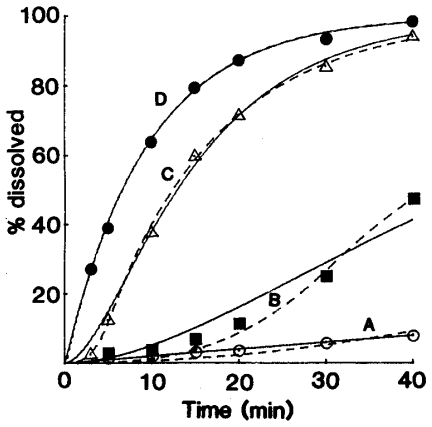


Fig. 1. Typical Dissolution Patterns of FFA (200 mg) Tablets

$C_s = 1025$ mg/l; $W_0 = 200$ mg; $V = 900$ ml. The full lines are the regression curves obtained using approach I and the broken lines are those obtained using approach II.

CMC-Ca (mg/tab.)	Compression pressure (t)	Experimental data	Regression line
5	1.5	⊙	A
5	0.8	■	B
0	0.2	△	C
5	0.2	●	D

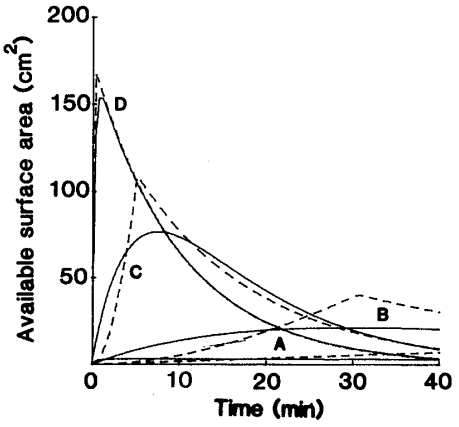


Fig. 2. The Typical $S(t)$ *vs.* t Patterns of FFA (200 mg) Tablets

$C_s = 1025$ mg/l; $W_0 = 200$ mg; $V = 900$ ml; $k = 0.127$ cm/min. The full lines are the regression curves obtained from approach I and the broken lines are those obtained from approach II. A—D are the same as in Fig. 1.

References and Notes

1) *a*) This paper forms Part IV of "Dissolution Profile in Relation to Available Surface Area"; *b*) Part III: S. Itai, S. Kouchiwa, M. Nemoto, H. Murayama and T. Nagai, *Chem. Pharm. Bull.*, **34**, 1264 (1986). This work was presented at the 104th and 105th Annual Meetings of the Pharmaceutical Society of Japan, Sendai and Kanazawa, April 1984 and 1985.
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6) Non-linear regressions were performed using the MULTI program devised by K. Yamaoka and U. Tanikawara.
7) K. Yamaoka, T. Nakagawa and T. Uno, *J. Pharmacokinet. Biopharm.*, **6**, 165 (1978).