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(21) International Application Number: PCT/US97/22737 (22) International Filing Date: 8 December 1997 (08.12.97) (30) Priority Data: 08/761,695 6 December 1996 (06.12.96) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: MITRA, Sekhar; 8700 Mason–Montgomery Road, Mason, OH 45040 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		(81) Designated States: BR, CA, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>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.</i>
(54) Title: INGESTIBLE PHARMACEUTICAL COMPOSITIONS FOR TREATING UPPER GASTROINTESTINAL TRACT DISTRESS (57) Abstract Ingestible pharmaceutical tablet compositions comprising pharmaceutical actives useful for treating upper gastrointestinal tract distress (e.g., antacid agents) and having a coating of 3–1–menthoxy propane 1,2–diol in amounts effective for providing a cooling sensation to the throat.		

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INGESTIBLE PHARMACEUTICAL COMPOSITIONS
FOR TREATING UPPER GASTROINTESTINAL
TRACT DISTRESS

BACKGROUND OF THE INVENTION

The present invention relates to ingestible pharmaceutical tablet compositions comprising pharmaceutical actives useful for treating upper gastrointestinal tract distress and having a coating of 3-l-menthoxy propane 1,2-diol ("MPD") in amounts effective for providing a cooling sensation in the throat.

Pharmaceutical compositions, such as antacids, useful for treating upper gastrointestinal tract distress (such as heartburn, indigestion, stomachache, etc.) are widely used. They vary depending on the active ingredients, and increasingly differ in the flavors, texture and even forms. The excipients for such compositions are chosen not only as appropriate for the dose form, but also to provide the best possible aesthetics for the compositions, including texture, flavor, after-taste, etc. Depending on the active used, and to some extent the excipients utilized, the time for the therapeutic effect of the active ingredient to be meaningful to the consumer will vary. Frequently, however, the time when the consumer actually begins to receive the benefit of the active ingredient and the time when the consumer perceives the product as starting to "work" are different. Dose form, flavorants, texture, etc. probably all contribute at least in part to this perception. Obviously, for the consumer in need of relief for upper gastrointestinal tract distress, perceiving that the product is working as quickly as possible after ingestion is of great benefit in addition to the true therapeutic relief eventually provided by the active ingredient.

In spite of the large amount of research directed to providing faster acting compositions for treating upper gastrointestinal distress, there continues to be a need for compositions which not only do act faster but also which are perceived by consumers as working faster. Surprisingly, it has been discovered that including the coolant MPD (which is very effective for providing a cooling sensation to the throat) as a coating on the tablet results in the perception by the consumer that the pharmaceutical composition is working. Thus, while this coolant has no apparent therapeutic activity, the signal it provides to the consumer in need of fast relief of upper gastrointestinal distress is of great benefit for the perception that relief is already being provided, possibly resulting in less possibility of drug overuse.

Even more surprising is that this improved signal of relief is recognized when compositions according to the present invention are compared against similar compositions containing menthol (which has a noticeably different cooling profile from MPD).

Thus, it is an object of the present invention to provide ingestible pharmaceutical compositions containing a pharmaceutical active useful for treating upper gastrointestinal tract distress (e.g., upset stomach, heartburn, indigestion) which are perceived as providing faster relief and/or greater perceived efficacy and/or longer duration of activity. Furthermore, an object is to provide methods for treating upper gastrointestinal distress by administering pharmaceutical compositions according to the present invention.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements are made at 25°C, unless otherwise specified.

SUMMARY OF THE INVENTION

The present invention is directed to ingestible pharmaceutical tablet compositions comprising: (a) a safe and effective amount of a pharmaceutical active useful for treating upper gastrointestinal tract distress; and (b) at least one excipient comprising an amount of 3-l-menthoxy propane 1,2-diol effective for providing a cooling sensation to the throat as a coating on such tablets.

The present invention is also directed to methods for treating upper gastrointestinal tract distress. These methods comprise orally administering to a human patient in need of such treatment a safe and effective amount of a pharmaceutical active useful for treating upper gastrointestinal tract distress and an amount of 3-l-menthoxy propane 1,2-diol effective for providing a cooling sensation to the throat.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical tablet compositions comprising: (a) at least one pharmaceutical active useful for treating upper gastrointestinal tract distress (preferably antacid actives); and (b) at least one excipient comprising 3-l-menthoxy propane 1,2-diol (hereinafter "MPD") as a coating on said tablet effective for providing a cooling sensation to the throat.

Pharmaceutical actives useful for treating upper gastrointestinal tract distress are those materials which are safe and effective when administered orally for treating disorders of the upper gastrointestinal tract (typically the stomach and/or esophagus) which result in symptoms of upper gastrointestinal tract distress (e.g.,

heartburn, stomachache, indigestion). Such actives include antacid agents and acid secretion prevention agents (e.g., H_2 receptor-blocking antisecretory agents). Antacid agents include, for example, aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium aluminosilicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, and mixtures thereof. Examples of acid secretion prevention agents include cimetidine, ranitidine, famotidine, omeprazole, lansoprazole, pantoprazole and mixtures thereof. Other useful pharmaceutical actives include bismuth-containing agents such as, for example, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, and mixtures thereof. A particularly preferred bismuth salt is bismuth subsalicylate.

Preferred for use herein are antacid agents. Preferred antacid agents are aluminum hydroxide, magnesium hydroxide, dihydroxy aluminum sodium carbonate, calcium carbonate, and mixtures thereof. Most preferred is calcium carbonate.

The tablet compositions of the present invention comprise a safe and effective amount of at least one pharmaceutical active useful for treating upper gastrointestinal tract distress. Typically the pharmaceutical active(s) comprise from about 1% to about 99%, by weight, of the pharmaceutical tablet compositions of the present invention, preferably from about 25% to about 60%, and most preferably from about 30% to about 50%.

The pharmaceutical tablet compositions of the present invention also comprise an amount of MPD as a coating on said tablets effective for providing a cooling sensation to the throat. This material is described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et al., incorporated herein by reference in its entirety. While not to be limited by theory, it is believed that the surprising benefits obtained by the use of MPD in the compositions of the present invention are the result of the unique cooling profile for this compound, which is very noticeable in the throat. MPD is commercially available, being sold by Takasago Perfumery Co., Ltd., Tokyo, Japan.

In addition, excipients may be included in the uncoated tablet of the present compositions. The term "excipients", as used herein, means one or more compatible solid or liquid filler diluents which are suitable for oral administration

to a human. The term "compatible", as used herein, means that the components of the compositions of the present invention are capable of being commingled with the pharmaceutical active, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compositions under ordinary use situations. Excipients must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human being treated.

Some examples of substances which can serve as excipients are sugars such as lactose, glucose and sucrose; starches such as corn-starch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; and alginic acid; as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, sweetening agents (including nonnutritive sweeteners such as aspartame and saccharin), tableting agents, stabilizers, antioxidants, cooling agents, and preservatives, can also be present. Other compatible pharmaceutical additives and actives which are not pharmaceutical actives useful for treating upper gastrointestinal tract distress (e.g., NSAID drugs; pain killers; muscle relaxants) may be included in the compositions of the present invention. Another agent found useful in the present compositions is an antifatulent such as simethicone. Also, it is to be noted that in addition, other materials having cooling properties may optionally be included within the excipients, such as menthol, menthol-like compounds such as N-ethyl-p-menthane-3-carboxamide ("WS-3", supplied by Sterling Drugs), as well as MPD and mixtures thereof in the uncoated tablet. Additionally, any of the excipients mentioned above may also be included in the coolant layer.

The choice of excipients to be used in conjunction with the pharmaceutical active of the present compositions is basically determined by the tablet dose form for the compositions. Excipients suitable for the preparation of tablet dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art. The only requirement is that the pharmaceutical active is available in safe and effective amounts.

The excipients employed in the present ingestible compositions are used at concentrations sufficient to provide a practical size to dosage relationship. Typically, excipients comprise from about 1% to about 99% by weight of the pharmaceutical tablet compositions of the present invention, preferably from about 40% to about 75%, and most preferably from about 50% to about 70%. Additionally, the MPD coating typically comprises from about 0.01% to about 0.50% by weight of the pharmaceutical tablet compositions of the present invention, preferably from about 0.02% to about 0.20%, and most preferably from about 0.04% to about 0.10%. Normally the amount of total coating material is from about 0.1 mg to about 40 mg per dose.

The present invention also relates to methods for treating upper gastrointestinal tract distress in humans. These methods comprise orally administering to a human in need of such treatment a safe and effective amount of a pharmaceutical active useful for treating upper gastrointestinal tract distress and an amount of MPD effective for providing a cooling sensation to the throat. Most preferred is administering a safe and effective amount of an ingestible pharmaceutical composition of the present invention.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as a limitation of the present invention as many variations thereof are possible without departing from the spirit and scope.

Example I

An ingestible pharmaceutical composition according to the present invention in the form of a chewable antacid tablet is prepared as follows:

<u>Ingredients</u>	<u>Weight %</u>
Granulated calcium carbonate ¹⁾	42.87%
Magnesium stearate	2.50%
Colored speckles	0.75%
Flavorants ²⁾⁵⁾	0.78%
MPD ³⁾⁵⁾	0.07%
WS-3 ⁵⁾	0.05%
Aspartame	0.198%
Sodium Saccharin ⁵⁾	0.102%
Mannitol ⁵⁾	Q.S.

- 1) Granulated calcium carbonate containing 93.3% calcium carbonate, 6.3% glucose and 0.4% gelatin; supplied by Whittaker Clark & Daniels, Philadelphia, Pa.
- 2) 3-l-menthoxy propane 1,2-diol, supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan.
- 3) N-ethyl-p-menthane-3-carboxamide, supplied by Sterling Drugs.
- 4) Granulate mannitol supplied by ICI Americas, Inc., Wilmington, Delaware.
- 5) Present as a coating on said tablets

The above ingredients are dry blended in a mixer until homogeneous, and then direct compressed in a tableting machine to approximately 8.5 Strong Cobb units hardness to produce chewable antacid tablets each weighing 1.25g (500mg calcium carbonate per tablet).

After the tableting process is completed, the tablets are coated with the two coolants and mannitol by applying them as a liquid solution.

Ingestion of one or two of these tablets by a human subject suffering from heartburn, acid indigestion and upset stomach associated with these symptoms provides effective relief for this upper gastrointestinal tract distress.

What is claimed is:

1. Ingestible pharmaceutical tablet compositions comprising:
a safe and effective amount of at least one pharmaceutical active useful for treating upper gastrointestinal tract distress in tablet form and as a coating on said tablet at least one excipient comprising an amount of 3-l-menthoxy propane 1,2-diol effective for providing a cooling sensation to the throat.
2. Ingestible pharmaceutical tablet compositions according to Claim 1 wherein the pharmaceutical active is selected from the group consisting of antacid agents, acid secretion prevention agents, bismuth-containing agents, and mixtures thereof.
3. Ingestible pharmaceutical tablet compositions comprising:
 - (a) from about 1% to about 99% of a material selected from the group consisting of at least one pharmaceutical active useful for treating upper gastrointestinal tract distress and mixtures of said active and excipients; and
 - (b) from about 1% to about 99% of at least one excipients as a coating on said tablet comprising an amount of 3-l-menthoxy propane 1,2-diol effective for providing a cooling sensation to the throat.
4. Ingestible pharmaceutical tablet compositions according to Claim 3 wherein the pharmaceutical active is selected from the group consisting of aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, cimetidine, ranitidine, famotidine, omeprazole, lansoprazole, pantoprazole, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, and mixtures thereof.

5. Ingestible pharmaceutical tablet compositions according to either of Claims 3 or 4 wherein the excipient further comprises one or more excipients selected from the group consisting of wetting agents, lubricants, tableting agents, flavoring agents, sweetening agents, coloring agents, stabilizers, antioxidants, cooling agents, preservatives, and mixtures thereof.
6. Ingestible pharmaceutical tablet compositions according to any of Claims 3-5 wherein the excipients comprise at least one cooling agent selected from menthol, menthol-like compounds, and mixtures thereof.
7. Compositions according to any of Claims 3-6 wherein the cooling agent comprises N-ethyl-p-menthane-3-carboxamide.
8. Ingestible pharmaceutical tablet compositions comprising:
 - (a) from about 25% to about 60% of at least one pharmaceutical agent useful for treating upper gastrointestinal tract distress selected from the group consisting of aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium aluminosilicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, cimetidine, ranitidine, famotidine, omeprazole, lansoprazole, pantoprazole, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgallate, and mixtures thereof;
 - (b) from about 40% to about 75% of excipients comprising an amount of 3-l-menthoxy propane 1,2-diol as a coating on said tablet effective for providing a cooling sensation to the throat, and at least one other excipient selected from the group consisting of wetting agents, lubricants, coloring agents, flavoring agent, sweetening agents, tableting agents, stabilizers, antioxidants, cooling agents, preservatives, and mixtures thereof.

9. Ingestible pharmaceutical tablet compositions according to Claim 8 wherein the pharmaceutical active is selected from the group consisting of aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxycarbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium aluminosilicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, and mixtures thereof, and wherein further the 3-l-menthoxy propane 1,2-diol as a coating on said tablet comprises from about 0.01% to about 0.50% by weight of the total composition.
10. Ingestible pharmaceutical tablet compositions according to either of Claims 8 or 9 wherein the pharmaceutical active comprises calcium carbonate.
11. Ingestible pharmaceutical tablet compositions according to any of Claims 8-10 wherein the 3-l-menthoxy propane 1,2-diol as a coating on said tablet comprises from about 0.02% to about 0.20% by weight of the composition.
12. Ingestible pharmaceutical tablet compositions according to any of Claims 8-11 wherein the excipients further comprise at least one cooling agent selected from menthol, N-ethyl-p-menthane-3carboxamide, and mixtures thereof.
13. Ingestible pharmaceutical tablet compositions according to any of Claims 8-12 in unit dose form.
14. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 1.
15. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 4.

16. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 7.
17. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 8.
18. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 9.
19. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 10.
20. A method for treating upper gastrointestinal tract distress in humans, said method comprises orally administering to a human patient in need of such treatment a safe and effective amount of a composition according to Claim 11.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 97/22737

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/10 A61K9/28

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	WO 94 25009 A (PROCTER & GAMBLE) 10 November 1994	1-7, 14-16
Y	see abstract see page 1, line 5-9 see page 3, line 24 - page 5, line 2 see page 5, line 13-19 see page 7, line 33-37 see page 8, line 27 - page 9, line 9 see page 9, line 17-20 see claims 1,4,7 --- -/--	8-13, 17-20

☒ 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

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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

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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

6 April 1998

Date of mailing of the international search report

24. 04.98

Name and mailing address of the ISA

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La Gaetana, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22737

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 244 670 A (UPSON JAMES G ET AL) 14 September 1993 see abstract see column 1, line 10-15 see column 2, line 27 - column 3, line 6 see column 3, line 34 - column 4, line 19 see example 1 see claims -----	8-13, 17-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/22737

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 14-20 are directed to a method of treatment of the human body , the search has been carried out and based on the alleged effects of the compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter: nal Application No

PCT/US 97/22737

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425009 A	10-11-94	CA 2161217 A CN 1122103 A EP 0695175 A JP 8509725 T NO 954146 A	10-11-94 08-05-96 07-02-96 15-10-96 18-10-95
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