Dissolution of Solid Dosage Form. VII.[1) Effect of Shape on the Dissolution of Nondisintegrating Single Component Tablet under Non-sink Condition

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Received October 13, 1995; accepted January 9, 1996

Effect of tablet shape on dissolution was examined as an example of the application of the z-law and Ln-z equations. The tablet shape can be altered systematically by changing the diameter and weight of tablet, since these equations were applicable for dissolutions with various optional initial amounts within the amount required to saturate the solution.

It was confirmed that the z-law and Ln-z equations efficiently treated the dissolution of tablet irrespective of the weight and size, *i.e.*, the diameter and thickness as well as crystalline particles. Both dissolution equations gave almost the same dissolution rate constants for a tablet of a fixed weight and size.

The dissolution rate constant changed with the tablet weight and size, and it was suggested that the latter factor probably had greater effect. The tablet size was then converted to the degree of isometricity or shape factor. Then, the effect of shape on the dissolution rate constants of tablets (k_z) was estimated using the z-law equation. The k_z-value of a long cylindrical tablet was large, and it decreased to reach a minimum value with decrease in tablet thickness and increase in diameter. The k_z-value increased to reach almost a fixed value of shallow cylindrical tablets as if it had been obtained by a rotating disk method.

The difference in the dissolution rate constants was examined using a specially devised tablet of which the flat-faced surface or curved surface was coated with wax. Dissolutions with these tablets suggested that the dissolution rate constant of the long cylindrical tablet was the larger of the two. Also, the way in which the flat-faced and curved surfaces contribute to the k_z-value was examined as a function of the ratio of flat-faced surface area ($2S_d$) to the whole surface area (S_o), *i.e.*, $2S_d/S_o$. The k_z-value decreased almost straightly within the $2S_d/S_o$-value reached to around 0.63, showing a close similar value where the $2S_d/S_o$-value was larger than around 0.73. Thus, it was suggested that the tablet form should be taken into consideration when necessary.

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

Previously, dissolution equations have been derived as a function of the initial amount, *i.e.*, the Ln-z equation and z-law equation which included the cube root law and negative two-thirds root law equations. Dissolution rate constants which were close in value were obtained irrespective of the initial amount and particle size by applying these equations to the dissolution of crystalline particles with various optional initial amounts.[2,3)

For a nondisintegrating single component tablet, the equation derived by postulating the isotropic dissolution of the tablet of an amount of 1/20 of the solubility or the amount required to saturate the solution was expressed in the same form of the cube root law equation or the negative two-thirds root law equation, respectively.[4) No shape factor was involved in these derived equations, and the effective surface area of tablet was given by the initial whole surface area per weight of the tablet as the specific tablet surface area. Also, an amount 1/20 of the amount required to saturate the solution was compressed to make a flat-faced nondisintegrating tablet, and dissolution rate constants of almost the same value were obtained irrespective of the initial amount using the z-law and Ln-z equations for the dissolution of several tablets.[1)

Originally, the cube root law and negative two-thirds root law equations were derived for crystal which remained predominantly spheroidal throughout its dissolution under the assumption that it is not necessary to postulate any definite geometrical shape for the particle undergoing dissolution.[5) Basically, these equations were expressed using the dissolution rate constant, solubility, specific surface area and initial amount, with a factor or coefficient concerning the shape of solute involved in the specific surface area.[4) The same expression was seen in the z-law and Ln-z equations, and these were applicable to the dissolution of both crystalline particles and tablets of which the shape far from spherical or cubic, even though these equations were expressed as a function of the specific surface area of particles with no regard to shape factor.[1,3) It was therefore thought that a factor or coefficient concerning the shape does not bring significant effect on the estimation of the dissolution rate constant directly. Hence, it was suggested that these equations can efficiently treat dissolution processes irrespective of sample weight and shape.

In a nondisintegrating single component tablet, the dissolution process may be affected by the weight and shape. Lai and Carstensen approximated crystalline particles that have needle or plate shapes by long or shallow cylinders, and examined the dissolution process of a non-isometric shape sample in relation to the cube root law equation[6); however, few papers have dealt with the effect of the shape or the degree of isometricity on this process. The cube root law equation or the negative two-thirds root law equation demands a fixed initial amount. The thickness of cylinder or tablet simultaneously changes in accordance with the diameter, so that the effect of the degree of isometricity or the contribution of the diameter or thickness on the dissolution

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cannot be clearly estimated. However, the z-law and Ln-z equations can be used to calculate the dissolutions irrespective of the shape and weight within the solubility as described above, so the degree of isometricity can be altered systematically by changing these features of the tablet, and it may be possible to estimate the contribution by treatment of the dissolution with a tablet with a systematically altered degree of isometricity.

Experimental

Materials Salicylic acid (SA: guaranteed reagent grade, Wako Pure Chemical Ind., Ltd.) was used, and hydrogenated castor oil (Kawaken Fine Chemical Co.) was used to make a wax coated specially devised SA tablet.

Preparation of Tablet An amount 6/12, 9/12, 10/12 and 12/12 of that required to saturate the solution (1.70 g) was used, and the weighed sample was compressed at a pressure of 2 t (type clean press correct 12 HUK, Kikusui Ind. Co.) to make a flat-faced tablet. These tablets were abbreviated as the $p_{6/12}$, $p_{9/12}$, $p_{10/12}$ and $p_{12/12}$ tablet, respectively. Tablet with diameters of 10.0, 16.0, 20.0 and 23.0 mm were abbreviated as d_{10}, d_{16}, d_{20} and d_{23} tablet, respectively. Thickness of the tablets thus differed in accordance with the weight of tablet.

Dissolution of Tablet The dissolution test followed the method described.[1] The test was initiated by placing a tablet 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 solvent amount constant throughout the test. The concentration of the sampled solution was estimated from the absorbance at 302.5 nm with a spectrophotometer (type UV-160, Shimadzu Ind. Co.).

Theoretical Analysis

The z-law equation is expressed as follows[3]:

$$(M/M_o)^z = 1 - zk_z C_s S_{sp} t \quad (1)$$

$$z = 1/3 - M_o/M_s \quad (2)$$

where M_s is the amount needed to saturate the solution, M_o is the initial amount, M ($= M_o - m$, m is the dissolved amount) is the remaining undissolved amount at time t, C_s is the solubility, S_{sp} is the specific surface area and k_z is the dissolution rate constant. Thus, the z-law equation is expressed as a function of the ratio of initial amount to the amount needed to saturate the solution, *i.e.*, M_o/M_s ($=p$). As the specific surface area is the surface area per unit amount, Eq. 1 is rewritten using the initial surface area (S_o) and the initial weight (M_o) of tablet as [1]:

$$(M/M_o)^z = 1 - zk_z C_s (S_o/M_o) t \quad (3)$$

Therefore, the dissolution process can be simulated by:

$$m_z = M_o[1 - \{1 - zk_z C_s (S_o/M_o) t\}^{1/z}] \quad (4)$$

where m_z is the simulated dissolved amount.

The Ln-z equation is expressed as follows[1,3b]:

$$\ln(M/M_o) = -k_{Ln} C_s (S_o/M_o) t \quad (5)$$

where k_{Ln} is the dissolution rate constant.

Shape Factor or Degree of Isometricity of Tablet Two kinds of shape factor or degree of isometricity which characterize the initial form of tablets are defined as follows:

1) Shape Factor, $f_{s/v}$: Following the definition of Lai and Carstensen,[6] the shape factor of tablet, $f_{s/v}$, was defined as:

$$f_{s/v} = S_o v^{-2/3} \quad (6)$$

S_o ($= \pi d^2/2 + \pi dh$) is the total initial surface area and v ($= \pi d^2 h/4$) is the initial volume of the tablet of diameter, d, and thickness, h. It is noted that for a spherical form $f_{s/v} = 6^{2/3}\pi^{1/3}$ and for a cubic form $f_{s/v} = 6$. The $f_{s/v}$-value increases with changes in tablet form from long to shallow cylinder, and a tablet is isometric when its diameter is equal to thickness.

2) Shape Factor, $f_{d/h}$: Using the surface area of two flat-faced and curved surfaces, the shape factor of tablet, $f_{d/h}$, was defined as:

$$f_{d/h} = 2S_d/S_h = d/2h \quad (7)$$

$2S_d$ ($= \pi d^2/2$) is the total initial surface area of the two flat-faced surfaces and S_h ($= \pi dh$) is the initial surface area of the curved surface. Hence, the $f_{d/h}$-value is given as the ratio of diameter to thickness of tablet. The $f_{d/h}$-value increases with changes in tablet form from long to shallow cylinder as well as the $f_{s/v}$-value described above.

Results and Discussion

Shape Factor and Dissolution Rate Constant Estimated Using the Negative Two-Thirds Root Law Equation When the initial amount is equal to that required to saturate the solution, the z-value is equal to $-2/3$, and the z-law equation is expressed as the negative two-thirds root law equation. Treatments of the dissolutions with the $p_{12/12}$ tablets using the negative two-thirds root law equation are shown in Fig. 1. The dissolution rate constants were estimated from the slope, and the relationship between the dissolution rate constants and the shape factors are shown in Fig. 2.

It was observed that the dissolution rate constants are likely to depend on the shape, even though details, especially beyond both ends, are not clear. Then, it was supposed that the one and only amount fixed by the negative two-thirds root law equation is insufficient for explanation.

Dissolution Rate Constants Estimated Using The z-Law and Ln-z Equations The z-law and Ln-z equations are applicable for dissolution with an optional initial amount.

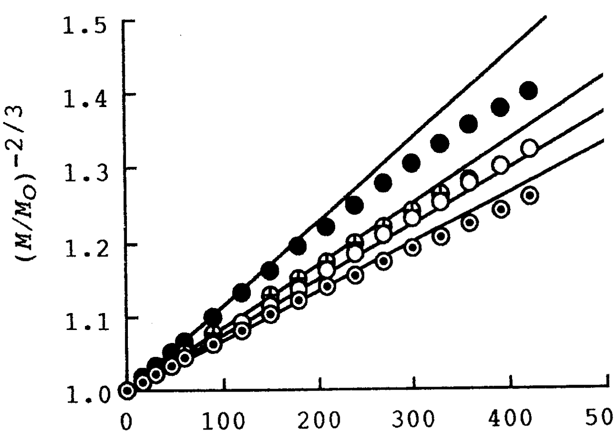

Fig. 1. Application of the Negative Two-Thirds Root Law Equation for Dissolutions with the $p_{12/12}$ Tablet

Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

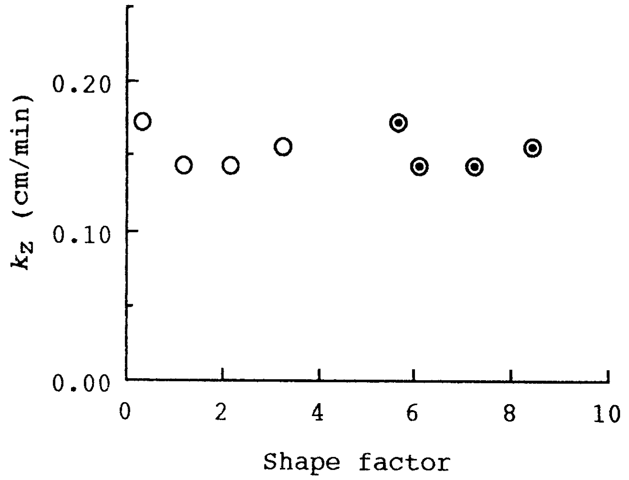

Fig. 2. Relationships between the Shape Factors ($f_{s/v}$ and $f_{d/h}$) and the Dissolution Rate Constants (k_z) Estimated Using the Negative Two-Thirds Root Law Equation for Dissolutions with the $p_{12/12}$ Tablet

Shape factor: ⊙, $f_{s/v}$; ○, $f_{d/h}$.

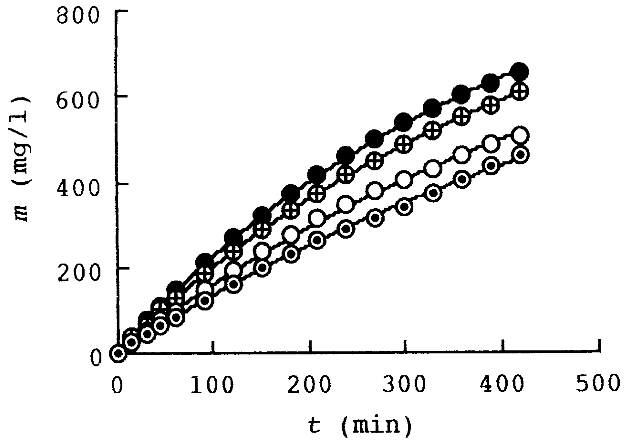

Fig. 3. Dissolution and Simulation Curves Using the z-Law Equation for Dissolutions with the $p_{9/12}$ Tablet

Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23};——, simulation curve (m_z).

The dissolution curves for the $p_{9/12}$ tablets are shown in Fig. 3 as an example, and treatments using the z-law equation are shown in Fig. 4. Fairly good straight lines appeared, and the dissolution rate constants (k_z) were estimated from the slope. The simulated values (m_z) estimated by use of the k_z-value and Eq. 4 are shown by the solid lines in Fig. 3. Where a fairly good applicability of the z-law equation is observed. Then, the k_z-values for the other tablets were estimated in the same manner, and these are shown in Fig. 5.

The k_z-values are relatively close to each other independent of tablet size for the dissolution with the $p_{6/12}$ tablets, whereas the k_z-values varied with tablet size at a fixed weight other than half of M_s. The variation in k_z-values decreased with increase in the diameter, and the k_z-values of the d_{23} tablets were similar irrespective of tablet weight.

Comparison of the values of measured and simulated dissolved amounts are shown in Fig. 6 as an example. The solid line in the figure shows that the simulated value is equal to the measured value. The simulated values estimated using the initial dissolution stage fit well with

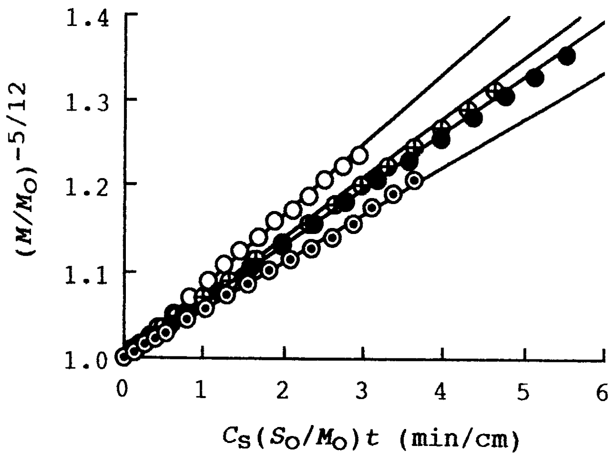

Fig. 4. Application of the z-Law Equation for Dissolutions with the $p_{9/12}$ Tablet

Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

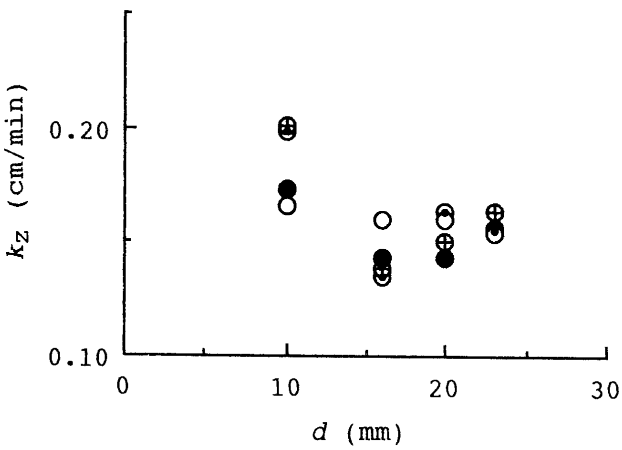

Fig. 5. Relationship between the Tablet Diameter (d) and the Dissolution Rate Constants (k_z)

Weight of tablet: ○, $p_{6/12}$; ⊙, $p_{9/12}$; ⊕, $p_{10/12}$; ●, $p_{12/12}$.

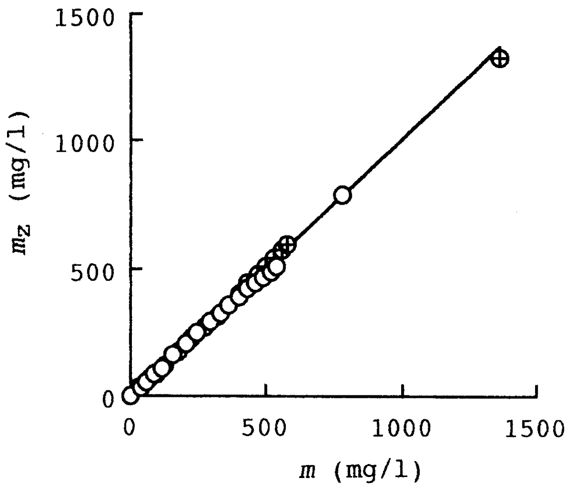

Fig. 6. Comparison of Simulated Values (m_z) Estimated Using the z-Law Equation and Measured Values (m) for d_{20} Tablets

Weight of tablet: ○, $p_{6/12}$; ⊕, $p_{10/12}$.

the measured values, and it was confirmed that the z-law equation is applicable irrespective of tablet size and weight. It was also assumed that the dissolution occurs from the geometric smooth surface and the change in diffusion layer

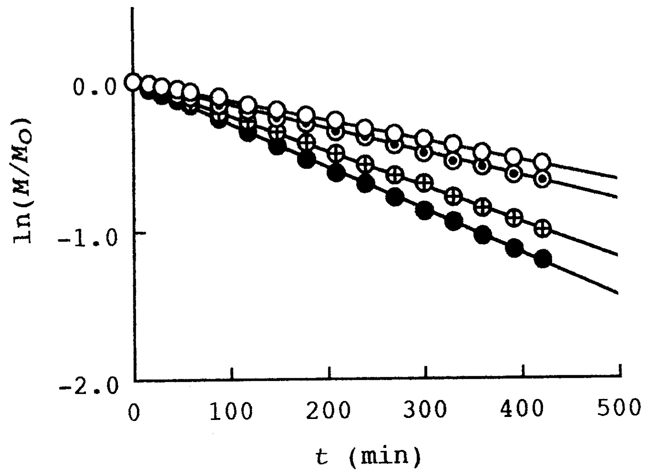

Fig. 7. Application of the Ln-z Equation for Dissolutions with the $p_{6/12}$ Tablet

Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

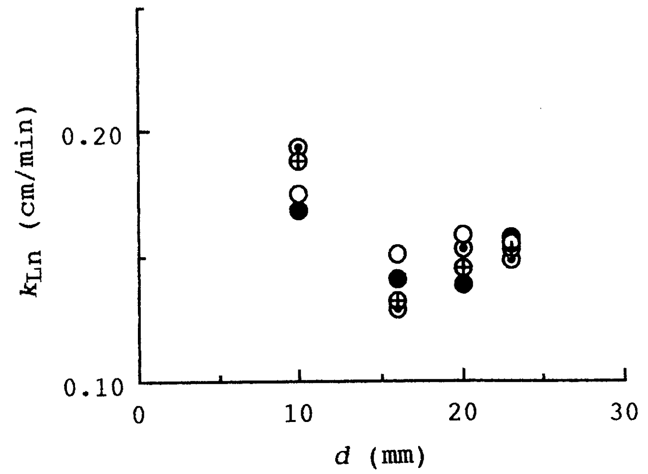

Fig. 8. Relationship between the Tablet Diameter (d) and the Dissolution Rate Constants (k_{Ln})

Weight of tablet: ○, $p_{6/12}$; ⊙, $p_{9/12}$; ⊕, $p_{10/12}$; ●, $p_{12/12}$.

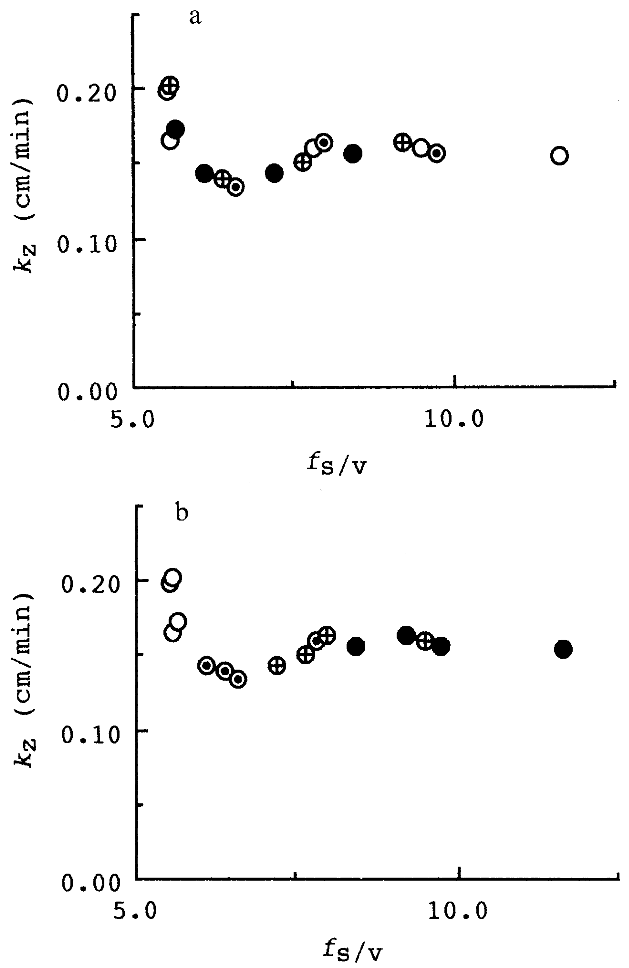

Fig. 9. Relationship between the Shape Factor ($f_{s/v}$) and the Dissolution Rate Constants (k_z)

a) Weight of tablet: ○, $p_{6/12}$; ⊙, $p_{9/12}$; ⊕, $p_{10/12}$; ●, $p_{12/12}$. b) Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

thickness when the dissolution time is short.

The dissolution rate constants were also estimated using the Ln-z equation. The applicabilities of this equation for the dissolutions with the $p_{6/12}$ tablets are shown in Fig. 7. As reported previously, the Ln-z equation can be used to estimate the dissolution rate constant for the dissolution with various optional initial amounts within M_s. However, as a simulation equation, this equation is useful only to the dissolution with an optional initial amount within around half of the tablet solubility.[1,3b)] The results shown in Fig. 7 confirm the applicability of the Ln-z equation irrespective of tablet diameter and thickness. The dissolution rate constants (k_{Ln}) obtained by applying the Ln-z equation are shown in Fig. 8. The k_{Ln}-values varied with tablet weight and size in the same manner as seen in Fig. 5 for the k_z-values.

Dissolution rate constants for the dissolution of crystalline particles and small tablets were similar independent of the initial amount and particle size.[1-3)] Here, it appeared that the dissolution rate constant for a fixed weight of tablet varied with the size, *i.e.*, the shape. However, the dissolution rate constants were believed to be satisfactorily estimated, since the simulated values fit well with the measured values and the dissolution rate constants obtained using the z-law and Ln-z equations were comparable at a fixed weight and size.

Shape Factors and Dissolution Rate Constants As described above, dissolutions of tablets were well treated by the two equations, irrespective of initial weight. However, the dissolution rate constant of tablet at a fixed weight is likely to change with its shape. Hence, the effect of degree of isometricity on the dissolution rate constant was estimated by examining the relationship between the shape factors defined by the initial tablet size and the dissolution rate constants (Figs. 9 and 10). The dissolution rate constant changed in almost the same manner with change in the $f_{s/v}$- and $f_{d/h}$-values. In crystalline particles, this constant may be less affected by particle size and initial amount, since the change in particle form may be minimal. A tablet , however, can be prepared in widely different forms, and there may be an effect of form on the dissolution rate constant. Here, the effect of the degree of isometricity on the dissolution rate constant was considered with the results shown in Fig. 10, since it is easier to imagine the tablet shape compared with Fig. 9. The dissolution rate constant (k_z) of tablet differed from shape to shape, even though tablet weight was the same.

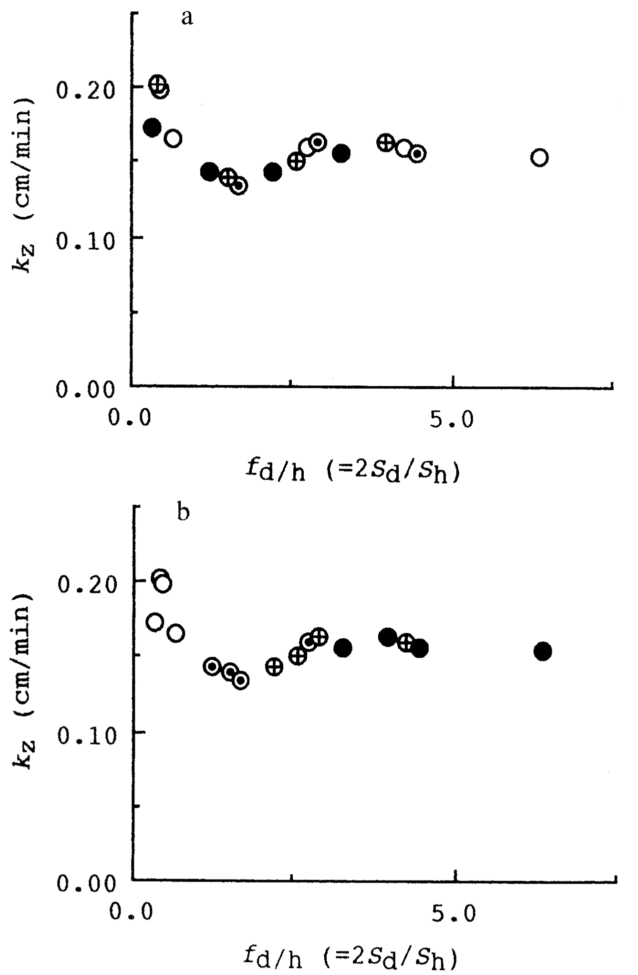

Fig. 10. Relationship between the Shape Factor ($f_{d/h}$) and the Dissolution Rate Constants (k_z)

a) Weight of tablet: ○, $p_{6/12}$; ⊙, $p_{9/12}$; ⊕, $p_{10/12}$; ●, $p_{12/12}$. b) Diameter of tablet: ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

The k_z-value of a long cylindrical tablet was large, and it decreased to reach a minimum value with increase in the $f_{d/h}$-value , *i.e.*, increase in the diameter and decrease in the thickness of tablet. The k_z-value increased to reach almost a fixed value when the flat-faced surface was more predominant. Hence, it was likely that the dissolution rate constant was more affected by change in the curved surface area than change in the flat-faced surface area of tablet.

Comparing the curved surface with the flat-faced surface in regard to the dissolution contribution, it was supposed that the former predominantly affects dissolution of a long cylindrical tablet, and the flat-faced surface dissolution of a shallow cylindrical tablet. However, it was also recognized that the dissolution rate constant estimated per unit surface area could be constant. The flat-faced surface or curved surface of SA tablet (1.70 g, 2.0 cm diameter and 0.41 cm thickness) was then coated with wax to make a specially devised tablet, and the dissolution test was carried out as described.[4)] The test on this tablet with a coated flat-faced or curved surface was treated using the following equations, respectively[4b)]:

$$(M/M_s)^{-1/2} = 1 + (1/2)k_h C_s(S_h/M_s)t \quad (8)$$

$$\ln(M_s/M) = k_d C_s(S_d/M_s)t \quad (9)$$

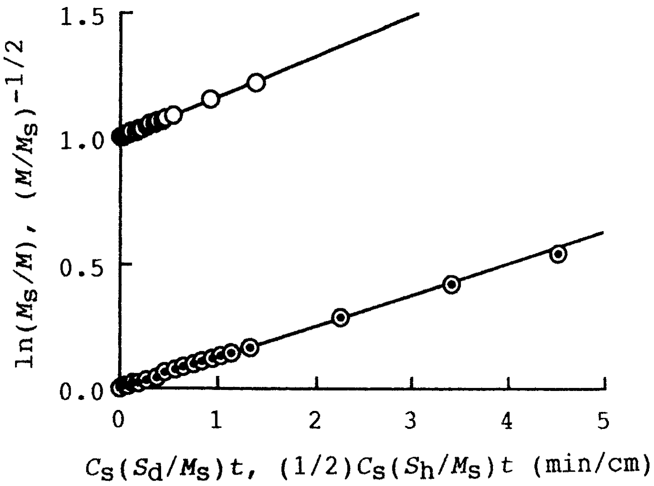

Fig. 11. Estimation of Dissolution Rate Constants of Specially Deviced $p_{12/12}$ Tablets

○, Eq. 8, dissolution from curved surface of tablet; ⊙, Eq. 9, dissolution from flat-faced surface of tablet.

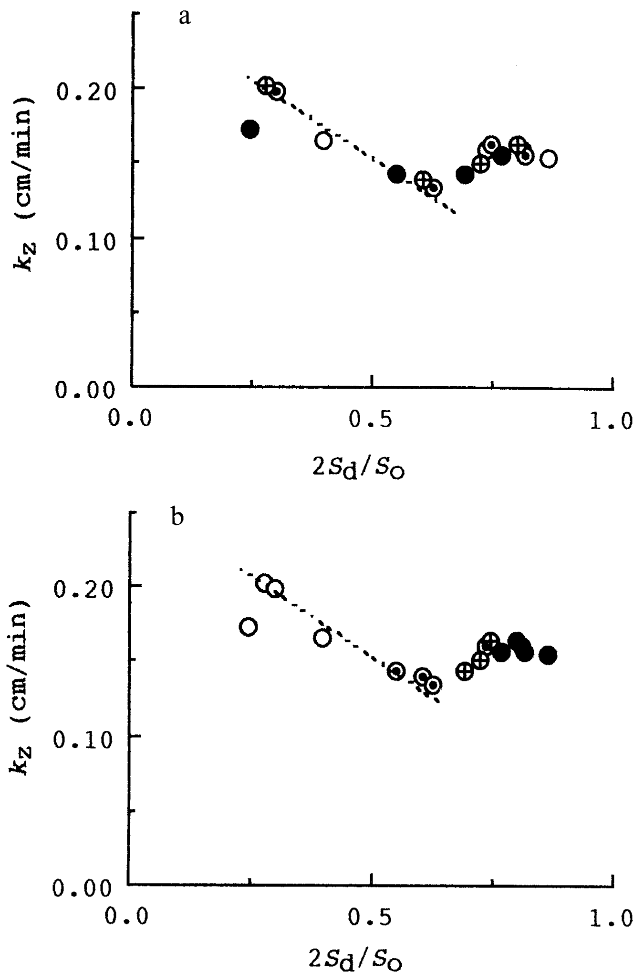

Fig. 12. Relationship between the Ratio of Flat-Faced Surface Area to the Whole Surface Area of Tablet ($2S_d/S_o$) and the Dissolution Rate Constants (k_z)

a) Weight of tablet: ○, $p_{6/12}$; ⊙, $p_{9/12}$; ⊕, $p_{10/12}$; ●, $p_{12/12}$. b) Diameter of tablet : ○, d_{10}; ⊙, d_{16}; ⊕, d_{20}; ●, d_{23}.

where k_h and k_d are the dissolution rate constants for dissolution from the curved and the flat-faced surface, respectively. The results are shown in Fig. 11 where the axis of abscissas expresses $(1/2)C_s(S_h/M_s)t$ or $C_s(S_d/M_s)t$

in accordance with Eq. 8 or Eq. 9, respectively. The k_h- and k_d-values estimated were 0.164 and 0.126 cm/min, respectively. Dissolutions with these specially devised tablets were treated using the z-law equation to compare the dissolution rate constant estimated by the same equation. The k_z-value for the coated tablet with a flat-faced surface and that with a curved surface were 0.164 and 0.143 cm/min, respectively. Thus, it appeared that the dissolution rate constant of a long cylindrical tablet is larger than that of a shallow cylindrical one. One reason the k_h-value is larger than the k_d-value was believed to be due to the orientation of SA particles in the tablet. Hence, SA was ground by hand, and was compressed to make the specially devised tablet described above. The dissolution rate constants estimated showed the same tendency, however, so it was suggested that the dissolution rate constant of the long cylindrical tablet was larger, even though the reason for the difference is not clear.

Finally, the way in which k_z-value is expressed by the contributions of k_h- and k_d-values was examined. Here, the k_h- and k_d-values are not those obtained with the specially devised tablet but ideal values leading to the results shown in Fig. 10. Expression of the k_z-value is postulated as follows:

$$k_z = k_h(S_h/S_o) + k_d(2S_d/S_o)$$
$$= k_h - (k_h - k_d)(2S_d/S_o) \quad (10)$$

According to Eq. 10, the results shown in Fig. 10 were redrawn as Fig. 12. The k_z-value decreased almost straightly within the $2S_d/S_o$-value reached around 0.63, and showed similar where the $2S_d/S_o$-value was larger than around 0.73. This suggested that the tablet form should be taken into consideration when necessary.

Conclusion

The z-law and Ln-z equations derived for the dissolution of particles with an optional initial amount were applied for the dissolution of a nondisintegrating single component tablet. It was confirmed that these equations efficiently treated tablet dissolution irrespective of weight and size, *i.e.*, tablet shape, and both equations gave almost the same dissolution rate constants for a tablet.

The tablet shape was altered systematically by changing the diameter and weight of tablet. Each tablet gave a different dissolution rate constant, and it was suggested that this constant was probably more affected by the shape than the weight. The dissolution rate constant of a long cylindrical tablet was large, and it decreased to reach a minimum value with increase in tablet diameter and decrease in thickness. In shallow cylindrical tablets it increased to reach almost a fixed value, as if it were obtained by a rotating disk method.

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