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(54) Title: ANTIACID PHARMACEUTICAL COMPOSITION IN THE FORM OF A SUSPENSION BASED ON SUCRALPHATE GEL		
(57) Abstract Antacid pharmaceutical compositions in the form of suspensions containing sucralphate gel as an active ingredient combined with suitable excipients and/or diluents.		

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ANTIACID PHARMACEUTICAL COMPOSITION IN THE FORM OF A SUSPENSION
BASED ON SUCRALPHATE GEL

Field of the invention

The present invention relates to antacid pharmaceutical
5 compositions in the form of suspensions containing sucralphate gel
as an active ingredient combined with suitable excipients and/or
diluent.

State of the art

Sucralphate, i.e. the complex of sulphated sucrose and aluminium
10 hydroxide, is an antiulcer drug. It exerts an inhibitory action
against pepsin and, as more recently found, a cytoprotective action.
In the solid state, sucralphate reacts with the acids of the stomach
giving a tacky mucosa-adhesive substance, denominated paste. Said
tacky substance is deemed essential to secure the antiulcer activity
15 of sucralphate: it adheres to the ulcers and maintains the pH of the
gastric microenvironment at ideal values for pepsin activity
inhibition.

Due to sucralphate basicity, 1 g of product can neutralize approx.
13 mEq hydrogen ions.

20 On addition to 0.1 N hydrochloric acid, sucralphate in powder form
rapidly becomes tacky and adhesive, and yields approx. 10% of its
antacid power within 2 to 3 minutes. After said initial yield, even
if the reaction medium is maintained under vigorous stirring, the
reaction with the acid becomes very slow as it is hindered by the

paste viscosity.

Therefore, although sucralphate is suitable for the treatment of ulcers, it cannot be used as an antiacid.

In fact, as well known to those skilled in the art, the therapeutic
5 activity of an antiacid preparation depends not only on its absolute
acidity neutralization, but also and especially on its acidity
neutralization rate in the gastric environment.

Advanced pharmacopoeias state that the therapeutic activity of an
antiacid preparation is a function of two basic parameters: reaction
10 rate and neutralization duration.

The first parameter, i.e. the reaction rate, concerns acidity
neutralization for a fast relief of the heartburn sensation
(pyrosis) generally accompanying gastric hyperacidity; the second
parameter, i.e. neutralization duration, concerns the development of
15 a buffer action maintaining for an appropriate time the gastric
lumen pH above the value at which said painful sensation is no more
felt.

As concerns the first parameter, sucralphate exerts a poor action:
paste formation considerably slows down its reactivity and,
20 therefore, a pH value compatible with pyrosis suppression cannot be
obtained. As concerns the second parameter, sucralphate is unable to
maintain the pH value reached for an appropriate time: theoretically
it can maintain the gastric environment buffered, but in fact,
against a continuous secretion of the gastric juice, it does not
25 exert any buffering action due to the low reactivity of the paste

that formed.

It follows that sucralphate can exert an antiacid action only if chemically transformed into a specific antiacid product, as disclosed in EP 437406. Therefore, sucralphate powder cannot
5 constitute an efficacious active ingredient of an antiacid preparation.

EP 286978 by the Applicant discloses sucralphate in the form of gel, with particles dimensional distribution practically at the limit of colloidal size, which secures a very high specific surface of the
10 product.

Sucralphate gel exerts a more potent antiulcer action than the powder form of general use and, when contacted with acids, does not form the paste already mentioned. The higher activity of the product was proved to result from its specific ability to adhere to the
15 mucosa, i.e. from the bioadhesion, taking place without any intervention of the acids.

The sucralphate gel aqueous suspension shows unique thixotropic-type rheological properties revealing a considerable surface activity of the particles, which very easily gives rise to interactions both
20 with one another and with the biological substrates.

Brief description of the drawings

Fig. 1 illustrates the change of pH on addition of 0.5N HCl to 1 g of sucralphate gel and, respectively, sucralphate powder at 25°C.

Fig. 2 shows the antiacid effectiveness by Rosset-Rice's test and
25 the results obtained with antiacid doses as per Examples 1, 2, 3,

and 4.

Fig. 3 shows the antiacid effectiveness by Rosset-Rice's test and the results obtained by testing doses of 1 g sucralphate powder, 1 g of sucralphate gel, and 2 g of sucralphate powder.

5 **Summary of the Invention**

It has surprisingly been found that sucralphate gel shows a rate of reaction with the acids and acidity neutralization power decidedly superior to sucralphate in the powder form, as elucidated in Fig. 1. This figure illustrates the change of pH on addition of 0.5N HCl
10 to 1 g of sucralphate gel and, respectively, sucralphate powder at 25°C.

It is an object of the present invention to provide antiacid pharmaceutical compositions in the form of suspensions containing sucralphate gel as an active ingredient, combined with suitable
15 excipients and/or diluents, particularly suitable for the treatment of pyrosis and gastroesophageal backflow.

Detailed description of the invention

According to US Pharmacopoeia USP XXII, an antiacid preparation is generally considered safe and effective when it obeys the safety and
20 effectiveness requirements ("Antiacid Effectiveness" requirements). To meet said requirements, the product has to pass a preliminary test meant to establish whether it may be defined antiacid or not. Said test consists in causing a single minimum dose of substance supposed to be antiacid to react with 0.5N hydrochloric acid for 10
25 minutes. Should the substance being tested under such conditions be

capable of bringing the solution pH to values above 3.5, the preparation will be considered antacid.

Should said preliminary test give positive results, a second test will be conducted to determine the acidity neutralization power of the substance. Said power must be such that the aforesaid single
5 minimum dose of the substance supposed to be antacid can neutralize at least 5 mEq of acid.

It has surprisingly been found by the Applicant that sucralphate gel at 37°C shows an acidity neutralization rate allowing it to pass the
10 USP XXII preliminary test.

In particular, in the preliminary antacid effectiveness test as per USP XXII, already a dose of 1.5 g brings pH to values exceeding 3.5. In the second antacid test, which is meant to determine the neutralization power, the said dose was found to neutralize 23 mEq
15 against the limit value of 20 to 25 mEq set by USP XXII.

Vice versa, in the preliminary test, the same dose of product containing commercially available sucralphate powder gives pH values ranging from 1.2 to 1.6. Evidence is thus provided that sucralphate powder is unable to exert an antacid action.

20 The sucralphate gel content in the suspension preferably ranges from 10 to 20% w/v.

In particular, the therapeutic compositions of the present invention contain 1.5 to 4 g sucralphate per dosage unit and, preferably, 2 g sucralphate per dosage unit.

25 Furthermore in water dispersion sucralphate gel is self-suspending:

in other words, no other suspending agent is needed to obtain stable suspensions. Therefore, sucralphate gel can be used as a suspending agent to prepare antacid suspensions in which other antacids are stably suspended.

- 5 The use of sucralphate gel as a suspending agent allows obtaining a safe and effective sucralphate-based antacid preparation matching two important goals. First, the antacid action of sucralphate gel may be strengthened by the addition of a dose of another antacid with the result that a more potent antacid action is obtained.
- 10 Second, the use of sucralphate in conjunction with another antacid active ingredient, such as for example magnesium hydroxide or salts thereof, brings a therapeutic benefit: i.e. the astringent effect on the intestine function typical of sucralphate is limited by the laxative effect typical of magnesium salts.
- 15 It follows that the claimed compositions may also contain another conventional antacid, if any, said antacid being preferably selected among magnesium hydroxide, magnesium carbonate and calcium carbonate.

In this case, 1 g of sucralphate was found to be sufficient for an
20 optimal antacid-suspending effect.

The preferred dose of sucralphate, when combined with another antacid active ingredient, preferably ranges from 1 to 3 g and the dose of said antacid active ingredient ranges from 0.250 to 0.750 g. The following examples of antacid preparations obtained according
25 to the present invention are conveyed by way of indication, not of

limitation.

EXAMPLE 1

One 10 ml dose of suspension contains:

	Sucralphate gel (corresponding to 927 mg $\text{Al}(\text{OH})_3$)	1.500 g
5	Methyl-p-hydroxybenzoate sodium salt	0.020 g
	Propyl-p-hydroxybenzoate sodium salt	0.010 g
	Sorbitol 70%	2.700 g
	Apple flavouring	0.014 g
	Purified water	q.s.

- 10 p-Hydroxybenzoates were dispersed in liquid sorbitol and wet sucralphate gel was added. The resulting mixture was dispersed to give a thick and fluid cream, which was added with the flavouring agent, made up to volume with water, turbine-stirred without air embodiment, to yield a fluid and translucent suspension.

15 EXAMPLE 2

One 15 ml dose of suspension contains:

	Sucralphate gel (corresponding to 1,324 mg $\text{Al}(\text{OH})_3$)	2.000 g
	Methyl-p-hydroxybenzoate sodium salt	0.030 g
	Propyl-p-hydroxybenzoate sodium salt	0.015 g
20	Sorbitol 70%	4.600 g
	Apple flavouring	0.014 g
	Purified water	q.s.

This suspension was prepared according to Example 1.

EXAMPLE 3

- 25 One 7.5 ml dose of suspension contains:

	Sucralphate gel (corresponding to 662 mg $\text{Al}(\text{OH})_3$)	1.000 g
	Magnesium hydroxide	0.281 g
	Methyl-p-hydroxybenzoate sodium salt	0.016 g
	Propyl-p-hydroxybenzoate sodium salt	0.008 g
5	Sorbitol 70%	2.300 g
	Apple flavouring	0.014 g
	Purified water	q.s.

This suspension was prepared according to Example 1.

EXAMPLE 4

10 One 7.5 ml dose of suspension contains:

	Sucralphate gel (corresponding to 662 mg $\text{Al}(\text{OH})_3$)	1.000 g
	Magnesium carbonate	0.400 g
	Methyl-p-hydroxybenzoate sodium salt	0.016 g
	Propyl-p-hydroxybenzoate sodium salt	0.080 g
15	Sorbitol 70%	2.300 g
	Apple flavouring	0.014 g
	Purified water	q.s.

This suspension was prepared according to Example 1.

20 The test as per USP XXII conducted on the formulation of Example 1 for the determination of the antacid effectiveness gave the following results:

preliminary antacid power ($\text{pH} > 3.5$): pH 3.65

neutralization power (>20.25 mEq): 23 mEq.

25 The test as per USP XXII conducted on the formulation of Example 2 for the determination of the antacid effectiveness gave the

following results:

preliminary antacid power (pH > 3.5): pH 3.85

neutralization power (>28.93 mEq): 27 mEq.

The test as per USP XXII conducted on the formulation of Example 3
5 for the determination of the antacid effectiveness gave the
following results:

preliminary antacid power (pH > 3.5): pH 5.6

neutralization power (>21.73 mEq): 27.0 mEq.

The test as per USP XXII conducted on the formulation of Example 4
10 for the determination of the antacid effectiveness gave the
following results:

preliminary antacid power (pH > 3.5): pH 5.6

neutralization power (>21.8 mEq): >28.3 mEq.

ROSSET-RICE DYNAMIC TEST

15 Rosset-Rice's dynamic test (N.E. Rosset and M.L. Rice,
Gastroenterology, 26, 940, 1954) was also conducted on the
preparations of the present invention further to prove the
effectiveness of the antacid dose of same. According to this test,
a 400 ml beaker containing water (70 ml) and 0.1N HCl (30 ml)
20 maintained at 37°C was fed with a dose of antacid. After addition
of 2 ml/min of 10N HCl the change in pH was measured under
continuous magnetic stirring (300 rpm/min).

The antacid dose is considered effective when a pH value of 3.0 is
reached within 10 minutes and maintained above said value for over
25 one hour.

With reference to the figures, the Rosset-Rice's test provided evidence that all products possessed antacid effectiveness.

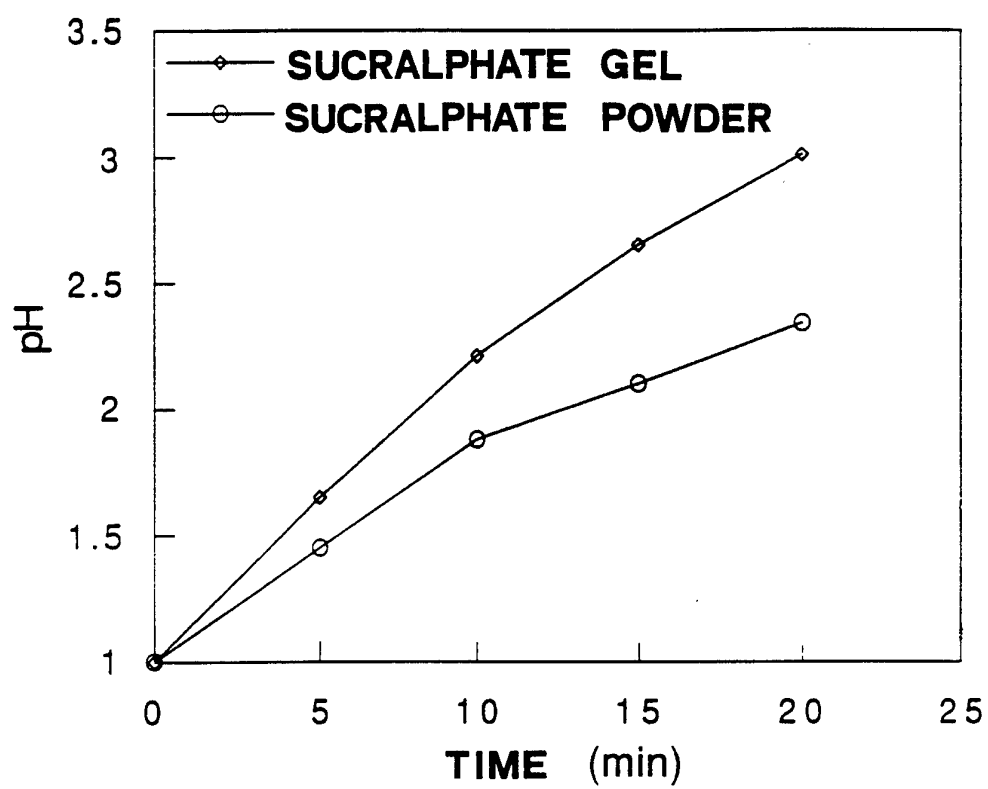
Sucralphate gel at a dose of 1 g shows some antacid power and sucralphate powder at a dose of 2 g reaches a pH value of 3 within
5 10 minutes, but cannot maintain said value for over 15 minutes, during which 2 ml/min HCl was added to simulate gastric secretion.

CLAIMS

- 1 1. Antacid pharmaceutical compositions in the form of suspensions
2 containing sucralphate gel as an active ingredient combined with
3 suitable excipients and/or diluents.
- 1 2. The pharmaceutical compositions according to claim 1 suitable for
2 the treatment of pyrosis and gastroesophageal backflow.
- 1 3. The pharmaceutical compositions according to claim 1 wherein the
2 sucralphate gel content in the suspension preferably ranges from 10
3 to 20% w/v.
- 1 4. The pharmaceutical compositions according to claim 1 wherein the
2 amount of sucralphate per dosage unit ranges from 1.5 to 4 g.
- 1 5. The pharmaceutical compositions according to claim 4 wherein the
2 amount of sucralphate per dosage unit is 2 g.
- 1 6. The pharmaceutical compositions according to claim 1 wherein
2 another antacid active ingredient of the conventional type, if
3 any, is also present.
- 1 7. The pharmaceutical compositions according to claim 6 wherein the
2 other antacid agent is selected among magnesium hydroxide,
3 magnesium carbonate and calcium carbonate.
- 1 8. The pharmaceutical compositions according to claim 6 wherein the
2 dose of sucralphate gel ranges from 1 to 3 g and the dose of the
3 other antacid active ingredient ranges from 0.250 to 0.750 g per
4 dosage unit.

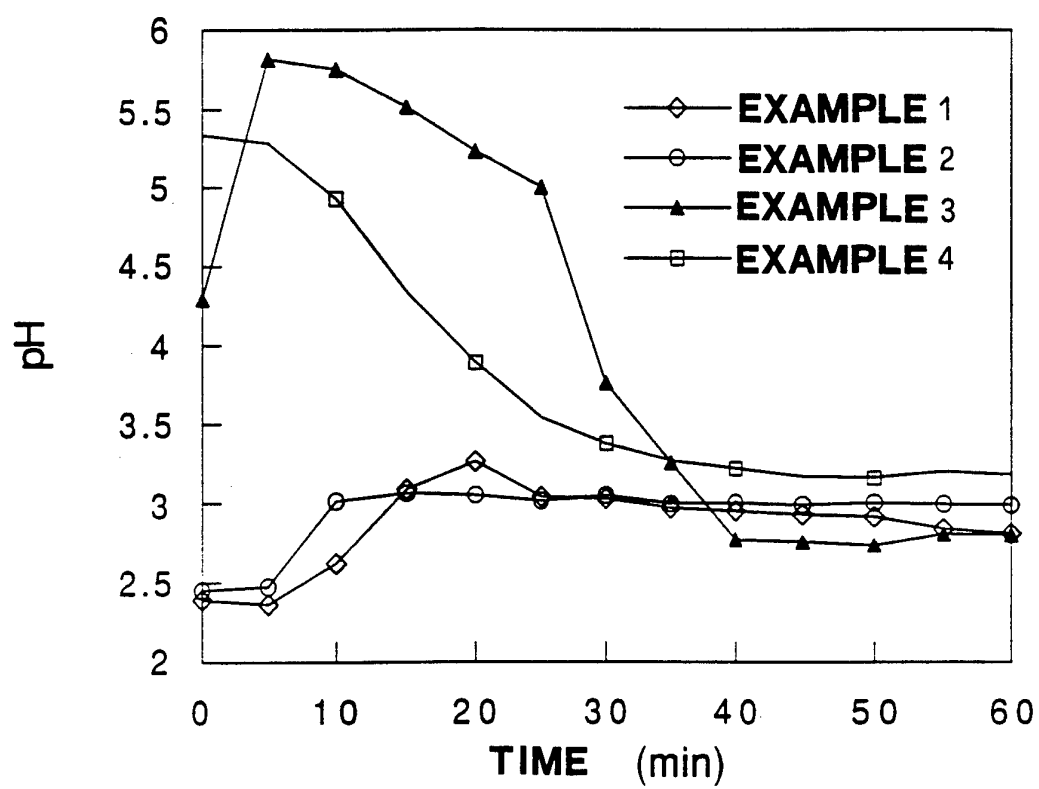
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FIG. 1



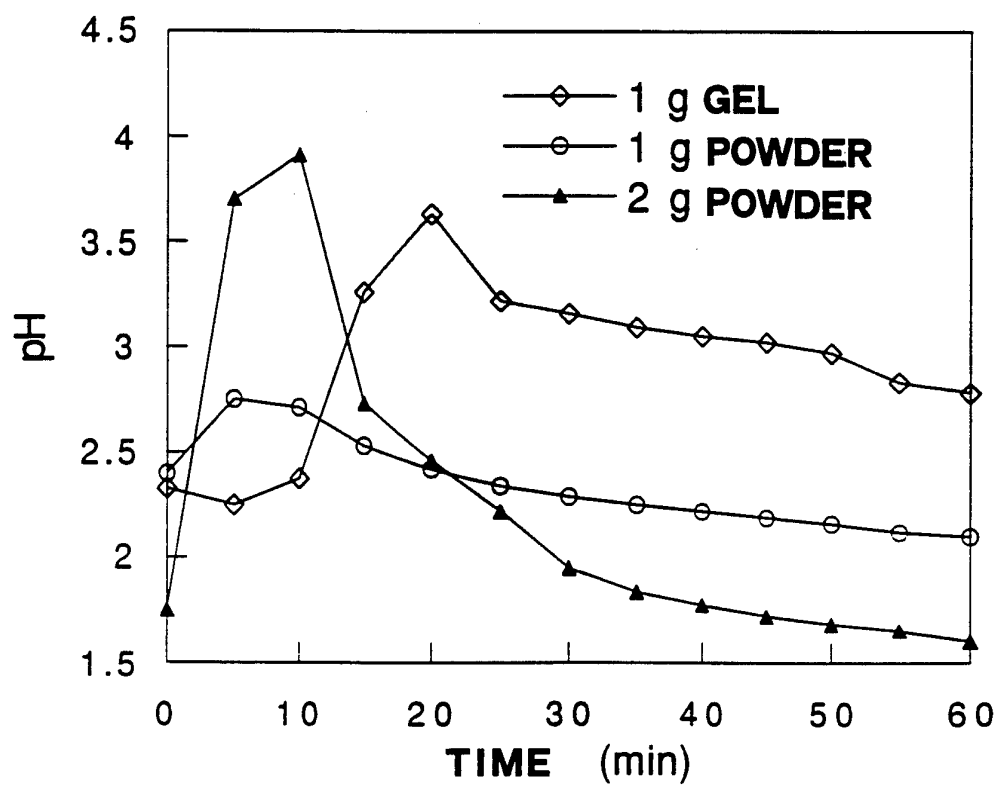
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FIG. 2



3/3

FIG. 3



INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/EP 94/02477

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/70 A61K9/08 A61K33/10 A61K33/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 245 855 (CHUGAI SEIYAKU K.K.) 19 November 1987 see page 3; example 1 see page 4; example 3 ---	1,2
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Inter. Patent Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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