Changes of Surface Area in the Dissolution Process of Crystalline Substances. V. Dissolution and Simulation Curves for Log-Normal Particle-Size-Distributed Model Systems

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The dissolution of log-normal particle-size-distributed model systems prepared with sieved *n*-propyl *p*-hydroxybenzoate crystalline particles was conducted under the sink condition. The log-normal particle-size-distributed systems were expressed as a generalized equation and distribution curve, and mixed systems were prepared following the generalized distribution curves. The dissolution of the mixed systems, composed of particles whose changes of surface area during the dissolution were not easy to measure, was carried out under the sink condition. These dissolution processes were simulated by the use of the relationship between the surface-producing rate constant and the initial particle size deduced with some components. The simulated values for the dissolution showed fairly good coincidence with those measured, and it is considered that the relationship between the surface-producing rate constant and the initial particle size is useful for prediction of the dissolution behavior of mixed systems.

Keywords paraben; *n*-propyl *p*-hydroxybenzoate; crystalline particle; dissolution; simulation; surface area; mixed system; log-normal particle size distribution

Introduction

The dissolution process is an important factor which influences the bioavailability of sparingly soluble drugs. Dissolution behavior of a powder or a tablet which immediately disintegrates depends on the particle size, and hence, particle surface area. Therefore, a method to evaluate or predict the dissolution process in terms of the surface area was sought, and the dissolution profiles and their simulation for mixed systems of sieved components on the basis of the changes of surface area during the dissolution process of component samples were reported.[1)]

Generally, estimation of the changes of surface area during the dissolution process becomes increasingly difficult with decreasing particle size. In the previous paper, the feasibility of estimation of the changes of surface area during the dissolution process by the use of the relationship between the surface-producing rate constant and the initial particle size was reported.[1b,c)] The relationship was thought to be useful for the simulation in terms of the surface area given by the initial particle size measured in advance. Mixed systems were prepared with relatively small particle size crystals whose changes of surface area during the dissolution are not easy to measure. Then the dissolution of the systems was carried out, and the dissolution process was simulated to confirm the applicability of the surface-producing rate constant. For mixed systems, the log-normal particle size distribution was expressed as a generalized equation and distribution curve independent of the mean particle size, and mixed systems were prepared with sieved components following the generalized distribution curves.

Experimental

Materials *n*-Propyl *p*-hydroxybenzoate (Pr-PHBA, 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 the use of J.I.S. sieves were used. The 14/20, 20/28 and 28/35 mesh fractions were abbreviated as Pr-PHBA (L), Pr-PHBA (M) and Pr-PHBA (S), respectively, in the previous paper.[1b,c)] Their Heywood's diameters measured by 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 of Mixed Systems A suitable amount of samples (equivalent to one-twentieth of the solubility) mixed of sieved components at various weight ratios was used. The mixed systems were prepared following the generalized log-normal particle size distribution curves. The dissolution test was carried out in the same manner as described in the previous papers.[1b,c)]

Results and Discussion

Log-Normal Particle-Size-Distributed Model Systems Consider a system containing spherical particles of diameters (D) which are distributed, on a number basis, so that $\ln D$ is normal with mean diameter (D_{mean}) and standard deviation (σ). The probability frequency ($F(D)$) of log diameter is given by:

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

As can be seen in Eq. 1, $F(D)$ is defined by the relative values of D and D_{mean} at a given σ-value. Hence, rearranging Eq. 1, the probability frequency can be expressed in the form

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

as a generalized equation independent of the mean diameter on a number basis. When D is equal to D_{mean}, the probability frequency ($F(D_{mean})$) is

$$F(D_{mean})=1/\sigma\sqrt{2\pi} \quad (3)$$

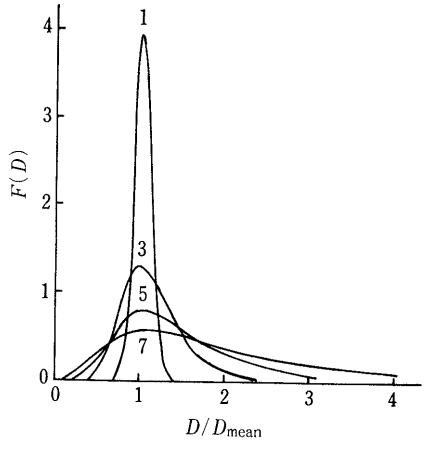

Fig. 1. Probability Frequency of Log-Normal Particle-Size-Distribution (Eq. 2)

1, $\sigma=0.1$; 3, $\sigma=0.3$; 5, $\sigma=0.5$; 7, $\sigma=0.7$.

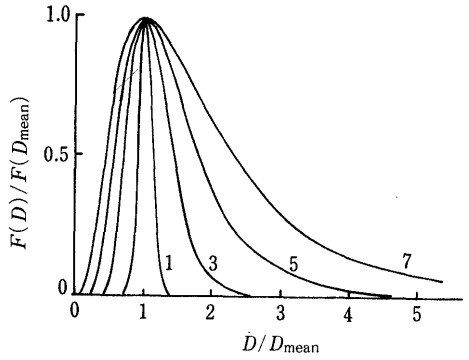

Fig. 2. Relative Probability Frequency of Log-Normal Particle-Size-Distribution (Eq. 4)
1, $\sigma=0.1$; 3, $\sigma=0.3$; 5, $\sigma=0.5$; 7, $\sigma=0.7$.

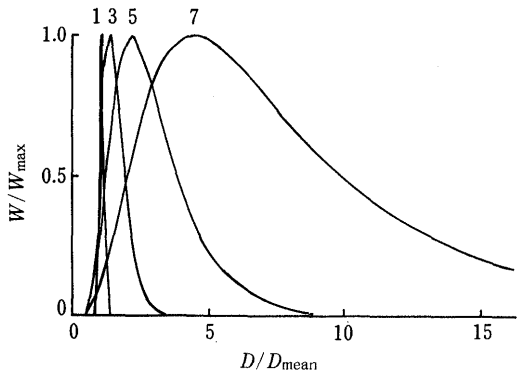

Fig. 3. Log-Normal Particle-Size-Distribution Curves
1, $\sigma=0.1$; 3, $\sigma=0.3$; 5, $\sigma=0.5$; 7, $\sigma=0.7$.

as the maximum probability frequency. Then the relative probability frequency is given by:

$$F(D)/F(D_{mean})=\exp[-\{\ln(D/D_{mean})\}^2/2\sigma^2] \quad (4)$$

The probability frequency and relative probability frequency thus expressed are shown in Figs. 1 and 2.

Taking account of the volume and density (ρ) of particles, the relative weight (W/W_{mean}) is expressed by:

$$W/W_{mean}=\{\pi D^3\rho F(D)/6\}/\{\pi D_{mean}{}^3\rho F(D_{mean})/6\} \quad (5)$$

and Eq. 5 can be rearranged in the form

$$W/W_{mean}=(D/D_{mean})^3\exp[-\{\ln(D/D_{mean})\}^2/2\sigma^2] \quad (6)$$

When Eq. 6 is expressed in logarithmic form, the following equations are obtained.

$$\ln(W/W_{mean})=3\ln(D/D_{mean})-\{\ln(D/D_{mean})\}^2/2\sigma^2 \quad (7)$$

$$\ln(W/W_{mean})=-(1/2\sigma^2)\{\ln(D/D_{mean})-3\sigma^2\}^2+9\sigma^2/2 \quad (8)$$

According to Eq. 8, 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 relative weight value. Then the diameter and weight of the maximum weight component are expressed as $D_{w.max}$ and W_{max}, respectively, and the relationship between the relative weight and D/D_{mean} is shown in Fig. 3.

Hence, log-normal particle size distribution curves can be expressed as generalized curves, and when the σ- and the D_{mean} or the $D_{w.max}$ values which characterize the distribution curve are given optionally, the log-normal particle-size-distribution curve can be defined. Then several model systems can be prepared by the use of the sieved samples

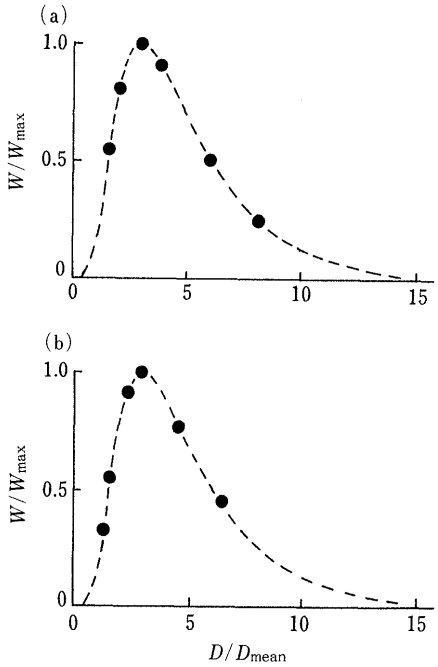

Fig. 4. Log-Normal Particle-Size-Distributed Model Systems ($\sigma=0.6$)
a) $D_{w.max}=0.0376$ cm; b) $D_{w.max}=0.0484$ cm.

following the generalized log-normal particle-size-distribution curves. Some examples are shown in Fig. 4.

Dissolution and Simulation for the Log-Normal Particle-Size-Distributed Model System The dissolution rate (dC/dt) given by Nernst[2] is expressed by:

$$dC/dt=(kS/V)(C_s-C) \quad (9)$$

where k(=the diffusion constant/the thickness of the diffusion layer) is the dissolution rate constant, S is the effective surface area for dissolution, V is the volume of solvent, C_s is the solubility and C is the concentration in the dissolution process. When the dissolution test of particles is carried out under the sink condition, the concentration is given by:

$$C=(kC_s/V)\int_0^t S(t)dt \quad (10)$$

as a function of the surface area produced during the dissolution process ($\int_0^t S(t)dt$). In the previous paper,[1b] the surface-producing properties during the dissolution process were examined,[3] and the surface-producing rate constant (α) was expressed in the form

$$\alpha=7.650\times10^{-4}/D_{H,i} \quad (11)$$

as a function of the initial particle size ($D_{H,i}$). Hence, when the surface-producing rate constant is applied for a dissolution of a mixed system, the concentration at time t should be expressed by:

$$C_t=(1/V)\Sigma w_{i,0}(1-e^{-\alpha_i t}) \quad (12)$$

where α_i and $w_{i,0}$ are the α-value and the initial amount of component i, respectively.

The dissolution profiles of mixed systems prepared following the generalized log-normal particle size distribution curves are shown in Fig. 5 as examples. In the previous papers,[1] the dissolution profile was simulated as the summation of the contributions of all the components by means of the measurement of the surface area produced during the

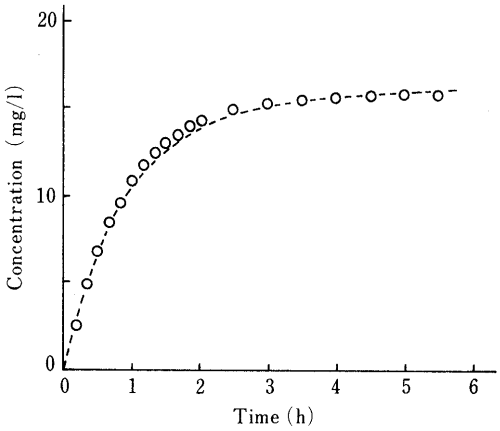

Fig. 5. Dissolution and Simulation Curves of Log-Normal Particle-Size-Distributed Model Systems

$\sigma=0.6$; $D_{w.max}=0.0484$ cm; ----; $C_\alpha=(1/V)\sum w_i(1-e^{-\alpha t})$.

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

Model system		$\bar{R}_\alpha \pm$S.D.	Model system		$\bar{R}_\alpha \pm$S.D.
σ	$D_{w.max}$ (cm)		σ	$D_{w.max}$ (cm)	
0.2	0.0376	0.969±0.037	0.3	0.0376	0.969±0.046
	0.0484	0.971±0.028		0.0484	1.015±0.057
	0.1044	1.026±0.064		0.0757	0.964±0.033
				0.1044	0.987±0.046
0.4	0.0376	0.985±0.027	0.5	0.0376	0.980±0.033
	0.0484	0.987±0.031		0.0484	0.971±0.039
	0.0757	0.991±0.037		0.0757	0.989±0.030
0.6	0.0376	0.981±0.037	0.7	0.0376	0.978±0.037
	0.0484	0.984±0.035		0.0484	0.975±0.042

dissolution (Eq. 10). However, the mixed systems examined here are composed of relatively small particle size crystals whose changes of surface area with the dissolution time are not easy to measure. Hence, the dissolution profile was simulated by the use of Eq. 12, and the result is shown by the broken line in Fig. 5. The simulated values are a little higher in the initial stage and a little lower in the middle stage of the dissolution than those measured (C). The validity of the simulation was estimated according to the previous papers.[1b,c] The ratio of C_α to C, *i.e.*, C_α/C $(=R_\alpha)$ was calculated, and the validity of the simulation was estimated from the mean value ($\bar{R}_\alpha$) and standard deviation (S.D.). The results obtained for the mixed systems examined are summarized in Table I.

The results summarized in Table I show that the mean value, *i.e.*, $\bar{R}_\alpha$ for the mixed systems deviates by a few percent from unity. In general, compared with the measured values, the simulated values were slightly higher in the initial stage and slightly lower in the middle stage of the dissolution. As described in the previous papers,[1] the dissolution profile might be simulated more satisfactorily if the surface-producing property of each component could be measured. However, a powder is usually composed of fine particles and the measurement of the dissolution properties for all of the components is not easy. Therefore, Eq. 12 was thought to be useful as an approximate method for simulation of the dissolution profile at least when the particle sizes of components are known.

Application of the Surface-Producing Rate Constant We have been treating the dissolution behavior in terms of the changes of surface area, and the dissolution behavior could be satisfactorily simulated as the summation of contributions of all the components.[1b,c] This method requires the measurement of the surface-producing properties, which was thought to be dependent on the particle size, for all the components. However, the smaller the particles size is, the more difficult the measurement of surface-producing property with the dissolution time becomes. Therefore, the surface-producing property was expressed as a function of particle size, and denoting by f the coefficient concerned with the particle shape, the surface-producing rate constant was deduced to be expressed in the form[1b]

$$\alpha=6kC_s/\rho f D_{H,i} \tag{13}$$

We examined the validity of the introduction of the relationship between the surface-producing rate constant and the initial particle size as well as the method by means of the summation of surface-producing properties of all the components. As a result, it was concluded that the introduction of the surface-producing rate constant was not unreasonable for the simulation of dissolution behavior under the sink condition.

The surface-producing rate constant was derived as a function of the initial particle size in our case, bacause we employed an image analyzer which evaluates particle size and surface area. The specific surface area (S_{sp}) is given by $6/\rho f D_{H,i}$, and the α-value should be expressed by:

$$\alpha=S_{sp}kC_s \tag{14}$$

Then the dissolution profile might be predicted by means of the following equation

$$C_\alpha=(1/V)\sum w_i\{1-\exp(-S_{sp}kC_s t)\} \tag{15}$$

when the particle size does not influence the solubility. Thus, according to Eq. 15, it is not necessary to estimate the particle size for the simulation method when the specific surface area can be obtained by a method such as the air permeation method, and hence, the applicability of Eq. 13 or Eq, 14 is thought to be dependent on the experimental situation.

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