

SUMMARY

Two procedures have been used in this laboratory for measurement of the expired $^{14}\text{CO}_2$ of rats and mice, in various drug metabolism studies and have been found to give rapid, consistent results.

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Some Physicochemical Properties of the Montmorillonites

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The swelling, moisture sorption, particle size, cation-exchange, and drug adsorption properties of selected montmorillonites were studied. The swelling of montmorillonite was found to depend on both adsorptive and osmotic phenomena. The study of the sorption of alkaloidal drugs by the clay showed that brucine was sorbed by both adsorption and ion-exchange reactions, forming a monomolecular layer on the interior surface of the clay; methapyrilene and triethylamine were sorbed by an ion-exchange reaction; and niacinamide was neither adsorbed nor ion-exchanged.

THE HYDROUS magnesium aluminum silicate minerals, montmorillonites, because of their unusual properties and widespread occurrence have attracted the attention of workers in many fields of application. These clays are extremely plastic when moist, swell in the presence of water, and can be dispersed in water forming thixotropic gels. Bentonite U.S.P. is a mineral composed of 90% montmorillonite (1).

The applications of the montmorillonites in the pharmaceutical field have been explored extensively. Magnesium aluminum silicate¹ and bentonite, alone or in combinations with other common suspending agents, have been studied for their use as suspending agents (2-5). Guth *et al.* prepared different types of bentonites by saturating the clay with Na^+ , K^+ , Ca^{2+} , Mg^{2+} , and H^+ . They used these various cation saturated bentonites to conduct a series of studies on the buffer capacity, cationic-exchange properties, and drug binding and release properties of bentonite (6-10). Many studies of montmorillonites as tablet disintegrants have been made, with the

work of Feinstein and Bartilucci (11) being the most recent.

Although the montmorillonite class of clay minerals is widely used in the field of pharmacy, little has been reported in the pharmaceutical literature concerning their basic physical and chemical properties and the relation between such properties and pharmaceutical applications and utility. It was, therefore, the purpose of this work to conduct a pharmaceutically oriented study of the physicochemical properties of the montmorillonites, so that the various present applications and limitations or restrictions of the clays might be better understood and future applications more accurately determined.

EXPERIMENTAL

The three commercial montmorillonites studied in this work were magnesium aluminum silicate, magnesium aluminum silicate F, and WG.² These three types of clay will be referred to as clay I, II, and III, respectively, in the remainder of this paper.

Magnesium aluminum silicate has a composition of 61.1% silicone dioxide, 13.7% magnesium oxide, 9.3% aluminum oxide, 2.9% sodium oxide, 2.7% calcium oxide, and smaller amounts of titanium, ferric, and potassium oxides, 1.8% carbon dioxide, and 7.2% water of combination (12). The moisture content of the material will increase if exposed to moist atmospheres. The various grades of

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

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

magnesium aluminum silicate have the same general composition of plain magnesium aluminum silicate, but differ primarily in mechanical treatments which have been employed to affect color, rehydration properties, aggregate particle size, and other gross properties of the various grades.

Magnesium aluminum silicate WG is a high viscosity grade of magnesium aluminum silicate in finer than 50-mesh powder form, which is easier to rehydrate than other grades (13). Magnesium aluminum silicate F is a microatomized (325 mesh) grade (13).

The magnesium aluminum silicates were selected for study from the montmorillonite class, based on their high relative purity and light color for clay minerals, small lot-to-lot variation, and the availability of grades of clay varying in aggregate particle size and other properties. The clays studied were all oven dried at 50° for 24 hr. prior to use to remove nonbound moisture which may have been sorbed by the materials during storage. The moisture content of the clays as supplied was between 6.2 and 7.5% and after drying was 3.4, 2.4, and 4.3% for clays I, II, and III, respectively. The starch contained 9.4% moisture before drying and 5.2% after. The physicochemical properties studied included swelling volume, moisture sorption, particle size, ion-exchange capacity, and drug binding.

Particle Size.—Electron microscopy³ was used to determine the particle-size distribution of the clays.

Three samples of each of the three grades of clay were used for the electron micrographic analysis. One picture, at a magnification power of 4000X, was taken of each sample, and the negative films were used to prepare 8 X 10-in. photographs. The Martin's diameters (14) of all the particles were measured on the enlarged photographs. The cumulative per cent of the particles was plotted on a probability scale against the logarithm of the Martin's diameter of the particles. The geometric mean diameters and the geometric standard deviations of the weight distribution were obtained from the graphs.

Swelling Volume.—The swelling of the montmorillonites was studied in media containing sodium chloride in 0, 0.005, 0.010, 0.025, 0.050, 0.10, 0.25, 0.50, and 1.00 *N* concentrations. Clay samples, weighing 2.00 Gm. each, were placed in 100-ml. amber glass jars. Fifty milliliters of medium was added to each jar, and the jars were capped and shaken for 2 hr. on a mechanical shaker. The contents of each jar were then transferred to a 100-ml. graduated cylinder, and additional saline medium was used to wash the jar and fill the graduated cylinder to volume. After 12 hr. of undisturbed hydration in the cylinders, the volume occupied by each hydrated clay gel was measured. This gel height volume was called the swelling volume. Each swelling volume was calculated from the average of three replicate determinations. For the purpose of comparison, the swelling of starch U.S.P. in each medium was also measured.

Moisture Sorption.—Three constant relative humidities were obtained by placing saturated solutions of calcium sulfate, sodium nitrite, and magnesium chloride, respectively, in 9-in. evaporating dishes in separate chromatographic chambers

sealed with glass sheets and stop-cock grease (15). The relative humidities in these chambers, measured by a Sedex hygrometer,⁴ were 98, 66, and 35%, respectively. The temperature in the chambers was 26 ± 2°. The moisture absorption of the clay samples, as commercially supplied and as compressed disks, and starch U.S.P. in the form of powdered material was studied. Starch could not be compressed as a disk. The disks, 0.5 in. in diameter and 0.5 Gm. in weight, were compressed with a force of 10,000 lb. (50,000 p.s.i.) for 3 min. with a Carver press.⁵ The moisture content of all samples was determined gravimetrically, initially, and after 7, 14, and 21 days of storage at each condition. The thickness and diameter of the disks were measured at the same time intervals and disk volumes were calculated.

Determination of the Exchangeable Cation of Montmorillonite with Radioactive Sodium.—A modified, inverse dilution technique was used to measure the amounts of exchangeable cation and free electrolyte in the clays. The experimental procedure was as follows.

(a) The ²²Na (10 μc.), in the form of a solution of NaCl in hydrochloric acid, was added to enough distilled water to make 1 L.

(b) The solution was divided into four 250-ml. portions in volumetric flasks. To these solutions was added enough sodium chloride to produce the equivalent of 0, 30, 60, and 100 mg. of Na₂O in 100 ml. of solution (plus the 1 μc. of ²²Na/100 ml.).

(c) The samples of the clays, weighing 1 Gm. each, were placed in 100-ml. dry-square bottles which had previously been soaked in dilute hydrochloric acid for 12 hr., washed, and dried.

(d) Fifty milliliters of the radioactive saline solutions were added to each bottle and the bottles capped and sealed with tape.⁶ The bottles were placed in a mechanical shaker and agitated for 3 hr.

(e) The clays were separated from the media by ultracentrifugation,⁷ with a force 100,000 times gravity.

(f) Three samples, each containing 2 ml. of the clear medium, were placed in 4-ml. sample vials. The radioactivity of each vial was measured with a crystal-well counter.⁸

Montmorillonite Reaction with Cationic Drugs.—Four cationic drugs were used to study the ion-exchange activity of the clays. They were methapyrilene hydrochloride, brucine sulfate, triethylamine hydrochloride, and niacinamide hydrochloride. The methapyrilene hydrochloride and brucine sulfate were analytical grade chemicals. The triethylamine and niacinamide hydrochlorides were prepared from the respective bases by reaction with hydrochloric acid followed by purification by recrystallization from alcohol, acetone, and ethyl acetate.

The alkaloidal salt was dissolved in alcohol U.S.P. The concentration of the alkaloid in the solution was adjusted so that the alkaloid in 50 ml. of solu-

⁴ Sedex Inc., Boston, Mass.

⁵ Fred S. Carver, Inc., New York, N. Y.

⁶ Scotch Tape No. 33, Minnesota Mining & Manufacturing Co., St. Paul, Minn.

⁷ Beckman Spinco Division, Stanford Industrial Park, Palo Alto, Calif.

⁸ Packard Instrument Co., LaGrange, Ill.

³ Philips EM 100, modified, electron microscope, North American Philips Co., Mount Vernon, N. Y.

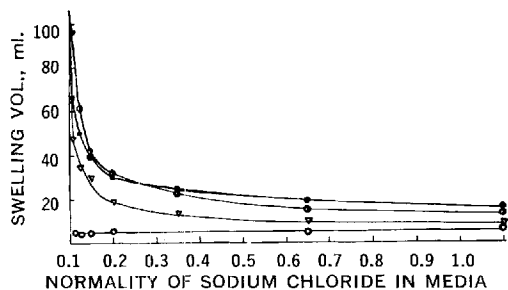


Fig. 1.—The swelling volumes of montmorillonites and starch in aqueous media containing various concentrations of sodium chloride. Key: ●, clay I; ●, clay II; ▽, clay III; ○, starch.

tion would be completely removed by 1 to 3 Gm. of clay by the ion-exchange reaction. The solution was divided into ten 50-ml. fractions. To these fractions were added different quantities of clay II, varying from 1 to 8 Gm. The clay was removed from the solution by centrifugation after it had been shaken for 3 hr. with the solution. Ten milliliters of the clear alcoholic fraction was pipeted into an aluminum weighing pan and evaporated to dryness on a hot plate at 50°. The weight of residue was plotted against the weight of clays added.

RESULTS

Particle Size.—The particle size (geometric mean diameter) of the discrete clay particles of clays I, II, and III was 0.15, 0.11, and 0.12 μ , respectively, with

a geometric standard deviation of 2.4 to 2.5 in each case. This does not reflect a significant difference between the discrete particle size of the various clay materials, although the aggregate particle size of each material as described earlier is quite different.

The surface area of each clay was also estimated using a gravimetric glycerol retention method (16). Based on an average of three replicate determinations for each clay, which were reproducible within $\pm 10\%$ for clay I and $\pm 5\%$ for clays II and III, the respective surface areas of the clays was 371, 339, and 300 M^2/Gm . This finding indicates that clay III, with the largest aggregate particle size (50 mesh), had the smallest available surface, and that microatomization of clay II also reduced its surface compared to clay I, according to the sorption procedure used.

Swelling Volume.—Figure 1 is a plot of the swelling volume of the three grades of clays and starch against the concentration of sodium chloride in the media. The swelling of the clays decreased as the concentration of electrolyte increased. This finding tended to substantiate the hypothesis of Norrish (17) that the second stage of swelling of a montmorillonite is essentially an osmotic one, since the increase in osmotic pressure of the medium caused a rapid decrease in the swelling of the clay. This could be a significant property when the clays are used as disintegrating agents for tablets and as suspending agents. In tablets containing large doses of strongly ionized chemicals, the chemicals might influence the swelling of the clay which, in turn, could decrease the disintegration rate; in suspensions, the strong electrolytes may affect the gel formation of the clays. The swelling of starch did not apparently depend on osmotic pressure and was

TABLE I.—MOISTURE SORPTION OF THE MONTMORILLONITES AND STARCH IN ATMOSPHERES OF VARIOUS RELATIVE HUMIDITIES

Material		Wt., Gm., and % Wt. Increase of Samples after Storage			
		Initial	7 Days	14 Days	21 Days
At 98% Relative Humidity					
Clay I	Wt.	2.007	2.470	2.572	2.528
	%	100	123.0	128.1	125.9
Clay II	Wt.	2.003	2.492	2.622	2.533
	%	100	124.4	130.9	126.5
Clay III	Wt.	1.972	2.439	2.517	2.451
	%	100	123.7	127.7	124.3
Starch	Wt.	5.704	6.382	6.532	6.416
	%	100	111.9	114.5	112.5
At 66% Relative Humidity					
Clay I	Wt.	2.058	2.235	2.240	2.236
	%	100	108.6	108.9	108.7
Clay II	Wt.	1.970	2.138	2.148	2.139
	%	100	108.5	109.0	108.6
Clay III	Wt.	2.018	2.182	2.185	2.180
	%	100	108.1	108.4	108.0
Starch	Wt.	5.548	5.691	5.754	5.702
	%	100	102.6	103.7	102.8
At 35% Relative Humidity					
Clay I	Wt.	2.030	2.090	2.089	2.088
	%	100	103.0	103.0	102.9
Clay II	Wt.	2.017	2.081	2.080	2.080
	%	100	103.2	103.2	103.2
Clay III	Wt.	2.053	2.118	2.115	2.115
	%	100	103.2	103.0	103.0
Starch	Wt.	5.547	5.584	5.597	5.546
	%	100	100.7	100.9	100.0

TABLE II.—SWELLING AND MOISTURE SORPTION OF COMPRESSED MONTMORILLONITES IN ATMOSPHERES OF VARIOUS RELATIVE HUMIDITIES

Material	Dimension	Initial	7 Days	14 Days	21 Days
		At 98% Relative Humidity			
Clay I	Vol., ml.	0.2484	0.4092	0.4192	0.3901
	Wt., Gm.	0.5008	0.6278	0.6412	0.6341
	Wt., %	100	125.4	128.0	126.6
Clay II	Vol., ml.	0.2503	0.3739	0.3829	0.3470
	Wt., Gm.	0.4927	0.6319	0.6464	0.6330
	Wt., %	100	128.5	131.2	128.5
Clay III	Vol., ml.	0.2473	0.4029	0.4253	0.3353
	Wt., Gm.	0.5157	0.6375	0.6605	0.6442
	Wt., %	100	123.6	128.1	124.9
At 66% Relative Humidity					
Clay I	Vol., ml.	0.2460	0.3076	0.2885	0.2907
	Wt., Gm.	0.4964	0.5318	0.5318	0.5310
	Wt., %	100	107.1	107.1	107.0
Clay II	Vol., ml.	0.2490	0.2765	0.2725	0.2761
	Wt., Gm.	0.4915	0.5200	0.5205	0.5202
	Wt., %	100	105.8	105.9	105.9
Clay III	Vol., ml.	0.2457	0.2897	0.2847	0.2891
	Wt., Gm.	0.5101	0.5374	0.5383	0.5376
	Wt., %	100	105.4	105.5	105.4
At 35% Relative Humidity					
Clay I	Vol., ml.	0.2449	0.2565	0.2575	0.2578
	Wt., Gm.	0.4886	0.4980	0.4979	0.4976
	Wt., %	100	101.9	101.9	101.8
Clay II	Vol., ml.	0.2458	0.2600	0.2505	0.2518
	Wt., Gm.	0.4907	0.4968	0.4923	0.4951
	Wt., %	100	101.2	100.3	100.9
Clay III	Vol., ml.	0.2473	0.2605	0.2598	0.2591
	Wt., Gm.	0.5110	0.5147	0.5146	0.5141
	Wt., %	100	100.7	100.7	100.6

TABLE III.—RADIOACTIVITY OF SODIUM CHLORIDE SOLUTIONS AFTER EQUILIBRATION WITH THE SODIUM IONS IN MONTMORILLONITE

Material		Na ₂ O Equivalent in 100 ml. of Soln., mg.			
		0	30	60	100
Clay I	c.p.m.	13,249	19,289	22,395	24,860
	% ^a	41.24	60.04	69.71	77.38
Clay II	c.p.m.	12,100	...	22,206	24,850
	%	37.66	...	69.12	77.35
Clay III	c.p.m.	16,839	...	24,040	25,898
	%	52.41	...	74.83	80.61

^a Per cent of original activity (32,126 c.p.m.) after average background count (219 c.p.m.) was subtracted.

TABLE IV.—Na₂O EQUIVALENTS IN MONTMORILLONITES

Material	Free Electrolyte, Na ₂ O	Exchangeable Electrolyte, Na ⁺	Equivalent mmole/Gm.
	Equivalent, mg./Gm.	Equivalent, mg./Gm.	
Clay I	13.08	18.63	0.601
Clay II	10.92	18.08	0.583
Clay III	17.83	16.19	0.523

not affected by the concentration of sodium chloride in the medium.

Moisture Sorption.—The hygroscopicity of a solid matrix has a direct effect on the stability of many active pharmaceutical ingredients. The hygroscopicity of clays may be influenced by their

chemical composition, the amount and type of exchangeable cation present, the particle size, and the surface area of the clay sample.

The results of the moisture sorption study are summarized in Tables I and II. At the same relative humidity condition, all three grades of montmorillonite sorbed approximately the same amount of moisture, although, physically each clay represents a different state of aggregation of the colloidal particles—flake, powder, and fine powder. The aggregate condition of the clays did not appear to affect the moisture sorption of the clays as supplied or as compressed disks. The clays in original powder form and the clays which had been compressed with a pressure of 50,000 p.s.i. for 3 min. also sorbed approximately the same amount of moisture in a period of 7 days or longer. This shows that moisture penetrates the compressed clay rather rapidly. The montmorillonites were found to swell (Table II)

in a humid atmosphere, with the volume of swelling approximately equal to the volume of the water absorbed.

Determination of the Exchangeable Cation of Montmorillonite with Radioactive Sodium.—Consider the case of a clay sample suspended in distilled water containing a trace of $^{22}\text{NaCl}$. The free electrolyte in the clay sample dissolves freely in the medium while the exchangeable cations attach to the clay particles. The ^{22}Na , being chemically identical to natural sodium, exchanges indiscriminately with the exchangeable sodium and the sodium in the medium. At equilibrium the relationship in Eq. 1 would exist.

$$\frac{\text{free Na in clay}}{\text{total Na in clay}} = \frac{\text{radioactivity in soln. at equilibrium}}{\text{initial radioactivity}} = \text{free electrolyte in clay, \%} \quad (\text{Eq. 1})$$

Consider another sample of clay suspended in saline solution containing a trace of $^{22}\text{NaCl}$ and x moles of NaCl . The free electrolyte in the clay sample dissolves freely in the medium and mixes with the sodium chloride originally in the medium. The ^{22}Na exchanges indiscriminately with the exchangeable sodium and the sodium in the medium. At equilibrium, the relationship in Eq. 2 is obtained.

$$\frac{\text{free Na} + x \text{ moles of Na}^+}{\text{total Na} + x \text{ moles of Na}^+} = \frac{\text{radioactivity in soln. at equilibrium}}{\text{initial radioactivity}} \quad (\text{Eq. 2})$$

Solving Eqs. 1 and 2, one can estimate the amount of exchangeable sodium and the amount of soluble electrolyte in the clays.

Table III expresses the radioactivity, in terms of c.p.m. and percentage of initial activity, of 2 ml. of the solutions of radioactive sodium chloride which had been mixed and ion-exchanged with the clays according to the procedure previously outlined.

Utilizing the data in Table III, the free electrolyte and exchangeable electrolyte contents were calculated and are summarized in Table IV.

This experiment shows that the sodium in montmorillonite exists as exchangeable cation as well as free electrolyte. The presence of free electrolyte in the clays may be due to the presence of electrolyte in natural water which is used to wash the clays. Comparing the ion-exchange property and the swelling volume of the clays, it appears that the ion-exchange capacity of the clay is not the major factor that influences the swelling of the clay.

Considering that the cation-exchange capacity of clay II is 0.583 (Table IV) and that the surface area of the same clay is 339 $\text{M}^2/\text{Gm}.$, the average distance between two ionized sites can be calculated to be about 10 Å. This is a reasonable estimation. It shows that the ion-exchange sites are distributed throughout the internal surface of the clay, and the cation-exchange activity takes place at the interior of the clay particles.

Montmorillonite Reaction with Cationic Drugs.—Figures 2 to 5 describe the sorption of the four drugs by montmorillonite. At first the drug concentration decreased very rapidly with the increased quantity

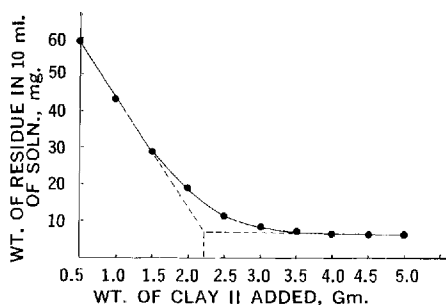


Fig. 2.—Sorption of methapyrilene by montmorillonite.

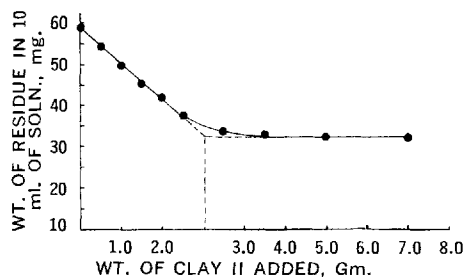


Fig. 4.—Sorption of triethylamine by montmorillonite.

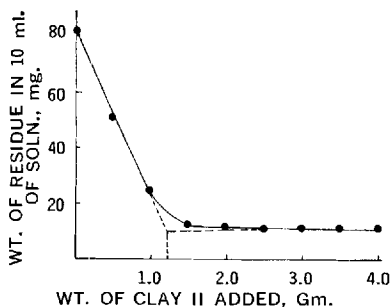


Fig. 3.—Sorption of brucine by montmorillonite.

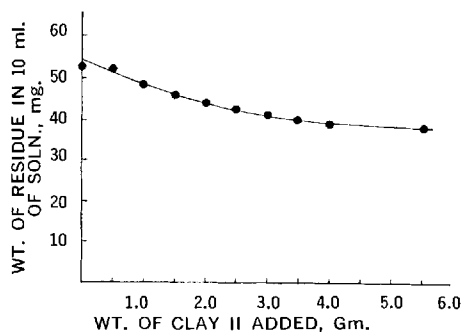


Fig. 5.—Sorption of niacinamide by montmorillonite.

TABLE V.—ABSORPTION OF ALKALOIDAL DRUGS BY CLAY II

	Methapyrilene HCl	Brucine Sulfate	Triethylamine HCl	Niacinamide HCl
Initial concn. of drugs, mg./ml.	5.89	8.11	4.90	5.45
Amt. of drug in 50 ml. of soln., meq.	0.989	0.915	1.780	1.718
Clay required to absorb all drug in 50 ml. of soln., Gm.	1.725	1.225	3.05	...
Ion-exchange capacity of clay, meq./Gm.	0.583	0.583	0.583	0.583
Drug exchanged with cation in clay, meq.	1.006	0.714	1.778	...
Drug adsorbed by clay, meq.	-0.017	0.201	0.002	...

of clay added. Finally, when all drug in the solution was removed by the clay, the weight of the residue-exchange product from the clay ceased to exchange with further addition of the clay. Each curve shows two distinct straight segments. The intersection at which the extensions of these two straight portions meet shows the weight of clay required to pick up all the drugs from the solution.

Table V illustrates the amounts of drug exchanged with the cations of the clay and the amount of drug adsorbed by the clay. The "initial concentrations of the drugs" and the amount of "clay required to absorb all of the drug in 50 ml. of solution" are obtained from Figs. 2-5. The "ion-exchange capacity of the clays" is obtained from the previous experiment. The "drug exchanged with the cation of the clay" is calculated by multiplying the "ion-exchange capacity" by "the amount of clay required to absorb all of the drug in 50 ml. of solution."

Table V shows that the clay quantitatively picks up methapyrilene and triethylamine by an ion-exchange reaction, and brucine partly by ion-exchange and partly by an adsorption reaction. Niacinamide was neither adsorbed by nor exchanged with the cations of the clay.

Brucine sulfate, being a large molecule, is picked up by the clay to an extent of 35% above the cation-exchange capacity of the clay; yet, triethylamine hydrochloride, being a small molecule, is picked up by the clay quantitatively with respect to the ion-exchange capacity of the clay. This is a further strong indication that the absorption of triethylamine by the clay is not a surface phenomenon of the clay. It is, instead, ion exchange.

Niacinamide, being an extremely weak acid, may dissolve in the alcohol in the form of niacinamide base, rather than the ionic form of its hydrochloride salt. Another possibility may be that the positive charge on the niacinamide cation may resonate and spread throughout the molecule, and weaken the charge of the cations, so that they cannot replace the original cations on the clay which are strongly charged. This may explain why niacinamide was not bound by the clay.

DISCUSSION AND CONCLUSIONS

The swelling of montmorillonite depends upon two main mechanisms—namely, adsorption and osmosis. The swelling by adsorption is illustrated by the adsorption of moisture, glycerol, and brucine

by the clay. The swelling of montmorillonite by osmosis can be illustrated by the depression of the swelling volume of the clays by electrolytes.

The data on the measurements of specific surface area of the clays are the best proof of particle swelling of clays by adsorption. The glycerol and brucine actually penetrate into the interior of the clay particles. The adsorption of glycerol, moisture, and brucine to the internal surface of the clay particles results in swelling of the particles of the clay. Since the initial swelling of the clay is essentially by adsorption, the disintegrating activity of the clay on tablets may be hypothesized as primarily due to the adsorption swelling rather than osmotic swelling of the clay. If this hypothesis is true, then, many other clays which are good adsorbents may also be good disintegrating agents.

The cation-exchange activity of montmorillonite occurs at the internal surface of the clay particles. The physical entrapment of the organic molecules between the silica-alumina-silica layers may explain the strong and partial irreversible binding of organic molecules by clays. One can further theorize that the entrapment of cationic drugs in the interior of the clay particles may be applied to stabilize some unstable drugs and to produce sustained-release medications.

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