MAGNESIUM TRISILICATE—ANTACID PROPERTIES AND CRYSTAL STRUCTURE

By J. Armstrong, A. S. Beidas, D. J. Craik and W. H. Stephenson

From The Pharmaceutical Development Department, The Plant Laboratory and The Chemical Division, Standards Department, Boots Pure Drug Co., Ltd., Beeston

According to Mutch[1], the particular value of magnesium trisilicate in the treatment of gastric hyperacidity and ulceration of the stomach and duodenum lies in its ability to give a quick primary neutralisation of the stomach acidity followed by a progressive secondary effect. Thus, ideally, a continuous antacid action should be exerted throughout the whole period of normal gastric digestion without the danger of the *p*H of the gastric contents being raised above the neutral point. This should be effected by the administration of a single dose of antacid. He defined medicinal magnesium trisilicate as a "chemically prepared substance with a composition represented by the formula $H_4Mg_2Si_3O_{10}$, and yielding a pure diffraction radiograph of sepiolite No. 1 or No. 2^2." A further advantage is the strong adsorptive effect exerted in the stomach and duodenum by either the un-neutralised excess of magnesium trisilicate or by the hydrated colloidal silica produced during the interaction with gastric acid: $Mg_2Si_3O_8 \cdot 2H_2O + 4HCl = 2MgCl_2 + 3SiO_2 + 4H_2O$. The British Pharmacopœia of 1953 contains a monograph on Magnesium Trisilicate in which standards for composition and acid neutralisation are prescribed. It has been found, however, that various magnesium tri-silicates of commerce, all of which complied with the B.P. monograph, gave very different antacid responses when tested by the *in vitro* procedure of Armstrong and Martin[3]. It is the purpose of this paper to draw attention to these differences in B.P. quality magnesium trisilicate, and also to the relationship which exists between the crystal structure of magnesium trisilicate and its antacid performance. This we feel extends the work of previous investigators[4,5,6].

For the investigation, six samples of magnesium trisilicate B.P. which showed marked difference in density were selected. The analytical data for these is given in Table I. These samples were examined by the technique of Armstrong and Martin[3] in which the requisite dose of antacid (1·5 g.) is added to 150 ml. of artificial gastric juice of *p*H 1·5, at 37° C., which is kept continuously stirred. The *p*H of the mixture is recorded at stipulated time intervals up to 10 minutes. After this time 20 ml. of the mixture, representing physiological loss from the stomach, is withdrawn and 20 ml. of artificial gastric juice added. The *p*H is again recorded at intervals up to the 10 minute "emptying time" and the withdrawal etc. is repeated until the *p*H readings indicate that all the antacid has been neutralised or is no longer effective. Under these conditions the antacid responses of the six products were markedly varied. These are represented graphically in Figure 1. A and B showed a slow initial effect, the maximum *p*H (4·5 and 5·0) being reached in 20 minutes after which

TABLE I

ANALYTICAL DATA FOR MAGNESIUM TRISILICATE SAMPLES TESTED

Sample	Per cent. MgO	Per cent. SiO$_2$	SiO$_2$/MgO ratio	Per cent. loss on ignition	ml. 0·05N HCl Neutralised B.P.					Apparent density
					15 min.	1 hr.	2 hrs.	4 hrs.	24 hrs.	
A	30·2	68·5	2·27	30·0	116	164	169	207	299	Light
B	31·3	66·1	2·15	20·7	121	170	191	235	312	Light
C	30·4	67·4	2·22	23·6	222	275	271	279	310	Heavy
D	30·5	67·2	2·20	27·6	207	268	283	289	322	Heavy
E	31·3	68·8	2·20	28·9	174	221	241	275	284	Medium
F	31·9	67·2	2·15	22·8	295	307	309	315	316	Light

time the acid neutralising effect was rapidly lost. C, D and E gave a rapid initial neutralisation, pH 6·75 to 7·0 being reached within 10 minutes the buffering effect being maintained for a further 60 minutes. The curves for C and E were practically superimposed and are represented as being identical for the sake of clarity. F exhibited the most powerful response, raising the pH to 6 to 7 within 4 minutes and maintaining the buffering effect for a period of 75 minutes.
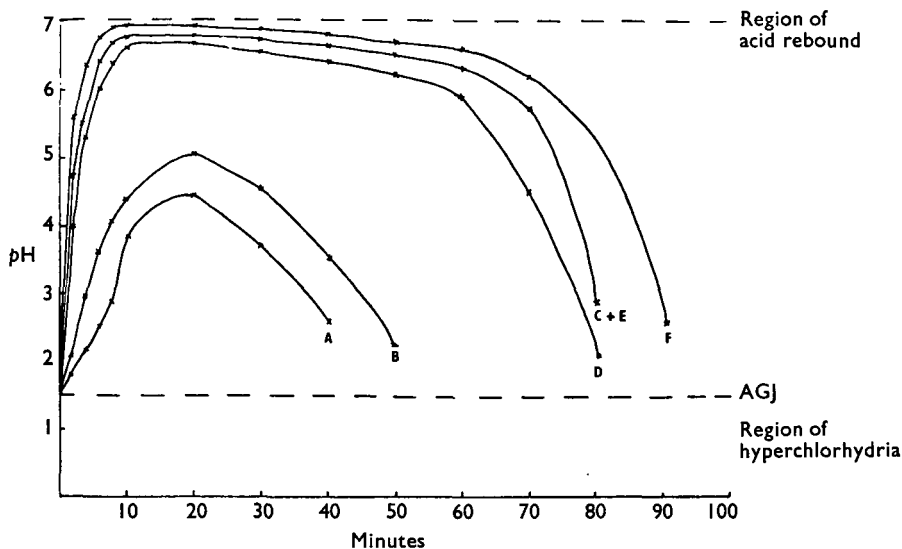

FIG. 1. Comparison of the antacid effect of samples of magnesium trisilicate. AGJ = Artificial gastric juice, pH 1·5, 37° C.

The B.P. acid absorption procedure was carried out on each powder, and in addition to the reading at 4 hours which is specified in the B.P. test the amount of acid neutralised after 15 minutes, 1 hour, 2 hours and 24 hours was determined. This data is also given in Table I and is shown graphically in Figure 2. Examination of the two sets of curves shows that there is but slight difference in the antacid performance as measured by the two methods.

These evaluations of the antacid properties of the various samples of magnesium trisilicate showed that A and B, although complying with the
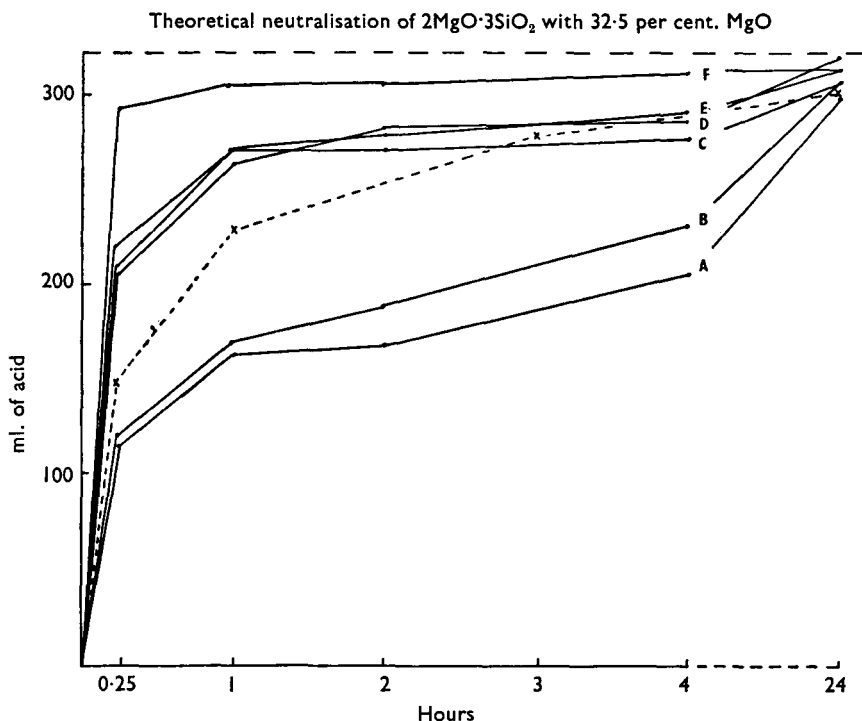
FIG. 2. Progressive neutralisation of 0·05N hydrochloric acid by magnesium trisilicate. × – – – × Curve transcribed from Mutch's graph (*Brit. med. J.*, 1936, 1, 205). Letters correspond to samples.

B.P. requirements had, in our opinion, fallen short of Mutch's criteria. It seemed that some other more fundamental factor was concerned in the antacid behaviour of the materials. As the bulk densities of the powders encompassed a fairly wide range this property was first investigated in relation to antacid effect. Bulk density as a factor was soon ruled out as Table I shows that no strict correlation existed between the density type and the antacid performance. F is a light grade product giving a good antacid control, whereas A and B are both light grade products giving poor antacid control. Particle size was next investigated using the ordinary microscope. This technique was not very successful due to the great tendency for clumping and agglomeration to occur, and was abandoned.

Examination of the material by means of the electron microscope showed a striking difference in the external form of the particles. This is demonstrated in the micrographs. Figure 3 is of meerschaum, a naturally occurring magnesium silicate dihydrate, $2MgO,3SiO_2 \cdot 2H_2O$. This is a form of sepiolite which occurs in a highly crystallised state, and the fascicular crystalline form of the material is well demonstrated. Figure 4 is an electron micrograph of A and when this is compared with meerschaum and kaolin (Figure 10) the nature of the crystal imperfections can

FIG. 3.   Meerschaum, × 12,500.
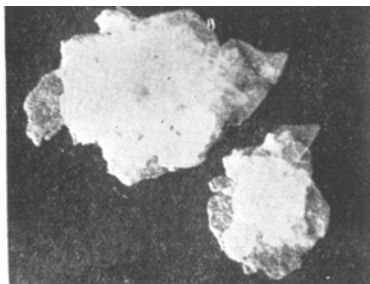

FIG. 4.   Sample A, × 12,500.
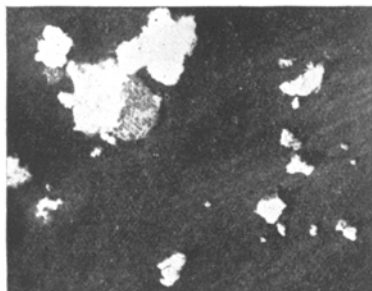

FIG. 5.   Sample B, × 12,500.

FIG. 6.   Sample C, × 12,500.
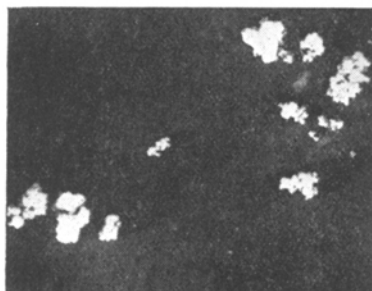

FIG. 7.   Sample D, × 12,500.
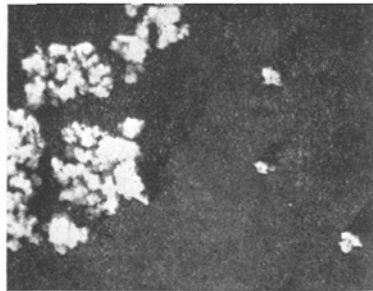

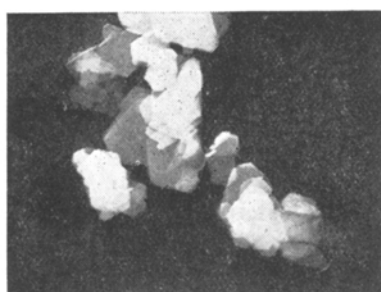FIG. 8.   Sample E, × 12,500.

FIG. 9.   Sample F, × 12,500.

FIG. 10.   Kaolin, × 12,500.

be appreciated. The distinctive sheets, evidenced by a comparative transparency and lack of shadow—typical of a layer-lattice silicate—are distorted and sometimes folded. B, Figure 5, resembles A and there is a gradation in the appearances of C, D, E and F which is well shown in Figures 6 to 9. These small particles do not seem to be homogeneous in
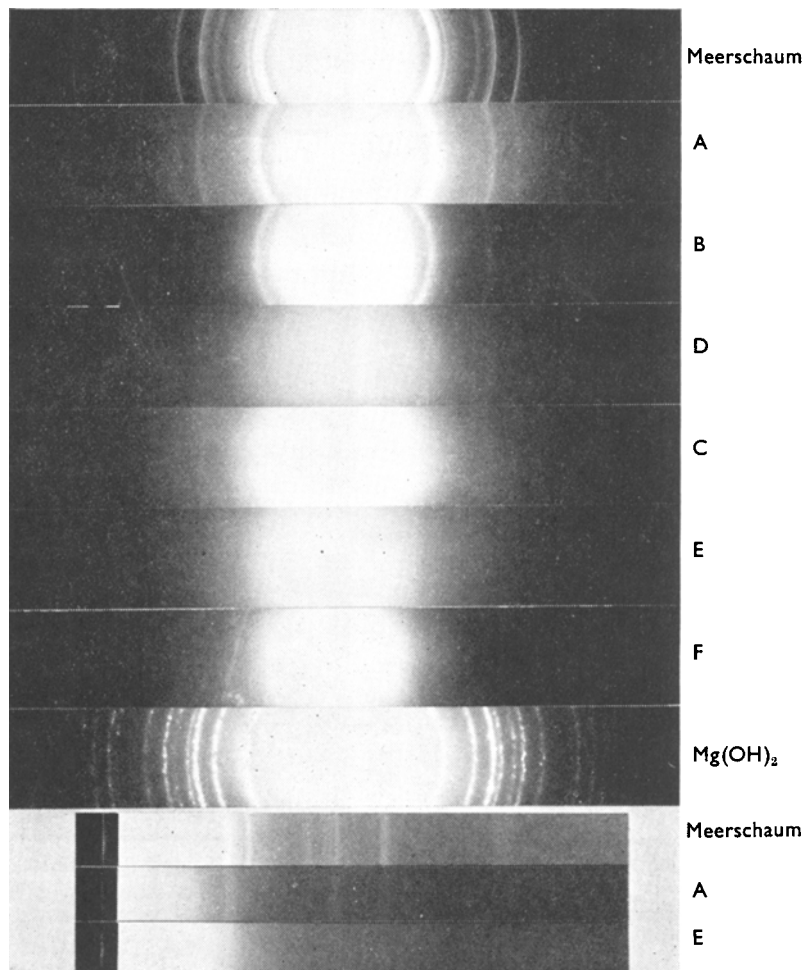
FIGS. 11 and 12.

structure, being rounded and irregularly shaped, and there is an absence of the "plate" formation seen in samples A and B.

The materials were then investigated from the viewpoint of crystal structure, electron and X-ray diffraction techniques being employed.

For the electron diffraction a thin layer of the powder was mounted on a collodion membrane and the patterns obtained by the use of 80 Kv. electrons. To ensure that the patterns recorded were truly representative

and not affected by any local non-homogeneity, several portions of the specimen were selected at random and the results compared. The electron diffraction patterns are shown in Figure 11. The materials were then heated to 900° C. for six hours and the residues examined by diffraction.

The X-ray diffraction studies were obtained by mounting the powder on a fine glass fibre using a water-based adhesive. Nickel-filtered copper radiation was used and long exposures were necessary. Three of the patterns are shown in Figure 12.

Diffraction patterns were also obtained for colloidal magnesium hydroxide and a mixture of this with silicic acid. These were quite different from the magnesium trisilicate patterns.

DISCUSSION

Comparison of the electron diffraction patterns of the six artificial samples of magnesium trisilicate with that of meerschaum (sepiolite) a natural form of magnesium trisilicate shows that the latter is highly crystalline, whilst the artificial samples are all, more or less, disordered crystallographically. Of these A is most crystalline, F is much less crystalline, while the other samples occupy an intermediate position. This variation is related to antacid activity. A low antacid activity is shown by samples which exhibit a "plate-like" appearance under the electron microscope and give a clear diffraction pattern (i.e., are the more crystalline). On the other hand a high antacid activity is possessed by samples which are less regular in appearance when examined under the electron microscope and which give a more diffuse type of diffraction pattern (i.e., are less crystalline). Meerschaum had a very low antacid activity when examined by the extended B.P. neutralisation test.

After the samples were heated to 900° C., all the residues of the trisilicates, including that of meerschaum, were found to be inactive in the acid absorption tests. When these residues were examined by the diffraction techniques, the pattern of each was seen to be identical in clarity as well as in spacing of the lines, all having been transformed to enstatite $MgOSiO_2$. This may be regarded as further evidence, particularly in the case of the less crystalline samples, for the original existence of the sepiolite structure. The fact that removal of the combined water has such an effect suggests that differences in structure may be the result of variable degrees of hydration. It was found that the loss of weight on ignition of the dry material was such as to make the number of "water molecules" n in the formula $2MgO\cdot3SiO_2\, n\, H_2O$, integral in the case of the more crystalline sample, but not in the case of the less crystalline materials. The results of X-ray diffraction substantiate those of electron diffraction. By greatly increasing the exposure, the outer lines in the patterns of E and F could be developed and they were then seen to be considerably broadened and diffuse. Magnesium hydroxide gave a pattern as sharp as that of meerschaum, but could not be mistaken for it.

The interplanar spacings were calculated from measurements on the X-ray diffraction patterns and are shown in Table II. The measurements

TABLE II

X-RAY DIFFRACTION DATA FOR NATURAL AND "ARTIFICIAL" MAGNESIUM TRISILICATE ETC.

Substance			Interplanar spacing in Ångstrom Units					
Meerschaum	4·67s	3·81m	3·40md	2·64s	2·30m	1·53m	1·31md	
Sample A, etc. ..	4·67s		d*	2·63s	d*	1·54m	d*	
Meerschaum after ignition	4·56md		3·24s	2·94s	2·55s			
Sample A, etc., after ig-								
nition	4·48m		3·22s	3·0s	2·62s			
Magnesium hydroxide ..	4·50s	2·26s	1·80s	1·58m	1·50w	1·38w	1·32w	1·19w

s = Strong.   m = Medium.   w = Weak.   d = Diffuse.   d* = Too weak and diffuse for measurement.

on the patterns of all the artificial samples and on the meerschaum (a form of sepiolite) conform with the lattice openings for sipiolite as quoted by Mutch[1] and also given by Migeon[7], although in some cases the measurements could only be approximate. Only one anomaly exists, the line corresponding to 4·6 A, indicating that the artificial forms resemble more the meerschaum than the sample of sepiolite used as a standard by Mutch[1].

CONCLUSIONS

1. Magnesium trisilicates which conform to the present B.P. requirements can vary markedly in their physical characteristics as well as in their efficiency as antacids.

2. Investigation has shown that the less crystalline the sample of magnesium trisilicate the higher the antacid efficiency when measured *in vitro*.

3. It would appear that antacid activity of magnesium trisilicate is associated with the degree of distortion of the crystal structure, and that this distortion is possibly related to the amount of "combined water" in the crystal and the way in which this is included in the lattice. A magnesium trisilicate with a high degree of distortion of its crystalline structure gives a better antacid control *in vitro* than does one which is more crystalline.

Our acknowledgments and thanks are due to Professor L. F. Bates, F.R.S., for permission to use the X-ray diffraction apparatus at the University of Nottingham, and to Miss P. C. Cutts, Mr. F. Hobson, Mr. S. Clunie, Mr. B. F. Miller and Mr. D. A. Meads for technical assistance.

REFERENCES

1. Mutch, *Brit. med. J.*, 1936, **1**, 143, 205, 254.
2. Mutch, *ibid.*, 1937, **2**, 735.
3. Armstrong and Martin, *J. Pharm. Pharmacol.*, 1953, **5**, 672.
4. Glass, *Quart. J. Pharm. Pharmacol.*, 1936, **9**, 445.
5. Surfleet and Porter, *ibid.*, 1940, **13**, 109.
6. Mukherjee, Das Gupta and Banerjee, *ibid.*, 1946, **19**, 14.
7. Migeon, *C.R., Acad. Sci., Paris*, 200, 946.

DISCUSSION

The paper was presented by MR. W. H. STEPHENSON.

DR. G. E. FOSTER (Dartford) said that there were several ways of making magnesium trisilicate. One was to add magnesium sulphate to a solution

of sodium silicate, silicic acid was first precipitated, subsequently magnesium hydroxide came down and combined with the acid. The composition of the magnesium trisilicate produced depended on the amount of alkali present in the sodium silicate. Another was to treat sodium silicate with acid, so precipitating silicic acid, and add the correct amount of magnesium hydroxide. It seemed the authors could tell the difference between magnesium trisilicate and mixtures of magnesium oxide and silicic acid. If such a mixture were left to mature so that the magnesium oxide had a chance to combine with the silicic acid, the X-ray pattern might change.

MR. N. BRUDNEY (London) said it seemed that the water content of magnesium trisilicate might have some influence on the antacid properties. Were the samples of magnesium trisilicate treated in any way before testing by the Armstrong and Martin technique? Had the technique been tried with a suspension of magnesium trisilicate, as that was often the way in which it was administered?

DR. F. HARTLEY (London) asked whether an attempt was being made to define what the crystallographic pattern of magnesium trisilicate should be? If not, had the authors any suggestions to make whereby the present B.P. specification could be improved to eliminate the less satisfactory samples?

MR. W. H. STEPHENSON, in reply, said that the investigation was an attempt to discover a brand of magnesium trisilicate which would be generally suitable for pharmaceutical purposes. The basic reaction mechanisms had not been investigated. He agreed that change of X-ray diffraction pattern of a mixture of magnesium oxide and silicic acid to that of a silicate type might occur, but he had no experimental evidence. The magnesium trisilicate had not been pretreated in any way. No suspensions had as yet been tried. With regard to a test which might be suitable for the B.P., if Mutch's magnesium trisilicate were taken as standard at least two points were required on the neutralisation curves. Probably the 15-minute and 3-hour times as postulated would be satisfactory. The higher the initial neutralisation the better, provided the lag neutralisation was maintained, and the pH of stomach contents kept up. For that reason samples E and F would be the type recommended. He would set standards of not less than 175 ml. of acid at 15 minutes rising to 300 ml. at the end of 3 hours. Such magnesium trisilicate should be satisfactory for all purposes.