Dissolution and Simulation Curves for Log-Normal Particle-Size-Distributed Model Systems

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Log-normal particle-size-distributed systems were expressed as a generalized equation and the relative diameter which gave the maximum relative weight was expressed as a function of the standard deviation of log-normal particle-size distribution. Generalized distribution curves independent of the mean particle size were then obtained. Several mixed model systems were prepared with sieved *n*-propyl *p*-hydroxybenzoate crystalline particles following the generalized distribution curves. The dissolution of model systems were conducted under sink and nonsink conditions, and the dissolution processes were simulated on the basis of cube root law equations. After the validity of the simulation method was confirmed, the method was applied to estimate the apparent mean diameters which partially define the isotropic dissolution processes of log-normal particle-size-distributed systems. The apparent mean diameter was then expressed as a function of the standard deviation of log-normal particle-size distribution.

Keywords paraben; *n*-propyl *p*-hydroxybenzoate; crystalline particle; dissolution; simulation; cube root law; mixed system; log-normal particle-size distribution

Introduction

Dissolution behavior of a powder or a tablet which immediately disintegrates depends on the particle size, and hence, surface area. Methods to evaluate or predict the dissolution process have been reported.[1] The dissolution profiles were well simulated on the basis of temporal changes of particle size and surface area during the dissolution. Among the simulation methods, the method by means of the cube root law equation which does not require the direct measurement of temporal changes in particle size gave comparable results with the method based on the direct measurement of changes of particle size.[1d]

It has been said that particles prepared by random process produced skewed distribution functions close to log-normal.[2] The dissolution properties of powders obeying log-normal particle-size distribution have been presented.[2,3] As described, particle-size distribution gradually changes with dissolution time, and dissolution properties had been strictly treated. However, the diameter which might define the dissolution property had never been suggested for log-normal distribution. Log-normal particle-size distribution was expressed as a generalized equation and distribution curves independent of the mean particle size.[1e] Also, the diameter of the maximum weight component in the weight-base log-normal particle-size distribution was expressed as a function of the standard deviation value, and it was supposed that the diameters which define the isotropic dissolution may be given by a function of the standard deviation value, even if it were valid in the initial dissolution stage. Examining with imaginary systems,[1c,d] it had been suggested that the simulation values coincided well with those of actual systems when imaginary components were chosen to reflect the original actual particle-size distribution pattern.

Hence, the mixed model systems were prepared with sieved crystals following the generalized particle-size-distribution curves. The simulation method based on the cube root law equation was examined with the dissolution of the mixed model systems, and then the method was applied to estimate the apparent mean diameters which may define the dissolution of the log-normal particle-size-distributed systems.

Experimental

Materials *n*-Propyl *p*-hydroxybenzoate (extra pure reagent, Kanto Chemical Co., Ltd.) separated into 14/20, 20/28, 28/35, 35/48, 48/65, 65/100 and 100/145 mesh fractions by means of J.I.S. sieves were used.[1b,e] Their Heywood's diameters measured using a LUZEX-500 image analyzer (NIRECO Co., Ltd.) were 0.134, 0.104, 0.076, 0.048, 0.038, 0.025 and 0.019 cm, respectively.

Dissolution Measurement A suitable amount of samples (equivalent or equivalent to one-twentieth of the solubility) mixed of sieved crystals at various weight ratios was used. The mixed sample was prepared following the generalized log-normal particle-size-distribution curves, and was added to a dissolution apparatus (type NTR-VS, Toyama Sangyo Co., Ltd.). The dissolution test was carried out in 1000 ml of water at a paddle rotation speed of 250 rpm at 25 °C. The concentration was estimated from the absorbance at 255 nm by means of sampling a small amount of the solution for a test under a nonsink condition, or flow cell set in a spectrophotometer (type 200-20, Hitachi Ind. Co.) *via* a pump for the test under a sink condition.[1b]

Results and Discussion

Application of Cube Root Law Equation Cube root law equations deduced were applied.[1d] The dissolution behavior carried out under the sink condition is expressed by:

$$M_{\mathrm{o}}^{1/3} - M^{1/3} = (2kC_{\mathrm{s}}/\rho f)(M_{\mathrm{o}}^{1/3}/D_{\mathrm{H,o}})t \tag{1}$$

$$(M/M_{\mathrm{o}})^{1/3} = 1 - (2kC_{\mathrm{s}}/\rho f)(t/D_{\mathrm{H,o}}) \tag{2}$$

Here, M_{o} is the amount used, M is the amount remaining in the solution ($= M_{\mathrm{o}} - m$, m is the amount dissolved), k is the dissolution rate constant ($=$ the diffusion constant/the thickness of the diffusion layer), C_{s} is the solubility, ρ is the density, f is the coefficient concerned with the shape and $D_{\mathrm{H,o}}$ is the initial diameter. The dissolution rate constant for Pr-PHBA obtained from the linear relationship expressed by Eq. 2 was 0.166 cm/min[1d] independent of the initial particle size where C_{s}, ρ and f were equal to 0.00033 g/ml, 1.28 g/cm^3 and 0.3690, respectively.[1a,b]

When the dissolution is carried out under a nonsink condition where the initial amount is equivalent to the amount needed to saturate the solution ($M_{\mathrm{o}} = C_{\mathrm{s}}V = M_{\mathrm{s}}$), in the same way as Niebergall *et al.* tried to simplify the treatment of dissolution behavior, the following equations are obtained.[1d,4]

$$M^{-2/3} = M_{\mathrm{o}}^{-2/3} + (4k/\rho fV)(M_{\mathrm{o}}^{1/3}/D_{\mathrm{H,o}})t \tag{3}$$

$$(M_{\mathrm{o}}/M)^{2/3} = 1 + (4kC_{\mathrm{s}}/\rho f)(t/D_{\mathrm{H,o}}) \tag{4}$$

According to Eq. 4, $(M_{\mathrm{o}}/M)^{2/3}$ *versus* $t/D_{\mathrm{H,o}}$ plot should
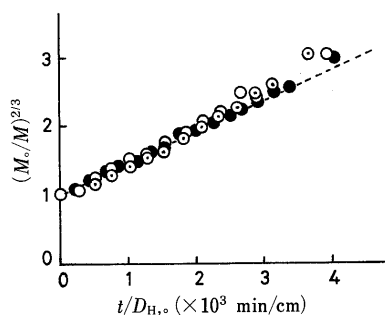
Fig. 1. Applicability of Cube Root Law Equation for Dissolution of Sieved Crystalline Particles

●, Pr-PHBA (14/20); ○, Pr-PHBA (48/65); ⊙, Pr-PHBA (100/145); ---, calculated value.

give one straight line independent of the initial particle size. Hence, the applicability of the equation was examined with the dissolution of sieved samples, and the results are shown in Fig. 1. The broken line in the figure shows the calculated values of Eq. 4. The measured values that fit well with the line within $(M_o/M)^{2/3}$ are equal to around 2.25 where the dissolved amount corresponds to about 70% of the initial amount. According to Eq. 1 or 2 for dissolution under the sink condition, the time when a given particle size crystalline dissolves can be calculated precisely. On the other hand, Eq. 3 or 4 for dissolution under the nonsink condition does not give such a definite time, and the broken line shown in Fig. 1 continues infinitely. Taking into account such property of the equations, the dissolution of sieved samples conducted under the nonsink condition was also supposed to be well expressed by Eq. 4.

Equations 2 and 4 derived for a monodisperse system have to be modified for a polydisperse system to simulate the dissolution of mixed model systems as follows.[1d, 5]

In a polydisperse system, the amount used and amount remaining in the solution are given by the summation of those of component i, i.e., $M_o = \Sigma w_{i,\circ}$ and $M = \Sigma w_i$, respectively.

In the case of the sink condition, the following equations were obtained from Eq. 1 by denoting $D_{H,i}$ the initial Heywood's diameter of component i.

$$w_i^{1/3} = w_{i,\circ}^{1/3} - (2kC_s/\rho f)(w_{i,\circ}^{1/3}/D_{H,i}) t \tag{5}$$

$$M^{1/3} = M_\circ^{1/3} - \Sigma \{(2kC_s/\rho f)(w_{i,\circ}^{1/3}/D_{H,i}) t\} \tag{6}$$

$$(M/M_\circ)^{1/3} = 1 - (2kC_s/\rho f) \Sigma \{(w_{i,\circ}/M_\circ D_{H,i}^3)^{1/3} t\} \tag{7}$$

$$\{M_\circ/\Sigma (w_{i,\circ}/D_{H,i}^3)\}^{1/3} = D_v \tag{8}$$

$$(M/M_\circ)^{1/3} = 1 - (2kC_s/\rho f D_v) t \tag{9}$$

Here, D_v is the mean volume diameter. Concerning D_v, dissolution and its simulation under the sink condition with various mixed systems other than the log-normal distribution pattern were examined, and 1.090 was obtained as the corrective coefficient.[1d] The following equations were then obtained from Eq. 7 or 9, respectively.

$$C_T = (1/V) \Sigma w_{i,\circ}[1 - \{1 - (2kC_s/\rho f D_{H,i}) t\}^3] \tag{10}$$

$$C_v = (M_\circ/V)[1 - \{1 - (2kC_s/1.090\rho f D_v) t\}^3] \tag{11}$$

The following equation in terms of the volume mean diameter, i.e., $D_w(=(\Sigma w_{i,\circ} D_{H,i})/M_\circ)$, was also examined. Here, the corrective coefficient was also examined as well as D_v, and 0.995 obtained was used.[1d]

$$C_w = (M_\circ/V)[1 - \{1 - (2kC_s/0.995\rho f D_w) t\}^3] \tag{12}$$

In the case of the nonsink condition, the following equations were obtained in the same manner.

$$M^{-2/3} = M_\circ^{-2/3} + \Sigma \{(4k/\rho f V)(w_{i,\circ}^{1/3}/D_{H,i}) t\} \tag{13}$$

$$(M_\circ/M)^{2/3} = 1 + (4kM_\circ/\rho f V) \Sigma \{(w_{i,\circ}/M_\circ D_{H,i}^3)^{1/3} t\} \tag{14}$$

$$(M_\circ/M)^{2/3} = 1 + (4kC_s/\rho f D_v) t \tag{15}$$

Hence, the following equations were obtained.

$$C_T = (1/V) \Sigma w_{i,\circ}[1 - \{1 + (4kC_s/\rho f D_{H,i}) t\}^{-3/2}] \tag{16}$$

$$C_v = C_s[1 - \{1 + (4kC_s/\rho f D_v) t\}^{-3/2}] \tag{17}$$

$$C_w = C_s[1 - \{1 + (4kC_s/\rho f D_w) t\}^{-3/2}] \tag{18}$$

These equations derived for the sink condition (Eqs. 10—12) and the nonsink condition (Eqs. 16—18) were used for the simulation of isotropic dissolution processes of mixed systems.

Dissolution and Simulation for the Log-Normal Particle-Size-Distributed Model Systems Consider a system containing spherical particles of diameters (D) which are distributed log-normally on a number basis, so that $\ln D$ is normal with the mean diameter (D_{mean}) and standard deviation (σ). The probability frequency ($F(D)$) and the relative probability frequence ($F(D)/F(D_{mean})$) were expressed by following generalized equations independent of the mean diameter on a number basis.

$$F(D) = (1/\sigma\sqrt{2\pi}) \exp[-\{\ln(D/D_{mean})\}^2/2\sigma^2] \tag{19}$$

$$F(D)/F(D_{mean}) = \exp[-\{\ln(D/D_{mean})\}^2/2\sigma^2] \tag{20}$$

Also, taking into account the volume and density of the particles, the relative weight (W/W_{mean}) can be expressed as follows.[1e]

$$W/W_{mean} = \{\pi D^3 \rho F(D)/6\}/\{\pi D_{mean}^3 \rho F(D_{mean})/6\} \tag{21}$$

$$\ln (W/W_{mean}) = -(1/2\sigma^2)\{\ln (D/D_{mean}) - 3\sigma^2\}^2 + 9\sigma^2/2 \tag{22}$$

According to Eq. 22, when $\ln(D/D_{mean})$ is equal to $3\sigma^2$, $\ln(W/W_{mean})$ is equal to $9\sigma^2/2$ and is the maximum value. When the diameter and weight of the maximum weight component are expressed as $D_{w.max}$ and W_{max}, respectively, the relative diameters which give the maximum relative weight are expressed by:

$$\ln \cdot \ln(D_{w.max}/D_{mean}) = \ln 3 + 2 \ln \sigma \tag{23}$$

Hence, when the σ- and the D_{mean} or the $D_{w.max}$ value are given optionally, the log-normal particle-size-distribution curve can be defined. Thus, several log-normal particle-size-distributed model systems can be prepared following the generalized log-normal particle-size distribution curves at a given σ-value, and examples are shown in Fig. 2.

The dissolution and simulation curves under a nonsink condition for the log-normal particle-size-distributed model system are shown in Fig. 3 as an example. The validities of the simulation methods were estimated from the mean value ($\bar{R}_T$, $\bar{R}_v$ and $\bar{R}_w$) of the ratios of simulated value to measured value (C), i.e., C_T/C ($= R_T$), C_v/C ($= R_v$) and C_w/C ($= R_w$) and standard deviation (S.D.).[1b] Results obtained are summarized in Tables I and II.

Generally, the $\bar{R}_T$-value is closer to unity than the $\bar{R}_v$- and $\bar{R}_w$-values. In the case of C_v, even though D_v was introduced in the derivation process of the cube root law equation, the $\bar{R}_v$-value is not always close to unity, and the deviation from unity increases with an increase in the σ-value. When
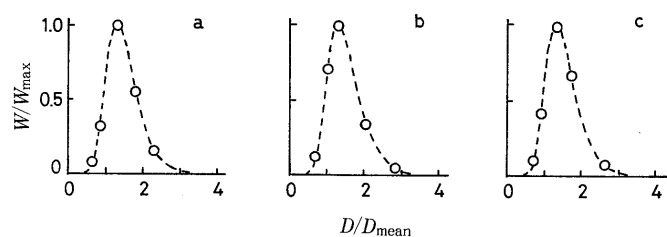
Fig. 2. Log-Normal Particle-Size-Distributed Model Systems ($\sigma = 0.3$)

$D_{w.max}$ (cm): a, 0.076; b, 0.048; c, 0.038. ---, generalized log-normal particle-size-distribution curve.
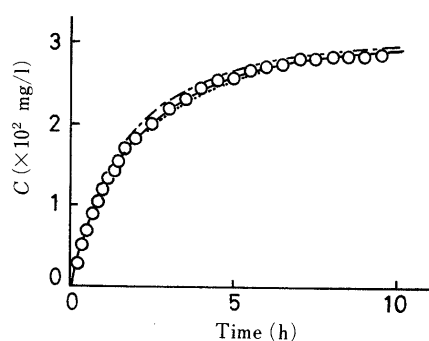

Fig. 3. Dissolution and Simulation Curves of Log-Normal Particle-Size-Distributed Model System

$\sigma = 0.3$; $D_{w.max} = 0.076$ cm; —, C_T; ---, C_v; —·—, C_w.

TABLE I. Evaluation of Simulated Values for Dissolution of Log-Normal Particle-Size-Distributed Model Systems under Nonsink Condition

	Model system				
σ	D_{mean} (cm)	$D_{w.max}$ (cm)	$\bar{R}_T \pm$ S.D.	$\bar{R}_v \pm$ S.D.	$\bar{R}_w \pm$ S.D.
0.2	0.0336	0.0376	1.029 ± 0.048	1.013 ± 0.038	1.027 ± 0.044
	0.0432	0.0484	1.018 ± 0.009	0.998 ± 0.017	1.015 ± 0.010
	0.0676	0.0757	1.004 ± 0.015	0.987 ± 0.021	0.997 ± 0.017
0.3	0.0285	0.0376	1.021 ± 0.029	1.042 ± 0.029	1.009 ± 0.022
	0.0366	0.0484	1.000 ± 0.027	1.010 ± 0.028	0.986 ± 0.041
	0.0573	0.0757	1.004 ± 0.018	1.042 ± 0.024	0.983 ± 0.020
0.4	0.0232	0.0376	1.031 ± 0.021	1.068 ± 0.019	1.011 ± 0.030
	0.0299	0.0484	1.012 ± 0.018	1.058 ± 0.013	0.984 ± 0.040
0.5	0.0178	0.0376	1.037 ± 0.038	1.100 ± 0.055	1.003 ± 0.029
	0.0228	0.0484	0.998 ± 0.024	1.067 ± 0.009	0.966 ± 0.063
0.6	0.0127	0.0376	1.048 ± 0.047	1.127 ± 0.064	1.002 ± 0.042
	0.0163	0.0484	1.004 ± 0.030	1.108 ± 0.038	0.951 ± 0.070
0.7	0.0087	0.0376	1.016 ± 0.022	1.107 ± 0.023	0.966 ± 0.072
	0.0111	0.0484	1.041 ± 0.020	1.165 ± 0.056	0.980 ± 0.060

TABLE II. Evaluation of Simulated Values for Dissolution of Log-Normal Particle-Size-Distributed Model Systems under Sink Condition

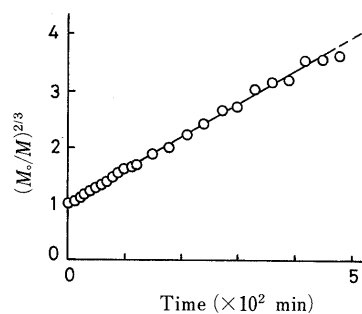|	Model system				
σ	D_{mean} (cm)	$D_{w.max}$ (cm)	$\bar{R}_T \pm$ S.D.	$\bar{R}_v \pm$ S.D.	$\bar{R}_w \pm$ S.D.
0.2	0.0336	0.0376	0.979 ± 0.020	0.960 ± 0.035	0.977 ± 0.024
	0.0432	0.0484	0.974 ± 0.026	0.951 ± 0.043	0.970 ± 0.032
	0.0932	0.1044	1.025 ± 0.033	1.016 ± 0.018	1.024 ± 0.025
0.3	0.0285	0.0376	0.979 ± 0.018	0.999 ± 0.011	0.972 ± 0.028
	0.0366	0.0484	1.007 ± 0.020	1.015 ± 0.016	0.997 ± 0.017
	0.0573	0.0757	0.964 ± 0.025	0.999 ± 0.015	0.945 ± 0.056
	0.0791	0.1044	0.992 ± 0.017	0.990 ± 0.019	0.990 ± 0.019
0.4	0.0232	0.0376	0.984 ± 0.032	1.018 ± 0.037	0.972 ± 0.061
	0.0299	0.0484	0.979 ± 0.019	1.011 ± 0.022	0.957 ± 0.056
	0.0467	0.0757	0.972 ± 0.025	1.021 ± 0.023	0.947 ± 0.069
0.5	0.0178	0.0376	0.966 ± 0.034	1.022 ± 0.032	0.947 ± 0.078
	0.0228	0.0484	0.952 ± 0.038	1.045 ± 0.029	0.926 ± 0.083
	0.0357	0.0757	0.971 ± 0.036	1.039 ± 0.034	0.943 ± 0.096
0.6	0.0127	0.0376	0.959 ± 0.042	1.028 ± 0.041	0.932 ± 0.099
	0.0163	0.0484	0.972 ± 0.019	1.062 ± 0.042	0.937 ± 0.080
0.7	0.0087	0.0376	0.965 ± 0.033	1.041 ± 0.037	0.933 ± 0.096
	0.0111	0.0484	0.960 ± 0.049	1.061 ± 0.060	0.920 ± 0.124

Fig. 4. Applicability of Cube Root Law Equation for Dissolution of Log-Normal Particle-Size-Distributed Model System

$\sigma = 0.3$; $D_{w.max} = 0.076$ cm.

the σ-value is small, the $\bar{R}_v$-value is close to unity, and simulations by means of Eqs. 11 and 17 were thought to be useful for the relatively symmetrical particle-size-distributed systems.[1d] In the case of C_w, D_w was introduced optionally in the cube root law equation, however, the treatment fitted well for the relatively symmetrical particle-size-distributed systems as well as for the treatment by means of the D_v-value. Here, the $\bar{R}_w$-value is closer to unity than the $\bar{R}_v$-value in a nonsink condition.

When the dissolution of these model systems were treated by means of the cube root law equation in the same manner as for a monodisperse system, a good linear relationship was obtained as shown in Fig. 4 as an example. The dissolution of the model system was then supposed to be defined by

a certain apparent mean diameter, at least in the initial dissolution stage. Hence, the apparent mean diameters (D_{app}) of the model systems were estimated from the slope of the straight line given by $(M_o/M)^{2/3}$ versus the t plot, and results are summarized in Table III. Also, the results obtained with the sink condition are summarized in Table IV. Following the same manner, the D_T-values were estimated by use of the C_T-value, and are also listed in these Tables. Here, the applicability of the equations change with the σ-value as Pederson et al. described.[3d] As was expected, the fitting range decreased with an increase in the σ-value. When the σ-value is equal to 0.2, the simulated values are fit with those measured until the amount dissolved reaches is ca. 90% of the initial amount. When the σ-value is equal to 0.7, it is decreased to ca. 20%.

As expected from the results shown in Tables I and II, the D_T-value is closer to the D_{app}-value than the D_v- and D_w-values. Hence, the simulation method by means of C_T was thought to be more useful than the other methods examined here, even though it required numerous calculations. Nevertheless, the simulation methods by use of D_v and D_w are very simple methods compared with that of C_T, and both methods were thought to be useful for dissolution with relatively symmetrical particle-size-dis-

TABLE III. Estimated Diameters from Dissolution of Log-Normal Particle-Size-Distributed Model Systems under Nonsink Condition

Model system		Diameter (cm)			
σ	$D_{w.max}$ (cm)	D_{app}	D_T	D_v	D_w
0.2	0.0376	0.0399	0.0406	0.0389	0.0409
	0.0484	0.0457	0.0455	0.0438	0.0459
	0.0757	0.0822	0.0815	0.0770	0.0825
0.3	0.0376	0.0379	0.0376	0.0320	0.0383
	0.0484	0.0472	0.0473	0.0416	0.0486
	0.0757	0.0797	0.0793	0.0662	0.0828
0.4	0.0376	0.0413	0.0390	0.0311	0.0401
	0.0484	0.0494	0.0497	0.0394	0.0524
0.5	0.0376	0.0415	0.0413	0.0303	0.0440
	0.0484	0.0476	0.0480	0.0357	0.0519
0.6	0.0376	0.0411	0.0415	0.0295	0.0456
	0.0484	0.0459	0.0492	0.0337	0.0560
0.7	0.0376	0.0451	0.0453	0.0302	0.0499
	0.0484	0.0512	0.0504	0.0332	0.0583

TABLE IV. Estimated Diameters from Dissolution of Log-Normal Particle-Size-Distributed Model Systems under Sink Condition

Model system		Diameter (cm)			
σ	$D_{w.max}$ (cm)	D_{app}	D_T	D_v	D_w
0.2	0.0376	0.0377	0.0403	0.0388	0.0408
	0.0484	0.0437	0.0453	0.0438	0.0459
	0.1044	0.1158	0.1104	0.1014	0.1085
0.3	0.0376	0.0345	0.0378	0.0319	0.0375
	0.0484	0.0453	0.0460	0.0414	0.0475
	0.0757	0.0704	0.0768	0.0663	0.0828
	0.1044	0.0990	0.1054	0.0969	0.1062
0.4	0.0376	0.0345	0.0358	0.0308	0.0392
	0.0484	0.0441	0.0471	0.0411	0.0519
	0.0757	0.0747	0.0800	0.0619	0.0821
0.5	0.0376	0.0316	0.0359	0.0298	0.0408
	0.0484	0.0406	0.0467	0.0395	0.0536
	0.0757	0.0599	0.0672	0.0531	0.0789
0.6	0.0376	0.0313	0.0364	0.0293	0.0434
	0.0484	0.0401	0.0435	0.0332	0.0515
0.7	0.0376	0.0329	0.0377	0.0298	0.0459
	0.0484	0.0384	0.0450	0.0332	0.0583

tributed systems as were partially examined before.[1d]

Apparent Mean Diameter for the Dissolution of Log-Normal Particle-Size-Distributed System As the $D_{w.max}$ value or the $D_{w.max}/D_{mean}$ value was defined by Eq. 23 in terms of the σ-value, an apparent mean diameter which defines the dissolution process of log-normal particle-size-distribution powder was also supposed to be expressed as a function of the σ-value. In the previous section, log-normal particle-size distribution was expressed by a generalized equation and curves, and hence, dissolution and its simulation with several model systems prepared following the generalized distribution curves were conducted. These results were treated on the basis of cube root law equation, and three kinds of diameters were introduced, i.e., D_v, D_w and D_T. As described before, each diameter came out in a different process. Therefore, whether or not it was valid to estimate the apparent mean diameter which defined the dissolution had to be confirmed.

To confirm the estimation method, D_{app}/D_{mean} versus D_{mean} plots for dissolution under the nonsink condition were
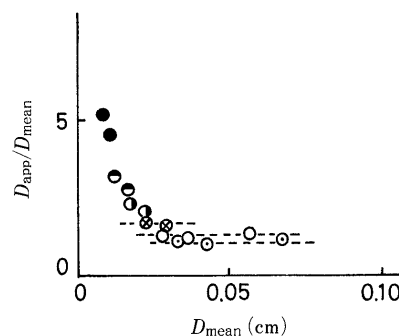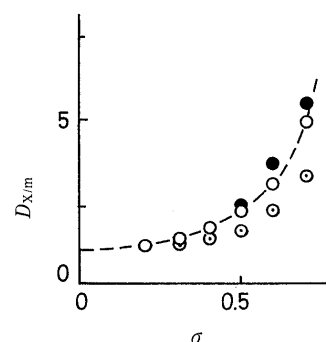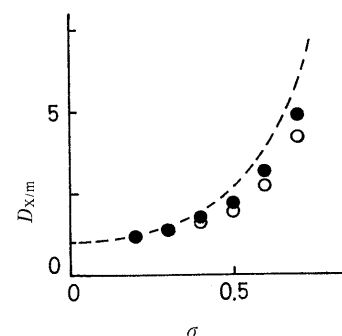

Fig. 5. Relationships between Diameters in Log-Normal Particle-Size-Distributed Model Systems

σ: ⊙, 0.2; ○, 0.3; ⊗, 0.4; ◑, 0.5; ◐, 0.6; ●, 0.7.

Fig. 6. Relationship between Relative Mean Diameters and Standard Deviation (σ) in Log-Normal Particle-Size-Distributed Model System

$D_{x/m}$: ○, $D_{T/m}$; ⊙, $D_{v/m}$; ●, $D_{w/m}$; – – –, $D_{app/m}$.

Fig. 7. Relationship between Relative Mean Diameters and Standard Deviation (σ)

$D_{x/m}$: ○, $D_{T/m}$ (sink); ●, $D_{T/m}$ (nonsink); – – –, $D_{T,^{\circ}/m}$.

examined as shown in Fig. 5. In the region where the σ-value is relatively large, the preparation of the model systems by the mixing of sieved crystals is restricted, and a definite D_{app}/D_{mean} value could not be obtained. However, in the region where the σ-value is small, the D_{app}/D_{mean} values show values close to each other independent of the D_{mean} value for a given σ-value. Hence, the D_{app}/D_{mean} value was also thought to be defined by the σ-value as well as the $D_{w.max}/D_{mean}$ value. Then the relative diameter at a given σ-value was obtained as the mean value ($D_{app/m}$), and is shown by the broken line in Fig. 6 where the other mean relative diameters ($D_{T/m}$, $D_{v/m}$ and $D_{w/m}$) are shown together for comparison. As can be seen in Fig. 6, the $D_{T/m}$ value and the $D_{app/m}$ value are very close to each other compared with the other relative diameters, and simulation by means
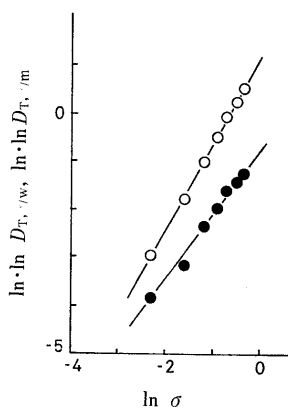
Fig. 8. Logarithmic Relationships between Relative Mean Diameters and Standard Deviation (σ) in Log-Normal Particle-Size-Distributed Systems

$\bigcirc$, $\ln \cdot \ln D_{T,°/m}$; $\bullet$, $\ln \cdot \ln D_{T,°/w}$.

of the C_T-method (Eqs. 10 and 16) was thought to be most suitable.

Then, the dissolutions of the actual log-normal particle-size-distributed systems were assumed. These dissolution processes were simulated as the summation of the concentration $(C_{T,°})$ calculated by the use of the D/D_{mean} value in the intervals of 0.1 following the calculation method of C_T (Eqs. 10 and 16), and the apparent mean diameter $(D_{T,°}/D_{mean})$ was estimated following the estimation manner of D_{app} and D_T. Here, the components, whose relative weight to W_{max} was less than 5%, were omitted. Concerning k, C_s, ρ and f for simulation, optional values were used, because these values were to be extinguished in the derivation process of the $D_{T,°}/D_{mean}$ value. The values thus obtained under sink and nonsink conditions showed close value to each other, so their mean values $(D_{T,°/m})$ are shown in Fig. 7. Similar treatments were also carried out with the systems where the components whose relative weight to W_{max} was less than 10% were omitted. The resultant values were only a few percent higher than those of the former treatment. The $D_{T/m}$ values are also shown in Fig. 7. The $D_{T/m}$ value in the sink condition is lower. However, when a large amount of samples was used, i.e., under a nonsinkcondition, the $D_{T/m}$ value accesses to the $D_{T,°/m}$ value. Hence, as described for examining with imaginary systems,[1d] when the dissolution measurement was carried out with a polydisperse system composed of many more components which reflect the original log-normal particle-size distribution, the $D_{T/m}$ value might become closer to the $D_{T,°/m}$ value. In other words, the $D_{T,°/m}$ value may define the dissolution behavior of the log-normal particle-size-distributed system at a given σ-value.

As the $D_{w.max}/D_{mean}$ value was expressed by Eq. 23 in terms of the σ-value, the $D_{T,°/m}$ and mean relative diameter of $D_{T,°}/D_{w.max}$, i.e., $D_{T,°/w}$ value were examined in the same

manner to clarify the relationships as shown in Fig. 8, and the following equations were obtained from the good linearity.

$$\ln \cdot \ln D_{T,°/m} = 1.209 + 1.833 \ln \sigma \tag{24}$$

$$\ln \cdot \ln D_{T,°/w} = -0.723 + 1.346 \ln \sigma \tag{25}$$

Equation 25 was obtained graphically as shown in Fig. 8. However, the equation could not be deduced from Eqs. 23 and 24, and it was thought that the applicability of Eq. 25 may be restricted within a certain σ region.

The dissolution of the log-normal particle-size-distributed system was simulated by means of the cube root law equation, and hence, the apparent mean diameter $(D_{T,°/m})$ was estimated without using the real values for k, C_s, ρ and f, since these values were to be extinguished in the estimation process of the apparent mean diameter. As a result, the $D_{T,°/m}$ values were well related with the σ-values as well as in the case of the $D_{w.max}/D_{mean}$ values. Hence, the $D_{T,°/m}$ value thus obtained was thought to be common for the isotropic dissolution of the log-normal particle-size-distributed powder, because the characteristic values of the powder were not involved in it as described above.

There still remains a problem as to temporal changes in composition, i.e., particle-size-distribution during dissolution. However, Brooke suggested that the truncation effect at the small end could, in many cases, be ignored without introducing large errors.[3c] When wide-range simulation of the dissolution process is requested, the $C_{T,°}$-method is thought to be more suitable as a similar simple method as presented by Matsuura.[3e] The cube root law is said to be applied for narrow particle-size-distribution.[3c] In the present treatment, the smaller the σ-value is, the wider the application range of the simulation method based on the apparent mean diameter becomes. Hence, it was thought that usage of the relationship between the $D_{T,°}/D_{mean}$ or $D_{T,°}/D_{w.max}$ and the σ-value is convenient for an approximate simulation method.

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