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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 329 CTOINFORMACION Folios: 38**SEÑOR****SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E. S. D.**

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**REF: EXPEDIENTE 10 082.162****TÍTULO SOLICITADO: FORMULACIONES FARMACEUTICAS DE  
FENILEFRINA Y COMPOSICIONES PARA  
ABSORCION TRANSMUCOSAL.****PUBLICACIÓN: Gaceta 632 de 20/09/2011, número de publicación  
1221.****SOLICITANTE: SCHERING - PLOUGH HEALTHCARE PRODUCTS,  
INC.****APODERADO: CARLOS REYNALDO OLARTE GARCIA.****TRÁMITE: SUSTENTACION DE OPOSICIÓN.**

**JOSÉ LUIS REYES VILLAMIZAR**, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 21 de julio de 2011, en los siguientes términos:

#### **I. RATIFICACIÓN**

- ❖ Teniendo en cuenta lo revelado en la reivindicación 17 de la solicitud colombiana en cuestión, en donde se hace mención de un método para administrar sistémicamente fenilefrina, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para*

*el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”.*

- ❖ Teniendo en cuenta que en las reivindicaciones 48 y 49 la solicitud colombiana en cuestión revela la combinación farmacológica entre fenilefrina y otros principios activos, es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich<sup>1</sup> en su opinión escrita a cerca de “Asociaciones y Patentes” en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica. En otras palabras, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.
- ❖ La patente americana US 2002/022057 publicada el 21 de febrero de 2002 y la patente americana US 2007/141147<sup>2</sup> publicada el 21 de junio de 2007, ya revelaban la elaboración de formulaciones para ser aplicadas a través de la mucosa oral, en donde dicha aplicación consiste en una rápida disolución de la formulación farmacéutica, especialmente de fenilefrina y otros fármacos descongestionantes, antitusivos y antihistamínicos. Específicamente se hace mención de la microencapsulación de fenilefrina para la elaboración de dichas formulaciones, estrategia tecnológica que se utiliza de la misma forma en la solicitud colombiana en trámite.

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<sup>1</sup> Profesora Regular Adjunta del Departamento de Farmacología de la Facultad de Farmacia y Bioquímica de la UBA y Directora Técnica y Gerente de Estudios Clínicos de DIFFUCAP-EURAND SACIFI

<sup>2</sup> En la oposición presentada en su momento el número de la patente indicado inicialmente (US 2007/003627) no es correcto. Procedemos a citar correctamente la patente que se toma como prueba de la carencia de nivel

## **II. COMPLEMENTO DE INFORMACION.**

En complemento a los argumentos dados en su momento en el respectivo escrito de oposición, para cualquier persona medianamente versada en la formulación de productos farmacéuticos es claro que las técnicas para la microencapsulación de fármacos se encuentran lo suficientemente descritas como para atribuírsele nivel inventivo a un producto que involucra un principio activo (o una combinación de los mismos dentro de dichas microcápsulas.

Es así como dicha persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que conseguir una liberación sostenida o controlada es en la actualidad la aplicación más frecuente que tiene la microencapsulación<sup>3</sup>. Gracias al recubrimiento con el material adecuado es posible conseguir no únicamente una cesión gradual y sostenida, sino que además se puede conseguir que se libere en forma de pulsos o a un determinado pH.

Así mismo, dicha persona medianamente versada en la formulación de productos farmacéuticos debe reconocer, que los materiales que pueden emplearse en microencapsular diversos fármacos se han venido diversificando, y que dentro de estos pueden incluirse las grasas, las proteínas y los polímeros<sup>4</sup>. Dentro de estos últimos se pueden clasificar los mencionados por la solicitud colombiana en cuestión, específicamente en sus reivindicaciones 30 a 40.

En cuanto a los diversos métodos de microencapsulación, en el estado de la técnica también se encuentran descrito lo suficientemente como para que cualquier persona medianamente versada en la elaboración de productos farmacéuticos pueda adaptarlo a través de los respectivos ensayos de preformulación y formulación, para incluir cualquier tipo de fármaco que requiera ser formulado de esta manera.

El mismo principio activo se puede presentar en diferentes formas, por ejemplo, como comprimido, cápsula o solución acuosa, para su administración parenteral,

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inventivo de la solicitud colombiana en cuestión y que en realidad es la patente americana US 2007/141147, tal y como aquí se indica.

<sup>3</sup> Vila Jato J.L. Tecnología Farmacéutica. Volumen I. Páginas 580 y 581.

los cuales, a su vez, se pueden formular utilizando diferentes excipientes, farmacéuticamente aceptables. En otras palabras, reivindicar presentaciones de fármacos ya existentes y reconocidos en el estado de la técnica como es el caso de la fenilefrina y demás principios activos mencionados por la solicitud colombiana en sus reivindicaciones 48 y 49; y que además mencionan excipientes reconocidos para elaborar dichas formulaciones farmacéuticas también reconocidas en el estado de la técnica (como en el caso de los polímeros para la microencapsulación), no pueden sustentar nivel inventivo alguno.

Prueba de que con anterioridad la fenilefrina, ha sido incluida en diversos tipos de formulaciones para absorberse a través de las mucosas, inclusive en combinación con otros fármacos, es el contenido de documentos tales como la patente americana US 623664 publicada el 18 de noviembre de 1986; la patente americana US 2003/0216420 publicada el 20 de noviembre de 2003; la patente americana US 2004/0122107 publicada el 24 de junio de 2004; la patente americana US 2007/0219253 publicada el 20 de septiembre de 2007 y la publicación internacional WO 2006/135254 publicada el 21 de diciembre de 2006.

Inclusive, en documentos como por ejemplo la patente americana US 2006/0193877 publicada el 31 de agosto de 2006 revela:

The present invention includes compositions and methods for the controlled release of active agents in a shelf-stable liquid formulation by blending one or more controlled release microbeads comprising one or more active agents, preparing a dense, thixotropic solution having a density that is at, or about, the density of the one or more microbeads comprising a thixotropic agent, water and one or more preservatives under conditions that reduce bubble formation and mixing the microbeads and the thixotropic solutions in a mixer that lacks scraping paddles.

(...)

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<sup>4</sup> Ibid. Páginas 581 y 582.

The one or more microbeads may include an enteric coat, a resin coat, a lacquer coat, a pH-sensitive coating, a biodegradable polymer matrix, a water soluble matrix, an ionic matrix, combinations and mixtures thereof. The one or more microbeads may also includes one or more polymers selected from cellulose, ethylcellulose, methylcellulose, propylcellulose, methoxypropylcellulose, cellulose nitrate, poly(vinyl alcohol), poly(vinyl chloride), polystyrene, polyethylene, polypropylene, poly(ethylene-co-vinyl acetate), poly(hydroxybutyric acid), poly(hydroxyvalerianic acid-co-hydroxybutyric acid), poly(lactic acid), poly(glycolic acid), poly(lactic acid-co-glycolic acid), poly( $\epsilon$ -caprolactones), poly( $\epsilon$ -caprolactone-co-DL-lactic acid), poly(maleic anhydride), polyamides, gelatin, chitosan, collagen, poly(hydroxyalkyl)-L-glutamines, poly( $\gamma$ -ethyl-L-glutamate-co-glutamic acid), poly(L-leucine-co-L-aspartic acid), poly(proline-co-glutamic acid), poly(alkyl 2-cyanoacrylates), polyurethanes, poly(methyl methacrylate), poly(methyl methacrylate-co-methacrylic acid) and poly(methacrylate-co-hydroxypropyl methacrylate), polystyrene, polistirex, polacrilex and salts, combinations and mixtures thereof.

(...)

[0013] The controlled-release liquid formulation may include a portion of the one or more beads with an immediate release profile and another portion with a controlled or delayed release profile. When using an ion-exchange matrix,

(...)

performance. The liquid formulations may be delivered to, and adapted for, oral, nasal, buccal, ocular, urethral, trans-mucosal, vaginal, topical or rectal delivery, although oral delivery is used mostly.

(...)

[0051] Decongestants useful with the present invention (along with a salt form) are phenylephrine (bitartrate, tannate, HBr, HCl), phenylpropanolamine (HCl) and pseudoephedrine (HCl). Furthermore, a number of herbal and/or natural decongestants are known in the art, all of which may be used with the present invention.

(...)

What is claimed is:

1. A method for preparing a liquid, controlled-release formulation comprising the steps of:

blending one or more controlled release microbeads comprising one or more active agents;

preparing a dense, thixotropic solution having a density that is at or about the density of the one or more microbeads comprising a thixotropic agent, water and one or more preservatives under conditions that reduce bubble formation; and

mixing the microbeads and the thixotropic solutions under conditions that minimize the introduction of bubbles in the liquid.

2. The method of claim 1, wherein the one or more microbeads comprise one or more of the following: an enteric coat, a resin coat, a lacquer coat, a pH-sensitive coating, a biodegradable polymer matrix, a water soluble matrix, an ionic matrix, combinations and mixtures thereof.

3. The method of claim 1, wherein the one or more microbeads comprise one or more polymers selected from the group consisting of cellulose, ethylcellulose, methylcellulose, propylcellulose, methoxypropylcellulose, cellulose nitrate, poly(vinyl alcohol), poly(vinyl chloride), polystyrene, polyethylene, polypropylene, poly(ethylene-co-vinyl acetate), poly(hydroxybutyric acid), poly(hydroxyvalerianic acid-co-hydroxybutyric acid), poly(lactic acid), poly(glycolic acid), poly(lactic acid-co-glycolic acid), poly( $\epsilon$ -caprolactones), poly( $\epsilon$ -caprolactone-co-DL-lactic acid), poly(maleic anhydride), polyamides, gelatin, chitosan, collagen, poly(hydroxyalkyl)-L-glutamines, poly( $\gamma$ -ethyl-L-glutamate-co-glutamic acid), poly(L-leucine-co-L-aspartic acid), poly(proline-co-glutamic acid), poly(alkyl 2-cyanoacrylates), polyurethanes, poly(methyl methacrylate), poly(methyl methacrylate-co-methacrylic acid) and poly(methacrylate-co-hydroxypropyl methacrylate), polystyrene, polystirex, salts, combinations and mixtures thereof.

Como se puede apreciar, en esta anterioridad ya se revelaba la inclusión de fenilefrina (y de otros fármacos) en formulaciones que comprenden macropartículas (microbeads) recubiertas que permiten la liberación inmediata o controlada de dichos farmacos de manera transmucosal. Nótese que los polímeros utilizados incluyen varios de los reivindicados por la solicitud colombiana en cuestión.

Nuevamente se hace evidente que la elaboración de formulaciones que se asocian con ciertos efectos, como liberación controlada de la droga en sangre, por lo general, forma parte de la capacidad habitual de una persona versada en formulación de productos farmacéuticos.

Por su parte la patente americana US 2005/0152967 publicada el 14 de julio de 2005 revela:

The present invention relates to novel mixed release pharmaceutical formulations that include a expectorant available for immediate release and a decongestant for extended release that provide for the symptomatic relief of cough associated with respiratory tract conditions such as the common cold, bronchial asthma, acute and chronic bronchitis.

(...)

[0014] In yet another embodiment, the present invention provides a time released phenylephrine that is formulated to provide maximum effective release over 2-8 hours using a combination of polymers and/or pharmaceutical glaze. It was found that when the phenylephrine were overcoated with immediate release gauifenesin the process was not only time consuming (since building up the bead with gauifenesin had adhesion problems), but also that overcoating of the gauifenesin on the phenylephrine slowed the release of the phenylephrine to an unacceptable level. Further attempts to

(...)

[0029] For oral, buccal, and sublingual administration, the pharmaceutical composition of the invention may be administered as either solutions or suspensions in the form of gelcaps, caplets, tablets, capsules or powders. For rectal

(...)

[0033] For example, suitable mixed or extended release polymers for use with the present invention include but are not limited to synthetic polymers such as poly(ethylene glycol), poly(ethylene oxide), partially or fully hydrolyzed poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers (poloxamers and meroxapols), poloxamines, carboxymethyl cellulose, and hydroxyalkylated celluloses such as hydroxyethyl cellulose and methylhydroxypropyl cellulose, and natural polymers such as polypeptides, polysaccharides or carbohydrates such as Ficoll®, polysucrose, hyaluronic acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, and proteins such as gelatin, collagen, albumin, or ovalbumin or copolymers or blends thereof. As used herein, "celluloses" includes cellulose and derivatives of the types described above; "dextran" includes dextran and similar derivatives thereof.

(...)

[0051] Substrate(s) for use with the present invention may be a powder or a multiparticulate, such as a granule, a pellet, a bead, a spherule, a beadlet, a microcapsule, a millisphere, a nanocapsule, a nanosphere, a microsphere, a platelet, a mimitablet, a tablet or a capsule. A powder may be a finely divided (milled, micronized, nanosized, precipitated, sprayed) to form of an active ingredient or additive molecular aggregates or a compound aggregate of multiple components or a physical mixture of aggregates of an active ingredient and/or additives. Such substrates may be formed of various materials known in the art, such as, for example: sugars, such as lactose, sucrose or dextrose; polysaccharides, such as maltodextrin or dextrans; starches; celluloses, such as microcrystalline cellulose or microcrystalline cellulose/sodium carboxymethyl cellulose; inorganics, such as dicalcium phosphate, hydroxyapatite, tricalcium phosphate, talc, or titania; and polyols, such as mannitol, xylitol, sorbitol or cyclodextrin.

(...)

[0058] Other additives include, binders (adhesives), i.e., agents that impart cohesive properties to powdered materials through particle-particle bonding, such as matrix binders (dry starch, dry sugars), film binders (polyvinylpyrrolidone (PVP), starch paste, celluloses, bentonite and sucrose), and chemical binders (polymeric cellulose derivatives, such as carboxy methyl cellulose, HPC and HPMC; sugar syrups; corn syrup; water soluble polysaccharides such as acacia, tragacanth, guar and alginates; gelatin; gelatin hydrolysate; agar; sucrose; dextrose; and non-cellulosic binders, such as PVP, PEG, vinyl pyrrolidone copolymers, pregelatinized starch, sorbitol, and glucose).

(...)

[0079] Phenylephrine for delayed release may be prepared using pharmaceutical glaze, polyvinylpyrrolidone and/or microcrystalline cellulose in combination with one or more inactive agents. For example, the phenylephrine may be allowed to roll and cure for 1-6 hours in the presence of the polyvinylpyrrolidone and microcrystalline cellulose. Optionally, a sustained release coating may be added to infuse and/or coat the active-polymer (phenylephrine-polyvinylpyrrolidone). Different levels of sustained release coating amounts may be added, with or without intervening layers of active and/or polymer. In one example, 10.93 Kgs of phenylephrine may be added to polyvinylpyrrolidone and pharmaceutical glaze. The phenylephrine-polyvinylpyrrolidone is allowed to roll and cure for 1-6 hours before sustained release coating (pharmaceutical glaze) is added.

(...)

12. The composition of claim 1, wherein the decongestant comprises phenylephrine as a sustained release bead, a layered sustained release bead or three or more layers of phenylephrine on a bead.

(...)

Como se puede apreciar, en esta anterioridad se revela la inclusión de fenilefrina en composiciones tipo microcápsulas en combinación con otros farmacos, que se obtienen a través de diversos polímeros, para su administración bucal o sublingual. Es importante resaltar el hecho que se menciona que dichas partículas pueden tener varias capas, que coincide con las características (multilamerales) descritas en la solicitud colombiana en cuestión, específicamente en su reivindicación 26.

Finalmente, no se deberían considerar admisibles las reivindicaciones relacionadas a parámetros farmacocinéticos, tales como las reivindicaciones 10 a 16 de la solicitud colombiana en cuestión, ya que como se mencionó anteriormente, la existencia o inexistencia del paso inventivo no se debe determinar exclusivamente sobre la base de dichos efectos obtenidos (una liberación sostenida en el tiempo), sino teniendo además en cuenta los conocimientos propios de una persona capacitada y experimentada en formulación farmacéutica, ya que, en términos generales, los procesos para preparar formulaciones con dichas características especiales, son bien conocidos como tales y de aplicación habitual.

### III. ANEXOS

- Todos los documentos mencionados en el acápite de Complemento de información.

Señor Superintendente,



**JOSE LUIS REYES VILLAMIZAR**  
C.C. 79.152.473 de Usaquén  
T.P. 44655 del C. S de la J.

**United States Patent** [19]  
**Schoenwald et al.**

[11] **Patent Number:** 4,623,664  
[45] **Date of Patent:** Nov. 18, 1986

[54] **OIL SUSPENDED PHENYLEPHRINE**

4,469,706 9/1984 Nathanson ..... 424/330

[75] **Inventors:** Ronald D. Schoenwald, Iowa City,  
Iowa; Du-Shieng Chien, Formosa,  
Taiwan

[73] **Assignee:** University of Iowa Research  
Foundation, Iowa City, Iowa

[21] **Appl. No.:** 793,138

[22] **Filed:** Oct. 31, 1985

[51] **Int. Cl.<sup>4</sup>** ..... A61K 31/135

[52] **U.S. Cl.** ..... 514/653; 514/912

[58] **Field of Search** ..... 514/653, 912

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*Primary Examiner*—Douglas W. Robinson

*Attorney, Agent, or Firm*—Zarley, McKee, Thomte,  
Voorhees & Sease

[57] **ABSTRACT**

An oil suspension, preferably sesame seed oil suspension, of the base form of phenylephrine as an ophthalmic medicament. Surprisingly, the base form of phenylephrine is much quicker absorbed into the eye than the conventional acid salt form. As a result, lower dosage levels can be used to achieve the same mydriatic effect, thus reducing the risk of adverse side effects from systemic absorption.

**11 Claims, 3 Drawing Figures**

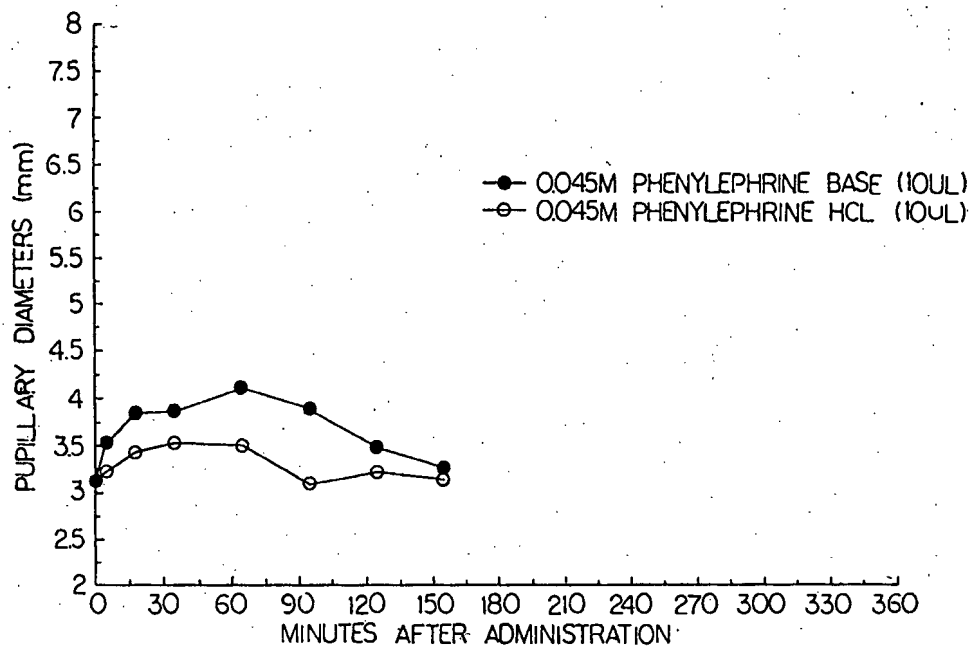


Fig. 1

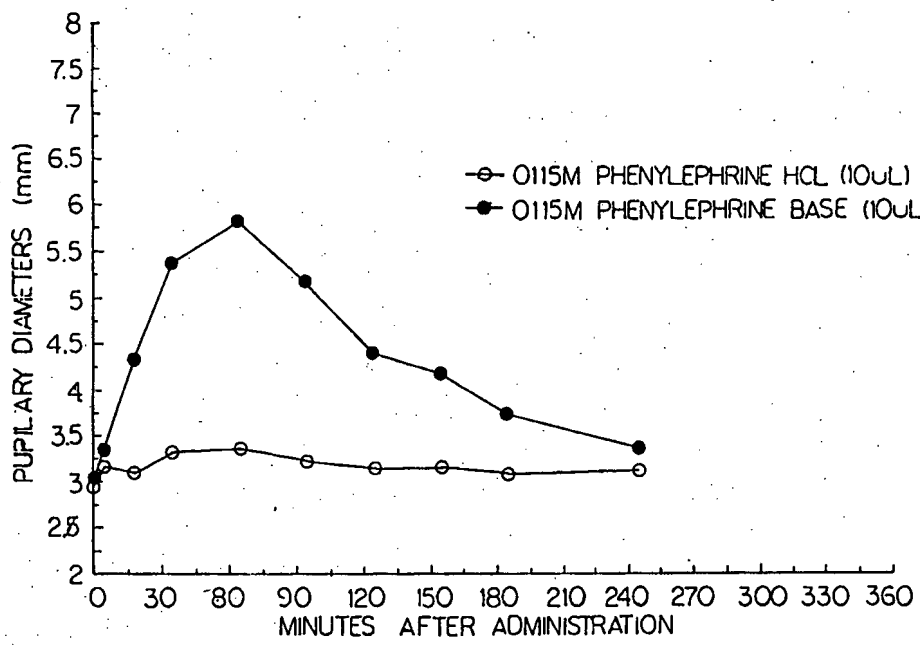


Fig. 2

13

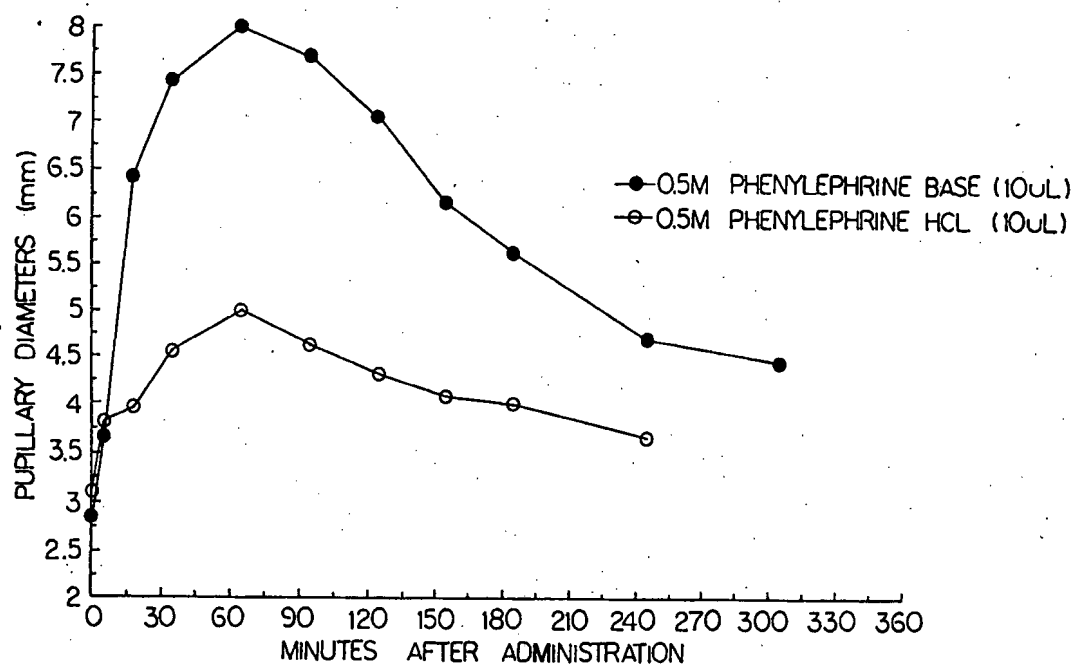


Fig. 3

OIL SUSPENDED PHENYLEPHRINE

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition containing the base form of phenylephrine. Phenylephrine has the formula 3-hydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol.

Phenylephrine is a well-known pharmaceutically active amine whose principal use in the field of ophthalmology is as a mydriatic. There are, however, certain known disadvantages associated with the use of phenylephrine as a mydriatic agent. Those disadvantages, involving systemic side effects, have limited the use of this highly effective drug. Thus, in spite of the fact that it is one of the most effective mydriatics available, its use is significantly limited because of the significant side effects which may occur in some individuals treated with phenylephrine. Those unwanted significant side effects range from hypertension, syncope, and even in some cases to myocardial infarction, leading to death.

Phenylephrine HCl is a very hydrophilic drug used in the eye for its mydriatic and capillary decongestion effects. Because of its hydrophilic characteristics, it poorly penetrates the epithelium of the cornea, therefore, a relatively high concentration, 2.5% or 10%, must be applied to the eye topically to achieve a potent effect. As a result of applying a large dose which is poorly absorbed, the earlier mentioned significant systemic side effects may occur. However, because phenylephrine is such an effective mydriatic agent, despite the potential risk of adverse side effects, there is a continuing need for its use. In the past there have been some attempts to prepare prodrugs of phenylephrine in order to minimize the side effect risk. While the preparation of prodrugs is often advantageous, it is not without disadvantages from time to time. For example, there is an increased cost factor with the preparation of prodrugs of phenylephrine. Accordingly, it can be seen that there is a continuing and real need for a technique which allows one to use phenylephrine in a topical ocular dose form which maximizes mydriatic effectiveness so that lower levels of the active drug can be employed.

Clearly, then, there is a need to reduce the systemic side effects of phenylephrine. Theoretically this could be accomplished by increasing the ocular absorption and thereby reducing systemic absorption. However, the reduction in systemic side effects is an indirect effect of improved ocular absorption. This is exemplified by the fact that even though ocular absorption may double from 2 to 4%, systemic absorption decreases from 98% to only 96%, which is not a significant decrease with respect to systemic side effects. Nevertheless, by increasing the absorption two-fold, the dose can be reduced by one-half to achieve the same therapeutic effect and in this manner systemic effects can be reduced substantially.

This invention has as its primary objective the development of new and useful phenylephrine topical compositions which when used at mydriatically effective levels allow a lower dosage level to be instilled in the eye, leading to decreased side effect risk.

Another objective of the present invention is to provide a safe and pharmaceutically effective mydriatic which is a combination of phenylephrine in the base form and a vegetable oil carrier.

Yet another objective of the present invention is to prepare a mydriatic composition for topical ocular

treatment, useful in ophthalmic diagnosis and surgery, which uses phenylephrine in the base form, allowing it to be more effectively absorbed than in the acid form.

Another objective of the present invention is to provide an ocular composition which will allow phenylephrine to be used in its base form to produce a local or systemic physiological effect, similar to that achieved by much higher concentrations of acid or salt forms of phenylephrine.

An even further objective is to develop a drug delivery system for phenylephrine, adopted to improve the drug absorption, and yet maintain drug potency.

The method and manner of accomplishing these and other objectives of the present invention will become apparent from the detailed description which will follow hereinafter.

SUMMARY OF THE INVENTION

This invention relates to topical phenylephrine composition useful as a mydriatic. Phenylephrine, in its base form, is suspended in an oil suspension, either a mineral oil or vegetable oil. As a result, when used topically, the oil suspension overwhelms the buffer capacity of the tears, so that the base form actually raises the pH of the tears thereby promoting the formation of the un-ionized base form phenylephrine which is preferentially absorbed into the eye quicker than the ionized acid or salt form. Since the base form is more quickly absorbed across the cornea than the acid form, lower dosage levels can be used, reducing the risk of adverse systemic effects.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a pupil dilation study for phenylephrine base form in comparison with phenylephrine acid form at the same molar concentration, 0.045 molar, and in the same sesame oil vehicle.

FIG. 2 shows a comparison study of phenylephrine and phenylephrine hydrochloride in sesame oil at 0.115 molar concentrations.

FIG. 3 shows a similar study at 0.5 molar concentrations of phenylephrine base and phenylephrine acid form in sesame oil.

DETAILED DESCRIPTION OF THE INVENTION

One successfully obtains the objects of the present invention by preparing a topical ocular medicament containing phenylephrine in an oil suspension system. Importantly, the phenylephrine must be in the base form, as opposed to the acid or acid salt form. In other words, the phenylephrine must be in the un-ionized form. In the past phenylephrine has always been used in its salt form since the latter is soluble and stable in buffered aqueous vehicles. In fact, the use of the base form in buffered aqueous vehicles produces the same amount of ionized species as produced from the salt form. Regardless of the initial pH of the phenylephrine salt (or base) form in the aqueous solution, the buffer capacity of the tears would overwhelm the pH of the instilled aqueous drop and poor absorption would result. In the past it has been common to use nontoxic salt forms of phenylephrine prepared by reacting it with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and the like. Such acid/salt forms can be used in aqueous systems or often in the form of a viscous gel for

placement in the conjunctival sac. However, the amount of phenylephrine used in such acid systems must necessarily be high, i.e. up to 10%. Conventionally, it had been thought necessary to achieve an effective mydriosis to use the high concentration of the acid form to overcome both the known poor penetration characteristics of the epithelium of the cornea and the natural buffering effect of tears.

It has now been surprisingly found that the base form of phenylephrine can be used to provide mydriatically effective topical dose compositions. In accordance with this invention, while applicant does not wish to be bound by any theory, it is believed that the base form of phenylephrine suspended in an oil suspension simply overwhelms the buffer capacity of the tears. As a result there is a high available amount of un-ionized phenylephrine which is preferentially absorbed. This only occurs in an oil suspension, not in aqueous systems, where because of the buffer capacity of tears, the pH remains unchanged.

Generally it has been found that the topical compositions of this invention may be satisfactorily prepared using either a mineral oil or an edible vegetable oil. Preferred oil suspensions include the usual triglyceride vegetable oils, preferably the edible oils such as sesame seed oil, cottonseed oil, soybean oil, coconut oil, rapeseed oil, peanut oil, olive oil, palm oil, palm kernel oil, corn oil, castor oil, sunflower seed oil, wallflower oil, and pilchard oil. The preferred oil is sesame seed oil.

The dosage of phenylephrine in the mydriatic composition of the present invention can comprise from about 0.25% by weight of the composition up to about 10% by weight of the composition which is to be topically applied to the eye. Preferably the composition is from about 0.5% by weight of the phenylephrine up to about 5% by weight of the phenylephrine. The balance of the composition is primarily the oil. However, besides the drug itself, other typically state of the art formulations such as stabilizing agents, wetting agents, antioxidants, preservatives, etc. may be added. For example, one may use from 0.25% to 0.5% of an anti-bacterial agent (chlorobutanol), from 0.01% to 0.05% of an anti-fungal agent (propylparaben, methylparaben), from 0.01% up to 0.05% of a wetting agent (poloxamer series) and from 0.01% to 0.05% of an anti-oxidant (alpha-tocopherol, BHA and BHT).

The following examples are offered to further illustrate but not limit the formulations of the present invention.

EXAMPLE 1

Formation of Phenylephrine Base

Phenylephrine HCl (0.3 g, 1.47 mmole) was dissolved in 3 ml of water in a test tube to which was added 1 ml of ammonia T.S. The interior of the test tube was rubbed with a glass rod to initiate the precipitation of the free base. The phenylephrine was separated by filtration and washed with about 1 ml of ice-cold water and finally dried over silica gel for 16 hours. IR (KBr) measurements were made to confirm the preparation of the phenylephrine base.

EXAMPLE 2

Preparation of an Oil Suspension of Phenylephrine and Phenylephrine HCl

| Ingredients                                | % (w/w composition) |
|--------------------------------------------|---------------------|
| Phenylephrine or phenylephrine HCl, U.S.P. | 1-10%               |
| Pluronic P-103*                            | 0.05%               |
| Chlorobutanol                              | 0.025-0.5%          |
| Methylparaben                              | 0.05%               |
| Propylparaben                              | 0.01%               |
| Alphatocopherol**                          | 0.05%               |
| Sesame Oil qs                              | 100%                |

\*polyethylenepolypropylene glycol or poloxamer P-103 (Wyandotte Corp., Wyandotte, Michigan)  
\*\*or other suitable oil soluble antioxidant, i.e., BHT 0.03% or BHA 0.02%

Preparation

The pluronic P-103 was added to phenylephrine or phenylephrine HCl and mixed well. Preferably, the drug powders are micronized. Each of the remaining ingredients were dissolved in about 80% of the sesame oil. If any of the ingredients are not fully dissolved, the sesame oil can be heated to about 50° for a few minutes. Upon cooling, any residual particles will be dissolved. About 10% of the sesame oil was added to the pluronic-drug mixture and triturated until the powder was wetted and well dispersed. The remainder of the sesame oil was added with stirring or trituration to form the final product which is dispensed to the patient's eye in drop form. Both phenylephrine and phenylephrine HCl form suspensions in sesame oil.

EXAMPLE 3

Mydriatic Experiments

The right eye of a normal adult New Zealand Rabbit (3-4 months) was used to measure mydriasis. A flood of diffuse light was placed at a fixed distance from the rabbit eye. The initial pupillary diameter prior to administering eye drops was about 3-4 mm. Changes in pupil diameter were measured from photographs taken with a 35 mm single lens reflex camera equipped with a close-up lens. Pupil diameters were measured at time 0 through about 5 hours. A dosing volume of 10 µl was administered to the right eye of a group of eight rabbits. A three day rest period was allowed between instillations of each formulation. Each rabbit received each formulation one time.

FIGS. 1-3 show the results of the tests demonstrated in Examples 1-3. There it can be seen that an equimolar concentration of phenylephrine and phenylephrine hydrochloride were compared at 0.045, 0.115 and 0.5 molar. These molarities represent 1, 2.5 and 10% w/v based upon phenylephrine hydrochloride. At each concentration, the phenylephrine base yielded a greater degree of mydriasis than the hydrochloride salt at all concentrations tested.

It can therefore be seen that one can now prepare topical ocular dose form compositions of phenylephrine containing phenylephrine at less than the ordinary 10% used in the acid form composition. Moreover, it is absorbed more quickly across the eye and achieves better dilation of the pupil than same level concentrations of the acid form. As a result, compositions can be dropped down in their phenylephrine content to within the range of from 1% to 5% and still get the same mydriatic

5

effect as those now commercially utilized. Because the concentration level is lower, the systemic side effect risk is also lower.

While not yet having been tested, it is possible that this same drug delivery system will work for other ocular drugs such as sodium sulfacetamide, pilocarpine, epinephrine, and in particular, whenever a weak base or weak acid drug is used in concentrations above 1%. Thus it can be seen that the invention accomplishes all of its stated objectives.

What is claimed is:

1. An ocular dilating composition, comprising:  
from about 0.5% by weight to about 5.0% by weight of the unionized base form of phenylephrine; and  
a non-toxic pharmaceutically acceptable oil selected from the group consisting of mineral oil and edible vegetable oil, said composition providing unionized base form of phenylephrine to the eye for preferential absorption in comparison with acid and salt forms of phenylephrine.
2. The composition of claim 1 wherein the oil is a mineral oil.
3. The composition of claim 1 wherein the base form of phenylephrine is from about 0.5% by weight to about 5% by weight of said composition.
4. The composition of claim 1 which includes from 0.25% by weight to 0.5% by weight of an anti-bacterial agent.

6

5. The composition of claim 1 which includes from about 0.1% by weight to 0.05% by weight of an anti-fungal agent.
6. The composition of claim 1 which includes from about 0.1% by weight to about 0.05% by weight of an anti-oxidant.
7. The composition of claim 1 which includes from about 0.1% by weight to about 0.05% by weight of a preservative.
8. The composition of claim 1 wherein the oil is a vegetable oil.
9. The composition of claim 8 wherein the oil is sesame seed oil.
10. A method of ocular drug delivery of phenylephrine which has a base form and acid/salt form, which comprises:  
placing said phenylephrine in its unionized base form; suspending from about 0.5% by weight to about 5.0% by weight of said phenylephrine in a non-toxic pharmaceutically acceptable oil selected from the group consisting of mineral oil and edible vegetable oil; and  
topically delivering a unit dose of said suspension which is unionized base form of phenylephrine to the eye for preferential absorption in comparison with acid and salt forms of said drug.
11. The method of claim 10 wherein said oil is a vegetable oil.

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**Kamm et al.** (43) **Pub. Date: Nov. 20, 2003**

(54) **PHARMACEUTICAL COMPOSITION FOR  
TREATING FECAL INCONTINENCE AND  
ANAL ITCH**

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(57) **ABSTRACT**

Fecal incontinence and anal itch can be treated by administration, more particularly by local application to the anus, of an  $\alpha$ -adrenergic blocker, nitric oxide synthase inhibitor, prostaglandin  $F_{2\alpha}$ , dopamine, morphine,  $\beta$ -blockers, and 5-Hydroxytryptamine. The patients who benefit most from the invention are those who have a normal or low maximum anal resting pressure and a structurally intact internal anal sphincter muscle, and patients who have had major bowel resection and reanastomosis.

[0076] 12 Patients were enrolled in the study of whom 10 have completed the study. 10 Patients are mainly troubled by nocturnal incontinence only, and 2 have both daytime and nocturnal incontinence.

[0077] Of the 10 completed studies, there were 7 women and 3 men, age range (34-67). Anorectal manometry was performed and laser doppler fowmetry on all patients. Incontinence score was determined. All these outcome measures were repeated after treatment with both trial creams (phenylephrine and placebo).

[0078] 6/10 (60%) patients had significant improvement of their symptoms with phenylephrine 10% compared to placebo. This correlated well with the rise in mean resting anal sphincter pressure in these patients after phenylephrine but not after placebo (29% increased after phenylephrine, v-8% on placebo compared to baseline, p<0.005). Incontinence scores improved by a mean of 45% after phenylephrine compared to 3% after placebo. No differences in anodermal blood flow were noted. The mean subjective improvement in symptoms reported by patients was 83% after placebo and 14% after placebo (p<0.01).

[0079] One patient had no measurable increase in anal sphincter pressure, though her incontinence score improved by 47% and subjectively she felt 75% better after phenylephrine compared to placebo. 3/10 patients had no improvement.

[0080] In summary, 7/10 patients with ileo-anal pouch had improvement of symptoms of incontinence after topical application of 10% phenylephrine cream, 6 of whom also had objective improvement i.e. measurement of anal sphincter pressure.

EXAMPLE 9

[0081] A 1% ointment was prepared by mixing 0.02 g of Nω-Nitro-L-arginine (obtained from Fluka—part of the Sigma group) in 19.8 g of unguentum merk base.

[0082] The ointment was then applied in and around the anal canal of twelve patients and the internal anal pressure measured by manometry (as discussed previously) before and shortly after application of the ointment. The patients suffered from passive and urge (P+U) incontinence, or constipation, and ultra-sound showed most patients to have an internal anal sphincter (IAS) and external anal sphincter (EAS) defect.

[0083] The results are given in Table 1 and show that nitric oxide synthase inhibitors such as N<sup>G</sup>-Nitro-L-arginine increase the resting internal anal sphincter pressure and relieve anal incontinence and anal itch.

TABLE 1

| Patient age/sex | Diagnosis     | Anal Ultra-sound | Internal Anal Pres-sure/Pre Appli-cation | Post Appli-cation |
|-----------------|---------------|------------------|------------------------------------------|-------------------|
| 1 24 M          | P + U Incont. | IAS & EAS Defect | 80                                       | 100               |
| 2 81 M          | P + U Incont. | IAS & EAS Defect | 40                                       | 50                |
| 3 97 M          | P + U Incont. | IAS & EAS Intact | 80                                       | 100               |
| 4 24 F          | Constipation  |                  | 80                                       | 100               |
| 5 37 F          | Constipation  |                  | 80                                       | 100               |

TABLE 1-continued

| Patient age/sex | Diagnosis        | Anal Ultra-sound                     | Internal Anal Pres-sure/Pre Appli-cation | Post Appli-cation |
|-----------------|------------------|--------------------------------------|------------------------------------------|-------------------|
| 6 38 F          | Constipation     |                                      | 60                                       | 80                |
| 7 37 M          | P + U Incont.    | s/p Sphincterectomy IAS & EAS Defect | 40                                       | 50                |
| 8 37 F          | Constipation     | IAS & EAS intact                     | 80                                       | 100               |
| 9 73 M          | P + U Incont.    | IAS & EAS Intact                     | 60                                       | 60                |
| 10 55 F         | P + U Incont.    | IAS & EAS Intact                     | 40                                       | 60                |
| 11 60 F         | P + U Incont.    | IAS & EAS Defect                     | 30                                       | 40                |
| 12 M            | P + U Incont.    | IAS & EAS Intact                     | 30                                       | 30                |
|                 | Viserol Myopathy |                                      |                                          |                   |

- What we claim is:
1. A method for the treatment of fecal incontinence or anal itch comprising topically administering in and/or around the anal canal of a patient a physiologically active agent selected from the group consisting of a adrenergic agonists, nitric oxide synthase inhibitors, prostaglandin F<sub>2α</sub>, dopamine, morphine, beta-blockers, and 5-Hydroxytryptamine.
  2. The method according to claim 1 wherein the active agent is selected from the group consisting of α adrenergic agonists, nitric oxide synthase inhibitors and prostaglandin F<sub>2α</sub>.
  3. The method according to claim 2 wherein the active agent is selected from the group consisting of phenylaph-rine, noradrenalin, methoxamine, dinaprost, carboprost, N<sup>G</sup>-monomethyl-L-arginine (L-NMMA), and N<sup>G</sup>-nitro-L-argi-nine methyl ester (L-NAME) and pharmacologically acceptable salts thereof.
  4. The method according to claim 3 wherein the active agent is selected from the group consisting of phenylephrine and pharmacologically acceptable salts thereof.
  5. The method according to claim 1 wherein the active agent is applied locally to the internal anal sphincter.
  6. The method according to claim 1 wherein the patients to be treated have a normal or low maximum anal resting pressure and a structurally intact internal anal sphincter muscle.
  7. The method according to claim 1 wherein the patients to be treated have had major bowel resection and reanasto-mosis.
  8. A rectally administrable topically acting pharmaceu-tical composition for local application in the treatment of fecal incontinence or anal itch comprising at least one active agent selected from the group consisting of a adrenergic agonists, nitric oxide synthase inhibitors, prostaglandin F<sub>2α</sub>, dopamine, morphine, beta-blockers, and 5-Hydrox-tryptamine together with a pharmacologically acceptable carrier, provided that the composition does not include a xanthine when the active agent is phenylephrine.
  9. A topical composition for local application in the treatment of fecal incontinence or anal itch comprising N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) together with a pharmacologically acceptable carrier.
  10. A topical composition for local application in the treatment of fecal incontinence or anal itch comprising phenylephrine in an amount of at least 10%.

11. The composition according to claim 10 in the form of a gel, ointment, cream emollient, lotion, powder, solution spray, paste, oil, suspension, enema, foam or suppository.

12. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, an internal anal sphincter pressure increasing amount of a physiologically active agent comprising an  $\alpha$  adrenergic agonist.

13. The method according to claim 12 wherein the active agent is selected from the group consisting of phenylephrine, noradrenalin and methoxamine and pharmacologically acceptable salts thereof.

14. The method according to claim 13 wherein the active agent is selected from the group consisting of phenylephrine and pharmacologically acceptable salts thereof.

15. The method according to claim 12 wherein the active agent is applied locally to the internal anal sphincter.

16. The method according to claim 12 wherein the patients to be treated have a normal or low maximum anal resting pressure and a structurally intact internal anal sphincter muscle.

17. The method according to claim 12 wherein the patients to be treated have had major bowel resection and reanastomosis.

18. The method according to claim 14 wherein the active agent is applied locally to the internal anal sphincter.

19. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient an internal anal sphincter pressure increasing amount of a physiologically active agent selected from the group consisting of phenylephrine, nor-adrenalin and methoxamine and pharmacologically acceptable salts thereof.

20. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, an internal anal sphincter pressure increasing amount of phenylephrine or a pharmacologically acceptable salt thereof.

21. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, a topical composition comprising at least 5% w/w of phenylephrine or a pharmacologically acceptable salt thereof.

22. A method for the treatment of fecal incontinence comprising topically administering in and/or around the anal canal of a patient, a topical composition comprising as the sole physiologically active agent a fecal incontinence treating amount of phenylephrine or a pharmacologically acceptable salt thereof.

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(54) **METHOD OF ALLEVIATING  
BAROMETRIC-INDUCED SYMPTOMS IN  
AIRLINE PASSENGERS**

(52) **U.S. Cl. .... 514/649**

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(57) **ABSTRACT**

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A method of alleviating the symptoms of ear and sinus cavity blockage in a descending aircraft, and a kit that provides the medications and instructions for a user to accomplish the method. The method contemplates ingesting a nasal decongestant at least one hour before the scheduled aircraft landing time, for non-specific shrinking of the nasal lining, and applying a nasal decongestant spray into the nose later in flight than the ingestion of the nasal decongestant, to shrink the nasal lining. The ingested and sprayed decongestants help to shrink the mucosa, including at least the nasal lining, to decrease the pain associated with blockage as an aircraft descends. The ingested nasal decongestant currently comprises pseudoephedrine, and the preferred dose is about 60 mg. The sprayed nasal decongestant currently comprises either phenylephrine or oxymetazoline, either of which may be in a concentration up to about 1%.

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**Publication Classification**

(51) **Int. Cl.<sup>7</sup> ..... A61K 31/137**

## METHOD OF ALLEVIATING BAROMETRIC-INDUCED SYMPTOMS IN AIRLINE PASSENGERS

### CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority of Provisional application serial No. 60/410,633, filed on Sep. 13, 2002.

### FIELD OF THE INVENTION

[0002] This invention relates to a method and kit for alleviating sinus and ear pain associated with landing in a commercial aircraft.

### BACKGROUND OF THE INVENTION

[0003] According to NBTA (FAA) estimates there were about 700 million emplanements in the U.S. alone in 2001. Factor in the Academy of Allergy, Asthma, and Immunology estimate that 20% of the population is affected by allergic diseases and incorporate the assumption that, at any given time, 5% of the population have a "cold" or are otherwise irritated (affected) by acknowledged poor air quality on aircraft, then there is the potential for over 170 million people to have significant ears and sinus difficulty while flying. Significant difficulty means the following: There is an intimate relationship between swelling in the nasal passages and potential blockages in the ears and sinus cavities. This typically takes place within the hour before landing (because of the pressurization characteristics of aircraft and the normal descent patterns of commercial aircraft). The most prominent symptoms are blockage of the sinuses. Blockage of the ears occurs when the pressurization of the aircraft drops below eight thousand feet, which usually occurs within about an hour of landing in commercial aircraft. This is the time at which appropriate preemptive treatments will be useful in obviating barometric-induced symptoms of ear blockage, which can range from just blockage to severe pain and actual hemorrhage or rupture of the eardrum. The same barometric scenario which produces blocked ears, also accounts for blocked sinuses and associated pain.

### SUMMARY OF THE INVENTION

[0004] There is a significant need for a safe and effective means of obviating these troublesome occurrences.

[0005] Accordingly, this invention features a method of alleviating the symptoms of ear and sinus cavity blockage in a descending aircraft, comprising ingesting a nasal decongestant at least one hour before the scheduled aircraft landing time, for non-specific shrinking of the nasal lining, and applying a nasal decongestant spray into the nose later in flight than the ingestion of the nasal decongestant, to shrink the nasal lining. The ingested and sprayed decongestants help to shrink the mucosa, including at least the nasal lining, to decrease the pain associated with blockage as an aircraft descends. The ingested nasal decongestant currently comprises pseudoephedrine, and the preferred dose is about 60 mg. The sprayed nasal decongestant currently comprises either phenylephrine or oxymetazoline, either of which may be in about a 1% concentration.

[0006] The ingestion step preferably takes place within about six hours of the scheduled aircraft landing time, and

the spray step preferably takes place within about one hour of the scheduled aircraft landing time.

[0007] In a more specific embodiment, the invention features a method of alleviating the symptoms of ear and sinus cavity blockage in a descending aircraft, comprising ingesting about 60 mg of pseudoephedrine at least one hour before the scheduled aircraft landing time, for non-specific shrinking of the nasal lining, and applying a nasal decongestant spray into the nose after the pseudoephedrine ingestion and within about one hour of scheduled landing time, to shrink the nasal lining.

[0008] This invention also features a kit for use in alleviating the symptoms of ear and sinus cavity blockage in descending aircraft, comprising a first medication comprising an oral nasal decongestant and a second medication comprising a nasal spray decongestant. The kit also includes instructions for the user to ingest a proper dose of the oral nasal decongestant at least one hour before the scheduled aircraft landing time, and to subsequently spray the nasal spray decongestant into at least one nostril within about one hour of the scheduled landing time.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0009] The invention is designed to overcome the major issues of what is called Eustachian tube and sinus blockage during an aircraft flight. It consists of a first medication, an oral nasal decongestant medication, taken as the flight starts if the flight is less than six hours. For longer flights, the oral medication is preferably taken about six hours before the scheduled landing time. A second medication, a nasal decongestant spray, is taken close to landing, typically within about one hour of the scheduled landing time. Included with the appropriate medication in a kit will be instructions for dosage and timing thereof, and medical information about safe usage and contraindications to usage. The invention preferably includes either two 60 mg. pseudoephedrine (e.g., Sudafed™) or four 30 mg. pseudoephedrine (e.g., Sudafed™) capsules, and one spray bottle of phenylephrine (e.g., Neosynephrine™) or oxymetazoline (e.g., Afrin™) at an appropriate typical dose, typically up to about 1% concentration.

[0010] More details about the composition of the invention, pharmacologically, are discussed below. The first (early in flight) medication is a nasal decongestant (called an alpha adrenergic agent) which, when taken orally, serves to shrink the nasal lining (mucosa) nonspecifically. A preferred medication is pseudoephedrine, and the adult dose is preferably 60 mg. Nonspecifically means it does not make a difference whether the swelling is secondary to an ordinary cold or an allergy. Pseudoephedrine is primarily used for the treatment of "cold" symptoms, but is often included, with an antihistamine, for the treatment of allergic congestion. The rationale for its use is to provide some decrease in normal nasal swelling as the flight progresses. There are continuing allusions to the poor air quality in aircraft. The major manifestations of this "poor quality" are nasal drying, congestion etc., resulting in nasal swelling that is alleviated by the pseudoephedrine.

[0011] The second (late in flight) medication is a topical nasal decongestant delivered as a nasal spray, typically one or two sprays into each nostril. This has the topical effect of

shrinking the lining of the nose and, ostensibly, the Eustachian tubes, which basically have the same type of tissue lining as the nose. Phenylephrine or oxymetazoline are the preferred choices. This topical is an adjunct to the systemic medication. The timing of the use of the nasal spray is designed to coincide with flight dynamics. The average landing pattern internationally is about an hour. It is during this landing period that most people experience both ear and sinus pressure symptoms. The rationale for the spray is that it defuses that congestion immediately and obviates the associated barometric otitis (ear pressure) and barometric sinus pressure.

[0012] The oral medication and the spray medication act adjunctively and additively to relieve the potential for ear and sinus symptoms associated with descent. This is the rationale for combining both the pill and the spray.

[0013] The effective substitutes for the sprays are limited. Under the current understanding of sprayable nasal decongestants, one either uses phenylephrine or oxymetazoline. With the withdrawal of phenylpropylene from the market, the only effective oral (pill) decongestant is pseudoephedrine. In the lexicon, both topical and oral decongestants are the same.

[0014] The invention can be presented for sale on a rack of pull-off, sealed plastic pouches. Attached to the rack will be a laminated copy of all pages of the use/safety manual, for perusal before purchase. The product will preferably contain enough medication for two flights (one round trip). The product will preferably contain the indications and rationale for usage, the method and timing of usage, and the medical contraindications of usage.

[0015] Other embodiments will occur to those skilled in the art and are within the following claims:

What is claimed is:

1. A method of alleviating the symptoms of ear and sinus cavity blockage in a descending aircraft, comprising:
  - ingesting a nasal decongestant at least one hour before the scheduled aircraft landing time, for non-specific shrinking of the nasal lining; and
  - applying a nasal decongestant spray into the nose later in flight than the ingestion of the nasal decongestant, to shrink the nasal lining;
  - wherein the ingested and sprayed decongestants help to shrink the mucosa, including at least the nasal lining, to decrease the pain associated with blockage as an aircraft descends.
2. The method of claim 1 wherein the ingested nasal decongestant comprises pseudoephedrine.
3. The method of claim 2 wherein the pseudoephedrine dose is about 60 mg.
4. The method of claim 1 wherein the sprayed nasal decongestant comprises phenylephrine.
5. The method of claim 4 wherein the phenylephrine is in up to about a 1% concentration.

6. The method of claim 1 wherein the sprayed nasal decongestant comprises oxymetazoline.
7. The method of claim 6 wherein the oxymetazoline is in up to about a 1% concentration.
8. The method of claim 1 wherein the ingestion step takes place within about six hours of the scheduled aircraft landing time.
9. The method of claim 1 wherein the spray step takes place within about one hour of the scheduled aircraft landing time.
10. A method of alleviating the symptoms of ear and sinus cavity blockage in a descending aircraft, comprising:
  - ingesting about 60 mg of pseudoephedrine at least one hour before the scheduled aircraft landing time, for non-specific shrinking of the nasal lining; and
  - applying a nasal decongestant spray into the nose after the pseudoephedrine ingestion and within about one hour of scheduled landing time, to shrink the nasal lining;
  - wherein the ingested and sprayed decongestants help to shrink the mucosa, including at least the nasal lining, to decrease the pain associated with blockage as an aircraft descends.
11. The method of claim 10 wherein the sprayed nasal decongestant comprises phenylephrine.
12. The method of claim 1 wherein the sprayed nasal decongestant comprises oxymetazoline.
13. A kit for use in alleviating the symptoms of ear and sinus cavity blockage in descending aircraft, comprising:
  - a first medication comprising an oral nasal decongestant;
  - a second medication comprising a nasal spray decongestant; and
  - instructions for the user to ingest a proper dose of the oral nasal decongestant at least one hour before the scheduled aircraft landing time, and to subsequently spray the nasal spray decongestant into at least one nostril within about one hour of the scheduled landing time;
  - wherein the ingested and sprayed decongestants help to shrink at least the nasal lining, to decrease pain associated with blockage as the aircraft descends.
14. The kit of claim 13 wherein the ingested nasal decongestant comprises pseudoephedrine.
15. The kit of claim 14 wherein the pseudoephedrine dose is about 60 mg.
16. The kit of claim 13 wherein the sprayed nasal decongestant comprises phenylephrine.
17. The kit of claim 16 wherein the phenylephrine is in up to about a 1% concentration.
18. The kit of claim 13 wherein the sprayed nasal decongestant comprises oxymetazoline.
19. The kit of claim 18 wherein the oxymetazoline is in up to about a 1% concentration.
20. The kit of claim 13 wherein the instructions comprise ingesting the first medication within about six hours of the scheduled aircraft landing time.

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(57) **ABSTRACT**

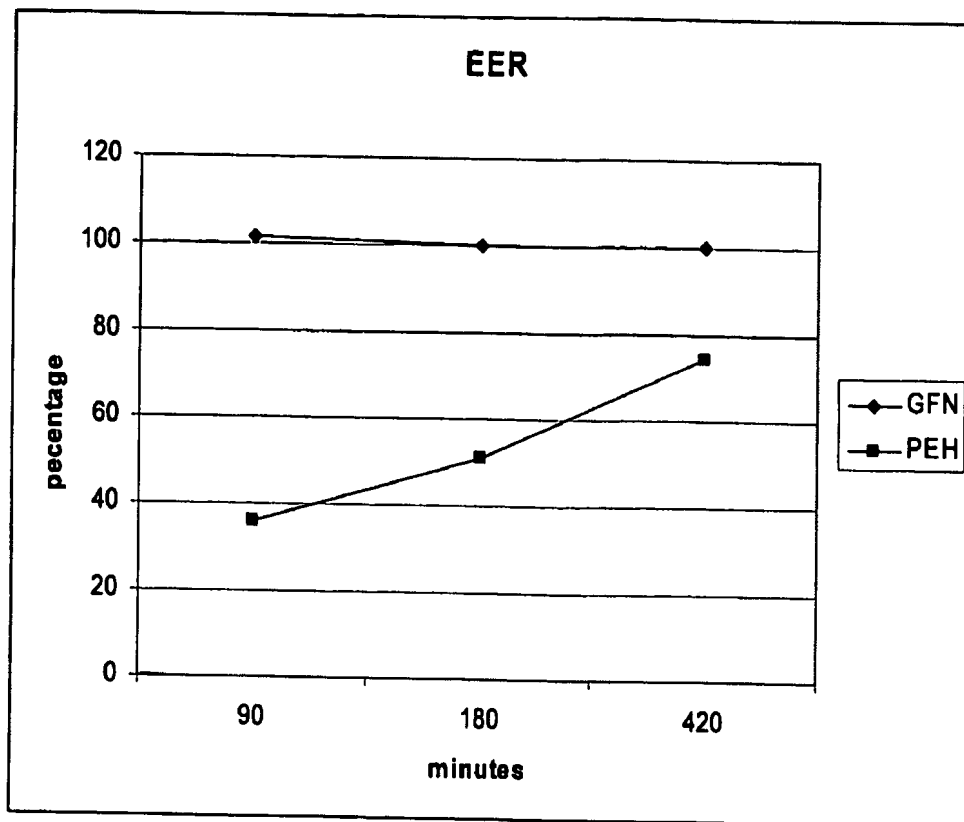
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**Related U.S. Application Data**

(63) **Continuation-in-part of application No. 10/764,177,**  
**filed on Jan. 23, 2004, which is a continuation of**

The present invention relates to novel mixed release pharmaceutical formulations that include a expectorant available for immediate release and a decongestant for extended release that provide for the symptomatic relief of cough associated with respiratory tract conditions such as the common cold, bronchial asthma, acute and chronic bronchitis.



| Expectorant    | Weight | Decongestant               | Weight |
|----------------|--------|----------------------------|--------|
| Guaifenesin DC | 421 mg | Phenylephrine              | 30 mg  |
|                |        | Microcrystalline Cellulose | 44 mg  |
|                |        | Magnesium Stearate         | 5 mg   |
| Gelcap         | 1      |                            |        |

[0098] A formulation for immediate release of an expectorant and extended release of a decongestant in an enveloped formulation, in a suppository:

| Expectorant      | Weight | Decongestant               | Weight |
|------------------|--------|----------------------------|--------|
| Guaifenesin DC   | 421 mg | Phenylephrine              | 15 mg  |
| Talc             | 5 mg   | PVPyrrole                  | 44 mg  |
|                  |        | Povidone                   | 6 mg   |
|                  |        | Microcrystalline Cellulose | 5 mg   |
|                  |        | Magnesium Stearate         | 5 mg   |
| Stearic Acid     | 2 mg   |                            |        |
| beeswax/glycerol | 1-2 gr |                            |        |

[0099] An effervescent tablet for immediate release of an expectorant and extended release of a decongestant in an enveloped formulation, in an effervescent tablet:

| First Effervescent Active | Weight | Decongestant Minicap       | Weight |
|---------------------------|--------|----------------------------|--------|
| Guaifenesin DC            | 421 mg | Phenylephrine              | 15 mg  |
| Talc                      | 5 mg   | PVPyrrole                  | 44 mg  |
|                           |        | Povidone                   | 6 mg   |
|                           |        | Microcrystalline Cellulose | 5 mg   |
|                           |        | Magnesium Stearate         | 5 mg   |
| Monosodium citrate        | 10 mg  |                            |        |
| Sodium bicarbonate        | 10 mg  |                            |        |

[0100] For immediate release of an expectorant and extended release of a decongestant in an enveloped formulation one may add the following ingredients, in a caplet:

| Expectorant    | Weight | Decongestant               | Weight |
|----------------|--------|----------------------------|--------|
| Guaifenesin DC | 421 mg | Phenylephrine              | 15 mg  |
| Talc           | 3 mg   | PVPyrrole                  | 44 mg  |
|                |        | Povidone                   | 6 mg   |
|                |        | Microcrystalline Cellulose | 5 mg   |
|                |        | Magnesium Stearate         | 5 mg   |

[0101] While this invention has been described in reference to illustrative embodiments, this description is not intended to be construed in a limiting sense. Various modifications and combinations of the illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to the description. It is therefore intended that the appended claims encompass any such modifications or embodiments.

1. A pharmaceutical composition comprising: an expectorant packaged for release of over 90% within about 90 minutes; and a decongestant packaged for extended release

wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes.

2. The composition of claim 1, wherein the decongestant comprises phenylephrine.

3. The composition of claim 1, wherein the expectorant comprises guaifenesin.

4. The composition of claim 1, wherein the pharmaceutical formulation is packed into a capsule.

5. The composition of claim 1, wherein the decongestant and the expectorant are packed into a capsule, caplet, softgel, gelcap, suppository, film, granule, gum, insert, pastille, pellet, troche, lozenge, disk, poultice or wafer.

6. The composition of claim 1, wherein over 80% of the expectorant is released within about 60 minutes.

7. The composition of claim 1, wherein immediate release is defined further as comprising release of over 90% of the expectorant within about 60 minutes.

8. The composition of claim 1, wherein the decongestant is packaged with PVPP and Povidone.

9. The composition of claim 1, wherein the decongestant is packaged with a talc and a stearate.

10. The composition of claim 1, wherein the expectorant comprises guaifenesin in a powder form.

11. The composition of claim 1, wherein the expectorant comprises 422 mg of 95% guaifenesin.

12. The composition of claim 1, wherein the decongestant comprises phenylephrine as a sustained release bead, a layered sustained release bead or three or more layers of phenylephrine on a bead.

13. The composition of claim 1, wherein the expectorant is superposed on the decongestant.

14. The composition of claim 1, comprising further one or more inactives.

15. A pharmaceutical composition consisting essentially of: an expectorant packaged for release of over 90% within about 90 minutes; a decongestant packaged for extended release wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes; and one or more inactive agents.

16. A capsule consisting essentially of: an expectorant packaged for release of over 90% within about 90 minutes; a decongestant packaged for extended release wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes; and one or more inactive agents.

17. A method of providing a dual-release formulation comprising: loading into a capsule an expectorant in a powdered form and a decongestant in an extended release form, wherein the capsule comprises one or more excipients selected from a polymer, a cellulose, a stearate, a talc, a lacquer and a pharmaceutical glaze.

18. A method of providing a dual-release formulation comprising: providing a expectorant packed for immediate release in a powder form; providing a nasal decongestant packed for extended release comprising, phenylephrine, PVP, cellulose and a pharmaceutical glaze, and loading the expectorant and the decongestant into a capsule

19. A pharmaceutical composition consisting essentially of: a guaifenesin packaged for release of over 90% within about 90 minutes; a phenylephrine packed for extended release; and one or more inactive agents selected from a polyvinyl polymer, microcrystalline cellulose, stearate, lacquer, talc and a pharmaceutical glaze, wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes.

20. A pharmaceutical composition consisting essentially of: an expectorant packaged for release of over 90% within about 90 minutes; a decongestant packaged for extended release wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes; and one or more inactive agents.

21. The composition of claim 20, wherein the decongestant comprises phenylephrine.

22. The composition of claim 20, wherein the expectorant comprises guaifenesin.

23. The composition of claim 20, wherein the pharmaceutical formulation is packed into a capsule.

24. The composition of claim 20, wherein the decongestant and the expectorant are packed into a capsule, caplet, softgel, gelcap, suppository, film, granule, gum, insert, pastille, pellet, troche, lozenge, disk, poultice or wafer.

25. The composition of claim 20, wherein over 80% of the expectorant is released within about 60 minutes.

26. The composition of claim 20, wherein immediate release is defined further as comprising release of over 90% of the expectorant within about 60 minutes.

27. The composition of claim 20, wherein the decongestant is packaged with a polyvinyl polymer and Povidone.

28. The composition of claim 20, wherein the decongestant is packaged with a talc and a stearate.

29. A pharmaceutical composition comprising: a guaifenesin salt packaged for release of over 90% within about 90 minutes; a phenylephrine salt packaged for extended release wherein between about 30 to 60% of the decongestant is available after 90 minutes, between about 50 to 70 percent is available at between about 150 and 210 minutes and wherein between about 60 to 80 percent is available after 360 minutes.

30. The composition of claim 29, wherein the decongestant comprises phenylephrine.

31. The composition of claim 29, wherein the expectorant comprises guaifenesin.

32. The composition of claim 29, wherein the pharmaceutical formulation is packed into a capsule.

33. The composition of claim 29, wherein the decongestant and the expectorant are packed into a caplet, softgel, gelcap, suppository, film, granule, gum, insert, pastille, pellet, troche, lozenge, disk, poultice or wafer.

34. The composition of claim 29, wherein over 80% of the expectorant is released within about 60 minutes.

35. The composition of claim 29, wherein immediate release is defined further as comprising release of over 90% of the expectorant within about 60 minutes.

36. The composition of claim 29, wherein the decongestant is packaged with a polyvinyl polymer and Povidone.

37. The composition of claim 29, wherein the decongestant is packaged with a talc and a stearate.

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26

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**Tengler et al.** (43) **Pub. Date: Aug. 31, 2006**

(54) **COMPOSITIONS AND METHODS OF MAKING SUSTAINED RELEASE LIQUID FORMULATIONS**

**Publication Classification**

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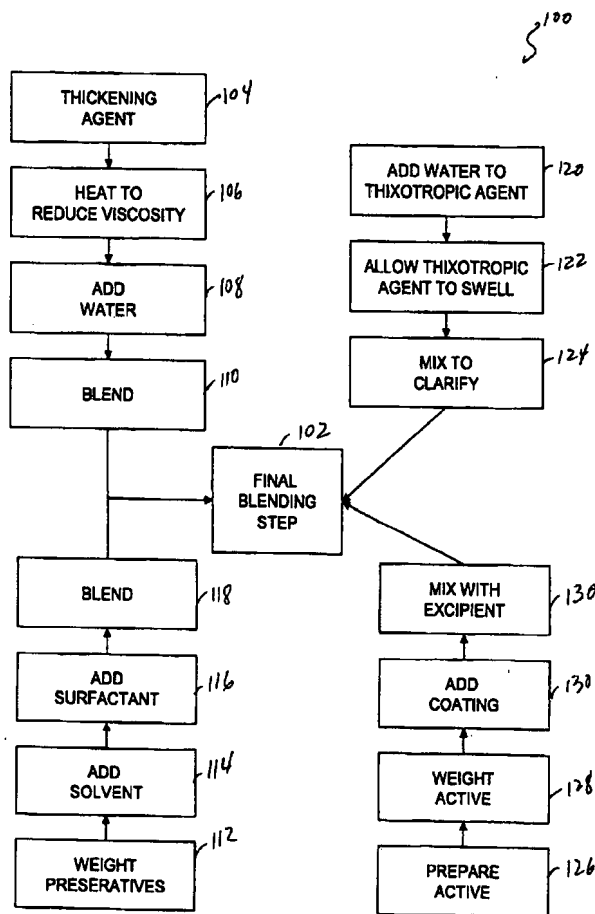
(57) **ABSTRACT**

The present invention includes compositions and methods for the controlled release of active agents in a shelf-stable liquid formulation by blending one or more controlled release microbeads comprising one or more active agents, preparing a dense, thixotropic solution having a density that is at, or about, the density of the one or more microbeads comprising a thixotropic agent, water and one or more preservatives under conditions that reduce bubble formation and mixing the microbeads and the thixotropic solutions in a mixer that lacks scraping paddles.

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tion was tested using, e.g., a standard low pH or a water dissolution profile assays. Briefly, the sustained release actives were tested for percent release by dissolution in a 37 degree Celsius water bath in one liter of deionized water into which 5.0 grams of potassium chloride was dissolved with paddles that mix the sample at 150 revolutions per minute (RPMs). A 5 milliliter test sample of the liquid formulation, neat or titrated, is added to the bath using a syringe (which may be washed in the water/KCl mix). Aliquots of 2 ml are sampled at, e.g., 0.5, 1, 3 and 8 hours. The results of a three active agent formulation and release are shown for three different samples in FIGS. 6-8.

[0112] It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

[0113] All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0114] All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

What is claimed is:

1. A method for preparing a liquid, controlled-release formulation comprising the steps of:

blending one or more controlled release microbeads comprising one or more active agents;

preparing a dense, thixotropic solution having a density that is at or about the density of the one or more microbeads comprising a thixotropic agent, water and one or more preservatives under conditions that reduce bubble formation; and

mixing the microbeads and the thixotropic solutions under conditions that minimize the introduction of bubbles in the liquid.

2. The method of claim 1, wherein the one or more microbeads comprise one or more of the following: an enteric coat, a resin coat, a lacquer coat, a pH-sensitive

coating, a biodegradable polymer matrix, a water soluble matrix, an ionic matrix, combinations and mixtures thereof.

3. The method of claim 1, wherein the one or more microbeads comprise one or more polymers selected from the group consisting of cellulose, ethylcellulose, methylcellulose, propylcellulose, methoxypropylcellulose, cellulose nitrate, poly(vinyl alcohol), poly(vinyl chloride), polystyrene, polyethylene, polypropylene, poly(ethylene-co-vinyl acetate), poly(hydroxybutyric acid), poly(hydroxyvalerianic acid-co-hydroxybutyric acid), poly(lactic acid), poly(glycolic acid), poly(lactic acid-co-glycolic acid), poly( $\epsilon$ -caprolactones), poly( $\epsilon$ -caprolactone-co-DL-lactic acid), poly(maleic anhydride), polyamides, gelatin, chitosan, collagen, poly(hydroxyalkyl)-L-glutamines, poly( $\gamma$ -ethyl-L-glutamate-co-glutamic acid), poly(L-leucine-co-L-aspartic acid), poly(proline-co-glutamic acid), poly(alkyl 2-cyanoacrylates), polyurethanes, poly(methyl methacrylate), poly(methyl methacrylate-co-methacrylic acid) and poly(methacrylate-co-hydroxypropyl methacrylate), polystyrene, polistirex, salts, combinations and mixtures thereof.

4. The method of claim 1, wherein reduced bubble formation comprises the step of using a diaphragm pump to combine the water and the thixotropic agent and one or more preservatives, colorants and flavorants.

5. The method of claim 1, wherein reduced bubble formation comprises the step of placing the recirculating tube below the surface of the liquid.

6. The method of claim 1, wherein reduced bubble formation comprises the step of adding liquids along the side of a vessel holding the liquid.

7. The method of claim 1, wherein reduced bubble formation comprises the step of sprinkling the beads onto the surface of the liquid.

8. The method of claim 1, wherein reduced bubble formation comprises the step of mixing the solution in the absence of one or more paddles that scrape the vessel.

9. The method of claim 1, wherein reduced bubble formation comprises the step of using a diaphragm pump to combine one or more of the water, the thixotropic agent, the one or more preservatives, colorants and flavorants.

10. The method of claim 1, wherein reduced bubble formation comprises the steps of:

placing the recirculating tube below the surface of the liquid;

adding liquids along the side of a vessel holding the liquid;

using a mixer that lacks scraping paddles.

11. The method of claim 1, wherein reduced bubble formation comprises the step of mixing the solution with a propeller mixer.

12. The method of claim 1, wherein reduced bubble formation comprises the step of mixing the solution with a propeller mixer at a speed that reduces cavitation.

13. The method of claim 1, wherein reduced bubble formation comprises the step of mixing the solution with a propeller that minimizes cavitation.

14. The method of claim 1, wherein a portion of the one or more beads comprises an immediate release profile and another portion comprise a delayed release profile.

15. The method of claim 1, wherein the thixotropic solution comprises a low-ionic strength.

16. The method of claim 1, wherein the formulation further comprises one or more flavorants, one or more

preservatives, one or more surfactants, one or more dissolved active agents, one or more buffers, one or more excipients, and mixtures and combinations thereof.

17. The method of claim 1, wherein the one or more active agents are pharmaceutical agents.

18. The method of claim 1, wherein the one or more active agents comprise vitamins, minerals, nutritional supplements, herbal extracts, gums, gels, oils, salts, mixtures and combinations thereof.

19. The method of claim 1, wherein the one or more active agents are pharmaceutical agents selected from protein, peptide, carbohydrate, polysaccharide, glycoprotein, lipid, hormone, growth factor, cytokine, interferon, receptor, antigen, allergen, antibody, antiviral, antifungal, antihelminthic, substrate, metabolite, cofactor, inhibitor, drug, pharmaceutical, nutrient, toxin, poison, explosive, pesticide, chemical warfare agent, biowarfare agent, biohazardous agent, infectious agent, prion, radioisotope, vitamin, heterocyclic aromatic compound, carcinogen, mutagen, narcotic, amphetamine, barbiturate, hallucinogen, combinations and mixtures thereof.

20. The method of claim 1, wherein the one or more active agents comprise a pharmaceutical agent, an enzyme, a cytokine, a growth promoting agent, an antibody, an antigen, a hormone, a vaccine, a cell, a live-attenuated pathogen, a heat-killed pathogen, a virus, a bacteria, a fungi, a peptide, a carbohydrate, a nucleic acid, a lipid, mixtures and combinations thereof.

21. The method of claim 1, wherein the one or more active agents is selected from wherein the one or more agents may be steroids, respiratory agents, sympathomimetics, local anesthetics, antimicrobial agents, antiviral agents, antifungal agents, antihelminthic agents, insecticides, antihypertensive agents, antihypertensive diuretics, cardiotonics, coronary vasodilators, vasoconstrictors,  $\beta$ -blockers, antiarrhythmic agents, calcium antagonists, anti-convulsants, agents for dizziness, tranquilizers, antipsychotics, muscle relaxants, drugs for Parkinson's disease, respiratory agents, hormones, non-steroidal hormones, antihormones, vitamins, antitumor agents, miotics, herb medicines, antimuscarinic, interferons, immunokines, cytokines, muscarinic cholinergic blocking agents, mydriatics, psychic energizers, humoral agents, antispasmodics, antidepressant drugs, anti-diabetics, anorectic drugs, anti-allergenic, decongestants, expectorants, antipyretics, antimigrane, anti-malarials, anti-ulcerative, peptides, anti-estrogen, anti-hormone agents, antiulcer agents, anesthetic agent, drugs having an action on the central nervous system, protein, peptide, carbohydrate, polysaccharide, glycoprotein, lipid, hormone, growth factor, cytokine, interferon, receptor, antigen, allergen, antibody, substrate, metabolite, cofactor, inhibitor, drug, pharmaceutical, nutrient, toxin, poison, explosive, pesticide, chemical warfare agent, biowarfare agent, biohazardous agent, infectious agent, prion, radioisotope, vitamin, heterocyclic aromatic compound, carcinogen, mutagen, narcotic, amphetamine, barbiturate, hallucinogen, and vaccines against virus, bacterium, fungi, helminth, cancer, *Salmonella*, *Streptococcus*, *Brucella*, *Legionella*, *E. coli*, *Giardia*, *Cryptosporidium*, *Rickettsia*, spore, mold, yeast, algae, amoebae, dinoflagellate, unicellular organism, pathogen, combinations and mixtures thereof.

22. The method of claim 1, wherein the one or more active comprises Pseudoephedrine, salts thereof or mixtures of salts thereof.

23. The method of claim 1, wherein the one or more active comprises an antihistamine.

24. The method of claim 1, wherein the one or more active comprises Chlorpheniramine, salts thereof or mixtures of salts thereof.

25. The method of claim 1, wherein the one or more active comprises Dextromethorphan, salts thereof or mixtures of salts thereof.

26. The method of claim 1, wherein the one or more active comprises Guaifenesin, salts thereof or mixtures of salts thereof.

27. The method of claim 1, wherein the one or more active comprises an analgesic.

28. The method of claim 1, wherein the one or more active comprises an antitussive.

29. The method of claim 1, wherein the one or more active comprises a narcotic.

30. The method of claim 1, wherein the one or more active are disposed on a polystyrene bead.

31. The method of claim 1, wherein the one or more active are disposed on a polypropylene bead.

32. The method of claim 1, wherein the one or more active are disposed on a polyethylene bead.

33. The method of claim 1, wherein the one or more active are disposed on a polacrilex bead.

34. The method of claim 1, wherein the one or more active are disposed on a PLA, PGA or PGLA bead.

35. A liquid formulation made by the method of claim 1.

36. The liquid formulation of claim 35, wherein the one or more active comprises pseudoephedrine, salts thereof or mixtures of salts thereof.

37. The liquid formulation of claim 35, wherein the one or more active comprises an antihistamine.

38. The liquid formulation of claim 35, wherein the one or more active comprises chlorpheniramine, salts thereof or mixtures of salts thereof.

39. The liquid formulation of claim 35, wherein the one or more active comprises dextromethorphan, salts thereof or mixtures of salts thereof.

40. The liquid formulation of claim 35, wherein the one or more active comprises guaifenesin, salts thereof or mixtures of salts thereof.

41. The liquid formulation of claim 35, wherein the one or more active comprises an analgesic.

42. The liquid formulation of claim 35, wherein the one or more active comprises an antitussive.

43. A method for preparing a liquid, controlled-release formulation comprising the step of blending one or more controlled release beads comprising one or more active agents with a dense, thixotropic solution having a density that is at or about the density of the one or more beads and a thixotropic agent, water and one or more preservatives under conditions that reduce bubble formation.

44. A liquid formulation made by the method of claim 43.

45. A method for preparing a liquid, controlled-release formulation comprising the step of blending a mixture comprising one or more controlled-release beads comprising one or more active agents, a thickening agent and a surfactant by mixing with a low cavitation propeller and recirculating the mixture under the surface of the mixture so as to minimize bubble formation.

46. A liquid formulation made by the method of claim 45.

47. The liquid formulation of claim 46, wherein the formulation comprises between about 15-45 mg phenyleph-

rine disposed in, on or about a resin, and between about 2-8 mg chlorpheneramine disposed in, on or about a resin per dose.

48. The liquid formulation of claim 47, further comprising between about 15-45 mg dextromethorphan disposed in, on or about a resin.

49. A method of preparing a liquid, controlled-release formulation comprising the step of blending a mixture comprising one or more active agents on or about a carrier a thickening agent under conditions that minimize the introduction of air.

50. The method of claim 49, wherein active agents and the carrier are encapsulated with a controlled release coating.

51. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of using a diaphragm pump to combine the active agents and the thickening agent.

52. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of placing the recirculating tube below the surface of the liquid.

53. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of adding liquids along the side of a vessel holding the liquid.

54. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of sprinkling the active agent disposed on the carrier onto the surface of the liquid.

55. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of mixing the solution in the absence of one or more paddles that scrape the vessel.

56. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of using a diaphragm pump to combine one or more of the water, the thixotropic agent, the one or more preservatives, colorants and flavorants.

57. The method of claim 49, wherein conditions that minimize the introduction of air comprise the steps of:

placing a recirculating tube below the surface of the liquid; and

adding liquids along the side of a vessel holding the liquid.

58. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of mixing the solution with a propeller mixer.

59. The method of claim 49, wherein conditions that minimize the introduction of air comprise the step of mixing the solution with a propeller mixer at a speed that reduces cavitation.

60. A method for preparing a liquid, controlled-release formulation comprising the step of blending a mixture comprising one or more controlled-release beads comprising one or more active agents on a carrier in a solution comprising a low ionic concentration and a thixotropic agent, under conditions that minimize the introduction of air bubbles.

\* \* \* \* \*



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30

(54) **DECONGESTANT / ANTIHISTAMINIC /  
EXPECTORANT COMPOSITIONS**

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(57) **ABSTRACT**  
Compositions consisting essentially of phenylephrine tan-  
nate, pyrilamine tannate, and guaifenesin which are effective  
when administered orally for the symptomatic relief of  
cough and nasal congestion associated with respiratory tract  
conditions such as the common cold, bronchial asthma,  
acute and chronic bronchitis are disclosed.

(21) Appl. No.: 10/665,220

# DECONGESTANT / ANTIHISTAMINIC / EXPECTORANT COMPOSITIONS

## FIELD OF INVENTION

[0001] The invention relates to a novel decongestant/antihistaminic/expectorant composition containing: phenylephrine tannate, pyrilamine tannate, and guaifenesin.

## BACKGROUND OF THE INVENTION

[0002] A considerable number of tannic acids occur in nature. Chemically, these acids are described as polymers of different hydroxybenzoic acids. Generally, when the term tannic acid is employed, as in the present case, the acid referred to is gallotannic acid: the internal ester of gallic acid also frequently referred to as tannin.

[0003] Tannic acid, a gallotannin, appears as an amorphous powder or glistening scales, or as spongy masses varying in color from yellowish-white to light brown. Tannic acid is very soluble in water, in alcohol, and in glycerol.

[0004] Tannic acids are usually obtained from glycosides which consist of several molecules of a tannic acid in combination with glucose.

[0005] Commercially available, tannic acid, also known as tannin, has a complex non-uniform chemistry, usually contains from about 5% to about 10% water by weight, has a molecular weight of about 1700, and is typically produced from Turkish or Chinese nutgall.

[0006] Phenylephrine, known chemically as (-)-1-m-hydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol, is a synthetic, optically active sympathomimetic amine. It is a white, odorless, non-hygroscopic, crystalline compound possessing a bitter taste. It has a melting point of 169 to 172° C. The frequently used hydrochloride salt has a melting point of 140 to 145° C. and is freely soluble in water and in alcohol. It is a directly acting sympathomimetic with strong  $\alpha$ -agonist and negligible  $\beta$ -agonist and central nervous activity. It is used as a nasal decongestant.

[0007] Pyrilamine is one of the oldest and most enduring antihistaminic drugs, known chemically as N[(4-methoxyphenyl)methyl]-N',N'-dimethyl-N-2-pyridinyl-1,2-ethanediamine. It is an oily liquid, and its preparation is disclosed in U.S. Pat. No. 2,502,151. Pyrilamine hydrochloride salt is very soluble in water and has a melting point of 143-143.5° C. The maleate salt is soluble in water and in alcohol, and it is slightly soluble in benzene and in ether; it has a melting point of 100-101° C.

[0008] Decongestant and antihistaminic compounds in the form of their free bases as well as their salts, e.g. hydrochloride, citrate, maleate, tannate, etc., are well known. Decongestants in the form of their tannate salts are very desirable because such salts are generally stable. Tannate salts are also desirable because they provide a prolonged release of the active ingredient free bases.

[0009] Tannate salts are typically prepared by reacting the free base, e.g. phenylephrine, pyrilamine etc. with tannic acid in the presence of a volatile solvent, usually isopropanol. Typically, in the conventional isopropanol route, the free base and the tannic acid will be present in the isopropanol at a concentration of about 20% based on the weight of the reaction mixture. The reaction mixture is stirred for

about one hour while maintaining the mixture at 60-70° C. The reaction mixture is cooled to room temperature and then filtered, washed with isopropanol, and then vacuum dried. Alternative routes to the tannate salts are described in U.S. Pat. No. 5,599,846 and U.S. Pat. No. 5,663,415, the disclosures of each of which are hereby incorporated by reference in their entireties.

[0010] Guaifenesin, known chemically as 3-(2-methoxyphenoxy)-1,2-propanediol, is a crystalline powder soluble in water and alcohol. It is readily absorbed from the gastrointestinal tract. It is indicated in the 23<sup>rd</sup> edition of USP Drug Information as an expectorant for the symptomatic relief of cough due to colds and minor upper respiratory infections.

## THE INVENTION

[0011] Research and development has shown that a unit dose for oral administration containing the novel combination of phenylephrine tannate, pyrilamine tannate, and guaifenesin can be produced. Phenylephrine tannate provides the nasal decongestion action. Guaifenesin has an expectorant action, which increases the output of respiratory tract fluid by reducing adhesiveness and surface tension. The increased flow of less viscous secretions promotes ciliary action and facilitates the removal of mucus. This changes a dry, unproductive cough to one that is more productive and less frequent. Pyrilamine tannate is an antihistaminic agent with a low incidence of sedative effects. It provides the desired relief from allergic rhinitis symptoms.

[0012] The compositions described herein are preferably designed to be taken twice a day with guaifenesin providing its expectorant action, phenylephrine tannate providing a prolonged nasal decongestant action, and pyrilamine tannate providing a prolonged antihistaminic action. The compositions of the present invention may be prepared for oral administration in the form of powders, capsules, elixirs, syrups, and in the preferred forms of tablets and suspensions.

[0013] Tablets containing the unique composition of phenylephrine tannate, pyrilamine tannate, and guaifenesin compositions of the present invention are prepared in a conventional manner by the addition of suitable pharmaceutical carriers including fillers, stabilizers, or antioxidants like ascorbic acid and sodium metabisulfite, diluents, colorants, lubricants and the like, as well as conventional and well known binding and disintegrating agents. In a preferred embodiment tablets would contain about 20 to 30 mg of phenylephrine tannate, about 40 to 80 mg pyrilamine tannate, and about 100 to 400 mg of guaifenesin per tablet. The tablet composition of the present invention containing dibasic calcium phosphate, microcrystalline cellulose, methylcellulose, polygalacturonic acid, talc, colorants, colloidal silicon dioxide and magnesium stearate, as described in Example 1 which follows, is illustrative of a tablet formulation of the present invention prepared by well known conventional tableting techniques such as those disclosed in U.S. Pat. Nos. 3,018,221; 2,798,024 and 2,757,124, the disclosures of each of which are hereby incorporated by reference in their entireties. In a particularly preferred embodiment the tablets contain about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 200 mg of guaifenesin. In another particularly preferred

31

32

embodiment the tablets contain about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 300 mg of guaifenesin.

EXAMPLE 1

[0014] Phenylephrine Tannate, Pyrilamine Tannate, and Guaifenesin Tablets

| Ingredient                                    | Milligrams per Tablet |
|-----------------------------------------------|-----------------------|
| Phenylephrine Tannate                         | 25.00                 |
| Pyrilamine Tannate                            | 60.00                 |
| Guaifenesin                                   | 200.00                |
| Calcium Phosphate Dibasic Dihydrate (DiTab ®) | 96.10                 |
| Microcrystalline Cellulose (ProSolv ®)        | 195.00                |
| Methylcellulose, 1500, USP                    | 39.00                 |
| Polygalacturonic Acid                         | 13.00                 |
| Talc, USP                                     | 12.00                 |
| FD&C Blue #1 Lake 29%                         | 5.00                  |
| FD&C Red #40 Lake 40%                         | 1.00                  |
| Colloidal Silicone Dioxide, NF                | 2.60                  |
| Magnesium Stearate, NF                        | 1.30                  |

[0015] Suspensions containing the unique composition of phenylephrine tannate, pyrilamine tannate and guaifenesin of the present invention are prepared in a conventional manner. In a preferred embodiment the suspensions of the present invention contain about 3 to 15 mg of phenylephrine tannate, about 25 to 35 mg pyrilamine tannate, and about 50 to 300 mg of guaifenesin, per 5 ml of suspension (one teaspoon). Additionally, the suspension formulations may contain colorants; natural and artificial flavors; glycerin; kaolin; pectin; magnesium aluminum silicate; methylparaben; benzoic acid; purified water; stabilizers like ascorbic acid and sodium metabisulfite; and sweeteners like saccharin, sucralose, and sucrose. Example 2, which follows, is illustrative of a suspension formulation of the present invention prepared by conventional well known compounding techniques. In a particularly preferred embodiment the suspensions contain about 5 mg of phenylephrine tannate, about 30 mg of pyrilamine tannate, and about 100 mg of guaifenesin, per 5 ml of suspension (one teaspoon). In another particularly preferred embodiment the suspensions contain about 5 mg of phenylephrine tannate, about 30 mg of pyrilamine tannate, and about 200 mg of guaifenesin, per 5 ml of suspension (one teaspoon).

EXAMPLE 2

[0016] Phenylephrine Tannate, Pyrilamine Tannate, and Guaifenesin Suspension

| Ingredient                      | Milligrams per 5 ml. |
|---------------------------------|----------------------|
| Phenylephrine tannate           | 5.00                 |
| Pyrilamine tannate              | 30.00                |
| Guaifenesin                     | 100.00               |
| Pectin, USP (Medium Viscosity)  | 57.00                |
| Kaolin, USP (Colloidal Powder)  | 680.00               |
| Magnesium Aluminum Silicate, NF | 35.00                |
| Benzoic Acid, USP               | 10.00                |
| Methylparaben, NF               | 2.50                 |
| Sucrose, NF                     | 1818.00              |
| Saccharin Sodium, USP           | 3.50                 |

-continued

| Ingredient                                 | Milligrams per 5 ml. |
|--------------------------------------------|----------------------|
| Glycerin, USP                              | 915.00               |
| Flavor Grape                               | 9.00                 |
| Dye Purple Shade R                         | 0.24                 |
| FD&C Blue #1 Dye                           | 0.48                 |
| Purified or Deionized Water, USP adjust to | 5 mL                 |

Sodium Hydroxide, Tannic Acid, Sodium Citrate, and Citric Acid may also be included in the formula for pH adjustment.

[0017] 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 warm-blooded animal that is preferably treated is a human.

[0018] 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.

[0019] In general, the named three active components are the only active components used in the composition.

[0020] It should be understood that the foregoing disclosure and examples will enable one of ordinary skill in the art to practice the best mode of the invention. However, it is anticipated that numerous variations will occur to those skilled in the art. 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 for the symptomatic relief of cough and nasal congestion associated with adverse respiratory tract conditions in warm-blooded animals in need of such treatment, said composition comprising pharmaceutically effective amounts of active ingredients, wherein said active ingredients consist of phenylephrine tannate, pyrilamine tannate, and guaifenesin.
2. The therapeutic composition of claim 1, in tablet form.
3. The therapeutic composition of claim 2, wherein each tablet contains about 20 to 30 mg of phenylephrine tannate, about 40 to 80 mg of pyrilamine tannate, and about 100 to 400 mg of guaifenesin.
4. The therapeutic composition of claim 2, wherein said tablet form contains about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 200 mg of guaifenesin.
5. The therapeutic composition of claim 2, wherein said tablet form contains about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 300 mg of guaifenesin.
6. The therapeutic composition of claim 1, in suspension form.
7. The therapeutic composition of claim 6, wherein said suspension form contains about 3 to 15 mg of phenylephrine tannate, about 25 to 35 mg of pyrilamine tannate, and about 50 to 300 mg of guaifenesin, per 5 ml of suspension.
8. The therapeutic composition of claim 6, wherein said suspension form contains about 5 mg of phenylephrine

tannate, about 30 mg of pyrilamine tannate, and about 100 mg of guaifenesin, per 5 ml of suspension.

9. The therapeutic composition of claim 6, wherein said suspension form contains about 5 mg of phenylephrine tannate, about 30 mg of pyrilamine tannate, and about 200 mg of guaifenesin, per 5 ml of suspension.

10. A method for symptomatically treating and relieving the distress of cough and nasal congestion associated with adverse respiratory tract conditions in warm-blooded animals, comprising orally administering to warm-blooded animals in need of such treatment the composition of claim 1.

11. The method of claim 10, wherein said composition is in tablet form.

12. The method of claim 11, wherein each tablet contains about 20 to 30 mg of phenylephrine tannate, about 40 to 80 mg of pyrilamine tannate, and about 100 to 400 mg of guaifenesin.

13. The method of claim 11, wherein said tablet form contains about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 200 mg of guaifenesin.

14. The method of claim 11, wherein said tablet form contains about 25 mg of phenylephrine tannate, about 60 mg of pyrilamine tannate, and about 300 mg of guaifenesin.

15. The method of claim 10, wherein said composition is in suspension form.

16. The method of claim 15, wherein said suspension form contains about 3 to 15 mg of phenylephrine tannate, about 25 to 35 mg of pyrilamine tannate, and about 50 to 300 mg of guaifenesin, per 5 ml of suspension.

17. The method of claim 15, wherein said suspension contains about 5 mg of phenylephrine tannate, about 30 mg of pyrilamine tannate, and about 100 mg of guaifenesin, per 5 ml of suspension.

18. The method of claim 15, wherein said suspension contains about 5 mg of phenylephrine tannate, about 30 mg of pyrilamine tannate, and about 200 mg of guaifenesin, per 5 ml of suspension.

19. The method of claim 10, wherein said oral administration is a twice a day administration.

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(54) Title: NOVEL PHARMACEUTICAL COMPOSITION AND ITS USE IN A METHOD FOR TREATMENT OF PATIENTS  
WITH UPPER RESPIRATORY MUCOSAL CONGESTION

(57) Abstract: A PHARMACEUTICAL COMPOSITION ABSTRACT The present invention relates to a pharmaceutical com-  
position including loratadine, its use in the treatment of upper respiratory mucosal congestion and a method of administration of  
the composition. Particularly, though not exclusively, the invention relates to a pharmaceutical composition including loratadine  
in an amount suitable for administration a maximum of 4 times a day, and a second active that is a hydroxyl-a-[(methylamino)  
methyl]-benzenemethanol, such 3-hydroxyl-a-[(methylamino) methyl]-benzenemethanol (phenylephrine), or salt thereof.

WO 2006/135254 A1

25

## 5 CLAIMS

1. A method of treating upper respiratory mucosal congestion by administering to a patient in need thereof a pharmaceutical composition including about 2.5 mg loratadine, or a corresponding amount in the form of a suitable salt thereof, four times a day.
- 10 2. A method according to claim 1 where the composition is administered qid.
3. A method according to claim 1 or 2 where the pharmaceutical composition further includes a hydroxy- $\alpha$ -[(methylamino) methyl]-benzenemethanol, or a suitable salt thereof.
- 15 4. A method according to any one of claims 1 to 3 where the pharmaceutical composition further includes 3-hydroxy- $\alpha$ -[(methylamino) methyl]-benzenemethanol (phenylephrine), or a suitable salt thereof.
- 20 5. A method according to any one of claims 1 to 4 where the pharmaceutical composition includes about 8 to 10 mg of phenylephrine free base or a corresponding amount in the form of a suitable salt thereof.
- 25 6. A method according to claim 5 where the phenylephrine salt is the hydrochloride salt.
7. A method according to any one of claims 1 to 6 where the pharmaceutical composition is in a solid dosage form.
- 30 8. A method of treating upper respiratory mucosal congestion using a pharmaceutical composition which includes about 8 to 10 mg phenylephrine free base, or a corresponding amount in the form of a suitable salt thereof, and about 2.5 mg loratadine, or a corresponding amount in the form of suitable salt thereof, wherein the patient is administered the composition four times a day.
- 35 9. A method according to claim 8 where the composition is administered qid.
10. A method according to claim 9 where the phenylephrine salt is the hydrochloride salt.
- 40 11. A method according to claim 10 where the composition includes 10 to 12.2 mg of the

5 hydrochloride salt.

12. A method according to any one of claims 8 to 11 where the method includes the  
administration of a pill, capsule or tablet containing about 8 to 10 mg phenylephrine and  
about 2.5 mg loratadine, or corresponding amounts in the form of suitable salts thereof,  
10 4 times a day.

13. The use of about 8 to 10 mg phenylephrine and about 2.5 mg loratadine, or  
corresponding amounts in the form of suitable salts thereof, in the manufacture of a  
medicament for administration to a patient 4 times a day for the treatment of upper  
15 respiratory mucosal congestion.

14. The use according to claim 13 where the medicament is manufactured for  
administration qid.

20 15. The use according to claim 14 where the phenylephrine is in a salt form.

16. The use according to claim 15 where the phenylephrine salt is the hydrochloride salt.

17. A pharmaceutical composition for the treatment of upper respiratory mucosal  
25 congestion containing phenylephrine, or a suitable salt thereof, and loratadine, or a  
suitable salt thereof, wherein the phenylephrine is present in an amount of about 8 to 10  
mg and the loratadine is present in an amount of about 2.5 mg.

18. A pharmaceutical composition according to claim 17 where the phenylephrine is in the  
30 form of the hydrochloride salt.

19. A pharmaceutical composition according to claim 17 or 18 where the pharmaceutical  
composition includes pharmaceutically acceptable non-active excipients and/or carriers.

35 20. A pharmaceutical composition according to any one of claims 17 to 19 where the  
pharmaceutical composition is a pill, capsule or tablet.

21. A pharmaceutical composition according to any one of claims 17 to 20 where  
pharmaceutical composition is 10.00 mg phenylephrine hydrochloride, 2.50 mg  
40 loratadine, 180.40 mg lactose, 140.00 mg maize starch, 10.365 mg pregelatinised

37

- 5 starch, 0.20 mg lake of quinoline yellow, 0.40 mg sodium metabisulphite, 0.14 mg  
disodium EDTA, 3.00 mg talc, and 3.00 mg magnesium stearate
22. A pack including pills, tablets or capsules containing a pharmaceutical composition  
including phenylephrine and loratadine, wherein the phenylephrine is present in an  
10 amount of about 10 mg and the loratadine is present in an amount of about 2.5 mg and  
wherein the pack includes instructions to administer the composition a maximum of 4  
times a day.
23. A pack according to claim 22 where the phenylephrine is in a salt form.
- 15 24. A pack according to claim 23 where the phenylephrine is in the form of the  
hydrochloride salt.
25. A pack according to any one of claims 22 to 24 where the 4 times a day administration  
20 is qid.
26. A pack according to claim 25 where the pack is a blister pack.
27. A container containing a syrup including loratadine and phenylephrine, or suitable salts  
25 thereof, at concentrations suitable for administration of about 2.5 mg loratadine and  
about 8 to 10 mg phenylephrine per unit dose, the container including instructions to  
administer an amount of syrup that will deliver about 2.5 mg loratadine and about 8 to  
10 mg phenylephrine per unit dose 4 times a day.
- 30 28. A container according to claim 27 where the phenylephrine is in a salt form.
29. A container according to claim 28 where the phenylephrine is in the form of the  
hydrochloride salt.
- 35 30. The use of about 2.5 mg loratadine in the manufacture of a medicament for the  
treatment of upper respiratory/mucosal congestion, wherein preferably the medicament  
is for administration a maximum of four times a day.
- 40 31. The use according to claim 30 where the use includes the use of 8 to 10 mg of  
phenylephrine, or a corresponding amount in the form of suitable salt thereof, in the

5 manufacture of the medicament.

32. A pharmaceutical composition for use in the treatment of upper respiratory mucosal  
congestion, the composition including 2.5 mg of loratadine together with  
pharmaceutically acceptable carriers and/or excipients.

10