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34. Hisashi Nogami,*1 Jun Hasegawa,*1 and Masatoshi Miyamoto*2 : Studies on Powdered Preparations. XX.*3 Disintegration of the Aspirin Tablets containing Starches as Disintegrating Agent.*4,5

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87 groups of tablets were made using 3 sieved fractions of aspirin and potato or corn starch varying formulation and compressional force. Disintegration of the tablet was investigated in detail by the thermal analysis reported previously. The relation between porous structure of tablet and disintegration was studied and the following conclusions were drawn from the results obtained.

1. The rate-determining step of the disintegration was the penetration of water into the porous structure of a tablet.
2. It was confirmed that starch can develop the capillary structure in aspirin tablet. This effect was observed when aspirin particles larger than starch grains were mixed with starch. The effect seemed to be larger at corn starch than potato starch.
3. There should be the critical amount of starch necessary for the disintegration depending upon the particle size or the specific surface area of ingredients. The smaller the particle size of aspirin, the more amount of starch was required for the tablet disintegration. The tablet of the smallest aspirin (11.9 μ in mean particle size) did not disintegrate by the addition of 20% of starch.
4. In the case of the tablets that disintegrated very rapidly and completely, the wall of the capillaries in the tablets was considered as starch. This may be the reason why the tablet with potato starch disintegrates more rapidly than with corn starch.
5. The model proposed for disintegration well explained why the tablet made from the medium aspirin particle (294 μ in mean volume-surface particle diameter) disintegrated more rapidly than that containing the largest aspirin (953 μ).

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When a drug is administered by oral route, the rapid absorption from intestinal tract and the maintenance of therapeutic level should be assured for higher availability of the medicine. The dissolution precedes the absorption when the drug is given in solid state excluding the pinocytosis for the absorption mechanism. The greater dissolution rate of drug, therefore, is favorable for the rapid development of medicinal effect and Eq. (1)[1] has been discussed by many investigators[2] from the standpoint mentioned above.

$$dC/dt = kS(C_s - C) \qquad (1)$$

where C is the concentration of drug at any time t, C_s the saturated concentration, S the surface area of solid, k a constant, and dC/dt the dissolution rate at a given condition.

When a drug is given by a dosage form of tablet, the tablet disintegrates in the intestinal tract, the surface area increases to the maximum value which is dependent on the disintegration characteristics of tablet and the particle size of ingredients, and

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*3 Part XIX : This Bulletin, in press.
*4 Taken in part from the thesis of Masatoshi Miyamoto for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo, 1964.
*5 Presented at the Kanto Local Meeting of Pharmaceutical Society of Japan Tokyo, July 1964.
1) A. A. Noyes, W. R. Whitney : J. Am. Chem. Soc., **19**, 930 (1897).
2) G. Levy : Am. J. Pharm., **135**, 78 (1963).

then dissolution and absorption of active ingredients follows for the development of pharmacological action.[3]

The starches from many origins are most widely used disintegrators in pharmaceutical industries which have the following merits, *i.e.*, chemically and pharmacologically inert character, low cost, and so on.[4,5] The mechanism why starches are useful as disintegrator, however, has not been confirmed, although the swelling properties of the substance have been supported by many investigators[4,6~8] but not in some cases as the origin of the adjuvant action. Some investigators believed that the starch developed the capillary structure of tablet[9~11] and that wetting of the capillary was accelerated by it.[12]

The basic formula used in preparing the granules, the degree of compression, the size, shape, weight, and hardness of the tablet, the particle size of the ingredient, granules and disintegrators, the type of compression machinery, the period of storage, the evaluation method of disintegration time, and moisture content of the granules were considered to affect the disintegration properties of tablets by Ward and Trachtenberg,[8] however, these factors are not independent but depend upon each other much complicatedly. The studies to find out the factors determining the disintegration of tablet, therefore, could not draw the distinct conclusion.[13~16] It has been estimated that the wettability or porous structure of the tablet relates to its disintegration characteristics from the following studies that the higher viscosity of the vehicle causes slow disintegration[11,17,18] and the lower surface tension of the medium by the addition of surfactants results in rapid disintegration.[11,19,20]

It may be considered that the disintegration characteristics are ruled by the correlation of two forces, *i.e.*, to hold the shape of tablet and to separate the constituent particles when disintegration vehicle penetrates the capillary of tablet,[21] however, it is impossible, at present to evaluate the two forces mentioned above separately.

Although the detailed mechanism may not be known, it is reasonable to consider that the mechanism of starch as disintegrator may be estimated by determining the relation of porous structure and disintegration time of tablet, since, assuming the two stages, *i.e.*, one that water contacts with the capillary wall of tablet and the other that water develops the action of starch as disintegrator, the close relation should be found if the former stage mentioned above is rate-determinant step and should not if not so. Therefore, it was our purpose to study the relation between the disintegration time and the porous structure of tablet which depends on the mean pore diameter and

3) K. Muenzel, W. Kaegi: Pharm. Acta Helv., **30**, 408 (1955).
4) E. Rotteglia, A. Marinone: Boll. Chim. Farm., **96**, 83 (1957).
5) R. P. Patel, D. T. Chikhlia; Indian J. Pharm., **25**, 220 (1963).
6) H. Sager: Pharm. Acta Helv., **24**, 334 (1949) (C. A., **44**, 2700i (1950)).
7) C. B. Granberg, B. E. Benton: J. Am. Pharm. Assoc., Sci Ed., **38**, 648 (1949).
8) J. B. Ward, A. Trachtenberg: Drug Cosmetic Ind., **91**, 35 (1962).
9) L. C. Curlin: J. Am. Pharm. Assoc., Sci. Ed., **44**, 16 (1955).
10) T. Bánó, T. Szarvas, L. Aradi: Pharm. Zentralhalle, **100**, 221 (1961).
11) H. Nogami, H. Fukuzawa, Y. Nakai: This Bulletin, **11**, 1389 (1963).
12) H. Matsumaru: Yakugaku Zasshi, **79**, 854 (1959).
13) E. A. Holstius, H. G. DeKay: J. Am. Pharm. Assoc., Sci. Ed., **41**, 505 (1952).
14) K. C. Kwan, F. O. Swart, A. M. Mattocks: *Ibid.*, **45**, 236 (1957).
15) V. Cid Krebs: Anales fac. quím. y farm., Univ. Chille, **11**, 204 (1959) (C. A., **54**, 25575f (1960)).
16) H. Burlinson, C. Pickering: J. Pharm. and Pharmacol., **2**, 630 (1950).
17) D. D. Abbott, E. W. Packman, E. W. Rees, J. W. E. Harrisson: J. Am. Pharm. Assoc., Sci. Ed., **48**, 19 (1959).
18) K. Muenzel, T. Kuhn: Pharm. Acta Helv., **37**, 509 (1962).
19) B. F. Cooper, E. A. Brecht: J. Am. Pharm. Assoc., Sci. Ed., **46**, 520 (1957).
20) L. Aradi: Acta Pharm. Hung., **31**, 272 (1961) (C. A., **56**, 4873f (1962)).
21) J. Hasegawa: Yakuzaigaku, **20**, 1 (1960).

the interfacial properties of capillary wall for the elucidation of mechanism of the disintegrator. The tablets of 87 groups of acetylsalicylic acid (Aspirin) of known particle size distribution were compressed directly by fixed upper punch forces with or without addition of potato or corn starch in four levels of concentration. The disintegration time was evaluated in detail by the thermal method as reported previously.[22] The rate-determining step of the disintegration was examined considering the factors mentioned above.

Experimental

Materials——Aspirin : 3 sieved fractions used were supplied from Nippon Kayaku Co., Ltd. Starches : J. P. grade potato and corn starches used were not further treated and kept in a sealed can after their moisture content was measured. The characteristics of the both tablet ingredients were given in Table I.

Table I. Properties of Aspirins and Starches used

	Aspirin			Starch	
	L	M	S	Corn	Potato
Volume-surface particle size[a] (d_{vs}) (mm.)	0.953	0.294	0.0119	0.0131	0.0248
Specific gravity[b] (37°) (g./ml.)	1.393[c]	1.393[c]	1.392[c]	1.463[d]	1.446[d]
Moisture content[e] (%)				12.8	17.4

a) Measured photographically.
b) Measured with the Weld pycnometer.
c) Replaced with liquid paraffine.
d) Replaced with xylene.
e) Weight loss after drying at 130° for 4 hr.

Table II. Formulary and Symbol of Sample Tablet

Aspirin	Compressional force (ton/tablet)	Without starch	Corn starch (%)					Potato starch (%)				
			2.50	5.00	10.0	20.0	100	2.50	5.00	10.0	20.0	100
L	0.50	L1	LC 11	LC 21	LC 31	LC 41	C1	LP 11	LP 21	LP 31	LP 41	P1
	1.0	L2	LC 12	LC 22	LC 32	LC 42	C2	LP 12	LP 22	LP 32	LP 42	P2
	2.0	L3	LC 13	LC 23	LC 33	LC 43	C3	LP 13	LP 23	LP 33	LP 43	P3
M	0.50	M1	MC11	MC21	MC31	MC41		MP11	MP21	MP31	MP41	
	1.0	M2	MC12	MC22	MC32	MC42		MP12	MP22	MP32	MP42	
	2.0	M3	MC13	MC23	MC33	MC43		MP13	MP23	MP33	MP43	
S	0.50	S1	SC 11	SC 21	SC 31	SC 41		SP 11	SP 21	SP 31	SP 41	
	1.0	S2	SC 12	SC 22	SC 32	SC 42		SP 12	SP 22	SP 32	SP 42	
	2.0	S3	SC 13	SC 23	SC 33	SC 43		SP 13	SP 23	SP 33	SP 43	

Formulary and Compression of Tablet——Fixed amount of aspirin and starch was mixed according to Table II, weighed 500± 1 mg., and fed to the die cavity. Neither of binder, filler, nor lubricant was incorporated. Tablets were compressed by manual operation with a single punch tableting machine, Kimura K-2, equipped with a set of 13 mm. flat-faced punches and die. To neglect the effect of compressing velocity and to keep the uniformity of the pressure distribution during compression, maximum compressional force, measured with a strain meter and the deviation of which was controlled within 5%, was maintained for 10 sec. In order to prevent the effect of sticking, the die wall and punch-surfaces were lubricated with saturated magnesium stearate solution in benzene and a group of 10 tablets was taken for the test sample after initial 3 compressions. 87 groups, 870 tablets, were stored in a closed container and a randomized group used for experiment.

Porosity of Tablets——Porosity was calculated from the dimension of tablets measured by a micrometer and the density of aspirin and starch given in Table I.

Mean Pore Size of Tablet——Mean pore size, which was the average value of 3 tablets, was obtained by air-permeametry experiment assuming the tortuosity of pores to be 2.5.[11]

Dissolution Rate and Disintegration Time——The both values were determined by thermal method.[22]

Three tablets were reacted with 300 ml. of 0.5*M* sodium citrate solution stirring at 500 r.p.m. at 37° in a Dewar's vessel and heat of dissolution (endothermic) was measured at adequate intervals. The detailed apparatus and the procedures were reported previously[23] but a little modification was employed using a stainless steel cage for the prevention of tablet crush by the stirrer. Thermal change, ΔT, is proportional to the quantity of aspirin dissolved, its differential coefficient by time, $d\Delta T/dt$, is proportional to the total surface area of the tablets at the instant, and the particle size distribution of disintegrated particles is obtained from the slope of the curve, $d^2\Delta T/dt^2-t$.[22]

Results and Discussion

Porous Structure of Tablets

A typical example of the relation between logarithmic compressional force and

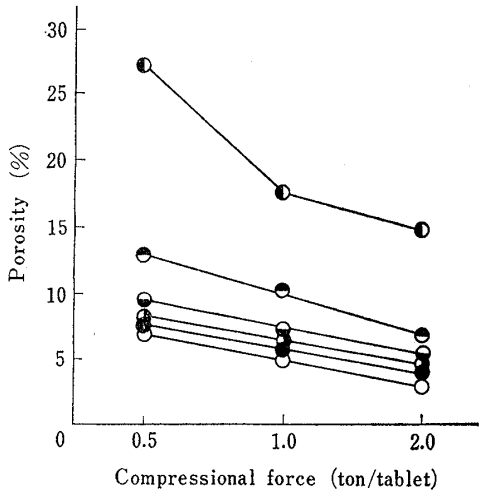

Fig. 1. The Effect of Compressional Force on the Porosity of Tablets

- ◐ Simple tablets of corn starch.
- ◓ Tablets of the largest aspirin, L, with 20% corn starch.
- ◒ Tablets of aspirin L with 10% corn starch.
- ◑ Tablets of aspirin L with 5% corn starch.
- ● Tablets of aspirin L with 2.5% corn starch.
- ○ Simple tablets of aspirin L.

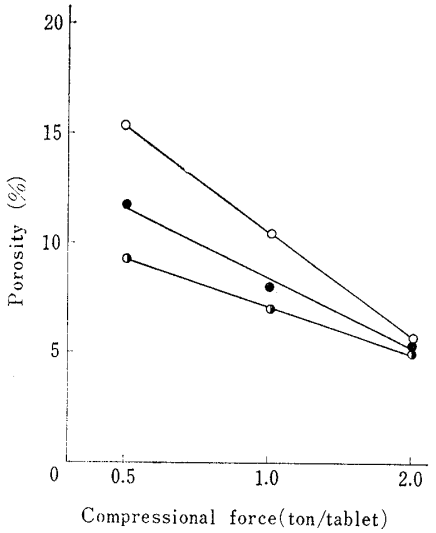

Fig. 2. The Effect of the Particle Size of Aspirin on the Relationship between the Compressional Force and the Porosity of Tablets

- ◑ Tablets of the largest aspirin, L, with 10% corn starch.
- ● Tablets of the medium aspirin, M, with 10% corn starch.
- ○ Tablets of the smallest aspirin, S, with 10% corn starch.

porosity is given in Fig. 1 where a linear relation which had been observed at sulfathiazole and aspirin tablets by Higuchi, *et al.*,[24,25] was found at the fixed ratio of aspirin and starch. The slope of the straight lines did not depend on the amount or kind of starches added when aspirin of the same particle size was compressed. The tablet containing potato starch, however, gave smaller porosity than that of corn starch, though the results were not shown in the figure and the results might be caused by the smaller particle size of corn starch.

The effect of particle size of aspirin on the porosity is given in Fig. 2 where the steeper slope was found at smaller particle. The relation between porosity and

22) Y. Nakai: This Bulletin, **8**, 641 (1960).
23) H. Nogami, J. Hasegawa, T. Nagai, M. Miyamoto: *Ibid.*, **10**, 747 (1962).
24) T. Higuchi, A. N. Rao, L. W. Busse, J. V. Swintosky: J. Am. Pharm. Assoc., Sci. Ed., **42**, 194 (1953).
25) T. Higuchi, L. N. Elowe, L. W. Busse: *Ibid.*, **43**, 685 (1954).

capillary diameter is shown in Fig. 3. The linear relation was found and the looser slope found at the smaller particle might be caused by the narrower interstices among smaller particles.

As mentioned in a literature,[26] the closer packing may be obtained when two kinds of spherical powder of different particle size having no inter-particle attractive force are mixed than the packing of each ingredient. In another words, the mixing of spherical particles of different size results in smaller porosity. If the mixing of aspirin and starch is the case, the minimum porosity should be found when smaller starch grains are added to larger aspirin particles. The result given in Fig. 4 did not show the minimum value in experimental conditions and the larger porosity observed with the increase of starch content on the contrary to the expectation. Such tendency mentioned above was shown in the pore diameter determined by air-permeation method. The tablet obtained by compressing the smallest aspirin particles showed different behavior given in Fig. 5 from Fig. 4.

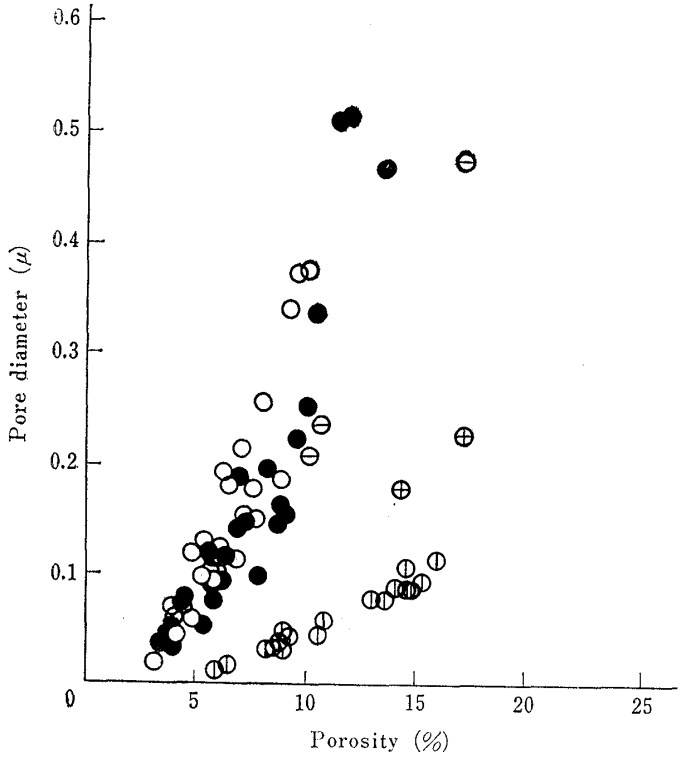

Fig. 3. Relationship between the Porosity and the Pore Diameter of Tablets

- ○ Tablets of the largest aspirin, L, with or without starch.
- ● Tablets of the medium aspirin, M, with or without starch.
- ⓘ Tablets of the smallest aspirin, S, with or without starch.
- ⊕ Simple tablets of corn starch.
- ⊖ Simple tablets of potato starch.

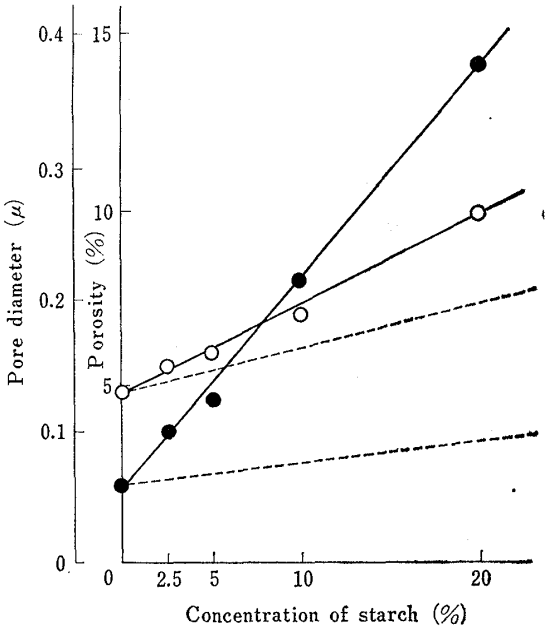

Fig. 4. Relationships between the Concentration of Corn Starch and the Porosity and between the Concentration of Corn Starch and the Pore Diameter of the Tablets of the Largest Aspirin, L, with Corn Starch compressed at 1.0 Ton per Tablet

○ Porosity; ● Pore diameter. Dotted lines were the values expected from the simple tablet of aspirin L and that of corn starch.

The circumstance might be explained as follows. It may be assumed that the surface of aspirin particles L and M is covered with small starch grains in mixed condition, but contrary in the case of the smallest aspirin particles, S, since the relation of particle size of ingredients is opposite as shown in Table I. The interaction

26) J. M. DallaValla : "Micromeritics. The Technology of Fine Particles," 2nd ed., Pitman Publ. Co. (1948).

between aspirin particle and starch grain which was observed in aspirin L and M seemed to enlarge the porosity of tablet and pore diameter as seen in Fig. 4, though the nature of the interaction could not be discussed from the experimental results

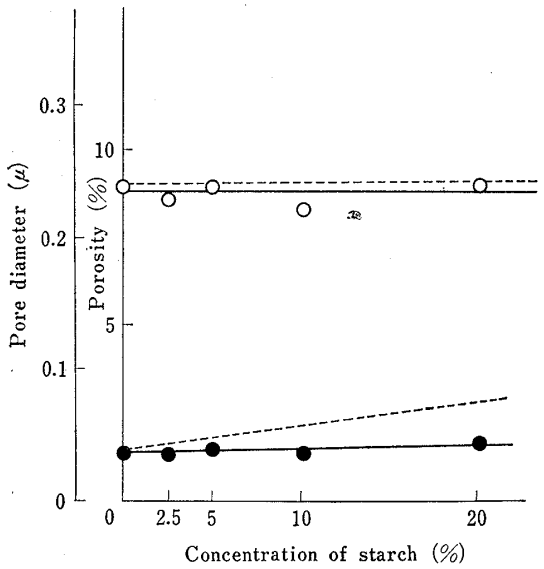

Fig. 5. Relationships between the Concentration of Potato Starch and the Porosity and between the Concentration of Potato Starch and the Pore Diameter of the Tablets of the Smallest Aspirin, S, with Potato Starch compressed at 1.0 Ton per Tablet

○ Porosity; ● Pore diameter. Dotted lines were the values expected from the simple tablet of aspirin S and that of potato starch.

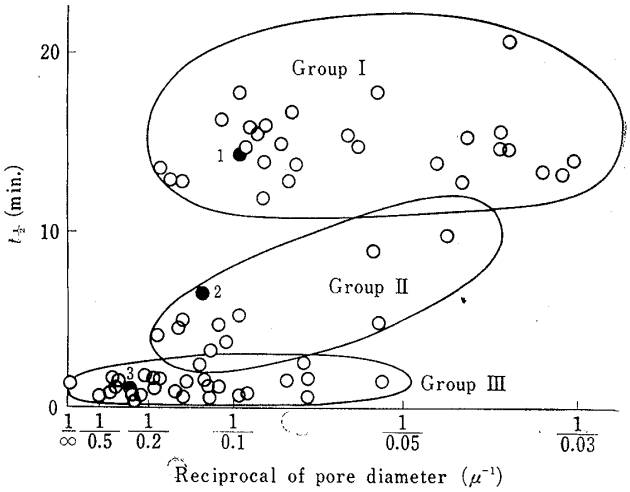

Fig. 6. Relationship between the Pore Diameter and the Dissolution Rate of Aspirin Tablets

●'s marked by 1, 2, and 3 were selected for the examples, whose thermal analysis curves were shown in Fig. 7.

presented. In the latter case of aspirin S, such interaction could not be manifested. It may be concluded, therefore, that the characteristics of starch to develop the porous structure in tablet distinguish themselves when starch is incorporated with coarse particles like aspirin L and M.

Dissolution Rate

As mentioned before, the therapeutic effect of tablet may depend on its dissolution properties. The dissolution characteristic of the dosage form is discussed in this paper comparing a parameter, $t_{1/2}$, which is the time to dissolve the 50% of aspirin contained,[27,28] *i.e.* to develop one-half of the heat of dissolution.

The relation of $t_{1/2}$ plotted against reciprocal of pore diameter is shown in Fig. 6 where the dissolution characteristics of tablet were classified into 3 groups in which the groups I and III had $t_{1/2}$'s independent of reciprocal pore diameter, however, $t_{1/2}$ related to reciprocal pore diameter in the group II. The classification was conducted not only subjectively, but also each group presented the characteristic behavior of disintegration as seen in Fig. 7 where ΔT or $d\Delta T/dt$ was plotted *versus* time. The representative of each group in Fig. 7 was the tablet shown by closed circles in Fig. 6, respectively. The results shown in Fig. 7 lead to the following considerations.

27) L. C. Schroether, J. E. Tingstad, E. K. Knoechel, G. G. Wagner : J. Pharm. Sci., **51**, 865 (1962).
28) G. Levy : *Ibid.*, **52**, 1039 (1963).

The curves (1) and (1′) in Fig. 7 were time plot of temperature change observed (dissolution rate) and its differential (change of surface area) of the tablet of the coarse aspirin, L, mixed with 2.5% of corn starch compressed at 2.0 ton force per tablet. As expected from the composition and compressional force of tablet, the surface area simply and slowly decreased. It meant the tablet examined did not disintegrate but dissolved gradually from the surface keeping the original shape of tablet. The whole tablets belonged to the group I showed the similar dissolution behavior mentioned above. It is reasonable, therefore, $t_{1/2}$ did not relate to pore diameter in the group I. The group contained the tablets of the fine particle, aspirin S, or the medium aspirin, M, and the coarse one, L, with little amount of the disintegrators.

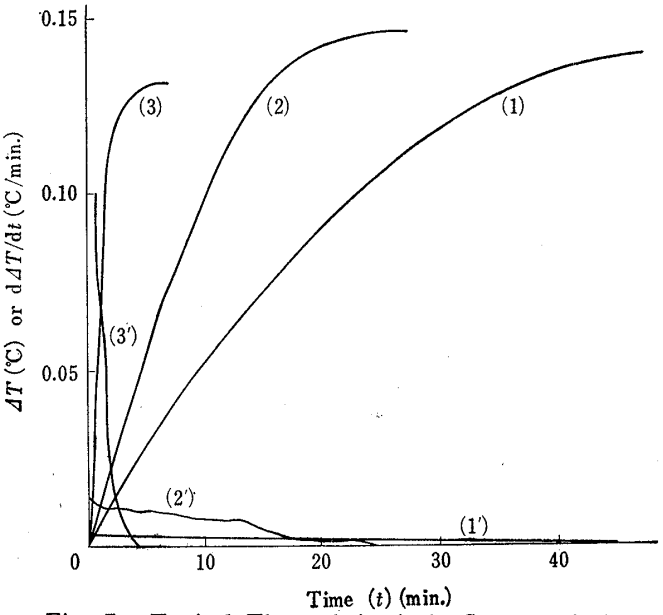

Fig. 7. Typical Thermal Analysis Curves of the Tablets representing Each Group

(1) and (1′): Tablet of the largest aspirin, L, with 2.5% corn starch compressed at 2.0 ton/tablet belonging to the group I. (2) and (2′): Tablet of aspirin L with 5% corn starch compressed at 1.0 ton/tablet belonging to the group II. (3) and (3′): Tablet of aspirin L with 10% potato starch compressed at 0.50 ton/tablet belonging to the group III. (1), (2), and (3): $\Delta T-t$. (1′), (2′), and (3′): $d\Delta T/dt-t$. ΔT and $d\Delta T/dt$ corresponded to the dissolved amount and the surface area, respectively.

It was considered that there might be a critical amount of disintegrator which depended upon the particle sizes of aspirin and starch or the relative surface areas of the components which related to the interfacial character of the capillary wall of tablets.

The curves (2) and (2′) in Fig. 7 showed disintegration properties of the tablet of the largest aspirin particle, L, with 5% of corn starch compressed at 1.0 ton. As seen from the comparison of curves (1′) and (2′), the effective surface for the dissolution during disintegration not simply decreased as (1′), but several maximal values were observed. It was estimated from disintegration behavior like (2′), that the tablet disintegrated into several pieces which were much larger than the constituents and disintegrated again into pieces during the dissolution process from the surface of the primary pieces, as mentioned by Berry and Ridout.[29] The group II contained the tablets of the aspirin S with excess disintegrator or the aspirins L and M with insufficient starches. It may be considered, generally, the $t_{1/2}$ related mainly to the pore diameter of the tablet in the group II even though it depended also on the dissolution or disintegration of the primary pieces formed.

The thermal analysis of the tablets of the largest aspirin, L, with 10% of potato starch compressed at 0.5 ton and of the medium aspirin, M, with 10% of corn starch compressed at 0.5 ton, both belonged to the group III, were given as the curves (3) and (3′) in Fig. 7 or Fig. 8. The heat absorption was completed rapidly during disintegration and the maximum surface area was observed around 40 sec. as seen in Fig. 8, where the mean particle size was about 0.35 mm., nearly same as that of the ingredient, aspirin M, when disintegration was finished. The particle size disintegrated, therefore,

29) H. Berry, C. W. Ridout: J. Pharm. and Pharmacol., **2**, 619 (1950).

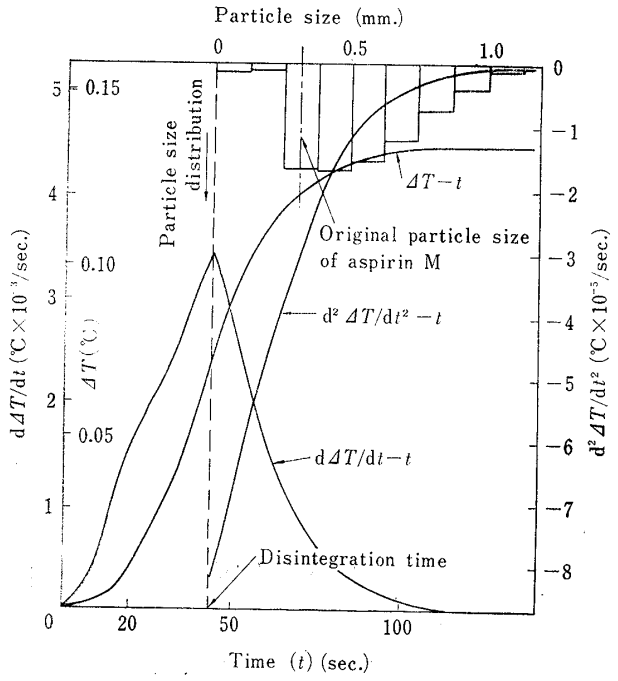

Fig. 8. Typical Thermal Analysis Curves of the Tablet representing the Group III (Tablet of the medium aspirin, M, with 10% corn starch compressed at 0.50 ton/tablet)

ΔT and $d\Delta T/dt$ corresponded to the dissolved amount and the surface area, respectively.

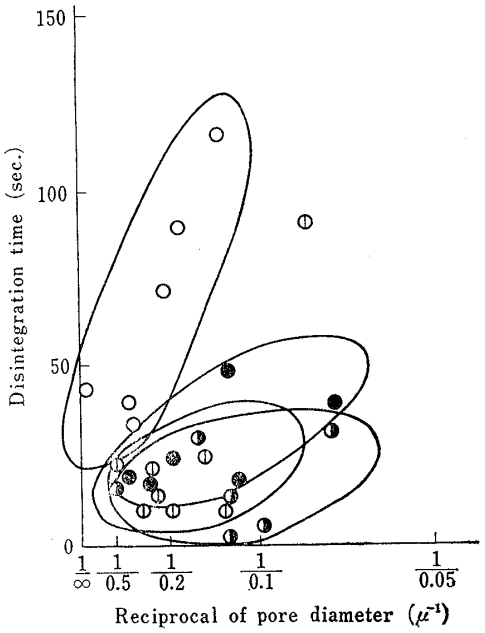

Fig. 9. Relationship between the Pore Diameter and the Disintegration Time of the Tablets of the Group III

- ○ Tablets of the largest aspirin, L, with corn starch
- ◑ Tablets of the medium aspirin, M, with corn starch.
- ● Tablets of aspirin L with potato starch.
- ◑ Tablets of aspirin M with potato starch.

was rate-determinant for dissolution and $t_{1/2}$ was independent of pore diameter in the group III.

The relation between reciprocal of pore diameter and disintegration time, the time to the maximum surface area for dissolution, of the tablets in the group III is given in Fig. 9. The effects of a) kind of starches and b) particle size of aspirin could be seen from Fig. 9. Each of these effects will be discussed later.

The Effect of Kind of Starch on Disintegration Time of the Tablets in the Group III

The linear relationship between reciprocal pore diameter and disintegration time was recognized on the both starches, though clearer at the tablets of the largest aspirin, L, with corn starch and those of aspirin L with potato starch but not the tablets of the medium aspirin, M, with corn starch and those of aspirin M with potato starch, and the slope was steeper at corn than potato starch in Fig. 9. Comparing the disintegration times of the tablets with the same size capillary, the more intensive disintegration effect than in corn starch was observed in potato starch, which was similar results obtained by Rácz, *et al.* who compared several starches as disintegrators in aspirin tablet.[30]

The structure of a tablet may be resembled as the suspended system of solid in solid where the granule containing active drug is surrounded by a continuous phase of

30) G. Rácz, Z. Kisgyorgy, J. Papp: Orvosi Szemle, **6**, 238 (1960) (C. A., **54**, 23184e (1960)).

disintegrator or lubricant.[31,32] The propriety of the model presented above might be supported by Higuchi, *et al.*[33] in their studies on tablet where the granules were isolated by lubricant, by Muenzel and Kaegi[34] who reported that the surface of granule was covered with talc, or by several investigators.[35~37]

The system in the study presented is simplified using just two components, aspirin and starch. The continuous phase of aspirin to aspirin in the aspirin tablet which is directly compressed may be interfered by the addition of starch. When the amount of starch added is over a limitation, the continuous phase in aspirin tablet may be replaced by starch as the phase conversion observed often in an emulsified system. It was estimated the phase conversion in tablet occurred by the addition of about 5% and 10% of starch to the aspirin particle L and M, respectively, calculated from the particle size of the components. The mean pore diameter determined by air-permeation is the summarized results of pores, assumed the same pore diameter, inner wall of which consists of a) starch only, b) starch and aspirin, and c) aspirin only. It is reasonable to assume, however, that the effective pores for disintegration of tablet are a) or b), but not c) since the contact angle between aspirin and water exceeds 90°[38] and it was observed actually that the aspirin tablet formed by direct compression without starch did not disintegrate. It is very natural to consider that the number of effective pore should be more in the tablet in which continuous phase is starch, *i.e.* containing much starch.

Assuming a laminar flow in a capillary and no effect of gravity, the penetrating time of liquid through pore is represented by Eq. (2) derived from Washburn's equation.[11]

$$t=\frac{4\eta L_e^2}{D_c\cdot\gamma\cdot\cos\theta} \qquad (2)$$

where t is time of penetration, η viscosity of liquid, L_e length of capillary, D_c pore diameter, γ surface tension of liquid, and θ contact angle of capillary wall.

When potato starch is used as disintegrator in the tablet of the group Ⅲ, the more rapid disintegration may be expected, since larger contact angle of potato than of corn starch was reported by Matsumaru[38] and the main constituent of capillary wall is estimated as starch. Made comparison between the tablets of aspirin L with corn starch and those with potato starch or the tablets of aspirin M with corn starch and those with potato starch in Fig. 9, the results agreed witn the expectation mentioned qualitatively. The larger swelling rate of corn starch than of potato starch has been reported,[6] therefore, it will be more natural to assume that the intensive disintegration effect of potato starch observed is caused by rapid penetration of water into the porous structure of tablet.

The Effect of Particle Size of Aspirin on Disintegration Time of the Tablets in Group III

It may be concluded from the results given in Fig. 9 that the tablets prepared from aspirin M disintegrated more rapidly than those prepared from aspirin L when

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32) H. Koehler, J. Hirschmann : Deut. Apotheker-Ztg., **102**, 1465 (1962).
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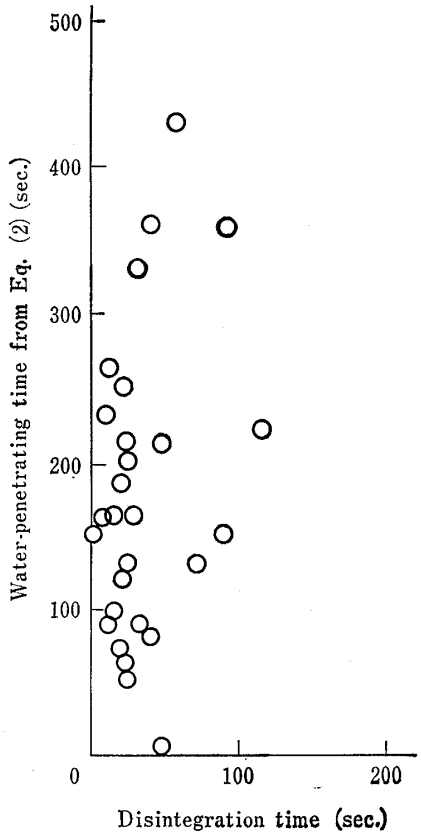

Fig. 10. Relationship between the Calculated Water-penetrating Time from Eq. (2) and the Disintegration Time

the disintegration time of tablets with same pore size was compared. The following consideration was made for the elucidation of this phenomenon.

The relation between the disintegration time (time to maximum surface area from 0-time in Fig. 8) and the water-penetrating time is given in Fig. 10. The water-penetrating time was calculated from Eq. (2) assuming $\eta=0.01$ poise, $\gamma=73$ dyne/cm., $L_e=2.5\times$ tablet thickness, and $\theta=85°$ for corn or 84.5° for potato starch,[38] although the influence of the particle size of aspirin could not be expected on the water-penetrating time. The results given in Fig. 9 and the much faster disintegration than calculated time given in Fig. 10 would suggest the following model of tablet disintegration. The model for the process of tablet disintegration is shown in Fig. 11.

The aspirin particle was mixed with starch grain as mentioned previously. The original particle size of aspirin would be reduced by the compression (aspirin tablets without starch in Table Ⅲ), but, the starch would not penetrate into the capillary newly formed by crushing. Water does not penetrate into a capillary formed between aspirin particles owing to the larger contact angle over 90° at the condition assumed. Therefore it may be expected that the original particle size should be found again when the disintegration proceeds smoothly and rapidly. The result given in Fig. 8 may be the evidence of assumption mentioned above.

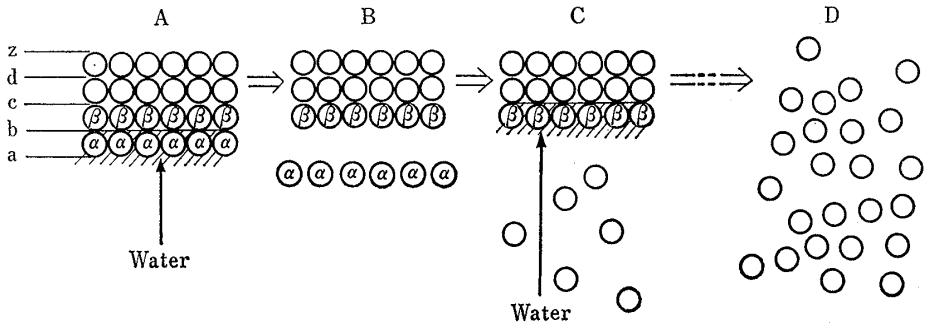

Fig. 11. A Model for the Process of Tablet Disintegration

The structure of tablet may be assumed as shown (A) in Fig. 11 where each particle may represent the original aspirin particle used for tablet formulation and not the actual particle existing in a compressed tablet. The one-directional water penetration is assumed as shown by an arrow in (A). As soon as water penetrates from "a" to "b" in (A), α-particles in the lowest layer separate from the tablet as shown in (B), then α-particles should not concern the process that water penetrates from "b" to "c". The process mentioned above is repeated on β-layer and so on. The number of the layers in a tablet is n, the tortuosity of the capillary in a tablet is 2.5, then the time for water penetration in the tablet may be written as Eq. (3) from Eq. (2).

$$t=\frac{4\eta(2.5\times D_A)^2}{D_c\cdot\gamma\cdot\cos\theta}\times n \qquad (3)$$

Table III. Mean Particle Size of the Ingredients after Compression by Permeametry (μ)[a]

Aspirin		L			M			S		
Compressional force (ton/tablet)		0.50	1.0	2.0	0.50	1.0	2.0	0.50	1.0	2.0
Starch 0%		20.1	13.4	10.0	16.5	14.9	16.0	6.76	5.40	—
Corn starch (%)	2.50	31.9	24.6	21.2	25.5	21.2	19.3	7.61	5.84	—
	5.00	34.5	29.4	25.3	32.0	28.1	24.9	7.83	5.66	—
	10.0	49.6	41.9	33.8	178	33.2	31.8	7.61	5.97	3.47
	20.0	—	51.1	39.8	—	42.6	38.0	8.60	7.01	4.49
	100	15.5	15.3	15.5						
Potato starch (%)	2.50	27.7	23.0	15.2	23.4	19.3	15.6	7.80	5.32	—
	5.00	29.6	25.1	20.6	24.3	21.2	19.8	7.89	5.59	—
	10.0	42.6	29.2	24.3	33.1	25.2	23.4	7.78	5.62	—
	20.0	52.2	42.5	36.3	59.1	28.8	26.7	9.54	6.00	—
	100	33.7	28.2	29.5						

a) Calculated from the air-permeation data using Kozney-Carman's equation.

where D_A is the diameter of aspirin particle in the tablet. As the thickness of the tablet, L, is expressed as

$$L = D_A \times n,$$

then Eq. (4) is obtained from Eq. (3).

$$t = \frac{25\eta}{\gamma} \times \frac{D_A L}{D_e \cdot \cos\theta} \qquad (4)$$

Assuming the equal contact angle, Eq. (4) shows the tendency that the smaller particle size and the larger pore diameter would result in more rapid water penetration. The relation between water-penetrating time calculated by Eq. (4) and disintegration time determined is given in Fig. 12.

The result shown in Fig. 12 may support the assumption mentioned above and the model proposed for the disintegration processes of a tablet.

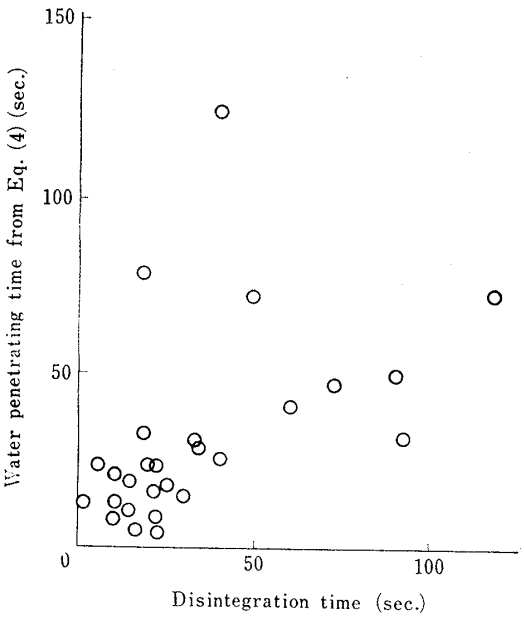

Fig. 12. Relationship between the Calculated Water-Penetrating Time from Eq. (4) and the Disintegration Time

Rate-determinant Process of Tablet Disintegration

From the proceeding discussion, it may be concluded that the process of water penetration into a tablet, rather than the process of separation of particles, determined the rate of disintegration of the tablets in the group III. Water penetration should be accelerated by the lower viscosity and higher surface tension of disintegration medium from Eqs. (2) and (4). The results obtained by some investigators [11,17~20,36] agreed the conclusion mentioned above. It does not mean, however, that starch does not affect the process of separation of ingredient particles, but this process will be finished within much shorter period than the one required for the water-penetrating process.

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