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Influence of Particle Size on Physicochemical Properties of Pharmaceutical Powders. IX.[1] Fluidity of Binary Mixtures of Potato Starch

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Sticky powders cause many troubles in pharmaceutical works. Aoki, *et al.* reported that fluidity of powders influenced on the process of the automatic packing to containers, equality of the packed weight to each container and the sieving rate of them.[3]

In the previous paper, the angle of repose of the mixture of the powder below critical size has been found to be smaller than that above the size.[4,5] The angle of repose of potato starch has also been reported to decrease remarkably by the addition of small proportion of magnesium alumino silicate, while that of the mixture of potato starch and boric acid or aspirin to be comparatively large.[4,6]

In the present work, fluidity of the binary mixtures of potato starch and about twenty kinds of the other pharmaceutical Powders of comparatively small particle diameters is studied and influence of the physical properties of the added powder on fluidity of the mixture is discussed.

Experimental

Specific gravities (ρ) and particle sizes of the used samples are tabulated in Table I. Measurement of specific gravities were made using model 930 Backman air comparison pycnometer. Surface mean diameters of the particles larger than 20μ were obtained by optical microscopic examination, and specific surface diameters of the smaller particles by air permeability method.[7] Carboxymethyl cellulose, calcium carboxymethyl cellulose and riboflavin particles are fibrous or stick-like, and the other particles are granular or blocky by optical microscopy.

One hundred grams of potato starch and addition were mixed for fifteen minutes in the cubic-type mixer rotating with the rate of 30 cycles per minute. Angles of repose (α) were measured by Nogami–Sugiwara's method (plate: 3×10 cm)[8], and the volume per gram of a sample in loosest packing (Vs) by the JIS standard funnel method.[9] The data of α and Vs for the mixtures of boric acid, aspirin or magnesium alumino silicate are the same as referred to in the previous paper.[4] Five grams of a sample in a measuring cylinder (1 cm in diameter) were tapped once a second with a tapping machine from the height of 1 cm. The same apparatus as that of Hayashi, *et al.* was used for the shear strength examination. Samples were compressed with the weight of 400 g and then by a hand in order to be packed as closely as possible before the measurement. Water was dropped from a burette at the rate of 1.2 g/min.[10] Surface area was measured by air permeability method.[7]

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1) Part VIII: N. Kaneniwa, A. Ikekawa, T. Ozaki, C. Shinya, N. Sugimoto, and Y. Hozumi, *Yakugaku Zasshi*, **88**, 1642 (1968).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) M. Aoki, S. Ogawa, S. Hayashi, M. Hirayama, and H. Nakajima, *Yakuzaigaku*, **27**, 98 (1967); M. Aoki, S. Ogawa, S. Hayashi, and M. Hirayama, *ibid.*, **27**, 183 (1967); K. Asahina, E. Sakamoto, A. Sugimura, and Y. Imai, *ibid.*, **27**, 319 (1968).
4) A. Ikekawa and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **16**, 1543 (1967).
5) M. Aoki and S. Hayashi, *Yakugaku Zasshi*, **87**, 1164 (1967).
6) D.J. Craik, *J. Pharm. Pharmacol.*, **10**, 73 (1958); D.J. Craik and B.F. Miller, *ibid.*, **10**, 136T (1958); M. Noda, C. Hayashi, M. Ito, S. Fukui, and S. Fujita, *Yakuzaigaku*, **20**, 50 (1960); M. Aoki, S. Ogawa, S. Hayashi, and M. Hirayama, *ibid.*, **27**, 18 (1967).
7) E. Suito, M. Arakawa, and M. Takahashi, *Kogyo Kagaku Zasshi*, **59**, 307 (1956).
8) H. Nogami, M. Sugiwara, and S. Kimura, *Yakuzaigaku*, **25**, 260 (1965).
9) JIS Z 2502–1958.
10) H. Hayashi and S. Minami, *Yakugaku Zasshi*, **84**, 229 (1964).

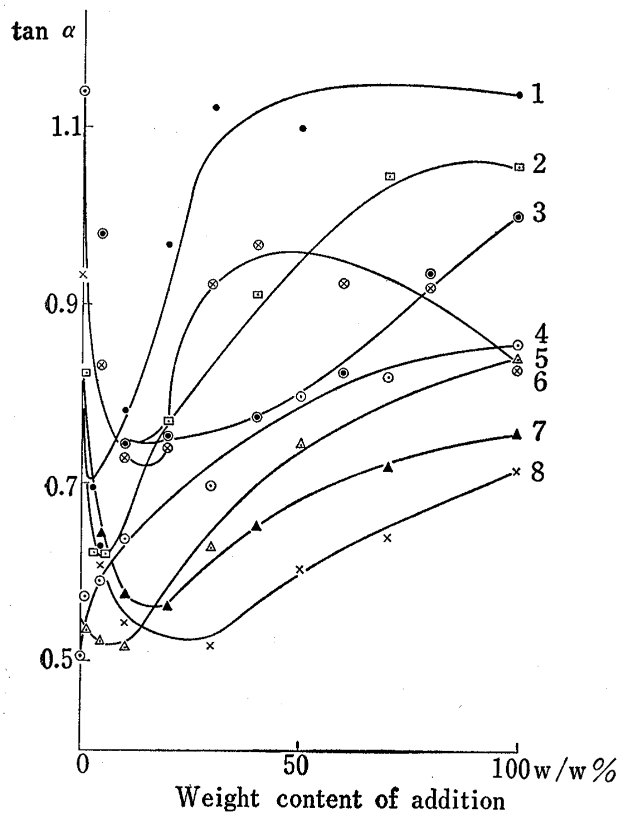

Fig. 1. Angle of Repose of Binary Mixture of Potato Starch in Various Proportions

addition
1 magnesium carbonate
2 kaoline
3 talc
4 magnesium oxide
5 dried aluminium hydroxide gel granules
6 sodium benzoate
7 magnesium stearate
8 synthetic aluminium silicate

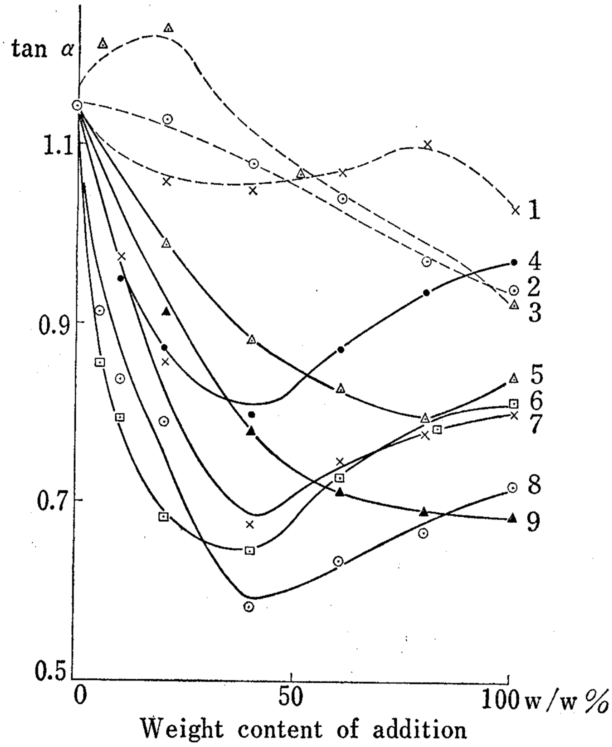

Fig. 2. Angle of Repose of Binary Mixture of Potato Starch in Various Proportions

addition
1 sublimed sulfur
2 stearic acid
3 riboflavin
4 carboxymethyl cellulose
5 powdered agar
6 dibasic calcium phosphate
7 calcium carboxymethyl cellulose
8 sodium stearate
9 powdered acacia

TABLE I

Sample	ρ(g/cm^3)	Mean diameter (μ)	α	V_s	K	C_i, μ_i	S_w
Potato starch	1.57	30.7					
Magnesium oxide	2.75	0.4	A	A	A	A	A
Magnesium carbonate	2.13	0.5	A	A	A	A	A
Magnesium alumino silicate	1.92	0.5	A	A	A	A	A
Kaoline	3.10	0.9	A	A	A	A	A
Talc	3.10	1.6	A	A	B_c	A	A
Dried aluminium hydroxide gel granules	2.09	321	A	A	A	B_a	A
Synthetic aluminium silicate	2.09	3.8	A	A	A	B_a	B
Magnesium stearate	1.21	0.6	A	A	A	B_a	A
Sodium benzoate	1.73	1.0	A	A	A	A	A
Sodium stearate	1.24	1.4	B	A	B_c	B_c	A
Dibasic calcium phosphate	2.56	7.9	B	B	A	B_a	C
Powdered acacia	1.59	17.3	B	B	A	A	B
Carboxymethyl cellulose	1.61	172	B	B	B_a	A	
Calcium carboxymethyl cellulose	1.68	119	B	B	C	A	
Powdered agar	1.60	15.1	B	B	C	B_c	B
Riboflavin	1.32	4.0	C	B	C	A	B
Stearic acid	1.07	112	C	C	B_c	C	
Sublimed sulfur	2.14	14.6	C	C	C	C	B
Boric acid	1.44	35.9	C	C	A	C	C
Aspirin (crushed)	1.35	38.9	C	C	C	B_c	C

Results and Discussion

1. Angle of Repose

It is suggested from Fig. 1 and 2 that powders added to potato starch are classified into the following three types.

Type A: The angle of repose of potato starch decreases remarkably by the addition of small proportion below 10 w/w%.[4,6]

Type B: The angle of repose of the mixture containing 10 w/w% of the addition is still large but that of the mixture containing about 40 w/w% of it is comparatively small.

Type C: The angle of repose of the mixture is comparatively large at any proportion.[4]

The classification of the powders added to potato starch based on α is shown in Table I.

2. The Loosest Packing

Fig. 3 and 4 show the following tendency. Porosity (ε) of potato starch decreases remarkably by the addition of small amount of the powder of type A. Although porosity of the mixture containing small proportion of the powder of type B is still large, that is smaller than the arithmetic mean value of ε of starch and the addition, while that of type C is larger than the arithmetic mean value.

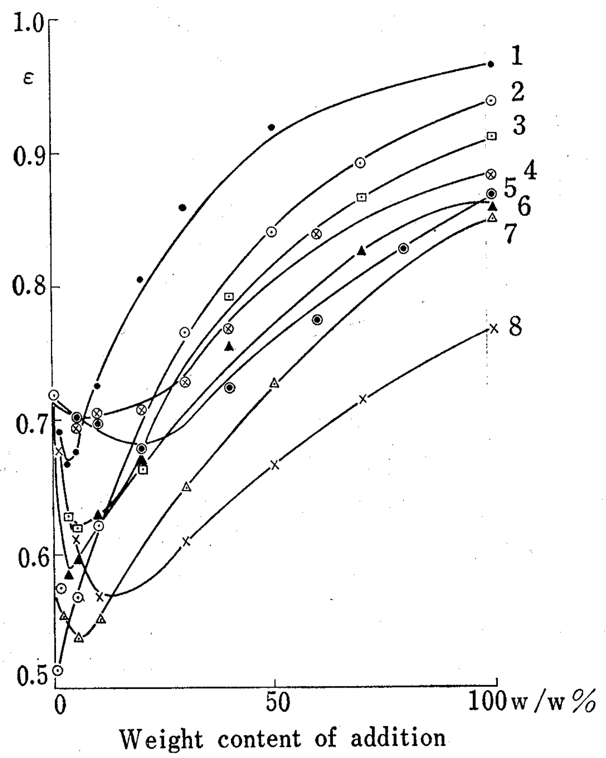

Fig. 3. Porosity in Loosest Packing of Binary Mixture of Potato Starch in Various Proportions

addition
1 magnesium carbonate
2 magnesium oxide
3 kaoline
4 sodium benzoate
5 talc
6 magnesium stearate
7 dried aluminium hydroxide gel granules
8 synthetic aluminium silicate

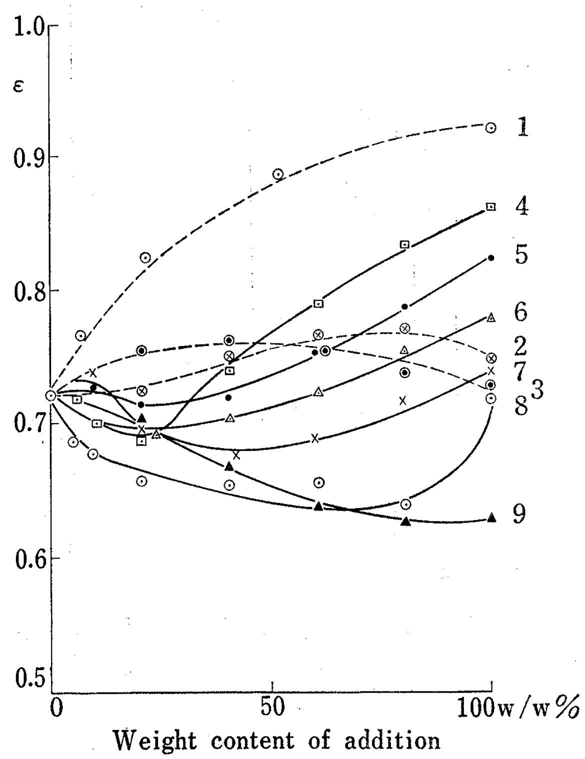

Fig. 4. Porosity in Loosest Packing of Binary Mixture of Potato Starch in Various Proportions

addition
1 riboflavin
2 sublimed sulfur
3 stearic acid
4 dibasic calcium phosphate
5 carboxymethyl cellulose
6 powdered agar
7 calcium carboxymethyl cellulose
8 sodium stearate
9 powdered acacia

Umeya's view on the packing of the binary mixtures of coarse and fine particles are as follows. The particles of them are supposed to be of the same material, uniform in size, spherical and the ratio of the particle size of the coarse powder to that of the fine powder (D_c/D_f) to be large enough. The volume per gram of coarse or fine powder in loosest packing is represented by the point of c′ or f′, respectively, and the true volume per gram (V) of the coarse powder by the point of c in Fig. 5. The value of V_s of the binary mixture varies on the line of c′ef′ with the increase of the proportion of the fine powder. The values of V_s and V of the coarse powder decrease on the line of c′F and cF, respectively, with the increase of the weight content of the fine powder. Therefore, S_1L_1 stands for the void volume per gram of the coarse powder and S_1M_1 for V_s of the fine powder. Then at the point of O_1, fine particles fill up the void space between coarse particles by S_1M_1 and coarse particles still have the void space of L_1M^1. At the point of O_2, the void space of coarse particles can admit only S_2L_2 of V_s of the fine particles and the remaining L_2M_2 is protruded. At the point of O_3, the void space of the coarse particles is completely filled up with all of V_s of the fine particles, and here the value of V_s of the mixture is minimum. The above view is applicable to the real mixtures of 7—30 of D_c/D_f. The point e approaches to the middle of c′f′, as the value of D_c/D_f approaches to one.[11]

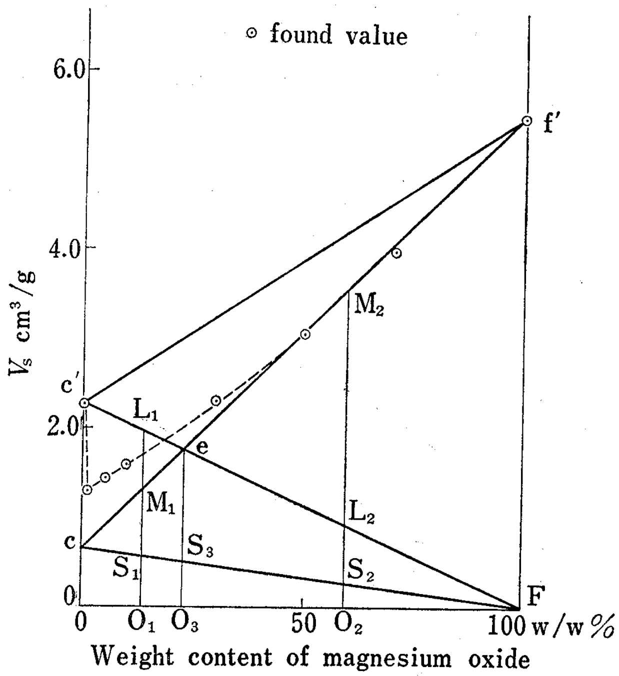

Fig. 5. Application of Umeya's Plot to Loosest Packing of Mixture of Potato Starch and Magnesium Oxide

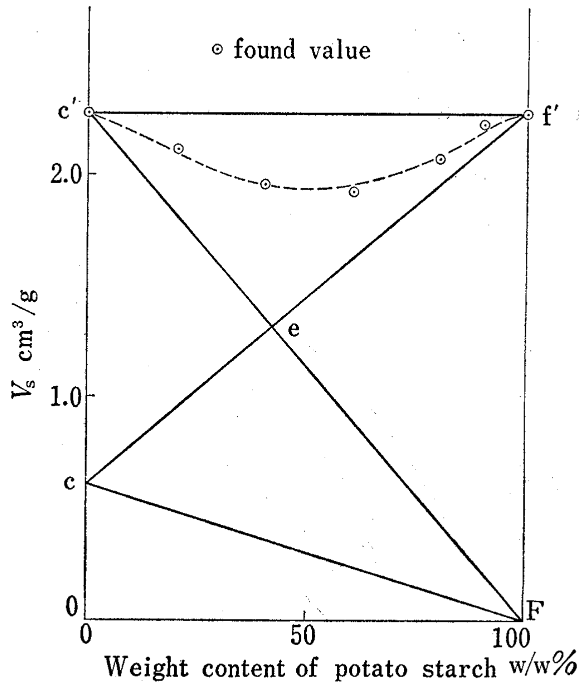

Fig. 6. Application of Umeya's Plot to Loosest Packing of Mixture of Potato Starch and Calcium Carboxymethyl Cellulose

By the application of Umeya's plot to our experimental results,[12] the powders added to potato starch are classified into the following three types, as the examples shown in Fig. 5, 6 and 7 (See Table I).

Type A: The found value of V_s of the mixture is smaller than the value on the line of c′e, when the weight content of the addition is small.

Type B: The found value of V_s of the mixture is within or on the lines of Δ c′ef′.

Type C: The found value of V_s of the mixture is larger than the value on the line of c′f′.

11) K. Umeya, *Huntai Kogaku Kenkyu Kaishi*, **2**, 205 (1965).
12) M. Aoki, S. Ogawa, S. Hayashi, M. Hirayama, and H. Nakajima, *Yakuzaigaku*, **27**, 322 (1968).

The classification of powders based on V_s is pararell to that based on α, in Table I.

Since the physicochemical property of the surface of potato starch particle is different from that of the added particle, shapes are not spherical and particles have size distribution in the real case, it may be reasonable that the value of V_s of the mixture is larger than the value on the line of c′f′, if the friction between the starch particle and the added particle is much larger than that between starch particles. Addition of small proportion of the powder of type A may influence markedly on physicochemical properties of starch particles and cause the decrease of the friction between starch particles.

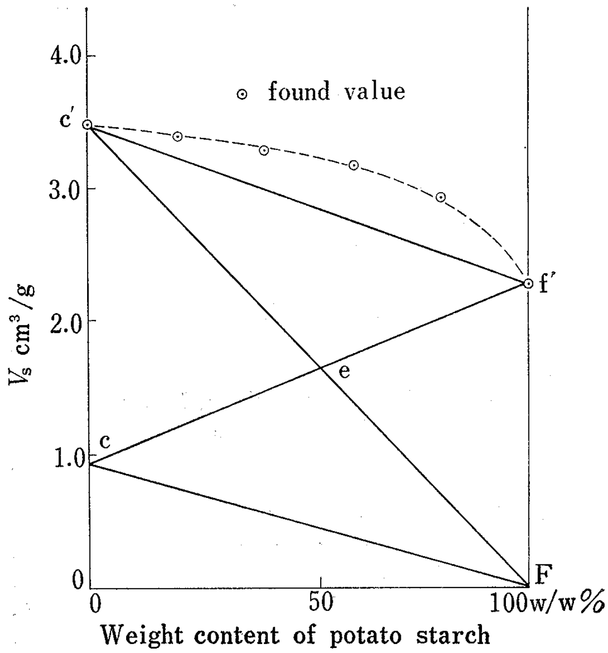

Fig. 7. Application of Umeya's Plot to Loosest Packing of Mixture of Potato Starch and Stearic Acid

3. Tapping

Equation (1) applied comparatively well to our data of tapping.[13)]

$$n/C = 1/a \cdot b + n/a \cdots \text{Kawakita's equation} \quad (1)$$

$$C = (V_o - V_n)/V_o$$

a, b: Constants

V_o: The volume per gram of a sample before tapping

V_n: The volume per gram of a sample after n tappings

Equation (2) is obtained by the transformation of the equation (1) using the term of ε_n, where ε_n is the porosity of a sample after n tappings.

$$-d\varepsilon_n/dn = \mathrm{K} \cdot \varepsilon_n^2, \ K = b(1-a)/a \quad (2)$$

In the previous papers,[13,14)] tapping constant K in the equation (2) is suggested to be smaller for the particles of larger friction. By the comparison of the value of K of the mixture (K_m) with those of potato starch (K_s) and the addition (K_a) in Table II, the following classification is applicable to the additions (See Table I).

Type A: $K_m \geq K_s, K_a$

Type B_a: $K_a < K_c \leq K_m < K_s$, or $K_s < K_c \leq K_m < K_a$

Type B_c: $K_a \leq K_m < K_c < K_s$, or $K_s \leq K_m < K_c < K_a$

Type C: $K_m < K_s, K_a$

K_c: The arithmetic mean value of K_s and K_a based on the ratio of the surface area of starch to that of the addition.

In Table I and II, the value of K_m for talc is small, in spite of the small values of α and V_s of the mixture, while that for boric acid is comparatively large, in comparison with the values

13) N. Kaneniwa and A. Ikekawa, *Yakuzaigaku*, **27**, 237 (1967).
14) A. Ikekawa and N. Kaneniwa, *Zairyo*, **17**, 480 (1968).

of a and V_s of the mixture. In the other powders, the classification based on the value of K corresponds with those based on a and V_s.

TABLE II

Sample	K_s, K_a	Weight content of addition	K_m	K_c
Potato starch	0.11			
Magnesium oxide	0.12	1 w/w%	0.87	
Magnesium carbonate	0.13	5	0.19	
Magnesium alumino silicate (NFL 1)	0.09	1	0.85	
Kaoline	0.06	5	0.29	
Talc	0.03	10	0.05	0.08
Dried aluminium hydroxide gel granules	0.81	5	1.15	
Synthetic aluminium silicate	0.14	30	0.26	
Magnesium stearate	0.12	20	0.12	0.12
Sodium benzoate	0.18	10	0.93	
Sodium stearate	0.61	40	0.15	0.65
Dibasic calcium phosphate	0.10	40	0.19	
Powdered acacia	0.55	20	0.65	
Carboxymethyl cellulose	0.24	40	0.16	0.12
Calcium carboxymethyl cellulose	0.35	40	0.10	
Powdered agar	0.32	20	0.04	
Riboflavin	0.05	20	0.03	
Stearic acid	0.27	40	0.12	0.22
Sublimed sulfur	0.17	20	0.03	
Boric acid	0.08	20	0.11	
Aspirin (crushed)	0.08	20	0.03	

4. Shear Strength Examination

Equation (3) applied comparatively well to our data of the shear strength examination.

$$F=\mu_i W+C_i \qquad (3)$$

F : Shear strength for a sample

W: The compressive load vertically imposed on the sample in the lower box

μ_i : Internal frictional coefficient

C_i: Cohesive force between particles

In Table III, the values of μ_i and C_i for the mixture (μ_{im}, C_{im}) are nearly pararrel to that of the angle of repose of the mixture, in spite of the variety of the relative humidity in which the measurement was made.

The values of μ_i and C_i for potato starch (μ_{is}, C_{is}) are dependent on R.H. Okada, *et al* found the following relations between μ_{is} and C_{is} and the moisture content of a sample (w).[15]

$$\mu=\mu_0 \exp(nw) \qquad (4)$$

$$C=C_0+mw \qquad (5)$$

n, m, μ_0, C_0: Constants

The values of μ_{is} and C_{is} in various R.H. were presumed by the equations (4) and (5). By the comparison of μ_{im} and C_{im} with μ_{is}, μ_{ia}, μ_{ic}, C_{is}, C_{ia} or C_{ic}, the following classification is made, where μ_{ia} and C_{ia} stand for μ_i and C_i of addition and μ_{ic} and C_{ic} for those of the arithmetic mean values of μ_{is} and μ_{ia} or C_{is} and C_{ia} based on the ratio of the surface area of the addition to that of starch (See Table I).

15) S. Okada and T. Abe, *Yakugaku Zasshi*, **83**, 39 (1963).

TABLE III

Sample	R.H. (%)	C_{is}, C_{ia}	μ_{is}, μ_{ia}	Weight content of Addition (w/w %)	C_{im}	μ_{im}
Potato starch	37	3.8	0.36			
	75	5.4	0.60			
Magnesium oxide	75	6.5	0.55	0.5	3.2	0.23
Magnesium carbonate	63	5.7	0.44	3	3.3	0.30
Magnesium alumino silicate (NFL 1)	73	5.5	0.60	1	3.1	0.27
Kaoline	50	4.6	0.50	5	3.3	0.31
Talc	45	3.0	0.37	20	3.0	0.32
Dried aluminium hydroxide gel granules	52	3.0	0.32	5	3.2	0.30
Synthetic aluminium silicate	45	2.5	0.27	10	2.1	0.31
Magnesium stearate	32	5.8	0.39	3	4.1	0.35
Sodium benzoate	67	8.3	0.75	10	2.0	0.33
Sodium stearate	50	3.4	0.36	20	6.2	0.32
Dibasic calcium phosphate	55	1.2	0.35	20	3.0	0.26
Powdered acacia	78	3.5	0.28	40	3.5	0.27
Carboxymethyl cellulose	60	2.5	0.36	40	1.9	0.36
Calcium carboxymethyl cellulose	57	3.0	0.32	40	3.0	0.32
Powdered agar	75	2.0	0.33	20	4.6	0.30
Riboflavin	55	4.1	0.45	20	3.6	0.37
Stearic acid	45	2.3	0·32	40	5.9	0.43
Sublimed sulfur	35	5.0	0.49	40	7.7	0.54
Boric acid	80	7.1	0.54	30	7.3	0.81
Aspirin (crushed)	71	3.4	0.48	20	5.6	0.46

C_{is}, C_{ia}, C_{im} : $\times 10^3$ dyne/cm^2

Type A : $\mu_{im} \leq \mu_{is}, \mu_{ia}$, $C_{im} \leq C_{is}, C_{ia}$

Type B_a: $\mu_{ia} < \mu_{im} \leq \mu_{ic} < \mu_{is}$, or $\mu_{is} < \mu_{im} \leq \mu_{ic} < \mu_{ia}$, $C_{ia} < C_{im} \leq C_{ic} < C_{is}$ or $C_{is} < C_{im} \leq C_{ic} < C_{ia}$

Type B_c: $\mu_{ia} < \mu_{ic} \leq \mu_{im} < \mu_{is}$ or $\mu_{is} < \mu_{ic} \leq \mu_{im} < \mu_{ia}$, $C_{ia} < C_{ic} < C_{im} < C_{is}$ or $C_{is} < C_{ic} < C_{im} < C_{ia}$

Type C : $\mu_{im} > \mu_{is}, \mu_{ia}$, $C_{im} > C_{is}, C_{ia}$

In Table I, talc, calcium carboxymethyl cellulose and riboflavin belong to type A on the shear strength examination, in spite of the small values of K_m, while the opposite is the case for boric acid. For the other powders, classification based on μ_{im} and C_{im} is pararrel to that based on the tapping.

5. Examination of Surface Area and Some Considerations

Additions are also classified into the following three types based on the values of surface area, as shown in Fig. 8 (See Table I).

Type A: $S_{wm} < S_{wc}$[4,16]

Type B: $S_{wm} \approx S_{wc}$

Type C: $S_{wm} > S_{wc}$[17]

S_{wm}: The found value of the surface area of the mixture.

S_{wc} : The arithmetic mean value of the surface area of starch and addition.

If no interaction exists between a starch particle and an added particle, S_{wm} is expected to be equal to S_{wc}. The mixture of type C on S_{wm} generally seems to be sticky in Table I. Probably correct value is not obtained for the surface area of the mixture of type C due to the deficiency in uniformity of the packing structure and so on, by air permeability method.[17]

16) O. Ohodaira, *Yakuzaigaku*, **25**, 195 (1965).
17) K. Shimizu, *Journal of Hokkaido Gakugei University*, **9**, 19 (1958).

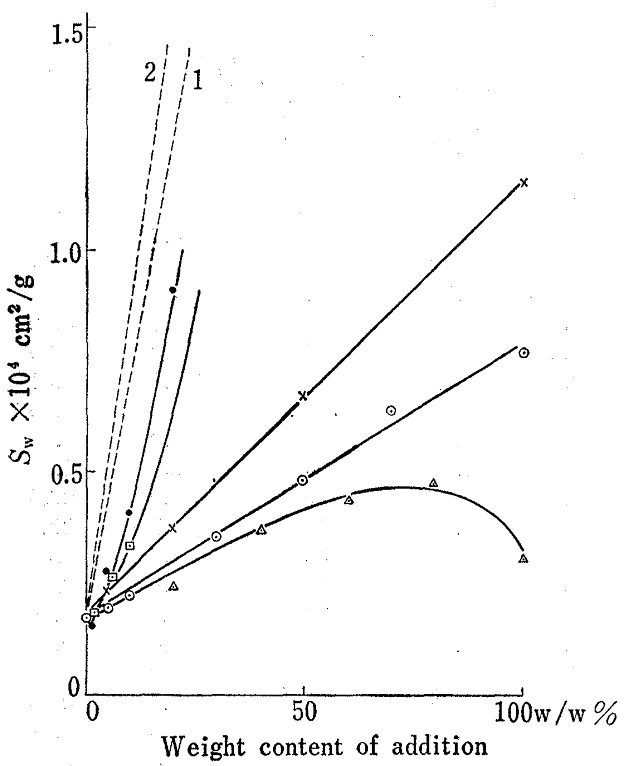

Fig. 8. Surface Area of Binary Mixtures of Potato Starch in Varying Proportions

——— S_{wm} addition
⊙ synthetic aluminium silicate
× riboflavin
△ dibasic calcium phosphate
⊡ magnesium oxide
● magnesium alumino silicate (NFL1)

- - - - - S_{wc} addition
1 magnesium oxide
2 magnesium alumino silicate (NFL1)

The particles of type A on S_{wm}, whose mixture generally shows good fluidity in Table I, are smaller than 2μ, with the exception of dried aluminium hydroxide gel granules. In the previous paper,[4] the angle of repose of the mixture containing small proportion of boric acid or aspirin below critical size is smaller than that of the mixture of them above the critical size. The above findings suggest that the fluidity of the mixture depends on the particle size of the addition. It is also suggested that the adhesive force of the added particle to a starch particle is one of the important parameters to control the fluidity of the mixture.[18] The decrease of the surface area of the mixture of type A may be due to the strong adhesive force of the added particle to the surface of a starch particle.

The shape and the physicochemical property of the surface of the added particle are also suggested to influence on fluidity of the mixture in Table I. In the previous paper,[4] NS1 and NSG1 are both magnesium alumino silicate granules of nearly the same mean diameter, but the former belongs to type A and the latter to type B on α and V_s of the mixture. Furthermore, NSG2, obtained by drying NSG1, belongs to type C on V_s.

In the previous paper,[4] magnesium alumino silicate particle is suggested to take moisture out of a starch particle by the measurement of the contact angles of liquids to the mixture. But in the present work, no suggestion was obtained from the contact angle measurement.

Acknowledgement Thanks are due to Miss T. Ozaki and Miss Y. Hozumi, students of School of Pharmaceutical Sciences, Showa University, for their experimental assistance.

18) N. Kaneniwa and A. Ikekawa, *Yakuzaigaku*, **28**, 29 (1968).