Dissolution of Solid Dosage Form. VI.[1] Dissolution of Nondisintegrating Single Component Tablets under Non-Sink Condition

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Nondisintegrating single component tablets were dissolved under a non-sink condition, and the applicability of equations derived for the dissolution of particles with optional initial amounts, *i.e.*, the z-law equation, Ln-z equation and Lg-z equation, was examined by comparing the dissolution rate constants and conformity of simulated value to measured value. The z-law equation expressed by a function of the initial amount used for dissolution measurement and solubility was reasonably applicable to the dissolutions of tablets with various initial amounts within solubility. The Ln-z equation well explained the dissolution process with initial amounts within around half of the solubility. The Lg-z equation, an extended application form of the z-law equation, was applicable to the dissolution with an initial amount close to the solubility. These application aspects for dissolutions of nondisintegrating single component tablets were almost the same as those observed for dissolution of particles reported previously, and it was confirmed that the z-law equation, the Ln-z equation and the Lg-z equation appropriately treated dissolutions carried out with optional initial amounts within solubility irrespective of whether particles or tablets. Once the dissolution rate constant was determined in advance, the dissolution process with optional initial amounts within solubility could be approximately predicted. It may become difficult to predict the dissolution process with increase in tablet weight, however.

Key words dissolution; simulation; tablet; non-sink condition; Ln-z equation; z-law equation

The rotating disk method is useful in determining an intrinsic dissolution rate constant. The dissolution process of a whole tablet cannot be predicted by this method, however, even when required from the viewpoint of practical use. Therefore, in postulating isotropic dissolution, equations were deserved for the dissolution of a nondisintegrating single component tablet under both a sink and a non-sink condition where the initial amount is equal to the amount required to saturate the solution; these were expressed in the form of the cube root law equation and the negative two-thirds root law equation, respectively.[2,3] Then, the validities of these equations were confirmed by comparing the dissolution measurements and their simulation; also, a nondisintegrating single component tablet was thought to behave like a single crystal.[3]

Three equations for the dissolution of a monodisperse crystalline system with optional initial amounts within solubility were previously derived as a function of the initial amount and solubility,[1,4] and were called the z-law, Ln-z and Lg-z equations. As described above,[2,3] a nondisintegrating single component tablet was thought to behave like a single crystal, so the applicability of the derived equations was examined by carrying out the dissolution of nondisintegrating single component tablets with optional initial amounts within the solubility. One-twentieth of the amount required to saturate the solution was compressed to make a flat-faced tablet, and the dissolution was measured using several tablets as a model of a monodisperse system. The applicabilities of the z-law, Ln-z and Lg-z equations was then estimated by comparing the dissolution rate constants and checking conformity of measured and simulated dissolution curves.

Experimental

Materials Salicylic acid (abbreviated SA, guaranteed reagent grade, Wako Pure Chemical Ind., Ltd.) was used.

Preparation of Tablet An amount 1/20 of that required to saturate the test solution (1.70 g)[3] was compressed at a pressure of 2 t (type clean press correct 12 HUK, Kikusui Ind., Co.) to make a flat-faced tablet of around 0.85 cm diameter and 0.12 cm thickness.

Dissolution of Tablet The dissolution test followed the method described previously.[3] The test was initiated by placing several tablets in 1000 ml of 0.1 N HCl (pH 1.0) at a paddle rotation speed of 250 rpm at 25 °C (type NTR-VS, Toyama Sangyo Co., Ltd.). A small amount of the solution was taken out periodically, and the same amount of solvent was replaced to keep the solvent amount constant throughout the test. The concentration of the sampled solution was determined from the absorbance at 302.5 nm with a type UV-160 spectrophotometer (Shimadzu Ind., Co.).

Theoretical Analysis

Equations derived for the dissolution of a monodisperse system are summarized as follows.[1,4] Following the diffusion layer model,[5] the dissolution rate (dC/dt) is expressed as

$$dC/dt = (k/V)S(C_s - C) \quad (1)$$

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.

The particle shape coefficient involves both the weight and surface area at the same time, and it was postulated that it does not have a significant effect on the estimation of the effective surface area during the dissolution process where the initial amount, M_0, decreased to amount M. Then, denoting by S_0 the initial effective surface area, by S_{sp} the initial specific surface area estimated from the initial particle size, the effective surface area, S, at time t is given as follows, since $S_0 = S_{sp} M_0$ and $S/S_0 = (M/M_0)^{2/3}$:

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

When C_s and C are expressed by the amount (M_s) required

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to saturate the solution and the amount (m) dissolved at time t, Eq. 1 can be rewritten as follows taking into account Eq. 2:

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

As $M_s/V=C_s$, and expressing the relative value, $M_0/M_s=p$, Eq. 3 is rewritten in the form

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{2/3}(1-pm/M_0) \quad (4)$$

When $(1-pm/M_0)$ can be expressed by a form of $(1-m/M_0)^q$, Eq. 4 can be expressed in a more simple form as:

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{2/3+q} \quad (5)$$

According to a popular approximation, the q-value is equal to the p-value when the m/M_0-value is much smaller than 1, and the q-value changes in accordance with the m/M_0-value at fixed p-value ($=M_0/M_s$). However, it was concluded that the q-value is temporarily substituted by the p-value, and Eq. 5 is rewritten as:

$$dm/dt=kC_sS_{sp}M_0(1-m/M_0)^{2/3+M_0/M_s} \quad (6)$$

or

$$-dM/dt=kC_sS_{sp}M_0^{\{1-(2/3+M_0/M_s)\}}M^{(2/3+M_0/M_s)} \quad (7)$$

In integrating Eq. 7, two integrated equations can be obtained in accordance with the value of $2/3+M_0/M_s$.

1. The z-law equation. When the M_0/M_s-value is a value other than 1/3, the following equation is obtained:

$$(M/M_0)^z=1-zk_zC_sS_{sp}t \quad (8)$$

Here, $z=1/3-M_0/M_s$, and the dissolution rate constant is expressed by k_z to distinguish it from one defined by the other dissolution equation.

2. The Ln-z equation. When the M_0/M_s-value is equal to 1/3, the following equation can be obtained:

$$\ln(M/M_0)=-k_{Ln}C_sS_{sp}t \quad (9)$$

Here, the dissolution rate constant is expressed by k_{Ln} to distinguish it from one defined by the other dissolution equation.

3. The Lg-z equation. The equation in the same form as the Langmuir equation which is efficient for the dissolution with the initial amount close to the solubility was obtained as an extended application form of the z-law equation. By setting q as equal to 4/3, an extended form of the z-law equation was expressed as

$$(M/M_0)^{-1}=1+k_zC_sS_{sp}t \quad (10)$$

Rearranging Eq. 10, the Lg-z equation was written as follows in the same form as the Langmuir equation.

$$m=M_0k_{Lg}C_sS_{sp}t/(1+k_{Lg}C_sS_{sp}t) \quad (11)$$

Here, the dissolution rate constant was expressed by k_{Lg} to distinguish it from one defined by the other dissolution equation. Also, by rearranging, Eq. 11 (or 10) is shown as follows:

$$M_0/m=1+(1/k_{Lg}C_sS_{sp})(1/t) \quad (12)$$

$$m/(M_0-m)=m/M=k_{Lg}C_sS_{sp}t \quad (13)$$

Essentially, Eqs. 10 and 13 give the same value of dissolution rate constant.

Results and Discussion

Applicability of the z-Law Equation In the dissolution of nondisintegrating single component tablets, the z-law equation is rewritten as follows, since the specific surface area is given by the initial surface area (S_0) and the initial amount (M_0) as S_0/M_0

$$(M/M_0)^z=1-zk_zC_s(S_0/M_0)t \quad (8')$$

where S_0 is estimated by using the diameter and thickness of tablets. Therefore, the dissolution process can be simulated by:

$$m=M_0[1-\{1-zk_zC_s(S_0/M_0)t\}^{1/z}] \quad (14)$$

The dissolution curves for tablets as a model of a monodisperse system and the treatment using the z-law equation are shown in Figs. 1 and 2, respectively.

Applying the z-law equation, a fairly good straight line was obtained for each dissolution measurement, and this equation was thought to be useful for the dissolution of

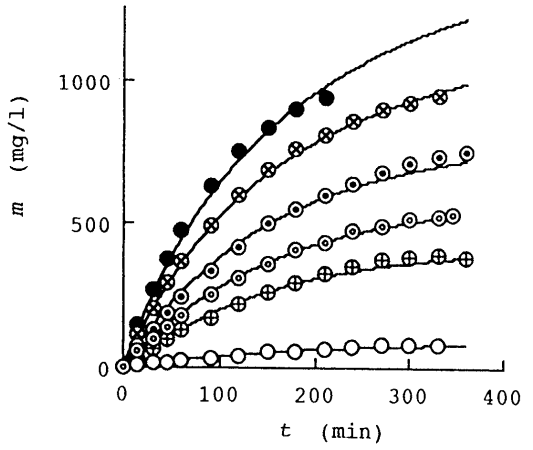

Fig. 1. Dissolution and Simulation Curves Using the z-Law Equation for Dissolution of Nondisintegrating Single Component Tablets

Initial amount (M_0/M_s): ○, 1/20; ⊕, 5/20; ◎, 7/20; ⊙, 10/20; ⊗, 15/20; ●, 20/20.

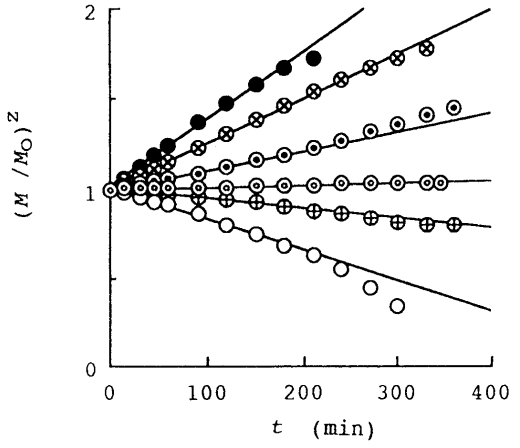

Fig. 2. Application of the z-Law Equation for Dissolution of Nondisintegrating Single Component Tablets

○, $p=1/20$, $z=7/24$; ⊕, $p=5/20$, $z=1/12$; ◎, $p=7/20$, $z=-1/60$; ⊙, $p=10/20$, $z=-1/6$; ⊗, $p=15/20$, $z=-5/12$; ●, $p=20/20$, $z=-2/3$.

nondisintegrating single component tablets, too. The dissolution rate constant (k_z) estimated from the slope of the line and the critical dissolved amount ($m_{c,m}$) which began to deviate from the line are summarized in Figs. 3 and 4, respectively. Here, the critical dissolved amount is expressed by the relative value as $m_{c,m}/M_0$.

The k_z-values are close to each other, and the $m_{c,m}/M_0$-value is around 0.7 irrespective of the initial amount. The simulated dissolution curves shown by the solid lines fitted well with the measured dissolution curves in Fig. 1. Therefore, applicability of the z-law equation for the dissolution of nondisintegrating single component tablets with various initial amounts within the solubility was believed satisfactory.

Applicability of the Ln-z Equation The Ln-z equation is rewritten as follows substituting S_0/M_0 for S_{sp} as in the z-law equation

$$\ln(M/M_0) = -k_{Ln}C_s(S_0/M_0)t \tag{9'}$$

Therefore, the dissolution process can thus be simulated by:

$$m = M_0[1-\exp\{-k_{Ln}C_s(S_0/M_0)t\}] \tag{15}$$

The dissolution curves of tablets with the initial amount within around two-thirds of the solubility and treatment by the Ln-z equation are shown in Figs. 5 and 6, respectively.

A fairly good straight line was obtained for the dissolution with the initial amount of half of the solubility, *i.e.*, $M_0=(1/2)M_s$. The dissolution with the other initial amount deviated downward or upward from the line in accordance with the initial amount as described.[1] The dissolution rate constant (k_{Ln}) estimated from the slope of the line and the critical dissolved amount ($m_{c,m}$) which began to deviate from the line are summarized in Figs. 3 and 4, respectively. As stated, the critical dissolved amount is expressed by the relative value.

The k_{Ln}-values are close to each other, and also, comparable to the k_z-values. The simulated dissolution curves are shown in Fig. 5. The $m_{c,m}/M_0$-value in the region from 1/4 to 1/2 of the solubility is relatively high as expected from the derivation condition for the Ln-z equation. Therefore, the Ln-z equation was viewed as efficient for the dissolution of tablets where the initial amount is at least within half of the solubility. Here, it was supposed that the applicable region of the Ln-z equation for tablet is a little narrower than that for crystalline particles.[1]

Applicability of the Lg-z Equation The Lg-z equation is rewritten as follows substituting S_0/M_0 for S_{sp}:

$$(M/M_0)^{-1} = 1 + k_zC_s(S_0/M_0)t \tag{10'}$$

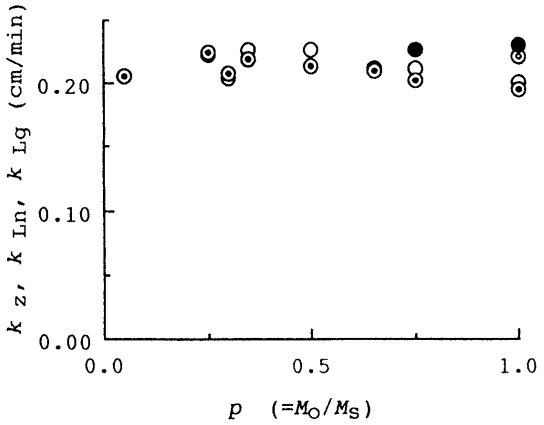

Fig. 3. Relationship between the Initial Amount ($p=M_0/M_s$) and the Dissolution Rate Constants

○, k_z; ⊙, k_{Ln}; ●, k_{Lg} (Eq. 12'); ◎, k_{Lg} (Eq. 13').

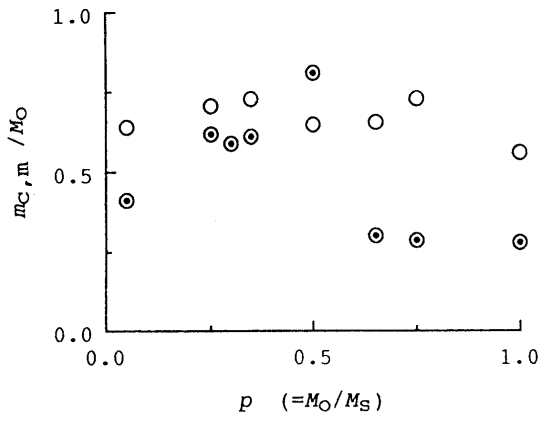

Fig. 4. Relationship between the Initial Amount ($p=M_0/M_s$) and the Measured Critical Amount Expressed by the Ratio to the Initial Amount ($m_{c,m}/M_0$)

○, estimated using the z-law equation; ⊙, estimated using the Ln-z equation.

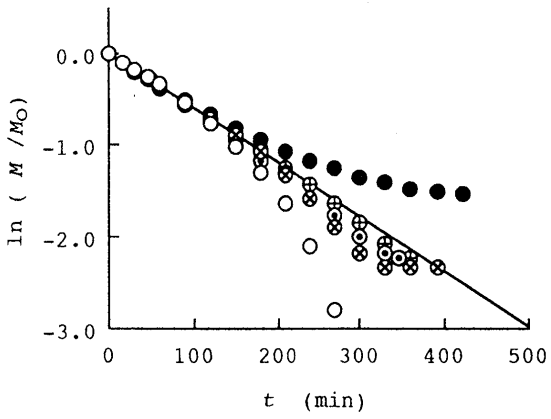

Fig. 5. Dissolution and Simulation Curves Using the Ln-z Equation for Dissolution of Nondisintegrating Single Component Tablets

Initial amount (M_0/M_s): ○, 1/20; ◎, 5/20; ⊗, 6/20; ⊙, 7/20; ⊕, 10/20; ●, 13/20.

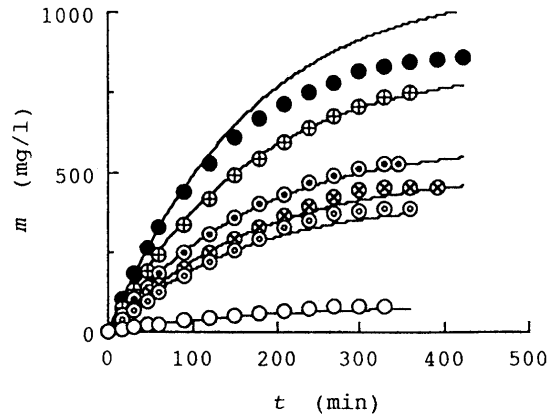

Fig. 6. Application of the Ln-z Equation for Dissolution of Nondisintegrating Single Component Tablets

Initial amount ($p=M_0/M_s$): ○, 1/20; ⊗, 6/20; ⊙, 7/20; ⊕, 10/20; ●, 13/20.

$$m=M_0k_{Lg}C_s(S_0/M_0)t/\{1+k_{Lg}C_s(S_0/M_0)t\} \quad (11')$$

$$M_0/m=1+\{1/k_{Lg}C_s(S_0/M_0)\}(1/t) \quad (12')$$

and

$$m/(M_0-m)=m/M=k_{Lg}C_s(S_0/M_0)t \quad (13')$$

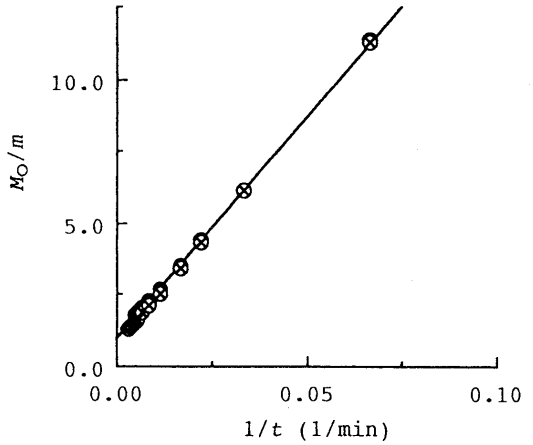

Fig. 7. Application of the Lg-z Equation (Eq. 12′) for Dissolution of Nondisintegrating Single Component Tablets

Initial amount ($p=M_0/M_s$): ⊗, 15/20; ●, 20/20.

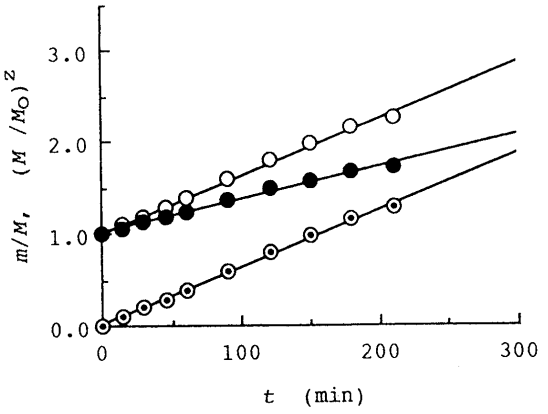

Fig. 8. Treatments of Dissolution of Nondisintegrating Single Component Tablets with an Initial Amount of Solubility

●, the negative two-thirds root law equation; ⊙, the z-law equation (Eq. 10′); ○, the Lg-z equation (Eq. 13′).

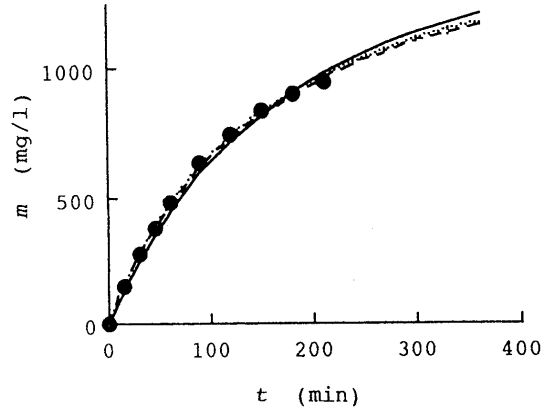

Fig. 9. Dissolution and Simulation Curves for Dissolution of Nondisintegrating Single Component Tablets with an Initial Amount of Solubility

——, the negative two-thirds root law equation; ------, the Lg-z equation (Eqs. 12′ and 11′); – –, the Lg-z equation (Eqs. 13′ and 11′).

The dissolutions with the initial amount around the solubility treated are shown in Figs. 7 and 8. Here, the treatment by the negative two-thirds root law equation is shown for comparison.

The dissolution with the initial amount of solubility showed a good straight line for each treatment. The dissolution rate constants estimated from the slopes are summarized in Fig. 3, and the dissolution and simulation curves are shown in Fig. 9. Comparing the simulation curves, the Lg-z equation gives a value close to that given by the negative two-thirds root law equation.

The simulation curves using Eqs. 12′ and 11′ for the dissolution with the initial amount around the solubility are shown in Fig. 10. A good straight line is seen for the dissolution with the initial amount of 3/4 of the solubility in Fig. 7. However, the simulated dissolution curve deviates from the measured one, and it was supposed that the Lg-z equation as an extended application form of the z-law equation is efficient only for the dissolution with initial amounts close to the solubility.

Tablet Weight and Dissolution Rate Constant An amount 5/20 of the solubility was compressed to make a flat-faced tablet about 1.6 cm diameter and 0.20 cm thickness. The tablet weight is five times that of the tablet

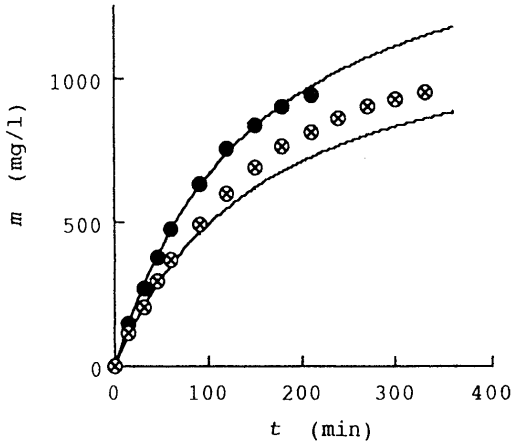

Fig. 10. Dissolution and Simulation Curves (Eqs. 12′ and 11′) for Dissolution of Nondisintegrating Single Component Tablets with an Initial Amount around the Solubility

Initial amount ($p=M_0/M_s$): ⊗, 15/20; ●, 20/20.

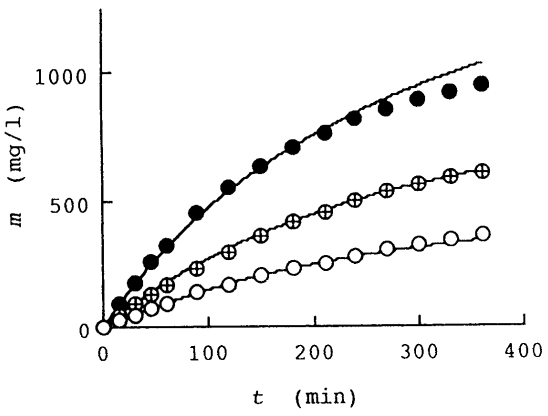

Fig. 11. Dissolution and Simulation Curves Using the z-Law Equation for Dissolution of Nondisintegrating Single Component Tablets

Tablet weight is equal to 5/20 of the solubility. Initial amount ($p=M_0/M_s$): ○, 5/20; ⊕, 10/20; ●, 20/20.

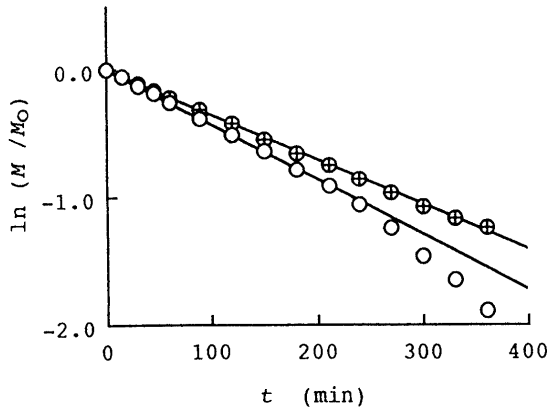

Fig. 12. Application of the Ln-z Equation for Dissolution of Non-disintegrating Single Component Tablets

Tablet weight is equal to 5/20 of the solubility. Initial amount ($p=M_o/M_s$): ○, 5/20; ⊕, 10/20.

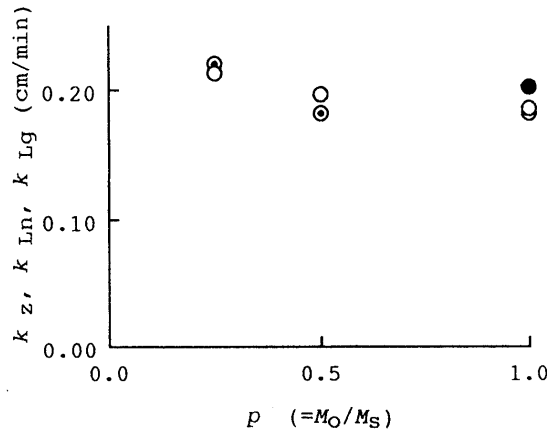

Fig. 13. Relationship between the Initial Amount ($p=M_o/M_s$) and the Dissolution Rate Constants

Tablet weight is equal to 5/20 of the solubility. ○, k_z; ⊙, k_{Ln}; ●, k_{Lg} (Eq. 13').

used in the above experiments, but the shape is almost the similar from the viewpoint of the ratio of diameter and thickness. Hence, effect of the tablet weight on the estimation of dissolution rate constant was examined. Dissolution curves are shown in Fig. 11. The dissolution rate constants are estimated using the z-law, Ln-z and Lg-z equations, and an example is shown in Fig. 12. The results obtained are shown in Fig. 13.

Simulation curves using the z-law equation are shown by the solid lines in Fig. 11. They fitted well with the measured curves, so these dissolution equations were thought to be useful irrespective of tablet weight. As shown in Fig. 13, the dissolution rate constants are relatively close to each other when compared at a given initial amount, but they decreased unexpectedly with increase in the initial amount, because the dissolution rate constant was expected to be less affected by particle or tablet number in a monodisperse system.[1,4] Comparing the results shown in Fig. 13 and Fig. 3, however, the dissolution with a single tablet gave a dissolution rate constant of almost the same value. It was then assumed that prediction of the dissolution process of small tablet size or weight is easy, but prediction may become difficult with increasing size or weight of tablet.

Conclusion

Equations derived for the dissolution of a monodisperse particle system with optional initial amounts were applied to the dissolution of nondisintegrating single component tablets as a model of the monodisperse system with various initial amounts, and the following was concluded.

The z-law equation was applicable for the dissolution with optional initial amounts other than one-third of the solubility. The dissolution rate constants (k_z) obtained were relatively similar irrespective of the initial amount, and the simulated dissolution curves fitted well with the measured dissolution curves.

The Ln-z equation gave the comparable dissolution rate constants (k_{Ln}) to k_z irrespective of the initial amount within the solubility. However, from the viewpoint of explanation or simulation of the dissolution process, the Ln-z equation was applicable to the dissolution with an initial amount within around half of the solubility.

The Lg-z equation as an extended application form of the z-law equation was efficient for a dissolution with an initial amount close to the solubility as well as the negative two-thirds root law equation.

The dissolution process of nondisintegrating single component tablets with an initial amount within solubility was well explained by the equations available for the dissolution of crystalline particles. In other words, the equations derived were applicable for the treatment of the dissolution of nondisintegrating single component tablets as well as crystalline particles, and the possibility of an approximate prediction of the dissolution process with various initial amounts within solubility was suggested when the dissolution rate constant was determined in advance using an optional initial amount. It was also suggested that these dissolution equations are applicable to dissolutions of substances of various shapes and sizes or weight within the solubility. In the case of tablet, however, it may become difficult to predict the dissolution process with increase in tablet size or weight, since the dissolution rate constant is likely to change with tablet weight from the viewpoint of hydrodynamic effect on the tablet.

References and Notes

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