applications for qualitative work. Bands in the 2.15 to 2.32 μ region have been shown to be useful for the quantitative measurement of amine hydrochloride salts. Primary amine salts were distinguished from secondary and tertiary amine salts on the basis of the presence of a 2.18 μ band and the absence of a band at 2.05 μ.

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Applications of the Montmorillonites in Tablet Making

By KEE-NENG WAI, H. GEORGE DEKAY, and GILBERT S. BANKER

The montmorillonites were studied for their use as disintegrants, binders, and lubricants for the manufacture of compressed tablets. It was found that the clays, although traditionally believed to be inert materials, agglomerated with several macromolecules commonly used as tablet binders. When added dry to prepared granulations, magnesium aluminum silicate F was an excellent disintegrant which produced tablets disintegrating twice as fast as those containing an equal amount of cornstarch. Furthermore, the clays contained a lower moisture content and were more compressible than starch. However, the other grades of montmorillonite studied were less effective as disintegrating agents than starch, and wet granulation of the clays with the diluents substantially decreased the effectiveness of these materials as disintegrants.

MONTMORILLONITE is the name given to a clay mineral first found near Montmorillon, France. Essentially, it has the composition $Al_2O_3 \cdot 4SiO_4 \cdot H_2O \cdot xH_2O$. Many minerals of similar properties, but distinctly different chemical compositions, have since been found (1). The clay minerals frequently exhibit properties which are highly desirable for any products used as disintegrants, binders, and fillers, or viscosity imparting agents. They have a high swelling volume in water, form gels at low concentrations, are chemically inert and stable to a wide range of temperatures, and are smooth, white to off-white fine powders. This study was undertaken to investigate the extent of application and limitations of the montmorillonite type of clays in tablet making, based on and in view of selected physical properties of the clays which were previously determined (2).

Bentonite and magnesium aluminum silicate[1] have been studied by several workers as tablet disintegrating agents. Granberg and Benton (3) reported that bentonite was an effective filler and disintegrating agent in thyroid tablets. Gross and Becker (4), on the other hand, found that neither bentonite nor magnesium aluminum silicate, in concentrations up to 17%, produced any disintegrating effect in tablets. However, Firouzabadian and Huyck (5) and Ward and Trachtenberg (6), who conducted comparative studies on the effectiveness of tablet disintegrants, found that magnesium aluminum silicates were among the best disintegrants studied. Nair and Bhatia (7) in another comparative study reported that sulfathiazole tablets containing magnesium aluminum silicate as the disintegrant appeared to have the most rapid distintegration time when most of the clay product was added after granulation and only a small portion before granulation. A suspension of 20% montmorillonite clay has been used as a granulating agent with reported disintegration activity (8).

EXPERIMENTAL AND RESULTS

The three commercial montmorillonites studied in this work will be referred to as clay I, II ,and III,[2] respectively. The composition and properties of these

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[1] Marketed as Veegum by the R. T. Vanderbilt Co., New York, N. Y.

[2] Marketed as Veegum, Veegum F, and Veegum WG by the R. T. Vanderbilt Co., New York, N. Y.

TABLE I.—COMPATIBILITY OF A 5% MONTMORILLONITE[a] DISPERSION WITH EQUAL VOLUMES OF VARIOUS OTHER TABLET ADJUNCTS

Granulating Agent	pH of Granulating Agent	pH of Granulating Agent with Clay	Appearance of Mixture
Distilled water	5	8	Smooth paste
Starch paste, 5%	6	8	Smooth paste
Starch paste, 2%	5	8	Smooth paste
Dextrose soln., 30%	4	8.5	Smooth paste
Algin,[b] 1%	7	9	Smooth paste
Propylene glycol alginate,[c] H.V., 1%	3	7	Smooth paste
Sodium alginate, 1%	5	8.5	Smooth paste
Simple syrup U.S.P.	5	7	Smooth paste
Acacia, 10%	5	7	Slightly agglomerated
Carboxymethylcellulose, 2.5%	5	8	Slightly agglomerated
Gelatin, 1%	5	8	Agglomerated
Methylcellulose 4000, 1%	5	8	Agglomerated
Polyvinylpyrrolidone, 5%	5	9	Agglomerated and separated

[a] Magnesium aluminum silicate WG. [b] Marketed as Keltose by Kelco Co. [c] Marketed as Kelcoloid by Kelco Co., Clark, N. J.

clays were reported in an earlier paper (2). The clays were oven dried at 50° for 24 hr. prior to use to remove nonbound moisture which may have been sorbed on storage.

Compatibility of Montmorillonite with Various Tablet Adjuncts.—The montmorillonites are frequently used in tablet matrices in combination with other tablet adjuncts with which the montmorillonites might be reactive. Such reactivity could affect tablet disintegration, drug availability, or manufacturing methods.

Two liters of a 5% dispersion of clay III were prepared in hot water. This preparation was permitted to hydrate for 24 hr. and was then divided into 100-ml. portions. To each portion, 100 ml. of another common or previously reported tablet binder was added. The change in pH and appearance of the mixed binders were observed and are summarized in Table I.

In spite of their relative chemical inertness, the montmorillonite clays were incompatible with certain common tablet adjuvants. The montmorillonites apparently interact with many macromolecules. The clays consistently increased the pH of the combined systems from 2 to 4 units. Hydrogen bonding between the clay and the polymer molecules and electrical discharge between two oppositely charged particles (or molecules) may explain the agglomeration phenomenon which frequently occurred between clay and polymer.

Disintegrating Action of Unwetted Montmorillonites.—Sixty-four batches of tablets were prepared, containing various concentrations of the three grades of clay, or starch, blended with a granulation of calcium sulfate. The relationships between the disintegration time and the concentrations of disintegrants, disintegration time and granule size, and between tablet hardness and disintegrant concentration were studied. The calcium sulfate granulation was prepared according to the following formula:

Calcium sulfate	10 Kg.
Ethylcellulose 47 cps. (5% solution in ethanol)	4 L.

The calcium sulfate was granulated in a dough mixer[3] and then passed through an oscillating granulator[3] fitted with a No. 12 screen. The granulation was air-dried. Through a series of hand sizing and screening processes, it was separated into granulations of the following size ranges:

Mesh Size	Quantity, Kg.
12–16	1
16–20	1
20–30	5
30–40	1
40–80	1

Ethyl cellulose was used in granulating the calcium sulfate to produce a granulation which did not readily disintegrate in water or simulated gastric juice. This granulation formula was used because the experiment was designed to study the efficiency of the clays as disintegrants when they were blended with prepared, insoluble, nondisintegrating granulations. Using this granulation, 100-Gm. samples of material were prepared by adding 0.5 Gm. of magnesium stearate and various concentrations (0, 0.5, 1, 2, 4, 8, 15, or 25%) of a disintegrating agent (clays I, II, III, and starch) to the granulation. These granulations were compressed into $^{5}/_{16}$-in. standard cup, 200-mg. tablets with a Colton 120 single punch machine.[4] Tablets of a hardness of about 4.5 to 5.5 Kg. were prepared when possible. Hardness was measured with a Dillon prototype tablet hardness tester[5] and is expressed as the average of 20 measurements. The average disintegration time of six tablets was determined in gastric juice U.S.P. by the official method. The results are summarized in Table II.

Figure 1 represents the relationship found between the disintegration time and the concentration of the four disintegrating agents. The straight lines were drawn with the assumption that the relationship holds when the concentration of the disintegrating agent is between 1 and 20%. The figure also illustrates that tablets containing clay II disintegrate about twice as fast as tablets containing cornstarch as a disintegrating agent in the same percentage. Starch, in turn, is a better disintegrating agent than clay III or clay I. The addition of 2% of clay II reduced the disintegration time of the tablets to below 5 min. The presence of 5% of clay II with

[3] F. J. Stokes Co., Philadelphia, Pa.

[4] Arthur Colton Co., Detroit, Mich.

[5] W. C. Dillon & Co., Van Nuys, Calif.

TABLE II.—THE DISINTEGRATION TIME, HARDNESS, AND WEIGHT OF TABLETS CONTAINING VARIOUS CONCENTRATIONS OF DISINTEGRATING AGENTS (DISINTEGRANTS ADDED DRY TO $CaSO_4$ GRANULATION)

Disintegrating Agent	Mesh Size of Granulation	Tests	Concn. of Disintegrating Agent, %: 0	0.5	1	2	4	8	15	25
Clay III	12–16	Disintegration time, sec.	1373	1343	1238	658	464	457	53	39
		Hardness, Kg.	4.4	4.7	5.1	5.0	5.2	5.1	3.0	3.6
		Wt., mg.	198	198	200	201	204	200	194	204
Clay III	16–20	Disintegration time, sec.	1655	1429	1089	866	219	74	42	34
		Hardness, Kg.	4.8	4.2	4.5	4.6	4.2	3.5	2.7	2.9
		Wt., mg.	199	197	199	200	205	204	210	210
Clay III	20–30	Disintegration time, sec.	1581	1198	1114	752	303	200	49	33
		Hardness, Kg.	4.4	4.3	4.8	4.8	4.6	3.8	4.4	4.0
		Wt., mg.	203	205	209	208	210	206	208	217
Clay III	30–40	Disintegration time, sec.	1221	1173	921	758	277	142	47	40
		Hardness, Kg.	4.7	4.9	5.1	5.0	4.1	5.5	4.9	4.9
		Wt., mg.	195	196	199	200	199	199	195	199
Clay III	40–80	Disintegration time, sec.	1025	947	811	433	228	62	30	27
		Hardness, Kg.	4.4	4.7	5.8	5.0	5.2	5.5	5.5	5.7
		Wt., mg.	202	197	199	202	205	204	200	203
Clay III	20–30 Replicate	Av. disintegration time, sec.	1581	1218	1035	693	298	136	44	35
Clay II	20–30	Disintegration time, sec.	1581	1403	690	282	75	21	10	61
		Hardness, Kg.	4.4	5.1	5.1	4.8	4.6	4.4	4.5	4.3
		Wt., mg.	203	201	200	200	201	200	200	197
Clay I	20–30	Disintegration time, sec.	1581	1434	1068	1150	477	197	66	29
		Hardness, Kg.	4.4	5.1	5.3	4.6	4.9	3.5	3.2	2.0
		Wt., mg.	203	200	201	203	201	197	198	200
Starch	20–30	Disintegration time, sec.	1819	1305	1071	485	133	57	36	12
		Hardness, Kg.	4.8	5.2	4.5	4.4	2.8	1.4	...	...
		Wt., mg.	199	200	197	200	202	196	197	196

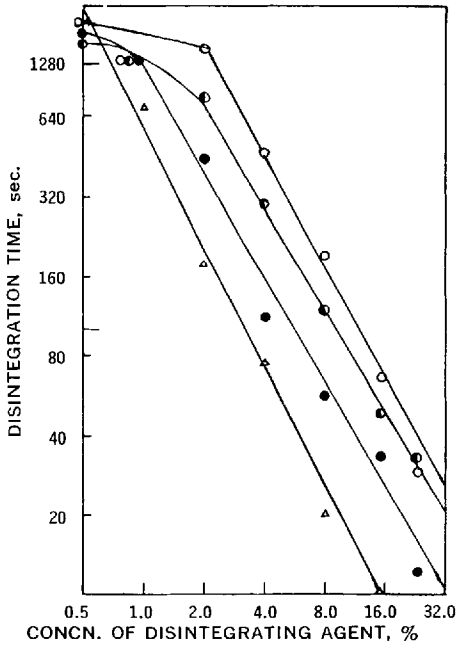

Fig. 1.—Disintegration time of $CaSO_4$–ethylcellulose tablets containing clays I, II, and III and starch as disintegrating agents (prepared from 20/30 mesh granulations). Key: ○, clay I; △, clay II; ◐, clay III; ●, starch.

the granulation reduced the disintegration time to below 1 min.

When the concentration of starch added dry with the lubricant was 8% or higher (Table II) it became very difficult to produce a tablet with a hardness above 5 Kg. Granulations containing more than 15% starch in powder form were practically incompressible, while fairly hard tablets could be produced with the concentration of clay II as high as 25%. Using clay III, in the coarser three granule sizes (Table II) a degree of tablet hardness appeared to be lost at clay concentrations of 8 to 15% or higher.

The particle-size distribution of the clay may be a factor which influences the disintegration rates of the tablets. Clay II had the smallest average particle size (completely passed a number 200 sieve) of the clays studied, and was the best disintegrant; clay I had the coarsest particles (average diameter equal to 373 μ by sieve analysis) and was the poorest disintegrant among the three clays studied (2). The ion-exchange capacity of the clays (0.601, 0.585, and 0.523 mmoles/Gm. for clays I, II, and III, respectively) and the swelling volume of the clays (21.3, 20.0, and 10.8 ml. in gastric juice) (2) showed no apparent relationship to the disintegration action of the clays.

The Disintegrating Action of Montmorillonites When Incorporated Within the Granulation.—The compatibility study (Table I) showed that the clays in this study agglomerated with many other commonly used tablet binders. It was hypothesized that this agglomeration might influence both the binding action of the binder and the disintegrating

action of the clays. Lactose and calcium sulfate were separately used as tablet fillers in this study to represent a soluble and an insoluble tablet matrix. The granulations were prepared as follows.

(*a*) A 10% suspension of clay I was prepared and was used alone, or was mixed with the other granulating agents and the mixture used to granulate the filler. The final granulations contained 1% clay by weight. If the mass was not adequately wet after adding sufficient clay suspension to provide 1% clay in the dry granulation, water was used to complete the massing operation.

(*b*) The fillers alone and with 1% clay added dry were granulated with the various syrup and gum granulating agents. These were the control samples against which the other clay-containing (clay added as granulating agent) tablets were compared. Each of the two diluents, with and without the addition of 1% clay, was also granulated with water alone.

Each batch of granulation contained 200 Gm. of lactose or 300 Gm. of calcium sulfate. The granulation masses were passed through a 12-mesh screen by hand, dried at room temperature for 48 hr., and resized through a 16-mesh screen. Magnesium stearate was added as the lubricant (0.5% for the calcium sulfate granulations and 0.25% for the lactose granulations). The tablets were compressed to a weight of 200 mg. using $^{5}/_{16}$-in. standard concave punches. A compression force was used which would yield tablets having a hardness of 2 to 3.5 Kg. for the calcium sulfate tablets and about 5 to 6 Kg. for the lactose tablets. The formula, granule hardness, disintegration time, hardness, and appearance of each batch of tablets were recorded (Table III). The dried granulations varied in per cent moisture content between 0.2 and 1.8%; most were between 0.4 and 1.2%.

According to Table III the following observations may be made.

(*a*) When the montmorillonite clays alone were used as the granulating agent-binder for calcium sulfate, soft granulations were obtained (formulas

TABLE III.—EVALUATION OF THE MONTMORILLONITES AS GRANULATION BINDERS ALONE AND IN COMBINATION WITH DIFFERENT GRANULATING AGENTS

Formula No.	Tablet Filler Base	Granulating Material	Hardness of Granules[a]	Av. Wt. of Tablets, mg.	Hardness of Tablets, Kg.	Disint. Time, sec.	Description of Tablets
1	$CaSO_4$	Water	Soft	197	1.3	278	Slight capping
2	$CaSO_4$	Clay I[c]	Soft	197	1.8	99	Slight capping
3	$CaSO_4$	Clay II[c]	Soft	205	2.1	80	Slight capping
4	$CaSO_4$	Clay III[c]	Soft	197	2.0	28	Slight capping
5	$CaSO_4$-I[b]	Water	Soft	205	2.3	94	Slight capping
6	$CaSO_4$	Clay I[d]	Medium	200	1.1	100	Slight capping
7	Lactose	Water	Medium	203	6.2	30	Satisfactory
8	Lactose	Clay I	Hard	205	5.9	242	Satisfactory
9	Lactose	Clay II	Hard	206	6.3	185	Satisfactory
10	Lactose	Clay III	Hard	202	6.2	233	Satisfactory
11	Lactose-I[b]	Water	Hard	205	5.0	125	Satisfactory
12	$CaSO_4$	Clay I and syr.[e]	Soft	204	3.5	1340	Satisfactory
13	$CaSO_4$	Syrup	Medium	200	3.4	1100	Satisfactory
14	$CaSO_4$-I	Syrup	Hard	203	3.3	710	Satisfactory
15	Lactose	Clay I and syr.	Hard	205	6.5	664	Satisfactory
16	Lactose	Syrup	Hard	205	4.2	215	Satisfactory
17	Lactose-I	Syrup	Hard	209	3.7	211	Satisfactory
18	$CaSO_4$	Starch[f]	Medium	203	2.4	63	Slight capping
19	$CaSO_4$	Clay I and starch	Medium	195	2.3	51	Satisfactory
20	$CaSO_4$-I	Starch	Medium	202	2.0	68	Satisfactory
21	Lactose	Starch	Hard	199	5.0	40	Satisfactory
22	Lactose	Clay I and starch	Hard	207	5.4	80	Satisfactory
23	Lactose-I	Starch	Hard	204	5.8	97	Satisfactory
24	$CaSO_4$	Acacia[g]	Medium	199	3.1	178	Satisfactory
25	$CaSO_4$	Clay I and acacia	Hard	207	3.5	140	Satisfactory
26	$CaSO_4$-I	Acacia	Hard	206	3.4	203	Satisfactory
27	Lactose	Acacia	Hard	202	4.8	53	Satisfactory
28	Lactose	Clay I and acacia	Hard	204	4.9	145	Satisfactory
29	Lactose-I	Acacia	Hard	202	4.6	119	Satisfactory
30	$CaSO_4$	MeCel[h]	Hard	210	2.1	3600	Slight capping
31	$CaSO_4$	Clay I and MeCel	Hard	206	2.4	2410	Slight capping
32	$CaSO_4$-I	MeCel	Medium	208	2.1	3600	Slight capping
33	Lactose	MeCel	Hard	207	4.3	257	Satisfactory
34	Lactose	Clay I and MeCel	Hard	207	4.9	67	Satisfactory
35	Lactose-I	MeCel	Hard	197	5.2	131	Satisfactory
36	$CaSO_4$	Sodium alginate[i]	Soft	206	1.8	119	Slight capping
37	$CaSO_4$	Clay I and sodium alginate	Soft	204	2.3	115	Slight capping
38	Lactose	Kelgin	Hard	203	5.8	103	Satisfactory
39	Lactose	Clay I and sodium alginate	Hard	206	4.6	125	Satisfactory
40	Lactose-I	Sodium alginate	Hard	203	4.6	134	Satisfactory

[a] Soft granules immediately powdered on handling. Medium granules partially powdered on handling. Hard granules could be handled without appreciable powdering. [b] One per cent of clay I was added dry to $CaSO_4$ or lactose before massing. [c] All clay granulating agents were used as 10% w/v suspensions. [d] Used 10% suspension of clay I as the only granulating agent without supplemental water. [e] Simple syrup U.S.P. [f] Ten per cent starch paste. [g] Ten per cent mucilage of acacia. [h] Ten per cent methylcellulose 4000 solution. [i] Two per cent mucilage of sodium alginate.

2–5, Table III). Capping of these tablets was observed during manufacture and on handling and hard tablets could not be prepared.

(*b*) Simple syrup, starch paste, and acacia were excellent granulating agents, producing hard calcium sulfate granulations. Starch, acacia, or methylcellulose, in equal volume combination with the clay suspension generally did not affect calcium sulfate granule hardness or tablet quality, but the combination granulating materials, although incompatible (Table I), did reduce disintegration time. Sodium alginate[6] reacted with the calcium ions of the calcium sulfate and could not be used successfully as a binder for this compound. All five tablet granulating agents tested appeared to be suitable for granulating lactose.

(*c*) The disintegration times of the tablets produced from formulas 1 to 6 in Table III shows that an addition of 1% of montmorillonite clays *via* the granulating agent, to calcium sulfate reduced the disintegration time of the calcium sulfate tablets from 278 sec. (formula 1) to less than 100 sec. (formulas 2–6).

(*d*) The clays in suspension form as a granulating agent permitted satisfactory granulations and tablets to be prepared of the soluble lactose formula; but so did water (formulas 7–11). One per cent of clay, added as granulating agent, greatly increased the disintegration time of the soluble lactose tablets (formula 7 *versus* 8–11). The clay decreased the time of disintegration of the lactose tablets containing methylcellulose as the binder (formulas 33–35). The slowly hydrating methylcellulose apparently prevents the water from penetrating to the core of the soluble tablets (No. 33 and 35). The methylcellulose was dehydrated and agglomerated in the presence of the clay (No. 34), which resulted in more rapid disintegration while not adversely affecting granule hardness or tablet quality. It is interesting to note that in the insoluble calcium sulfate tablets the combination of methylcellulose and clay, even though incompatible (Table I), also produced tablets superior to those obtained when methylcellulose was used singly.

(*e*) It is obvious from Tables I and III that the combination of compatible granulating agent plus clay suspension as binder (syrup plus clay or starch paste plus clay) offered no apparent advantage. In the syrup–clay systems the combination produced the longest disintegration time with both diluents (formulas 12 and 15), while the clay–starch combination tablets (No. 19 and 22) were either not substantially better or were poorer than tablets prepared from starch paste alone. Acacia and methylcellulose agglomerated with the clay, and the disintegrating action of the combination systems were usually superior to the gum or polymer alone, while the combination systems retained adequate binding properties (formulas 24–29 and 30–35).

The clays were also studied for their use as tablet disintegrating agents when added to the granulation internally with the diluent in concentrations ranging from zero to 25%. Four granulating agents (20% glucose, 5% acacia, half strength simple syrup, 10% clay I suspension) and water and the four disintegrating agents (the three clays plus starch) were studied. Three hundred grams of calcium sulfate and disintegrating agent were mixed and moistened with 80 ml. of one of the selected granulating agents, the mass passed through a 20-mesh screen, oven dried at 100°F. for 24 hr., sized to 20 mesh, and lubricated with 1% magnesium stearate. Tablets were compressed to 200 mg. at a hardness of from 3.5 to 5.0 Kg.

Increasing the montmorillonite clay concentrations from 1–16% with each granulating agent failed to produce an equivalent consistent decrease in disintegration times, which varied inconsistently from about 10 to 30 min. *versus* 5 to 12 min. for starch. This showed that wetting the clay type disintegrating agents during the granulation process reduces the activity of the disintegrating agents. Compared to starch the clays were all relatively poor disintegrating agents when wet granulated together with the filler.

The loss of disintegration activity of the montmorillonite clays after wet granulation may be explained in two ways. First, the clays and the binder may form an adhesive gel on disintegration and thus resist falling through the screen of the disintegration tester. Although the tablets disintegrated, they remained partially suspended inside the basket and, according to U.S.P. specification, disintegration was incomplete. Second, certain granulating agents may form a film surrounding clay particles and reduce the rehydration rate of the clay.

CONCLUSIONS

Montmorillonite suspensions alone were poor granulating agents producing inadequate granule binding.

Although montmorillonite clays are relatively inert chemically, they interact with many organic macromolecules. This interaction reduces but does not destroy the binding properties of certain tablet binders while the interacted systems may produce superior tablets with more rapid disintegration than either binder alone.

The clays are not good disintegrating agents when they are added as a dry powder to the filler and are wet granulated. They are good disintegrating agents and may be superior to starch when added dry to completed granulations, in which case the disintegration time and the concentration of clay added demonstrate an inverse second-order relationship.

[6] Marketed as Kelgin by the Kelco Co., Clark, N. J.

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