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217. Hisashi Nogami,*1 Hisashi Fukuzawa, and Yoshinobu Nakai*2: Studies on Tablet Disintegration. I. The Effect of Penetrating Rate on Tablet Disintegration.

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The penetrating of liquid into a tablet is the first step in the process of tablet disintegration though the mechanism of disintegration is so complicated and has not been completely determined. The effect of wetting rate on granule disintegration was experimented by Aoki, *et al*[1] and it was concluded that the adsorption speed of water into a granule affected on the granule disintegration.

In this experiment, the relationship between the rate of penetration and the tablet disintegration was examined. The penetration of a liquid into a capillary is expressed by the following equation.[2]

$$L^2 = \frac{R\gamma\cos\theta}{2\eta}\,t \qquad (1)$$

where L is the penetrated length of capillary, R the radius of capillary, γ the surface tension of liquid, η the viscosity of solution and t the time. The effect of η, γ, $\cos\theta$ and R on the disintegration were examined and the equation of penetrating was discussed theoretically to apply the equation for tablet disintegration.

Experimental

The Measuring of Viscosity——Ostwald viscometer was used at 37°.

The Measuring of Surface Tension——Du noüy tensiometer was used.

The Measuring of Penetration——The penetrated length of powder bed which was padded in a vertical hold glass tube was measured.

The Measuring of the Mean Capillary Diameter existed in a Tablet——The permeametry apparatus commonly used for the measuring of particle size of powder was used as shown in Fig. 1. The side of a tablet was coated and set in a small glass funnel by solid paraffin.

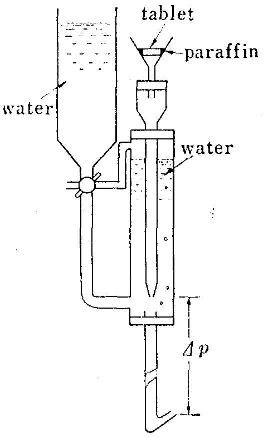

Fig. 1. Apparatus of Air Permeametry to measure the Mean open Capillary Diameter of Tablet

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1) M. Aoki, T. Fukuda: Yakuzaigaku, **20**, 106 (1960).

2) E.H. Washburn: Phys. Rev., **17**, 273 (1921).

Material Used——Aspirin : J. P. VII.

MgO : Reagent class.

Tablet of MgO : Flat faced tablets 13 mm. in diameter were compressed by an oil press.

Sodium dioctyl sulfosuccinate : Reagent class.

The human gastric juice : The gastric juice was drawn by a catheter at about 10 A. M. from the subjects who ate no breakfast. The gastric juice was separated in two layer in a test tube. Each layer was filtrated by a glass filter and their viscosities were measured.

Tablets of calcium *p*-aminosalicylate and aspirin : Market products.

Result and Discussion

The Effect of Viscosity on the Disintegration

It is assumed from equation (1) that the high viscosity of a solution may take a long time to disintegrate since the penetrating rate decreases in high viscosity solution. The rate of penetration in the powder bed and the disintegration of tablet were measured with calcium *para*-aminosalicylate (PAS-Ca) in the solutions of various concentrations of methyl cellulose 400. The result of penetrating rate is shown in Fig. 2. The coefficient of penetration, $R\gamma\cos\theta/2\eta=F$, in each concentration can be given by the inclination of the linear relationship between L^2 and t. The coefficient of penetration, the viscosity, the surface tension and the tablet disintegration time of PAS-Ca in each solution are shown in Table I.

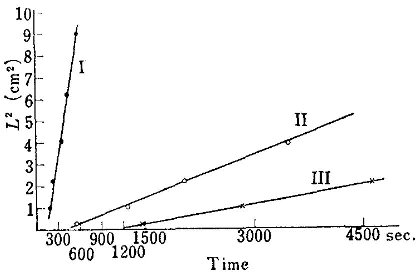


Fig. 2. Effect of Viscosity on the Rate of Penetration

PAS-Ca powder in methylcellulose 400 solution at 37° $F=R\gamma\cos\theta/2\eta$

I : water $\eta=0.6947$ $F=2.13\times10^{-2}$

II : 0.8% methyl cellulose 400 solution $\eta=7.384$ $F=1.3\times10^{-3}$

III : 1% methyl cellulose 400 solution $\eta=12.513$ $F=0.567\times10^{-3}$

Table I. Effect of Viscosity on the Rate of Penetration and the Tablet Disintegration Time

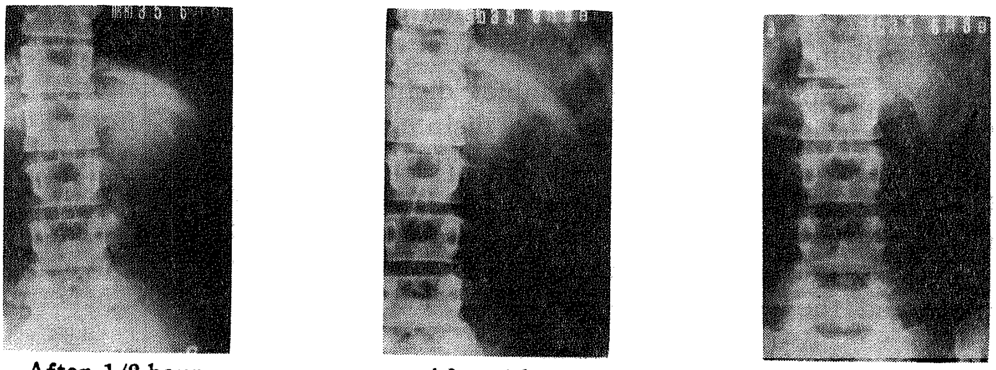
PAS-Ca 37°

Concn. of M. C. 400 (%)	Viscosity C. P.	Ratio of $\gamma\cos\theta$ pure water = 1	$F=\dfrac{R\gamma\cos\theta}{2\eta}\times10^4$	Disintegration time (min.)
(pure water) 0	0.6947	1	213	3
0.8	7.3840	0.7	13	90
1.0	12.5130	0.5	5.7	160

It could be seen from Table I that the greater the viscosity of the solution, the more the rate of penetration decreased and the disintegration time increased. The effect of $\gamma\cos\theta$ on this result might be negligible since the value of $\gamma\cos\theta$ was not significantly varied in each solutions as compared with the value of viscosity.

The disintegration of PAS-Ca tablets in the human gastrointestinal tract was examined by X ray. Some of the figures of X ray films of tablet are shown in Fig. 3, and the number of undisintegrated tablets were counted, half, one and four hours after 10 tablets used as shown in Table II.

In this test, the effect of water ingested with the tablet on disintegration was examined by the same subjects. On the first day the tablets were used with water and on the second day with no water half hour after the lunches of the same menu were eaten.



After 1/2 hour After 1 hour After 4 hour

Fig. 3. X Ray Film of PAS-Ca Tablets in Gastro-intestinal Tract
Ten tablets were ingested with no water by subject No. 2 in Table II.

Table II. Disintegration of PAS-Ca Tablets in Gastro-intestinal Tract examined by X ray

Method to ingest tablets	Number of undisintegrated tablets counted on X ray films				
	No water was ingested with tablet			Water was ingested with tablets	
Time / Subject	30 min.	1 hr.	4 hr.	1 hr.	4 hr.
1	10	3½	0	0	0
2	5~6	4~5	4	0	0
3	0	0	0	0	0
4	8	4	0	0	0
5	5	4	0	0	0
6	3	0	0	1	0

Ten tablets were ingested at 30 minutes after meals.
Disintegration times of these tablets measured by U.S.P. method were 3′44″~11′40″.

Disintegration time of the tablets used with no water was apparently longer than the one used with water and the time of the U.S.P. method.

The viscosity of human gastric juice was measured. The gastric juice was separated in two layers in a test tube and the viscosities of the upper and lower layers were about 1.1 c.p. and 10~20 c.p. respectively.

When tablets were used with no water, tablets might drop into the high viscosity solution of gastric juice and the disintegration time might be longer though the viscosity of gastric juice might vary by the kind of meals, the time after a meal and etc.

The tests of tablet disintegration in the human and the artificial gastric juice were examined by Abbott, *et al.*3) Their result showed that the disintegration time was longer in the former than in the latter and was increased by the greater concentration of mucoid in the test solution. Abbott's result might depend upon the high viscosity of solution given by the addition of mucoid with respect to our experiment described above.

The adsorption rate of aspirin tablet was examined by Levy4) and as a result it was found that the rapid adsorption was given by the intake of large quantities of water with the tablets.

This result might be affected by the rapid disintegration given by water used with tablets.

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3) D.D. Abbott, *et al.* : J. Am. Pharm. Assoc. Sci. Ed., **48**, 19 (1959).
4) G. Levy : J. Pharm. Sci., **50**, 388 (1961).

The Effect of Contact Angle and Surface Tension on the Rate of Penetration and the Tablet Disintegration

The effect of contact angle upon a tablet disintegration was examined in several reports,[5,6] and it was concluded that the disintegration was not affected by contact angle, however a surfactant varies not only with a contact angle but also with a surface tension of solution. It can be found in the equation (1) that the rate of penetration depends upon both surface tension and the cosine of contact angle, and the rate cannot be decided by only the value of contact angle. In this experiment the effects of the contact angle and the surface tension of surfactants on the rate of penetration were measured.

For practical purposes, two methods for the measurement of surfactant effect on a tablet disintegration are in common use. One is merely the addition of a surfactant to a test solution and the other involves the coating of a powder or granule by surfactant before compressing.

By the first method, the rates of penetration of calcium carbonate and carbon black were measured by Kuno[7] in the solution of various surfactants, and the rates of surfactant solutions were smaller than the one of pure water for all kind of surfactant.

This result showed that the value of surface tension decreased though the cosine of contact angle increased in a surfactant solution.

Granule disintegration was examined in polyoxyethylene monostearate solution by Aoki, *et al.*[1] and no effect of the surfactant on a granule disintegration was given.

By the second method, the effect of surfactants on a tablet disintegration was measured by Cooper, *et al.*[6]

Their results showed that the tablets coated by a surfactant disintegrated rapidly only when the tablet contained a disintegrator.

In this experiment the effect of sodium dioctylsulfosuccinate (Aerosol OT) on the rate of penetration was measured with the powder bed of magnesium oxide and aspirin by the first and second method. The result of magnesium oxide is shown in Fig. 4.

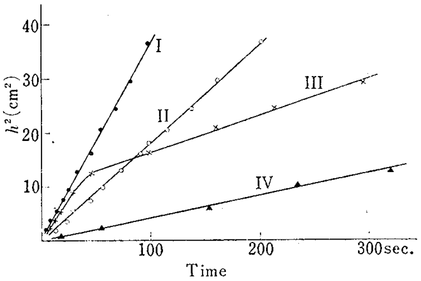

Fig. 4. Effect of AOT on Penetration with Magnesium Oxide Powder

Magnesium Oxide 50/100 Mesh

$F = R\gamma \cos\theta/2\eta$

Ⅰ : MgO-water $F=0.354$
Ⅱ : MgO-0.02% AOT solution $F=0.169$
Ⅲ : MgO coated by AOT-water
Ⅳ : MgO-0.2% AOT solution $F=0.0406$

The result showed that the penetrating rate of surfactant solution was smaller than of pure water, and that in the great concentration of a surfactant the rate decreased. The effect of viscosity on the penetrating rate was negligible since there was little difference of the viscosities between the pure water and the surfactant solutions. A knick point was observed on the relationship between L^2 and t when water penetrated into the powder bed which was coated by the surfactant. This knick point might be due to the lowering of surface tension given by the dissolving of the surfactant on the way of penetrating. The penetrating rate of aspirin powder was shown in Fig. 5. The penetrating rate of aspirin was greater in the surfactant solution than the pure water in contrast with magnesium oxide.

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[5] M. Aoki, T. Fukuda : Yakuzaigaku, **18**, 232 (1958).
[6] B.E. Cooper, E.A. Brecht : J. Am. Pharm. Assoc. Sci. Ed., **46**, 520 (1957).
[7] H. Kuno, R. Abe : J. Indust. Chem. Japan, **61**, 1445 (1958).

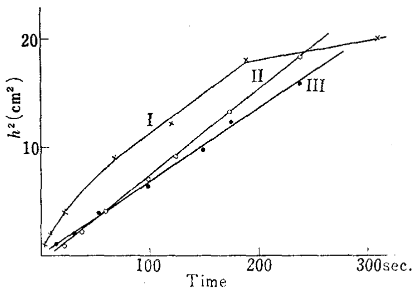

Fig. 5. Effect of AOT on Penetration with Aspirin
Aspirin 50/100 mesh
I : Aspirin coated by AOT-water
II : Aspirin-0.02% AOT solution $F=0.0809$
III : Aspirin-water $F=0.0679$

In pure water, the penetrating rate of the aspirin powder which was coated by surfactant was greater than the rate of the pure aspirin powder at the initial step of penetrating. The increase of the rate for aspirin given by the surfactant might be due to the fact that the contact angle of aspirin crystal to water was nearly 90°[10)] and the cosine of contact angle was greatly increased by the surfactant compared with the decrease of surface tension.

The knick point of the relationship between L^2 and t was observed in aspirin as same as in magnesium oxide. When the effect of surfactants on a tablet disintegration was measured by Cooper[6)] with the series of succinate ester, the disintegration time was decreased by a longer chain of alkyl radicals of the esters which coated the capillary surface of a tablet. The disintegration time decreased in following order of alkyl radicals, that is, amyl, hexyl, and octyl. The water solubility of the esters were 40.7, 35.4, and 1.8 g./100 ml. at 30° respectively.

The relation between a solubility and a rate of solution is given as[8)]

$$dC/dt=kS(C_s-C) \qquad (2)$$

where C is the concentration at time t, C_s the saturated concentration, S the surface of solid and k the rate constant. The rate constant k is depend upon the thickness of diffusion layer and the diffusion constant. The thickness of diffusion layer may not be so different among each ester for the same movement of liquid as penetrating. The difference of diffusion constant among the esters may not be so great as compared with the difference of the solubilities. The rate constant k, therefore, may be in same order for the series of succinate esters, so it can be seen from equation (2) that the greater the solubility of esters, the further the rate of solution may be increased. Therefore Cooper's result may be due to the solution rate of each ester since the greater concentration of surfactant makes a disintegration time to increase as experimented above.

Summarizing the effect of surfactant of a tablet disintegration, a rapid disintegration generally may not be given by a surfactant since both surface tension and contact angle are involved in factors of penetrating rate. The effect can be expected only when the contact angle of medicine to water is great and nearly equal or larger than 90°.

The Effect of Capillary Diameter on Penetrating Rate and Tablet Disintegration

It can be seen from equatin (1) that a rapid penetration is given by a large capillary diameter.

On tableting, the effect of compressional force on the distribution of capillary diameter was measured by Higuchi[9)] and Matsumaru[10)] by the gas adsorption method. The type of the capillaries existed in tablet was considered by Matsumaru[8)] as the blind capillary which was closed at one end and ink bottle type.

[8)] A.A. Noyes, W.R. Whittney: J. Am. Chem. Soc., **19**, 930 (1897).
[9)] T. Higuchi: J. Am. Pharm. Assoc., Sci. Ed., **42**, 194 (1953).
[10)] H. Matsumaru: J. Pharm. Soc. Japan, **78**, 1205 (1958).

An open capillary diameter, however, must be measured in order to examine the relationship between a penetrating rate and a disintegration since equation (1) can be applied for only an open capillary.

In this experiment, a mean diameter of the open capillary existed in a tablet was measured by air permeametry.

The calculations of the open capillary by the permeametry were given by Kozeny-Carman,[11] Otto Bartsch,[12] and Fujii.[13] The principle of the calculations is the same and based on Poiseiulle equation and so Kozeny-Carman equation well known is used as follows.

$$D_c=\frac{4}{\rho S_w}\left(\frac{\varepsilon}{1-\varepsilon}\right) \tag{3}$$

$$S_w=\frac{14}{\rho}\sqrt{\frac{\Delta P\cdot A\cdot t}{\eta\cdot L\cdot Q}\,\frac{\varepsilon^3}{(1-\varepsilon)^2}} \tag{4}$$

From equation (3) and (4)

$$D_c=\frac{2}{7}\sqrt{\frac{\eta\cdot L\cdot Q}{\Delta P\cdot A\cdot t\cdot \varepsilon}} \tag{5}$$

where D_c is the capillary diameter, ρ the density of powder, S_w the specific surface area of powder, ε the porosity, η the viscosity of air, L the thickness of powder bed, Q the penetrated air volume at the time t, A the cross section area of the powder bed and P the pressure difference of both heads of the powder bed. Using a general permeametry apparatus, a tablet was set in place of powder bed and a mean capillary diameter was calculated by equation (5).

The effect of compressional force on the mean capillary diameter was examined with magnesium oxide tablet as follows. The granule contained 5% potato starch as disintegrator and 3% starch paste as binder and was sieved by 10/20 mesh. The effect of compressional force on capillary was shown in Fig. 6. The relationship between the capillary diameter and the tablet disintegration time measured by U.S.P. method

Table III. Effect of Compressional Force on the Open Capillary Diameter with Magnesium Oxide Tablets

Compressional force (ton/cm^2)	Thickness of tablet (cm.)	Porosity	Time to permeate 100 ml. air ($\times 10^4$sec.)		D_c (μ)
0.5	0.300	0.670	1.757		0.191
	0.300	0.670	1.645		0.191
	0.300	0.670	1.435		0.209
				mean	0.197
1.0	0.270	0.620	6.060		0.100
	0.265	0.624	5.220		0.107
	0.260	0.623	5.760		0.101
				mean	0.102
1.5	0.235	0.572	7.060		0.089
	0.240	0.566	8.760		0.083
				mean	0.086
2.0	0.230	0.566	12.000		0.069
	0.230	0.560	12.600		0.069
	0.230	0.561	11.400		0.071
				mean	0.069

Granule: disintegrator 5%, binder 3%.

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[11] P.C. Carman: J. Soc. Chem. Ind., **57**, 225 (1938).
[12] O. Bartsch: Ber. Deutch. Karam. Ges., **14**, 519 (1933).
[13] K. Fujii: J. Ceramic Assoc. Japan, **42**, 757 (1934).

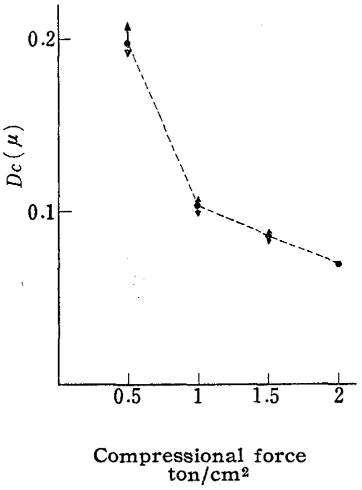


Fig. 6. Relation between Compressional Force and Capillary Diameter

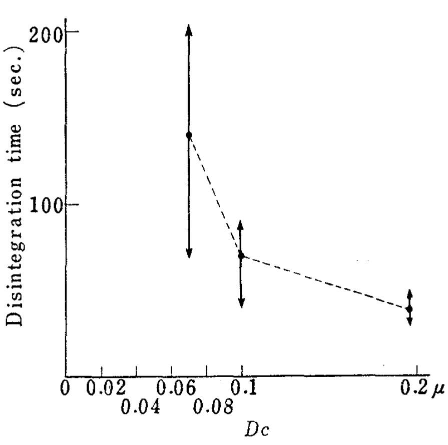


Fig. 7. Relation between Capillary and Disintegration Time

were shown in Fig. 7. It can be seen from these results as follows. The distinguished decrease of capillary diameter was recognized between 0.5 ton and 1 ton of compressional force. This result agreed with the one of Matsumaru.[8] A rapid disintegration was given by a large capillary diameter but a linear relationship between capillary diameter and a disintegration time was not obtained.

The effect of disintegrator quantity on capillary diameter was measured and the result was shown in Table IV. This result showed that a large quantity of disintegrator gave an increase of capillary diameter and a distinguished difference was recognized between 0% and 5% of disintegrator. It can be said therefore that a disintegrator gives a large capillary diameter and a rapid penetration of water in tablet. This effect of disintegrator on capillary diameter may be one of the factors of the tablet disintegration mechanism.

Table IV. Effect of Disintegrator on the Mean Open Capillary Diameter with Aspirin and Magnesium Oxide Tablets

Quantities of disintegrator / Material	0% (μ)	5% (μ)	10% (μ)
Aspirin	0.36	0.72	1.14
	0.47	0.96	1.43
	—	—	1.23
Magnesium oxide	0.07	0.27	0.30
	0.09	0.29	0.32

Disintegrator : potato starch.
Compressiomal force : 0.5 ton/cm², direct compression.

When the effect of surfactant on a disintegration was examined by Cooper,[6] it was concluded that only surfactant didn't give a rapid disintegration and the combination of the surfactant and disintegrator gave a good effect on disintegration.

This result can be explained from the result described above as follows, that is, a large capillary diameter enough to penetrate a liquid rapidly was not given by surfactant only and even the dissolution of surfactant lets the penetrating rate decrease.

Theoretical Discussion of Penetrating Rate to Apply it for Tablet Capillary

The rate of penetration is given for the capillary of uniform diameter as follows

$$dL/dt = R^2 \cdot P/8 \cdot \eta \cdot L \qquad (6)$$

where L is the penetrated capillary length, R the radius of capillary, η the viscosity of liquid and P the force of penetration given as

$$P=(2\gamma\cos\theta/R)-g\cdot d\cdot L\cdot\sin\alpha \qquad (7)$$

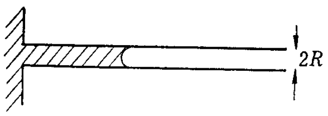
where g is the accellation of gravity, d the density of liquid and α the inclination of capillary to water surface. The next relation can be given from equation (6) and (7)

$$dL/dt=(2R\gamma\cos\theta-R^2\cdot g\cdot d\cdot L\cdot\sin\alpha)/8\eta L \qquad (8)$$

The types of capillaries were considered as shown in Fig. 8 and the rate of penetration was discussed with each case. When the capillary laid horizontally as shown in Fig. 8-A, α was equal to zero and the rate of peneiration $[dL/dt]_A$ was expressed by equation 9.

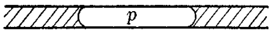
$$[dL/dt]_A=R\gamma\cos\theta/4\eta L \qquad (9)$$

A. The penetration when one opening of uniform radius is in atmosphere

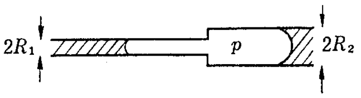


$[dl/dt]_A=R\gamma\cos\theta/4\eta l$

B. The penetration when both openings are in liquid

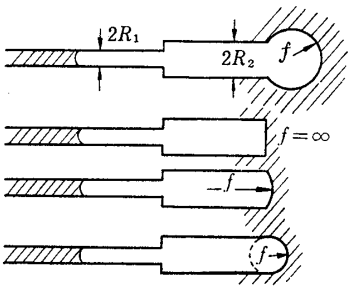


C. The penetration when both openings of radii R_1 and R_2 are in liquid



$[dl/dt]_C=[dl/dt]_A\cdot n-1/n$
$R_2/R_1=n$

D. The penetration when it bubbles at the opening of radius R_2



$[dl/dt]_D\geqq[dl/dt]_{D\min}$
$[dl/dt]_{D\min.}=[dl/dt]_C$
$\therefore\ [dl/dt]_D\geqq[dl/dt]_A\cdot n-1/n$
$f=R_2$: f is minimum

E. The penetration in capillary net of a tabilet

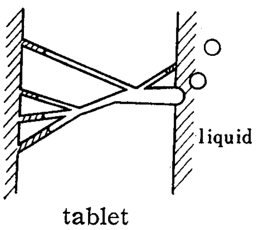


Fig. 8. The Rates of Penetration in various Cases of Capillaries

The rate of penetration is given by this equation when one opening of a capillary is in atomosphere but not given when both openings are in liquid as in shown in Fig. 8-B. The air pressure P closed in capillary and the penetrating force in equilibrium at the following relation

$$P=2\gamma\cos\theta/R$$

and thereafter a liquid cannot penetrate more deeply. When a tablet is dropped into water, a liquid penetrates from both openings of capillary and equation (9) cannot be applied for the penetration.

The capillary of tablet was calculated by permeametry as uniform diameter. When the capillary is composed of two radii R_1 and R_2 as shown in Fig. 8-C and R_2 is equal to $nR_1 (n>1)$, the penetrating rates in capillaries R_1 and R_2 are calculated as follows. In capillary R_2, the rate decreases due to the air pressure P and extends to zero at the following condition

$$P=P_2=2\gamma \cos\theta/R_2 \tag{10}$$

where P_2 is the penetrating force in capillary R_2, so a liquid cannot penetrate more deeply in capillary R_2. In capillary R_1, the liquid can penetrate since the next relation is given

$$P_1=2\gamma \cos\theta/R_1>P \tag{11}$$

where P_1 is the penetrating force in capillary R_1.

So a liquid penetrates in the capillary of smaller diameter R_1 and regresses in the capillary of larger diameter R_2.

The rate of penetration in capillary R_1 is given by the following relation.

$$dL/dt=R_1^2(P_1-P_2)/8\eta L \tag{12}$$

From the equation (10), (11), and (12), the rate is given by

$$dL/dt=R_1^2(2\gamma\cos\theta/R_1-2\gamma\cos\theta'/R_2)/8\eta L \tag{13}$$

where θ' is a regressive contact angle of solid to a liquid. When θ' is nearly equal to θ, the following relation is given

$$dL/dt=[(R_1/4\eta L)\gamma\cos\theta](R_2-R_1)/R_2$$

therefore the rate of penetration in capillary R_1, $[dL/dt]_C$, is expressed by

$$[dL/dt]_C=(R_1\gamma\cos\theta/4\eta L)\cdot(n-1)/n \tag{14}$$

From equations (9) and (14), the relation between $[dL/dt]_C$ and $[dL/dt]_A$ can be given as

$$[dL/dt]_C=[dL/dt]_A\cdot(n-1)/n \tag{15}$$

It can be found that the penetrating rate in the capillary of smaller radius R_1 is equal to $(n-1)/n$ of the rate which is given in the uniform capillary R_1 opened in atomosphere at one opening. Therefore $[dL/dt]_C$ takes a nearer value to $[dL/dt]_A$ according as n takes a greater value.

The penetrating rate $[dL/dt]_D$ was examined when it bubbled at capillary opening after a liquid was exhausted from capillary R_2. $[dL/dt]_D$ is given by

$$[dL/dt]_D=(R_1^2\gamma\cos\theta/4\eta L)\cdot(1/R_1-1/f) \tag{16}$$

where f is the curvature of bubbles. When f is equal to R_2 as shown in Fig. 6-D, the value of f is minimum and the rate of penetration $[dL/dt]_{D\ \text{min.}}$ is given as follows.

$$\begin{aligned}[dL/dt]_{D\text{min.}}&=(R_1^2\gamma\cos\theta/4\eta L)\cdot(1/R_1-1/R_2)\\&=[dL/dt]_C\end{aligned} \tag{17}$$

Therefore the next relations are given by equations (15), (16), and (17)

$$[dL/dt]_D \geqq [dL/dt]_{D\min.} = [dL/dt]_C = [dL/dt]_A (n-1)/n \qquad (18)$$

So it can be seen that the rate of penetration $[dL/dt]_D$ is not smaller than $(n\text{-}1)/n$ of the rate $[dL/dt]_A$.

The capillaries existed in the tablet may be connected with each other and may compose the nets of capillaries as shown in Fig. 8-E. It bubbles only at the opening of greatest diameter in a net of capillary and the value of $(n\text{-}1)/n$ may be near to one for the most part of capillaries in the net. So the rate of penetration in a tablet may be near to the rate $[dL/dt]_A$ of a uniform single capillary opened in atmosphere at one opening.

The number of openings from which it bubbles gives the number of the isolated capillary nets in a tablet. There may not be so many nets in a tablet since bubbling is observed in some places when a tablet is placed in a liquid.

Summary

The effects of the penetrating rate on tablet disintegration were examined. Viscosity, surface tension, contact angle of liquid and the mean capillary diameter of tablet were measured and their effects on disintegration were discussed.

In high viscosity solution, the rate of penetration decreased and the disintegration was not well. The viscosity of gastric juice was measured and tablet disintegration in human gastro-intestinal tract was examined by X ray. It was estimated that a tablet disintegration might be affected by the viscosity of gastric juice.

The rate of penetration of powder in a surfactant solutions and the penetration of the powder coated by surfactant in pure water were measured. The effect of surfactant on disintegration could not be generally expected due to the decrease of surface tension.

The mean diameter of open capillary in a tablet was measured by air permeametry. The diameter was decreased by a large compressional force in tableting and increased by a large quantity of disintegrator.

The equation of penetrating rate was discussed theoretically to apply it for the penetrating in tablet capillary. It was concluded that Washburn's equation of penetrating rate could be applied to the penetrating in the capillary of a tablet.

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