



(12) UK Patent (19) GB (11) 2 192 131 (13) B

(54) Title of Invention

Pharmaceutical compositions containing calcium salts

(51) INT CL⁴; A61K 31/10

(21) Application No
8715216.1

(22) Date of filing
29 Jun 1987

(30) Priority data

(31) 8609515

(32) 1 Jul 1986

(33) FR

(43) Application published
6 Jan 1988

(45) Patent published
4 Apr 1990

(73) Proprietor(s)
Sandoz Ltd

(Incorporated in
Switzerland)

35 Lichtstrasse
CH-4002 Basle
Switzerland

(72) Inventor(s)
John-Marc Gailly
Daniel Gomez
Martine Burgulere
Andre Gens
Jean Remy

(74) Agent and/or
Address for Service
B.A Yorke & Company
Coomb House
7 St John's Road
Isleworth
Middlesex TW7 6NH

(52) Domestic classification
(Edition J)
A5B BJA B180 B27Y B272
B28Y B285 B40Y B401 B402
B841
U1S S1318

(56) Documents cited
None

(58) Field of search

As for published application
2192131 A viz:
UK CL A5B
INT CL⁴ A61K
updated as appropriate

PHARMACEUTICAL COMPOSITIONS CONTAINING CALCIUM SALTS

The present invention relates to pharmaceutical compositions containing calcium salts, especially for oral administration.

5 Calcium salts are well known for the treatment of calcium deficiencies and their symptoms. For an acceptable and effective therapy, calcium pharmaceutical compositions based on such salts must have a high content of calcium ions in order to facilitate the assimilation
10 into the body of a sufficient amount of calcium. Moreover, for permanent calcium therapy in practice only oral administration comes into question. One well-established oral calcium pharmaceutical composition comprises an effervescent tablet containing calcium
15 gluconolactate (also known as calcium lactogluconate and calcium lactategluconate) , calcium carbonate, sodium bicarbonate, citric acid and sucrose. Before administration the tablet is dissolved in a glass of water to give a sparkling (effervescent) drink. For permanent therapy,
20 such a composition with its sodium and sucrose content may be unsatisfactory for subjects only allowed to take foods and medicines having a low content of sodium ions or for diabetic subjects. Moreover, the sparkling drink may lead to digestive and gastric disorders.

After extensive testing we have now found an advantageous stable, sugar-free and sodium-free or substantially sodium-free calcium composition which not only provides a high dose of calcium ions per unit dosage but is easily and quickly dissolved in water. It also may be formulated to contain as few excipients as possible which could induce side effects.

In one aspect, the present invention provides a stable, sugar-free and sodium-free or substantially sugar and sodium-free calcium pharmaceutical composition, comprising a calcium organic salt, calcium carbonate and a non-aromatic organic polycarboxylic acid.

In another aspect the present invention provides a process comprising mixing the above constituents.

Appropriate calcium organic salts used in the compositions of the invention, preferably have calcium ion contents of above 5 or even 10 percent. They include for example calcium glucoheptonate, calcium ascorbate, calcium gluconate, calcium lactate, calcium gluconolactate, calcium citrate, calcium fumarate and calcium levulinate. Preferably, the calcium organic salt is the calcium salt of gluconic acid and/or lactic acid, particularly calcium gluconate, calcium lactate and calcium gluconolactate, more preferably calcium gluconolactate. These calcium organic salts are known; calcium gluconolactate may be prepared for example as described in the US Patent No. 1 267 760. Calcium gluconolactate has a calcium content of about 12-13%, e.g. 12,92% by weight.

The organic polycarboxylic acid used in the compositions of the invention is preferably a low molecular weight acid, e.g. of up to 6 carbon atoms, and conveniently fumaric acid or an organic hydroxy polycarboxylic acid such as tartaric acid, malic acid or citric acid. The organic polycarboxylic acid is preferably citric acid. Preferably the acids are used in anhydrous form.

The compositions of the invention provide high amounts of calcium ions. Per dosage , the total amount of calcium organic salt and calcium carbonate is chosen to provide conveniently from about 200 mg to about 1000 mg of calcium ions, preferably about 500 mg. The weight ratio of calcium organic salt to calcium carbonate is conveniently from 35:1 to 5:1, preferably between 25:1 and 8:1 , and may be for example ca. 23:1 or 10:1.

The weight ratio of calcium carbonate to the organic polycarboxylic acid is conveniently from 1:3 to 1:6, for example from 1:3.5 to 1:4.5, and is preferably of about 1:4.

The pH of the aqueous solution produced on dissolving the compositions of the invention is conveniently between 3.6 and 4, for example from 3.75 to 3.92 , in e.g. 100 ml water.

Preferably the compositions of the invention contain a non-carbohydrate sweetener agent. Appropriate non-carbohydrate sweetener agents include L-aspartyl-L-phenylalanine methylester (known as Aspartame, Registered Trademark), cyclamic acid or its calcium salt or preferably a saccharinate, e.g. ammonium or especially calcium saccharinate.

When the compositions of the invention contain a non-carbohydrate sweetener agent, the weight ratio of the non-carbohydrate sweetener agent to calcium carbonate is preferably from about 1:5 to 1:20, particularly
5 from 1:7.5 to 1:15.

The compositions of the invention preferably may contain flavouring agents such as lemon, orange, grape fruit, raspberry, strawberry, black currant or apricot flavours, preferably lemon.

10 If desired, the compositions of the invention may contain up to 0.2% by weight of a flowing agent, preferably colloidal silica (known for example under the name Aerosil, Registered Trademark).

The compositions of the invention may be
15 completely sodium and sugar-free or may contain, in the light of additional excipients present, only insignificant amounts of sodium. Preferably, such compositions are free of excipients containing sodium and are entirely sodium free.

20 The compositions of the invention are preferably in the form of a powder. The compositions in the powder form may e.g. have a particle size diameter of from 20 to 1000 microns, preferably from 50 to 750 microns; more especially, at least 80% of the powder has a
25 particle size diameter of from 60 to 500 microns. Such powders may be prepared according known methods, e.g. by dry mixing of the different constituents, for example

in a tumbler mixer / blender. In order to obtain a good distribution of the mixture, each constituent may be processed e.g. sieved, before the mixing operation to obtain an similar average particle size for each constituent. Conveniently, the constituents which are present in a low amount in the final composition, such as the non-carbohydrate sweetener agent and the flavouring agent, are diluted in part of the organic polycarboxylic acid or in the calcium salts before mixing with the other constituents.

A particularly preferred composition according to the invention, is a sugar-free and sodium-free composition comprising calcium gluconolactate, calcium carbonate, citric acid, a non-carbohydrate sweetener agent, preferably calcium saccharinate or aspartame and optionally a flavouring agent, preferably in the weight ratio indicated above for the different constituents. Preferably such a composition is in a powder form.

The resulting powders are not hygroscopic and possess good flowing properties. Surprisingly, the compositions of the invention dissolve well in water in a beaker and in a very short time, for example under 1 minute or even 30 seconds, compared to 3 minutes for the prior art effervescent tablet mentioned above. The compositions of the invention dissolve with only a slight effervescence and give a non-sparkling solution without deposit on the sides of the beaker. They have a good gastric and digestive tolerance. They may be dissolved as indicated in the examples hereinafter.

Clinical tests have shown that the compositions of the invention are well tolerated and have a very acceptable taste. The calcium ions are absorbed well. The compositions of the invention avoid the unfavourable effects on hormones, e.g. PTH, somatotropin C, CRGHP (calcitonin precursor).

The compositions of the invention may be used in therapy for hypocalcaemia to provide high dosages of calcium ions, for example to satisfy the increased demand for calcium in pregnant and lactating women and in growing children, the treatment of osteoporosis, in the treatment of osteopathies, the treatment of rickets and osteomalacia as an adjuvant to specific therapy, in the treatment of tetany and latent tetany, and as a supportive treatment in the treatment of allergic conditions. Due to the absence of sodium and sucrose, the compositions of the invention are particularly appropriate for subjects taking a food regime having a low sodium content or for diabetics. As the resulting solutions are not significantly effervescent, the compositions of the invention are very well accepted for permanent treatments, for example, of osteoporosis.

The compositions of the invention are conveniently in unit dosage forms. The calcium content in the unit dosage may vary depending on e.g. the therapeutic need and may contain the equivalent of e.g. from 200 to 1000 mg calcium, for example 500 mg calcium ions. Preferably, the compositions of the invention in powder form are packed in a sachet for the delivery of a unit dosage, for example 500 mg of calcium. Preferably, the packing comprises paper, aluminium and/or polyethy-

lene or another thermosetting agent. The paper is preferably a paper of 30 to 60 g/m², e.g. 40 g/m². Aluminium is preferably an aluminium sheet of 9 to 25 microns in thickness, e.g. 9 microns.

- 5 Polyethylene is preferably of 20 to 50, e.g. 25 g/m².
The sachet packing comprises preferably 3 layers of paper (outer), aluminium and polyethylene sheets.

Preferably, the weight of the composition in unit dosage form is about 4 to 5 g. Per unit dosage form, the amount of acid is about 0.6 to 0.7 g, e.g. 0.62 to 0.65 g,
10 unless no flavouring agent is present. When a flavouring agent is present, it is preferably about 0.85 to 1.5, e.g. 1.2 to 1.3 g.

Ammonium and calcium saccharinate are also known as saccharin ammonium salt and saccharin calcium salt.

The following examples in which the temperatures are in degrees Centigrade, illustrate the present invention.

EXAMPLE 1

A powder having the following composition is prepared :

Unit dose content in g

5		Composition A
	Calcium gluconolactate	2.940 ¹⁾
	Calcium carbonate	0.300 ²⁾
	Citric acid (anhydrous)	1.220
	Ammonium saccharinate	0.020
10	Flavour-lemon or orange (powder)	0.020
	Total	4.500

1) corresponds to 379.85 mg calcium ions

2) corresponds to 120.12 mg calcium ions

- 15 In a mixer of 140 litres 29.4 kg of
 calcium gluconolactate, 3 kg of calcium carbonate
(sieved through 0.8 mm mesh) and 12.2 kg of granulated
anhydrous citric acid are mixed together for 5 minutes
(mixture I). To 1.6 kg of this mixture, 0.2 kg of
20 ammonium saccharinate and 0.2 kg of lemon or orange
flavour are added and the resulting mixture is mixed
for 5 minutes (mixture II). Mixtures I and II are
sieved (1 mm mesh) and mixed together for 10 minutes,
to give 45 kg of composition A. The mixture suffices for
25 the filing of 10 000 sachets each containing 4.5 g

of the composition A indicated above and containing about 500 mg calcium ions.

EXAMPLE 2

The following compositions B to H may be prepared in analogous manner to that described in Example 1.

Unit dose content in g.

	B	C	D
Calcium gluconolactate	3.405	2.940	3.250
Calcium carbonate	0.150	0.300	0.200
10 Citric acid (anhydrous)	0.625	1.215	0.880
Aspartame	-	0.025	-
Ammonium saccharinate	0.020	-	0.020
Flavour-lemon or orange (powder)	-	0.020	0.050
15 Total	4.200	4.500	4.400

Unit dose content in g.

	E	F
Calcium gluconolactate	3.405	2.940
Calcium carbonate	0.150	0.300
20 Citric acid (anhydrous)	0.625	1.220
Calcium saccharinate	0.020	0.020
Flavour-lemon or orange (powder)	-	0.020
Total	4.200	4.500

Unit dose content in g.

	G	H
Calcium gluconolactate	2.940	3.405
Calcium carbonate	0.300	0.150
5 Citric acid (anhydrous)	1.220	0.625
Aspartame	0.020	0.020
Flavour-lemon or orange (powder)	0.020	-
Total	4.500	4.200

10 The compositions obtained in examples 1 to 2 are
filled into sachets made from multilayer sheets comprising
40 g/m² paper, 9 microns thick aluminium and 25 g/m²
thick polyethylene in a sachet filling and packaging
machine (e.g. type Wolkogon) producing 80 filled sachets
15 (7 cm²) every minute. The sachet edges are sealed by heat.

The sealed sachets are then packed in groups of 6 units in cardboard boxes. They can be stored for a long period of time without significant alteration of the composition.

- 5 To use, the opened sachet content is dissolved in water or, for the non-flavoured compositions, in an aqueous beverage, e.g. orangeade or lemon squash, or fruit juice. Advantageously, the sachet content is poured into a vessel, water or the dissolution liquid
10 being then added to give a quick dissolution of the composition. The amount of liquid to be used to dissolve the content of one sachet may vary according to the user's taste; to achieve complete dissolution, the content of these sachets will be advantageously dissolved
15 in an amount of liquid greater than about 30 ml (e.g. 70-80 ml), if necessary with stirring.

The content of these sachets dissolves in 20 to 30 seconds to give a clear sediment-free solution having an agreeable taste.

Characteristics of compositions

- 20 A and B prepared according the above Examples are indicated hereinafter:-

		Composition A	Composition B
	Flowing rate (100g of powder)	5 seconds	7 seconds
	Compactness volume (100 g of powder)		
5	V ₀ (Poured volume)	144 ml	150 ml
	V ₁₀ (Tapped volume)	132 ml	140 ml
	V ₅₀₀ (Tapped volume)	114 ml	118 ml
	Dissolution rate (100 ml)	1 min.	1 min.
10	pH of the solution (100 ml)	3.75	3.92
	<u>Particle size diameter</u>	A	B
	less than 63 microns	4.1 %	4.3 %
		A	B
	next fraction greater than 63 microns	15.5 %	19.2 %
	next fraction greater than 100 microns	17.4 %	22.8 %
15	next fraction greater than 160 microns	17.2 %	19.3 %
	next fraction greater than 250 microns	31 %	27.6 %
	next fraction greater than 500 microns	14.65%	7.8 %

Flowing rate test

100 g of powder are introduced in a standardized funnel and the time measured for the powder to flow through into a graduated cylinder. For powders having good flowing properties, the flowing time is less than 10 seconds.

Tapped volume test

The volume of the powder in the graduated cylinder from the flowing rate test is determined before tapping (V_0) and after 10 (V_{10}) and 500 tappings (V_{500}). For powders having good flowing properties, the difference $V_{10}-V_{500}$ must be less than 25 ml.

CLAIMS :

- 1) A process for preparing a stable, sugar free and sodium free or substantially sodium free calcium pharmaceutical composition comprising mixing a calcium
5 organic salt, calcium carbonate and a non-aromatic organic polycarboxylic acid.
- 2) A process according to claim 1 wherein the calcium organic salt is calcium gluconate, calcium lactate or calcium gluconolactate.
- 10 3) A process according to claim 1 or 2, wherein the weight ratio of the calcium organic salt to calcium carbonate is between 35:1 and 5:1.
- 4) A process according to any preceeding claim, wherein the total content of calcium ions is about 500 mg
15 per unit dosage.
- 5) A process according to any preceeding claim, wherein the non-aromatic organic polycarboxylic acid is citric acid.
- 6) A process according to any preceeding claim,
20 wherein the weight ratio of calcium carbonate to organic polycarboxylic acid is between 1:3 and 1:6.

- 7) A process according to any preceeding claim,
wherein the composition contains a non-carbohydrate
sweetener agent.
- 8) A process according to claim 7, wherein the
5 non-carbohydrate sweetener agent is L-aspartyl-L-phenyl-
alanine.
- 9) A process according to any preceeding claim,
wherein the composition contains a flavouring agent.
- 10) A process according to any preceeding claim,
wherein the resulting composition is ground to a powder.
- 10 11) A process according to any preceeding claim,
wherein the powder is in the form of unit dosage having
a calcium content which is the equivalent of between 200 and
1000 mg calcium ions.
- 12) A process according to any preceeding claim,
15 wherein the composition is packed in a sachet.
- 13) A composition whenever produced by a process
according to anyone of claims 1 to 12.
- 14) A stable , sugar free and sodium free or
substantially sodium free calcium pharmaceutical composi-
20 tion , comprising a calcium organic salt, calcium
carbonate and a non-aromatic organic polycarboxylic
acid.

- 15) A pharmaceutical composition according to claim 14, wherein the calcium organic salt is calcium gluconate, calcium lactate or calcium gluconolactate.
- 5 16) A pharmaceutical composition according to claim 14 or 15, wherein the weight ratio of the calcium organic salt to calcium carbonate is comprised between 35:1 and 5:1.
- 10 17) A pharmaceutical composition according to anyone of claims 14 to 16, wherein the total content of calcium ions is about 500 mg per unit dosage.
- 18) A pharmaceutical composition according to anyone of claims 14 to 17, wherein the non-aromatic organic carboxylic acid is citric acid.
- 15 19) A pharmaceutical composition according to anyone of claims 14 to 18, wherein the weight ratio of calcium carbonate to organic polycarboxylic acid is between 1:3 and 1:6.
- 20 20) A pharmaceutical composition according to anyone of claim 14 to 19, wherein the composition contains a non-carbohydrate sweetener agent.
- 21) A pharmaceutical composition according to claim 20, wherein the non carbohydrate sweetener agent is L-aspartyl-L-phenylalanine.

- 22) A pharmaceutical composition according anyone
of claims 14 to 21, wherein the composition contains
a flavouring agent,
- 23) A pharmaceutical composition according anyone
5 of claims 14 to 22, wherein the composition is in
powder form.
- 24) A pharmaceutical composition according anyone
of claims 14 to 23, wherein the powder is in the form
of unit dosage having a calcium content which is the
10 equivalent of between 200 mg and 1000 mg calcium ions.
- 25) A pharmaceutical composition according anyone
of claims 14 to 24, packed in a sachet.
- 26) A sugar-free and sodium free composition
comprising calcium gluconolactate, calcium carbonate,
15 citric acid and a non-carbohydrate sweetener agent.
- 27) A composition according to claim 26 in powder
form.
- 28) A oral calcium composition substantially as
hereinbefore described with reference to anyone
20 of the examples.
-

REGISTER ENTRY FOR GB2192131 /

Form 1 Application No GB8715216.1 filing date 29.06.1987 /

Priority claimed:

01.07.1986 in France - doc: 8609515

Title IMPROVEMENTS IN OR RELATING TO CALCIUM SALTS

Applicant/Proprietor

SANDOZ LTD, Incorporated in Switzerland, 35 Lichtstrasse, CH-4002 Basle,
Switzerland / [ADP No. 00703264018]

Inventors

JOHN-MARC GAILLY, 92 rue Guy de Maupassant, F-45100 Orleans, France
[ADP No. 03957883001]

DANIEL GOMEZ, 11 rue de Limare, F-45000 Orleans, France
[ADP No. 03957891001]

MARTINE BURGUIERE, Residence les Floralties, rue Eugene Turbat, F-45100
Orleans, France [ADP No. 03957909001]

ANDRE GENS, 760 Avenue de Loiret, F-45160 Olivet, France
[ADP No. 03957917001]

JEAN REMY, 100 rue de l'oree du Bois, F-45590 St Cyr en Val, France
[ADP No. 03957925001]

Classified to

A5B U1S

A61K

Address for Service

B A YORKE & CO, Coomb House, 7 St John's Road, Isleworth, Middlesex, TW7
6NH, United Kingdom [ADP No. 00001800001]

Publication No GB2192131 dated 06.01.1988

Examination requested 29.06.1987

Patent Granted with effect from 04.04.1990 (Section 25(1)) with title
PHARMACEUTICAL COMPOSITIONS CONTAINING CALCIUM SALTS.

**** END OF REGISTER ENTRY ****

OA80-01
FG

OPTICS - PATENTS

19/11/92 14:51:28
PAGE: 1

RENEWAL DETAILS

PUBLICATION NUMBER

GB2192131 /

PROPRIETOR(S)

Sandoz Ltd, / Incorporated in Switzerland, 35 Lichtstrasse, CH-4002
Basle, Switzerland /

DATE FILED

29.06.1987 /

DATE GRANTED

04.04.1990 /

DATE NEXT RENEWAL DUE

29.06.1993

DATE NOT IN FORCE

DATE OF LAST RENEWAL

06.05.1992

YEAR OF LAST RENEWAL

06

STATUS

PATENT IN FORCE /