CONVENTION APPLICATION FOR A PATENT

COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

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SOCITE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES,
of 264 rue du Faubourg Saint Honore 75008 Paris,
France

hereby apply for the grant of a Patent for an invention entitled:
NEW MODIFIED CLAYS, PREPARATION THEREOF AND THERAPEUTICAL COMPOSITIONS CONTAINING THE SAME

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered
82 12448
for a patent or similar protection made in United Kingdom
on 29th April 1982

Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,
50 Queen Street, Melbourne, Victoria, Australia.

DATED this 27th day of April 1983

SOCIITE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES

by
Wayne McMaster

To:
The Commissioner of Patents.
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In support of the Convention Application made by

SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES

(hereinafter referred to as the applicant) for a Patent

for an invention entitled,

NEW MODIFIED CLAYS, PREPARATION THEREOF AND THERAPEUTICAL COMPOSITIONS CONTAINING THE SAME

I, (a) GERARD BEAFOUR
of 264 rue du Faubourg Saint Honore, 75008 Paris, France
do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in
United Kingdom
on the 29th day of April 1982, by

SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES

3. (b) Mr. PLANTEFIEVE Jean-Claude
11 rue du Vallon 28500 VERNONILLET (FRANCE)
Mr. RENE Michel
2 rue de Civry 75016 PARIS (FRANCE)

are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The applicant is the assignee of the said actual inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Paris, France
this 25th day of February 1983

To: THE COMMISSIONER-GENERAL FOR PATENTS

Edwin Waters & Sons, Melbourne

Signature

Gérard BEAFOUR
The General Manager
Modified clays comprising a sheet-silicate clay - with a plate separation of from 1.5 to 1.6 nm, with a cation exchange capacity of from 170 to 1700 mEq per 100 g, with a reduction of the plate separation to from 1.2 to 1.4 nm when heated to 490°C - combined with 0.05 to 0.5 part in weight of magnesium hydroxide per part of clay, i.e. containing from about to 5 to about 33% of magnesium hydroxide and in which the characteristic X-ray spectrum of magnesium hydroxide is no more present, and acidic addition products of the same with carbonic, citric, tartaric, phosphoric and silicic acids.
A preparation process of the modified clays of claim 1 consisting in treating at a temperature between 50°C and about 140°C, possibly under pressure, one part of a purified sheet-silicate clay presenting a plate separation of from 1.2 to 1.5 nm, a cation exchange capacity at least 80 mEq per 100 g and a reduction of the plate separation to from 0.9 to 1 nm on heating to 490°C, by 0.05 to 0.5 part of magnesium hydroxide for about 3 hours to about 24 hours.

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

A clay, especially a 50°C
change of a complete
plate with a change of 40°C

as an

of a

The following statement is a full description of this invention, including the best method of performing it known to U.S.
The invention relates to modified clays to be used as active ingredients in medicaments.

Clays are used in therapy, notably to bring about a partial neutralization of too high stomach acidity. 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. This is the case, for example, with magnesium hydroxide.

The modified clays according to the invention comprises a sheet-silicate clay, and has a plate separation of from 1.5 to 1.6 nm (nanometers), a cation exchange capacity of from 170 to 1700 m equiv (milli-equivalents or mEq) per 100 g, and a reduction of the plate separation to from 1.2 to 1.4 nm when heated to 490°C, in combination with from 0.05 to 0.5 part of magnesium hydroxide per part of clay (which means, containing from about 5 to about 33 % of magnesium hydroxide).

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 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 active ingredient of the medicament combines neutralizing power with a clay structure in a stable composition. It is a
distinct entity; the characteristic X-ray spectrum of
the magnesium hydroxide disappears on its formation, and
its action is different from that of a mixture in the
cold of the same constituents.

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.

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 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 the stones or hard particles and then suspended
in water in a rotativ tube. 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
dispersion is between 2 and 3.

Stirring is maintained for about one hour and then
the dispersion is diluted and sent to a sery of
hydrocyclones in which is separated the portion of clays
to be used, i.e. the one passing through sieves with a
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, a cation exchange capacity above 80 mEq per 100 g and a reduction plate separation to from 0.9 to 1 nm, on heating to 490°C.

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.

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. The 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 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 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. Mg(OH)$_2$ rate : 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.

Substantially the same product is obtained by treating the same starting material for 2 hours at 120°C. Mg(OH)$_2$ rate : 19.35 %.

Example 3

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. Mg(OH)$_2$ rate : 21.04 %.

Example 4

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. Mg(OH)$_2$ rate : 23.07 %.

Example 5

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. Mg(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: 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: 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 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 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.

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 (average weights of the rats: 200 g).

An experimentation has been conducted on 4 batches each of 20 rats:

- a first batch of control female rats receiving only physiological serum, in 3 doses of one ml at 8, 12 and 16 hours;
- a second batch of 20 female rats receiving 3 times a day, at 8 hours, 12 hours, 16 hours, an oral dose of 5 g/kg, suspended in 1 ml of water and administered by intragastric route;
- 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.

All the animals have been weighed before the experimentation and at the end of the same; the average weight of the female rats increased by 2.67 % compared to the control females, whereas the average weights of male rats decreased by 2.93 % compared with the control males.

Accordingly, no significant variation of weight could be noticed during this experimentation. Moreover, no death intervened during this experimentation.

It can be concluded that the composition of the invention is deprived of any noticeable toxicity.
DETERMINATION OF ANTI-ACID ACTIVITY

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

1) In vitro experimentation.

This experimentation 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 have been used, i.e. 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 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.

In this experimentation, which was performed according to the technic 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 at pH 3 by automatic addition of hydrochloric acid and the graphic representing the acid demand plotted against the time is recorded continuously and automatically; hydrochloric acid was 0.1 N. From the amounts of acid are determined the used amounts of mEq of each product, the corresponding percentage and the available amounts of mEq at various times.

The results are reported in the following table wherein it appears clearly that:
<table>
<thead>
<tr>
<th>Time h mn</th>
<th>Reference Composition</th>
<th>Tested Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Used mEq</td>
<td>Available mEq</td>
</tr>
<tr>
<td>0</td>
<td>5.8 14</td>
<td>35.8</td>
</tr>
<tr>
<td>2</td>
<td>16.3 39</td>
<td>25.3</td>
</tr>
<tr>
<td>3</td>
<td>19.3 46</td>
<td>22.3</td>
</tr>
<tr>
<td>5</td>
<td>31.6 76</td>
<td>10.0</td>
</tr>
<tr>
<td>6</td>
<td>39.5 95</td>
<td>2.1</td>
</tr>
<tr>
<td>7</td>
<td>40.5 97</td>
<td>1.1</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
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<td>41.3 99</td>
<td>0.3</td>
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<tr>
<td>1 00</td>
<td>-</td>
<td>-</td>
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<tr>
<td>1 30</td>
<td>41.6 100</td>
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<tr>
<td>2 00</td>
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<td>2 30</td>
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</tr>
<tr>
<td>2 45</td>
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</tr>
</tbody>
</table>
at about 7 minutes, the reference composition is quite completely neutralized;

the composition of the invention requires about 2 h 45 for being neutralized.

The compound of the invention has a far more longer action and a very progressive pace of neutralization compared to the reference composition.

2) In vivo experimentation.

This experimentation 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 or the composition according to the invention.

All the 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, was determined the time after administration during which the pH value in the stomach was superior or equal to 5 (tested compound gave longer times for 7 patients, equal times for 3, and shorter time for 2), and superior or equal to 3.5 (tested compound gave longer times for 9 patients, equal times for 2 and shorter time for 1).

The result has, in vivo, 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
Dn is quite more favourable for the tested composition if same amounts of mEq of both compositions were used.

COATING POWER

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

This experimentation has been conducted comparatively on the composition of the invention, on the rat 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.

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 of the invention.

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

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 and opened along the large curve of the same, they were thus placed in recipients containing physiologic serum and smoothly rinsed.

The amount of protective coat is thus estimated
by quote 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:

1°) compound of the invention : 2.5

2°) clay used as starting material : 1.9

3°) gel of magnesium and aluminium hydroxide : 0.5.

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 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 therapeutical administration, such as powder, tablets, gel or suspension, for instance.

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

As examples of suspensions, for instance, may be given:
Composition of the invention
(Example 3)
Citric acid 1.900 g
Methyl Parahydroxybenzoate 0.008 g
Pr pyl Parahydroxybenzoate 0.004 g
Ethyl alcohol at 95° 0.065 g
Saccharose 1.30 g
CO₂ (sufficient amount for pH 9±0.5) about 0.040 g
Purified water, sufficient amount for 9 ml
This suspension is contained in an individual bag.

Composition of the invention
(Example 6)
Tartaric acid 1.900 g
Methyl Parahydroxybenzoate 0.070 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.

Composition of the invention
(Example 4)
Methyl Parahydroxybenzoate 1.900 g
Menthol 0.010 g
Ethyl alcohol at 95° 0.001 g
Saccharose 0.065 g
CO₂ (sufficient amount for pH 8.5±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)
Phosphoric acid 1.400 g
Sorbitol 0.100 g
Pectine 0.250 g

This dose is contained in an individual bag.

As example of tablets, may be given:

10 5°) Composition of the invention
(Example 5)
Mannit: 1.400 g
Starch 0.250 g
Magnesium Stearate 0.100 g
Silicic acid 0.030 g
Talc 0.100 g
Saccharose : sufficient amount for
Menthol 0.0005 g

In human therapy, it may be administered from 1 to
12 bags or tablets per diem.
1.400 g
0.100 g
0.250 g
0.050 g
-------
1.800 g

1.400 g
0.250 g
0.100 g
0.030 g
0.100 g
0.020 g
0.0005 g

2 g
from 1 to
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1°) Modified clays comprising a sheet-silicate clay — with a plate separation of from 1.5 to 1.6 nm, with a cation exchange capacity of from 170 to 1700 mEq per 100 g, with a reduction of the plate separation to from 1.2 to 1.4 nm when heated to 490°C — combined with 0.05 to 0.5 part in weight of magnesium hydroxide per part of clay, i.e. containing from about to 5 to about 33 % of magnesium hydroxide and in which the characteristic X-ray spectrum of magnesium hydroxide is no more present, and acidic addition products of the same with carbonic, citric, tartaric, phosphoric and silicic acids.

2°) A preparation process of the modified clays of claim 1 consisting in treating at a temperature between 50°C and about 140°C, possibly under pressure, one part of a purified sheet-silicate clay presenting a plate separation of from 1.2 to 1.5 nm, a cation exchange capacity at least 80 mEq per 100 g and a reduction of the plate separation to from 0.9 to 1 nm on heating to 490°C, by 0.05 to 0.5 part of magnesium hydroxide for about 3 hours to about 24 hours.

3°) A therapeutic composition of matter comprising as an essential ingredient therein, a sufficient amount of a modified clay of claim 1.

DATED this 27th day of April 1983.
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