THE ROUTINE DETERMINATION OF THE ANTACID EFFICIENCY OF ALUMINIUM HYDROXIDE GELS

By P. R. Clemow and J. W. Lowry
From the Laboratories of John Wyeth and Brother Ltd.

Received April 28, 1954

The test for neutralising capacity specified in the monographs of the British Pharmaceutical Codex 1949 for aluminium hydroxide gel and dried aluminium hydroxide gel does not give a complete picture of the antacid action of the gels for two reasons. Firstly there is a large excess of acid present throughout the test, which is not normally the case *in vivo* and secondly the only determination made is of the total amount of acid neutralised at the end of the test period. This test eliminates the very poor quality dried gels but does not give any information on the rate at which the neutralisation occurs, and this is important in determining the therapeutic value of the gels. Many tests have been devised[1–8] to assess antacid efficiency but nearly all of these have had as their aim the comparison of a wide range of antacid substances. The work reported in this paper was undertaken to devise a routine test for aluminium hydroxide gels only and this limitation of scope has meant that some of the refinements of these general methods could be eliminated, provided that reproducibility could be obtained. The most recent methods published were those described at the British Pharmaceutical Conference 1953 by Armstrong and Martin[6]; Gore, Martin and Taylor[7]; and Brindle[8] and these three will be discussed in more detail as they have put more emphasis on the preparations of aluminium.

The method of Armstrong and Martin demands continuous and close attention for a period as long as 90 minutes, a period which is possibly unreal physiologically and very demanding both of time and labour for routine purposes. In addition, the acid medium contains pepsin, which, being a natural product, cannot be guaranteed to give completely consistent behaviour from one delivery to the next. Finally the adjustment of the initial *p*H of the hydrochloric acid by dilution means that varying strengths of acid will be used and consequently varying quantities will be required to neutralise equivalent amounts of antacid. The use of "room temperature" by Gore, Martin and Taylor is difficult to justify as even in this country it could range from 15° C. to 25° C. and elsewhere the range could be even greater. As will be seen later, close temperature control is essential. The strength of acid used for the initial solution is lower than that used by other investigators and lower than the 0·5N to 0·1N[9,10] usually accepted as the concentration of gastric juice. Brindle pointed out that the artificial gastric juice used by him was variable in its initial *p*H and there is the possibility (which has not been investigated) that there was some effect on the intermediate values found during the test. This

uncertainty cannot be permitted in a test where standards of quality are to be established.

The aim of our investigation was to establish a suitable simple technique for routine use. For this, the following points needed consideration:— (1) The amount and form of the alumina. (2) The quantity and strength of the acid. (3) The use or omission of enzymes and buffering agents. (4) Temperature of test. (5) Rate of stirring. (6) Duration of test. (7) Reproducibility of results. (8) Discrimination.

(1) *Amount and Form of Alumina*

For this work the quantities chosen were the maximum B.P.C. doses, namely 0·6 g. of dried gel and 8 ml. of the liquid, each equivalent to approximately 0·3 g. of Al_2O_3. The form of the alumina should be that in which it is administered, namely liquid—perhaps diluted with water—powder or tablet. For the majority of these experiments dried powder was used, the whole of it having been rubbed through a 100-mesh sieve. The remainder of the experiments were carried out using liquid gel.

(2) *Quantity and Strength of Acid*

The first and perhaps most obvious idea would be to use the quantity present in the stomach but this is actually far from constant. For example Adams, Ensel and Myers[9] found the volume of acid in the fasting stomach could vary from 30 ml. to 300 ml. and Kay[11] has shown that the *average* amount of hydrochloric acid present can range from 70 mg. (as HCl) in normal persons to 265 mg. in duodenal ulcer cases. A better line would be to take a quantity of acid which bears some relation to the amount of alumina used, such as, for example, an equivalent amount, so that the results obtained might also give some indication of neutralising capacity. The dried gel must have a neutralising capacity (B.P.C.) better than 200 ml. of 0·1N acid per g. This is equivalent to a minimum of 240 ml. of 0·05N acid for 0·6 g., so 250 ml. of 0·05N would be a convenient amount to take for the test. The choice of 0·05N for acid strength is probably reasonable although strengths up to 0·1N are mentioned for "appetite juice"[9,10]. The minimum neutralising capacity of the liquid gel is one-tenth that of the dried material so that the most appropriate quantity to take when testing liquid gels would be 6 ml. rather than the maximum dose of 8 ml. However, as the maximum dose was chosen as our guide, the 8 ml. quantity has been retained in these tests, using 250 ml. of 0·05N hydrochloric acid, or its equivalent, in all cases.

(3) *Enzymes and Buffering Agents*

There is some case for the use of enzymes and buffering agents such as pepsin and peptone for the reason that their presence gives a better representation of stomach conditions. There are several arguments against their use, some of which have already been stated but to permit a more definite conclusion to be reached some experiments were made with such additions, and the results are discussed later.

(4) *Temperature of Test*

The natural choice is 37° C., the physiological temperature, and this means that a thermostat bath is required. If, however, the temperature coefficient of the reaction is not considerable then conditions approximating to "room temperature" could be used without precise control. A series of tests was made at different temperatures to establish whether or not close temperature control was necessary.

(5) *Rate of Stirring*

This was an unknown factor in the test and 3 different rates of stirring were tried.

(6) *Duration of Test*

For routine purposes the test should be completed in the minimum of time and in any case it would be meaningless to continue the test for longer than the antacid would be in the stomach. According to Mutch[4], even massive doses of buffering agents do not exert their effect for more than about 1 hour, presumably because of loss to the duodenum. Thus the test should certainly be completed within an hour and, except for experiments on the effects of temperature, all tests were concluded within 60 minutes.

(7) *Reproducibility of Results*

This is an important point and a controlling factor in establishing the exact conditions required. It was confirmed by repeated tests on well-mixed bulk samples.

(8) *Discrimination*

Good discrimination is a valuable characteristic as it enables limits to be set which can easily be maintained. For this reason considerable importance was attached to the need for a test having this property.

Methods of Testing and Apparatus

The simplest form of test would be the addition of alumina gel to a suitable quantity of acid and the measurement of *p*H at intervals. This becomes quite a practical proposition once the characteristic curves of a number of suitable gels have been established, because for further testing, the *p*H at a few chosen time intervals is all that is needed to indicate the quality of a gel. This has been developed as Method I. An alternative procedure which would also give some information on the behaviour of the gel when in considerable excess, would be to simplify the Armstrong and Martin method, by reducing the number of additions of acid and not withdrawing any of the mixture. Thus two additions of 5 ml. of 0·5N acid to 150 ml. of 0·05N acid would give the equivalent of the 250 ml. of 0·05N acid chosen as a suitable amount for the test. The reason for suggesting stronger acid for the additions is that volume and temperature changes would be small and the time taken reduced. This has been developed as Method II.

For all these experiments a 250-ml. squat form Pyrex beaker was used to hold the acid medium and the test was carried out in a thermostat bath. A glass stirrer having two blades, about 3·5 cm. overall diameter, was used to agitate the mix, and the *p*H electrodes, glass and calomel respectively, were arranged so that measurements of *p*H could be made at frequent intervals without interrupting the stirring. The procedure was to measure the acid medium into the beaker, heat to just below the test temperature and put the beaker into the thermostat bath. The stirrer and electrodes were then put into position and the stirrer left running until the correct temperature had been obtained, when the initial *p*H of the solution was measured. The weighed quantity of sample was then added quickly and *p*H readings were taken at measured intervals of time.

Experimental

Method I

The first 2 sets of experiments were planned to test the effects of stirring and temperature and for this series 0·6 g. of dried gel was used in 250 ml. of 0·05N hydrochloric acid.

Rate of Stirring. 3 rates of stirring were tried, 120 r.p.m., which kept the powder in suspension but did not give much turbulence, 240 r.p.m., which seemed to be reasonably vigorous, and 350 r.p.m., which was the fastest speed attainable without splashing. As will be seen from Table I, the variations in rate of stirring have very little effect. The wider difference at 15 minutes is largely due to the velocity of reaction at this stage when only a few seconds are needed for a change of 0·1 *p*H unit.

TABLE I

Effect of stirrer speed on the velocity of reaction of alumina gel with acid

Speed of Stirring r.p.m.	Time in Minutes						
	0	5	10	15	20	25	30
	*p*H readings						
120	1·36	1·60	1·95	2·55	3·55	3·70	3·70
240	1·38	1·61	2·00	2·80	3·65	3·75	3·80
350	1·36	1·61	2·00	2·70	3·65	3·75	3·77

Variations of Temperature. To investigate the need for temperature control, 6 temperatures were chosen, 15°, 20° and 25° C. being used for the "room temperature" set and 32°, 37° and 42° C. for the higher range. The curves given in Figure 1 show quite clearly the considerable effect of temperature differences. The time taken to reach a given *p*H is increased by about 50 per cent. for every 5° C. fall in temperature. Such a high temperature coefficient means that there must not be more than about 0·5° C. variation from the specified temperature, and in view of the time taken to attain full buffering effect at "room temperature" (100 to 180 minutes) there is much advantage in specifying 37° C. One interesting

fact is the rise in the final *p*H with fall in temperature; at 42° C. the peak *p*H is 3·7 and at 15° C. it is 4·1.

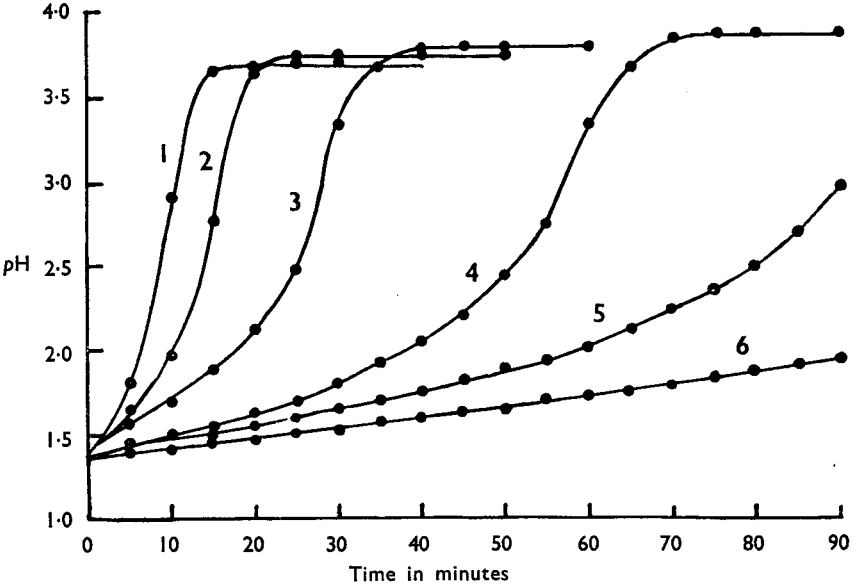

FIG. 1. The effect of temperature on the rate of reaction of dried aluminium hydroxide in 0·05N hydrochloric acid. 1 at 42° C.; 2 at 37° C.; 3 at 32° C.; 4 at 25° C.; 5 at 20° C. and 6 at 15° C.

Discrimination. A number of samples of dried alumina gel from various sources were assayed and their neutralisation capacities determined (see Table II). These were then tested at 37° C. with a stirrer speed of about 240 r.p.m. The curves obtained are given in Figure 2 and show quite clearly that the neutralisation capacity does not give complete information because, for instance, samples B and C, which differ by about 20 per cent. according to the B.P.C. test, have nearly identical reaction rates. Similarly, samples B and E, of similar neutralisation capacity have very different characteristics. The slow action of sample D would render it of doubtful value for the rapid relief of hyperacidity although it conforms to the

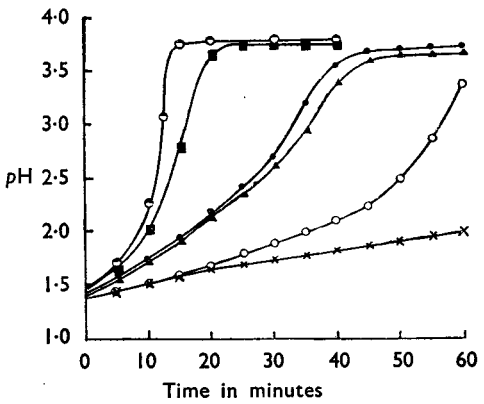

FIG. 2. The reaction rates of various dried aluminium gels, using method I.

■—■ Sample A ×—× Sample D
●—● „ B ○—○ „ E
▲—▲ „ C ◒—◒ „ F

existing requirements of the B.P.C. The spacing of the curves gives a very clear picture of the discriminating power of the test.

TABLE II

ASSAYS AND NEUTRALISATION CAPACITIES OF THE DRIED ALUMINA GELS

	Sample					
	A	B	C	D	E	F
Assay—Al_2O_3, per cent. ..	50·5	50·3	50·5	50·4	50·0	50·8
Neutralisation Capacity (ml. of 0·1N acid/g.) ..	258	270	219	210	270	280

Enzymes and Buffers. Another series using 0·05N acid containing 0·15 per cent. each of pepsin, peptone and sodium chloride as used by Brindle shows very much less difference between the various samples and much lower *p*H values even after 60 minutes. Similarly, when 3 of these samples were tested in acid containing 0·15 per cent. of pepsin alone, which is similar to the Armstrong and Martin acid medium, the slowing down of the reaction gave a less distinct classification. These results are compared in Table III. Thus from the point of view of routine testing the omission of pepsin and similar materials is an advantage as differences can be more readily detected and, as Rossett and Flexner[1] showed, comparable results are obtained from *in vivo* tests and *in vitro* tests using hydrochloric acid without the addition of physiological substances.

TABLE III

RATE OF REACTION WHEN ENZYMES AND SIMILAR SUBSTANCES ARE ADDED TO THE ACID MEDIUM. METHOD I

(a) 250 ml. of 0·05N hydrochloric acid with 0·15 per cent. each of pepsin, peptone and sodium chloride.

	Time in Minutes					
	0	10	20	30	40	60
Sample	*p*H readings					
A	1·44	1·64	1·80	1·94	2·06	2·31
B	1·40	1·57	1·63	1·72	1·80	1·94
D	1·40	1·56	1·62	1·72	1·82	2·00
E	1·46	1·56	1·60	1·62	1·67	1·76

(b) 250 ml. of 0·05N hydrochloric acid with 0·15 per cent. of pepsin.

A	1·42	1·66	1·92	2·20	2·48	3·15
D	1·36	1·52	1·59	1·67	1·73	1·90
E	1·38	1·50	1·54	1·58	1·62	1·72

Reproducibility. 4 additional tests were made on sample A and also on samples B and E. The results are given in Table IV. The tests on stirring rate were made on sample A and Table I could accordingly be considered as a further set of figures. It will be seen that close agreement can be obtained. The poorest results were obtained with sample E, a relatively inactive gel, at the point of most rapid change of *p*H.

Method II

For the second type of test, in which there was an initial excess of antacid, 150 ml. of 0·05N acid was used at the start and after 20 minutes 5 ml. of 0·5N acid was added, followed 10 minutes later by a further 5 ml., giving a total quantity of acid equivalent to 250 ml. of 0·05N as before. The same samples of dried gel were tested as above and the curves obtained are given in Figure 3. Although the shape of the curves is quite different, the relative positions of the lines is unchanged except that sample E now

approaches closely to the behaviour of B and C in the final 15 minutes of the test. Considering the test as a whole, however, the gels would be given the same relative placings.

TABLE IV

REPRODUCIBILITY OF METHOD I

Sample	Time in Minutes								
	0	5	10	15	20	30	40	50	60
	*p*H readings								
A	1·38	1·66	2·00	2·75	3·66	3·75			
A	1·38	1·64	2·00	2·85	3·67	3·80			
A	1·36	1·63	2·00	2·73	3·70	3·78			
A	1·40	1·64	1·96	2·49	3·56	3·71			
B	1·40	1·59	1·76	1·94	2·18	2·99	3·65	3·72	3·74
B	1·39	1·58	1·74	1·94	2·17	3·04	3·66	3·70	3·72
B	1·35	1·56	1·76	1·96	2·17	2·88	3·64	3·70	3·73
B	1·40	1·61	1·77	1·96	2·19	2·89	3·63	3·72	3·75
E	1·36	1·44	1·50	1·60	1·70	1·90	2·16	2·59	3·42
E	1·35	1·41	1·49	1·61	1·71	1·88	2·13	2·38	3·10
E	1·36	1·44	1·52	1·61	1·72	1·94	2·20	2·58	3·43
E	1·38	1·43	1·51	1·60	1·70	1·88	2·12	2·41	2·86

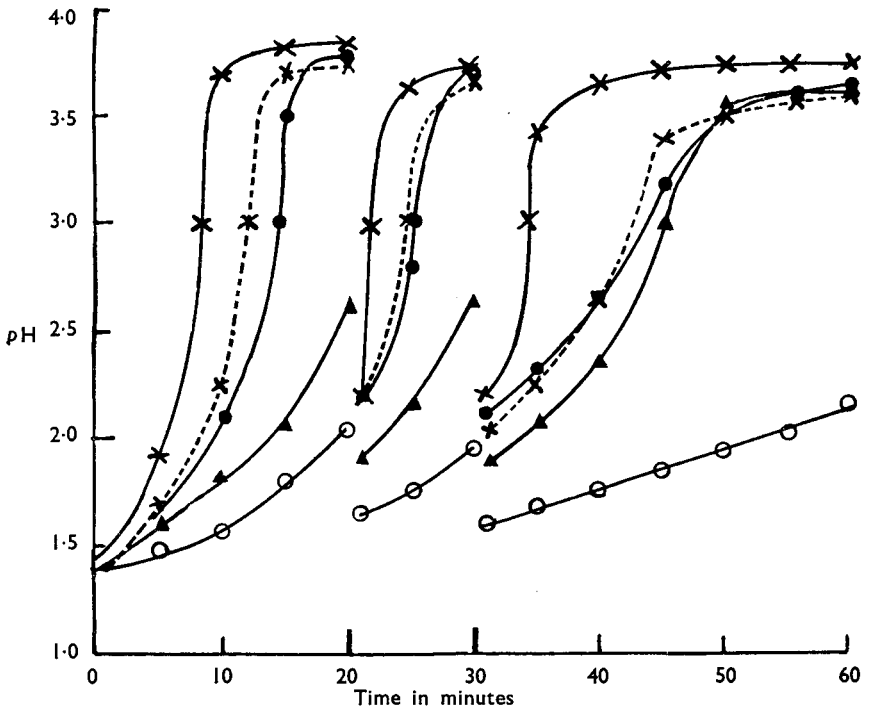

FIG. 3. The reaction rates of various dried alumina gels using method II. To avoid confusion the lines joining the 20 and 21 minute and the 30 and 31 minute points, have been omitted.

×——× Sample A ○——○ Sample D
×---× „ B ▲——▲ „ E
●——● „ C

Enzymes and Buffers

Only 3 samples were tested by Method II with added pepsin and with added pepsin, peptone and sodium chloride (in the 0·05N acid only). The effect on the reaction rate was closely similar to that found in Method I as will be seen in Table V.

TABLE V

RATE OF REACTION WHEN ENZYMES AND SIMILAR SUBSTANCES ARE ADDED TO THE ACID MEDIUM. METHOD II

(a) 150 ml. of 0·05N hydrochloric acid with 0·15 per cent. each of pepsin, peptone and sodium chloride.

	Time in Minutes							
	0	10	20	21	30	31	40	60
Sample	*p*H readings							
A	1·38	1·76	2·07	1·71	1·95	1·65	1·85	2·30
D	1·36	1·57	1·71	1·52	1·59	1·42	1·52	1·71
E	1·38	1·55	1·61	1·42	1·49	1·35	1·45	1·61

(b) 150 ml. of 0·05N hydrochloric acid with 0·15 per cent. pepsin.

A	1·36	1·90	3·30	1·97	2·81	1·90	2·30	3·45
D	1·39	1·62	1·77	1·55	1·72	1·52	1·59	1·90
E	1·36	1·56	1·72	1·50	1·66	1·48	1·59	1·86

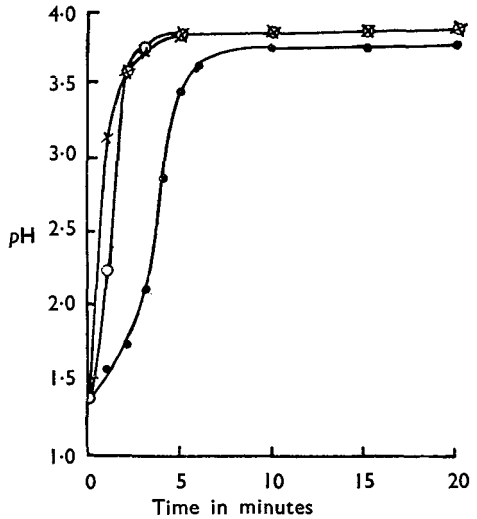

FIG. 4. The reaction rates of 3 samples of liquid alumina gels using method I.

●—● Sample 1.
×—× „ 2.
○—○ „ 3.

Liquid Gels

3 liquid gels were tested by Method I, without the addition of pepsin etc. The weight per ml. of liquid gel is about 1·015 g. to 1·020 g. so that a negligible error is introduced by using 8 g. instead of 8 ml. The gel was diluted with 8 ml. of water before addition so that more complete transference could be achieved. This is quite permissible as the gel is usually diluted before administration. Figure 4 gives the results and shows that the reaction is so rapid that little distinction is possible between different samples.

DISCUSSION

For the purposes of a routine test the use of 0·05N hydrochloric acid rather than artificial gastric juice is quite permissible because the aim of the test is to establish the relation between different samples of closely similar

material. The use of additives aimed at producing artificial gastric juice have been shown to give no advantage in the performance of such a test and are probably a disadvantage as they reduce the overall range of the readings and hence the discrimination. If they had a significant effect on the relative placings of the samples these disadvantages would be offset but no such effect was found.

Taking the maximum B.P.C. dose of gel as a starting point, a convenient form of test is the first one described. The alternative form of test, where a considerable excess of antacid is present during the first 20 minutes, has attractions at first sight as it seems to be closer to the conditions existing *in vivo*. For routine purposes it seems to offer no advantage as it would need an elaborate set of limits. The *p*H would have to be specified at several time intervals if the test is to have real value.

Thus the most suitable method of testing is as follows: Take 8 g. of liquid gel or 0·6 g. of dried gel (or equivalent amounts if in another form) and add quickly to 250 ml. of 0·05N hydrochloric acid at 37° ± 0·5° C. in a 250 ml. beaker provided with a stirrer and electrodes for *p*H measurement. Maintain brisk agitation and determine the *p*H at intervals. The *p*H of the acid, which should have a factor between 0·98 and 1·02 should be between 1·35 and 1·40 at 37° C. Suitable limits for dried gel could be, for example, that a *p*H not less than 3·0 should be attained in 20 minutes and a *p*H not less than 3·5 in 30 minutes. At no time should the *p*H exceed 4·0. For the liquid gel the corresponding values could be a *p*H not less than 3·5 in 10 minutes and not more than 4·0 at any time.

Summary

(1) *In vitro* methods for assessing the therapeutic value of antacids have been discussed in relation to the routine evaluation of aluminium hydroxide gels.

(2) Experiments based on these tests and the conclusions drawn from the discussion have been carried out with a view to establishing a suitable routine test.

(3) A form of test has been given in detail and limits have been suggested.

We thank the Directors of John Wyeth and Brother Ltd. for permission to publish this work and express our indebtedness to the Wyeth chemists in the United States whose work formed the basis for the proposed routine method.

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