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Modified Clays

The invention relates to modified clays useful as
5 active ingredients in medicaments, to processes for
their preparation and to therapeutic compositions
containing them.

Clays are used in therapy, notably to bring about a
partial neutralization of too high stomach acidity.
10 They have a moderate neutralizing power, which means the
patient has to take several grams of product to obtain
the desired effect. Other anti-acid products generally
have a too rapid speed of neutralization, and do not
provide sufficient permanence for the desired effect.
15 This is the case, for example, with magnesium hydroxide.

The invention provides a modified clay comprising the
product of reaction between a sheet-silicate clay and
from 0.05 to 0.5 part by weight of magnesium hydroxide
per part by weight of the sheet-silicate clay, the
20 modified clay having a plate separation of from 1.5 to
1.6 nm reducing to from 1.2 to 1.4 nm when heated to
490°C and a neutralizing power of from 170 to
1700 milliequivalents per 100 g; or an acid addition
product of such a modified clay with a therapeutically
25 acceptable acid.

Such clays have a high neutralizing power and a good speed of neutralization with residual activity. In fact, the clays have been found active for from some
5 tens of minutes to several hours depending on the proportions of starting material used for its preparation and the time and temperature of the reaction. The modified clay combines neutralizing power with a clay structure in a stable composition.

10 The modified clay according to the invention is a reaction product of the sheet-silicate clay and the magnesium hydroxide, and not merely a mixture thereof; its action is different from that of a mixture thereof, and it does not exhibit the characteristic X-ray spectrum of the magnesium hydroxide.

15 The plate separation of the clay is variable as a function of the number of molecules of water, and of the nature and quantity of fixed cations.

20 The modified clays according to the invention can be prepared from a suitable starting clay by treatment in an aqueous phase, possibly under pressure, with magnesium hydroxide added in an appropriate proportion. If the materials used are not dry or perfectly pure (apart from impurities which do not affect the process), the quantities used are adjusted so as to put the

quantities of the active ingredients within the necessary ranges. In particular if the clay is in the form of a mud such as can be obtained at the end of the usual purification process, the concentration of the
5 clay in this mud is taken into account. Generally, the clay will be in the form of a mud for the purification of the raw materials if necessary.

This purification is performed as follows:

The mineral is roughly crushed in order to eliminate
10 the stones or hard particles and then suspended in water in a rotating tube. The aqueous dispersion thus obtained is treated by a chemically pure and strong inorganic acid, under stirring at room temperature, the addition of the acid being made until the pH of the
15 dispersion is between 2 and 3.

Stirring is maintained for about one hour and then the dispersion is diluted and sent to a series of hydro-cyclones in which is separated the portion of clays to be used, i.e. the one passing through sieves with a
20 mesh opening of 0.1 mm.

The separated fraction is either used as such or sent to a thickener for increasing its concentration and dried at a temperature inferior to 200°C.

A suitable starting clay is a sheet-silicate clay having a plate separation of from 1.2 to 1.5 nm reducing to from 0.9 to 1 nm when heated to 490°C, and a cation exchange capacity above 80 mEq per 100 g.

- 5 As to the magnesium hydroxide, the dry material can have a less satisfactory purity than certain pastes or suspensions, so it is preferred to use these latter forms of the material and calculate the equivalent quantity which is necessary.
- 10 The reaction temperature should be at least 50°C, and depending on the quality of the clay initially used, could be up to 120°C or even more, the limit being in practice defined by industrial operating conditions and the start of the transformation of the clay. Ther
- 15 period of the reaction is a function of the temperature and pressure. The progress of the reaction is tested by the disappearance of the spectrum lines of magnesium hydroxide (Brucite) on a sample of the mixture.

- In the following examples, modified clays according to
- 20 the invention are prepared in autoclaves from samples each weighing 14 g, containing 2.5 g of clay (smectite) but variable quantities of neutralizing agent, the said 14 g being reached by the addition of water. The quantities of magnesium hydroxide are always given for
- 25 one part of clay. After placing the sample in the autoclave and closing, the treatment is as follows:

Example 1

Magnesium hydroxide paste : 0,606 g corresponding
to 0,200 g of pure product (0.08 part). Reaction
temperature 90°C. Reaction time 24 hours. $\text{Mg}(\text{OH})_2$ rate :
5 6.45 %.

Example 2

Magnesium hydroxide paste : 1.819 g corresponding
to 0.600 g of pure product (0.24 part). Reaction
temperature 90°C. Reaction time 24 hours.

10 Substantially the same product is obtained by
treating the same starting material for 2 hours at 120°C.
 $\text{Mg}(\text{OH})_2$ rate : 19,35 %.

Example 3

15 Magnesium hydroxide paste : 2.019 g corresponding
to 0.606 g of pure product (0.265 parts). Reaction
temperature 90°C. Reaction time 24 hours. $\text{Mg}(\text{OH})_2$ rate
21.04 %.

Example 4

20 Magnesium hydroxide paste : 2.273 g corresponding
to 0.750 g of pure product (0.30 part). Reaction
temperature 120°C. Reaction time 3 hours. $\text{Mg}(\text{OH})_2$ rate :
23.07 %.

Example 5

25 Magnesium hydroxide paste : 2.278 g corresponding
to 0.900 g of pure product (0.36 part). Reaction
temperature 120°C. Reaction time 4 hours. $\text{Mg}(\text{OH})_2$ rate :
26.47 %.

Example 6

Magnesium hydroxide paste : 3.183 g corresponding
to 1.050 g of pure product (0.42 part). Reaction
temperature 125°C. Reaction time 4 hours. Mg (OH)₂ rate :
5 29.58 %.

Example 7

Magnesium hydroxide paste : 3.638 g corresponding
to 1.200 g of pure product (0.48 part). Reaction
temperature 142°C. Reaction time 4 hours. Mg(OH)₂ rate :
10 32.43 %.

After the end of the reaction in each case, the
autoclave is cooled and the product recovered in the form
of a mud. In order to use the product as such, after
washing and drying it is ground to powder. It can then be
15 placed in capsules for oral administration. However, as
the product is very basic, it is generally preferred to
treat it with carbon dioxide or a therapeutically
acceptable acid in order to lower the pH to from 7.5 to
9, after which the product is washed and dried, and can
20 be used either in the form of a powder for putting in
suspension or pressed to make tablets. Citric, tartaric,
phosphoric and silicic acids are therapeutically
acceptable and examples of acids which can be used in
this way.

25 Various determinations and experimentations have
been conducted to show the interest of the composition of
the invention ; toxicity has been determined on rats and
experimentation on anti-acid activity and coating power
are also reported.

TOXICITY

The toxicity of the composition of the invention has been determined on Wistar rats, both male and female, for 5 days at the oral daily dose of 15 g/kg. 5 (average weight of the rats : 200 g).

Tests were conducted on 4 batches, each of 20 rats:

- a first batch of control female rats receiving 3 times a day, at 8, 12 and 16 hours, a dose of 1 ml of physiological serum only; 10
- a second batch of female rats receiving 3 times a day, at 8, 12 and 16 hours, an oral dose of 5 g/kg, suspended in 1 ml of water and administered by intra-gastric route;
- 15 - a third batch of control male rats treated as the first batch above, and
- a fourth batch of male rats treated as the second batch above.

20 All the animals were weighed before the test and at the end of the test; the average weight of the female rats increased by 2.67% compared to the control females, whereas the average weight of the male rats decreased by 2.93 % compared with the control males.

25 Accordingly, no significant variation of weight could be noticed during the test. Moreover, no death occurred during the test.

It can be concluded that the composition of the

invention is devoid of any noticeable toxicity.

DETERMINATION OF ANTI-ACID ACTIVITY

The anti-acid activity has been determined by two methods:

5 1) In vitro.

 This test was conducted comparatively with a known substance presently on the market and which is a mixture of aluminium and magnesium hydroxides; comparable doses of both compositions were used, i.e.
10 2 bags containing 31.2 mEq of ion exchange capacity for the modified clay according to the invention and 1 dose of the reference compound, containing 41.6 mEq of ion exchange capacity.

 It should be noticed that the reference compounds
15 contained about 25% more of ion exchange capacity than the modified clay of the invention; however, the comparison has been conducted in that way in order to compare the effectively used therapeutical doses.

 This test was performed according to the technique
20 of Fordtran JS (Reduction of acidity by diet, antacids, and anticholinergic agents; In Gastro-intestinal disease; Pathophysiology, diagnosis, management; Sleisenger MH and Fordtran JS, Saunders, Philadelphia, 1973, p 718-742). Each sample of product was maintained
25 at pH 3 by automatic addition of 0.1 N hydrochloric acid and the graph representing the acid demand plotted against the time is recorded continuously and automatically. From the amounts of acid are determined the used amounts of mEq of each product, the corresponding
30 percentage and the available amounts of mEq at various times.

The results are reported in the following Table.

TABLE

Time h mn		Reference Composition			Tested Composition		
		Used mEq		Available mEq	Used mEq		Available mEq
		mEq	%		mEq	%	
	0	5.8	14	35.8	5.9	19	25.3
	2	16.3	39	25.3	-	-	-
	3	19.3	46	22.3	-	-	-
	5	31.6	76	10.0	10.8	35	20.4
	6	39.5	95	2.1	-	-	-
	7	40.5	97	1.1	-	-	-
	10	-	-	-	14.2	46	17.0
	20	-	-	-	18.8	60	12.4
	30	41.3	99	0.3	21.8	70	9.4
1	00	-	-	-	26.7	86	4.5
1	30	41.6	100	0	29.0	93	2.2
2	00	-	-	-	30.8	99	0.4
2	30	-	-	-	31.1	100	0.1
2	45	-	-	-	31.2	100	0

From these results, it will be seen that, at about 7 minutes, the reference composition is almost completely neutralized, whereas the composition of the invention requires about 2 h 45 for neutralization. The compound of the invention has a far longer action and a very progressive pace of neutralization compared to the reference composition.

2) In vivo

This test was conducted on 12 people and consisted in the intra gastric pH determination at various times after the administration of either the same reference composition of the composition according to the invention.

All patients received both compositions, one on the first day after a standard meal, and a second one the day after, after the same standard meal; administration was effected in double blind.

In both cases, the time after administration during which the pH value in the stomach was greater than or equal to 5 was determined. The tested compound gave longer times for 7 patients, equal times for 3, and shorter times for 2. The time after administration during which the pH value in the stomach was greater than or equal to 3.5 was also determined. The tested compound gave longer times for 9 patients, equal times for 2 and a shorter time for 1.

The results in vivo have the same orientation as in vitro but appears a little less favourable. It should be however noticed that the tested composition contained a lower amount of mEq than the reference composition.

The comparative results would surely have been

more favourable for the tested composition, if same amounts of mEq of both compositions were used.

COATING POWER

5 The coating power or covering power has been determined on rats' gastric mucous (male Wistar rats, weight about 250 g).

10 This test was conducted comparatively on the composition of the invention, on the starting clay used as raw material for the preparation of the same and with a commercialized reference compound consisting of a gel of magnesium and aluminium hydroxides.

15 For the composition of the invention, the dose used was 10 ml of the suspension prepared for the composition of Example 3; for the treatment with the clay used as starting material, the suspension has been prepared containing the same amount of clay as the composition of the invention and for the gel of magnesium and aluminium hydroxide, the dose was of 10 ml per kilo which is equivalent to the dose used for the composition
20 of the invention.

The rats were divided in three batches, each of eight rats, and treated as follows:

25 The appropriate dose of each product was administered intragastrically to each rat of each batch and ten minutes later, the rats were killed by diethyl ether. The stomachs were taken, opened along their large curve, placed in recipients containing physiologic serum and smoothly rinsed.

30 The amount of protective coat was estimated by number from 0 to 4 in relationship with the coated area and the amount of product (0 : no coating at all).

Average values for these three batches were as follows:

compound of the invention: 2.5

clay used as starting material : 1.9

gel of magnesium and aluminium hydroxide : 0.5.

- 5 Accordingly it should be remarked that the commercialized compound is of poor value for the coating of the rats' gastric mucous; the composition of the invention affords it better protection than the clay used as starting material, however the
10 amount of mineral is the same in both cases.

PRESENTATION - POSOLOGY

- The compound according to this invention may be presented in any suitable form for therapeutic administration, such as powder, tablets, gel or
15 suspension.

 In human therapy, a unit dose may contain from 1 to 5 g of dry substance.

 As examples of suspension, for instance, may be given:

25

1)	Composition of the invention	
	(Example 3)	1.900 g
	Citric acid	0.008 g
	Methyl Parahydroxybenzoate	0.008 g
5	Propyl Parahydroxybenzoate	0.004 g
	Ethyl alcohol at 95°	0.065 g
	Saccharose	1.30 g
	CO ₂ (sufficient amount for pH 9 $\pm$ 0.5)	
	about	0.040 g
10	Purified water, sufficient amount for	9 ml

This suspension is contained in an individual bag.

2)	Composition of the invention	
	(Example 6)	1.900 g
	Tart ric acid	0.070 g
15	Methyl Parahydroxybenzoate	0.010 g
	Ethyl alcohol at 95°	0.070 g
	Saccharose	1.000 g
	Purified water, sufficient amount for	9 ml

This suspension is contained in an individual bag.

20	3)	Composition of the invention	
		(Example 4)	1.900 g
		Methyl Parahydroxybenzoate	0.010 g
		Menthol	0.001 g
		Ethyl alcohol at 95°	0.065 g
25		Saccharose	0.050 g
		CO ₂ (sufficient amount for pH 8.5 $\pm$ 0.5)	
		about	0.025 g
		Purified water, sufficient amount for	8 ml

This suspension is contained in an individual bag.

As example of powder form, may be given :

4	Composition of the invention (Example 2)	1.400 g
	Phosphoric acid	0.100 g
5	Sorbitol	0.250 g
	Pectine	0.050 g

		1.800 g

This dose is contained in an individual bag.

As example of tablets, may be given :

10	5)	Composition of the invention (Example 5)	1.400 g
		Mannitol	0.250 g
		Starch	0.100 g
		Magnesium Stearate	0.030 g
15		Talc	0.100 g
		Silicic acid	0.020 g
		Menthol	0.0005 g
		Saccharose : sufficient amount for a tablet of	2 g

20 In human therapy, there may be administered from
1 to 12 bags or tablets per day.



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CLAIMS:

1. A modified clay comprising the product of reaction between a sheet-silicate clay and from 0.05 to 0.5 part by weight of magnesium hydroxide per part by weight of the sheet-silicate clay, the modified clay having a plate separation of from 1.5 to 1.6 nm reducing to from 1.2 to 1.4 nm when heated to 490°C and a neutralizing power of from 170 to 1700 milliequivalents per 100 g; or an acid addition product of such a modified clay with a therapeutically acceptable acid.

2. A process for the preparation of a modified clay according to claim 1, the process comprising reacting, at a temperature of from 50°C to 140°C for a period of from 3 to 24 hours, a purified sheet-silicate clay having a plate separation of from 1.2 to 1.5 nm reducing to from 0.9 to 1 nm when heated to 490°C and a cation exchange capacity at least 80 milliequivalents per 100 g with 0.05 to 0.5 part by weight of magnesium hydroxide per part by weight of the sheet-silicate clay.

3. A process for the preparation of a modified clay according to claim 1, the process being substantially as described herein with reference to any of the Examples.



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4. A therapeutic composition of matter comprising
as an essential ingredient therein, a modified clay
of claim 1.
