Title: DIPHENHYDRAMINE TANNATE COMPOSITIONS AND METHODS OF USE

Abstract: A therapeutic composition comprises diphenhydramine tannate in the substantial absence of other active ingredients. The composition has utility in providing symptomatic relief of sneezing, itchy, watery eyes, itchy nose or throat and runny nose due to hay fever (allergic rhinitis) or other respiratory allergies.
DIPHENHYDRAMINE TANNATE
COMPOSITIONS AND METHODS OF USE


Field of Invention

The invention relates to novel antihistaminic tannate compositions with diphenhydramine tannate as the lone active ingredient.

Background of the Invention

Tannins are water-soluble phenolic metabolites of plants with a molecular weight of 5 - 5000 Da. Physicochemically, tannins are complex polymers, which can be classified as two major types: the condensed tannins and hydrolyzable tannins. Hydrolyzable tannins or tannic acids are referenced in the various pharmacopeias and are composed of gallic acid or
its condensation product ellagic acid esterified to the hydroxyl groups of glucose. Each hydrolyzable tannin molecule is usually composed of a core D-glucose and 6 to 9 galloyl groups.

In nature, there is an abundance of mono and di-galloyl esters of glucose with a molecular weight of about 900. These are not considered to be tannins. At least 3 hydroxyl groups of the glucose must be esterified to exhibit a sufficiently strong binding capacity to be classified as tannin.

Tannic acid, also known as tannin, is commercially available with a water content of about 5% to about 10% by weight and a molecular weight of about 1700. It is typically produced from Turkish or Chinese nutgall and has a complex, non-uniform chemistry.

Diphenhydramine is known chemically as 2-(benzhydroxy)-N,N-dimethylethylamine. The methods of preparation of the drug are described in U.S. Patent Nos. 2,421,714 and 2,397,799. Diphenhydramine Hydrochloride salt has a melting point of 166-170 degrees C and is soluble in water, somewhat less soluble in alcohol. The pH of a 1% aqueous solution is about 5.5. Diphenhydramine belongs to the class of ethanolamine H1 receptor blockers, and possesses in addition to antihistaminic activity, a significant anticholinergic effect, which makes it highly effective in treating for the symptomatic relief of sneezing, itchy, watery eyes, itchy nose or throat and runny nose due to hay fever (allergic rhinitis) and other respiratory allergies. It has lower incidences of gastrointestinal side effects than compositions containing other antihistamine compounds by themselves or in combination with diphenhydramine. Diphenhydramine also possesses a pronounced tendency to induce sedation.
The present invention relates to a therapeutic composition comprising a pharmaceutically effective amount of diphenhydramine tannate in the substantial absence of other active ingredients.

**Summary of the Invention**

The present invention relates to a therapeutic composition comprising as an active ingredient a pharmaceutically effective amount of diphenhydramine tannate in the substantial absence of other active ingredients. Such a composition may be useful for the symptomatic relief of sneezing, itchy, water eyes, itchy nose or throat and runny nose commonly associated with hay fever (allergic rhinitis) or other respiratory allergies.

The therapeutic composition may further include an excipient. That excipient may be selected from a group consisting of microcrystalline cellulose, lactose, sugar, magnesium aluminum silicate, xanthan gum, polyvinylpyrrolidone, cellulose, starch, starch hydroxypropyl methylcellulose, sucrose, saccharin sodium, calcium phosphate, talc, magnesium stearate, artificial flavor, kaolin, pectin, glycerine, sodium citrate, sodium phosphate monobasic and dibasic, citric acid, methylparaben, sodium benzoate, benzoic acid, coloring agents, purified water and mixtures thereof.

The composition may be provided in any appropriate form for administration to a warm-blooded animal including but not limited to liquid dosage form, semi-solid dosage form, solid dosage form, tablet form and capsule form.

The composition may also be defined as consisting essentially of a pharmaceutically effective amount of diphenhydramine tannate.
In accordance with still another aspect of the present invention, a method is provided for symptomatically treating respiratory allergies in a warm-blooded animal. That method comprises administering to the warm-blooded animal a pharmaceutically effective amount of diphenhydramine tannate in substantial absence of other active ingredients. Advantageously, such a composition exhibits a number of unique advantages characterized by efficient and effective relief of the symptoms of respiratory allergies in the substantial absence of adverse side effects.

**Detailed Description of the Invention**

Antihistamine compounds in the form of their free bases as well as their salts, e.g. hydrochloride, maleate, tannate, etc. are well known. Frequently it is desirable to utilize the antihistamine in the form of its tannate salt, because such salt is generally quite stable and may be administered in such form without any side effects. In addition, the tannate salt of the active is a significantly larger molecule, which affords absorption of the active over prolonged intervals of time, reducing the sedative action, frequency of administration and thereby improves patient compliance in comparison to other salt forms of antihistamines.

Antihistamines in the form of their tannate salts can be prepared by following a number of different procedures. In a first approach, the free base, e.g. diphenhydramine, etc. is reacted with tannic acid in the presence of a volatile solvent, isopropanol. Typically, in the conventional isopropanol route, the antihistaminic free base and the tannic acid will be present in the isopropanol at a concentration based on the weight of the reaction mixture. The reaction mixture is stirred for about one hour while maintaining the mixture at 60-70 degrees C. The reaction mixture is cooled
to room temperature and then filtered, washed with isopropanol and then vacuum dried.

A second approach to prepare the antihistamine tannates, is to contact the free base form of the drug with tannic acid in the presence of water for a suitable period of time and at a maximum temperature. The antihistamine tannate salt needs to be isolated and purified by freeze-drying and then subsequently introduced into pharmaceutically effective dosage forms.

A third and better approach to prepare the antihistamines in the form of their tannate salts is disclosed in our copending U.S. Patent Application serial no. 10/119,285 filed April 9, 2002, entitled "Process For Preparing Tannate Liquid And Semi-Solid Dosage Forms", the full disclosure of which is incorporated herein by reference. In this approach, an aqueous solution or the powder form of the drug is reacted with a tannic acid mixture in liquid or powder form. The tannate salt prepared by this method can be isolated and purified by filtration, drying or centrifugation or can be directly incorporated into suitable pharmaceutically effective dosage forms without being subjected to high temperatures that can produce undesirable decomposition products.

The tannate salt of the antihistamine can also be prepared without the use of organic solvents, which would be desirable from an environmental standpoint. This also allows one to eliminate organic solvents as a possible contaminant in the final dosage product. In addition, a commercially available USP/NF grade salt or the free base of the antihistamines can be used with USP/NF grade tannic acid to prepare the tannate salt. This insures that the stoichiometry of the active ingredient may be properly matched to the tannic acid. As a result, the potency of the
finished product is less variable and, therefore, more precise dosing is possible.

The diphenhydramine ingredient used is the free base or salt having anionic functional groups such as bitartrate, maleate, citrate, chloride, bromide, acetate and sulfate. The source of the tannic acid is natural or synthetic.

The preferred dispersing agent is chosen from the group such as magnesium aluminum silicate, xanthan gum and cellulose compounds. The thickening agents employed include kaolin, pectin, xanthan gum and cellulose compounds.

The excipients commonly used in the formulations are as follows: microcrystalline cellulose, lactose, sugar, magnesium aluminum silicate (MAS), xanthan gum, polyvinylpyrrolidone, cellulose, starch, starch hydroxypropyl methylcellulose, sucrose, saccharin sodium, calcium phosphate, talc, magnesium stearate, artificial flavors, kaolin, pectin, glycerin, sodium citrate, sodium phosphate monobasic and dibasic, citric acid, sodium benzoate and benzoic acid, methylparaben, coloring agents (e.g. FD&C Red No. 40 and FD&C Blue No. 1), purified water and mixtures thereof.

The composition of the present invention contains diphenhydramine tannate in the substantial absence of other active ingredients such as other tannate salts. Such compositions are particularly effective for treating symptoms commonly associated with respiratory allergies while avoiding adverse side effects including but not limited to gastrointestinal upsets. Such compositions are particularly useful in treating children as they avoid exposure of the patient to other drugs that are unnecessary to provide effective treatment and might otherwise produce undesired side effects.
The compositions of the present invention may be prepared for oral administration in the form of elixirs, syrups and the preferred forms of suspensions formulated so that ideally each 5 mL (approximately 1 teaspoon) of suspension would contain approximately 12.5 to 50 mg, preferably 25 mg of diphenhydramine tannate, at a pH range of 2.5 - 9.0, preferably from 6.0 - 7.5.

Suspensions of the compositions of the present invention are prepared such that each 5 mL (one teaspoon) contains 25 mg of diphenhydramine tannate. The suspension formulations additionally contain sodium benzoate, coloring, natural and artificial flavors, xanthan gum, magnesium aluminum silicate, methyl paraben, purified water, saccharin, sodium hydroxide, tannic acid and sucrose or sorbitol. Example 1, which is illustrative of a typical suspension formulation of the present invention, is prepared as follows:

**EXAMPLE 1**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Milligrams per 5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine Tannate</td>
<td>25.0</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>27.5</td>
</tr>
<tr>
<td>Magnesium Aluminum Silicate</td>
<td>40.0</td>
</tr>
<tr>
<td>Sodium Benzoate</td>
<td>5.0</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>10.0</td>
</tr>
<tr>
<td>Sucrose</td>
<td>50.0</td>
</tr>
<tr>
<td>Saccharin Sodium</td>
<td>5.0</td>
</tr>
<tr>
<td>Glycerin</td>
<td>375.0</td>
</tr>
</tbody>
</table>
Artificial Strawberry Flavor 15.0
FD&C Red #40 3.0
Purified Water, USP (Deionized) adjust to 5 mL

Tannic acid may also be used for pH adjustment. Monobasic sodium phosphate, USP, and Dibasic sodium phosphate, USP, Anhydrous may also be included in the formula for pH adjustment.

Tablets containing the unique tannate compound of the present invention are prepared by the addition of suitable pharmaceutical carriers including filler, diluents, colorants, lubricants and the like as well as conventional and well known binding and disintegrating agents. A typical tablet composition of the present invention containing starch, dibasic calcium phosphate, coloring agent, microcrystalline cellulose, magnesium aluminum silicate, magnesium stearate, methylcellulose, sucrose, HPMC and talc as described in Example 2 is prepared as follows:

EXAMPLE 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Milligrams per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine Tannate</td>
<td>25.0</td>
</tr>
<tr>
<td>Starch, NF</td>
<td>4.5</td>
</tr>
<tr>
<td>HPMC</td>
<td>6.7</td>
</tr>
<tr>
<td>Magnesium Aluminum Silicate</td>
<td>6.7</td>
</tr>
<tr>
<td>Dibasic Calcium Phosphate</td>
<td>13.7</td>
</tr>
<tr>
<td>Compressible sugar (DIPAC)</td>
<td>244.2</td>
</tr>
</tbody>
</table>
Microcrystalline cellulose
(Avicel PH 102) 157.0
Talc 13.5
FD&C Blue #2 Aluminum Lake 2.7
Magnesium Stearate 13.5

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, kinds of concurrent treatment, if any, frequency of treatment and effect desired. Typically, from about 25 to about 50 mg of the diphenhydramine are administered to adults and children over twelve years of age every four to six hours up to a maximum of about 300 mg in any twenty-four hour period. From about 12.5 to about 25 mg of the diphenhydramine are administered to children from about six to about twelve years of age every four to six hours up to a maximum of about 150 mg in any twenty-four hour period.

It should be understood that the above examples are illustrative of the best mode only of the invention herein disclosed. Given the present disclosure, it is anticipated that numerous variations will occur to those skilled in the art. For example, the composition could be prepared for administration in a nasal spray form if desired. A latitude of modification, substitution and change is intended and in some instances, some features of the invention will be employed without a corresponding use of other features. Accordingly, it is intended that the spirit and scope of the invention disclosed herein should be limited only by the following claims.
What is claimed is:

1. A therapeutic composition comprising as an active ingredient a pharmaceutically effective amount of diphenhydramine tannate in substantial absence of other active ingredients.

2. The therapeutic composition of claim 1, further including an excipient.

3. The therapeutic composition of claim 2, wherein said excipient is selected from a group consisting of microcrystalline cellulose, lactose, sugar, magnesium aluminum silicate, xanthan gum, polyvinylpyrrolidone, cellulose, starch, starch hydroxypropyl methylcellulose, sucrose, saccharin sodium, calcium phosphate, talc, magnesium stearate, artificial flavor, kaolin, pectin, glycerine, sodium citrate, sodium phosphate monobasic and dibasic, citric acid, methylparaben, sodium benzoate, benzoic acid, coloring agents, purified water and mixtures thereof.

4. The therapeutic composition of claim 1, in a liquid dosage form.

5. The therapeutic composition of claim 1, in a semisolid dosage form.

6. The therapeutic composition of claim 1, in a solid dosage form.

7. The therapeutic composition of claim 1, in a tablet form.

8. The therapeutic composition of claim 1, in a capsule form.
9. A therapeutic composition, consisting essentially of a pharmaceutically effective amount of diphenhydramine tannate.

10. The therapeutic composition of claim 9, further including an excipient.

11. The therapeutic composition of claim 10, wherein said excipient is selected from a group consisting of microcrystalline cellulose, lactose, sugar, magnesium aluminum silicate, xanthan gum, polyvinylpyrrolidone, cellulose, starch, starch hydroxypropyl methylcellulose, sucrose, saccharin sodium, calcium phosphate, talc, magnesium stearate, artificial flavor, kaolin, pectin, glycerine, sodium citrate, sodium phosphate monobasic and dibasic, citric acid, methylparaben, sodium benzoate, benzoic acid, coloring agents, purified water and mixtures thereof.

12. The therapeutic composition of claim 9, in a liquid dosage form.

13. The therapeutic composition of claim 9, in a semisolid dosage form.

14. The therapeutic composition of claim 9, in a solid dosage form.

15. The therapeutic composition of claim 9, in a tablet form.

16. The therapeutic composition of claim 9, in a capsule form.

17. A method for symptomatically treating respiratory allergies in a warm-blooded animal, comprising administering to said warm-blooded
animal a pharmaceutically effective amount of diphenhydramine tannate in substantial absence of other active ingredients.

18. A method for symptomatically treating respiratory allergies in a warm-blooded animal, consisting essentially of administering to said warm-blooded animal a pharmaceutically effective amount of diphenhydramine tannate.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

<table>
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<tr>
<th>IPC(7)</th>
<th>461K 9/00, 9/48, 9/20</th>
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<tr>
<td>US CL</td>
<td>424/400, 451, 452, 464, 465</td>
</tr>
</tbody>
</table>

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

B. DOCUMENTS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)


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 practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>Y</td>
<td>US 6,509,492A (VENKATARAMAN) 21 January 2003 (21.01.2003), column 6, line 48 through column 10, line 46.</td>
<td>1-18</td>
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<tr>
<td>Y</td>
<td>5,665,415A (CHOPDEKAR et al) 02 September 1997 (02.09.1997), column 2, line 20 through column 4, line 67.</td>
<td>1-18</td>
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<tr>
<td>Y</td>
<td>US 6,287,597A (GORDZIEL) 11 September 2001 (11.09.2001), column 2, line 10 through column 4, line 37.</td>
<td>1-18</td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search: 13 June 2003 (13.06.2003)

Date of mailing of the international search report: 17 July 2003

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Form PCT/ISA/210 (second sheet) (July 1998)
Continuation of B. FIELDS SEARCHED Item 3:
WEST
diphenhydramine tannate, tannic acid, allergy, respiratory, antihistamine, oral