Dissolution of Solid Dosage Form. IV.[1] Equation for the Non-sink Dissolution of a Monodisperse System

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An equation for the dissolution of a monodisperse system with an optional initial amount was derived from the Nernst equation. The derived equation was given as a function of the initial amount used for the dissolution test, and was expressed by a form which included the cube root law and negative two-thirds root law equations. Hence, the derived equation is herein abbreviated as the z-law equation following the cube root law and negative two-thirds root law equations. The dissolution measurements of monodisperse crystalline particles using various initial amounts within the amount required to saturate the solution were carried out, and these dissolution processes were treated by use of the z-law equation. The applicability or validity of the z-law equation for the dissolution of monodisperse crystalline particles with optional initial amounts was estimated by a simulation of the dissolution process. As a result, it was suggested that the z-law equation more efficiently explains the dissolution process than the cube root law equation for the treatment of dissolution under sink condition. Also, applicability of the z-law equation was fairly good for dissolution under non-sink condition. Hence, the derived general dissolution equation, *i.e.*, the z-law equation, was thought to be efficient for the treatment of dissolution of a monodisperse system with optional initial amounts within solubility.

Keywords dissolution; non-sink equation; simulation; crystalline particle; cube root law; negative two-thirds root law

Usually, dissolution properties, including the dissolution rate constant, were examined by use of the disk method, cube root law equation and negative two-thirds root law equation. Hence, estimation of the dissolution process could be examined only for dissolution measurements carried out in accordance with these conditions.[2,3] Among the above equations, the cube root law and negative two-thirds root law equations were useful for dissolution of powder or particles. However, it is often necessary from the viewpoint of practical use to estimate the dissolution process as it will be carried out with an initial amount not defined by those equations. Thus, dissolution measurements with various initial amounts which will not completely saturate the dissolution medium, so-called dissolution measurements under non-sink condition, were carried out, and these processes were treated by non-sink dissolution equation deduced precisely from the original Hixson–Crowell treatment.[4,5] However, it is relatively hard to carry out such a non-sink dissolution equation because some of the functions included.

Hence, the derivation of a general dissolution equation as an approximate simple dissolution equation was attempted. The derived general dissolution equation was given as a function of the initial amount, and was expressed by a form which included the cube root law and negative two-thirds root law equations. Expressing the index in the derived general equation as z, the equation is herein abbreviated as the z-law equation after the equations of cube root law and negative two-thirds root law. The applicability and validity of the z-law equation were examined by the dissolution of monodisperse crystalline particles using optional initial amounts within solubility, and the dissolution processes were simulated.

Experimental

Materials *n*-Propyl *p*-hydroxy benzoate crystalline particles (extra pure reagent, Kanto Chemical Co., Ltd.) 20/28 mesh fraction, separated by the use of J.I.S. sieves, was used. The sample was abbreviated as Pr-PHBA(M). The Heywood's diameter, measured by the use of a LUZEX-500 image analyzer (NIRECO Co., Ltd.), was 0.104 cm.[6] Particle density was 1.28 g/cm^3, the coefficient concerned with the particle shape was 0.369, and solubility in water at 25 °C was 0.330 g/l.[6]

Dissolution of Crystalline Particles For the dissolution measurement under non-sink condition, a weighed optional 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 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 test. The concentration of the sampled solution was estimated by the absorbance at 255 nm. A UV-160 spectrophotometer (Shimadzu Ind., Co.) was used.

Theoretical Analysis

The general dissolution equation for a monodisperse system as an approximate simple dissolution equation was derived as follows. The dissolution rate ($\mathrm{d}C/\mathrm{d}t$) given by Nernst[7] is expressed as

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

where k (=the diffusion coefficient/the thickness of the diffusion layer) is the dissolution rate constant, V is the solvent volume, S is the effective surface area at time t, and C_s is the solubility. When the dissolution measurement of a monodisperse system was carried out with initial amount, M_0, the M_0 decreased to amount M at time t, and the initial particle size, D_0, decreased to D. When the surface area at the initial dissolution time is expressed as S_0, S_0 and S of the monodisperse system can be expressed as follows[1,6,8]

$$S_0=S_{sp}M_0=(6/\rho f D_0)(\pi f^3 D_0^3 \rho N/6) \tag{2}$$

$$\begin{aligned} S&=S_{sp}'M=(6/\rho f D)(\pi f^3 D^3 \rho N/6)\\ &=(6/\rho f D_0)(D_0/D)(\pi f^3 D_0^3 \rho N/6)(D/D_0)^3 \end{aligned}$$

$$=S_{sp}M_0(D/D_0)^2$$

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

Here, S_{sp} is the specific surface area, ρ is the density of particle, f is the coefficient concerned with particle shape and N is the particle number.

Inserting Eq. 3, Eq. 1 can be expressed as

$$dC/dt=(k/V)S_{sp}M_0(M/M_0)^{2/3}(C_s-C) \quad (4)$$

When C_s and C are expressed by particle amount M_s and m, respectively, Eq. 4 can be given as

$$dm/dt=(k/V)S_{sp}M_0(M/M_0)^{2/3}(M_s-m) \quad (5)$$

When M is introduced in Eq. 5, Eq. 5 can be rewritten as follows

$$-dM/dt=(k/V)S_{sp}M_0(M/M_0)^{2/3}\{M_s-(M_0-M)\} \quad (6)$$

In Eq. 6, the cube root law equation can be obtained when $M_0 \ll M_s$,[3,5] and the negative two-thirds root law equation can be obtained when $M_0=M_s$.[9] Also, a precise dissolution equation was derived from Eq. 6.[4]

Here, a general dissolution equation as an approximate simple dissolution equation was derived from Eq. 5. Introducing M_0-m as M and with p defined as M_0/M_s, Eq. 5 can be rewritten as follows

$$dm/dt=(k/V)S_{sp}M_0(1-m/M_0)^{2/3}M_s(1-pm/M_0) \quad (7)$$

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{2/3}(1-pm/M_0) \quad (8)$$

In Eq. 8, the cube root law equation can be obtained when the p-value is extremely small, and the negative two-thirds root law equation can be obtained when the p-value is equal to 1, as described before. Therefore, it is suggested that a general dissolution equation may be obtained when the p-value can be taken into account. If the value of $(1-pm/M_0)$ can be expressed as a function of $(1-m/M_0)$, it is easy to integrate Eq. 8. Hence, the following approximate treatment for $(1-pm/M_0)$ was tried.

It was assumed, in order to simplify Eq. 8, that $(1-pm/M_0)$ can be expressed by a form of $(1-m/M_0)^q$, *i.e.*,

$$(1-pm/M_0)=(1-m/M_0)^q \quad (9)$$

Mathematically, the q-value changes when the p and m/M_0 values change, or the p-value changes with the changing values of q and m/M_0. Here, changes in the p-value with an increased m/M_0-value at a fixed q-value was calculated, and the values calculated within the m/M_0-value being equal to 0.95 are shown in Fig. 1. The p-value at a fixed q-value increased with an increasing m/M_0-value. The p-value should be equal to q at $m/M_0=0$, and reach 1 when the m/M_0-value is 1. However, it can be seen in Fig. 1 that each q-value required to satisfy Eq. 9 can be defined by a small region of the p-value. In other words, the p-value may fix the q-value, and the dissolution process can be estimated by the q-value defined by initial amount, *i.e.*, the p-value. Hence, the q-value was substituted by the p-value as an approximate simple treatment. So Eq. 8 can be rewritten as

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{2/3}(1-m/M_0)^p \quad (10)$$

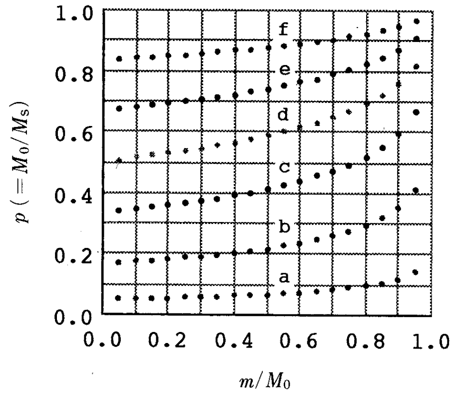

Fig. 1. Changes in the p-Value with the m/M_0-Value at a Given q-Value
a, $q=1/20$; b, $q=1/6$; c, $q=1/3$; d, $q=1/2$; e, $q=2/3$; f, $q=5/6$.

By rearranging Eq. 10, the following equations were obtained:

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{(2/3+p)} \quad (11)$$

$$-dM/dt=kC_sS_{sp}M_0(M/M_0)^{(2/3+M_0/M_s)} \quad (12)$$

$$-dM/dt=kC_sS_{sp}M_0^{\{1-(2/3+M_0/M_s)\}}M^{(2/3+M_0/M_s)} \quad (13)$$

Hence, by rearranging the equation after integration of Eq. 13, the following equation for the dissolution of a monodisperse system with an optional initial amount can be obtained when the p-value is a value other than 1/3.

$$(M/M_0)^{\{1-(2/3+M_0/M_s)\}}=1-\{1-(2/3+M_0/M_s)\}kC_sS_{sp}t \quad (14)$$

In Eq. 14, the cube root law equation can be obtained when M_0 is extremely small, and the negative two-thirds root law equation can be obtained when $M_0=M_s$. When an optional initial amount was used for the dissolution test, the dissolution process should be expressed by Eq. 14 by inserting the M_0/M_s-value.

Here, with z denoting the value of $\{1-(2/3+M_0/M_s)\}$ or $(1/3-M_0/M_s)$ and k_z the dissolution rate constant, the derived general dissolution equation was expressed as follows:

$$(M/M_0)^z=1-zk_zC_sS_{sp}t \quad (15)$$

Thus, the derived general dissolution equation was hereafter abbreviated as the z-law equation, after the equations of cube root law and negative two-third root law.

Results and Discussion

Applicability of the z-Law Equation The dissolution profiles of Pr-PHBA(M) using an optional initial amount are shown in Fig. 2. The initial amounts used for the dissolution test were expressed by a relative value, p (initial amount, M_0/the amount necessary to saturate the solution, M_s).

Following standard practice, the cube root law equation was applied for a dissolution test with a p-value of 1/20. The applicability of the z-law equation was examined as follows. In the case of dissolution with a p-value of 1/4, the z-value is given by 1/3 minus 1/4. Here, the applied z-law equation was

$$(M/M_0)^{1/12}=1-(1/12)k_zC_sS_{sp}t \quad (16)$$

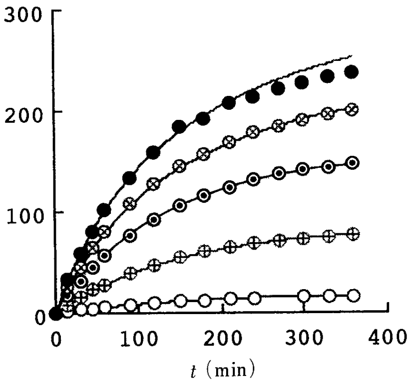

Fig. 2. Dissolution and Simulation Curves for Pr-PHBA (M)

○, $p=1/20, z=1/3$; ⊕, $p=1/4, z=1/12$; ⊙, $p=1/2, z=1/6$; ⊗, $p=3/4, z=-5/12$; ●, $p=1, z=-2/3$.

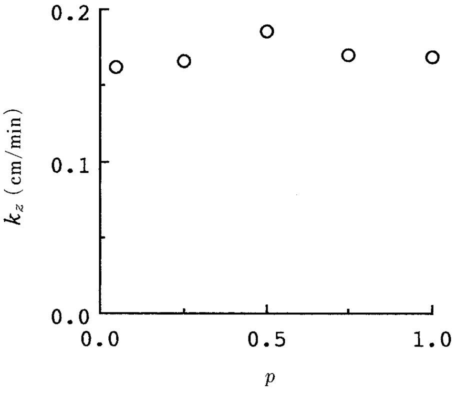

Fig. 4. Changes in the k_z-Value with the p-Value Estimated by Using the z-Law Equation with the Value of $q=p$

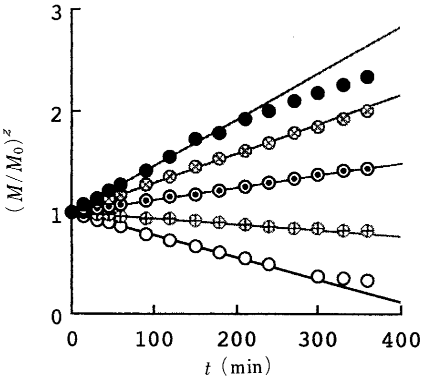

Fig. 3. Applicability of the Cube Root Law, Negative Two-Thirds Root Law and z-Law Equations

○, $p=1/20, z=1/3$; ⊕, $p=1/4, z=1/12$; ⊙, $p=1/2, z=1/6$; ⊗, $p=3/4, z=-5/12$; ●, $p=1, z=-2/3$.

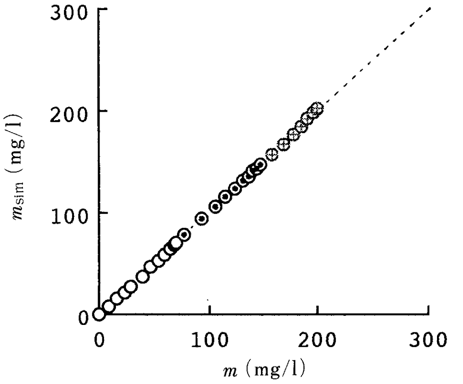

Fig. 5. Relationships between the Values Simulated by Using the z-Law Equation and the Measured Values

○, $p=1/4, z=1/12$; ⊙, $p=1/2, z=1/6$; ⊕, $p=3/4, z=-5/12$; ----, $m_{\text{sim}}=m$.

When the p-value is 1/2,

$$(M/M_0)^{-1/6}=1+(1/6)k_zC_sS_{\text{sp}}t\,, \tag{17}$$

and when the p-value is 3/4,

$$(M/M_0)^{-5/12}=1+(5/12)k_zC_sS_{\text{sp}}t \tag{18}$$

Results of treatment using these equations are shown in Fig. 3.

A fairly good straight line was obtained for each dissolution test, and the z-law equation was thus thought to be useful. The dissolution rate constant (k_z) was estimated from the slope of the line, and the k_z-value obtained for each dissolution test is shown in Fig. 4 as a function of the initial amount, *i.e.*, the p-value.

The k_z-value showed a consistent value of around 0.17 cm/min. Hence, each dissolution process was simulated by use of the k_z-value, *i.e.*,

$$m_{\text{sim}}=M_0\{1-(1-zk_zC_sS_{\text{sp}}t)^{1/z}\} \tag{19}$$

and was shown by a solid line in Fig. 2. Comparisons of the simulated values (m_{sim}) and measured values (m) are shown in Fig. 5. The broken line shown in Fig. 5 represents $m_{\text{sim}}=m$. According to Figs. 2 and 5, the simulated values showed fairly good coincidence with the measured values, despite a small deviation which appeared in the dissolution process (Fig. 3) and the k_z-value (Fig. 4). Hence, the z-law equation was thought to be very efficient for explaining the dissolution process carried out with an optional initial amount within solubility.

Application of the z-Law Equation In deriving the z-law equation, the q-value was assumed to be equal to the p-value in order to confirm its validity as a simple method. However, the q-value covered only a small range of the p-value, as shown in Fig. 1, so it was supposed that a more suitable q-value, other than the p-value, may exist around the p-value which would better explain the dissolution process. Hence, the dissolution process was examined by setting several q-values around the p-value, and the results obtained are shown in Fig. 6.

Usually, sink dissolution with the p-value below 1/20 was treated by use of the cube root law equation. However, when the p-value is equal to 1/20, the z-value should be around 7/24, since the z-value is given as $1/3-1/20=6.8/24$. Hence, it was expected that the z-law equation with a z-value of 7/24 would explain the dissolution process more accurately than the cube root law equation, *i.e.*, the z-value of 1/3 (=8/24). Here, as can be seen in Fig. 6a, the dissolution process using a z-value of 7/24 fits better than that of 8/24. Also, it was observed that explanation of dissolution process increased in effectiveness with a decreasing z-value, and the whole dissolution process measured here was satisfactorily expressed by a straight line

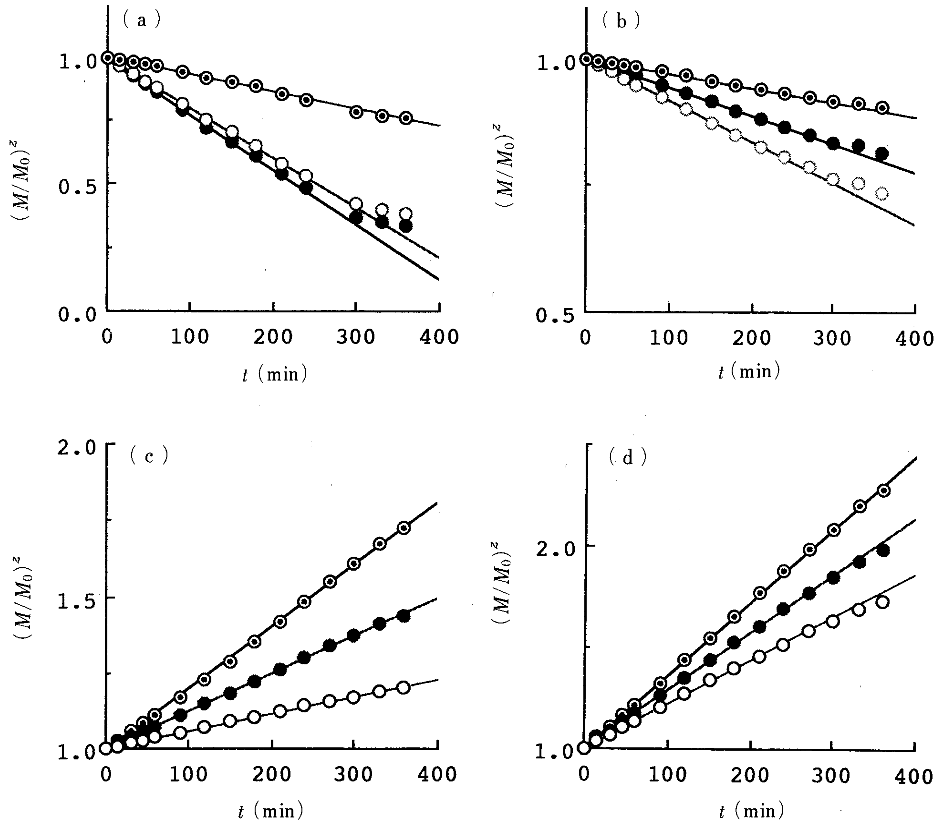

Fig. 6. Application of the z-Law Equation with Various z-Values

(a) $p=1/20$, ●, $z=8/24$; ○, $z=7/24$; ⊙, $z=2/24$ (b) $p=1/4$, ○, $z=3/24$; ●, $z=2/24$; ⊙, $z=1/24$ (c) $p=1/2$, ○, $z=-1/12$; ●, $z=-2/12$; ⊙, $z=-3/12$ (d) $p=3/4$, ○, $z=-8/24$; ●, $z=-10/24$; ⊙, $z=-12/24$.

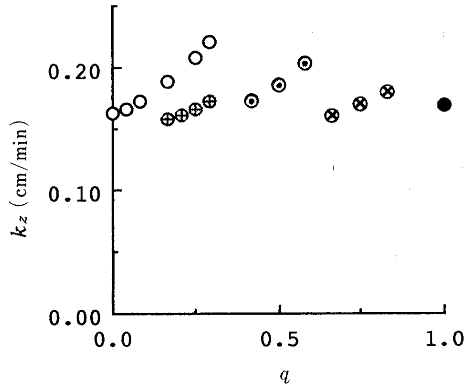

Fig. 7. Changes in the k_z-Value Estimated by Using the z-Law Equation with Different q-Values

○, $p=1/20$; ⊕, $p=1/4$; ⊙, $p=1/2$; ⊗, $p=3/4$; ●, $p=1$.

when the z-value was equal to about 1/24. Thus, it was suggested that the z-law equation derived by taking into account the initial amount should be applied for dissolution tests, even if the dissolution measurement were carried out under sink condition. The difference in the explainable dissolution process may be caused by setting the q-value to be equal to the p-value, because the q-value agrees with the p-value in Eq. 9 when the m/M_0-value is small, *i.e.*, the initial dissolution stage. Also, the same aspects were observed in dissolution tests with p-values of 1/4, 1/2 and 3/4, as shown in Fig. 6. The k_z-values obtained by setting various q-values are shown in Fig. 7.

Considering the derivation process of the z-law equation, the q-value is not always equal to the p-value, and the z-value should be $1-(2/3+q)$ or $1/3-q$ according to Eqs. 8 and 9. Thus, in the case of treament by means of the z-law equation with various q-values, the k_z-value and the explainable dissolution process increased with increasing the q-value, or, by decreasing the z-value, as can be seen in Figs. 6 and 7. Hence, it was thought that the q-value can be settled freely around the p-value for the z-value as needed. However, the simulated values (m_{sim}) coincided fairly well with the measured value (m), as shown in Figs. 2 and 5, and the dissolution process can be fairly accurately estimated by use of the z-law equation originally defined by $q=p$.

Conclusion

A general dissolution equation as an approximate simple dissolution equation was derived as a function of the initial amount used in a dissolution measurement. The derived equation was expressed by a form which included the cube root law and negative two-thirds root law equations, and was abbreviated as the z-law equation. Applying the derived dissolution equation, *i.e.*, z-law equation, to dissolution measurements with various initial amounts, the validity of the z-law equation was confirmed. Once the dissolution rate constant has been determined from dissolution measurement with a given initial amount, it is easy to predict or simulate the dissolution process with an optional initial amount by use of the z-law equation with a dissolution rate constant determined previously, since the dissolution rate constant is almost the same independent of the initial amount. Hence, the z-law equation was thought to be very efficient for the explanation or simulation of dissolution processes with optional initial amounts within solubility.

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