[Chem. Pharm. Bull. 31(3)1030—1039(1983)]

The Rate of Penetration of Liquid into Tablets. II.[1] Influence of Second Ingredient and Mixing Ratio

EIHEI FUKUOKA, SHINTARO KIMURA* and MIDORI YAMAZAKI

Faculty of Pharmaceutical Science, Toho University, 2-2-1 Miyama Funabashi-shi Chiba 274, Japan

(Received July 20, 1982)

The influence of a second ingredient having a high contact angle on liquid penetration into tablets was tested and compared with the result obtained for powder. The contact angles of hydrophobic substances and mixed powders with excipients were measured by Kossen's method.

The liquid penetration into powders and tablets of magnesium oxide and bromvalerylurea in various mixing ratios could be described by Washburn's equation. The penetration into mixed powders of magnesium silicate with bromvalerylurea, in spite of the large porosity of the powders, was delayed compared with that into the tablets. The penetration, however, was facilitated by the replacement of magnesium silicate with phenobarbital. The penetration into tablets of microcrystalline cellulose (M.C.C.) and magnesium stearate could not be described by Washburn's equation, as was the case for tablets prepared from M.C.C. A theoretical explanation for the experimental equation $L=Kt$, which had previously been introduced for the M.C.C. tablets, is discussed. The penetration into the tablets could be described by this equation when the amount of second ingredient in M.C.C. was small. When the amount of second ingredient was increased, however, the penetration into the tablets could not be described by Washburn's equation or by the equation $L=Kt$. The penetration into the mixed powders was fairly well described by Washburn's equation.

Keywords——penetration rate; tablet; powder; binary system; mixing ratio; drug; contact angle; swelling; contraction; Washburn's equation

A direct and simple method to measure the penetration rate of liquid into compressed tablets was reported previously.[1] In the case of binary mixtures, in which the contact angle of the second ingredient cannot be regarded as zero, such factors as mean capillary radius and contact angle of the mixture change with the component ratio. Little work has been done on liquid penetration into a multi-component system. Ganderton[2] examined the effect of magnesium stearate on the penetration by measuring the time required for 0.1 ml of water to be absorbed into the tablet. However, he did not discuss the results in terms of the contact angle, penetration length, and mean capillary radius in Washburn's equation (Eq. 1) for binary systems:

$$L^2=\gamma r t \cos\theta/2\eta \qquad \text{(Eq. 1)}$$

where L is the penetration length at time t, r is the average radius of the capillary, θ is the contact angle, and γ and η are the surface tension and viscosity of the liquid, respectively.

Further, the influence of other drugs (which also have high contact angles and in certain cases larger amount may be mixed with excipient than magnesium stearate) on the penetration has not been investigated. The capillary radius (r) can be calculated by substituting L and θ into Eq. 1; however, it is very difficult to measure θ of powdered substances directly. The present investigation was intended to clarify the influence of a second ingredient having a relatively high contact angle on liquid penetration into tablets and powder columns.

Experimental

Materials——Magnesium oxide, magnesium silicate, and microcrystalline cellulose (M.C.C.) were chosen as excipients and only the fraction that had passed through a 200 mesh sieve was used. Bromvalerylurea,

phenobarbital, magnesium stearate, and aspirin were chosen as the second ingredients and the 100/200 mesh fractions were used. The materials used were all of J.P.IX grade.

Preparation of Tabletes and Powder Samples——The second ingredient was mixed at 20, 40, 60, or 80 (w/w)% concentration with the excipient for 5 min in a glass micro V-type mixer (100 ml capacity). An accurately weighed amount (0.25 g) of mixture was compressed with an oil press at a pressure of 215 kg/cm^2 to prepare the compressed tablet (1.3 cm in diameter and 0.14—0.18 cm in thickness) using flat-faced punches. The preparation of powder columns was carried out as described previously.[1]

Measurement of Contact Angle——It is very difficult to measure directly the contact angle of a substance when a large crystal cannot be obtained. Kossen *et al.*[3] developed an equation, which accommodates the change of porosity, to estimate the contact angle from the drop height on a compressed disk of powdered substance. The contact angles of the substances were measured with an apparatus of the type shown in Fig. 1 and evaluated from Kossen's[3] equation (Eq. 2):

$$\cos\theta=\left\{\frac{Bh^2}{3(1-\varepsilon)\left(1-\frac{B}{2}h^2\right)}\right\}^{\frac{1}{2}} \qquad \text{(Eq. 2)}$$

where h is the height of a sufficiently large drop of liquid on a compressed disk (3.0 cm in diameter and 0.5—0.6 cm in thickness), the void spaces of which are saturated with the liquid, ε is the porosity of the disk, and

$$B=\rho\, g/2\gamma$$

where ρ is the density of the liquid, g is the acceleration constant of gravity, and γ is the surface free energy of liquid against its vapor. All measurements were carried out at 24±2°C and were repeated at least five times.

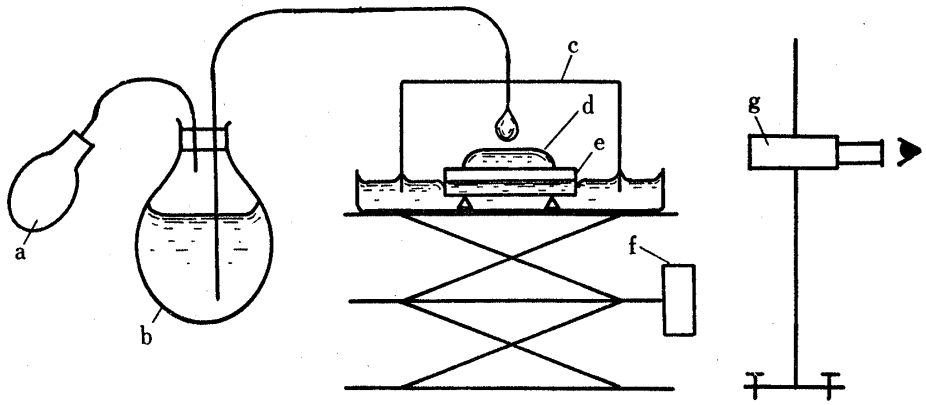

Fig. 1. Kossen's Apparatus used to measure Contact Angles of Powdered Substances

a, rubber bulb b, liquid container; c, glass cover; d, large drop of liquid; e, compressed disk of powdered substance; f, jack; g, cathetometer.

Measurement of Penetration Rate——The apparatus and procedure were the same as in the previous report.[1] Washburn's equation (Eq. 1) was used to analyze the results obtained with both the tablet and powder. All measurements of penetration were carried out at 24±2°C and were repeated five times.

Results and Discussion

Examination of the Independency of Contact Angle from Porosity, and the Amount of Scatter in Contact Angle

The contact angles of the substances calculated from Eq. 2 must be independent of the porosity of disks, since the contact angle is peculiar to the substance. To confirm this, pulverized aspirin and bromvalerylurea were compressed at various compression pressures into disks of different porosity. Figure 2 illustrates the influence of porosity on the contact angles. Standard deviations calculated from five measurements are also illustrated in the figure to indicate the amount of scatter. As shown in Fig. 2, the amount of scatter in θ (from 4.7 to

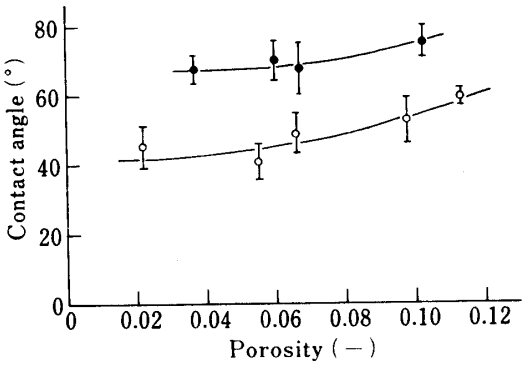

Fig. 2. Influence of Porosity on Contact Angles of Powders, and Amount of Scatter in Contact Angle

●, bromvalerylurea; ○, aspirin; ⊥, standard deviation.

14.8% coefficient of variation) was comparatively large and a slight dependence of θ on the porosity was recognized. These results suggest that Kossen's[3] method is not wholly satisfactory, but there exists no alternative method to obtain the contact angles of pulverized substances. If the contact angles are measured with disks prepared under constant compression pressure (215 kg/cm^2), as in the present investigation, the results may be usable for the estimation of apparent capillary radius.

Penetration of Liquid into Binary Mixtures

1) Magnesium Oxide and Organic Drug—Physical properties of powders and tablets of bromvalerylurea and magnesium oxide in different mixing ratios are listed in Table I. Scanning electron microscopic photographs of bromvalerylurea before and after compression are shown in Fig. 3.

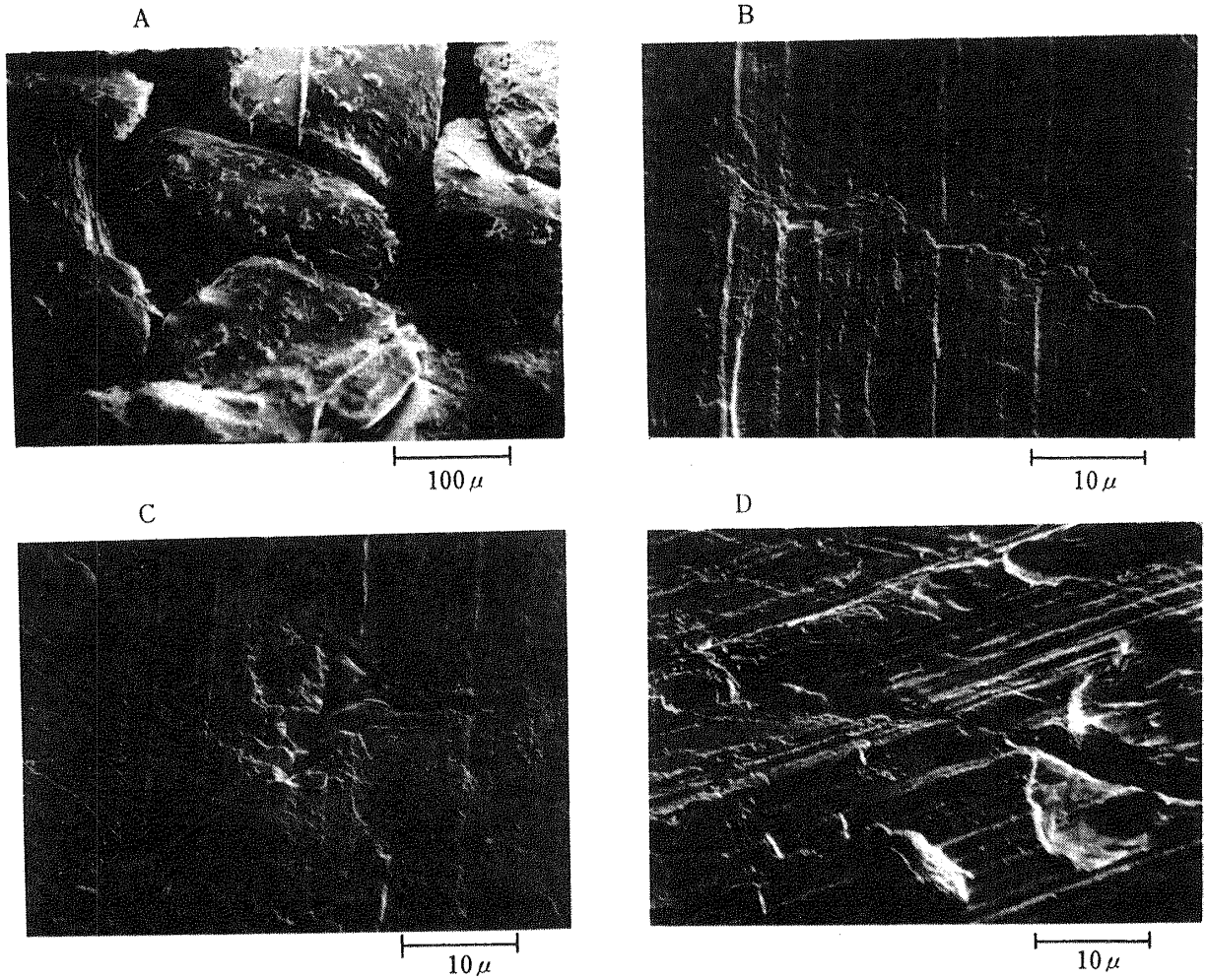

Fig. 3. Scanning Electron Microscopic Photographs of Bromvalerylurea (A) before and (B, C, and D) after Compression

Micro particles can be seen in the crevices at the boundries between particles. The many parallel lines or grooves are the replica of grooves on the surface of the punches.

The extremely small porosity of the tablet prepared from bromvalerylurea shown in Table I suggests that bromvalerylurea is friable and may be crushed; then it would be compacted closely during the compression to form the tablet. Figure 3 also suggests that the particles were packed closely, and boundaries between particles after compression are only recognizable under high magnification.

TABLE I. Physical Properties of Tablets and Powders consisting of Magnesium Oxide and Bromvalerylurea at Various Mixing Ratios

Concentration of bromvalerylurea in magnesium oxide (%)	Specific gravity	Porosity of tablets	Porosity of powders	Contact angle (°)
0	3.65	0.693	0.932	0
20	3.25	0.594	0.891	20.3
40	2.84	0.565	0.828	30.9
60	2.44	0.459	0.761	42.2
80	2.03	0.319	0.625	55.5
100	1.63	0.059	0.521	92.8

The tablets were prepared at 215 kg/cm² and the powders were compacted by tapping into glass tubes.

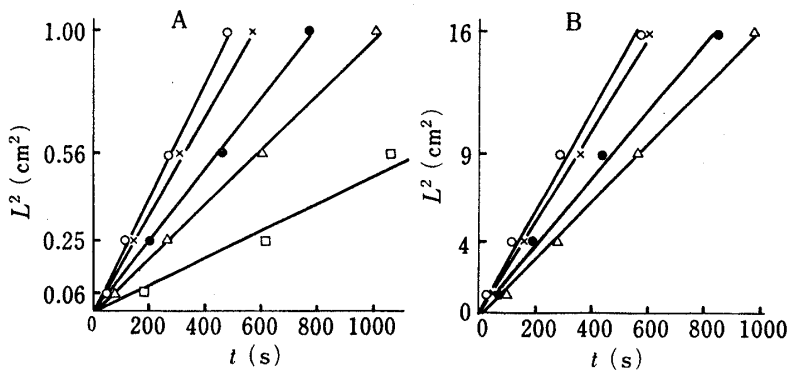

Fig. 4. Influence of Concentration of Bromvalerylurea in Magnesium Oxide on Liquid Penetration obtained with (A) Tablets and (B) Powders

Bromvalerylurea concentrations (%) in magnesium oxide were as follows: ○, 0%; ×, 20%; ●, 40%; △, 60%; □, 80%.

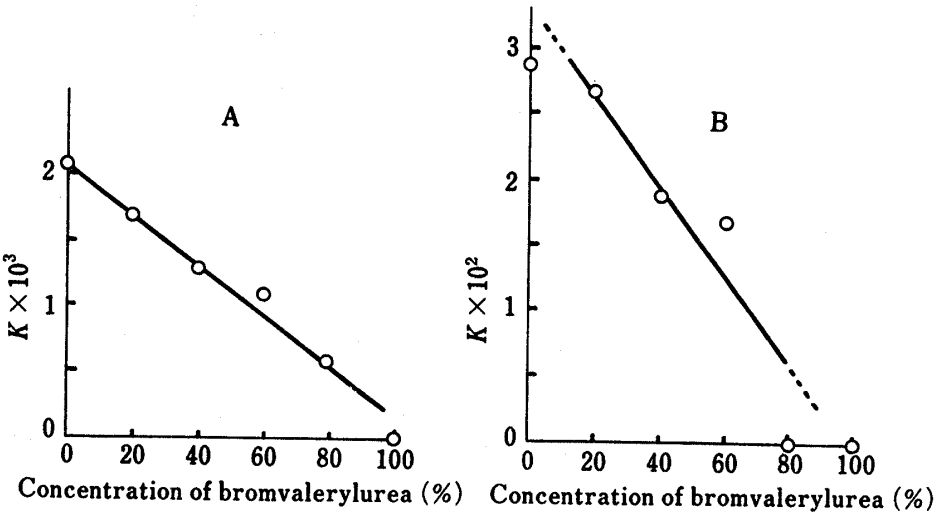

Fig. 5. Relation between Slope (K) and Concentration of Bromvalerylurea in Magnesium Oxide obtained with (A) Tablets and (B) Powders

The penetration into both powders and tablets of magnesium oxide and bromvalerylurea could be described by Washburn's equation (Eq. 1), since L^2 *vs.* t plots were practically linear, passing through the origin, as illustrated in Fig. 4. No penetration occurred, with tablet or powder, in bromvalerylurea (the contact angle of which is above 90°). Penetration into the mixed powder of magnesium oxide with 80% bromvalerylurea, however, could not be observed, probably because the magnesium oxide particles were isolated among the large numbers of hydrophobic bromvalerylurea particles.

The slope, K, (which corresponds with the term $r\gamma \cos\theta/2\eta$ in Eq. 1) of these linear relations changed with the ratio of contents. The K values were plotted against the mixing ratio in order to compare the tablet with the powder, as shown in Fig. 5.

K values in both the powders and tablets decreased with increase of the mixing ratio, as is clear from Fig. 5. The capillary radius values calculated by substituting K and θ (Table I) into Eq. 1 are listed in Table II. Although the difference in porosity between the tablets and powders was approximately two-fold at most (Table I), the difference in capillary radius between them was more than 15-fold (Table II), except for pure bromvalerylurea. Such a significant difference in the capillary radius suggests that the relation between the porosity and mean capillary radius calculated from Eq. 2 is not always parallel. It is considered that during the preparation of compressed tablets, the number of fine capillaries may have been increased.

Table II. Comparison of Apparent Capillary Radius of Tablets (r_t) and Powder (r_p) consisting of Magnesium Oxide and Bromvalerylurea at Various Mixing Ratios

Concentration of bromvalerylurea in magnesium oxide (%)	r_t (cm)	r_p (cm)
0	5.1×10^{-7}	8.9×10^{-6}
20	4.5×10^{-7}	7.2×10^{-6}
40	3.8×10^{-7}	5.4×10^{-6}
60	3.2×10^{-7}	5.8×10^{-6}
80	2.7×10^{-7}	—
100	—	—

The tablets were prepared at 215 kg/cm² and the powders were compacted by tapping into glass tubes.

2) **Magnesium Silicate and Organic Drugs**——The physical properties of mixtures of magnesium silicate and bromvalerylurea are listed in Table III. The slopes (K) of the linear relations between L^2 and t were plotted against the mixing ratio, as shown in Fig. 6.

Table III. Physical Properties of Tablets and Powders consisting of Magnesium Silicate and Bromvalerylurea at Various Mixing Ratios

Concentration of bromvalerylurea in magnesium silicate (%)	Specific gravity	Porosity of tablets	Porosity of powders	Contact angle (°)
0	3.28	0.697	0.816	21.7
20	2.95	0.632	0.783	29.1
40	2.62	0.558	0.706	33.8
60	2.29	0.445	0.637	41.3
80	1.96	0.297	0.558	52.3
100	1.63	0.059	0.517	92.8

The tablets were prepared at 215 kg/cm² and the powders were compacted by tapping into glass tubes.

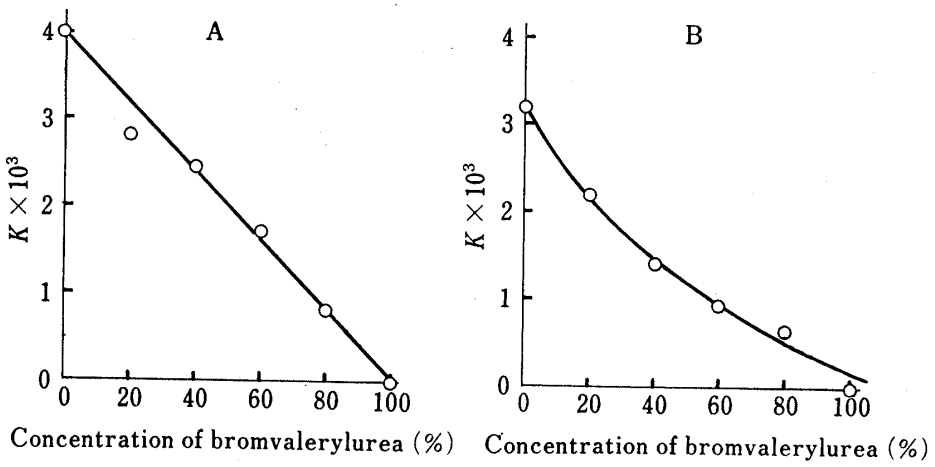

Fig. 6. Relation between Slope (K) and Concentration on Bromvalerylurea in Magnesium Silicate obtained with (A) Tablets and (B) Powders

Although the tablets gave an approximately linear relation between K and the mixing ratio (Fig. 6-A), the linearity was less good with powders (Fig. 6-B). Further, the powders showed rather small K values compared with the tablets, in spite of the large porosity, as shown in Table III. These findings also suggest a difference in the mechanism of penetration between the powder and tablet. We have previously[1] reported that liquid penetration into magnesium silicate was retarded by a contraction of the powder bed. It is clear that liquid penetration into binary systems containing magnesium silicate may be significantly affected by both the contraction of the powder bed and the contact angle.

The physical properties of mixtures of magnesium silicate and phenobarbital are listed in Table IV.

Table IV. Physical Properties of Tablets and Powders consisting of Magnesium Silicate and Phenobarbital at Various Mixing Ratios

Concentration of phenobarbital in magnesium silicate (%)	Specific gravity	Porosity of tablets	Porosity of powders	Contact angle (°)
0	3.28	0.697	0.806	21.7
20	2.89	0.400	0.782	34.6
40	2.50	0.354	0.715	37.3
60	2.11	0.281	0.614	37.7
80	1.72	0.179	0.515	46.5
100	1.33	—	0.487	50.0[a] 70.0[b]

a) Extrapolated. *b*) The literature value.[4]
The tablets were prepared at 215 kg/cm² and the powders were compacted by tapping into glass tubes.

Phenobarbital is so difficult to compress into a disk that Kossen's method could not be used; thus the contact angle was obtained by extrapolation of the results for mixtures at various mixing ratios and the result is given in Table IV together with the literature value.[4] Phenobarbital was shown to have a small influence on the contact angles of the binary mixtures compared with bromvalerylurea (Table III).

The slopes (K) of the linear relations between L^2 and t were plotted against the (phenobarbital and magnesium silicate) mixing ratio, as illustrated in Fig. 7. There is some scatter in the results obtained with tablets (Fig. 7-A), but a tendency for K to decrease with increasing

ratio of ingredient having high contact angle was noted. The mixed powders (Fig. 7-B), in contrast, showed a steep increase in K with increasing phenobarbital content. Interestingly, this indicates that the penetration rate is facilitated in a mix of powder having comparatively high contact angle, in contrast with the experimental results in the preceding section.

The reason for this phenomenon is considered to be as follows. With increasing phenobarbital content, magnesium silicate, which contracts as it wets, is replaced by phenobarbital (which does not contract), while the influence of phenobarbital on contact angles is relatively weak as mentioned above. The results shown in Fig. 7 can be explained well if the influence of contractibility is larger than that of contact angle.

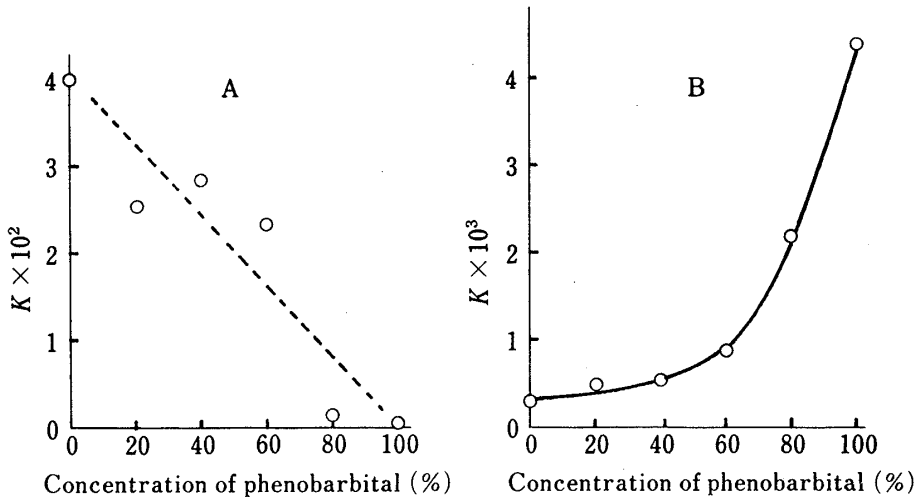

Fig. 7. Relation between Slope (K) and Concentration of Phenobarbital in Magnesium Silicate obtained with (A) Tablets and (B) Powders

3) **M.C.C. and Organic Drugs**——The contact angles of binary mixtures containing M.C.C. also could not be estimated by Kossen's method[3] due to the swelling of M.C.C. in the tablet on wetting.

The results obtained for mixtures of M.C.C. and magnesium stearate are shown in Fig. 8. The penetration into the tablets could not be described by Eq. 1, as is clear from Fig. 8-A.

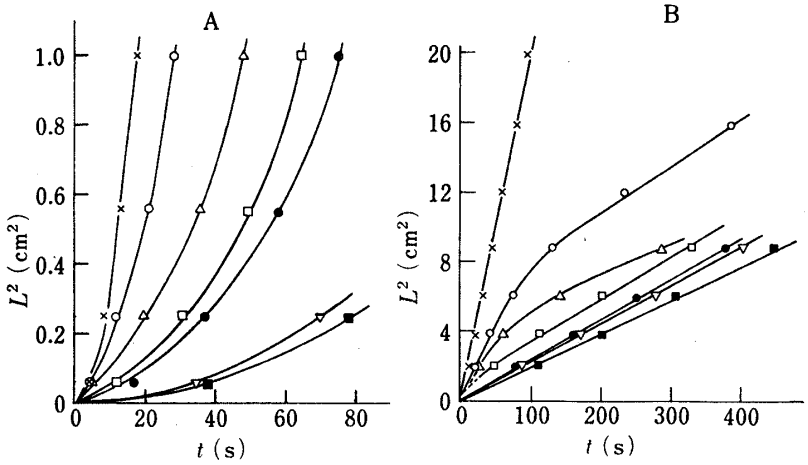

Fig. 8. Influence of Concentration of Magnesium Stearate in M.C.C. on Liquid Penetration obtained with (A) Tablets and (B) Powders

Magnesium stearate concentrations (%) in M.C.C. were as follows:
×, 0%; ○, 0.5%; △, 1%; □, 2%; ●, 4%; ▽, 6%; ■, 8%.

The behavior of the powders, on the other hand, was fairly well described by Eq. 1 except for the 0.5—1% magnesium stearate mixtures, as shown in Fig. 8-B. The penetration rate into M.C.C. was noticeably decreased by admixture of magnesium stearate even at concentrations as low as those usually used as a lubricant in the tableting process.

As described previously,[1] the L^2 *vs.* t plots for tablets of M.C.C. prepared at different compression pressures gave concave plots, as illustrated in Fig. 9-A. However, L *vs.* t plots for the same samples gave linear relations rather than Washburn plots, as illustrated in Fig. 9-B. A theoretical explanation of this phenomenon, however, is not available.

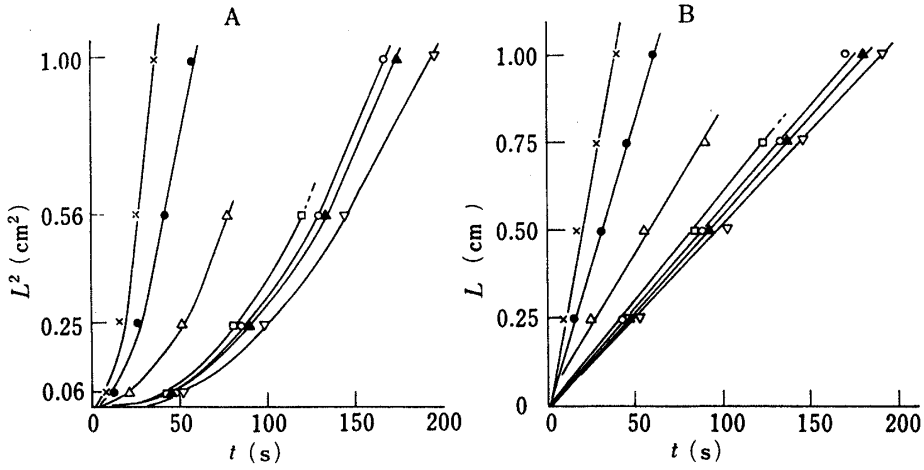

Fig. 9. (A)L^2 *vs.* t Plots and (B) L *vs.* t Plots for M.C.C. Tablets prepared at Different Compression Pressures

×, 215 kg/cm^2; ●, 430 kg/cm^2; △, 645 kg/cm^2; □, 860 kg/cm^2; ○, 1075 kg/cm^2; ▲, 1290 kg/cm^2; ▽, 1505 kg/cm^2.

The penetration rate, V, in a capillary having radius r is predicted by Hagen–Poiseuille's equation (Eq. 3):

$$V=\frac{dL}{dt}=\frac{r^2}{8\eta L}\left(\frac{2\gamma\cos\theta}{r}-\rho gL\right) \qquad \text{(Eq. 3)}$$

where L is the penetration length at time t, θ is the contact angle of the substance, g is the acceleration constant of gravity, γ, η, and ρ are the surface tension, viscosity, and specific gravity of the liquid, respectively. Since L is so small in the case of tablets that the term ρgL is negligible, Eq. 4 can be used:

$$V=r\gamma\cos\theta/4\eta L \qquad \text{(Eq. 4)}$$

Provided that large capillaries or cracks are generated in the tablet as a result of swelling or weakening of binding forces between particles, the viscosity resistance to liquid flow at these enlarged capillaries or cracks may be markedly decreased and may be ignored. The length from the top of the crack to the top of penetration (Fig. 10), consequently, may be defined as L^*. If these cracks grow with progress of the penetration, L^* can be postulated to be constant; then Eq. 4 becomes Eq. 5:

$$V=r\gamma\cos\theta/4\eta L^* \qquad \text{(Eq. 5)}$$

where L^* is a constant. Eq. 5 can be integrated as follows:

$$\int_0^L dL=\int_0^t(r\gamma\cos\theta/4\eta L^*)dt$$

$$L=(r\gamma\cos\theta/4L^*)t \qquad \text{(Eq. 6)}$$

since $r\gamma \cos\theta/4\eta L^*$ is a constant, let this be k, and then Eq. 6 is reduced to Eq. 7:

$$L=kt \qquad \text{(Eq. 7)}$$

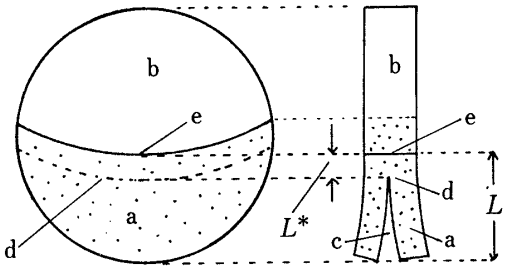

Fig. 10. Penetration Model involving Generation of Cracks to explain Liquid Penetration into M.C.C. Tablet

a, wetted portion; b, unwetted portion; c, crack; d, top of crack; e, top of penetration; L, penetration length; L^*, length from the top of crack to the top of penetration.

When L is plotted against t, linear relations as shown in Fig. 9-B should be obtained and the slope should correspond to k in Eq. 7.

The same plots as above for mixtures of M.C.C. and magnesium stearate are shown in Fig. 11. The tablets showed good linearity and their behavior could be described well by Eq. 7, whereas the powders did not give linear plots. This suggests that the assumptions on which Eq. 5 for the M.C.C. tablets is based are applicable to binary systems containing M.C.C. The reason why penetration into the powder column could not be described by Eq. 7 is presumably that no cracks can be generated in the powder column regardless of whether a single system or binary system is used.

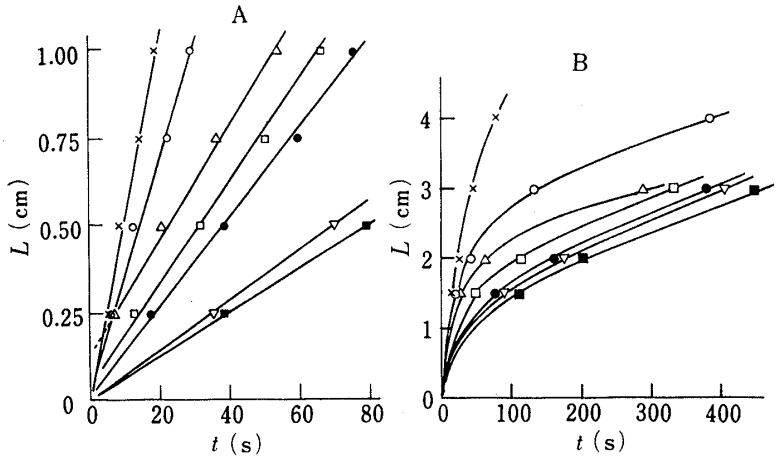

Fig. 11. L *vs.* t Plots for the Same Samples as in Fig. 8 (Mixture of M.C.C. and Magnesium Stearate) obtained with (A) Tablets and (B) Powders

Magnesium stearate concentrations (%) in M.C.C. were as follows: ×, 0%; ○, 0.5%; △, 1%; □, 2%; ●, 4%; ▽, 6%; ■, 8%.

The L^2 *vs.* t plots for M.C.C. and aspirin mixtures are shown in Fig. 12. Although the behavior of the tablets could not be described by Eq. 1 (Fig. 12-A), that of the powders could be described fairly well, except for the mixed powder of M.C.C. with 80% aspirin and pure aspirin (Fig. 12-B). No penetration occurred in the tablet of pure aspirin. The L *vs.* t plots for the same samples are shown in Fig. 13. Unexpectedly, neither the powders nor the tablets showed linearity. These results suggest that L^* in Eq. 7 is not constant in a binary system unless the concentration of the second ingredient is low enough, *e.g.* tablets consisting of M.C.C. and a small amount of magnesium stearate (Fig. 11). When the amount of the second ingredient is increased, the swelling ingredient (M.C.C.) is replaced with non-swelling materials, so the generation of cracks is appreciably hindered or retarded. It is for this reason that both Eq. 2 and Eq. 7 are inapplicable to tablets composed of various mixing ratios of M.C.C. and aspirin. Interestingly, this is in contrast with the behavior of binary mixtures containing

magnesium silicate in powder columns, the contraction of which was hindered by the second ingredient, while liquid penetration into the column was, conversely, facilitated (Fig. 7).

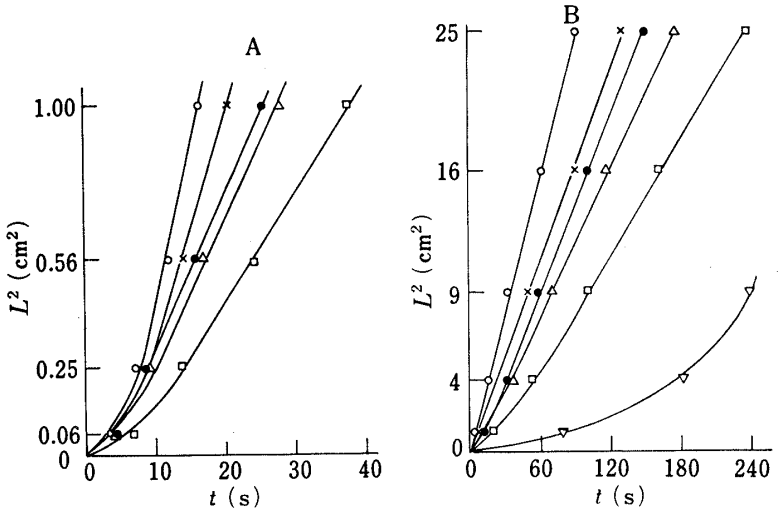

Fig. 12. Influence of Concentration of Aspirin in M.C.C. on Liquid Penetration obtained with (A) Tablets and (B) Powders

Aspirin concentrations (%) in M.C.C. were as follows:
○, 0%; ×, 20%; ●, 40%; △, 60%; □, 80%; ▽, 100%.

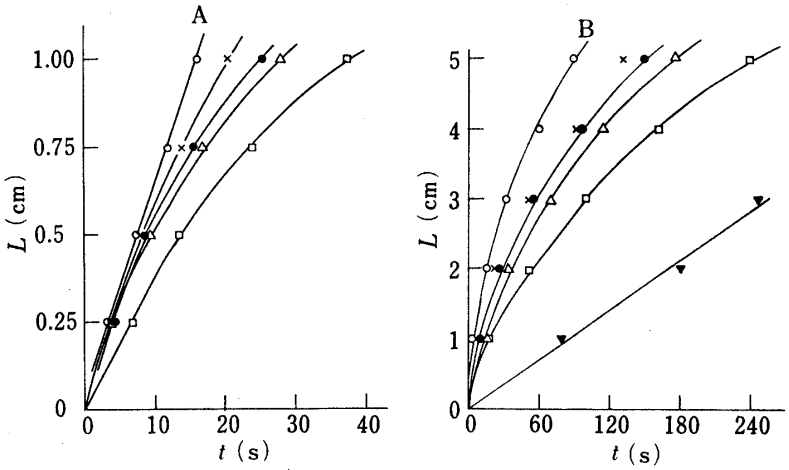

Fig. 13. L *vs.* t Plots for the Same Samples as in Fig. 12 (Mixture of M.C.C. and Aspirin) obtained with (A) Tablets and (B) Powders

Aspirin concentrations (%) in M.C.C. were as follows:
○, 0%; ×, 20%; ●, 40%; △, 60%; □, 80%; ▼, 100%.

In conclusion, in order to understand the various phenomena which take place during liquid penetration into tablets, it is necessary to study not only the liquid penetration into tablets but also that into the powder, and to compare the results. In this way, the mechanism of the penetration of liquid into the tablets can be elucidated.

References

1) Part I: E. Fukuoka, S. Kimura and M. Yamazaki, *Chem. Pharm. Bull.*, **29**, 205 (1981).
2) D. Ganderton, *J. Pharm. Pharmacol.*, **21**, Supple., 9S (1969).
3) N.W.F. Kossen and P.M. Hertjes, *Chem. Eng. Sci.*, **20**, 593 (1965).
4) C.F. Lerk, A.T.M. Scoonen and J.T. Fell, *J. Pharm. Sci.*, **65**, 843 (1976).