PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/415, 9/00, 9/14, 33/12

A1

(11) International Publication Number: **WO 95/05173**

(43) International Publication Date: 23 February 1995 (23.02.95)

(21) International Application Number: PCT/US94/09204

(22) International Filing Date: 16 August 1994 (16.08.94)

(30) Priority Data:

08/107,126	17 August 1993 (17.08.93)	US
08/288,711	12 August 1994 (12.08.94)	US

(71) Applicant: APPLIED ANALYTICAL INDUSTRIES, INC. [US/US]; 1206 N. 23rd Street, Wilmington, NC 28405 (US).

(72) Inventors: CALDWELL, Henry, C.; 37 Mercer Hill Road, Ambler, PA 19002 (US). DESAI, Ashok, J.; 3412 Hampshire Drive, Wilmington, NC 28409 (US).

(74) Agents: GARRETT, Arthur, S. et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, 1300 I Street, N.W., Washington, DC 20005-3315 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ORAL COMPOSITIONS OF H_2-ANTAGONISTS

(57) Abstract

Chewable tablets of H_2-antagonists which are tasteless in the mouth, but give good release of active ingredients are prepared using calcium carbonate and a supportive magnesium aluminum silicate. Also contributing to the formulation are such non-essentials as xylitol and fruit acids.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

Description

ORAL COMPOSITIONS OF H_2 - ANTAGONISTS

This invention relates to pharmaceutically elegant compositions of therapeutic compounds having H_2-antagonist activity especially adapted for convenient oral administration.

Background of the Invention

Magnesium aluminum silicates have been known in the pharmaceutical art to be useful to mask the bitter taste of a variety of medicinal agents. U.S. Patent No. 3,140,978 (M. R. Zentner), together with related patents such as 3,248,290, 3,337,402, 3,337,403, as well as U.S. Patent No. 4,711,774 (J. Denick Jr.), together with 4,716,033, 4,717,565, 4,758,424, 4,758,425 and 4,761,274, describe the adsorption of medications of many therapeutic classes onto magnesium aluminum silicates as well as the suspensions, granulations, lozenges, chewable tablets and the like prepared from the resulting complexes using standard formulation methods. None of these mention the use of H_2-antagonists as the active therapeutic agent.

Other specific applications of magnesium aluminum silicates to formulation procedures are disclosed in U.S. Patent Nos. 3,432,593 (M. Shepard), 3,567,819 and 4,753,800. These also are of a specific aim and are believed cumulative as well to the two basic references of Zentner and Denick mentioned above.

U.S. Patent No. 4,719,228 (D. Rawlins) discloses the use of selected synthetic silicas to form free flowing powder products of a number of therapeutic classes of drugs including antiulcer drugs. No reference to H_2-antagonists is made here.

The scientific literature contains studies of the use of silicate clays in formulating various drugs of different chemical types and the nature of the binding forces involved. In general, the release of the active ingredient from such formulations is uncertain but is

often retarded by clay admixture, J.W. McGinity et al., J. Pharm. Sc. 65, 896; J.T. Carstensen et al., J. Pharm. Sc. 60 733. Certain electrolytes such as sodium and magnesium chloride are reported to facilitate the release of antibiotics from clay adsorbates, J.W. McGinity et al., J. Pharm. Sc. 64, 1567.

An effervescent tablet containing ranitidine as the active H_2-antagonist agent has been reported. This pharmaceutical form, which contains sodium acid pyrophosphate, an acid salt, demonstrated substantial reduced bioavailability of the active ingredient (54%). K.M. Koch et al., Pharm. Res. 10 1027 (1993).

U.S. Patent No. 5,219,563 (S.J. Douglas) reports adsorbates of ranitidine on synthetic ion exchange resin.

Disclosure of the Invention

This invention relates to pharmaceutical oral compositions containing one or more H_2-antagonist drugs. These compositions do not exhibit a bitter taste in the mouth and distribute the active ingredient substantially in the gastrointestinal tract. The composition contains, as essential ingredients, an H_2-antagonist - magnesium aluminum silicate complex and calcium carbonate. The dosage unit form is any which would normally expose the bitter H_2-antagonist to the taste of the patient but is preferably a chewable tablet. For larger doses, it may be a sachet, lozenge or packaged flavored granules.

Best Mode for Carrying Out the Invention

Most drugs which have H_2-antagonist activity, and are thereby useful for treating various gastrointestinal disorders such as ulcers, dyspepsia or gastrointestinal reflux indications, have a bitter taste. The H_2-compounds are preferably administered orally. For the usual prescription use, the oral product forms of these compounds are capsules or coated tablets. Certain segments of the patient population prefer more easily ingested product forms. This is most evident in the over-the-counter market. One of the most useful of such

product forms is the chewable or frangible tablet, lozenge or troche. Examples of the preparation of chewable products are found in U.S. Patent No. 4,711,774 which is cited in the Background section above.

As stated above, the pharmaceutical art has long recognized that the natural or processed magnesium aluminum silicates adsorb a wide variety of medicaments to some degree. Natural clays such as attapulgite and montmorillonite have been used, but, in our hands, these are not as satisfactory for use with H_2-antagonists as are the processed silicates known by the trade name "Veegum". The latter are also described in detail in the above cited prior art and are widely accepted for pharmaceutical use.

The literature describes the nature of silicate-drug binding and the uncertain release of various active ingredients from the adsorbate complex. Mechanical and chemical methods of increasing the reliability of release are many but, more often than not, unsuccessful. Ionic additives such as the halide salts have not been successful due to the side effects due to large ingestions of such salts.

This invention is based on several discoveries which are unique with the use of H_2-antagonists. Firstly, the H_2-antagonist compounds form tasteless adsorbates with magnesium aluminum silicate readily and substantially completely. Secondly, the addition of a selected quantity of calcium carbonate dramatically improves the release of active ingredient from the silicate adsorbate, but does not cause overt side effects such as substantial release of carbon dioxide by effervescence. This is so especially when the formulations are prepared with acid addition salts of the biologically active ingredients or with added solid acid formulation aids such as the fruit acids, for example citric acid, within the granules in the formulation process. The complex between the active biological ingredient and the magnesium aluminum silicate

is usually formed in situ, that is, during the formulation of the dosage unit composition.

The composition of this invention, therefore, is in its preferred form a chewable tablet comprised essentially of a therapeutically effective but non-toxic dosage unit quantity of an H_2-antagonist complex formed with a magnesium aluminum silicate, which complex is usually prepared during formulation, and a quantity of calcium carbonate.

The magnesium aluminum silicate which is the support component of this combination is preferably the commercial product known as "Veegum" supplied by R.T. Vanderbilt Company, Inc. Analysis of the commercial product is carried out as oxide contents. No control of the particle size of the commercial grade of product has been found necessary. Comprehensive descriptions of the product are in the Zentner-Denick patents noted above.

The exact quantity of the silicate support is not critical to the invention as long as enough is present to completely adsorb the drug component in situ. An excess is most convenient and preferred with ranges of from 10 - 30% by weight of the dosage unit. Magnesium aluminum silicates have been used in the literature to delay the release of other active ingredients in time release products when used in excess. This is in contrast to the present invention which affords good quick release of drug.

The H_2-antagonist, in either the base or its acid addition salt form as appropriate, is preferably selected from those approved for use in either the prescription or over-the-counter pharmaceutical markets. The dosage units will contain either a full therapeutic dose or a partial dose for a subject in need of relief so that from 1-5 units may be administered per day to obtain satisfactory treatment of symptoms. The non-prescription products usually contain a lower dose, often about half the quantity. Examples of active H_2-antagonists and suggested

doses are cimetidine (300 mg), nizatidine (150 mg), roxatidine (acetate), famotidine (20 mg), ranitidine (150 mg), tiotidine, lamtidine, mifentidine, zaltidine, KV-1257 or loxtidine (Handbook Exp. Pharmacol. 97 573-748 (1991), "Histamine and Histamine Antagonists").

The daily dose range of active ingredient is a nontoxic but H_2-antagonist effective quantity and may be chosen from 40 to 1600 mg. The dosage units may range from 10 - 800 mg of active ingredient depending on the known individual activity and market of the H_2-antagonist drug. The units are administered from 1-5 times daily orally to a patient in need of H_2-antagonist treatment. The H_2-antagonist may be present either as the base if appropriate or as a salt thereof with a nontoxic, pharmaceutically acceptable acid. Usually, the dose and the form which is commercially available is conveniently used. Surprisingly, the H_2-antagonist-silicate adsorbate is formed substantially completely during formulation despite which base or salt form of the active H_2-antagonist is selected.

Preferably, the calcium carbonate is selected from the range of 75-500 mg per dosage unit.

The calcium carbonate supplemented product is preferably used in non-toxic quantities in up to 5 units per day. A general range of calcium carbonate content of the oral product is from about 1-35% by weight of the chewable tablet products. For example, for a 1500 mg. tablet as much as 500 mg. of calcium carbonate may be present. Overt evolution of carbon dioxide has not been observed when the compositions contact water. One skilled in the art will recognize that the size of chewable tablets may be larger than that of normal compressed tablets.

A variety of other pharmaceutical additives may be optionally used in the composition of this invention in addition to the essential ingredients described above. Among these are bulking agents, flavoring agents,

granulating agents, buffering agents, coloring agents, preservatives, confectioneries and the like. Reference may be made to U.S. Patent No. 4,711,774 for more specific formulation information.

Especially useful optional ingredients are the solid fruit acids such as citric, malic or tartaric acids in up to 3% by weight for good stability and palatability of the chewable tablet as well as xylitol or mannitol as a sweetening-bulking agent in up to 70% by weight. Citric acid as well as xylitol are particularly advantageous since each contributes unexpectedly well to the palatability of the chewable tablets. When such acids are used for this purpose, quantity of calcium carbonate and acid should be selected to insure good release, but not to cause overt carbon dioxide evolution. The absence of the acid component gives acceptable products as well.

The chewable tablets of this invention are prepared by mixing the H_2-antagonist compound with magnesium aluminum silicate in a weight ratio chosen from the range of 1 to 1 down to 1 to 10 with an optional sweetening agent in a mixer, adding water to form the complex and granulate. The dried and milled granules are mixed with the calcium carbonate, bulking-sweetening agents and tabletting aids then compressed into tablets.

The chewable pharmaceutical products are taken by the subject in need of H_2-antagonist treatment orally from 1 to 5 times daily as required to satisfy the acceptable daily dosage regimen of active ingredients. It should be particularly noted that the antacid component of the chewable tablet may also contribute to lowering the acid content of the gastrointestinal tract. The dosage units should be prepared and used with this in mind.

The method of analysis used and detailed hereafter is the ultraviolet dissolution method as reported in the USP XXII (p. 3074). Usually times for pulling samples were 15, 30, 45, 60 minutes. The ultraviolet wave lengths vary, of course, with the active ingredient. Cimetidine

is at 218 nm. Nizatidine and ranitidine are at 314 nm. Famotidine is at 265 nm.

The following embodiments of this invention are designed to illustrate and teach the specific use of the invention but not to limit its scope.

Example 1

Ingredients	% By Weight A	B	C	D
Nizatidine USP	5	-	-	-
Cimetidine USP	-	5	-	-
Ranitidine USP	-	-	5	-
Famotidine USP	-	-	-	2
Magnesium Aluminum Silicate NF	25	25	25	10
Sodium Saccharin NF	.25	.25	.25	.125
Mannitol NF	Q.S.	Q.S.	Q.S	Q.S.
Xylitol NF	Q.S.	Q.S.	Q.S.	Q.S.
Colloidal Solicon Dioxide NF	1	1	1	1
Magnesium Stearate NF	1.5	1.5	1.5	1.5
Flavors	Q.S.	Q.S.	Q.S.	Q.S.
Purified water*				
	100	100	100	100

* Remove during processing

Method of Manufacturing

1. Mix drug with magnesium aluminum silicate and sodium saccharin in a planetary mixer for five minutes.
2. Add water until a uniform granulation occurs.
3. Dry the granules.
4. Size the granules into fine powder.
5. Add mannitol, xylitol and colloidal silicon dioxide and mix for ten minutes.
6. Add magnesium stearate and mix for five minutes.
7. Compress into chewable tablets.

Example 2

Ingredients	% By Weight A	B	C	D
Nizatidine USP	5	-	-	-
Cimetidine USP	-	5	-	-
Ranitidine USP	-	-	5	-
Famotidine USP	-	-	-	2
Magnesium Aluminum Silicate NF	25	25	25	10
Calcium Carbonate	5	5	5	5
Sodium Saccharin NF	.25	.25	.25	.125
Mannitol NF	Q.S.	Q.S.	Q.S.	Q.S.
Xylitol NF	Q.S.	Q.S.	Q.S.	Q.S.
Colloidal Solicon Dioxide NF	1	1	1	1
Magnesium Stearate NF	1.5	1.5	1.5	1.5
Flavors	Q.S.	Q.S.	Q.S.	Q.S.
Purified water*				
	100	100	100	100

* Remove during processing

Method of Manufacturing

1. Mix drug with magnesium aluminum silicate and sodium saccharin in a planetary mixer for five minutes.
2. Add water until a uniform granulation occurs.
3. Dry the granules.
4. Size the granules into fine powder.
5. Add mannitol, xylitol, calcium carbonate, colloidal solicon dioxide to and mix for ten minutes.
6. Add magnesium stearate and mix for five minutes.
7. Compress into chewable tablets.

If the operator wishes an acid agent such as a fruit acid, for example, citric, malic or tartaric acid in the formulation, this is added to the manufacturing process at Step 1 before the granulation process, usually at about 1.5%.

The following comparative examples were selected to illustrate the enhanced release of active ingredient from the granules/tablets of this invention using the preparative and testing procedures described above.

Example 3

The percentage of cimetidine dissolved in water using the U.S.P. method II at 50 RPM to 60 minutes from granules with added citric acid (3%), calcium carbonate (75 mg) and without calcium carbonate.

Time	Without $CaCO_3$	With $CaCO_3$
15	39.9	67.5
30	44.6	74.4
45	46.9	78.8
60	48.3	82.8
75	51.6	104.3

Example 4

Ranitidine Hydrochloride (75 mg base) with Calcium Carbonate (75 mg)

Time	Without $CaCo_3$	With $CaCo_3$
15	30.3%	44.0%
30	36.6%	51.4%
45	36.9%	53.7%
60	37.6%	56.8%
∞	40.4%	63.6%

Example 5

Nizatidine with and without calcium carbonate compared at 0 time and 1 month stability (40°; 75%RH), citric acid (1.5%) added to all samples.

Time	Without $CaCO_3$	Stability	With $CaCO_3$	Stability
15	30.3	30.0	77.6	45.7
30	34.8	34.5	82.3	60.3
45	36.6	37.42	84.2	67.2
60	38.8	39.4	85.3	70.0
75	42.9	44.1	94.4	90.3

Example 6

Nizatidine granules compared in water with tablet with 1.5% citric acid and tablet with 1.5% of citric acid and 37.5 mg of calcium carbonate.

Time	Gran	Tab (1.5% C.A.)	Tab (C.A. plus $CaCO_3$)
0	0	0	0
30	88.8	39.1	97

Example 7

The process of Example 1 is used with 25% by weight of magnesium aluminum silicate, 5% of nizatidine, 0.25% of sodium saccharin and 1.2% of citric acid. The granules, before tabletting, were compared with the tabletted product and with the chewable tablet with 5% of calcium carbonate.

Time	Gran	(Without $CaCO_3$)	(With $CaCO_3$)
0	0	0	0
30	37	45	92.2
60	39.2	47	93
75	47.4	47.4	95.7

Claims

1. An oral pharmaceutical dosage unit composition for inducing H_2-antagonist activity, which composition is designed for at least partial release of its H_2-antagonist ingredient in the mouth, consisting essentially of from 1-35% by weight of said composition of calcium carbonate and of a complex which is prepared from a nontoxic but therapeutically effective quantity of said H_2-antagonist ingredient and an excess of aluminum magnesium silicate.
2. The composition of claim 1 in which said complex is prepared during formulation of said composition and the aluminum magnesium silicate is selected from the range of 10-30% by weight of said composition.
3. The composition of claim 2 in which the composition is a chewable tablet.
4. The composition of claim 1 in which famotidine, ranitidine or cimetidine is the drug.
5. The composition of claim 1 in which nizatidine is the drug.
6. The composition of claim 1 in which xylitol or mannitol is present as a bulking -sweetening agent.
7. The composition of claim 2 in which the calcium carbonate is present in from 75 to 500 mg.
8. The composition of claim 2 in which up to 3% by weight of citric, malic or tartaric acid is present.
9. The composition of claim 8 in which 5% by weight of calcium carbonate is present.
10. The composition of claim 9 in which said active ingredient is nizatidine.
11. The composition of claim 9 in which said active ingredient is ranitidine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/09204

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 A61K9/00 A61K9/14 A61K33/12

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 Y	WO,A,92 17164 (THE PROCTER & GAMBLE COMPANY) 15 October 1992 see claims 1-5 see page 5, line 1 - line 11 see example 1	1-4,6,7 5
Y	US,A,5 229 137 (M. MICHAEL WOLFE) 20 July 1993 see claims 13,15,16,18,20,21 see column 4, line 33 - line 57	5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1994	12. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US 94/09204

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9217164	15-10-92	AU-A-	1761492	02-11-92
		BR-A-	9205827	28-06-94
		CZ-A-	9302260	13-04-94
		EP-A-	0578768	19-01-94
		HU-A-	65881	28-07-94
		JP-T-	6506682	28-07-94
		US-A-	5244670	14-09-93
US-A-5229137	20-07-93	AU-B-	4225093	29-11-93
		WO-A-	9321932	11-11-93