Dissolution of Solid Dosage Form. V.[1] New Form Equations for the Non-sink Dissolution of a Monodisperse System

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The derivation of equations available for the treatment of a dissolution process of a monodisperse system with an optional initial amount within solubility was attempted. Two kinds of dissolution equations were derived as a function of the initial amount used in the dissolution test by using MacLaurin's expansion. When the initial amount is equal to one-third of the solubility, a semilogarithm form dissolution equation was deduced and was abbreviated as the Ln-z equation. When the initial amount is an amount other than one-third of the solubility, the derived equation was expressed by a form which included the cube root law and negative two-thirds law equations, and was abbreviated as the z-law equation. Also, the Langmuir form dissolution equation was obtained as an extended application form of the z-law equation, and was abbreviated as the Lg-z equation.

Since the applicability or validity of the z-law equation was examined in a previous paper, the applicabilities of the Ln-z equation and the Lg-z equation were examined in this paper. As a result, it was suggested that the dissolution rate constant of a substance can be determined by dissolution measurement with an optional initial amount, and once the dissolution rate constant is determined in advance, the dissolution process of the substance with any optional initial amount within solubility can be approximately predicted.

Key words dissolution; simulation; z-law equation; cube root law; negative two-thirds law; nonsink dissolution

Hixson and Crowell derived the cube root law and negative two-thirds law equations based on special conditions in terms of the initial amount.[2] Since then, the dissolution of crystalline particles or powder has been calculated using these equations, and the validity of each equation was confirmed.[3] The cube root law equation was derived for dissolution with an initial amount up to around one-twentieth of the solubility, and the negative two-thirds law equation was derived for dissolution with an initial amount needed to saturate the solution. Calculations using both dissolution equations give dissolution rate constants of almost the same value as each other,[1,4] and, for example, the dissolution process of those dissolutions with an initial amount of solubility can be predicted or simulated by the negative two-thirds law equation using the dissolution rate constant obtained by applying the cube root law equation to the dissolution measurement carried out with an initial amount within one-twentieth of the solubility. However, when the initial amount is an amount other than those defined by the above equations, it is impossible to predict or simulate the dissolution process, even though it is necessary from the viewpoint of practical use. Hence, in the previous paper,[1] the derivation of a dissolution equation for the dissolution of a monodisperse system with an optional initial amount within solubility was tried, and a simple form equation abbreviated as the z-law equation, which included the cube root law and the negative two-thirds law equations, was obtained when the initial amount is an amount other than one-third of the solubility. Hence, applying the z-law equation expressed as a function of the initial amount, once the dissolution rate constant of a substance has been determined by the dissolution measurement with a favorable initial amount, it is easy to predict or simulate the dissolution process with any optional initial amount within solubility of the substance when the other dissolution conditions, *i.e.*, temperature, stirring speed and so on are fixed.

Here, a semilogarithm form dissolution equation was obtained for dissolutions with the initial amount of one-third of the solubility. Also, after logarithming both sides of the z-law equation, the semilogarithm form dissolution equation can be obtained by introducing a simple approximation based on MacLaurin's expansion. Hence, the derived semilogarithm form dissolution equation was abbreviated as the Ln-z equation, and its applicability or validity was estimated by dissolution measurements and simulation of the dissolution processes. It was therefore suggested that the Ln-z equation is an efficient equation for explaining the dissolution process of any dissolution carried out with an initial amount of one-third of the solubility, and is also an efficient equation for a dissolution with an initial amount up to around two-thirds of the solubility, especially around one-third of the solubility.

Moreover, the Langmuir form dissolution equation was deduced as an extended application form of the z-law equation, and was abbreviated as the Lg-z equation. Subsequently, the applicability or validity of the equation was examined.

Experimental

Materials *n*-Propyl *p*-hydroxy benzoate crystalline particles (extra pure reagent, Kanto Chemical Co., Ltd.) 14/20, 20/28 and 28/35 mesh fractions separated by the use of J.I.S. sieves were used. The samples were abbreviated as Pr-PHBA(L), (M) and (S), respectively. The Heywood's diameters measured by the use of a Luzex-500 image analyzer (Nireco Co., Ltd.) were 0.134, 0.104 and 0.076 cm, respectively.[5] Particle density is 1.28 g/cm^3, the coefficient concerning particle shape is 0.369, and solubility in water at 25 °C is 0.330 g/l.[5]

Dissolution of Crystalline Particles Dissolution measurements were carried out following the method of the previous paper.[1] A weighed initial amount of sieved sample was added to a dissolution apparatus (type NTR-VS, Toyama Sangyo Co., Ltd.), and the dissolution test was carried out in 1000 ml of water at a paddle rotation speed of 250 rpm at

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25 °C. A small amount of the solution was sampled, and by adding the same amount of water, the amount of solvent was kept constant throughout the dissolution measurement. The concentration of the sampled solution was estimated by the absorbance at 255 nm measured by the use of a type UV-160 spectrophotometer (Shimadzu Ind. Co.).

Theoretical Analysis

Semilogarithm Form Dissolution Equation The cube root law and negative two-thirds law equations for the isotropic dissolution of particles or powder were expressed as a function of the initial particle size and particle density.[2,3] Therefore, these equations were expressed by using the specific surface area in accordance with the initial particle size.[6] Following the same idea, the specific surface area was introduced in the Nernst dissolution equation. The dissolution rate ($\mathrm{d}C/\mathrm{d}t$) is expressed as[7]

$$\mathrm{d}C/\mathrm{d}t=(k/V)S(C_s-C) \tag{1}$$

where k (=the diffusion coefficient/the thickness of the diffusion layer) is the intrinsic dissolution rate constant, V is the solvent volume, S is the effective surface area at time t, and C_s is the solubility. In the dissolution measurement of a monodisperse system, the initial amount, M_0, decreased to amount M; the initial particle size, D_0, decreased to D; and the specific surface area, S_{sp}, changed to S'_{sp} at time t. Though the particle shape coefficient represents the weight and surface area at the same time, it was postulated that it does not have significant effect on the estimation of the specific surface area during the dissolution measurement, and the effective surface area at time t is given as follows, since $S/S_0=(M/M_0)^{2/3}$ and $S_0=S_{sp}M_0$.

$$S=S_{sp}M_0(M/M_0)^{2/3} \tag{2}$$

Hence, when C_s and C are expressed by the amount (M_s) needed to saturate the solution and the amount (m) dissolved at time t, Eq. 1 can be expressed as follows by taking into account Eq. 2.

$$\mathrm{d}m/\mathrm{d}t=(k/V)S_{sp}M_0(M/M_0)^{2/3}(M_s-m) \tag{3}$$

or

$$-\mathrm{d}M/\mathrm{d}t=(k/V)S_{sp}M_0(M/M_0)^{2/3}\{M_s-(M_0-M)\} \tag{4}$$

In Eq. 4, the cube root law equation can be obtained when $M_0 \ll M_s$, and the negative two-thirds law equation can be obtained when $M_0=M_s$.[2] Therefore, it was suggested that Eq. 3 or 4 may give a more simple or handy dissolution equation than that reported[8] when the relative value of M to M_s is taken into account in Eq. 3 or 4.

Introducing the relative value, p $(=M_0/M_s)$ and $M/M_0=1-m/M_0$, Eq. 3 is rewritten in the form

$$\mathrm{d}m/\mathrm{d}t=(k/V)S_{sp}M_0(1-m/M_0)^{2/3}M_s(1-pm/M_0) \tag{5}$$

as a function of p. As M_s/V is the solubility (C_s), if it were ascertained that $1-pm/M_0$ can be expressed in a form of $(1-m/M_0)^q$, Eq. 5 can be expressed in a more simple form

$$\mathrm{d}m/\mathrm{d}t=(k/V)S_{sp}M_0(1-m/M_0)^{2/3}M_s(1-m/M_0)^q \tag{6}$$

and hence,

$$\mathrm{d}m/\mathrm{d}t=kC_sS_{sp}M_0(1-m/M_0)^{(2/3+q)} \tag{7}$$

Therefore, the relationship between the p-value and the q-value was examined as follows:

$$1-pm/M_0=(1-m/M_0)^q \tag{8}$$

By logarithming Eq. 8, following equation is obtained:

$$\ln(1-pm/M_0)=q\ln(1-m/M_0) \tag{9}$$

According to a popular approximation using MacLaurin's expansion, Eq. 9 can be simplified as follows by using the first term when the value of m/M_0 is small enough to regard $1 \gg m/M_0$ and when contributions of the following terms in the polynomial are small enough to neglect.

$$-pm/M_0=q(-m/M_0) \tag{10}$$

In this case, the q-value is equal to the p-value. As examined previously,[1] the q-value changes in accordance with the m/M_0-value at a fixed p-value. However, the q-value was temporarily substituted by the p-value as a simple treatment, even though changes in the q-value should be taking into account with a decreasing m/M_0-value. Hence, Eq. 7 is rewritten as:

$$\mathrm{d}m/\mathrm{d}t=kC_sS_{sp}M_0(1-m/M_0)^{(2/3+p)} \tag{11}$$

Using M $(=M_0-m)$ and p $(=M_0/M_s)$, Eq. 11 is expressed as follows:

$$-\mathrm{d}M/\mathrm{d}t=kC_cS_{sp}M_0(M/M_0)^{(2/3+p)} \tag{12}$$

$$-\mathrm{d}M/\mathrm{d}t=kC_sS_{sp}M_0{}^{\{1-(2/3+M_0/M_s)\}}M^{(2/3+M_0/M_s)} \tag{13}$$

In the case of integrating Eq. 13, two kinds of integrated equations can be obtained in accordance with the value of $2/3+M_0/M_s$. When the M_0/M_s-value is equal to 1/3, the value of $2/3+M_0/M_s$ is equal to 1, and Eq. 13 is expressed as:

$$-\mathrm{d}M/\mathrm{d}t=kC_cS_{sp}M_0{}^0M^1 \tag{14}$$

Hence, the following semilogarithm form equation can be obtained by rearranging the equation after the integration of Eq. 14:

$$\ln(M/M_0)=-k_{Ln}C_sS_{sp}t \tag{15}$$

or

$$\ln\{M_0/(M_0-m)\}=k_{Ln}C_sS_{sp}t \tag{16}$$

Here, the dissolution rate constant in a semilogarithm form dissolution equation was expressed by k_{Ln} to distingush it from one defined by the other dissolution equation. Hence, dissolution process can be simulated by the following equation.

$$m=M_0\{1-\exp(-k_{Ln}C_sS_{sp}t)\} \tag{17}$$

When the M_0/M_s-value is a value other than 1/3, the following equation can be obtained by rearranging the equation after the integration of Eq. 13:

$$(M/M_0)^{\{1-(2/3+M_0/M_s)\}}=1-\{1-(2/3+M_0/M_s)\}kC_sS_{sp}t \tag{18}$$

In Eq. 18, the cube root law equation can be obtained when M_0 is so extremely small compared with M_s that the M_0/M_s-value can be negligible as zero, and the negative two-thirds law equation can be obtained when $M_0=M_s$. Therefore, Eq. 18, expressed by a function of the initial amount, was suggested to be efficient for calculating the dissolution process independent of a sink or non-sink condition. Hence, denoting by z the value of $\{1-(2/3+M_0/M_s)\}$ or $(1/3-M_0/M_s)$ and by k_z the dissolution rate constant to distinguish it from one defined by the other dissolution equation, Eq. 18, given as a function of the initial amount used in a dissolution measurement, was expressed in a general form as the z-law equation.$^{1)}$

$$(M/M_0)^z = 1 - zk_z C_s S_{sp} t \tag{19}$$

The logarithm of the z-law equation is expressed as

$$z\ln(M/M_0) = \ln(1 - zk_z C_s S_{sp} t) \tag{20}$$

Here, when the absolute value of $zk_z C_s S_{sp} t$ is small enough to assume it to be $1 \gg |zk_z C_s S_{sp} t|$, which can occur at the initial dissolution stage, Eq. 20 can be expressed as follows by the same treatment described in Eq. 10 (MacLaurin's expansion).

$$z\ln(M/M_0) = -zk_z C_s S_{sp} t \tag{21}$$

By rearrangement, Eq. 21 becomes Eq. 15 or 16. Thus, the semilogarithm form dissolution equation was abbreviated as the Ln-z equation. A similar equation was obtained from a change in the surface area in dissolution under the sink condition.$^{5,6a)}$ Estimations of the dissolution rate constants by using the cube root law equation and negative two-thirds equation gave almost the same value as each other. Also, the values of C_s and S_{sp} are fixed at a given condition for a substance independent of the initial amount (M_0).$^{1)}$ Hence, the dissolution stage which adheres to the Ln-z equation is easily supposed to change in accordance with the z-value, *i.e.*, the initial amount. When a dissolution with an optional initial amount is treated by the Ln-z equation as an approximate dissolution equation, the closer the initial amount is to one-third of the solubility, the more the dissolution stage should adhere to the Ln-z equation.

Langmuir Form Dissolution Equation In the derivation process of the z-law equation or the Ln-z equation, the q-value was assumed to be equal to the p-value in order to confirm its validity for a simple treatment. Therefore, the existence of a more suitable q-value to explain the dissolution process other than the p-value was examined previously.$^{1)}$ As a result, the applicability of the z-law equation was improved when the q-value was a little higher than the p-value. Hence, it was supposed that the q-value can be set freely around the p-value in case of necessity. Then, the following equations were obtained as an extended application form of the z-law equation, when the q-value in Eq. 7 is equal to 4/3,

$$-dM/dt = kC_s S_{sp} M_0^{-1} M^2 \tag{22}$$

and hence,

$$(M/M_0)^{-1} = 1 + kC_s S_{sp} t \tag{23}$$

An extended application form of the z-law equation, *i.e.*, Eq. 23 can be rearranged as follows:

$$M(1 + kC_s S_{sp} t) = M_0 \tag{24}$$

Here, denoting by k_{Lg} the dissolution rate constant to distinguish it from one defined by the other equation, and by adding $M_0 k_{Lg} C_s S_{sp} t$ to both sides of Eq. 24, the following dissolution equation expressed by the same form of the Langmuir equation which is popularly used for adsorption phenomena can be obtained

$$(M_0/M)(1 + k_{Lg} C_s S_{sp} t) = M_0 k_{Lg} C_s S_{sp} t$$
$$M_0 - M = m = M_0 k_{Lg} C_s S_{sp} t/(1 + k_{Lg} C_s S_{sp} t) \tag{25}$$

Then, the following is obtained by rearranging Eq. 25.

$$M_0/m = 1 + (1/k_{Lg} C_s S_{sp})(1/t) \tag{26}$$

Also, Eq. 24 or Eq. 26 can be rewritten as

$$m/(M_0 - m) = m/M = k_{Lg} C_s S_{sp} t \tag{27}$$

Hence, the dissolution equation as an extended application form of the z-law equation is abbreviated as the Lg-z equation, and the dissolution process for a dissolution with an initial amount around solubility may be predicted or simulated by the use of Eq. 25. Here, when the dissolution rate constant (k_z) is obtained by applying Eq. 23, the dissolution process can be also estimated by the use of Eq. 25 by substituting k_z for k_{Lg}.

Results and Discussion

Applicability of the Ln-z Equation Dissolution curves obtained using the initial amount of one-third of the solubility, and treatment by means of the Ln-z equation (Eq. 15) are shown in Figs. 1 and 2, respectively.

Expected linear relationships were obtained. The slope

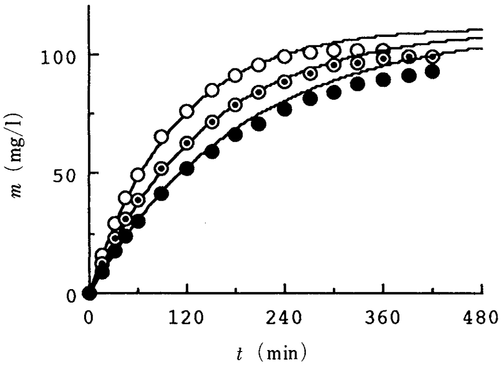

Fig. 1. Dissolution and Simulation Curves Using the Ln-z Equation ($k_{Ln}=0.170$ cm/min) for Dissolution with an Initial Amount of 1/3 of Solubility

○, Pr-PHBA(S); ⊙, Pr-PHBA(M); ●, Pr-PHBA(L).

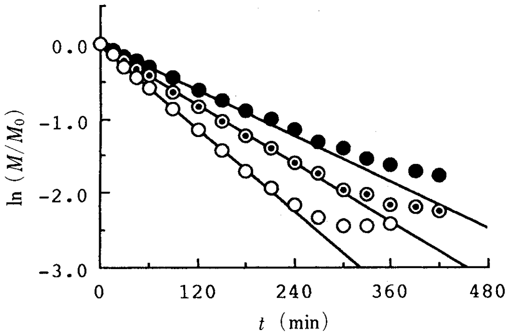

Fig. 2. Application of the Ln-z Equation for Dissolution with an Initial Amount of 1/3 of Solubility

○, Pr-PHBA(S); ⊙, Pr-PHBA(M); ●, Pr-PHBA(L).

of the line is equal to $-k_{Ln}C_sS_{sp}$ and the k_{Ln}-values estimated for Pr-PHBA(L), (M) and (S) are 0.164, 0.166 and 0.168 cm/min, respectively. These values coincided well with the value (0.166 cm/min) obtained by applying the cube root law equation and the negative two-thirds equation,[4] but they are a little smaller than the average value (0.170 cm/min) obtained by applying the z-law equation.[1] Therefore, the dissolution processes were simulated by using the value of 0.170 as the k_{Ln} and the Ln-z equation (Eq. 17) to confirm the general applicability of the equation, and these are shown in Fig. 2 by the solid lines. The simulated values are a little larger than the measured values, as expected. However, seeing the small deviation between them, the Ln-z equation appears to be efficient for a calculating the dissolution with an initial amount of one-third of the solubility and for predicting the dissolution process using the dissolution rate constant obtained beforehand.

Application of the Ln-z Equation As described before, the Ln-z equation was also deduced from the z-law equation by applying simple mathematical approximation when $1 \gg |zk_zC_sS_{sp}t|$. The values of k_z, C_s and S_{sp} are supposed to be fixed by the conditions for a given substance.[1] When the dissolution measurement was carried out with an optional initial amount for a given substance, the dissolution stage which satisfies the condition, *i.e.*, $1 \gg |zk_zC_sS_{sp}t| = |(1/3-p)k_zC_sS_{sp}t|$ may change in accordance with the initial amount, *i.e.*, *p*. According to a commom calculation, this condition is supposed to be satisfied within the absolute value of $zk_zC_sS_{sp}t$ being equal to around 1/20. Hence, the critical dissolution time (t_c) which satisfies the condition, *i.e.*, $|zk_zC_sS_{sp}t| = 1/20$, was calculated as a function of the initial amount, and then, the critical dissolved amount ($m_{c,c}$) was calculated by use of the z-law equation and t_c. The results obtained are shown in Fig. 3.

Here, the calculated critical dissolved amount is expressed by the relative value as $m_{c,c}/M_0$. The values of t_c and $m_{c,c}/M_0$ increase with increasing the *p*-value to reach a maximum where the *p*-value is equal to around 1/3, then they decrease with increasing the *p*-value. Hence, of course, the applicability or accuracy depends on the *p*-value, and it is suggested that the dissolution process carried out with a *p*-value of around 1/3, which should be treated by the z-law equation, can be efficiently treated by the Ln-z equation.

The dissolution profiles of Pr-PHBA(M) using optional initial amounts are shown in Fig. 4, which also includes the previously reported profiles.[1] The initial amount used for the dissolution test was expressed by the relative value, $p\ (=M_0/M_s)$.

These dissolution processes, which should be treated by using the z-law equation, were treated by use of Eq. 15 to examine the applicability of the Ln-z equation as an approximate or efficient equation. The results are shown in Fig. 5.

The solid straight line in Fig. 5 expresses the treatment of the dissolution measurement with the initial amount of $p=1/3$, and the others treated in the same manner are relatively close to the line. Then, the dissolution rate constants (k_{Ln}) were estimated from each straight line obtained at the initial dissolution stage, and the measured critical dissolved amount ($m_{c,m}$) was obtained as the dissolved amount which began to deviate from each straight line. The values of $m_{c,m}$ and k_{Ln} are summarized in Figs. 6 and 7, respectively. The $m_{c,m}/M_0$-value changed with the changing *p*-value in the manner expected (Fig. 3), and the k_{Ln}-value tends to decrease with an increasing *p*-value.

The k_z-values obtained by use of the z-law equation are also shown in Fig. 7 for comparison. The k_z-values are

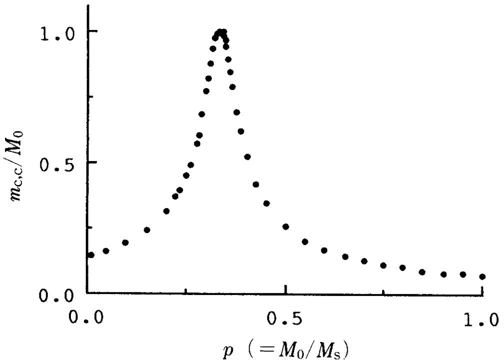

Fig. 3. Relationship between the *p*-Value and the Calculated Critical Dissolved Amount Expressed by the Ratio to the Initial Amount ($m_{c,c}/M_0$) for Pr-PHBA(M)

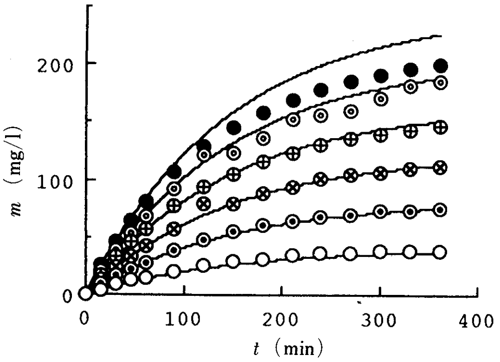

Fig. 4. Dissolution and Simulation Curves Using the Ln-z Equation for Pr-PHBA(M)

○, $p=1/8$; ⊙, $p=1/4$; ⊗, $p=3/8$; ⊕, $p=1/2$; ◎, $p=5/8$; ●, $p=3/4$.

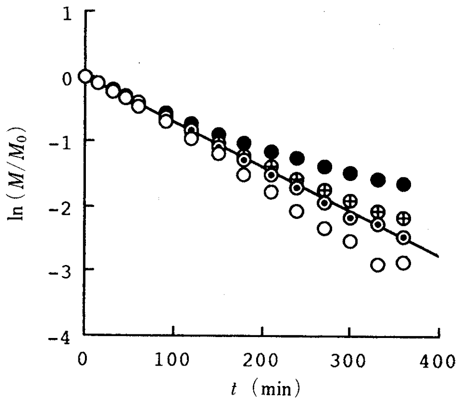

Fig. 5. Application of the Ln-z Equation for the Dissolution of Pr-PHBA(M)

○, $p=1/8$; ⊙, $p=1/4$; ⊕, $p=1/2$; ●, $p=3/4$. ——, $p=1/3$.

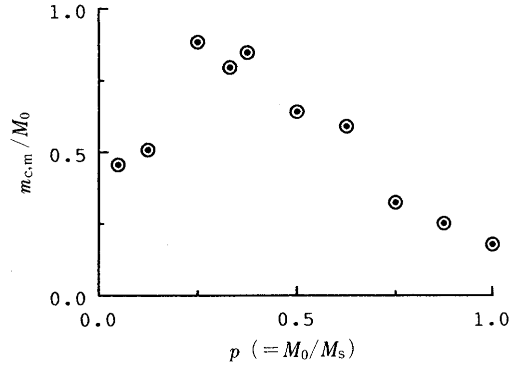

Fig. 6. Relationship between the p-Value and the Measured Critical Dissolved Amount Expressed by the Ratio to the Initial Amount ($m_{c,m}/M_0$) for Pr-PHBA(M)

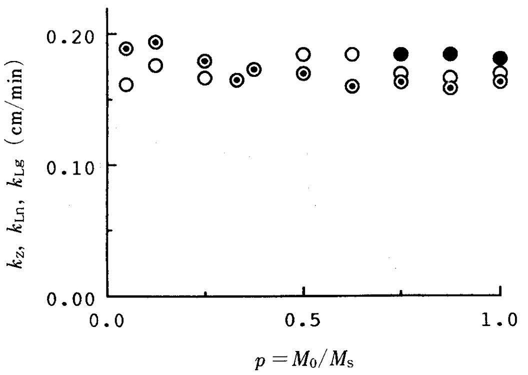

Fig. 7. Relationship between the p-Value and Dissolution Rate Constants for Pr-PHBA(M)

⊙, k_{Ln}; ○, k_z; ●, k_{Lg}.

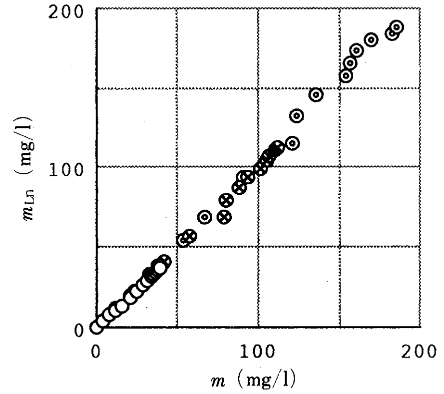

Fig. 8. Relationship between the Measured Value (m) and Simulated Value (m_{Ln}) Using the Ln-z Equation for the Dissolution of Pr-PHBA(M)

○, $p=1/8$; ⊗, $p=3/8$; ⊙, $p=5/8$.

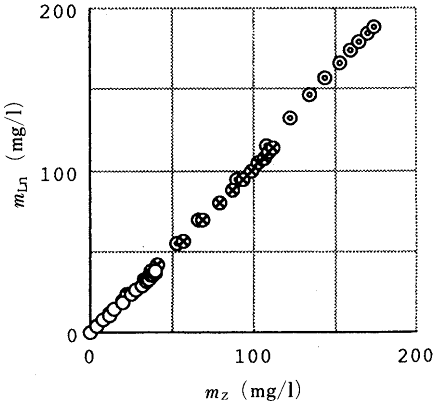

Fig. 9. Comparison of Simulated Values Using the Ln-z Equation (m_{Ln}) and the z-Law Equation (m_z) for the Dissolution of Pr-PHBA(M)

○, $p=1/8$; ⊗, $p=3/8$; ⊙, $p=5/8$.

close each other, though a little deviation appeared when the p-value was equal to around one-fourth of the solubility. The k_{Ln}-value at $p=1/20$ was a little higher than the k_z-value (0.170 cm/min). Even though the k_{Ln}-value gradually decreased with an increasing p-value, they were comparable to the k_z-value. Hence, the dissolution processes were simulated by use of the k_{Ln}-value (0.170 cm/min) and the Ln-z equation, and are shown in Fig. 4 by solid lines.

The value of $m_{c,m}/M_0$ was relatively high for dissolution when the initial amount was within $p=2/3$. The Ln-z equation can be obtained when the p-value is equal to 1/3, and seems to be an approximate equation for an initial dissolution stage of the z-law equation at the same time. The z-value is given as $\{1-(2/3+M_0/M_s)\}$, the z-value decreases from 1/3 to $-2/3$ in accordance with an increasing M_0/M_s-value, and the z-value is equal to $-1/3$ when $M_0/M_s=2/3$. As an approximate equation, the Ln-z equation was applicable for dissolution under the sink condition where the z-value is 1/3.[1,4a)] Considering the absolute value, *i.e.*, 1/3, it was mathematically supposed that the Ln-z equation may be applicable when the z-value is equal to $-1/3$, too. Therefore, the Ln-z equation may be applicable for dissolution with an initial amount up to around 2/3 of solubility, at least, and its validity was suggested from the simulation results shown in Fig. 4. To confirm this idea, the applicability or validity was examined by comparing the simulated values (m_{Ln}) by the use of Eq. 17 with the measured values (m) as shown in Fig. 8. Comparing these results, the simulated values for the dissolution with an initial amount within $p=5/8$ fitted well with measured values. Hence, the $m_{c,m}$-value estimated (Fig. 7) is a kind of apparent value or region which adheres to the Ln-z equation, and deviation from the straight line in Fig. 6 may be caused by from a mathematical treatment, *i.e.*, a logarithm which expands the scale of a small M/M_0-value at an advanced dissolution time.

Also, comparisons of the simulated values by means of the Ln-z equation and the z-law equation are shown in Fig. 9 to examine whether the Ln-z equation is a handy equation.

The simulated values by means of the Ln-z equation and the z-law equation coincide fairly well with each other.

Hence, it was suggested that the Ln-z equation is also efficient for the treatment of the dissolution test carried out with an initial amount within around two-thirds of solubility, which should be treated by means of the z-law equation.

Applicability of the Lg-z Equation Since the Lg-z equation was obtained from an extended application form of the z-law equation for dissolution carried out using an initial amount of solubility, the applicability of the Lg-z equation was examined by comparing it with the negative

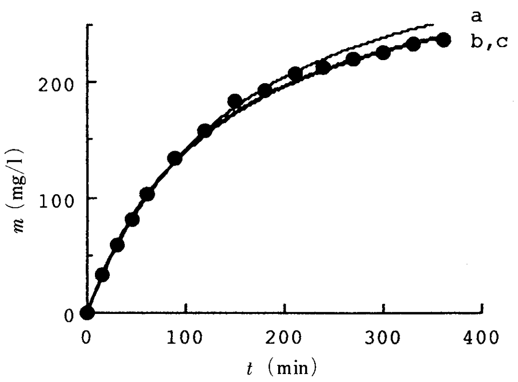

Fig. 10. Dissolution and Simulation Curves for Pr-PHBA(M) with an Initial Amount of Solubility

Simulation curve: a, the negative two-thirds law equation; b, the Lg-z equation (Eq. 26); c, the z-law equation (Eq. 23).

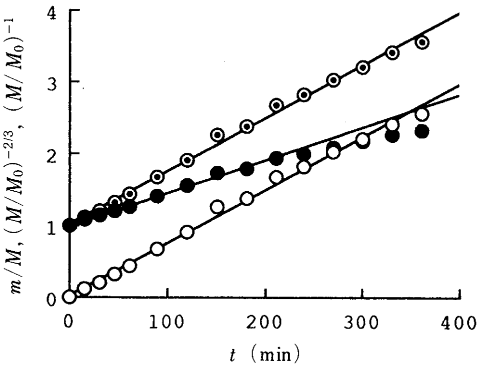

Fig. 11. Treatments of the Dissolution of Pr-PHBA(M) with an Initial Amount of Solubility

●, the negative two-thirds law equation; ○, the Lg-z equation (Eq. 27); ⊙, the z-law equation (Eq. 23).

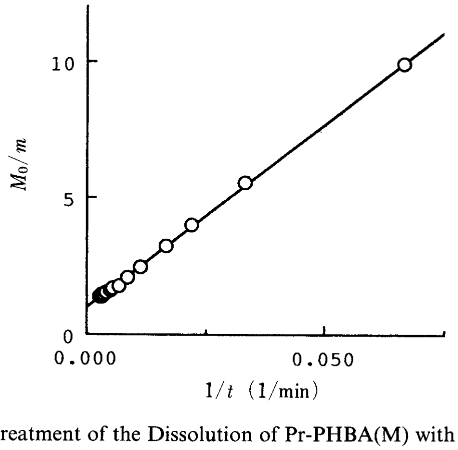

Fig. 12. Treatment of the Dissolution of Pr-PHBA(M) with an Initial Amount of Solubility Using the Lg-z Equation (Eq. 26)

two-thirds law equation. The dissolution curve and the results treated by using these equations are shown in Figs. 10, 11 and 12, respectively. Also, treatment by means of Eq. 23, which has the same definitions as Eq. 27, is shown at the same time.

The dissolution rate constants estimated by applying the negative two-thirds law equation as a z-law equation and the Lg-z equation expressed in the forms of Eq. 26 and Eq. 27 are 0.169, 0.185 and 0.182, respectively. The simulation curves resulting from these equations are shown in Fig. 10. The dissolution rate constant estimated by means of the Lg-z equation is slightly larger than that estimated by means of the negative two-thirds law equation or the z-law equation, but the simulated values fit well with the measured values. Hence, the Lg-z equation obtained as an extended application form of the z-law equation was supposed to be efficient.

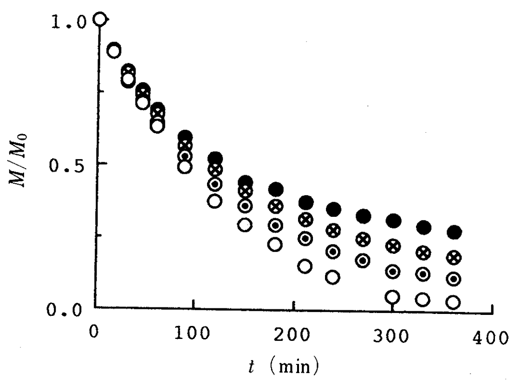

Fig. 13. Time Courses of M/M_0 for Pr-PHBA(M)

○, $p=1/20$; ⊙, $p=1/3$; ⊗, $p=3/4$; ●, $p=1$.

Also, the Lg-z equation was examined by the dissolution measurement with an initial amount around solubility, and the k_{Lg}-values obtained are shown in Fig. 7. As a result, it was suggested that the Lg-z equation is efficient for a dissolution with an initial amount which is very close to solubility.

Initial Amount and Applicability of Dissolution Equations The relative values of M/M_0 estimated from the dissolution measurements versus the dissolution time are shown in Fig. 13.

As can be seen in Fig. 13, the time course of M/M_0 depends on the initial amount used for the dissolution measurement. Calculations by means of the cube root law and negative two-thirds law equations give almost the same dissolution rate constant,[4] even though the initial amounts and the time course of M/M_0 are quite different. The solubility, specific surface area and dissolution rate constant are considered not to be affected by the amount used for the dissolution measurement for a given substance, and each time course of M/M_0 is specific to the initial amount. So, as a simple method, dissolution with an optional initial amount should be treated by an equation which expresses the time course of M/M_0 by a straight line. Therefore, it seems that the cube root law equation or the negative two-thirds equation demands its own specific power to express the time course of M/M_0 by a straight line.

Obviously, the Ln-z equation demands a specific time course of M/M_0 defined by the initial amount, *i.e.*, $M_0=(1/3)M_s$, for satisfying the application. When the M_0-value is smaller than $(1/3)M_s$, the time course of M/M_0 is lower than that defined by the initial amount of $(1/3)M_s$. Hence, the logarithm values of M/M_0 deviate downward from the line estimated by the Ln-z equation, and the k_{Ln}-value is apt to increase, as can be seen in Figs. 5 and 7. On the other hand, when the M_0-value is larger than $(1/3)M_s$, the logarithm values of M/M_0 deviate upward, and the k_{Ln}-value is apt to decrease in the same manner. The same situation was considered for application of the Lg-z equation and z-law equation expressed by a function of the initial amount. Even though the dissolution test was carried out under the sink condition, the time course of M/M_0 should depend on the initial amount. So the dissolution rate constant estimated by using the cube root law equation should be affected by the initial amount and should apparently change with the initial amount within the sink condition. Such deviation caused by the initial amount was seen in a paper reported by Niebergall *et. al.*[3b)] Therefore, it was supposed that the dissolution process should be treated by its own suitable equation in relation to the initial amount. Hence, the equations derived by taking into account the initial amount were suggested to be efficient.

Conclusion

Applying the z-law equation to dissolution with optional initial amounts, the dissolution rate constants (k_z) obtained were relatively close to each other, independent of the initial amount. The dissolution rate constant (k_{Ln}) obtained by applying a semilogarithm form dissolution equation, *i.e.*, the Ln-z equation, were comparable to k_z. As far as the dissolved amount was concerned, dissolutions carried out with initial amounts within around two-thirds of the solubility were relatively well estimated by the Ln-z equation. Hence, the Ln-z equation was suggested to be efficient as a handy equation to estimate dissolution when the initial amount is within around two-thirds of the solubility.

Langmuir form dissolution equation, *i.e.*, the Lg-z equation as an extended application form of the z-law equation was efficient for dissolution with the initial amount close to the solubility.

Once the intrinsic dissolution rate constant of a substance was determined in advance, a possibility of an approximate prediction of the dissolution process of the substance with any optional initial amount within solubility was suggested.

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