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Effect of Compression Pressure and Formulation on the Available Surface Area of Flufenamic Acid in Tablets[1)]

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The effects of compression pressure and a disintegrant on the dissolution profile of flufenamic acid (FFA) in tablets were evaluated in relation to the time course of the available surface area ($S(t)$). The ratios of $S(t)$ generated by time t to the total $S(t)$ generated during the dissolution process ($F(t)$), which it was possible to obtain from dissolution tests on the tablets as well as on granules before compression, were well regressed to the Weibull distribution and the log-normal distribution. The scale parameter (a) and the shape parameter (b) of the Weibull distribution increased as the compression pressure was increased, and also as the level of disintegrant was decreased. With regard to the regression to the log-normal distribution, the standard deviation (σ) of the $S(t)$-generated pattern increased as the compression pressure was increased, whereas it was unaffected by the level of disintegrant. By using the probability parameters thus obtained, the $S(t)$-generation patterns of FFA (200 mg) tablets at various compression pressures were simulated. When the compression pressure was low, and the disintegrant level was high, the patterns had a well-defined peak value, which was consistent with the disintegration time of the tablets.

Keywords——dissolution profile; available surface area; Weibull distribution; log-normal distribution; non-linear regression; compression pressure; flufenamic acid; computer simulation

The effect of compression pressure on the dissolution of drugs contained in tablets is one of the most important factors to be considered in relation to the bioavailability of the preparations. Many studies[2–5)] have therefore been carried out to elucidate the relationship between the dissolution process, which includes disintegration and deaggregation, and the hardness of tablets. However, most of these studies have been restricted to the use of data directly obtained from dissolution tests or disintegration tests. When the compression pressure is increased, changes in bonding, cleavage or crushing of particles of the drug in tablets may occur, thus altering the available surface area ($S(t)$) of the drug. In our previous study, time course equations were derived for $S(t)$ generated in the dissolution process and the influence of the manufacturing process on the dissolution of flufenamic acid (FFA) in tablets[6)] and that of wetting factors on the dissolution behavior of FFA powders[1b)] were evaluated. In the present paper, tablets containing 200 mg of FFA were prepared by compression at various pressures (from 0 to 1.5t/tab.) and the dissolution rates were measured by using method II of the USP dissolution test (paddle method). Then, by the use of the previous method,[6)] the $S(t)$-generation patterns for each tablet could be obtained quantitatively.

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), carboxymethyl cellulose calcium (CMC-Ca), hydroxypropyl cellulose (HPC-L), magnesium stearate (St. Mg) and polysorbate 80 were all of JP X grade. All other chemicals were of reagent grade.

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TABLE I. The Manufacturing Process and Formulas for FFA (200 mg) Tablets

Ingredient (mg/tab.)		Manufacturing process
FFA[a]	200	mixing—kneading—sieving (0.8 cm)—drying—sieving (24 mesh)—mixing—tableting[c] (10 mmϕ)
LA	q.s.	
CMC-Ca	[b]	
HPC-L	5	
Pur. water	45	
St. Mg	2	sieving (60 mesh)
	300mg/tab.	

a) True density (ρ) = 1.49 g/cm^3, specific surface area (S_w) = 580 cm^2/200 mg. *b*) Amount of CMC-Ca: 0, 5, 10, 15 or 25 mg/tab. *c*) Compression pressure: 0.2, 0.5, 0.8 and 1.5 t/tab.

Preparation of FFA (200 mg) Tablets——The wet granulation method was applied to prepare samples containing 200 mg of FFA and various amounts (0—25 mg) of CMC-Ca per tablet. The manufacturing process and formulas for the samples are shown in Table I. A total of 200 g of FFA, LA and CMC-Ca was blended in a suitable mixing device for 5 min. Then, 50 ml of 10% (w/v) HPC-L aqueous solution was added to the mixtures and kneaded for 5 min. The wet granules were sieved through a 0.8-cm screen using a speed mill and dried in a stationary-type dry box for 5 h at 60 °C. The dry granules were sieved through a 24-mesh screen and mixed with 2 g of St. Mg sieved through a 60-mesh screen. The mixtures were tabletted on an instrumented 19-station press (Correct 19; Kikusui Seisakujyo Co., Ltd.) using various compression pressures (0.2—1.5 t/tab.).

Dissolution Study——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, agitated at 100 rpm at 37 °C. At appropriate intervals, 2 ml of sample solution was withdrawn through a membrane filter (pore size: 0.45 μm) and immediately diluted with 49 ml of the test medium. The absorbance was determined at 288 nm on a spectrophotometer and the FFA concentration was calculated from the absorbance of the standard solution. The dissolution test was performed twice, and the reproducibility was within the limits of experimental error.

Rotating Disk Method——In order to determine the rate constant per unit area (k), the rotating disk method was applied. An FFA disk having a diameter of 2 cm was fixed perpendicularly to a rotating shaft so that only one of the plane surfaces was available (surface area = 3.14 cm^2). The rotating shaft was placed in a USP dissolution test apparatus and rotated at 100 rpm in pH 6.8 phosphate buffer containing 10^{-2}% (w/v) polysorbate 80. At appropriate intervals, 2 ml of sample solution was withdrawn and diluted with 18 ml of the test medium. The FFA concentration was calculated in the same manner as described for the dissolution study.

Determination of Solubility (C_s)——To about 1 g of FFA in a flask, 30 ml of phosphate buffer containing 10^{-2}% (w/v) polysorbate 80 was added, and the mixture was incubated for 2 d at 37 °C. The solubility (C_s) of FFA was determined in the same manner as described for the dissolution study.

Measurement of Disintegration Time——The disintegration time of each sample in pH 6.8 phosphate buffer containing 10^{-2}% (w/v) polysorbate 80 was measured using a JP X disintegration test apparatus.

Results and Discussion

Determination of k

The results of the dissolution test of the FFA disk using the rotating disk method are shown in Fig. 1. An approximately linear relationship was found between time and the dissolved amount of FFA. If $C_s \gg C$ (sink condition) and the surface area is constant, from the rearrangement and integration of the Noyes-Whitney equation,[7] we have

$$C = k \cdot S \cdot C_s / V \cdot t \qquad (1)$$

where C is the solute concentration, S the surface area, and V the solvent volume. Then, linear regression of the experimental data produces Eq. 2.

$$C = 0.454t + 0.624 \qquad r = 0.998 \qquad (2)$$

Since the values of S, C_s and V in this experiment were 3.14 cm^2, 1025 mg/l and 900 ml,

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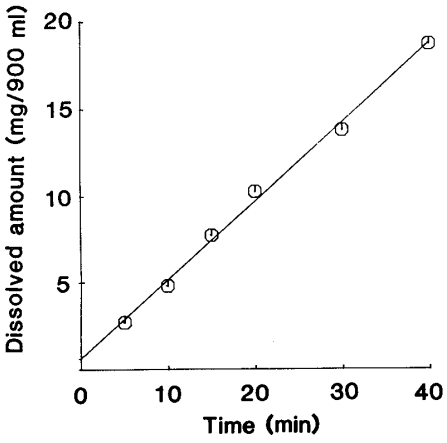

Fig. 1. Dissolution Rate of an FFA Disk Using the Rotating Disk Method
$C_s = 1025$ mg/l; $S = 3.14$ cm^2; $V = 900$ ml.

respectively, $k = 0.127$ cm/min was obtained from Eqs. 1 and 2.

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

In our previous study,[6] time course equations for $S(t)$ generated in the dissolution process and the dissolution rate in relation to $S(t)$, as shown in Eqs. 3 and 4, were derived,

$$S(t) = V/k \cdot \ln\{C_s/(C_s - W_o/V)\} \cdot dF(t)/dt \tag{3}$$

$$C = C_s[1 - \exp[-[\ln\{C_s/(C_s - W_o/V)\} \cdot F(t)]]] \tag{4}$$

where $F(t)$ is interpreted as the ratio of the cumulative surface area which has been made available for dissolution up to time t to the total surface area which is made available during the dissolution process.[8] $F(t)$ at any time can be calculated from the experimental data of the dissolution test, as shown in Eq. 5, where W_o is the initial amount of drug in the tablet.

$$F(t) = \ln\{C_s/(C_s - C)\}/\ln\{C_s/(C_s - W_o/V)\} \tag{5}$$

Furthermore, since $F(0) = 0$ and $F(\infty) = 1$, $F(t)$ can be interpreted as a cumulative probability distribution, as shown in Eq. 6,

$$F(t) = \int_0^t \phi(t)dt \tag{6}$$

where $\phi(t)$ is the probability distribution. In the present paper, the Weibull distribution (Eq. 7) and log-normal distribution (Eq. 8) were selected as $\phi(t)$, because they cover extensive distribution patterns and do not coincide with each other,[6]

$$\phi(t) = b/a \cdot t^{b-1} \cdot \exp\{-(t^b/a)\} \tag{7}$$

$$\phi(t) = 1/(2\pi \cdot \sigma \cdot t)\exp[-\{(\ln t - \ln \mu)^2/(2 \cdot \sigma^2)\}] \tag{8}$$

where a, b, μ and σ are the scale parameter, the shape parameter, the logarithmic mean of t and the standard deviation, respectively. Then, the Weibull distribution and log-normal distribution of $F(t)$ are written as:

$$F(t) = 1 - \exp\{-(t^b/a)\} \tag{8}$$

$$F(t) = 1/(2\pi \cdot \sigma) \cdot \int_0^{\ln t} \exp\{-(\ln t - \ln \mu)^2/(2 \cdot \sigma^2)\} d(\ln t) \tag{9}$$

Since $F(t)$ at any time during the dissolution process of FFA (200 mg) tablets could be obtained from Eq. 5, the best-fitting parameters for Eqs. 8 and 9 could be found by using non-

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TABLE II. Probability Parameters of Weibull and Log-Normal Distributions for $F(t)$ of FFA (200 mg) Tablets

CMC-Ca amount (mg/tab.)	Compression pressure (t)	Weibull distribution			Log-normal distribution		
		a	b	AIC	μ	δ	AIC
0	0	9.80	0.996	−72.7	6.18	1.15	−58.8
	0.2	74.8	1.49	−69.8	13.4	0.779	−107.3
	0.5	1.35×10^3	1.20	−93.2	3.11×10^2	1.41	−75.7
	0.8	4.49×10^2	0.859	−89.9	3.33×10^3	2.70	−89.5
	1.5	7.61×10^2	0.903	−67.8	5.05×10^3	2.69	−67.6
5	0	11.9	1.05	−76.6	6.73	1.10	−53.3
	0.2	11.7	1.05	−70.4	6.70	1.09	−62.7
	0.5	21.6	1.19	−48.3	8.83	.0.978	−54.9
	0.8	1.36×10^4	2.43	−97.5	44.9	0.629	−84.9
	1.5	6.94×10^2	1.08	−74.3	1.93×10^3	2.62	−39.6
10	0	4.98	0.890	−59.0	3.70	1.23	−47.9
	0.2	4.98	0.927	−39.4[a]	4.15	1.09	−25.9[a]
	0.5	9.28	1.08	−71.3	5.06	1.03	−72.6
	0.8	34.2	1.43	−67.6	8.45	0.815	−66.4
	1.5	9.04×10^2	2.08	−71.2	21.0	0.551	−65.0
15	0	3.24	0.746	−62.7	2.76	1.42	−53.4
	0.2	5.22	0.972	−61.5	3.46	1.11	−55.2
	0.5	7.80	1.03	−69.9	4.72	1.07	−73.4
	0.8	17.1	1.27	−62.8	8.44	0.816	−66.4
	1.5	3.07×10^2	1.85	−77.4	17.4	0.607	−62.5
25	0	2.82	0.863	−48.3	2.09	1.19	−54.1
	0.2	4.41	0.908	−47.1	3.18	1.16	−55.5
	0.5	5.85	1.05	−56.3	3.53	1.03	−62.8
	0.8	11.9	1.15	−58.8	5.70	0.980	−72.2
	1.5	48.9	1.55	−49.3	8.98	0.755	−50.2

a) $n=1$; the other values were obtained from the regression of data, obtained in 2 trials.

linear regression (simplex method).[9] The results are shown in Table II, where the fit of the experimental data was estimated in terms of Akaike's information criterion (AIC),[10] as shown in Eq. 10,

$$\mathrm{AIC}=N\cdot\ln(Re)+2P \tag{10}$$

where N, Re and P are the number of experimental data points, the residual sum of the squares and the number of parameters in the estimated model. Since each AIC in Table II had a large minus value, $F(t)$ values of FFA (200 mg) tablets were considered to be well-regressed to both the Weibull and log-normal distributions. The scale parameter (a) and the shape parameter (b) increased as the compression pressure was increased, and also as the level of disintegrant was decreased. With regard to the regression to the log-normal distribution, the logarithmic mean (μ) increased as the compression pressure was increased, and also as the level of disintegrant was decreased, whereas the standard deviation (σ) was only affected by the compression pressure, being unaffected by the level of disintegrant.

The experimental data for the dissolution rate of FFA (200 mg) tablets are shown in Table III. The dissolution rate was greatly affected by the amount of CMC-Ca and compression pressure, especially when the amount was less than 5 mg per tablet and the compression pressure was more than 0.8 t. The theoretical dissolution rates in relation to $S(t)$,

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TABLE III. 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

calculated with Eq. 4, are shown in Tables IV and V, for the Weibull distribution and log-normal distribution, respectively. There was little difference between the experimental data and the regression data of the two probability distributions, so that the time course patterns of $S(t)$ obtained by Eq. 3 were assumed to be reasonable. The time courses of the $S(t)$ value during the dissolution process obtained by non-linear regression to the Weibull and log-normal distributions are shown in Tables VI and VII, respectively. Most of the time course patterns of $S(t)$ in Tables VI and VII had a maximum. Furthermore, the time when $S(t)$ became maximum (t_{max}) was delayed, and the maximum value was decreased, as the compression pressure became higher, as well as when the amount of CMC-Ca became lower. That is, the $S(t)$ values of tablets containing less than 5 mg of CMC-Ca and compressed with 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. Typical dissolution patterns are shown in Fig. 2, and the $S(t)$ patterns obtained by non-linear regression to the Weibull and log-normal distributions are shown in Figs. 3 and 4. In Fig. 2, the full lines and the broken lines represent the regression curves of the Weibull and log-normal distributions, respectively.

The Available Surface Area of Granules before Compression

Besides compression pressure, the dispersion of granules prepared by wet granulation is also an important factor in determining the bioavailability of solid dosage forms. If it is assumed that spherical particles dissolve isotropically under sink conditions and that

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TABLE IV. The Theoretical Dissolution Rate in Relation to $S(t)$ Obtained by Non-linear Regression to the Weibull Distribution

CMC-Ca amount (mg/tab.)	Compression pressure (t)	% dissolved Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	10.8	20.3	28.7	42.7	66.4	80.0	88.1	95.7	98.4
	0.2	1.5	4.1	7.4	15.2	36.6	56.1	71.3	89.3	96.6
	0.5	0.1	0.2	0.3	0.6	1.3	2.1	3.0	4.8	6.7
	0.8	0.3	0.5	0.6	1.0	1.8	2.5	3.2	4.5	5.8
	1.5	0.1	0.3	0.4	0.6	1.2	1.7	2.2	3.1	4.0
5	0	9.0	17.7	25.6	39.4	63.9	78.5	87.2	95.5	98.4
	0.2	9.1	17.9	26.0	39.9	64.5	79.1	87.7	95.7	98.6
	0.5	5.1	11.2	17.4	29.4	54.2	71.3	82.4	93.7	97.9
	0.8	—	—	0.1	0.4	2.2	5.8	11.3	27.2	46.7
	1.5	0.2	0.3	0.5	0.9	1.9	3.0	4.0	6.2	8.3
10	0	20.1	33.7	44.3	59.9	80.9	90.4	95.1	98.6	99.6
	0.2	20.1	34.4	45.7	62.0	83.5	92.5	96.5	99.2	99.8
	0.5	11.4	22.4	32.3	48.9	75.0	87.9	94.3	98.7	99.7
	0.8	3.2	8.5	14.6	27.7	57.5	77.7	89.3	98.0	99.7
	1.5	0.1	0.5	1.2	3.5	13.8	29.0	46.0	75.3	91.7
15	0	29.0	43.4	53.4	66.9	83.8	91.3	95.0	98.2	99.3
	0.2	19.2	34.0	45.7	62.9	85.0	93.8	97.4	99.5	99.9
	0.5	13.4	25.2	35.5	52.0	76.9	88.9	94.6	98.8	99.7
	0.8	6.4	14.6	23.1	39.2	69.0	85.4	93.6	98.9	99.8
	1.5	0.4	1.3	2.8	6.9	22.6	41.5	59.4	84.5	95.6
25	0	32.5	50.6	62.9	78.1	93.3	97.7	99.2	99.9	100.0
	0.2	22.3	37.5	49.0	65.2	85.6	93.7	97.2	99.4	99.9
	0.5	17.4	32.4	44.8	63.3	86.8	95.3	98.3	99.8	100.0
	0.8	9.0	18.8	28.1	44.4	72.0	86.4	93.6	98.7	99.7
	1.5	2.3	6.5	11.8	24.1	54.6	76.6	89.3	98.4	99.8

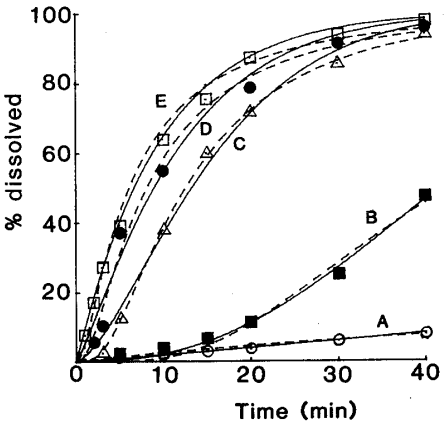

Fig. 2. The Typical Dissolution Patterns of FFA (200 mg) Tablets

$C_s = 1025$ mg/l; $W_0 = 200$ mg; $V = 900$ ml. The full lines are regression curves of the Weibull distribution and the broken lines are those of the log-normal distribution.

CMC-Ca (mg/tab.)	Compression pressure (t)	Experimental data	Regression line
5	1.5	⊙	A
5	0.8	■	B
0	0.2	△	C
5	0.5	●	D
5	0.2	⊡	E

solubility is independent of particle size, the diameter X of a particle at time t during the dissolution process is described by:[11]

$$X = X_0 - (2 \cdot k \cdot C_s/\rho) \cdot t \qquad (11)$$

where X_0 is the initial diameter of a particle and ρ is the density of FFA ($= 1.49$ g/cm^3). On the other hand, the X_0 of particles having a specific surface area of S_w is written as:

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TABLE V. The Theoretical Dissolution Rate in Relation to $S(t)$ Obtained by Non-linear Regression to the Log-Normal Distribution

CMC-Ca amount (mg/tab.)	Compression pressure (t)	% dissolved Time (min)								
		1	2	3	5	10	15	20	30	40
0	0	6.4	18.0	28.9	45.7	68.9	80.0	86.2	92.4	95.4
	0.2	0.1	0.8	3.1	11.5	38.2	58.8	72.2	86.5	92.9
	0.5	—	—	0.1	0.2	0.9	1.8	2.9	5.5	8.2
	0.8	0.2	0.4	0.6	0.9	1.8	2.6	3.3	4.6	5.7
	1.5	0.1	0.2	0.3	0.6	1.2	1.7	2.3	3.2	4.6
5	0	4.7	15.0	25.4	42.3	66.8	78.8	85.5	92.2	95.3
	0.2	4.6	14.8	25.3	42.4	67.1	79.1	85.8	92.5	95.5
	0.5	1.5	7.2	15.0	30.6	58.1	73.1	81.8	90.6	94.6
	0.8	—	—	—	—	1.0	4.6	11.1	28.5	45.7
	1.5	0.2	0.5	0.8	1.3	2.5	3.6	4.6	6.3	7.8
10	0	15.9	33.5	46.2	62.6	81.0	88.6	92.4	96.1	97.7
	0.2	10.7	27.5	41.2	59.8	81.0	89.3	93.4	96.9	98.3
	0.5	6.5	20.3	33.2	52.6	76.8	86.9	91.9	96.3	98.0
	0.8	0.5	4.3	11.4	28.4	61.1	78.1	87.0	94.7	97.5
	1.5	—	—	—	0.5	9.9	29.5	49.5	76.4	89.1
15	0	26.0	44.0	55.4	68.9	83.5	89.6	92.7	95.9	97.4
	0.2	14.6	33.7	47.9	65.8	84.7	91.7	94.9	97.7	98.8
	0.5	8.2	23.2	36.4	55.2	78.0	87.4	92.1	96.3	98.0
	0.8	0.5	4.4	11.4	28.5	61.2	78.1	87.0	94.7	97.5
	1.5	—	—	0.2	2.3	19.9	43.3	62.0	83.3	92.4
25	0	29.2	51.6	64.8	78.9	91.6	95.7	97.4	98.9	99.4
	0.2	17.6	37.3	51.0	67.9	85.4	91.9	95.0	97.7	98.7
	0.5	12.3	31.6	46.7	66.0	86.0	92.9	95.9	98.3	99.2
	0.8	4.3	15.8	28.0	47.7	74.1	85.4	91.1	96.0	97.9
	1.5	0.2	2.7	8.2	24.0	58.7	77.4	87.0	95.1	97.9

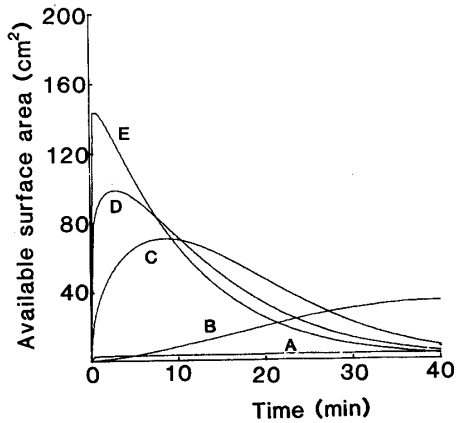

Fig. 3. Typical $S(t)$ *vs.* t Patterns of FFA (200 mg) Tablets Obtained by Regressing $F(t)$ to the Weibull Distribution

$C_s = 1025$ mg/l; $W_o = 200$ mg; $V = 900$ ml; $k = 0.127$ cm/min. A—E are the same as in Fig. 2.

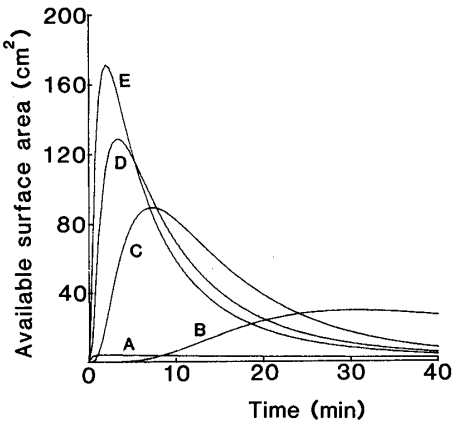

Fig. 4. Typical $S(t)$ *vs.* t Patterns of FFA (200 mg) Tablets Obtained by Regressing $F(t)$ to the Log-Normal Distribution

$C_s = 1025$ mg/l; $W_o = 200$ mg; $V = 900$ ml; $k = 0.127$ cm/min. A—E are the same as in Fig. 2.

$$X_o = 6/(\rho \cdot S_w) \tag{12}$$

Furthermore, the particle number (N_o) of FFA in a tablet is described by:

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TABLE VI. The Time Course of $S(t)$ during the Dissolution Process of FFA (200 mg) Tablets Obtained by Non-linear Regression to the Weibull Distribution

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	171.4	185.6	164.4	118.1	55.0	29.8	17.8	7.8	4.0
	0.2	3.4	22.5	46.7	82.6	82.6	58.5	38.9	17.3	8.3
	0.5	0.1	0.4	0.7	1.3	2.5	3.2	3.7	4.1	4.3
	0.8	2.8	2.9	2.9	2.8	2.5	2.3	2.1	1.9	1.7
	1.5	1.7	1.8	1.9	1.9	1.8	1.6	1.6	1.4	1.3
5	0	139.8	170.9	159.9	121.1	58.9	32.1	19.2	8.3	4.2
	0.2	138.3	171.3	161.0	122.3	59.2	32.1	19.2	8.2	4.1
	0.5	59.2	111.5	128.0	119.3	70.1	40.7	24.9	10.8	5.4
	0.8	—	—	—	0.5	6.4	16.0	24.0	29.8	27.0
	1.5	4.1	4.2	4.2	4.0	3.5	3.2	2.9	2.5	2.2
10	0	319.0	247.8	184.5	140.1	109.0	40.5	19.6	11.0	2.2
	0.2	270.3	253.3	202.1	124.9	45.8	21.1	11.2	4.1	1.8
	0.5	194.3	223.4	196.6	134.1	53.9	25.6	13.8	5.0	2.2
	0.8	27.5	88.8	126.0	137.8	83.0	44.1	24.2	8.4	3.4
	1.5	—	0.1	0.8	8.4	50.6	69.4	62.4	33.9	15.8
15	0	376.8	237.1	161.9	89.1	32.6	15.9	9.2	4.0	2.1
	0.2	333.1	275.5	205.8	117.9	39.4	17.3	8.9	3.1	1.4
	0.5	225.6	234.0	196.8	128.9	50.5	24.0	13.0	4.8	2.2
	0.8	27.8	89.2	126.4	137.8	82.9	44.0	24.2	8.4	3.4
	1.5	—	1.0	5.7	27.6	75.1	73.6	55.4	25.4	11.1
25	0	479.2	290.1	184.8	88.8	24.4	9.8	4.8	1.6	0.7
	0.2	362.2	274.9	198.3	110.4	36.6	16.2	8.5	3.1	1.4
	0.5	316.9	288.0	220.8	126.7	40.2	16.7	8.1	2.6	1.0
	0.8	145.6	199.1	189.6	139.7	70.3	28.9	15.5	5.6	2.4
	1.5	13.4	63.3	106.3	135.5	90.6	48.4	26.1	8.5	3.2

$$N_0 = W_0 \cdot S_w/(\pi \cdot X_0^2) \tag{13}$$

Then, if the particles were perfectly wetted, the ideal $S(t)$ pattern for W_0 g of FFA can be written as:

$$S(t) = N_0 \cdot \pi \cdot X^2 = W_0 \cdot S_w \cdot \{1-(k \cdot C_s \cdot S_w/3) \cdot t\}^2 \tag{14}$$

Since initial $S(t)$ cannot be determined from the Weibull distribution when $b<1$, log-normal distribution was applied to determine the $S(t)$ patterns of the granules before compression. The ideal $S(t)$ pattern, as well as the $S(t)$ patterns of the granules before compression obtained by non-linear regression to the log-normal distribution are shown in Fig. 5. If the FFA in granules is perfectly wetted and dispersed, the $S(t)$ will be zero at about 8 min. However, due to granulation, the rate of decrease of $S(t)$ was delayed, especially when the amount of CMC-Ca was less than 5 mg per 300 mg (the weight of one tablet).

Quantitative Analysis of the Available Surface Area for FFA (200 mg) Tablets

By using the probability parameters of the Weibull distribution, the following expressions can be obtained,[1b)]

$$T_{20} = \sqrt[b]{a \cdot \ln 1.25} \tag{15}$$

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TABLE VII. The Time Course of $S(t)$ during the Dissolution Process of FFA (200 mg) Tablets Obtained by Non-linear Regression to the Log-Normal Distribution

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	158.9	143.2	129.2	105.3	63.4	38.3	23.2	8.5	3.1
	0.2	34.0	46.7	55.2	65.5	70.5	61.1	46.9	21.8	8.1
	0.5	1.5	1.8	1.9	2.1	2.4	2.6	2.7	2.9	3.0
	0.8	3.3	3.0	2.8	2.6	2.4	2.2	2.2	2.0	1.9
	1.5	2.1	1.9	1.8	1.7	1.6	1.6	1.5	1.4	1.4
5	0	140.5	132.9	123.7	105.0	66.8	41.3	25.2	9.1	3.2
	0.2	142.7	134.8	125.2	106.0	66.8	41.0	24.8	8.8	3.1
	0.5	91.1	97.9	99.1	94.6	72.1	49.9	32.8	12.9	4.6
	0.8	0.3	0.8	1.5	3.1	8.2	14.1	20.2	30.1	34.0
	1.5	2.7	2.8	2.9	3.0	3.2	3.3	3.3	3.3	3.4
10	0	253.2	197.7	160.8	111.8	50.5	24.6	12.4	3.4	1.0
	0.2	263.7	209.2	170.6	117.4	49.9	22.3	10.3	2.3	0.5
	0.5	181.0	169.6	154.6	124.2	66.3	33.6	16.6	3.8	0.8
	0.8	70.3	90.2	100.9	106.3	88.7	56.9	31.5	7.1	1.2
	1.5	4.0	8.4	12.9	22.0	41.9	54.5	57.7	42.5	19.9
15	0	292.8	199.3	149.7	95.0	39.8	19.6	10.4	3.4	1.2
	0.2	266.2	217.2	179.1	123.4	50.2	20.8	8.7	1.6	0.3
	0.5	201.2	179.7	158.8	122.5	62.0	30.8	15.1	7.4	0.8
	0.8	121.3	134.7	136.7	126.4	80.6	43.2	20.9	4.0	0.6
	1.5	10.4	18.6	25.9	38.4	58.7	64.0	58.0	32.3	12.0
25	0	371.7	252.9	182.6	102.5	29.1	9.3	3.2	0.4	0.1
	0.2	284.2	218.6	174.3	115.7	46.1	19.6	8.7	1.8	0.4
	0.5	262.0	225.9	191.0	133.4	51.2	18.9	6.8	0.8	0.1
	0.8	153.9	154.1	146.6	124.8	72.1	37.9	18.8	4.2	0.8
	1.5	53.8	75.7	89.8	103.8	94.3	62.5	34.1	6.6	0.8

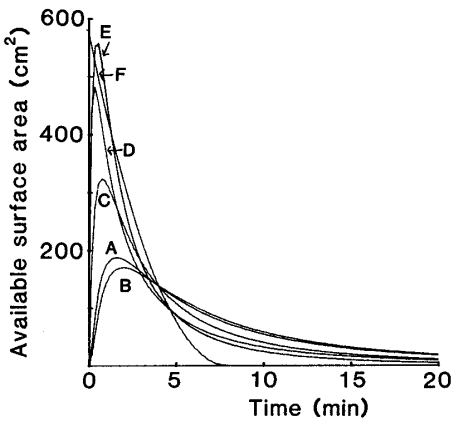

Fig. 5. The $S(t)$ *vs.* t Patterns of the Granules before Compression

$C_s = 1025$ mg/l; $W_0 = 200$ mg; $V = 900$ ml; $k = 0.127$ cm/min; $S_w = 580\,cm^2/200$ mg. A, CMC-Ca = 0 mg/300 mg; B, CMC-Ca = 5 mg/300 mg; C, CMC-Ca = 10 mg/300 mg; D, CMC-Ca = 15 mg/300 mg; E, CMC-Ca = 25 mg/300 mg; F, Ideal $S(t)$ pattern calculated from Eq. 14.

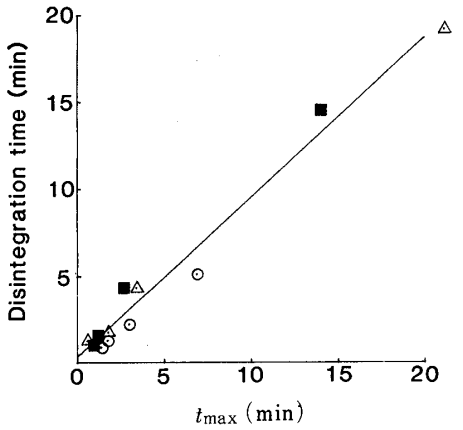

Fig. 6. Disintegration Time *vs.* t_{max} Plots for FFA (200 mg) Tablets

△, CMC-Ca = 10 mg/tab.; ■, CMC-Ca = 15 mg/tab.; ⊙, CMC-Ca = 25 mg/tab.

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TABLE VIII. The Time Values in Relation to $S(t)$ of FFA (200 mg) Tablets

CMC-Ca amount (mg/tab.)	Compression pressure (t)	Weibull					Log-normal	
		T_{20} (min)	T_{50} (min)	T_d (min)	t_{max} (min)	S_{max} (cm^2)	t_{max} (min)	S_{max} (cm^2)
0	0	2.19	6.85	9.85	—	—	1.65	1.88×10^2
	0.2	6.61	14.2	18.1	8.58	71.2	7.30	89.6
	0.5	1.16×10^2	2.99×10^2	4.06×10^2	91.2	3.21	42.6	4.26
	0.8	2.13×10^2	7.98×10^2	1.22×10^3	—	—	2.27	2.94
	1.5	2.95×10^2	1.03×10^3	1.55×10^3	—	—	3.64	1.90
5	0	2.53	7.46	10.6	0.58	1.42×10^2	2.01	1.71×10^2
	0.2	2.49	7.34	10.4	0.57	1.44×10^2	2.04	1.71×10^2
	0.5	3.75	9.72	13.2	2.83	99.1	3.39	1.29×10^2
	0.8	27.1	43.2	50.2	40.4	34.0	30.2	29.8
	1.5	1.07×10^2	3.04×10^2	4.27×10^2	38.4	3.35	2.02	4.23
10	0	1.13	4.02	6.07	—	—	0.82	3.23×10^2
	0.2	1.12	3.81	5.65	—	—	1.26	2.77×10^2
	0.5	1.96	5.60	7.87	0.71	1.82×10^2	1.75	2.25×10^2
	0.8	4.14	9.15	11.8	5.10	1.08×10^2	4.35	1.40×10^2
	1.5	12.8	22.1	26.4	19.2	57.8	15.5	69.5
15	0	0.65	2.17	4.83	—	—	0.37	4.83×10^2
	0.2	1.17	3.75	5.47	—	—	1.01	3.33×10^2
	0.5	1.71	5.15	7.35	0.24	2.12×10^2	1.50	2.42×10^2
	0.8	2.87	7.01	9.35	2.76	1.37×10^2	4.34	1.40×10^2
	1.5	9.82	18.1	22.1	14.5	64.1	12.0	78.6
25	0	0.58	2.17	3.32	—	—	0.51	5.64×10^2
	0.2	0.98	3.42	5.13	—	—	0.83	3.67×10^2
	0.5	1.29	3.79	5.38	0.30	2.79×10^2	1.22	3.23×10^2
	0.8	2.34	6.26	8.62	1.47	1.56×10^2	2.18	2.00×10^2
	1.5	4.67	9.71	12.3	6.30	1.06×10^2	5.08	1.36×10^2

TABLE IX. Disintegration Time of FFA (200 mg) Tablets in pH 6.8 Phosphate Buffer Containing 10% (w/v) of Polysorbate 80

CMC-Ca amount (mg/tab.)	Disintegration time (min) Compression pressure (t)			
	0.2	0.5	0.8	1.5
0	1.80 ± 0.12[a)]	151 ± 17.2	148 ± 18.6	359 ± 6.1
5	0.71 ± 0.07	3.28 ± 0.48	45.6 ± 5.1	175 ± 4.1
10	0.58 ± 0.08	1.78 ± 0.12	3.39 ± 0.23	21.1 ± 0.58
15	0.89 ± 0.03	1.12 ± 0.04	2.61 ± 0.27	13.9 ± 1.33
25	1.29 ± 0.12	1.66 ± 0.11	2.90 ± 0.29	6.80 ± 0.57

a) Mean ± S.D. ($n=6$).

$$T_{50}=\sqrt[b]{a\cdot\ln 2} \tag{16}$$

$$T_d=\sqrt[b]{a} \tag{17}$$

where T_{20}, T_{50} and T_d are the times when 20%, 50% and 63.2%, respectively, of the available surface area has been generated during the dissolution process. Furthermore, the peak time (t_{max}) when $S(t)$ is maximum can be determined by using Eqs. 18 and 19, for the Weibull and log-normal distributions, respectively.[6)]

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$$t_{max}=\sqrt[b]{a(b-1)/b} \tag{18}$$

$$t_{max}=\exp(\ln\mu-\sigma^2) \tag{19}$$

These time values, as well as the maximum values of $S(t)$ (S_{max}) for FFA (200 mg) tablets are shown in Table VIII. When the compression pressure was low, and the amount of CMC-Ca high, well-defined t_{max} values could be obtained, and there was little difference between the data determined by the Weibull and log-normal distributions. The initial $S(t)$ increase was considered to be due to tablet disintegration and deaggregation, and the subsequent decrease in $S(t)$, after t_{max}, was considered to be due to FFA dissolution. Furthermore, there was little difference between the T_{20}, T_{50} and T_d values of granules before compression (compression pressure = 0 t) and those of tablets compressed at 0.2 t, whereas when the compression pressure was more than 0.5 t, these time values increased abruptly as the compression pressure was increased. That is to say, the aggregation of granules by compression affected the $S(t)$ of FFA tablets when the compression pressure was more than 0.5 t. The relationship between t_{max} and the disintegration time (DT) of FFA (200 mg) tablets was therefore investigated. The disintegration times of FFA (200 mg) tablets are shown in Table IX, and the DT *vs.* t_{max} plot is shown in Fig. 6, where t_{max} was selected from the better fitting value of the two probability distributions. A good correlation ($r=0.985$) was found to exist between DT and t_{max}, the equation being:

$$t_{max}=0.920DT+0.384 \tag{20}$$

Furthermore, since the slope of the line had a value close to 1 and the y-intercept was close to zero, the t_{max} was found to be almost equal to the disintegration time.

In conclusion, by applying non-linear regression to probability distributions, the time course of $S(t)$ during the dissolution process of FFA (200 mg) tablets compressed at various compression pressures could be elucidated. The compression pressure and the level of disintegrant were found to be important factors affecting the time course of $S(t)$ for FFA in tablets.

References and Notes

1) *a*) This paper forms Part III of "Dissolution Profile in Relation to Available Surface Area"; *b*) Part II: S. Itai, M. Nemoto, S. Kouchiwa, H. Murayama and T. Nagai, *Chem. Pharm. Bull.*, **33**, 5464 (1985).
2) S. Kitazawa, I. Johno, S. Teramura and J. Okada, *J. Pharm. Pharmacol.*, **27**, 765 (1975).
3) S. Kitazawa, I. Johno, T. Minouchi and J. Okada, *J. Pharm. Pharmacol.*, **29**, 453 (1977).
4) N. Kitamori and T. Makino, *J. Pharm. Pharmacol.*, **31**, 501 (1979).
5) S. Esezobo and V. Ambujam, *J. Pharm. Pharmacol.*, **34**, 761 (1982).
6) S. Kouchiwa, M. Nemoto, S. Itai, H. Murayama and T. Nagai, *Chem. Pharm. Bull.*, **33**, 1641 (1985).
7) A. W. Noyes and W. Whitney, *J. Am. Chem. Sci.*, **19**, 930 (1897).
8) J. G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).
9) Non-linear regressions were performed using the MULTI program devised by K. Yamaoka and U. Tanikawara.
10) K. Yamaoka, T. Nakagawa and T. Uno, *J. Pharmacokinet. Biopharm.*, **6**, 165 (1978).
11) J. T. Carstensen and M. N. Musa, *J. Pharm. Sci.*, **61**, 223 (1972).

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