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WO 2004/000283 A1

(54) Title: POPPING ORAL ADMINISTRATION FORM

(57) Abstract: Disclosed are popping pharmaceutical oral administration forms, which comprise an active ingredient, and pressurized gas trapped within cavities in a pharmaceutically acceptable material in a manner that allows the gas to escape from the administration form upon dissolution or shattering of said form. Such an oral administration form may be popular with children that will prefer it on other ones, which do not pop. Methods for preparation of such oral administration forms are also disclosed.

POPPING ORAL ADMINISTRATION FORM

FIELD OF THE INVENTION

This invention relates to oral administration forms and to processes for their preparation.

BACKGROUND OF THE INVENTION

Gasified particles are known in the art as particles that comprise a core material, which encapsulates a pressurized gas that escapes as the core material dissolves or shatters.

Processes for making gasified particles are known in the art of candy making. For example, processes for making gasified confections are described in the following publications: U.S. Patent Nos. 3,985,909, 3,985,910 and 4,001,457.

U.S. Patent No. 4,289,794 describes a method for preparing gasified candy whereby a sugar melt is gasified at superatmospheric pressure and then is cooled below its fusion temperature under superatmospheric pressure to form a gasified candy. As the gasified candy is wetted in the mouth the candy melts and the gas escapes producing an entertaining popping sensation.

WO 99/64555 describes laundry detergent products that include gasified particles, and may also include other materials such as bleaching agents and conventional detergent composition adjuvants. The gasified particles that are used in the laundry detergent are said to increase the rate of product dissolution in the wash water and add desirable product aesthetics in the form of colored speckles. In addition, the gasified particles can provide both audible and olfactory signals to the consumer that the product is working.

Another use of gasified particles is described in U.S. Patent No. 6,310,014 wherein a composition comprising a gasified solid and an anhydrous liquid base is

described. Such composition is said to be useful for personal and household care and to deliver an audible cracking or popping sound during use.

Gasified particles are also known for use in cosmetic treatments, particularly hair treatments as described in EP 1059076. The cosmetic compositions contain gasified particles and the gas is released on contact with water or moisture.

Effervescent pharmaceutical compositions for oral administration are also known in the art. An effervescent pharmaceutical composition includes compounds which evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent pharmaceutical composition to water or other fluids.

Pharmaceutical compositions comprising an effervescent agent are described for example, in US Patent Nos. 6,350,470 and 5,178,878 and in EP 1082106.

SUMMARY OF THE INVENTION

The present invention provides, according to the first aspect thereof, an oral administration form comprising an active ingredient and a pressurized gas, said pressurized gas being trapped in cavities within a pharmaceutically acceptable material, in a manner that allows its escape upon dissolution or shattering of the administration form. The active ingredient may be included in the material trapping the pressurized gas in the cavities thereof. An administration form according to the invention may comprise more than one active ingredient, and it preferably comprises a pharmaceutically acceptable carrier.

The term "pressurized gas" refers to a gas at a pressure more than 1 atmosphere.

The oral administration form of the present invention may further comprise coloring, flavoring and other pharmaceutical or neutraceutical excipients.

It should be noted that the term *"administration form"* should be construed in a broad sense and includes any form administered for the purpose of achieving a therapeutic effect in humans or animals. It may be sold as a pharmaceutical administration form carrying a label as to the intended indication, whether as a

prescription drug or over the counter, or it may be sold without any specific indication, for example as a neutraceutical (neutraceuticals are often referred to as *"food additives" or "food supplements"*).

"An oral administration form" is an administration form, the swallowing of which is permissible. Such an administration form is usually intended to be given through the mouth, for swallowing, for treating the mouth cavity, etc.

The term *"active ingredient"* should be construed in a broad sense as including any ingredient considered to have a therapeutic effect when delivered to a subject in need thereof. The active ingredient may be an analgesic, an antipyretic agent, an anti-inflammatory agent, a vitamin, an expectorant, an antibiotic, an anti-hypertensive, an anti-histamine, etc. Thus, it may be a drug such as paracetamol, diphenhydramine, dextromethorphan, lidocaine, loratadine, ibuprofen, pseudoephedrine, enalapril, calcium carbonate, etc, a vitamin or mineral such as vitamin C, vitamin E, biotin, selenium, zinc, etc, a food additive such as echinacea, propolis, soy extract, etc. or a veterinary active ingredient such as nitroscanate, abamectin, ivermectin, etc. The active ingredient may be taste masked, for instance by coating or microencapsulation.

Non limiting examples of suitable materials for trapping therein the gas are sugars such as glucose, fructose, sucrose, lactose, maltose, corn syrup and mixtures thereof.

The gas trapped in the cavities may be any pharmaceutically acceptable inert gas. The term *"inert"* indicates that the gas does not react with the pharmaceutically acceptable material, in the cavities of which the pressurized gas is trapped and the other ingredients included in the administration form during preparation, storage or use. Non limiting examples of gases suitable for the preparation of the oral administration form are carbon dioxide, nitrogen, air, helium, argon, and neon.

An oral administration form according to the present invention may have benefits in many circumstances, for instance, it may be popular with children that will like the popping sensation and will be more willing to take a popping

administration form than one that does not create a popping sensation. The escape of the gas does not only produce a pleasant sensation but may also stimulate saliva production, thereby providing additional saliva to aid dissolution in the mouth. Similarly, it may be used to enhance dissolution of tablets or powders in a drinking liquid. Such tablets may be useful for the elderly or swallow-problem population. It may be used in semi-solids, oils, suspensions or solid preparations to enhance disintegration or dissolution of the active ingredients either in the mouth or in the stomach or intestine.

Particles which contain trapped pressurized gas may be coated by any suitable material that would protect them from direct contact with water or moisture during storage. However, such a coating material should dissolve when the escape of the gas is required. Suitable coating materials may be for instance, cocoa butter that melts in the mouth, biodegradable polymers typically used for gastrointestinal delivery of drugs (such as enteric polymer that dissolves in the intestine), etc.

The oral administration form according to the present invention may have different forms, such as a tablet, powder, pellets, capsule, syrup, oil, suspension, gel, drops and various candy-like forms.

In one non-limiting example, candy-like administration form may be a chocolate bar including gasified particles and an active ingredient.

The present invention further provides a method for preparing a gasified oral administration form according to the present invention, the method comprising:

i) preparing a mixture comprising (a) an active ingredient, and (b) a pharmaceutically acceptable material trapping pressurized gas within cavities thereof; and

ii) processing the mixture to obtain an administration form, said processing being under conditions that permits said gas to escape upon dissolution or shattering of the administration form.

The mixture mentioned in (i) above may comprise more than one active ingredient.

According to one embodiment, the mixture prepared in (i) also comprises a pharmaceutically acceptable ingredient (c) that melts in the mouth, such as cocoa butter. According to this embodiment, the mixture obtained in (i) includes the ingredients (a) and (b) of the mixture, homogeneously dispersed in ingredient (c), and the processing mentioned in (ii) includes casting of the mixture into molds and cooling obtain the gasified oral administration form.

According to another embodiment, the mixture prepared in (i) is of powders, and the processing mentioned in (ii) includes compressing the mixture to produce a tablet.

The present invention further provides a method for preparing a gasified oral administration form comprising:

i) melting a pharmaceutically acceptable material to obtain a melt;

ii) adding a gas and at least one active ingredient and optionally a pharmaceutically acceptable excipient into the melt under superatmospheric pressure to obtain a liquid pharmaceutical composition;

iii) casting the liquid pharmaceutical composition into a mold under superatmospheric pressure;

iv) solidifying the cast pharmaceutical composition under conditions suitable to obtain a gasified oral administration form; and releasing the pressure.

The solidification mentioned above in (iv) may be done in a mold having the form of a desired administration form, for instance, a tablet.

Alternatively, the gasified pharmaceutical composition obtained by the above method in (iii) may be processed to an oral administration form according to the present invention by the following steps:

(iv) solidifying said gasified pharmaceutical composition to obtain a solid gasified pharmaceutical composition;

(v) grinding the solid gasified pharmaceutical composition to obtain a popping powder;

(vi) optionally adding excipients to said powder and mixing them together; and

(vii) processing the obtained powder or mixture to obtain an oral administration form which produces popping sensation when it is wetted.

The active ingredient used in any of the above methods may be coated or microencapsulated with a taste-masking material, enteric polymers, humidity protective materials, oxidation protective materials etc.

According to an additional aspect of the invention there is provided a method for orally administering an active ingredient to a patient. The method comprising orally administering to the subject an oral administration form according to the present invention. This method may be used for oral administration of drugs to subjects reluctant to take pharmaceutical compositions that do not create a popping sensation upon wetting.

Further provided by the invention is a method for treating a patient by orally administering to him an administration form according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

In order to understand the invention and to see how it may be carried out in practice, several specific embodiments will now be described, by way of non-limiting examples only.

Example 1 - Preparation of Paracetamol tablets 500mg

The following ingredients were used in the preparation of the above-mentioned tablets:

Ingredient mg/tab

Coated Paracetamol 540.0 mg

Popping Candy 300.0 mg

Cross Povidone 30.0 mg

Magnesium Stearate 15.0 mg

Aspartame 10.0 mg

Flavor 10.0 mg

Process for the preparation: all the above-mentioned ingredients were mixed together to obtain a uniform mixture that was compressed conventionally to obtain a tablet.

Example 2 – Preparation of Calcium carbonate lozenges 300mg

The following ingredients were used in the preparation of the above-mentioned lozenges:

Ingredient mg/loz.

Calcium Carbonate 300.0 mg

Sucrose 100.0 mg

Lactose 100.0 mg

Corn Syrup 50.0 mg

FD&C Red # 40 0.02 mg

Carbon Dioxide q.s.

Grape Flavor 20.0 mg

Process for the preparation: sucrose, lactose, coloring agent and corn syrup were melted. Calcium carbonate and flavor were added and mixed together with the molten mixture. Carbon dioxide was bubbled into the molten mixture under superatmospheric pressure. Then, still under superatmospheric pressure, the melt mass was cast to lozenges-shaped molds and cooled.

Example 3 – Preparation of Pseudoephedrine hydrochloride powder for reconstitution

The following ingredients were used in the preparation of the above-mentioned powder:

Ingredient mg/g

Coated beads of pseudoephedrine hydrochloride 200.0 mg

Fructose 275.0 mg

Lactose 275.0 mg

Liquid Glucose 225.0 mg

Nitrogen q.s.

Cherry flavor 20.0 mg

FD&C Blue # 1 0.002 mg

FD&C Red # 40 0.001 mg

Saccharin sodium 5.0 mg

Process for the preparation: fructose, lactose and liquid glucose were melted. Flavor, sweetener and coloring agents were added and mixed together with the molten mixture. Nitrogen was bubbled into the obtained molten mixture under superatmospheric pressure. Then, the molten mixture was cooled under superatmospheric pressure and then the pressure was released. The obtained solid mixture was ground to obtain a popping powder.

Psuedoephedrine beads were mixed together with the obtained popping powder to yield pseudoephedrine hydrochloride powder.

Example 4- Preparation of Ivermectin 3mg capsules

The following ingredients were used in the preparation of the above-mentioned capsules:

Ingredient mg/caps.

Ivermectin 3.0 mg

Popping candy 100.0 mg

Magnesium stearate 1.5 mg

Microcrystalline cellulose 150.0 mg

Process for the preparation: all the above-mentioned ingredients were mixed together to yield a uniform mixture. The obtained mixture was filled inside hard gelatin capsules.

Example 5 – Preparation of Propolis melt bar

The following ingredients were used in the preparation of the above-mentioned bar:

Ingredient mg/Bar

Propolis Extract 200.0 mg

Popping Candy 1000.0mg

Cocoa Butter 800.0 mg

Chocolate Flavor 20.0 mg

Process for the preparation: Cocoa butter was melted and while cooling, propolis extract, chocolate flavor and the popping powder were added. The semi-solid mass was cast inside chocolate bar molds to yield the desired bars.

Example 6 – Preparation of Lidocaine Gel

The following ingredients were used in the preparation of the above-mentioned gel:

Ingredient % w/w

Lidocaine base 0.2%

Popping Candy (coated with cocoa butter) 20.0%

Propylene Glycol 30.0%

Carbomer 1.0%

Sodium Hydroxide q.s.

Water to 100.0%

Process for the preparation: Carbomer and water are heated and mixed. Sodium Hydroxide is added to form a liquid gel. While cooling, the rest of the materials are added.

Example 7: Preparation of Ibuprofen 250mg Tablet

Ingredient mg/tab

Coated Ibuprofen 270mg

Hard Fat 500mg

Strawberry Flavor 3mg

Aspartame 5mg

Popping Candy 200mg

Process for the preparation

Ibuprofen, Strawberry flavor and Aspartame are mixed in Hard Fat heated to 45°C. The mixture is cooled to 38°C and Popping Candy is added. Mixture is filled inside pre-cooled blisters.

Example 8: Preparation of Amoxycillin 250mg Tablet

Ingredient mg/tab

Amoxycillin 250mg

Hard Fat 600mg

Vanilla Flavor 3mg

Aspartame 5mg

Popping Candy 250mg

Process for the preparation:

Amoxycillin, Vanilla flavor and Aspartame are mixed in Hard Fat heated to 45°C. The mixture is cooled to 38°C and Popping Candy is added. Mixture is filled inside pre-cooled blisters.

CLAIMS:

1. An oral administration form comprising an active ingredient and a pressurized gas, said pressurized gas being trapped in cavities within a pharmaceutically acceptable material, in a manner that allows its escape upon dissolution or shattering of the administration form.
2. An oral administration form according to Claim 1, wherein said pharmaceutically acceptable material comprises said active ingredient.
3. An oral administration form according to Claim 1, comprising more than one active ingredient.
4. An oral administration form according to any one of the preceding claims, including a pharmaceutically acceptable carrier.
5. An oral administration form according to any one of the preceding claims, wherein said active ingredient includes a prescription drug.
6. An oral administration form according to any one of claims 1 to 4, wherein said active ingredient includes a drug sold over the counter.
7. An oral administration form according to any one of claims 1 to 4, wherein said active ingredient is a neutraceutical.
8. An oral administration form according to any one of the preceding claims, suitable for veterinary use.
9. An oral administration form according to any one of the preceding claims, wherein said active ingredient includes a vitamin, an expectorant, an analgesic, an antipyretic, an anti-inflammatory, an antibiotic, an anti-hypertensive, or an anti-histamine agent.
10. An oral administration form according to Claim 9, wherein said active ingredient includes a vitamin, an expectorant, an analgesic, an antipyretic, an anti-inflammatory, an antibiotic, or an anti-hypertensive agent.

11. An oral administration form according to Claim 1, wherein said active ingredient is selected from paracetamol, diphenhydramine, dextromethorphan,

loratadine, lidocaine, ibuprofen, pseudoephedrine, enalapril and calcium carbonate.

12. An oral administration form according to Claim 1, wherein said active ingredient includes a vitamin or a mineral.

13. An oral administration form according to Claim 12, wherein said vitamin or mineral is selected from vitamin C, vitamin E, biotin, selenium and zinc.

14. An oral administration form according to Claim 7, wherein said neutraceutical is selected from echinacea, propolis and soy extract.

15. An oral administration form according to Claim 8, wherein said active ingredient is selected from nitroscanate, abamectin and ivermectin.

16. An oral administration form according to any one of the preceding claims, wherein said active ingredient is coated by a coating.

17. An oral administration form according to Claim 16, wherein said coating comprises taste-masking materials, biodegradable polymers, enteric polymers, humidity protective materials and/or oxidation protective materials.

18. An oral administration form according to Claim 17, wherein said coating is a taste masking coating.

19. An oral administration form according to any one of the preceding claims, having a form of a tablet, powder, pellets, capsule, syrup, oil, suspension, gel, drops, or candy-like form.

20. An oral administration form according to any one of the preceding claims, wherein said pharmaceutically acceptable material is selected from sugars, corn syrup or mixtures thereof.

21. An oral administration form according to any one of the preceding claims, wherein said gas is selected from carbon dioxide, nitrogen, air, helium, argon, and neon.

22. A method for preparing an oral administration form according to Claim 1 comprising:

(i) preparing a mixture comprising (a) an active ingredient, and (b) a pharmaceutically acceptable material trapping pressurized gas within cavities thereof; and

(ii) processing said mixture to obtain an administration form that permits said gas to escape upon dissolution or shattering of the administration form.

23. A method according to claim 22, wherein the mixture prepared in (i) also comprises a pharmaceutically acceptable ingredient that melts in the mouth, the ingredients (a) and (b) of the mixture being homogeneously dispersed therein, and the processing mentioned in (ii) includes casting of the mixture into molds and cooling, to obtain the gasified oral administration form.

24. A method according to claim 22, wherein the mixture prepared in (i) is of powders, and the processing mentioned in (ii) includes compressing the mixture to produce a tablet.

25. A method according to any one of Claims 22 to 24 , wherein the mixture in (i) comprising more than one active ingredient.

26. A method according to Claim 22, wherein the mixture obtained in (i) further comprises other excipients.

27. A method for preparing a gasified oral administration form comprising:

(i) melting a pharmaceutically acceptable carrier material to obtain a melt;

(ii) adding a gas and at least one active ingredient into the melt under superatmospheric pressure to obtain a liquid pharmaceutical composition;

(iii) casting the liquid pharmaceutical composition into a mold under superatmospheric pressure; and

(iv) solidifying the cast pharmaceutical composition under conditions suitable to obtain a gasified oral administration form.

28. A method according to Claim 27, wherein in (ii) a pharmaceutically acceptable excipient is also added into the melt.

29. A method for preparing a gasified oral administration form comprising:

(i) melting a pharmaceutically acceptable carrier material to obtain a melt;

(ii) adding a gas and at least one active ingredient into the melt under superatmospheric pressure to obtain a liquid pharmaceutical composition;

(iii) casting the liquid pharmaceutical composition into a mold under superatmospheric pressure;

(iv) solidifying the liquid pharmaceutical composition to obtain a gasified solid pharmaceutical composition;

(v) grinding the gasified solid pharmaceutical composition to obtain a popping powder; and

(vi) processing the obtained powder to obtain an oral administration form which produces popping sensation upon wetting.

30. A method according to Claim 29, wherein in (ii) a pharmaceutically acceptable excipient is also added into the melt.

31. A method according to Claim 29, wherein an excipient is added to the popping powder obtained in (v) to be processed in (vi).

32. A method for treating a subject comprising administering to said subject a pharmaceutical administration form according to Claim 1.

33. A method according to Claim 32, wherein said pharmaceutical administration form is of a prescription drug.

34. A method for administration of an active ingredient to a subject in need thereof, said method comprising orally administering to said subject an oral administration form according to Claim 1.

35. A method according to Claim 34, wherein said subject is reluctant to swallowing pharmaceutical administration forms that do not produce popping sensation upon wetting.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00519

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K47/26 A61K47/08 A61K47/16

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 7 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)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 271 206 A (FARIEL HARRY F ET AL) 2 June 1981 (1981-06-02) column 3, line 29 - line 46 claims 1-11	1-35
X	US 4 289 794 A (KLEINER FREDRIC ET AL) 15 September 1981 (1981-09-15) cited in the application column 2, line 53 - line 66 column 4, line 25 - line 32 claims 1-8	1-35
X	EP 0 371 228 A (MEIJI SEIKA KAISHA) 6 June 1990 (1990-06-06) page 3, line 21 - line 25 claims 1-4	1-35

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[X] Further documents are listed in the continuation of box C.

[X] 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
23 October 2003	30/10/2003

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	Hedegaard, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00519

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 263 328 A (PARADA MAYA ET AL) 21 April 1981 (1981-04-21) claim 1	1-35
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P,X	WO 02 062152 A (SCHOONMAN ANNEMARIE ;CHMIEL OLIVER (CH); NESTLE SA (CH); DARBYSHIR) 15 August 2002 (2002-08-15) claims 1-47	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 03/00519

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. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy. Although claims 32-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00519

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