Influence of Internal Structure on Kinetics of Drug Release from Wax Matrix Tablets

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To examine the influence of the internal structure of a wax matrix tablet on *in vitro* drug release, the release rates of several tablets consisting of various proportions of drug and wax were compared with the water penetration rates from the compressed and lateral surfaces of the tablets. The penetration rates from the lateral surface were found to be much faster than those from the compressed surface in all cases. A theoretical equation involving a two-dissolving-direction was derived on the basis of the boundary retreating concept. The retreating rate constants deduced from the dissolution results were well coincident with the values directly determined by the needle penetration method, suggesting good applicability of the proposed equation. The results suggest that the tortuosity of the water channels created in a tablet during dissolution is generally smaller in the horizontal direction than that in the vertical direction. This would be caused by the drug particles or granules being elongated in the horizontal direction by compression.

Keywords wax matrix tablet; hydrogenated castor oil; isoniazid; sustained release; internal structure; boundary retreat

Introduction

Incorporation of a drug into an inert wax matrix is known as a means of preparation of sustained release medicaments.[1,2] This technique has often been used in the manufacture of sustained release tablets because it offers many additional advantages, such as comparatively low manufacturing cost, improved humidity resistance, good physical–chemical stability, and reduction of unpleasant taste.

Concerning the mechanism of drug release from a matrix system, Higuchi[3] was the first to treat theoretically the matrix model and to show that the drug amount released per unit surface area is proportional to the square root of time. Cobby *et al.*[4] and Fessi *et al.*[5] extended Higuchi's square root law to the matrix tablet by introducing the boundary retreating concept in which the dissolution boundary layer retreats to the inside of the tablet as drug release proceeds. Their proposed equations seem to accurately express the overall drug release behavior.

However, earlier theories regarded the whole matrix as a homogeneous phase, and, as a matter of convenience, the equations were developed assuming that drug release occurs at the same rate from every surface of a tablet. This assumption does not seem reasonable in more practical cases, because it is generally known that tablets usually have a somewhat asymmetric internal structure[6] or density distribution[7,8] due to the plastic deformation and/or fracture of components. Usually, the drug particles, when compressed vertically, can be elongated horizontally by plastic deformation, or in another case, the fractured drug crystals can be rearranged along a horizontal direction.[6] In those cases, the drug release rate would differ between compressed surfaces and lateral surface, because the asymmetric internal structure would provide a different tortuosity to both directions of matrix after leaking of the drug, even though the resultant fractional voidage would be the same.

The objectives of the present study were to examine the difference in boundary retreat rate between the compressed surfaces and the lateral surface of a matrix tablet and to propose a reasonable expression for the total release rate. In this paper, a modification of Cobby's equation is made on the basis of the two-dissolving-direction model. To demonstrate its applicability to a series of wax matrix tablets, the boundary retreat rates calculated from the dissolution data are compared with the values directly determined by the needle penetration method.

Theoretical Analysis

For the leaching type release mechanism from a planar matrix system, a diffusion equation was proposed by Higuchi[3]:

$$Q=\sqrt{\frac{D\varepsilon}{\tau}(2A-\varepsilon C_s)C_s t} \tag{1}$$

where Q is the amount of drug released per unit surface area, D is the diffusion coefficient of the drug in the permeation fluid, ε is the porosity of the matrix, τ is the tortuosity of the matrix, A is the concentration of solid drug in the matrix, C_s is the solubility of drug in the dissolution medium, and t is time. In this system, the dissolution boundary distance retreating from the surface, after time t, X_t, is expressed as:

$$X_t=\frac{2Q}{2A-\varepsilon C_s} \tag{2}$$

Then, from Eqs. 1 and 2, X_t can be rewritten as:

$$X_t=K_b t^{1/2} \tag{3}$$

and,

$$K_b=2\sqrt{\frac{D\varepsilon C_s}{\tau(2A-\varepsilon C_s)}} \tag{4}$$

where K_b is the boundary retreat rate constant.

Kinetic Expression for Cylindrical Matrix Tablet **1) Symmetric Case** When the internal structure of a wax matrix tablet is homogeneous and the configuration of drug particles in the tablet is entirely symmetric (Fig. 1A), the drug can be released at the same rate from every surface of the tablet, so that the boundary retreat rate is regarded as constant at any point on the surface. A kinetic expression for drug release behavior in this case was proposed by Cobby *et al.*[4] If the amount of drug existing in the diffusive passage is negligible compared with the amount released ($2A \gg \varepsilon C_s$), the fraction of the drug released at time t, f_t, can be expressed as:

$$f_t=(q+2)K_r t^{1/2}-(2q+1)(K_r t^{1/2})^2+q(K_r t^{1/2})^3 \tag{5}$$

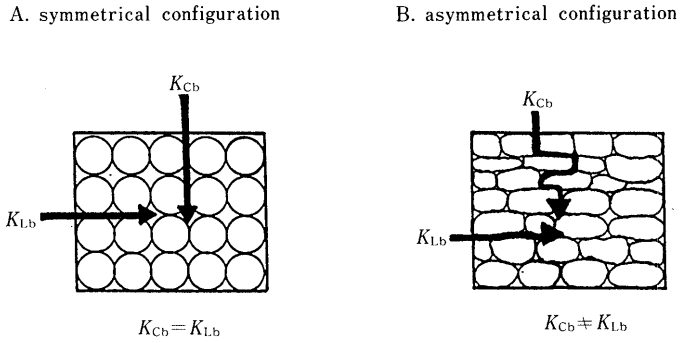

Fig. 1. Internal Structure of a Wax Matrix Tablet

K_{Cb} and K_{Lb} are the boundary retreat rate constants from the vertical and horizontal directions, respectively.

$$q=r_0/h_0\,,$$

and

$$K_r=K_b/r_0$$

where r_0, h_0 and q are initial tablet radius, initial tablet half-thickness and a ratio factor (usually, $q>1$), and K_r is the release rate constant.

2) Asymmetric Case When the internal structure of a matrix tablet has an asymmetric configuration, a drug can be released from the compressed surfaces and the lateral surface at different rates (Fig. 1B). This can happen when the tortuosity of the water channels formed during drug release differs depending on the direction from the releasing surfaces due to deformation of the drug particles. In this case, the distances of dissolution boundary from the lateral and the compressed surfaces can be expressed by:

$$X_{Ct}=K_{Cb}t^{1/2} \tag{6}$$

$$X_{Lt}=K_{Lb}t^{1/2} \tag{7}$$

where X_{Ct} and X_{Lt} are the distances of dissolution boundary from the compressed and the lateral surfaces at time t, respectively. K_{Cb} and K_{Lb} are the boundary retreat rate constants from the compressed and the lateral surfaces, respectively. Thus, half-height and the radius of unreleased portion after time t is:

$$h_t=r_0/q-X_{Ct} \tag{8}$$

$$r_t=r_0-X_{Lt} \tag{9}$$

The volume of unreleased portion, V_t, is expressed by:

$$V_t=2\pi r_t^2 h_t=2\pi(r_0-X_{Lt})^2(r_0/q-X_{Ct}) \tag{10}$$

Substituting Eqs. 6 and 7 into Eq. 10 gives:

$$V_t=2\pi(r_0-K_{Lb}t^{1/2})^2(r_0/q-K_{Cb}t^{1/2}) \tag{11}$$

Therefore, the fraction of solute released at time t:

$$f_t=1-\frac{V_t}{V_0}=1-\frac{q}{r_0^3}(r_0-K_{Lb}t^{1/2})^2(r_0/q-K_{Cb}t^{1/2}) \tag{12}$$

When $K_{Cb}=K_{Lb}$, Eq. 12 can be reduced to Eq. 5.

Experimental

Materials Isoniazid JP (INZ) was obtained from Yukigosei Yakuhin Kogyo Co., and pulverized to about 7 μm prior to use. Hydrogenated castor oil (HCO) was obtained from Kawaken Fine Chemical Co. (K_3wax®; mp 84—88 °C), and used as received.

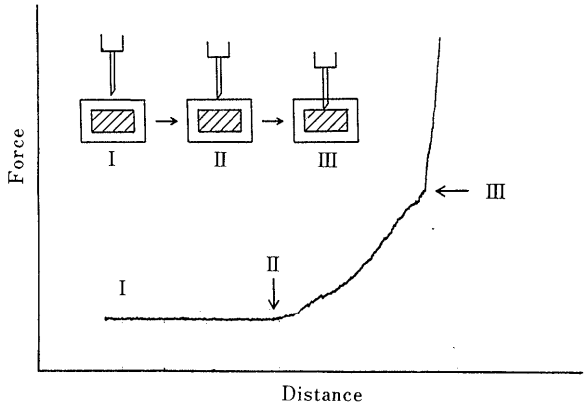

Fig. 2. Schematic Diagram of the Needle Penetration Method and Typical Recording

Clear, ghost portion (wax only); hatched, unreleased portion (wax and drug). I, Needle does not contact tablet; II, needle comes in contact with released portion in tablet; III, needle comes in contact with unreleased portion in tablet.

Granulation Melt granulation method was applied. Pulverized INZ and HCO powder were mixed together in various proportions. One hundred grams of the powder blend was melted in a vessel at 95—98 °C under continuous agitation. The homogeneous mass was cooled to room temperature and then pulverized using a pestle and a mortar. The granules obtained were sized by passing them through a 20 mesh-sieve. Five lots of granules consisting of drug and wax at ratios of 90 : 10, 85 : 15, 80 : 20, 75 : 25 and 70 : 30, were prepared by the same procedure.

Tabletting Five hundred milligrams of the granules was compressed by a reciprocating press (Autograph IS-5000, Shimadzu Seisakusyo) using a flat-faced punch and die with a diameter of 10 mm. Applied force and punch velocity were 1273 kg/cm^2 and 10 mm/min, respectively, for all the tablets. For one-planar-surface dissolution test, the lateral and one side of the planar surfaces of each tablet formulation were covered by HCO using the press-coating technique; namely, one tablet was placed at the center of the bottom of the die, one gram of HCO powder was added to it, and then the content was compressed at 850 kg/cm^2. To examine the effect of tablet size on dissolution behavior, tablets with diameters of 7, 8, 9, 10, 11 and 12.5 mm were prepared using one particular batch of granules (drug-to-wax ratio; 80 : 20) under the same tabletting conditions. The weight of each tablet was controlled to assure the same thickness.

Dissolution Test Dissolution tests were conducted according to the paddle method described in JP XI. Nine hundred milliliters of distilled water thermostated at 37 °C was used as the dissolution fluid, and stirred with a paddle at the rate of 100 rpm. A sinker was applied to prevent flotation of the tablet. In a one-planar-surface dissolution test, plate glass was applied to the wax coated planar surface of each sample tablet to prevent flotation, and it was placed at the bottom of the vessel keeping the dissolution surface upward. The amount of drug released was spectrophotometrically assayed at 310 nm.

Needle Penetration Method After dissolution for a predetermined period, the tablet was removed from the vessel, and the penetration distance of dissolution fluid into the tablet was determined by a newly developed needle penetration method. A needle (2.54 cm in length and 0.51 mm in diameter) was fixed on a tensile tester (Autograph AGS-100A; Shimadzu Seisakusyo) and moved onto the surface of the tablet at the rate of 0.5 mm/min. Changes in the detected penetration force were monitored on a recorder as a function of distance. Figure 2 is the schematic representation of the needle penetration process and the chart output on a recorder. When the tip of the needle reached the tablet surface, the stress gradually increased due to the friction generated between the moving needle and the ghost portion of the tablet. But once the needle came into contact with the unreleased portion, the force abruptly increased. The penetration distance, therefore, was regarded as the distance between II and III. The determination was repeated six times at different positions on the compressed surface and the lateral surface of each tablet. The relative standard deviation was less than 5%.

Determination of Tablet Properties Weight, diameter and thickness of each tablet were determined using an ordinary balance and gages. Porosity of the tablet after drug release, ε, was calculated from the tablet weight, W, the geometrical volume, V, composition ratio of HCO in tablet, f, and

the true density of HCO, ρ, (1.03, which was determined with an air comparison pycnometer), according to Eq. 13.

$$\varepsilon = 1 - \frac{Wf\rho}{V} \tag{13}$$

Results and Discussion

Formulas of the wax matrix tablets examined in this study and various parameters required for the kinetical analysis of dissolution behavior are summarized in Table I.

One-Planar-Surface Dissolution Study In order to precisely examine the relation between the drug release rate and the boundary retreat rate, the drug release behaviors from a one-planar-surface were studied. Figure 3 shows the $\sqrt{t} - f_t$ plots of INZ release from the one-planar-surface of the wax matrix tablets, R_p-1, R_p-2, R_p-3, R_p-4 and R_p-5, which consist of wax and drug in different proportions. It was found that each dissolution profile exhibited a good straight line over the long range from 0 to 0.95. Also, it was clearly shown that drug release rate decreased with increasing wax content. These prove that the drug release from the wax matrix thoroughly obeys the diffusion theory proposed by Higuchi.

The distance from the surface of tablet to the dissolution boundary was directly determined by the needle penetration method after dissolution for various periods, and the determined values (X_t) were compared with the values calculated from the cumulative released amount for the corresponding time using Eq. 2. In the calculation, the solubility of INZ was regarded as 0.195 g/ml, which was obtained from the solubility experiments in water at 37 °C.

TABLE I. Formulas and Various Parameters of the Wax Matrix Tablets Used in This Study

R_p	INZ:HCO	Weight (g)	Diameter (cm)	Thickness (cm)	A[a] (g/cm^3)	Porosity[b]
1	90:10	0.501	1.003	0.484	1.179	0.869
2	85:15	0.497	1.003	0.485	1.107	0.805
3	80:20	0.501	1.002	0.497	1.023	0.744
3a	80:20	0.250	0.702	0.507	1.019	0.745
3b	80:20	0.319	0.803	0.493	1.022	0.744
3c	80:20	0.396	0.904	0.484	1.020	0.745
3d	80:20	0.597	1.104	0.487	1.024	0.744
3e	80:20	0.773	1.256	0.488	1.023	0.744
4	75:25	0.500	1.002	0.501	0.949	0.684
5	70:30	0.501	1.002	0.511	0.870	0.627

a) Drug concentration in the matrix. b) Total porosity after dissolution.

The mean X_t value and standard deviation calculated from six measurements for each formulation are shown in Table II. As can be seen, variation of each X_t value was small, and both values of X_t were fairly close to each other at any given time point. Then, K_b values were calculated using the mean X_t values by the linear regression according to Eq. 3 (Table II). The K_b values obtained from the two methods were found almost coincident to each other. This result indicates that the drug release from wax matrix practically obeys the boundary retreat theory, and also proves that X_t can be successfully determined directly by the needle penetration method.

Whole-Surface Dissolution Study Figure 4 shows the

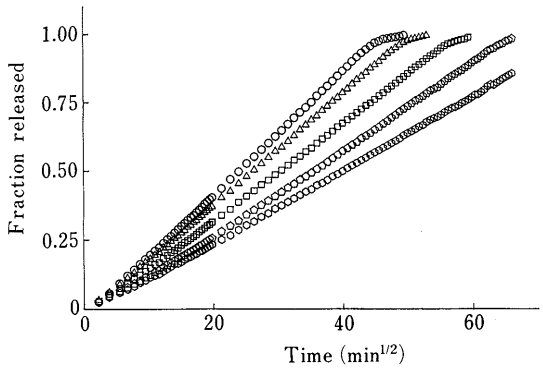

Fig. 3. Drug Release Profiles from One-Planar-Surface of Wax Matrix Tablets Consisting of INZ and HCO in Various Proportions

INZ:HCO ratio: ○, 90:10; △, 85:15; □, 80:20; ⬠, 75:25; ⬡, 70:30.

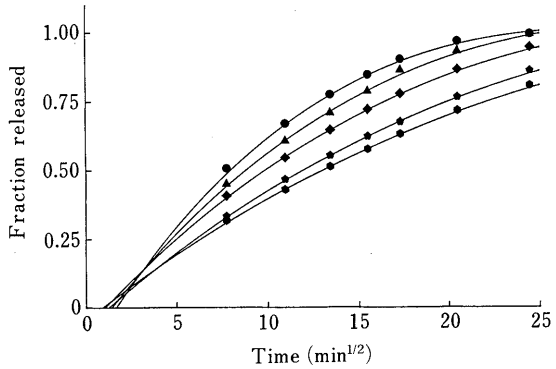

Fig. 4. Drug Release Profiles from Whole Surface of Wax Matrix Tablets Consisting of INZ and HCO in Various Proportions

Solid lines represent simulation curves. INZ:HCO ratio: ●, 90:10; ▲, 85:15; ◆, 80:20; ⬟, 75:25; ⬢, 70:30.

TABLE II. Comparison of Penetration Distance (X_t) by Needle Penetration Method and That Calculated from One-Planar-Surface Dissolution

Time (min)	R_p No. 1		2		3		4		5	
	Diss.[a]	Penet.[b]	Diss.	Penet.	Diss.	Penet.	Diss.	Penet.	Diss.	Penet.
30	0.46±0.01	0.46±0.02	0.44±0.01	0.45±0.02	0.38±0.01	0.40±0.01	0.33±0.01	0.37±0.02	0.30±0.01	0.31±0.01
60	0.69±0.01	0.69±0.03	0.64±0.01	0.65±0.03	0.54±0.01	0.60±0.03	0.47±0.01	0.53±0.03	0.42±0.01	0.47±0.02
120	1.01±0.01	1.05±0.04	0.95±0.01	0.96±0.04	0.08±0.01	0.84±0.01	0.66±0.01	0.75±0.03	0.62±0.01	0.63±0.02
180	1.27±0.01	1.29±0.03	1.20±0.01	1.24±0.03	1.02±0.01	1.07±0.03	0.83±0.02	0.92±0.02	0.78±0.01	0.78±0.03
240	1.49±0.01	1.51±0.04	1.38±0.01	1.39±0.02	1.20±0.01	1.31±0.01	0.97±0.02	1.08±0.02	0.91±0.01	0.93±0.03
K_b ($\times 10^{-3}$ cm/min$^{1/2}$)	10.33	10.52	9.53	9.66	8.24	8.92	6.42	7.03	6.09	6.13
Lag time (min$^{1/2}$)	1.1	1.1	1.0	0.9	1.0	1.1	0.5	0.2	0.7	0.5

Each value represents mean±S.D. of six measurements. a) Calculated by Eq. 2. b) Determined by the needle penetration method.

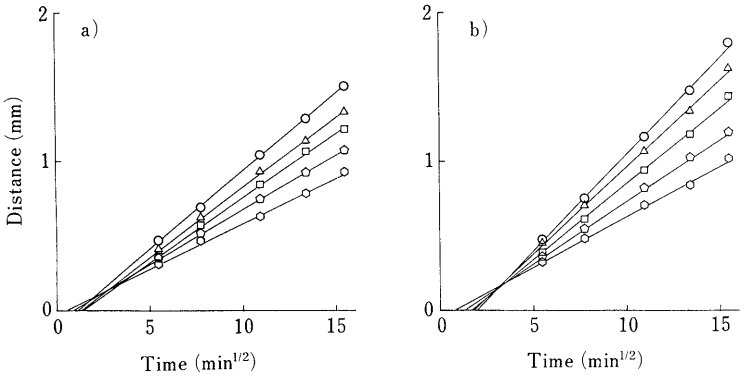

Fig. 5. Changes of Needle Penetration Distance with the Square Root of Time

a) Compressed surface; b) lateral surface. INZ : HCO ratio: ○, 90 : 10; △, 85 : 15; □, 80 : 20; ⬠, 75 : 25; ⬡, 70 : 30.

$\sqrt{t}-f_t$ plots of INZ release from the whole-surface of five wax matrix tablets consisting of wax and drug in different proportions. The profiles did not exhibit a linear line, so that Higuchi's square root equation appeared not to be applicable for the expression of overall drug release behavior. This is mainly due to the fact that the dissolution surface area in the matrix decreases as drug release proceeds. But the internal structure of the tablet may also contribute to this phenomenon, because particles in the matrix would be elongated in the horizontal direction by the receipt of compression force from the vertical direction; so, the drug release rate may differ depending on the dissolving direction.

Thus, to see if some difference of boundary retreat rate actually exists between compressed and lateral surfaces of a tablet, X_t was determined by the needle penetration method after dissolution for a certain period. The results are shown as the $\sqrt{t}-X_t$ profile in Figs. 5a and 5b.

As apparent in both figures, X_t linearly increased with the square root of time in all cases. This indicates that the mechanism of drug release from any surface of a tablet basically obeys the diffusion theory. When the retreating rate from the compressed surface was compared with that from lateral surface in each tablet, it was noted that the retreating rate from the lateral surface was obviously faster in all cases. These results well support the above-mentioned hypothesis in which the drug release from matrix tablets can differ depending on dissolving surface. Another notable finding in Fig. 5 was that a clear lag time existed in all cases, though it was not long. Therefore, for more precise estimation of K_{Cb} and K_{Lb}, this lag time must be taken into consideration. Then, as a more practical and rational expression form, Eq. 12 can be rewritten by introducing lag time, t_{CL} and t_{LL}, to:

$$f_t=1-\frac{q}{r_0^3}\{r_0-K_{Lb}(t^{1/2}-t_{LL})\}^2\{r_0/q-K_{Cb}(t^{1/2}-t_{CL})\} \quad (14)$$

From all the dissolution data shown in Fig. 4, K_{Cb}, K_{Lb}, t_{CL} and t_{LL} were computed by a non-linear regression using the SIMPLEX method. The fitting curves are shown in Fig. 4 by solid lines for each tablet formulation. Excellent agreement was found between the observed values and the calculated values in all cases; the residual sum of square of the calculated value for five tablets, R_p-1, R_p-2, R_p-3, R_p-4 and R_p-5, was 1.5×10^{-3}, 1.7×10^{-3}, 1.2×10^{-3}, 1.5×10^{-3}, 3.0×10^{-3}, respectively. The calculated values of the parameters are listed in Table III with the observed values

TABLE III. Comparison of Boundary Retreat Rate Constants Calculated and Those Directly Determined by Needle Penetration Method

	Parameters	R_p No. 1	2	3	4	5
Calculated[a]	K_{Cb} ($\times10^{-3}$ cm/min$^{1/2}$)	10.28	8.69	8.58	7.18	5.99
	K_{Lb} ($\times10^{-3}$ cm/min$^{1/2}$)	14.14	9.91	9.54	8.14	6.63
	t_{CL} (min$^{1/2}$)	2.0	0.2	1.7	1.7	0.2
	K_{LL} (min$^{1/2}$)	1.1	0.8	1.2	2.0	1.5
Direct[b] measurement	K_{Cb} ($\times10^{-3}$ cm/min$^{1/2}$)	10.46	9.22	8.62	7.24	6.03
	K_{Lb} ($\times10^{-3}$ cm/min$^{1/2}$)	13.50	11.98	10.69	8.42	6.81
	t_{CL} (min$^{1/2}$)	1.1	1.0	1.2	0.6	0.3
	t_{LL} (min$^{1/2}$)	2.1	1.9	2.0	1.2	0.7

a) Computed by Eq. 16. *b*) Determined by the needle penetration method.

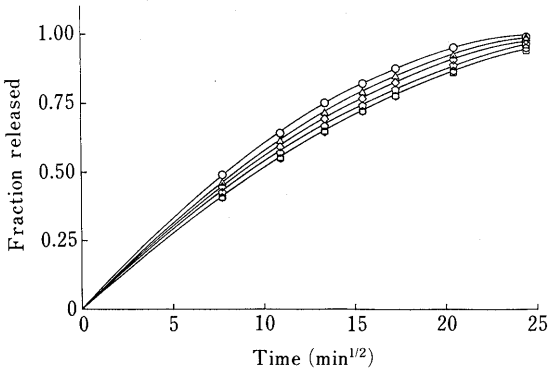

Fig. 6. Comparison of the Drug Release Profiles of Wax Matrix Tablets with Various Diameters

Diameter: ○, 7 mm; △, 8 mm; ◇, 9 mm; ⬠, 10 mm; ⬡, 11 mm; □, 12.5 mm.

obtained from Figs. 5a and 5b.

There was a good coincidence between the values calculated and directly determined, suggesting the good applicability of the proposed equation. Another important finding in this examination was that the K_{Cb} value of each formulation was very close to the K_b value directly obtained from the one-planar-surface dissolution study (Table II). This proves that the calculated value is correct.

Effect of Tablet Size To more strictly examine the applicability of the proposed equation to the drug release from wax matrix tablets, and to highlight the difference in applicability between the proposed equation and Cobby's equation, the effect of tablet size on dissolution behavior was studied. Figure 6 shows the drug release profiles of five

Table IV. Comparison of Calculated Boundary Retreating Rate Constants in Wax Matrix Tablets with Various Diameters

Parameters	R_p No.					
	3a	3b	3c	3	3d	3e
K_{Cb} ($\times 10^{-3}$ cm/min$^{1/2}$)	9.13	8.93	8.94	8.58	8.95	8.96
K_{Lb} ($\times 10^{-3}$ cm/min$^{1/2}$)	9.97	9.89	9.73	9.54	9.84	9.82
t_{CL} (min$^{1/2}$)	0.0	0.1	0.9	1.7	2.6	1.4
t_{LL} (min$^{1/2}$)	2.3	2.5	1.6	1.2	0.0	0.0

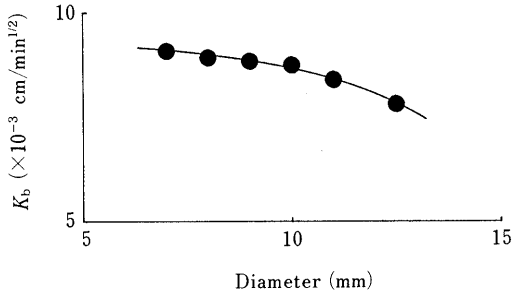

Fig. 7. Change of K_b Values Calculated by Cobby's Equation Depending on Tablet Diameter

kinds of wax matrix tablets, R_p-3, 3a, 3b, 3c and 3d, each of which has the same ratio of HCO and INZ but a differing radius. The drug release rate obviously increased with the decrease in shape factor, q.

To determine how the q value affects the boundary retreated rates of the two surfaces, K_{Cb} and K_{Lb} values were calculated according to Eq. 14 by computer calculation, and the values of both parameters are listed in Table IV. The calculation provided almost the same values of each parameter irrespective of the size of tablet. This indicates that the drug release rates from the unit area of the compressed and lateral surfaces were not affected by tablet size; hence, the total dissolution behavior would change depending on the ratio of the area of the two surfaces. Then, an analogous calculation was done using Cobby's modified equation, Eq. 15, in which his original equation Eq. 5 was modified to a more practical form by introducing the term of lag time, t_L.[4b]

$$f_t=(q+2)K_r(t^{1/2}-t_L)-(2q+1)K_r^2(t^{1/2}-t_L)^2+qK_r^3(t^{1/2}-t_L)^3 \quad (15)$$

Figure 7 shows a plot of the calculated Cobby K_b values to tablet diameter. The values showed a systematic decrease with increasing tablet radius. If Cobby's equation was completely satisfiable, the K_b values would be constant irrespective of tablet size or shape. This is therefore a notable discrepancy of Cobby's equation. Because of the observed discrepancy in Cobby's calculated K_b value, the K_b obtained in the one-planar-surface dissolution study is considered to represent the mass-transfer rate in one particular direction from the inside to the compressed surface of a tablet, whereas the K_b obtained from whole-surface dissolution study represents the average rate from the inside to every position on the surface. Although the differences of values shown in Fig. 7 are not very large, this is clear evidence that the boundary retreat rates are different depending on the direction in which dissolution proceeds.

Quantitative Evaluation of the Systematic Disorder of Internal Structure As above mentioned, the observed difference between K_{Cb} and K_{Lb} values represents the difference of drug release rate from the compressed surface and the lateral surface. The ratio of the two rate constants, K_{Cb}/K_{Lb}, can be an index representing the extent of asymmetric drug release.

K_{Cb}/K_{Lb} can be rewritten from Eq. 4 as,

$$K_{Cb}/K_{Lb}=\sqrt{\tau_L/\tau_C} \quad (16)$$

where τ_C and τ_L are the tortuosity of the channels from the dissolution boundary surface to the compressed and lateral surfaces, respectively. Since the tortuosity is intimately related to the internal structure of the matrix, the ratio of τ_L/τ_C can be used for quantitative evaluation of the disorder in the internal structure of an individual tablet.

Table V. τ_L/τ_C Ratio of Various Wax Matrix Tablets

R_p	INZ : HCO	Diameter (cm)	τ_L/τ_C
1	90 : 10	1.003	0.53
2	85 : 15	1.003	0.77
3	80 : 20	1.002	0.81
3a	80 : 20	0.702	0.85
3b	80 : 20	0.803	0.81
3c	80 : 20	0.904	0.85
3d	80 : 20	1.104	0.83
3e	80 : 20	1.256	0.83
4	75 : 25	1.002	0.77
5	70 : 30	1.002	0.81

Table V summarizes the τ_L/τ_C ratios of the tablets with different wax-drug proportions or different diameters. All values except that of R_p-1 were comparatively close to each other, and ranged from 0.77 to 0.85. This suggests that the tablet generally has a tighter structure in the direction from the center to the compressed surface than to the lateral surface. It also suggests that such biased internal structure is basically less affected by wax-drug proportion or tablet diameter, as long as the compression force applied per unit surface area is the same. However, it was noted that R_p-1, which contains less HCO, showed a considerably smaller value of τ_L/τ_C, suggesting that the tablet had a relatively large distortion in its internal structure. This probably was caused by the fact that INZ crystals were much more easily to be oriented in the horizontal direction. From the fact that the increase of HCO resulted in the increase of τ_L/τ_C, HCO may work to prevent the orientation of INZ crystals due to its plastic property.

The smaller value of τ_L/τ_C implies that the tablet potentially has a more lamellar structure; hence, the tablet with a smaller value of τ_L/τ_C would have a greater tendency toward lamination, which may result in breaking during shipping or occasionally in abrupt drug release after oral administration. To avoid various problems resulting from structural defects in a matrix tablet, the internal distortion should be quantitatively evaluated. The approach outlined provides a useful means by which to determine the degree of distortion in internal tablet structure, in addition to providing a precise explanation of the drug release mechanism.

Conclusion

The results of this investigation showed that: i) The drug

release behavior from the one-planar-surface of INZ-HCO tablets obeys the square root law; ii) The boundary retreating distance can be directly determined by the needle penetration method; iii) The boundary retreating rate constants differ in the lateral surface and compressed surface; iv) The difference in the rate constants is thought to be caused by the asymmetric configuration of drug particles in the tablet; v) The proposed equation utilizing two rate parameters (Eq. 14) well expresses the overall dissolution behavior of the wax matrix tablet; and vi) The ratio of the two rate constants can be used for quantitative evaluation of the systematic distortion of the internal structure of wax matrix tablets.

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