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Influence of Particle Size on Physicochemical Properties of Pharmaceutical Powders. IV.[1] On Packing of Pharmaceutical Powders. (2)[1]

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Fifteen kinds of pharmaceutical powders are tapped in air and in solvents, and the following equation is proposed for the tapping of these samples.

$$d(\varepsilon_0-\varepsilon_n)/dn=p\{\log 1/(\varepsilon_0-\varepsilon_n)\}^q-r$$

Coefficients p, q and r are related to the apparent friction, that is, internal friction and cohesive force between particles of powders.

In the previous paper, about ten kinds of tapping formulas and powder compression formulas were discussed for the tapping of fifteen kinds of organic and inorganic pharmaceutical powders. Five of them, proposed by Kuno, Kawakita, Yoshioka, Balshin and Jones, were found to apply comparatively well, but no formula was applicable for all the cases investigated in our work.[1]

In this paper, a new tapping formula will be proposed and parameters will be discussed on the basis of the results obtained from studies on fluidity and packing of sodium borate and boric acid powders.[3-5]

Table I

Sample	Surface mean diameter (μ)	Specific gravity (g/cm^3)
Zinc oxide	below 1	5.47
Kaoline	1.7	2.35
Bentonite	1.8	2.23
Magnesium oxide	3.5[a]	2.75
Heavy magnesium oxide	1.5[a]	3.65
Dibasic calcium phosphate	24.8	2.31
Spray-dried magnesium alumino silicate	45.7	2.01
Synthetic aluminium silicate	1.9	2.01
Lactose	13.8	1.54
Spray-dried lactose	64.9	1.53
Microcrystalline cellulose	64.9	1.55
Carboxymethyl cellulose[b]	172	1.53
Carboxymethyl cellulose calcium[b]	119	1.50

a) The particle sizes of magnesium oxide and heavy magnesium oxide powders are reported to be about 0.1 μ, but by optical microscopy, agglomerate of the particles may be measured.

b) By optical microscopy, the shape of particles of carboxymethyl cellulose and carboxymethyl cellulose calcium powders are fibrous and the other powder particles larger than 10 μ are granular.

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1) Part III: N. Kaneniwa and A. Ikekawa, *Yakuzaigaku*, **27**, 232 (1967).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo*.
3) N. Kaneniwa, A. Ikekawa, and H. Aoki, *Chem. Pharm. Bull.* (Tokyo), **15**, 1441 (1967).
4) A. Ikekawa, H. Aoki, K. Masukawa, and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **15**, 1626 (1967).
5) A. Ikekawa and N. Kaneniwa, *Zairyo*, **16**, 314 (1967).

Experimental

Experimental data discussed in this paper are the same as referred to in the previous paper.[1]

Sodium borate powders are tapped in toluene and carbon tetrachloride, boric acid in carbon disulfide, and the other thirteen kinds of powders tabulated in Table I in cyclohexane and air.

Results and Discussion

Distribution of porosity in the layer of fine powders in a measuring cylinder was examined by the tapping of the sample composed of the several layers of starch (white) and bentonite (gray), and that of large particles by the sample of the several layers of brown sands and fused alumina (white alumdum). Particles in the upper layer were packed more compactly than those in the lower layer. Porosity of the powders at the top of the layer was approximately by 10—20 percents smaller than that of the powders at the bottom of the layer. In this paper, mean value of porosity of the total layer is to be discussed.

In the previous papers,[4,5] $(\varepsilon_0-\varepsilon_c)$ has been suggested to be directly related to the cohesive force between particles of powders, where ε_0 is the porosity in loosest packing of the particles smaller than the critical size and ε_c that of the larger particles. Furthermore, Yoshioka, *et al.*[6] proposed the following relation between the bulk density of powders ρ_σ and the imposed pressure σ,

$$\rho_\sigma=\rho_0(1+k\sigma^n),$$

where ρ_0 is the bulk density without imposed pressure and k, n are constants. If ε_n and ρ_n are the porosity and the bulk density after n tappings, respectively, and ρ is the true density of the samples, the following relation applies between them.

$$\varepsilon_0-\varepsilon_n=1/\rho\cdot(\rho_n-\rho_0)$$

The above findings suggest that $(\varepsilon_0-\varepsilon_n)$ is the value related to the force imposed on the powders in the loosest state, in order to obtain the state corresponding to ε_n. Therefore $(\varepsilon_0-\varepsilon_n)$ might be related to the work done by n tappings against the friction of powders in order to transform packing constitution. Then, the gradient of the tangent line of the $(\varepsilon_0-\varepsilon_n)-n$ curve, $d(\varepsilon_0-\varepsilon_n)/dn$, might concern the work done by one tapping at each point of the curve. As shown in Fig. 1, the value of $d(\varepsilon_0-\varepsilon_n)/dn$ decreases gradually with the increase of $(\varepsilon_0-\varepsilon_n)$, for the tapping effect opposes the force imposed on the loosest state.

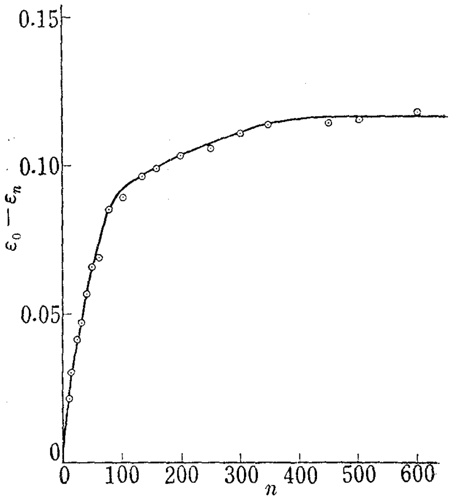

Fig. 1. Relation between Porosity and Tapping Number n for Tapping of Sodium Borate Powders (Mean Particle Diameter: 279 μ) in Carbon Tetrachloride

The relation between $(\varepsilon_0-\varepsilon_n)$ and $d(\varepsilon_0-\varepsilon_n)/dn$ is now investigated. Straight lines are obtained for all cases by the log–log plot of $d(\varepsilon_0-\varepsilon_n)/dn$ and log $1/(\varepsilon_0-\varepsilon_n)$, if the axis of $d(\varepsilon_0-\varepsilon_n)/dn$ is removed adequetly to plus direction, as shown in Figs. 2 and 3 for some examples. Consequently the relation between $d(\varepsilon_0-\varepsilon_n)/dn$ and $(\varepsilon_0-\varepsilon_n)$ is represented as follows.

$$d(\varepsilon_0-\varepsilon_n)/dn=p\{\log 1/(\varepsilon_0-\varepsilon_n)\}^q-r \quad (1)$$

$p,\ q,\ r$: Constants

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[6] N. Yoshioka and K. Tsuzuki, *J. Res. Assoc. Powder Techn.*, **1**, 23 (1964).

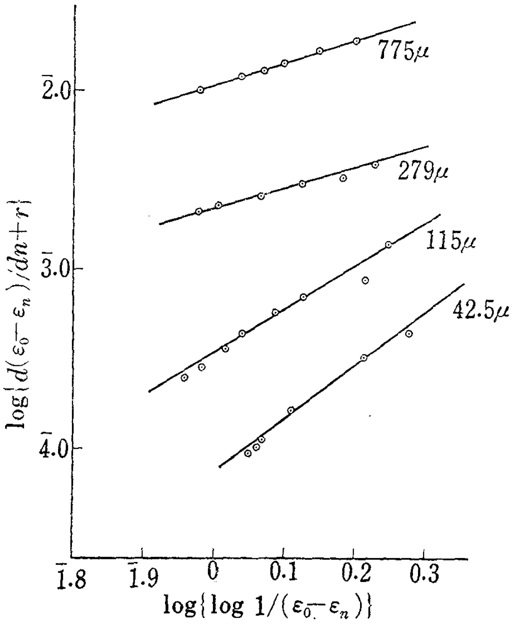

Fig. 2. Relation between $(\varepsilon_0-\varepsilon_n)$ and $d(\varepsilon_0-\varepsilon_n)/dn$ for Tapping of Sodium Borate Powders in Carbon Tetrachloride

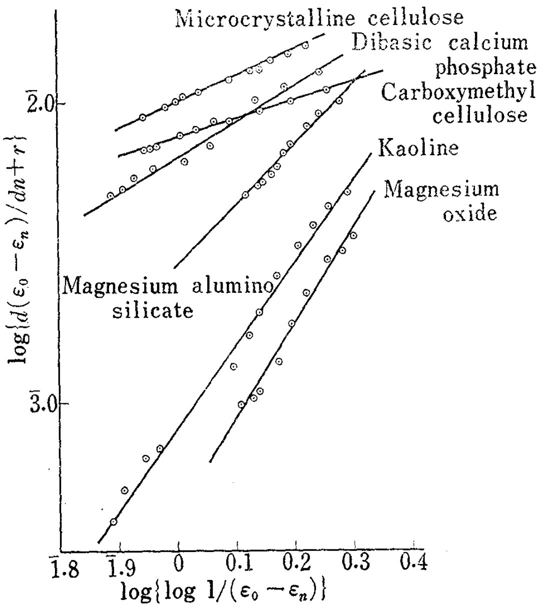

Fig. 3. Relation between $(\varepsilon_0-\varepsilon_n)$ and $d(\varepsilon_0-\varepsilon_n)/dn$ for Tapping of Pharmaceutical Powders in Air

Closest packing is obtained by sufficient tapping. The numerical values of $(\varepsilon_0-\varepsilon_f)$ are calculated by substituting zero for $d(\varepsilon_0-\varepsilon_n)/dn$ in the equation (1), where ε_f is the porosity at the closest packing. Equation (1) is proved to be adequate by the identity of the calculated and experimentally obtained values of $(\varepsilon_0-\varepsilon_f)$, as shown in Table II and III.

TABLE II

Sample	Sodium borate		Sodium borate		Boric acid	
Solvent	Carbon tetrachloride		Toluene		Carbon disulfide	
Mean particle dameter (μ)	$(\varepsilon_0-\varepsilon_f)_f$	$(\varepsilon_0-\varepsilon_f)_c$	$(\varepsilon_0-\varepsilon_f)_f$	$(\varepsilon_0-\varepsilon_f)_c$	$(\varepsilon_0-\varepsilon_f)_f$	$(\varepsilon_0-\varepsilon_f)_c$
42.5	0.210	0.210	0.221	0.216		
68.5					0.276	0.284
81.0	0.272	0.270	0.157	0.158	0.171	0.162
96.5	0.244	0.240	0.145	0.137	0.185	0.190
115	0.237	0.256	0.120	0.115	0.177	0.169
137	0.216	0.221	0.110	0.101	0.149	0.151
163	0.204	0.208	0.083	0.078	0.150	0.151
214	0.170	0.140	0.073	0.070	0.140	0.141
235	0.141	0.152	0.082	0.078	0.130	0.134
279	0.125	0.122	0.079	0.077	0.117	0.113
324	0.147	0.151	0.082	0.078	0.117	0.113
385	0.121	0.120	0.081	0.081	0.095	0.103
460	0.120	0.110	0.069	0.070	0.097	0.098
545	0.114	0.119	0.069	0.069		
650	0.129	0.131	0.068	0.073		
775	0.112	0.111	0.068	0.073		

First of all, we investigated parameters p, q and r for sodium borate and boric acid powders tabulated in Table IV and discussed the influence of cohesive force and internal friction between particles of powders on these parameters.

TABLE III

Solvent Sample	Air $(\varepsilon_0-\varepsilon_f)_f$	Air $(\varepsilon_0-\varepsilon_f)_c$	Cyclohexane $(\varepsilon_0-\varepsilon_f)_f$	Cyclohexane $(\varepsilon_0-\varepsilon_f)_c$
Zinc Oxide	0.052	0.054	0.031	0.031
Kaoline	0.166	0.176	0.058	0.059
Bentonite	0.133	0.133	0.090	0.087
Magnesium oxide	0.052	0.052	0.029	0.029
Heavy magnesium oxide	0.057	0.057	0.042	0.058
Dibasic calcium phosphate	0.167	0.169	0.191	0.186
Magnesium alumino silicate	0.050	0.048	0.067	0.065
Synthetic aluminium silicate	0.141	0.140	0.103	0.103
Microcrystalline cellulose	0.157	0.196	0.106	0.108
Carboxymethyl cellulose	0.135	0.135	0.133	0.133
Carboxymethyl cellulose calcium	0.147	0.149	0.152	0.151
Lactose	0.145	0.145	0.204	0.214
Spray-dried lactose	0.130	0.131	0.160	0.165

TABLE IV

Sample Solvent Mean particle diameter (μ)	Sodium borate Carbon tetrachloride p	 q	 r	Sodium borate Toluene p	 q	 r	Boric acid Carbon disulfide p	 q	 r
42.5	0.84×10^{-4}	2.68	0.30×10^{-4}	2.36×10^{-5}	2.04	1.00×10^{-5}			
68.5							3.70×10^{-4}	3.04	0.50×10^{-4}
81.0	1.85	2.49	0.45	12.4	1.95	8.10	4.25	2.76	2.80
96.5	2.02	2.09	0.74	21.2	1.74	15.6	6.82	2.63	2.88
115	3.51	2.19	1.11	59.2	1.20	53.5	15.0	2.25	8.35
137	3.72	1.93	1.65	104	1.19	101	15.7	2.40	9.85
163	5.21	1.94	2.48	355	1.08	398	43.8	1.90	30.2
214	11.7	1.56	7.80	406	0.96	467	62.5	1.68	48.0
235	16.6	1.27	14.2	353	1.20	401	62.1	1.55	48.7
279	22.1	1.02	20.2	462	0.83	504	54.3	1.80	49.2
324	50.2	1.11	40.4	536	0.97	600	56.0	1.74	50.8
385	68.5	1.13	62.3	355	1.26	396	101	1.80	108
460	73.1	1.31	69.2	578	0.90	657	186	1.76	189
545	77.3	1.23	69.8	513	1.02	598			
650	101	1.04	89.0	499	1.16	580			
775	106	1.28	99.5	449	1.07	496			

In all cases, p and r conspicuously decreased and q increased with decrease of D in the region of small diameter. By the logarithmic plot of p, q and r *vs* D, the presence of the critical particle size is also found for p, q and r in all cases as shown in Fig. 4, and therefore, the following equations apply between p, q, r and D.

$$\left.\begin{array}{ll} D\leqq D_{cp} & p=a_p\exp(b_pD) \\ D\geqq D_{cp} & p=a_p'\exp(b_p'D) \end{array}\right\} \qquad (2)$$

$$\left.\begin{array}{ll} D\leqq D_{cq} & q=a_q\exp(-b_qD) \\ D\geqq D_{cq} & q=a_q'\exp(-b_q'D) \end{array}\right\} \qquad (3)$$

$$\left.\begin{array}{ll} D\leqq D_{cr} & r=a_r\exp(b_rD) \\ D\geqq D_{cr} & r=a_r'\exp(b_r'D) \end{array}\right\} \qquad (4)$$

$a_p,\ a_p',\ a_q,\ a_q',\ a_r,\ a_r',\ b_p,\ b_p',\ b_q,\ b_q',\ b_r,\ b_r',\ D_{cp},\ D_{cq},\ D_{cr}$: Constants

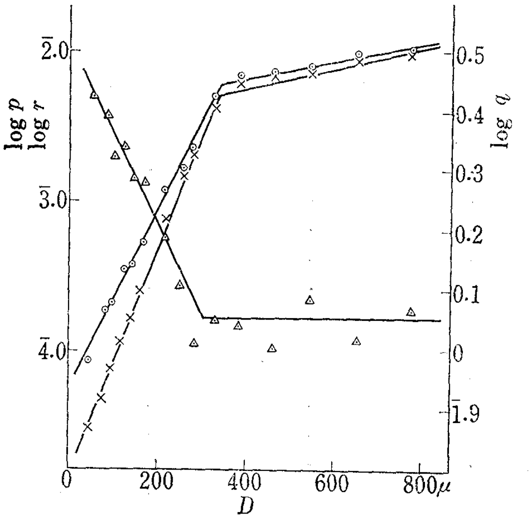

Fig. 4. Influence of Particle Size on Parameters p, q and r for Tapping of Sodium Borate Powders in Carbon Tetrachloride

—⊙— p, —△— q, —×— r

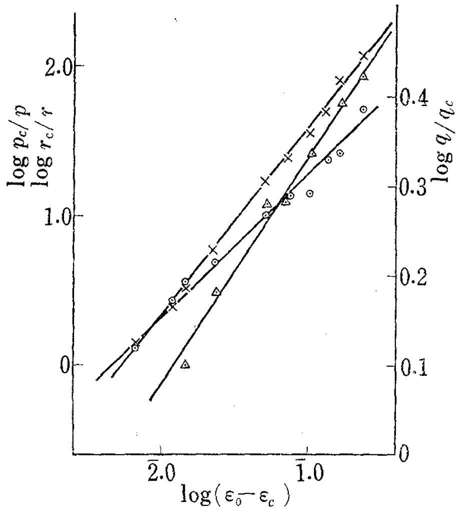

Fig. 5. Relation between $(\varepsilon_0-\varepsilon_c)$ and p_c/p, q/q_c or r_c/r for Tapping of Sodium Borate Powders in Carbon Tetrachloride

—⊙— p_c/p, —△— q/q_c, —×— r_c/r

Table V

Sample Solvent	Sodium borate Carbon tetrachloride	Sodium borate Toluene	Boric acid Carbon disulfide
D_{cp}	350	165	170
D_{cq}	300	160	180
D_{cr}	340	165	160
D_{cII}*	330	160	180

* from the previous paper[4]

As shown in Table V, the critical particle diameters for p, q and r are identical with those obtained in loosest packing in each solvent in the previous paper,[4] respectively. This finding suggests that p, q and r are connected with apparent friction between powder particles. It is also suggested that cohesive force markedly influences these parameters in the region below critical size.

In any case, linear relations are obtained between logarithm of p_c/p, q/q_c or r_c/r and log $(\varepsilon_0-\varepsilon_c)$ in each solvent as shown in Fig. 5, where p_c, q_c or r_c is the value on the extended part of the straight lines for the region above the critical size obtained by the logarithm plot of p, q and r *vs* D. Accordingly the following equations are applicable.

$$p_c/p=M_p(\varepsilon_0-\varepsilon_c)^{\gamma_p} \qquad (5)$$

$$q/q_c=M_q(\varepsilon_0-\varepsilon_c)^{\gamma_q} \qquad (6)$$

$$r_c/r=M_r(\varepsilon_0-\varepsilon_c)^{\gamma_r} \qquad (7)$$

M_p, M_q, M_r, γ_p, γ_q, γ_r : Constants

Equations (5), (6) and (7) illustrate that p_c/p, q/q_c and r_c/r are related to cohesive force between powder particles.

The numerical values of M_p, M_r, γ_p, and γ_r are larger in toluene than in carbon tetrachloride, but those of M_q and γ_q are nearly identical, for sodium borate powders. This fact suggests that p and r depend on the characteristics of the solvent, such as viscosity and specific gravity.

The same tendency is also found for the coefficients of equation (1) for the tapping of sodium borate powders in air, although it can not be discussed in detail because the closest packing occurred after only a few tappings.

We now examine the parameters p, q and r for the samples tabulated in Table I. In Figs. 6 and 7, q or $\log p$ and $\log r$, obtained by the tapping of samples in air, are plotted *vs* $\tan \alpha$, where α is angle of repose by Nogami–Sugiwara's method .[3] As $\tan \alpha$ becomes larger, q tends to become larger and p or r to smaller, for organic and inorganic powders, respectively, with the exception of zinc oxide. This tendency is also shown for sodium borate and boric acid powders. In the case of zinc oxide, q becomes exceptionally smaller and p or r larger in comparison with the other inorganic powders. This finding may be due to the fact that the specific gravity of zinc oxide is much larger than that of the other samples.

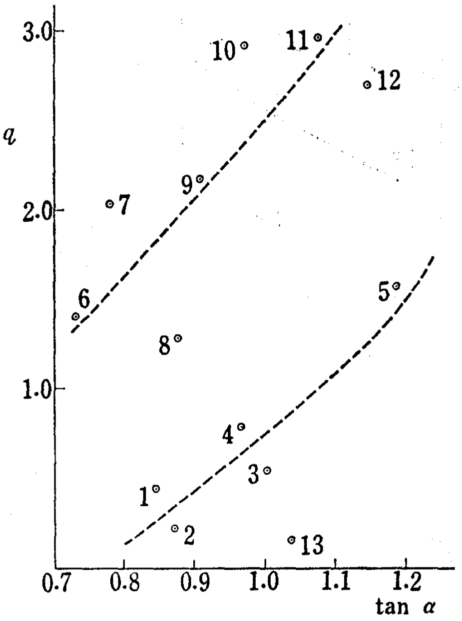

Fig. 6. Relation between $\tan \alpha$ and q for Tapping of Pharmaceutical Powders in Air

1 spray-dried lactose
2 carboxymethyl cellulose calcium
3 carboxymethyl cellulose
4 microcrystalline cellulose
5 lactose
6 synthetic aluminium silicate
7 magnesium alumino silicate
8 dibasic calcium phosphate
9 heavy magnesium oxide
10 magnesium oxide
11 bentonite
12 kaoline
13 zinc oxide

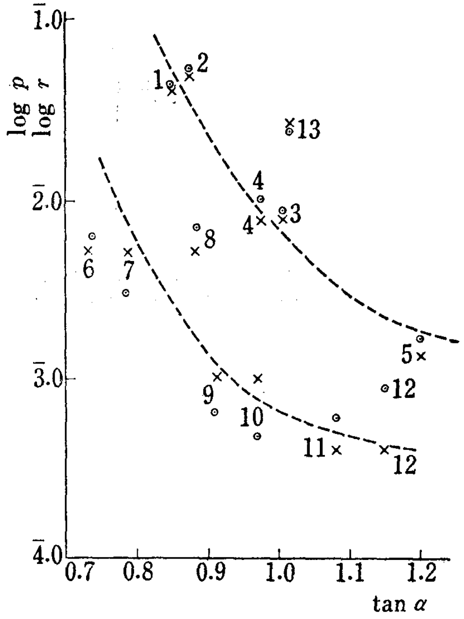

Fig. 7. Relation between $\tan \alpha$ and p or r for Tapping of Pharmaceutical Powders in Air

p : ⊙ r : ×

1 spray-dried lactose
2 carboxymethyl cellulose calcium
3 carboxymethyl cellulose
4 microcrystalline cellulose
5 lactose
6 synthetic aluminium silicate
7 magnesium alumino silicate
8 dibasic calcium phosphate
9 heavy magnesium oxide
10 magnesium oxide
11 bentonite
12 kaoline
13 zinc oxide

The following tendency is also shown in Figs. 8 and 9. The value of q increases gradually with the increase of ε_0 and more so in cyclohexane than in air. Meanwhile, p and r decreases gradually with the increase of ε_0 and less so in cyclohexane than in air.

Correlation between $\tan \alpha$ and ε_0 in air is found by comparing Figs. 6, 7 and 8, 9, and such a correlation is also found for sodium borate and boric acid powders.[3-5] Otsubo and Nakajima also reported correlation between them for many other powders.[7,8] Consequently

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[7] T. Otsubo, *J. Res. Assoc. Powder Techn.*, **1**, 20 (1964); *ibid.*, **2**, 179 (1965).
[8] E. Nakajima, *Yakugaku Zasshi*, **81**, 717 (1961).

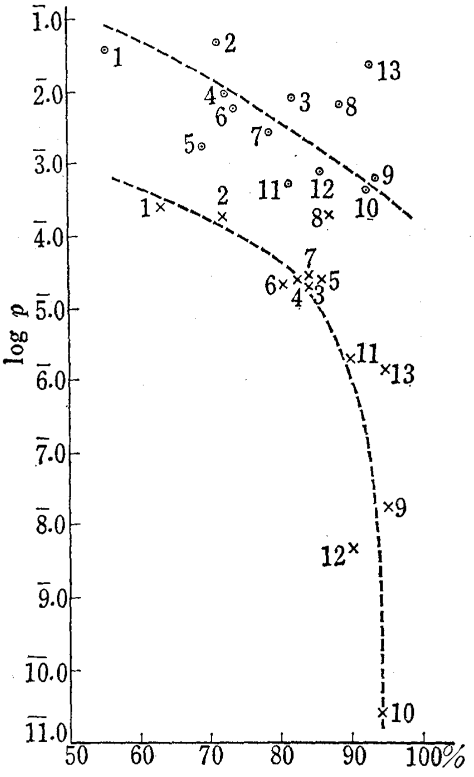

Fig. 8. Relation between p and Porosity in Loosest Packing

—⊙— in air —×— in cyclohexane

1	spray-dried lactose
2	carboxymethyl cellulose calcium
3	carboxymethyl cellulose
4	microcrystalline cellulose
5	lactose
6	synthetic aluminium silicate
7	magnesium alumino silicate
8	dibasic calcium phosphate
9	heavy magnesium oxide
10	magnesium oxide
11	bentonite
12	kaoline
13	zinc oxide

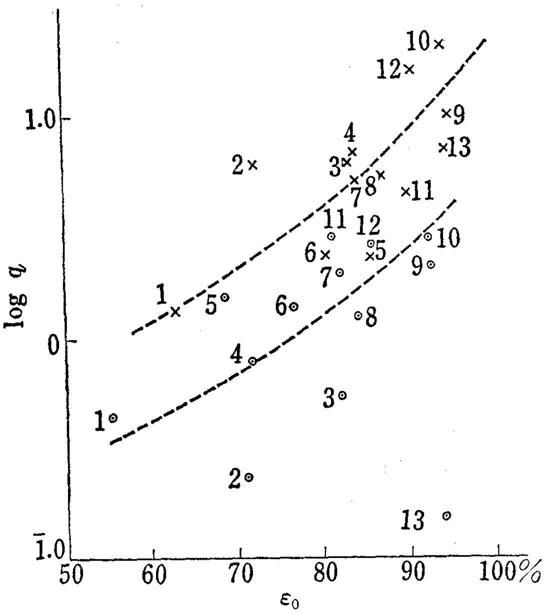

Fig. 9. Relation between q and Porosity in Loosest Packing

—⊙— in air —×— in cylcohexane

1	spray-dried lactose
2	carboxymethyl cellulose calcium
3	carboxymethyl cellulose
4	microcrystalline cellulose
5	lactose
6	synthetic aluminium silicate
7	magnesium alumino silicate
8	dibasic calcium phosphate
9	heavy magnesium oxide
10	magnesium oxide
11	bentonite
12	kaoline
13	zinc oxide

p, q and r might also be related to the apparent friction, that is, internal friction and cohesive force between particles of powders.9) It is suggested from Figs. 8 and 9 that p, q and r also depend on the characteristics of solvents such as viscosity and specific gravity.

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9) M. Arakawa, *J. Res. Assoc. Powder Techn.*, Rinjigo, 15 (1966).