

THE ASSAY OF PHARMACEUTICAL CLAYS

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WILFRED SMITH has described¹ a method of estimating the montmorillonite content of clays by measuring the amount of barium ions adsorbed from normal barium chloride solution, subsequently eluted with ammonium chloride solution, precipitated and weighed as barium sulphate. There is need for a simpler and quicker method of assay, since the barium method is complicated and requires great care in execution; moreover, some of the results found by it are much higher than one would expect. Plesch and Robertson² have described a method of measuring the adsorption of basic dyes on to ionogenic surfaces; this differentiated between physical and chemical adsorption. By choice of conditions the cation exchange capacity of clays could apparently be measured. The present authors therefore set out to confirm this work, using as test materials the same series of clays as was used by W. Smith, in the hope that a simpler and more accurate method of assay could be worked out for pharmaceutical clays. The clays were also subjected to a number of simple tests, which, when taken together, are of some diagnostic value, namely, apparent specific gravity, colour, and reaction with universal indicator solution.

APPARENT SPECIFIC GRAVITY

Method.—The British Standard Specification method of measuring the apparent specific gravity of powders^{3,4} requires about 42 g. of powder for a test. As such large quantities are frequently not available, an apparatus made by W. B. Nicolson (Scientific Instruments), Ltd., Glasgow, was used. This requires a very much smaller quantity of powder and gives results of comparable accuracy. It is a development of an apparatus first made by the Fullers' Earth Union, Ltd., and consists of a 25 ml. graduated cylinder securely held on a platform, which is caused to fall through 0.5 cm. on to a hard surface by means of a cam.

The powder is first shaken strongly in a bakelite-capped glass bottle and poured carefully through a funnel into the glass cylinder until the 25 ml. mark is reached. The vessel is then allowed to fall 10 times at 5-second intervals and the volume is read after a further 10 seconds. The whole test is repeated a second time with the same or a new sample, and if the apparent specific gravity (weight/volume) of the two tests differs by more than 0.005, the test is repeated and the aberrant result discarded. The average of the accepted values is taken. For assay work this test is accurate enough, though for certain research purposes the clay may be first dried at 105°C. and lightly brushed through a 30-mesh sieve instead of shaking in a bottle. In the present tests the clays were tested as received, but their moisture contents were separately measured, as recorded in Table I.

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TABLE I
APPARENT SPECIFIC GRAVITY, MOISTURE CONTENT, COLOUR AND UNIVERSAL INDICATOR
REACTION OF A NUMBER OF CLAYS

Clay	Apparent Specific Gravity	Moisture per cent.	Natural Colour	Universal Indicator Reaction (on dry powder)
1. Kaolin, heavy BP	0.311	0.7	white	orange, pH 5 to 5.5 pale yellow, pH 6.5 to 7 yellow-green, pH 7 to 7.5
2. Kaolin, light BP	0.256	0.5	white	
3. Osmokaolin	0.312	0.8	white	
4. Floridin, Filtrol	0.546	10.0	drab	brown red, olive border brown
5. Floridin xs	0.447	10.0	mauve	
6. Floridin xxs	0.578	11.0	drab	
7. Kaogel	0.606	13.7	white	green, pH 8.5 brown, olive border brown, olive border
8. White earth A	0.792	12.4	pink-buff	
9. White earth B	0.818	12.9	light drab	
10. Surrey powder	0.763	13.3	brown drab	olive green brown-red, green border
11. Redhill natural earth ...	0.875	11.3	grey drab	
12. Fulbent 182	0.792	11.1	drab	crimson, pale green border blue-green, pH 9
13. Fulbent 150	0.810	10.5	drab	
14. 249	0.437	15.7	grey-white	red crimson, pale green border
15. KN 11	0.441	15.8	buff-white	
16. YB 20	0.571	10.9	drab	olive green scarlet, olive border faint brown brown-red, green border
17. CT 200	0.680	13.0	brown	
18. SP 4	0.900	9.1	dark grey, greenish	
19. Lloyd's reagent (I) ...	0.605	10.9	light pink-brown	
20. Bentonite Clay Spur (I)	0.661	14.1	very light drab	
21. North African bentonite	0.835	13.4	white	bright green, pH 8 brown with olive tinge.

Results.—The apparent specific gravities fall into several fairly distinct groups which reflect differences in mineralogical composition and fineness of grinding.

TABLE II

Number of Clay	Type of Clay	Apparent Specific Gravity	Chief Mineral	Fineness
1, 2, 3 ...	Kaolins	<0.4	Kaolinite	ca. 300 mesh
4, 5, 6 ...	Floridins	0.4—0.6	attapulgite	ca. 40 mesh
14, 15 ...	Activated earths	0.4—0.5 (or wider range)	montmorillonite (acid-treated)	(large surface)
16, 17, 19, 21...	Finely-ground Fuller's earth and bentonite	0.55—0.7	montmorillonite	ca. 200 mesh
10, 11 ... 12, 13, ... 8, 9 ...	Normally ground Fuller's earth, bentonite & white earths	} 0.7—0.9	montmorillonite	ca. 100 mesh

The apparent specific gravity test alone separates the kaolins from the white earth with which they might be confused. The Floridins tested were in the form of a fine sand; montmorillonite of the same particle size would give an apparent specific gravity of about 0.9 or over; the low values of Floridin are characteristic of the clay mineral attapulgite.

COLOUR

The colours of clays are difficult to describe. They may be compared with one another or with known samples if small samples are squashed

together under a sheet of glass. Surprisingly small differences in colour may be detected in this way. For research purposes a photoelectric brightness tester may be used. In the table of results, "drab" is used to describe a yellowish grey, and "buff" a light biscuit brown with a much lower grey component.

REACTION WITH UNIVERSAL INDICATOR

Method.—A small pile of clay is compressed with a spoon to make a shallow smooth basin. 3 drops of B.D.H. Universal Indicator solution are dropped into the centre of the basin. The chromatographic colour scheme after about 2 minutes is described.

Results.—Kaolins show a single colour indicative of their *pH*. The activated earth 249 shows a strong red colour, but the other activated earth KN11 is very similar to the synthetic bentonite Fulbent No. 182 in showing a crimson centre with a pale green border, though Fulbent No. 150 and clay spur bentonite are strongly alkaline (bluish green and bright green respectively). The natural Fuller's earth CT200 also has a scarlet centre and olive border; it is a naturally acid clay. Most of the other clays show fairly characteristic colours and commonly have a ring of different colour around them. The test, first used by the Fullers' Earth Union, Ltd., is a useful one for comparing an unknown with a known sample of earth, but it is not easy to understand all the colour changes observed. It will help in some cases to detect an acid-activated Fuller's earth.

MOISTURE CONTENT

The moisture content was determined by drying for 2 hours or more at 105°C. to constant weight. The kaolins are sharply distinguished from all the other earths.

METHYLENE BLUE ADSORPTION

Method. Preparation of dye solution.—Methylene blue is unfortunately unobtainable as a chemical of constant and known purity. Not only may chemical impurities be present, but the water of hydration is not constant, though the compound is sometimes given in text-books as being $C_{16}H_{18}N_3SCl \cdot 3H_2O$. The equivalent weight of the pure anhydrous dye is 319.9. The dye therefore requires to be standardised for accurate work either by titrimetric reduction (Davidson⁶), by reference to a standard solution of methylene blue, or by standardisation with a clay whose exchange capacity has been accurately measured by another method.

Nevertheless, Davidson showed that the different samples of methylene blue which he used (B.D.H. Standard Stain), after recrystallisation from water and air-drying, contained only about 0.7 per cent. of chemical impurity besides the water of hydration, which could be estimated by drying at 105°C. for 4 to 22 hours. For assay work we recommend estimating the moisture content of the dye only and neglecting the small amount of chemical impurity which is found in the best grades of

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methylene blue. This counteracts to some extent the tendency of the test to give slightly low results compared with barium ion exchange.

A nominally 0.3 per cent. solution of dye has been found to be the most generally useful concentration; this is obtained by weighing out 3 g. of the air-dry dye, dissolving it in about 800 ml. of hot water, transferring when cool to a 1-l. measuring flask, and adjusting to the litre mark with water when the solution has come to room temperature. After being well shaken, the solution is ready for use. For china clays, a nominally 0.1 per cent. solution is more convenient to use.

Preparation of clay.—Granular or very coarse clays are ground to pass a 100-mesh sieve. As the moisture content of the clay has to be determined by drying for 2 hours or more to constant weight at 105°C., the dried sample may be used for the dye adsorption test. Very occasionally this gives slightly low results, but they are reproducible. In the present series the moist clays were used in the tests.

Dispersibility.—The dispersibility of the clay in water is first tested by shaking about 0.2 g. of the clay with 5 ml. of water in a test-tube. Clays going into a homogeneous suspension quite readily require no further treatment, but those displaying a reluctance to disperse or a tendency to swell (e.g., bentonites, "Fulbent," or "Kaogel") must be shaken with 5 ml. of water in a glass-stoppered bottle and left overnight before the treatment with the dye. Allowance must be made for the dilution of the dye by this amount of water.

Dye adsorption test.—A suitable weight of clay is transferred to a glass-stoppered bottle, and if necessary 5 ml. of water is added, as stated above. An exact quantity of standard dye, e.g., 50 ml. of 0.3 per cent. dye—though we worked with 25 ml. usually, is added by pipette, and the mixture shaken for 20 minutes. By the use of a box or a shaking machine a number of tests may be carried out simultaneously.

The suspension is filtered through a 15-cm. Whatman's No. 4 filter-paper into a boiling tube, the first light-coloured runnings are rejected and the remaining filtrate shaken well when the bulk of the liquid has been collected. Small volumes (e.g., 2 ml.) of the filtrate are then measured by pipette into a 100-ml. measuring cylinder, and water is added until the diluted solution exactly matches one of several standard solutions of dye when they are compared in matched tubes. These matching solutions are made up by the exact dilution of the standard dye solution used in the adsorption tests, for example, 0.005, 0.0025, 0.001 and 0.0005 per cent. solutions. Alternatively the colour of the filtrates may be measured photoelectrically.

Weight of clay.—The weight of dry clay required for this test is that which, after the adsorption under specified conditions has taken place, leaves in the filtrate between 0.5 and 15 per cent. of the original dye ("excess dye"), the clay having adsorbed the remainder. This means that several tests will have to be made before the excess dye falls within the limits set, but the preliminary tests—colour, apparent specific gravity and indicator test—usually give one some idea of the nature

of the clay and therefore approximately of the exchange capacity to be expected. In our tests the results were obtained by an average of three tests per sample.

Pharmaceutical kaolins	4-6 milliequivalents per 100 g.		
Attapulgites ("Floridins")	ca. 20	"	" "
Fuller's earths	50 to 70	"	" "
White earths	ca. 75	"	" "
Activated earths	ca. 50	"	" "
Synthetic bentonites	ca. 80	"	" "
Natural bentonites	80 to 100	"	" "

The cation exchange capacity in milliequivalents per 100 g. of dry clay is worked out in the following manner:—

$$\left(\frac{\text{percentage of dye initially} - \text{percentage of dye in filtrate}}{\text{equivalent weight of dye}} \times \frac{100}{\text{volume of dye used in ml.}} \right) \times \text{percentage purity of dye} \times \text{dry weight of earth}$$

Example.—Fuller's earth, YB20.

Percentage of dye initially	0.3
Percentage of dye in filtrate	0.01
Percentage of dye adsorbed	0.29
Moisture content of dye	20.6 per cent.
Purity of dye taken as	79.4 per cent.
Milliequivalent of dye	0.3199 (anhydrous)
Volume of dye solution used	25 ml.
Weight of clay (moist)	0.301 g.
Moisture content of clay	10.9 per cent.
Dry weight of clay	0.301 × 0.891 g.

The ionic exchange capacity therefore is:—

$$\frac{0.29 \times 79.4}{0.3199 \times 4 \times 0.301 \times 0.891} = 67.1 \text{ milliequivalents per 100 g.}$$

Examination of test procedure.—Ionic exchange adsorption proceeds much more quickly than physical adsorption. The following series shows the effect of different times of contact on the result, using YB20 and solutions at room temperature, 18.5°C.

4 minutes' shaking	62.3 milliequivalents per 100 g.
10 " "	63.0 " "
20 " "	65.2 " "
40 " "	67.1 " "
120 " "	67.3 " "

From these results it was concluded that 20 minutes' shaking at room temperature was likely to be a measure mainly of chemisorption. It is of interest that Borland and Reitemeier⁷ have recently shown by using radioactive calcium, ⁴⁵Ca, that the cations of an element in solution are in

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kinetic equilibrium with the exchangeable cations of the same element and that the equilibrium is complete or virtually so after shaking for $\frac{1}{2}$ to 1 hour, the technique not permitting the study of shorter periods.

Strength of solution.—The effect of the initial concentration of dye should be much less marked with chemisorption than with physical adsorption. The following tests were carried out at 20 minutes' contact and at 18.5°C., using YB20 as before:—

Initial dye concentration per cent.	Dye adsorbed m. eq./100 g.
0.30	63.3
0.25	63.3
0.20	62.0
0.15	59.2
0.10	59.7
0.05	61.7

The error of weighing increases with decreasing initial concentration of dye. If this is taken into account, it appears that the values obtained are not greatly affected by the initial concentration of the dye and are probably a true measure of chemical rather than physical adsorption. In

TABLE III
IONIC EXCHANGE CAPACITIES OF CLAYS MEASURED BY METHYLENE BLUE ADSORPTION
AND BY BARIUM ION EXCHANGE

Clay	Dye		Weight of Clay (moist) g.	Filtrate Strength per cent.	Excess Dye per cent.	Exchange Capacity milliequivalents per 100 g. clay	
	Volume ml.	Strength per cent.				Methylene Blue	Barium ions (Smith)
1. Kaolin, heavy BP ...	20	0.1	1.123	0.0003	0.3	4.44	4.28 ^a
2. Kaolin, light BP ...	20	0.1	1.083	0.0003	0.3	4.59	4.28
3. Osmokaolin ...	25	0.2	2.187	0.006	0.3	5.55	5.41
4. Floridin, Filtrol ...	25	0.3	1.097	0.045	15.0	16.03 ^b	21.43
5. Floridin xs ...	25	0.3	1.537	0.08	26.7	9.87 ^b	19.46
6. Floridin xxs ...	25	0.3	0.935	0.035	11.7	19.75 ^b	21.00
7. Kaogel ...	30	0.312	0.210	0.025	8.0	118.0	90.1
8. White earth A ...	25	0.3	0.254	0.0325	10.8	74.6	95.7
9. White earth B ...	25	0.3	0.267	0.03	10.0	71.9	65.3
10. Surrey Powder ...	25	0.3	0.317	0.0425	14.2	58.1	93.2
11. Redhill natural earth ...	25	0.3	0.420	0.045	15.0	42.5	79.9
12. Fulbent 182 ...	30	0.312	0.293	0.03	9.6	80.7	240.5
13. Fulbent 150 ...	30	0.312	0.298	0.03	9.6	78.8	276.0
14. 249 ...	25	0.3	0.389	0.036	12.0	50.0	60.0
15. KN 11 ...	25	0.3	0.435	0.01	3.3	49.1	55.3
16. YB 20 ...	25	0.3	0.301	0.01	3.3	67.1	120.2
17. CT 200 ...	25	0.3	0.337	0.015	5.0	60.3	68.6
18. SP 4 ...	25	0.3	0.417	0.00125	0.42	48.9	71.5
19. Lloyd's reagent (1) ...	25	0.3	0.326	0.045	15.0	54.5	97.3
20. Bentonite Clay Spur (1)	30	0.312	0.243	0.01	3.22	107.7	100.3
21. North African Bentonite	30	0.312	0.293	0.035	11.2	81.3	76.2

a. Or 3.60; not known which of two samples was sent.
b. Ground to pass 100 mesh sieve.

all cases there was only a small amount of dye left over in the filtrate by adjustment of the weight of clay.

Excess dye.—Owing to the fact that van der Waals or physical adsorption is greatly affected by differences of time of contact and temperature, results show a considerable amount of scatter when the amount of dye used is much in excess of that required to satisfy the cation exchange capacity. The following results show the usual relationship. Again YB20 is the clay used.

Excess dye in filtrate per cent.	Dye adsorbed m. eq./100 g.
55.0	81.1
28.8	71.4
18.3	69.2
10.0	65.8
3.3	65.2

Temperature.—When the excess of dye is small, temperature has little effect on the results, at least between 16° and 75°C.

DISCUSSION

The cation exchange values, measured by methylene blue adsorption, appear to be fairly reliable between 2 and 12 per cent. excess of dye. For general assay purposes an excess between 0.5 and 15 per cent. is probably accurate enough.

The experimental error within the accepted range of excess dye is difficult to judge from the number of experiments done (about 100). Results with the two Fulbent samples show that a high degree of reproducibility is sometimes possible:—

Fulbent 182	16.0 per cent. excess of dye	72.7 m.eq./100 g.
	9.6 " " " " "	70.7 " "
Fulbent 150	17.9 " " " " "	71.4 " "
	9.6 " " " " "	69.4 " "

The experimental error is believed to be within 5 per cent. for small values to 2 per cent. for high values.

Of course, aberrant results are commoner when the excess of dye is greater than in the accepted range, since the van der Waals component of the adsorption is much affected by temperature, time of contact, dispersion of clay, as well as the concentration of initial dye solution and of clay in suspension. The physical adsorption of different clays behaves differently in its response to these factors, as has been explained by Plesch and Robertson². Thus, 249, the only strongly acid earth, shows a very rapid rise in amount of dye adsorbed with increase in excess of dye. The only other activated earth, KN11, which is much less acid, shows a much smaller physical component of adsorption when the excess of dye is high. Most of the natural Fuller's earths and bentonites show a small and similar rise in adsorption with increasing excess of dye.

Comparison with barium exchange results.—The three kaolins tested show 2 to 3 per cent. higher dye adsorptions than the barium results. The

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results for the Floridin earths are all rather lower than the published figures for attapulgite, about 25 to 30 m.eq./100 g.; the result found by Plesch and Robertson by the methylene blue method was 25.0. There is reasonably good agreement between the values in the case of the three kaolins, Floridin XXS, Fuller's earth CT200, white earth B, activated earths 249 and KN11, bentonite Clay Spur (1), and North African bentonite, nearly half the specimens.

Cation exchange capacities measured by the barium method are much higher than the methylene blue results in the case of Redhill natural Fuller's earth, Surrey Powder, YB20, SP4, and Lloyd's Reagent, in fact, 88, 60, 80, 46 and 78 per cent. higher, respectively. With White Earth B (28 per cent. higher) the difference is not so marked. Indeed with 249 and KN11, the activated earths, one might have expected an even higher result by the barium method, because these clays contain residual sulphate ions from the process of activation.

Results by the barium method are very much higher than those by the dye method in the case of Fulbent 182 (198 per cent.) and Fulbent 150 (252 per cent.). The explanation may be that with these synthetic bentonites some barium ions may have been precipitated as barium carbonate when the clay was treated with barium chloride. The test with Universal Indicator showed that No. 150 was very alkaline. On the other hand methylene blue appears to be much less affected by comparatively large changes in alkalinity. One reason why the rather alkaline sodium-montmorillonite, bentonite, gives higher exchange capacities than those of calcium-montmorillonites, *e.g.*, Fuller's earths, is that sodium-montmorillonite dries with a different amount of water of hydration from that of the calcium-clays.

The cation exchange capacity of Redhill Fuller's earth is unexpectedly lower than that of Somerset Fuller's earth SP4 which contains less montmorillonite; this is shown by both methods. The two activated earths have lower exchange capacities than Surrey Powder; both methods agree here too. It is known that the process of activation reduces the exchange capacity of Fuller's earth while greatly increasing the specific surface.

Lloyd's reagent gives almost the same result as Surrey Powder; it is said to consist of the finest particle size fractions of Fuller's earth. Its apparent specific gravity lies between those of the other two finely ground Fuller's earths, YB20 and CT200, both of which leave only a small residue on a 200 mesh sieve. This is the fineness favoured for pharmaceutical Fuller's earth. YB20 and CT200 have rather higher exchange capacities than Surrey Powder and SP4, of normal commercial grinding, YB20 having the highest exchange capacity among the Fuller's earths. The result of YB20 obtained by the barium method is apparently much too high.

SUMMARY

1. The estimation of cation exchange capacity of clays by barium ion exchange as a pharmaceutical assay method is shown to be not without pitfalls.

2. Adsorption of methylene blue offers an alternative method which gives more reliable results and which is capable of being carried out with much simpler equipment and at far greater speed.

3. By measuring the apparent specific gravity of the sample of clay and observing its colour and reaction with Universal Indicator solution, a rough guide to the nature of the clay may be obtained, and this enables one to reduce the number of dye adsorption tests required to establish the cation exchange capacity.

4. The main disadvantage of the methylene blue determination is the difficulty of establishing the purity of the dye. This can be done by chemical means; but the chemical impurities in the highest grades of dye supplied by the makers are not believed to be large or variable enough to invalidate a method which shows promise in the pharmaceutical assay of clays. Only the moisture content of the dye need be estimated.

REFERENCES

1. Smith, *J. Pharm. Pharmacol.*, 1947, **20**, 367.
2. Plesch and Robertson, *Nature*, 1948, **161**, 1020.
3. *B.S.S.* 1460:1948.
4. Ault, *J. Soc. chem. Ind.*, 1948, **67**, 313.
5. Robertson, *Disc. Farad. Soc.*, 1949, No. 7, 163.
6. Davidson, *J. Textile Inst.*, 1947, **38**, (12), 1408.
7. Borland and Reitemeier, *Soil Sci.*, 1950, **69**, 251.