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(54) **Title**: FORMULATION FOR SOFT ANTICHOLINERGIC ANALOGS

(57) **Abstract**: Topical formulations comprising soft glycopyrrolates are useful for treating excessive sweating conditions in subjects, such as humans suffering from hyperhidrosis. Preferably, at least one soft anticholinergic agent is provided in an effective amount or concentration in an anhydrous formulation that can inhibit excessive perspiration resulting from a condition such as hyperhidrosis.

FORMULATION FOR SOFT ANTICHOLINERGIC ANALOGS

BACKGROUND

[0001] Various anticholinergic compounds and formulations for those compounds have been previously described. Muscarinic receptor antagonists are frequently used therapeutic agents that inhibit the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells as well as in peripheral ganglia and in the central nervous system (CNS). However, their side effects, which can include dry mouth, photophobia, blurred vision, urinary hesitancy and retention, drowsiness, dizziness, restlessness, irritability, disorientation, hallucinations, tachycardia and cardiac arrhythmias, nausea, constipation, and severe allergic reactions, often limit their clinical use. Topical administration of anticholinergic agents to targeted areas, such as sweat glands, where the localized blockage of muscarinic receptors will be of clinical benefit, would be a desirable therapeutic strategy. However, currently used topical anticholinergics can exhibit unwanted systemic side effects which can limit the dosage that can be safely administered.

[0002] Glycopyrrolate is among the quaternary ammonium anticholinergics which have reduced CNS-related side effects as they cannot cross the blood-brain barrier; however, because glycopyrrolate is eliminated mainly as unchanged drug or active metabolite, its topical administration is often associated with common undesirable anticholinergic systemic side effects. To increase the therapeutic index of anticholinergics, the soft drug approach has been applied in a number of different designs starting from various lead compounds, but there is a need for yet other new soft anticholinergics with clinically meaningful biological activity. These novel muscarinic antagonists, just as all other soft drugs, are designed to elicit their intended pharmacological effect at the site of application, but to be quickly metabolized into their designed-in, inactive metabolite upon entering the systemic circulation and rapidly eliminated from the body, resulting in reduced systemic side effects and an increased therapeutic index.

[0003] Soft anticholinergic zwitterions have been described in US Patent Publication No. 2012/0141401 (now USP 8,568,699), and its related patents,

USP 8,071,693; 7,538,219; and 7,417,147. Soft anticholinergic esters have been described in US Patent Publication No. 2012/0177590 (now USP 8,628,759) and its related patents USP 8,147,809; 7,576,210; and 7,399,861. Although these published applications and patents identified the potential for the zwitterion or ester forms of anticholinergics to be used for treating hyperhidrosis, the fact that activity and duration of action against hyperhidrosis are unexpectedly high herein, based on a comparison to published mydriasis data, was not known or previously described.

[0004] Each of the US Patent Publication Nos. 2012/0141401 (USP 8,568,699) and 2012/0177590 (USP 8,628,759), and their related patents USP 8,147,809; 8,071,693; 7,576,210; 7,538,219; 7,417,147; and 7,399,861 are hereby incorporated by reference in their entireties.

[0005] Hyperhidrosis is an idiopathic pathological condition characterized by excessive, uncontrollable sweating beyond that required to cool the body. A hyperfunction of the sweat glands and a disturbance of their cholinergic stimulation have been described as possible causes of this condition. It is known to affect approximately 3% of the population. Hyperhidrosis not only may result in intense social embarrassment, but also may even interfere with a person's occupation.

[0006] Hyperhidrosis most often involves one or several areas, especially the hands, axillae, feet or face, although it can even involve the whole body. Axillary hyperhidrosis is the most common form, followed by palmar hyperhidrosis. Antiperspirants alone are generally not effective in treating this excessive perspiration. Oral medications are occasionally beneficial, but may have side effects. Other therapeutic alternatives include surgical procedure such as endoscopic thoracic sympathectomy. Although the surgery affords permanent benefit in some 40% to 90% of affected individuals, it is invasive, requires general anesthesia and is not without potential side effects. As many as 50% of persons who have undergone thoracic sympathectomy develop compensatory and annoying sweating of the trunk or thighs. Botulinum A neurotoxin (BOTOX), which blocks the action on sweat glands of acetylcholine that is released by the autonomic nerves, has proven effective in hyperhidrosis. Minute amounts of

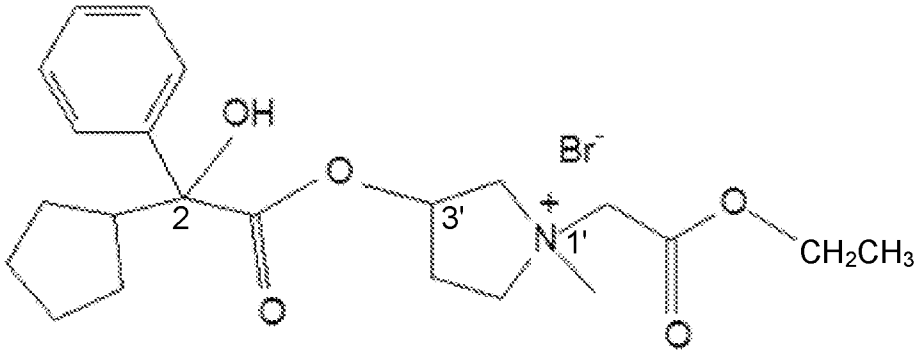
BOTOX injected into the palms or axillae of affected individuals result in statistically significant benefit. The effect lasts for several months but requires repeated injections and is often not a suitable alternative for pediatric patients. Iontophoresis has limited efficacy and cannot be used for axillary areas.

[0007] A non-invasive, convenient and effective treatment having high sweat reduction activity, long duration and with fewer side effects would be a welcome alternative for treating hyperhidrosis. An improved method of treating hyperhidrosis has recently been described in copending United States Patent Application No. 14/213,242, filed March 14, 2014 (inventors BODOR and ANGULO), incorporated by reference herein in its entirety.

[0008] Topical formulations comprising soft anticholinergic analogs, such as soft ester analogs of glycopyrrolate, have been previously proposed for use in treating hyperhidrosis; however, stable, pharmaceutically acceptable formulations of such esters which can meet regulatory requirements or provide commercially viable shelf-life for such products have been elusive. Thus, what is needed in the art is a stable, pharmaceutically acceptable, and commercially viable formulation for a topically administered composition comprising a soft anticholinergic analog.

SUMMARY

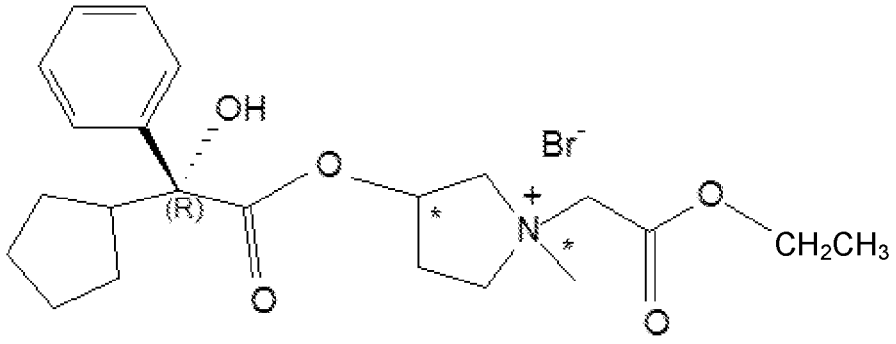
[0009] The subject application concerns topical formulations for treating excessive sweating conditions in subjects, such as humans suffering from hyperhidrosis. A composition herein comprises at least one soft anticholinergic agent, which is a soft ester analog of glycopyrrolate, in an effective amount or concentration that can inhibit excessive perspiration resulting from a condition such as hyperhidrosis. One embodiment is a topical composition comprising: (a) at least one compound having the formula (1):



(1)

said compound having the R, S, or RS stereoisomeric configuration at the 2 position and 1' and 3' positions, or being a mixture thereof, and (b) anhydrous ethanol, provided that said topical composition is anhydrous.

[0010] One preferred embodiment of a topical composition comprises: (a) at least one compound having the following stereospecific formula (2):



(2)

said compound having the R stereoisomeric configuration at the 2 position and having the R, S, or RS stereoisomeric configuration at the 1' and 3' positions (designated by asterisks), or being a mixture thereof, and (b) anhydrous ethanol, provided that said topical composition is anhydrous.

[0011] Another embodiment provides a topical pharmaceutical composition comprising (a) one or more compounds of the foregoing formula (2), (b) anhydrous ethanol and (c) one or more pharmaceutically acceptable carriers or excipients, provided that said topical composition is anhydrous. Yet another

embodiment provides a topical composition comprising (a) and (b) above; (c) optionally, at least one gelling or viscosity controlling ingredient; and (d) optionally at least one additional carrier or excipient; provided that said topical composition is anhydrous and comprises from about 1% to about 25% of the compound of formula (2), said composition having greater storage stability compared to a composition comprising an aqueous solvent or aqueous buffer.

[0012] Methods of treating or inhibiting or ameliorating excessive sweating, including conditions such as hyperhidrosis, using a topical composition as described herein, are also included. The methods of copending United States Patent Application No. 14/213, 242, filed March 14, 2014, are of particular interest and advantage when carried out by administering a topical formulation comprising an ethyl ester of formula (2) above and anhydrous ethanol, provided that said topical formulation is anhydrous.

[0013] A composition of the subject application can be formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension, aerosol, patch, wipes or emulsion, or the like, and is formulated for topical application for the treatment, inhibition or amelioration of hyperhidrosis. More preferably, a composition as defined above is formulated as an anhydrous ethanol topical gel, which can provide certain advantages, including superior stability or increased shelf-life for the composition, as well as the benefit of minimizing or eliminating the need for a separate preservative in the composition.

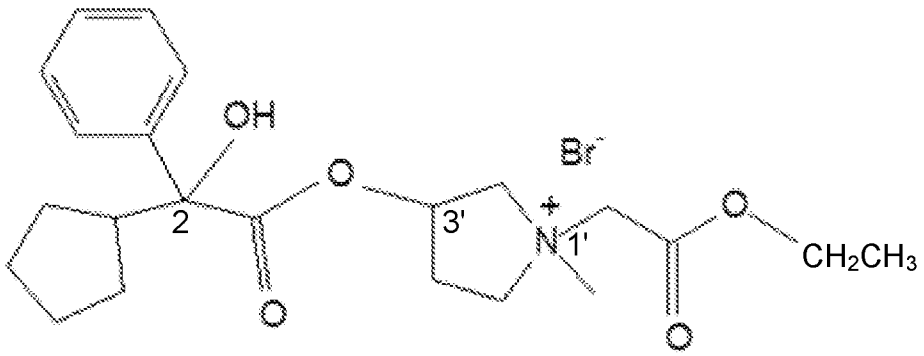
[0014] Additional advantages for a topical anhydrous ethanol gel composition herein include properties such as fast drying time, limited residue on the skin or clothing, and facilitation of a capability to be dispensed in metered amounts of product per application. A particular formulation can further mask stickiness properties that some soft anticholinergics, such as certain compounds described herein, may have.

[0015] One formulation comprises about 0.1% to about 30% of the compound in 70-99.9% of the non-aqueous solvent, ethanol. The formulation can further include one or more additional carriers or excipients, including a gelling or viscosity controlling excipient, which itself is anhydrous, that is non-aqueous.

[0016] The compounds of formulas (1) and (2) are ethyl esters. As esters, these compounds are subject to transesterification, which is the process of exchanging the alkyl group of the ester with the alkyl group of an alcohol/alkanol. This reaction is catalyzed by acid or base or even enzymatically. Unfortunately, transesterification can lead to an interchange of a significant amount of the drug's ester group for a less desirable, less biologically acceptable group. For example, use of anhydrous methanol as solvent for the ethyl ester leads to unacceptable formation of a significant amount of methyl ester mixed with ethyl ester. Use of anhydrous ethanol, on the other hand, leads only to formation of ethyl ester as a product of transesterification. Further, by using anhydrous ethanol, and by making certain that the composition itself is anhydrous, it is possible to avoid hydrolysis of the active ingredient's ethyl ester group.

[0017] There is thus provided in one aspect herein a method for treating, inhibiting or ameliorating hyperhidrosis in a subject which comprises:

(A) providing a topical composition comprising: (a) from about 1% to about 25% of a compound having the formula (1):



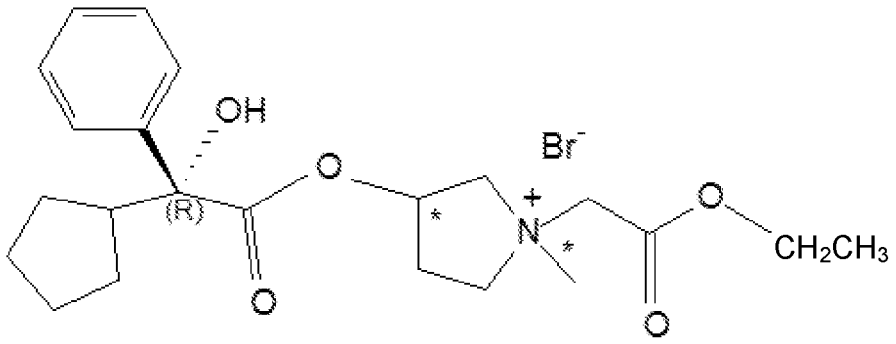
(1)

said compound having the R, S or RS stereoisomeric configuration at the 2 position and 1' and 3' positions, or being a mixture thereof; (b) anhydrous ethanol; (c) optionally, at least one gelling or viscosity-controlling ingredient; and (d) optionally, at least one additional carrier or excipient; provided that said topical composition is anhydrous; and

(B) topically administering the composition to a subject suffering from excessive sweating, such as hyperhidrosis.

[0018] There is further provided in another aspect herein a method for treating, inhibiting or ameliorating hyperhidrosis in a subject which comprises:

(A) providing a topical composition comprising: (a) from about 1% to about 25% of a compound having the formula (2):



(2)

said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS stereoisomeric configuration at the 1' and 3' positions, or being a mixture thereof, (b) anhydrous ethanol; (c) optionally, at least one gelling or viscosity-controlling ingredient; and (d) optionally, at least one additional carrier or excipient; provided that said topical composition is anhydrous; and

(B) topically administering the composition to a subject suffering from excessive sweating, such as hyperhidrosis.

[0019] Advantageously, the method can provide reduction of excessive sweating for up to about 48 hours. Moreover, surprisingly, topical administration of the composition can unexpectedly provide a reduction in sweat production, as compared to baseline conditions, for at least about six (6) hours by an amount which is substantially equivalent to the reduction of sweat production resulting from administration of a composition comprising an equivalent concentration of glycopyrrolate, also compared to baseline conditions. Soft ester analogs of glycopyrrolate were previously believed to require up to 5-10 times the concentration of glycopyrrolate to provide substantially equivalent activity.

[0020] A preferred method of treating hyperhidrosis in a subject in need of same or for treating, inhibiting or ameliorating excessive sweating therein,

comprises administering the instant composition in accord with the methods of United States Patent Application No. 14/213,242. In accord therewith, the composition as defined herein comprising a compound of formula (2) above is administered to skin of a subject suffering from hyperhidrosis, before bedtime, such that, compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours; and such that sweat production is reduced by an amount substantially equivalent to an amount that sweat production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising the same concentration of glycopyrrolate, and with an improved safety profile compared to topical glycopyrrolate. In particular, at 5% drug concentration, no systemic anticholinergic side effects were observed for the soft ester in testing described in the '242 application. Also, no systemic anticholinergic side effects were observed in clinical studies at 5% or 10% as described hereinbelow.

[0021] The present method is preferably carried out by topically administering the composition to a human subject, to the skin of the subject at a superficial anatomic area in need of sweat reduction. Preferably, the anatomic area for application or administration of the composition is selected from a hand palm area, a foot plantar area, a groin area, an axilla area, and a facial area of the subject.

[0022] The subject method can reduce sweat production by about 25% to about 99%, preferably by about 30% to about 90%, more preferably by at least 50%, which can be a clinically significant endpoint for an indication for treating hyperhidrosis.

[0023] As previously described, the method can employ the composition formulated as a solid or semisolid, powder, gel, cream, lotion, foam, solution, suspension, aerosol, patch, wipes or emulsion, or the like and can comprise from about 0.1% to about 30% concentration of the compound, preferably from about 1% to about 25% concentration of the compound, more preferably about 1% to about 20% concentration of the compound, and most preferably about 2% to about 10% concentration of the compound of formula (1) above, preferably of formula (2).

[0024] A method in accordance with the present description can comprise topically administering to a subject as needed (prn), a composition as defined herein. Administrations are preferably at least one time per week, more preferably at least three to four times per week (e.g., every other day), or can be administered more frequently such as once daily (QD), for example, before bedtime (typically, at night) or after the subject awakens (typically in the morning, and preferably after a bath or shower); twice daily (BID), e.g., every 10-12 hours; thrice daily (TID), e.g., every 6-9 hours; four times daily (QID), e.g., every 3-5 hours; with a preferred upper limit of about 6-8 doses or applications per day.

[0025] Surprisingly, the subject method, after single or multiple applications, can reduce sweat production for a period of from about 4 hours to about 24 hours, and preferably for a period of from about 6 hours to about 12 hours.

[0026] A preferred composition herein comprises:

one or more soft glycopyrrolate analogs of formula (1) or (2) as active ingredient; and
anhydrous ethanol (as non-aqueous solvent for the active ingredient);
provided that said composition is anhydrous.

[0027] As described herein, the subject formulation is preferably a gel. Accordingly a more preferred composition comprises:

one or more soft glycopyrrolate analogs of formula (1) or (2) as active ingredient;
anhydrous ethanol (as non-aqueous, pharmaceutically acceptable solvent for the active ingredient); and
one or more gelling or viscosity-controlling agents,
provided that said formulation is anhydrous.

[0028] The soft glycopyrrolate analog of formula (1) or (2) is a soft anticholinergic ethyl ester. The use of the matching non-aqueous solvent ethanol avoids mixtures of esters which can result from transesterification when an alcohol such as methanol is used as solvent for the ethyl ester. Moreover, the absence of water results in much greater storage stability.

[0029] Advantageously, anhydrous ethanol can provide for a self-preserving composition, which can provide microbial stability to the composition without added preservatives.

[0030] Anhydrous ethanol can also inhibit bacterial growth and provide deodorant properties to the composition.

[0031] A further advantage of a composition according to the present description is provided by the fact that the non-aqueous solvent, anhydrous ethanol, is volatile, especially at localized temperatures generated by body heat so that, when it is topically applied to a subject, it provides a rapidly drying composition.

[0032] A preferred gelling or viscosity controlling agent can be a modified cellulose, e.g., hydroxypropyl cellulose (HPC), such as the commercially available KLUCEL™, which can preferably provide viscosity of the composition of from about 100 to about 10,000 cps.

DETAILED DESCRIPTION

[0033] Throughout this specification, the following definitions, general statements and illustrations are applicable.

[0034] The patents, published applications and scientific literature referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entireties to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

[0035] As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the

context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a composition, the term "comprising" means that the composition includes at least the recited features or components, but may also include additional features or components.

[0036] The terms "consists essentially of" or "consisting essentially of" have a partially closed meaning, that is, they do not permit inclusion of steps or features or components which would substantially change the essential characteristics of a process or composition; for example, steps or features or components which would significantly interfere with the desired properties of the compounds or compositions described herein, i.e., the process or composition is limited to the specified steps or materials and those which do not materially affect the basic and novel characteristics of the process or composition.

[0037] The terms "consists of" and "consists" are closed terminology and allow only for the inclusion of the recited steps or features or components.

[0038] As used herein, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

[0039] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

[0040] As used herein, the recitation of a numerical range for a variable is intended to convey that the variable can be equal to any values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2,

can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0, 0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

[0041] In the specification and claims, the singular forms include plural referents unless the context clearly dictates otherwise. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

[0042] Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present description pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th Ed., McGraw Hill Companies Inc., New York (2001).

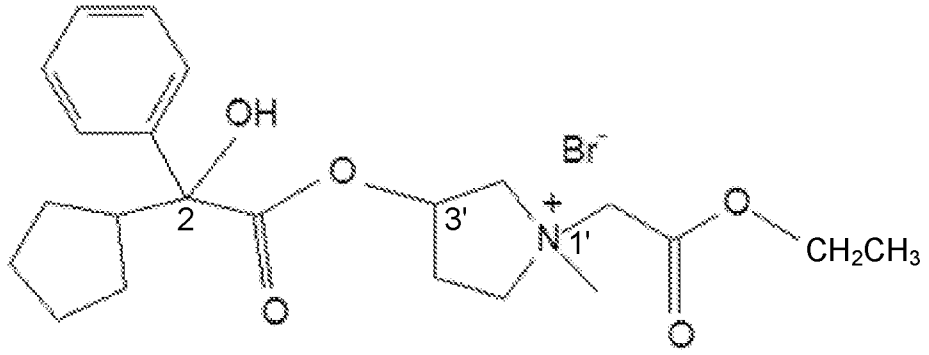
[0043] As used herein, "treating" means reducing, hindering or inhibiting the development of, controlling, inhibiting, alleviating and/or reversing the symptoms in the individual to which a composition comprising a compound of formula (1) or (2) has been administered, as compared to the symptoms of an individual not being administered the compound or composition. A practitioner will appreciate that the combinations, compositions, dosage forms and methods described herein are to be used in concomitance with continuous clinical evaluations by a skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

[0044] The subject compounds or compositions can also prevent the symptoms, or prevent the occurrence of the symptoms, in the individual to which a composition comprising a compound of formula (1) or (2) above has been administered, as compared to the symptoms of an individual not being administered the compound or composition. This is not a prevention of hyperhidrosis or excessive sweating in the absolute sense, it does not prevent the medical condition, as it does not even address the condition's cause; rather it

inhibits the manifestation of the condition for the period of time (hours) for which the administered dose is effective.

[0045] The methods described herein are intended for use with any subject/patient that may experience their benefits. Thus, the terms "subjects" as well as "patients," "individuals" and "warm-blooded animals" include humans as well as non-human subjects, such as animals that may experience excessive sweating.

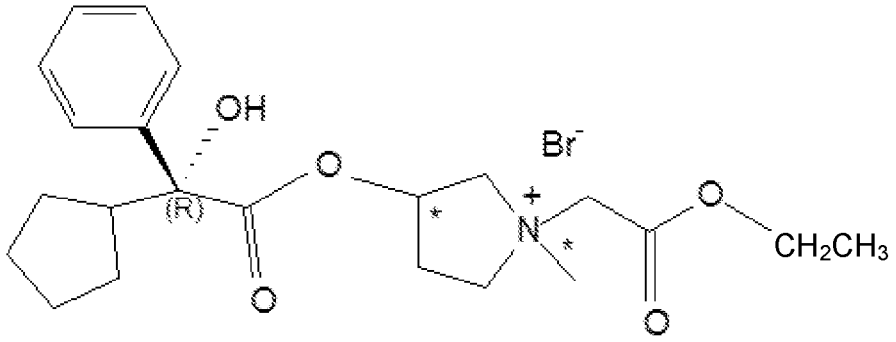
[0046] Compounds useful in a composition herein include those of the formula (1):



(1)

The compound has the R, S, or RS stereoisomeric configuration at the 2 position and at the 1' and 3' positions, or is a mixture thereof.

[0047] Compounds having the R configuration with respect to chiral center 2 are of particular interest for use in the instant compositions. For example, a preferred compound useful in a composition herein has the stereospecific formula (2):



(2)

said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS stereoisomeric configuration at the 1' and 3' positions (designated by asterisks), or being a mixture thereof.

[0048] The following compounds are of particular interest for use in a composition of the present description:

(i) 3-(2-cyclopentylphenylhydroxyacetoxy)-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(ii) 3-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(iii) 3'(R)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(iv) 3'(S)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(v) 1'(R)-3'(S)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(vi) 1'(S)-3'(S)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide;
(vii) 1'(R)-3'(R)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide; and
(viii) 1'(S)-3'(R)-[2(R)-cyclopentylphenylhydroxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethylpyrrolidinium bromide.

[0049] It is noted that the above compounds are identical to those originally disclosed with a correct, but different, naming scheme, in US Provisional Patent Application No. 61/952,505 filed March 13, 2014. The compounds were previously and respectively disclosed as:

(i) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(ii) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(iii) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(iv) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(v) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(vi) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;
(vii) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide; and
(viii) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

[0050] The above compounds (i)-(viii) can be used alone or two or more of the above compounds can be used in combination in a single composition. Various methods of making the instant compounds are described in the art.

[0051] An anticholinergically effective amount of such an agent inhibits the effect of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites. Subjects in need of a method of eliciting an anticholinergic response are those suffering from conditions which respond to treatment with an anticholinergic agent, including subjects suffering from excessive sweating or hyperhidrosis.

[0052] The compound of formula (1) or (2) is typically administered in the form of a pharmaceutical composition comprising an anticholinergically effective

amount of the compound, anhydrous ethanol and a non-toxic pharmaceutically acceptable carrier or excipient, provided that the composition itself is also anhydrous. Pharmaceutically acceptable carriers, or diluents, are well-known in the art. The carriers may be any inert material, organic or inorganic, powders, liquid, or gases suitable for administration, such as: alcohol such as hexylene glycol, gelatin, gum arabic, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like, provided that the ingredients are anhydrous.

[0053] It has been discovered that the instant formulations, having advantageous properties, result when no water or aqueous carrier is added to the formulation. Thus, a composition herein is an anhydrous formulation. By the term "anhydrous", is meant the ordinary scientific meaning of the word, that is, that no water or aqueous excipient is added to the formulation.

[0054] Such compositions may also contain conventional additives such as solvents, stabilizers, wetting agents, emulsifiers, buffers, binders, disintegrants, fragrances, lubricants, glidants, antiadherents, propellants, and the like, just so long as the additives and compositions are anhydrous, that is, free of water to the extent required to avoid significant negative impact on the storage stability of the composition (by hydrolysis of the ester drug).

[0055] The active ingredient is dissolved in anhydrous ethanol as a solvent, in which the compound is soluble or at least slightly soluble. It is preferred that the apparent pH of the composition be acidic (i.e. apparent pH <7).

[0056] The composition herein can be formulated as a solid, semi-solid, or liquid, such as in the form of powders, solutions, lotions, creams, gels, semi-solid sticks, foams, sprays, aerosols, solutions, suspensions or emulsions, patches, wipes and the like, and is formulated for topical administration. By way of illustration only, for treating hyperhidrosis, a topical preparation formulated as an anhydrous antiperspirant stick, gel, spray, cream, solution, foam, emulsion or the like can be preferred.

[0057] In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the

other ingredients. The active compound can be milled to a particle size of less than 200 mesh.

[0058] Some examples of suitable topical carriers or excipients, to be added to the compound of formula (1) or (2) in absolute ethanol, include alcohols such as hexylene glycol and propylene glycol, dimethicone, e.g. dimethicone 350 cSt, dimethicone copolyol, Dimethiconol Blend 20, dimethiconol 20 cSt, cyclomethicone, e.g. cyclomethicone 5-NF, PGE, allantoin, glycerin, vitamin A and E oils, mineral oil, PPG2, myristyl propionate, isopropyl myristate, C_{12-15} alkyl lactate, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, and methyl cellulose, and mixtures thereof. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; and preserving agents such as methyl- and propylhydroxy-benzoates. The compositions can be formulated so as to provide quick, modified, sustained or delayed release or activity of the active ingredient after administration and/or application to the subject by employing procedures known in the art. The use of a separate preserving agent can be avoided by judicious selection of other ingredients, as discussed in more detail below.

[0059] The composition may additionally contain one or more optional additives such as colorants, perfumes, or the like. In practice, each of these optional additives should be compatible with the active compound. Compatible additives are those that do not prevent the use of or result in the degradation of the compound in the manner described herein.

[0060] For purposes of illustration, liquid formulation dosages are expressed based on a percent solution (g/100 ml) or percent concentration (w/v) unless otherwise stated. For solid formulation dosages, the percent concentration can be expressed as mg/mg, or w/w concentrations unless otherwise stated. A person of ordinary skill in the art would readily understand the percent concentration in the context of the type of formulation described.

[0061] In general, a therapeutically effective or anticholinergically effective amount of a compound of formula (1) or (2) herein is from an about 1% solution (10 mg/ml) to an about 30% solution (300 mg/ml). Preferably, the topical composition dose is from about 1% concentration to about 25% concentration, or more preferably from about 1% concentration to about 20% concentration, especially from 2% to 10%, and is most preferred using a dose application volume of approximately 0.5 to about 1.0 ml or 2.0 ml of a composition comprising about 3% to about 6%, e.g., about 5%, of the compound per treated area. The exact dosage of a compound in the instant composition can vary depending on its potency, the mode of administration, the application area, the age and weight of the subject and the severity of the condition to be treated. The daily dosage may be administered singly or multiply one to four times daily or more.

[0062] Administration prior to bedtime (in accord with a preferred method of treating hyperhidrosis herein) does not imply at night or a particular hour or time of day; rather, before or prior to bedtime means that the composition is preferably administered, generally within about 1-2 hours prior to a person's normal rest or sleep (typically 4 to 10-hour) period. A before bedtime administration time can provide a preferred response or activity of the active compounds of formulas (1) and (2), in accord with the method of prior copending United States Patent Application No. 14/213,242.

[0063] Administration of a composition as described herein can provide a substantially identical or similar clinical (sweat reduction) response in a subject, as compared to administration of a composition containing the same concentration of glycopyrrolate. Thus, the results of this discovery are surprising in view of previously published mydriatic studies which suggested that the subject compounds in a composition were required to be present in concentration from 5 times to 10 times the concentration of a glycopyrrolate composition exhibiting a similar or substantially identical clinical response.

[0064] In addition, administration of a second dose within about 6-10 hours following the initial dose can also be a preferred method of administration or dosing regimen.

[0065] The topical composition for treating hyperhidrosis can be a liquid solution, semi-solid, or solid. Solutions are prepared in the usual way, e.g. with the addition of excipients as well as the anhydrous ethanol solvent and can include preservatives such as p-hydroxybenzoates, or stabilizers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, and other organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into vials, ampules, bottles, tubes, syringes, or the like.

[0066] However, the anhydrous composition can have the advantage of minimizing, or eliminating, the need for an additional preservative to be included in the formulation. Thus, one preferred embodiment of a composition is a substantially "preservative-free" composition. By "preservative-free" is meant that the composition, although containing ethanol and even possibly another organic solvent which may provide some preserving properties, has no additional preservative component, added specifically for its preservative property to the composition.

[0067] Additional carriers or excipients may be used in a composition herein, including, for example, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. hexylene glycol or glycerol), carriers such as natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulfite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

[0068] Compositions herein can be formulated using known techniques, and are generally accepted as being formulated with commonly known excipients, including preservatives if needed. For example, the patent literature describes that soft glycopyrrolate compounds are at least partially water-soluble. Accordingly, soft glycopyrrolates compounds, such as soft anticholinergic analogs (e.g., esters) were earlier described as capable of being formulated in buffer (aqueous or water-based) solutions. However, aqueous components

added to the formulation increase the hydrolysis products found in the composition, and decrease the stability of the active compound, and consequently decrease the shelf-life of the product compared to anhydrous formulations comprising a soft anticholinergic analog (ester) as an active ingredient.

[0069] Moreover, decreased stability and increased hydrolysis products found for a soft anticholinergic analog (ester) formulated in an aqueous or water-based composition would suggest or even require an added preservative to be included in the composition.

[0070] In addition to the general preference or need to decrease exposure to preservative chemicals by the subject being treated, certain ingredients, such as the antioxidant/pH adjuster ascorbic acid, can have additional disadvantages when topically applied. For example, an aqueous preparation comprising ascorbic acid was found to produce a pink-colored residue on the skin of individuals after a few to several hours following exposure to the preparation.

[0071] A preservative-free composition, which is also an ascorbic acid-free composition, can therefore provide a further advantage of maintaining a colorless preparation following application and during residence on the skin of a subject. A composition comprising citric acid as an antioxidant/pH adjuster did not result in a pink colored residue following application of the composition to the skin; therefore a composition herein can include citric acid as an antioxidant.

[0072] Experimental data demonstrate that aqueous or water-based compositions result in the presence of increased hydrolysis products in the composition, and decreased stability of the composition, which leads to reduced shelf-life for a product comprising the composition. Adequate shelf-life is an advantageous factor for regulatory approval, as well as commercial success for a topical gel composition.

[0073] The HPLC experimental data presented in EXAMPLE 1 below also demonstrate the reduction of hydrolysis products Identified, and increased stability for a product comprising an anhydrous topical gel in accordance with the subject description.

EXAMPLE 1 - PROOF OF CONCEPT

[0074] Aqueous, or water-based, topical formulations are the most common in view of the availability of gel-forming components which interact with water to form hydrogels. The following experiments were conducted using the compound, (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide, (compound (iii) in the above list), which is designated as "BBI-4000" for convenience of reference.

[0075] Various formulations of approximately 2% BBI-4000 were made and their stabilities assessed. The solvent systems were as follows:

(a) solvent content: 100% water;

(b) solvent content: 60% water/40% ethanol;

(c) solvent content: 30% water/70% ethanol;

(d) solvent content: 100% ethanol.

Each sample was assessed at baseline; after 7 days at 25°C/60% humidity; and after 7 days at 40°C/75%humidity. The percentage change from baseline for 40°C after 7 days was calculated in each case. HPLC analysis was conducted as described in EXAMPLE 2 below.

[0076] Testing conclusively showed that, of the four solvent systems tested, only 100% ethanol (i.e. absolute or anhydrous ethanol) was capable of providing a composition which essentially maintained the baseline amount of BBI-4000 even after 7 days at the elevated temperature of 40°C. There is clearly a dramatic difference in the stability of the anhydrous ethanol formulation compared to the water-containing formulations. The results are shown in TABLE I below.

TABLE I

Formulation	**Solvent Content: 100% Water**			
Condition / Timepoint	Baseline	Day 7 @ 25°C/60%	Day 7 @ 40°C/75%	Change from Baseline (40°C/75%)
BBI-4000 Assay	1.99%	1.91%	1.80%	reduction 9.5%
BBI-4000 Main Hydrolysis Products (RRT-0.79-0.84)	0	1.90%	7.42%	
Formulation	**Solvent Content: 60% water, 40% ethanol**			
Condition / Timepoint	Baseline	Day 7 @ 25°C/60%	Day 7 @ 40°C/75%	Change from Baseline (40°C/75%)
BBI-4000 Assay	1.99%	1.94%	1.89%	reduction 5%
BBI-4000 Main Hydrolysis Products (RRT-0.79-0.84)	0	0.83%	3.40%	
Formulation	**Solvent Content: 30% water, 70% ethanol**			
Condition / Timepoint	Baseline	Day 7 @ 25°C/60%	Day 7 @ 40°C/75%	Change from Baseline (40°C/75%)
BBI-4000 Assay	1.99%	1.95%	1.89%	reduction 5%
BBI-4000 Main Hydrolysis Products (RRT-0.79-0.84)	0	0.84%	3.50%	
Formulation	**Solvent Content: 100% Ethanol**			
Condition / Timepoint	Baseline	Day 7 @ 25°C/60%	Day 7 @ 40°C/75%	Change from Baseline (40°C/75%)

BBI-4000 Assay	2.02%	2%	2.01%	reduction <1%
BBI-4000 Main Hydrolysis Products (RRT-0.79-0.84)	0	0	0	

EXAMPLE 2 - AQUEOUS FORMULATIONS

[0077] The following Table II shows the components included in an aqueous formulation comprising BBI-4000, a soft anticholinergic ethyl ester, prepared and subjected to hydrolysis and stability testing:

TABLE II

Material	Lot Number (% w/w)				
	BB-61-1	BB-62-1	BB-63-1	BB-64-1	BB-65-1
BBI-4000	2.00	2.00	2.00	2.00	2.00
Hydroxyethyl Cellulose	1.00	1.00	1.00	1.00	1.00
Hexylene Glycol	5.00	5.00	5.00	5.00	5.00
Benzyl Alcohol	1.00	1.00	1.00	1.00	1.00
Ethanol 95%	26.31	26.32	26.32	26.32	26.32
Polysorbate 80	1.00	1.00	1.00	1.00	1.00
Dimethiconol Blend 20	2.50	2.50	2.50	2.50	2.50
Dibasic Sodium Phosphate, Dried		0.09	0.09	0.09	
Monobasic Sodium Phosphate, Anhydrous		0.53	0.53	0.53	

Citric Acid, Anhydrous					0.20
Trisodium Citrate Dihydrate					1.16
Water	61.19	60.56	60.56	60.56	59.83
2N HCl	to pH 5	to pH 4.5	to pH 5	to pH 5.5	to pH 5
2N NaOH	to pH 5	to pH 4.5	to pH 5	to pH 5.5	to pH 5

[0078] An HPLC method was developed at a commercial laboratory for assaying the soft anticholinergic analog, and related substances (including hydrolysis products):

Apparatus

- High performance liquid chromatography (HPLC) system Chromatography data system
- XBridge Shield RP18,4.6 x 150 mm, 3.5 µm HPLC column
- Analytical balance capable of weighing to 0.00001 g
- Ultrasonic bath
- Volumetric flasks, 1, 5 mL
- Syringe Filter: 25 mm, 0.45 µm, HPF Millex-HV, Millipore or suitable alternative

Reagents, Supplies, Media and Solutions:

- BBI-4000 standard
- Water, HPLC grade
- Acetonitrile (can), Optima grade
- Trifluroacetic acid (TFA), Fisher
- Mobile Phase "A": 0.1% TFA in Water
- Mobile Phase "B": 0.1% TFA in Acetonitrile
- Auto Sampler Flush: 1:1 Water:Acetonitrile

- Diluent: Acetonitrile

BBI-4000 Standard Preparation (2 mg/mL in Diluent):

[0079] The standards were prepared in duplicate by weighing 2.0 ± 0.1 mg of BBI-4000 into 1 mL volumetric flasks. Dissolved and diluted to volume with acetonitrile and mixed by inversion.

Sample preparation (BBI-4000 gels):

[0080] Gel samples were prepared in duplicate at a target concentration of 2 mg/mL in a 5-mL volumetric flask. Added 1.5 ml H_2O and mixed to disperse the sample. Diluted to volume with acetonitrile and filtered an aliquot through a syringe filter.

HPLC Conditions:

[0081] The liquid chromatographic system was set-up as follows:

HPLC Column: XBridge Shield RP18, 4.6 x 150 mm, 3.5 µm
Column Temp.: 25 ± 1 °C
Sample Temp.: ambiant
Flow Rate: 1.5 mL/min
Injection Volume: 10 µL
UV Detection: 220 nm
Run Time: 20 minutes

[0082] The HPLC assay was conducted on formulations at differing pH values, and the results were reviewed for "Time-Zero" and at 7 days at 40°C:

[0083] The BBI-4000 content was determined. By Day 7, the assay number decreased, indicating hydrolysis of the BBI-4000 and some hydrolytic degradation products were noticeably increased (the two zwitterion stereoisomers, identified by RRT 0.84 and RRT 0.80), indicating lack of stability of this formulation system. Adjustment of pH, by itself, although providing a lower percent of hydrolytic degradation in the buffered formulation, did not resolve the issue.

[0084] A second experiment was conducted using a preparation comprising 2% of a soft glycopyrrolate ethyl ester (SGE) in an aqueous buffer system, which was tested for stability at refrigerated, 25°C (RT), and 40°C, for 7 days, and showed the same trend or similar results.

[0085] Thus, independent of pH, when water or aqueous buffer is present, the SGE is relatively rapidly degraded by hydrolysis and is substantially reduced in less than one week.

EXAMPLE 3 - ANHYDROUS FORMULATIONS

[0086] For preparing an anhydrous formulation, it is noted that no water or aqueous solution is added to the preparation.

[0087] The anhydrous formulations are based on: ethanol (solvent), hexylene glycol (moisturizer), and hydroxypropyl cellulose (HPC, gelling agent), in varying amounts or ratios. Each formulation was given an identification number as follows:

69-1 = without antioxidant
73-2 = without antioxidant but with polysorbate 80
72-2 = adding propylene glycol and polysorbate 80
78-1 and 78-2 = different quantities of HPC
79-1 = with ascorbic acid as antioxidant/acidifying agent
79-2 = with Vitamin E as antioxidant
84-1 = with citric acid as antioxidant/acidifying agent

Repeat-dose Studies up to 14 days

[0088] A 14-day dermal and systemic toxicity and toxicokinetics study in Göttingen Minipigs was conducted and completed using a formulation based on Formulations 79-1 and 84-1, above, but having a relatively high concentration of the active drug for testing tolerability. Specifically, the composition of the preparation used in this study included BBI-4000 as active ingredient (except in the vehicle-only control), hydroxypropyl cellulose as a gelling agent, hexylene glycol as an emollient, ascorbic acid or citric acid as antioxidant / pH adjuster and ethanol as the anhydrous vehicle.

[0089] Three groups of one male and one female animal were included in the main study, Group 1 receiving vehicle, Group 2 receiving BBI-4000 gel at 10% concentration and Group 3 receiving BBI-4000 gel at 20% concentration. All groups received 2 mL of gel formulation, once a day, for 14 consecutive days, applied to approximately 10% of their body surface area on their backs.

[0090] The study included daily observations of the site of application and scoring of erythema and edema (if present), daily general examinations including heart rate as well as pupil size assessment at days 1, 2, 3, 5, 7, 10 and 14. The frequent observations of heart rate and pupil size were intended to identify any potential systemic anticholinergic effect. Main organs were evaluated during necropsy and histopathology evaluation was completed for treated and untreated skin. Blood samples for chemistry and hematology analysis were collected as well as PK samples.

[0091] The results indicated that the composition was well-tolerated, there was no evidence of erythema or edema in the treated skin of any of the animals. Daily observation did not report any abnormality in heart rate or any other parameter. Pupil size assessments were reported as normal at all times in all animals. Blood chemistry and hematology parameters were reported within normal ranges. The necropsy did not reveal any abnormalities in any of the animals.

[0092] Histopathology analysis for the skin treated with an anhydrous composition comprising BBI-4000 was unremarkable and identical to non-treated and vehicle treated skin. All skin samples from the different groups were similar, with minor nonspecific changes that do not appear to be related to treatment. Mild, superficial inflammation reported in the dermis of most skin samples from all groups and from the non-treated areas suggests this finding is not drug or composition related, but associated with the caging of the animals.

[0093] The estimated BBI-4000 dose applied to the skin in this study was 40 mg/kg/day for Group 3 and 20 mg/kg/day for Group 2.

[0094] The PK analysis revealed variable, dose related systemic exposure of BBI-4000. The highest concentration was observed at 2 hours after Day-14

dosing in a minipig receiving the 20% BBI-4000 concentration. Most of the PK values for the carboxylic acid metabolite were below the lowest limit of quantification (LLOQ = 4.75 ng/mL for this assay), consistent with the short half-life of this metabolite. Group 1 (vehicle) did not report any value above the LLOQ, as expected.

[0095] It was noted during the study that a reddish formulation residue was observed in the skin of all animals receiving the ascorbic acid-containing formulation. Although the residue could be removed with wiping from the skin, this type of residue would not be acceptable to a human subject; therefore, additional formulations were evaluated. A new experiment was conducted in 2 new pigs with a new formulation removing the ascorbic acid, adding citric acid instead. Testing of the citric acid-containing formulation was also well tolerated and no reddish or pink-colored residue was observed.

[0096] The following formulations, shown in Table III, were tested for stability:

Table III

Component	A 84-1 % (w/w)	B 84-2 % (w/w)	C 84-3 % (w/w)
BBI-4000	10	10	10
KLUCEL™ MF (Hydroxypropyl Cellulose)	1.25	1.25	1.25
Hexylene Glycol	10	10	10
DIMETHICONOL BLEND 20	2.5	2.5	2.5
BHT	--	0.1	--
Propyl Gallate	--	--	0.05
Citric Acid, Anhydrous	0.1	0.1	0.1
Ethanol (200 proof) (Anhydrous Ethanol)	76.15	76.05	76.1

[0097] KLUCEL™ MF hydroxylpropyl cellulose (HPC) is available commercially from a variety of sources. DOW CORNING® DIMETHICONOL BLEND 20 is a unique blend of silicone gum (6%) in dimethicone. BHT is butylated hydroxytoluene also known as dibutylhydroxytoluene.

[0098] BBI-4000 and non-BBI-4000 levels determined at time "zero" are shown in Table IV, below:

Table IV

Day 0 Results		BB-84-1		BB-84-2		BB-84-3	
BBI-4000	Assay (Wt %)	9.81%		9.89%		9.72%	
	TAN %	98.19%		95.15%		92.17%	
Non-BBI-4000 by HPLC (%)		RRT	Area%	RRT	Area%	RRT	Area%
		RRT 0.80	0.67%				
		RRT 0.96	0.10%	RRT 0.80	0.62%	RRT 0.64	6.07%
		RRT 1.09	0.86%	RRT 0.96	0.07%	RRT 0.80	0.69%
		RRT 1.48	0.19%	RRT 1.09	0.79%	RRT 0.96	0.09%
				RRT 1.49	0.16%	RRT 1.09	0.81%
				RRT 2.05	0.90%	RRT 1.49	0.17%
				RRT 2.07	2.31%		
Total Non-BBI-4000 by HPLC (%)		1.82%		4.85%		7.83%	

[0099] BBI-4000 and non-BBI-4000 levels determined at 7 days, under accelerated conditions, 40°C, are shown in Table V, below:

Table V

Day 7 Results		BB-84-1		BB-84-2		BB-84-3	
BBI-4000	Assay (Wt %)	10.32%		10.18%		10.08%	
	TAN %	97.89%		94.75%		93.84%	
Non-BBI-4000 by HPLC (%)		RRT	Area%	RRT	Area%	RRT	Area%
		RRT 0.80	0.59%	RRT 0.80	0.42%	RRT 0.64	4.28%
		RRT 0.82	0.03%	RRT 0.91	0.16%		
		RRT 0.91	0.17%	RRT 0.96	0.15%	RRT 0.80	0.58%
		RRT 0.96	0.29%	RRT 1.09	0.96%	RRT 0.96	0.20%
		RRT 1.08	0.04%	RRT 1.49	0.18%	RRT 1.09	0.90%
		RRT 1.09	0.80%	RRT 1.50	0.02%	RRT 1.49	0.18%
		RRT 1.49	0.19%	RRT 2.05	0.88%	RRT 1.50	0.02%
		RRT 1.50	0.01%	RRT 2.07	2.49%		
Total Non-		2.11%		5.25%		6.16%	

BBI-4000 by HPLC (%)				

[0100] All formulations showed good stability, however fewer non-BBI-4000 materials were identified in formulations where antioxidants propyl gallate or BHT were absent from the formulation.

[0101] Further stability testing has been completed for a 3-month time-frame, using Formulation No. 84-1, tested at three temperatures: accelerated (40°C), room temperature (25°C), and refrigerated (about 4°C). Formulation No. 84-1 was specifically prepared using the following preparation instructions:

a) Combine the hexylene glycol and ethanol in a suitable container and mix.
b) Add the citric acid and stir to dissolve.
c) Add the active (BBI-4000) and stir to dissolve.
d) Add the KLUCEL™ MF and stir to dissolve, to increase viscosity of the product.
e) Lastly, add the DIMETHICONOL BLEND 20 and briefly disperse.
f) Homogenize the mixture of steps a) through e). For small batches, homogenation can be carried out by passing/mixing between 2 syringes connected with a micro-emulsifying needle. For larger batches, an overhead or inline homogenizer may be required.

[0102] The results of the 3-month stability study are provided in Table VI, below:

Table VI Stability of Formulation A 84-1

Day/ Temperature	0	7D-40C	14D-40C	30D-40C	30D-5C	90D-5C	30D-25C	90D-25C
Assay BBI-4000 (%)	9.81	10.32	10.21	10.25	9.32	10.50	10.26	10.63
Total Non-BBI-4000 by HPLC (%)	1.82	2.12	2.12	3.48	2.77	2.35	3.29	3.87

[0103] The formulation 84-1, having the formulation shown in Table VII, showed good stability and was tested in vivo.

TABLE VII

Component	**A 84-1** % (w/w)
BBI-4000	10
KLUCEL™ MF (Hydoxypropyl Cellulose)	1.25
Hexylene Glycol	10
DIMETHICONOL BLEND 20	2.5
Citric Acid, Anhydrous	0.1
Ethanol (200 proof) (Anhydrous Ethanol)	76.15

[0104] In the following clinical study, the A 84-1 formulation above was modified slightly. For 5% and 10% BBI-4000 gels, respectively, 0.001% anhydrous citric acid was used and the amount of ethanol adjusted accordingly (81.25% for the 5% gel and 76.25% for the 10% gel).

EXAMPLE 4 - Clinical Study

Study BBI-4000-CL-101: A Single-Center, Randomized, Double-Blind, Vehicle Controlled Study to Evaluate the Safety and the Effect on Sweat

Production of Topically Applied BBI-4000 Gel in Subjects with Hyperhidrosis

Study Design and Inclusion Criteria

[0105] Study BBI-4000-CL-101 was a Phase 1, randomized, double-blind, vehicle-controlled study of BBI-4000 gel conducted in 24 subjects with axillary hyperhidrosis. The study was conducted at a single center in the Dominican Republic. This study was not conducted under a US IND, but was undertaken in full compliance with applicable regulations of the Dominican Republic and with good clinical practice guidelines.

[0106] The objectives of this exploratory study were to evaluate the safety, local tolerability, and the effects on sweat production of topically applied BBI-4000 gel. A preliminary assessment of systemic exposure based on the pharmacokinetics of BBI-4000 was also conducted following topical application of the gel.

[0107] The drug product used in this study was an anhydrous semi-transparent gel with a composition including BBI-4000, hydroxypropylcellulose, hexylene glycol, DIMETHICONOL BLEND 20, citric acid, and ethanol.

[0108] The study consisted of 2 consecutive cohorts, where Cohort 1 established acceptable tolerability of 5% BBI-4000 gel (applied to one axilla) prior to enrolling a separate group of subjects into Cohort 2:

- **Cohort 1**: 6 subjects received 5% BBI-4000 gel in one axilla and vehicle in the other once daily (at night) for 14 consecutive days, based on a randomized, split-body design.
- **Cohort 2**: 18 subjects (6 in each treatment group) were randomized to receive 5% BBI-4000 gel, 10% BBI-4000 gel, or vehicle (control) to both axillae once daily (at night) for 14 consecutive days, based on a parallel-group design.

[0109] Subjects were 18 to 45 years of age, in good general health, with a diagnosis of primary axillary hyperhidrosis based on the following criteria at baseline:

- HDSS of 3 or 4 (HDSS = Hyperhidrosis Disease Severity Score)
- Gravimetric test indicating at least an average of 100 mg of sweat production in each axilla in 5 minutes at rest (at 25°C to 27°C)
- Bilateral and symmetrical hyperhidrosis

[0110] Subjects with prior axillary use of botulinum toxin (within 2 years) or receiving any anticholinergic medication were not eligible to participate in the study. All female subjects of child-bearing potential were required to use a medically acceptable method of contraception while on active treatment.

[0111] Subjects were not allowed to use any antiperspirant 7 days prior to baseline assessments and for the duration of the study.

Study Assessments and Endpoints

Assessment of Local Tolerability

[0112] Local tolerability to topical BBI-4000 was assessed by the investigator (erythema, dryness, and scaling) and study subjects (burning and itching).

[0113] The investigator graded the severity of erythema, dryness, and scaling for each axilla based on a 4-point scale, where "0" was absent, "1" was minimal (barely perceptible), "2" was mild, "3" was moderate, and "4" was severe.

[0114] Subjects graded the severity of any burning or itching based on a 4-point scale, where "0" was absent, "1" was minimal (an awareness, but no discomfort), "2" was mild, "3" was moderate, and "4" was severe.

Assessment of Safety

[0115] Safety was assessed by AEs, serious AEs (SAEs), or unexpected AEs; vital signs (blood pressure and heart rate); and clinical laboratory measures (hematology, chemistry, and urinalysis). Clinically relevant laboratory findings were to be collected as AEs (AEs = adverse events).

Assessment of Efficacy

[0116] Efficacy was assessed by the change in gravimetrically measured sweat production and the change in hyperhidrosis disease severity scale (HDSS) from baseline to Day 15 (end of therapy).

[0117] For the gravimetric assessment, sweat production was measured by placing filter paper (pre-weighed) on the axilla for 5 minutes while the subject was in a semi-reclining position at room temperature. The filter paper was covered with plastic during exposure to the axilla, and was then weighed following the 5-minute exposure period to calculate the amount of sweat produced.

[0118] For the HDSS, subjects rated the severity of their hyperhidrosis on a 4-point scale (1,2, 3, or 4) based on the level of interference with their daily activities. A score of 1 indicated that "my sweating is never noticeable and never interferes with my daily activities" and a score of 4 indicated that "my sweating is intolerable and always interferes with my daily activities".

Key Results of Study BBI-4000-CL-101

[0119] All subjects completed the study, including the follow-up visit at Day 16, and received 14 days of study treatment in accordance with the study protocol. All subjects were included in the analysis of study assessments (evaluable population). The subjects in Cohort 1 (split-body) had no AEs reported and tolerated well the 5% BBI-4000 gel and vehicle with only minimal to mild dryness and erythema reported in a couple of subjects during the study.

[0120] The results from Cohort 2 subjects, who received study drug in both axillary areas in a parallel design, are considered the most informative data from this study and are the focus of the following sections.

[0121] This was an exploratory study not powered to achieve statistically significant differences in the efficacy parameters measured, but to provide an early indication of safety, tolerability, and the potential treatment effect of topically applied BBI-4000.

Baseline Demographics and Disease Characteristics

[0122] Subjects in Cohort 2 ranged from 18.6 to 43.7 years of age, with a median age of $\leq$31 years in each treatment group. All subjects were Hispanic/Latino. No imbalances were noted between treatment groups with regard to gender, race, or ethnicity.

[0123] Measures of sweat production at baseline were generally similar between treatment groups and consistent with axillary hyperhidrosis. Median sweat production was > 200 mg (both axillae) in a 5-minute period for all treatment groups based on baseline gravimetric assessment. All subjects had an HDSS score of 3 or 4 at baseline.

Local Tolerability

[0124] Investigator and subject-based assessments of local tolerability indicated that 5% and 10% BBI-4000 gel topically applied to the axilla region was well tolerated over the 14-day treatment period. Dryness, erythema, itching and burning were occassionally reported by 1 or 2 subjects, they were minimal and did not lead to discontinuation of the therapy in any individual.

Safety

[0125] No AEs were reported by any subjects during the conduct of the study, and no deaths or serious AEs were reported.

[0126] There were no changes in laboratory parameters that were considered clinically relevant through the follow-up period (Day 16), as indicated by no reports of laboratory-related AEs by the investigator.

[0127] There were no clinically relevant changes from baseline in vital signs (blood pressure and heart rate) for any treatment group in either cohort during the study.

Efficacy

[0128] BBI-4000 formulation showed achievement of a greater reduction in gravimetrically measured sweat production and a greater improvement in HDSS assessments, when compared to vehicle. Although the overall reduction in sweat production and the HDSS improvement endpoints suggest than BBI-4000 10% gel performed better than BBI-4000 5% gel, it is difficult to make a definitive conclusion regarding differences in the magnitude of effect of the 2 active arms with this small sample size. Results for the key endpoints that have been commonly associated with a clinically meaningful improvement (i.e., reduction in sweat product of at least 50% and ≥ 2-point improvement in HDSS) are here

provided for the aggregate number of subjects exposed to BBI-4000 in comparison to vehicle.

[0129] The proportion of subjects treated with BBI-4000 who had at least a 50% reduction in sweat production at Day 15 was 75% (9 of 12) compared with 33% (2 of 6) of subjects who received vehicle. In addition 8 of 12 (67%) subjects receiving BBI-4000 reported a ≥ 2-point improvement in HDSS at Day 15, compared with 2 of 6 (33%) in the vehicle group. This reduction in HDSS score represents a meaningful change from intolerable or barely tolerable hyperhidrosis to tolerable or never noticeable hyperhidrosis for these subjects.

EXAMPLE 5 - FURTHER ANHYDROUS FORMULATIONS

[0130] Other formulations were developed, as set forth in the following table.

TABLE VIII

Component	Composition (% w/w)				
	Gel 2	Gel 3	Gel 4	Gel 5	Gel 6
Hydropropyl Cellulose	1.250	1.250	1.250	1.250	1.250
BBI-4000	5.000	5.000	5.000	5.000	5.000
Hexylene Glycol	10.000	10.000	10.000	10.000	10.000
Citric Acid, Anhydrous	0.001	0.001	0.001	0.001	0.001
Talc	0.500	-	-	-	-
C12-15 Alkyl Lactate	-	2.500	-	-	-
Dimethicone copolyol	-	-	1.000	-	-
Magnesium stearate	-	-	-	0.001	-

Isopropyl myristate (IPM)	-	-	-	-	2.500
Ethanol, Anhydrous	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100
Visual appearance at t=0	Translucent, med-high viscosity, smooth	Clear colorless, low viscosity, smooth	Clear colorless, low viscosity, smooth	Clear colorless, low viscosity, smooth	Clear colorless, low viscosity, smooth
Assessed for short-term stability	√	√	√	√	√

By way of example, the amount of BBI-4000 can alternatively be 10.000, 15.000 or 20.000 (% w/w), with the quantity of anhydrous ethanol adjusted accordingly.

[0131] Other formulations in accord herewith are listed in Table IX below.

TABLE IX

Component	Composition (% w/w)				
	Gel AA	Get BB	Gel CC	Gel DD	Gel EE
Hydropropyl Cellulose	1.250	1.250	1.250	1.250	1.250
BBI-4000	10.000	10.000	10.000	10.000	10.000
Hexylene Glycol	10.000	10.000	10.000	10.000	10.000
Citric Acid, Anhydrous	0.001	0.001	0.001	0.001	0.001
Dimethicone, e.g. 350 cSt	1.000	0.500	-	1.000	1.000
Cyclomethicone, e.g. 5-NF	1.000	1.000	1.000	-	-
Isopropyl myristate	-	-	2.500	-	2.500
Myristyl propionate	-	-	-	2.500	-
Ethanol, Anhydrous	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100

By way of example, the amount of BBI-4000 can alternatively be 5.000 % w/w, 15.000 % w/w or 20.000 % w/w, with the amount of anhydrous ethanol adjusted accordingly.

[0132] The following is a general formulation for particularly preferred embodiments of the subject composition.

FORMULATION

Component	Amount
BBI-4000	1% to 20% w/w
Hexylene Glycol	10% w/w
Hydroxypropyl Cellulose	1.25% w/w
Citric Acid, Anhydrous	0.001 % w/w
Dimethiconol Blend 20 or Isopropyl Myristate	2.5% w/w
Anhydrous Ethanol	qs to 100 %w/w

Additional preferred embodiments include dimethicone or cyclomethicone, separately or in combination, in place of Dimethiconol Blend 20, optionally together with isopropyl myristate, in the above formulation.

[0133] In these compositions, isopropyl myristate is preferred over Dimethiconol Blend 20 for two reasons. The first reason is related to transfer and scale-up of manufacturing process. It has been found difficult to stabilize the droplets of Dimethiconol Blend 20 in the formulation when attempting to increase the batch size and transfer the manufacturing process. Over time, a small amount of Dimethiconol Blend 20 coalesces at the bottom of the container in small droplets. The change to isopropyl myristate (IPM) eliminates this. The second reason is related to FDA acceptance of Dimethiconol Blend 20. While Dimethiconol Blend 20 is an

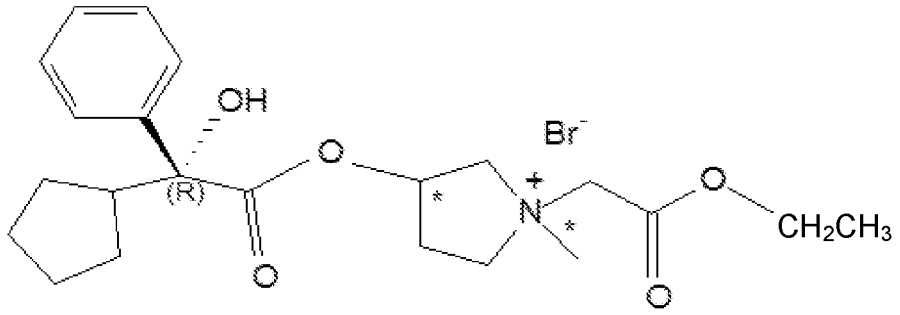
acceptable ingredient in cosmetic preparations, it has not been previously approved in pharmaceutical formulations. The FDA accepted its use in clinical studies, but additional studies might be needed to qualify it in a final formulation. The change to isopropyl myristate eliminates the need to conduct this additional testing as IPM has been approved in other pharmaceutical preparations, Dimethiconol Blend 20 was not detrimental to the function of the formulation; however, isopropyl myristate provides benefits to scale-up and commercialization. After evaluating a number of alternatives, isopropyl myristate was selected based upon its ability to reduce tack during drying as well as provide similar in vitro permeability. It also provided a formulation with a similar chemical stability profile to Dimethiconol Blend 20. The isopropyl myristate formulation was compared to the Dimethiconol Blend 20 formulation in a preclinical animal study. The isopropyl myristate formulation demonstrated an increase in permeation in mini-pigs relative to the Dimethiconol Blend 20 formulation. Two upcoming studies in humans are planned. The first study will compare the pharmacokinetics of 5% and 15% BBI-4000 gels containing isopropyl myristate with 15% BBI-4000 gel containing Dimethiconol Blend 20. The second study will evaluate/confirm the efficacy of BBI-4000 gel containing isopropyl myristate.

[0134] While certain preferred and alternative embodiments have been set forth for purposes of disclosure, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, this specification is intended to cover all embodiments and combinations and modifications thereof which do not depart from the spirit and scope of the following claims.

WHAT IS CLAIMED IS:

1. A topical composition for treating, inhibiting or ameliorating excessive sweating, said composition comprising the following ingredients:

(a) a compound having the formula:



(2)

said compound having the R stereoisomeric configuration at the 2 position and the R, S or RS stereoisomeric configuration at the 1' and 3' positions, or being a mixture thereof;

(b) anhydrous ethanol;

(c) optionally, at least one gelling or viscosity-controlling ingredient; and

(d) optionally, at least one additional carrier or excipient;

provided that said topical composition is anhydrous and comprises from about 1% to about 25 % w/w or w/v of the compound of formula (2), said composition having greater storage stability compared to a composition comprising an aqueous solvent or aqueous buffer, said ingredients being present

in amounts such that the product of any transesterification is the same as the compound of formula (2).

2. The composition of claim 1, comprising at least about 70% w/w or w/v anhydrous ethanol.

3. The composition of claim 1 or 2, comprising from about 70% to about 99.99% w/w or w/v anhydrous ethanol.

4. The composition of claim 1, 2 or 3, comprising from about 70% to about 85% w/w or w/v anhydrous ethanol.

5. The composition of any one of claims 1-4, wherein at least one gelling or viscosity-controlling ingredient is present.

6. The composition of any one of claims 1-5, wherein at least one additional carrier or excipient is present.

7. The composition of any one of claims 1-6, wherein the compound of formula (2) is selected from the group consisting of:

(i) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ii) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iii) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iv) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(v) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vi) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vii) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide; and

(viii) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

8. The composition of any one of claims 1-7, wherein the compound of formula (2) is at a concentration of from about 1% w/v or w/w to about 20% w/v or w/w of the composition.

9. The composition of claim 8, wherein the compound of formula (2) is at a concentration of from about 2% w/v or w/w to about 10% w/v or w/w.

10. The composition of any one of the preceding claims, packaged into a multiple dose container that meters a dose of from about 0.5 ml to about 1.0 ml of the composition for each application.

11. The composition of any one of the preceding claims, packaged into a single or unit dose container that delivers a single or unit dose of about 0.5 ml to about 1.0 ml of the composition for each application.

12. The composition of any one of the preceding claims, wherein the compound of formula (2) is (2R, 3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

13. The composition of any one of claims 5-12, wherein the gelling or viscosity-controlling ingredient is hydroxypropyl cellulose.

14. The composition of any one of claims 5-13, further comprising citric acid.

15. The composition of any one of claims 5-14, further comprising hexylene glycol.

16. The composition of any one of claims 5-15, further comprising a 6% silicone gum blend in dimethicone.

17. The composition of any one of claims 5-15, further comprising at least one member selected from the group consisting of dimethicone, cyclomethicone, myristyl propionate, isopropyl myristate and C_{12}-C_{15} alkyl lactate.

18. The composition of claim 17, wherein the cyclomethicone is cyclomethicone 5-NF and/or where the dimethicone is dimethicone 350 c5t.

19. The composition of any one of claims 5-15, further comprising isopropyl myristate.

20. Use of a composition as claimed in any one of claims 1-19 in treating hyperhidrosis in a subject by topically administering to skin of an area of a subject suffering from hyperhidrosis, before bedtime, such that, compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours; and such that sweat production is reduced by an amount substantially equivalent to an amount that sweat production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising the same concentration of glycopyrrolate, and with an improved safety profile compared to topical glycopyrrolate.

21. Use of a composition as claimed in any one of claims 1-19 in treating hyperhidrosis in a subject by topically administering to skin of an area of a subject suffering from hyperhidrosis, such that, compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours; and such that sweat production is reduced by an amount substantially equivalent to an amount that sweat production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising the same concentration of glycopyrrolate, and with an improved safety profile compared to topical glycopyrrolate.

22. A method of treating hyperhidrosis in a subject, said method comprising topically administering a composition as claimed in any one of claims 1-19 to skin of an area of a subject suffering from hyperhidrosis, before bedtime, such that, compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours; and such that sweat production is reduced by an amount substantially equivalent to an amount that sweat

production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising the same concentration of glycopyrrolate, and with an improved safety profile compared to topical glycopyrrolate.

23. A method of treating hyperhidrosis in a subject, said method comprising topically administering a composition as claimed in any one of claims 1-19 to skin of an area of a subject suffering from hyperhidrosis, such that, compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours; and such that sweat production is reduced by an amount substantially equivalent to an amount that sweat production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising the same concentration of glycopyrrolate, and with an improved safety profile compared to topical glycopyrrolate.

24. The composition of any one of claims 1-19, for use in the treatment of hyperhidrosis, wherein said composition is to be topically administered in a one to four times daily regimen to an affected skin area of a subject.

25. The composition for use according to claim 24, wherein said composition is to be topically administered to an affected skin area of the subject, within 1-2 hours prior to the subject's sleep period.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/43380

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 491/08, A01N 43/42 (2016.01)
CPC - A61K 9/0019, A61K 9/0048, A61K 9/0075, A61K 9/2059
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07D 491/08, A01N 43/42 (2016.01)
CPC - A61K 9/0019, A61K 9/0048, A61K 9/0075, A61K 9/2059

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 546/91

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patent, Google Web
Search terms used - anticholinergic composition anhydrous ethanol hyperhidrosis Glycopyrrolate storage stability ester hydrolysis excess
Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/144075 A1 (BODOR LABORATORIES, INC.) 18 September 2014 (18.09.2014); pg 4, ln 19-20, 24-25, pg. 17, ln 1-5	1-3
A	US 2014/0151255 A1 (Johnston et al.) 05 June 2014 (05.06.2014); entire document	1-3
A	US 6,433,003 B1 (Bobrove et al.) 13 August 2002 (13.08.2002); entire document	1-3
A	US 2003/0064040 A1 (Lukacsko) 03 April 2003 (03.04.2003); entire document	1-3
A	Kirk et al. "Esterification and Esters, Organic" Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed. February 1994. vol 9, ISBN-10 0471526770, http://vigoschools.org/~mmc3/AP%20Lab/ap%20lab%20documents/Esterfication.pdf; pg. 24, para 8	1-3

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2016 (15.09.2016)	13 OCT 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/43380

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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(51)Int.Cl.
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A01N 43/42(2006.01)

权利要求书3页 说明书26页

(54)发明名称

软性抗胆碱能药类似物的制剂

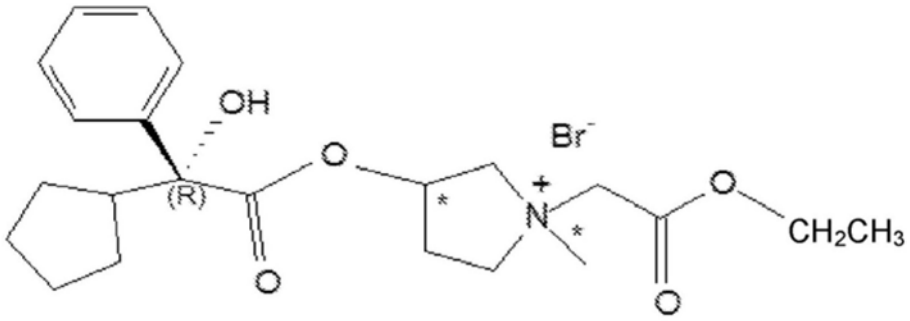
(57)摘要

包含软性格隆溴铵的局部用制剂可用于治疗受试者(如患有多汗症的人)的出汗过多状况。优选地,在无水制剂中以有效量或浓度提供至少一种软性抗胆碱能剂,所述无水制剂能抑制因诸如多汗症的状况引起的汗脱。

CN 108137612 A

1.一种用于治疗、抑制或缓解出汗过多的局部用组合物，所述组合物包含以下成分：

(a)具有下式的化合物：



(2)

所述化合物在2位具有R立体异构构型并且在1'和3'位具有R、S或RS的立体异构构型，或者是其混合物；

(b)无水乙醇；

(c)任选地，至少一种胶凝成分或粘度控制成分；和

(d)任选地，至少一种另外的载体或赋形剂；

条件是所述局部用组合物是无水的并且包含约1％至约25％w/w或w/v的式(2)的化合物，与包含水性溶剂或水性缓冲剂的组合物相比，所述组合物具有更高的储存稳定性；所述成分以使得任何酯交换的产物与式(2)的化合物相同的量存在。

2.如权利要求1所述的组合物，其包含至少约70％w/w或w/v的无水乙醇。

3.如权利要求1或2所述的组合物，其包含约70％至约99.99％w/w或w/v的无水乙醇。

4.如权利要求1、2或3所述的组合物，其包含约70％至约85％w/w或w/v的无水乙醇。

5.如权利要求1-4中任一项所述的组合物，其中存在至少一种胶凝成分或粘度控制成分。

6.如权利要求1-5中任一项所述的组合物，其中存在至少一种另外的载体或赋形剂。

7.如权利要求1-6中任一项所述的组合物，其中式(2)的化合物选自以下化合物组成的组：

(i)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(ii)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(iii)(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(iv)(2R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(v)(2R,1'R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(vi)(2R,1'S,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

(vii)(2R,1'R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;和

(viii)(2R,1'S,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓。

8.如权利要求1-7中任一项所述的组合物,其中式(2)的化合物的浓度为所述组合物的约1%w/v或w/w至约20%w/v或w/w。

9.如权利要求8所述的组合物,其中式(2)的化合物的浓度为约2%w/v或w/w至约10%w/v或w/w。

10.如前述权利要求中任一项所述的组合物,其被包装到多剂量容器中,所述多剂量容器计量剂量为约0.5ml至约1.0ml的所述组合物供每次涂敷用。

11.如前述权利要求中任一项所述的组合物,其被包装在单剂量或单位剂量容器中,所述单剂量或单位剂量容器递送单剂量或单位剂量为约0.5ml至约1.0ml的所述组合物供每次涂敷用。

12.如前述权利要求中任一项所述的组合物,其中式(2)的化合物是(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓。

13.如权利要求5-12中任一项所述的组合物,其中所述胶凝成分或粘度控制成分是羟丙基纤维素。

14.如权利要求5-13中任一项所述的组合物,其还包含柠檬酸。

15.如权利要求5-14中任一项所述的组合物,其还包含己二醇。

16.如权利要求5-15中任一项所述的组合物,其还包含在聚二甲基硅氧烷中的6%硅氧烷胶共混物。

17.如权利要求5-15中任一项所述的组合物,其还包含选自由聚二甲基硅氧烷、环甲基硅酮、丙酸肉豆蔻酯、肉豆蔻酸异丙酯和乳酸C_{12}-C_{15}烷基酯组成的组中的至少一种。

18.如权利要求17所述的组合物,其中所述环甲基硅酮是环甲基硅酮5-NF和/或其中所述聚二甲基硅氧烷是聚二甲基硅氧烷350c5t。

19.如权利要求5-15中任一项所述的组合物,其还包含肉豆蔻酸异丙酯。

20.如权利要求1-19中任一项所述的组合物在治疗受试者的多汗症中的用途,所述组合物通过在就寝前局部施用于受试者的患多汗症区域的皮肤,使得与未处理的基线状况相比,汗液产生持续至少六(6)小时减少至少25%;并使得汗液产生减少的量基本上相当于施用包含相同浓度的格隆溴铵的组合物后与未处理的基线状况相比汗液产生减少的量;并且与局部用格隆溴铵相比具有改善的安全性状况。

21.如权利要求1-19中任一项所述的组合物在治疗受试者的多汗症中的用途,所述组合物通过局部施用于受试者的患多汗症区域的皮肤,使得与未处理的基线状况相比,汗液产生持续至少六(6)小时减少至少25%;并使得汗液产生减少的量基本上相当于施用包含相同浓度的格隆溴铵的组合物后与未处理的基线状况相比汗液产生减少的量,并且与局部用格隆溴铵相比具有改善的安全性特性。

22.一种治疗受试者的多汗症的方法,所述方法包括在就寝前向受试者的患多汗症区域的皮肤局部施用如权利要求1-19中任一项所述的组合物,使得与未处理的基线状况相比,汗液产生持续至少六(6)小时减少至少25%;并使得汗液产生减少的量基本上相当于施

用包含相同浓度的格隆溴铵的组合物后与未处理的基线状况相比汗液产生减少的量，并且与局部用格隆溴铵相比具有改善的安全性特性。

23.一种治疗受试者的多汗症的方法，所述方法包括向受试者的患多汗症区域的皮肤局部施用如权利要求1-19中任一项所述的组合物，使得与未处理的基线状况相比，汗液产生持续至少六(6)小时减少至少25％；并使得汗液产生减少的量基本上相当于施用包含相同浓度的格隆溴铵的组合物后与未处理的基线状况相比汗液产生减少的量，并且与局部用格隆溴铵相比具有改善的安全性特性。

24.如权利要求1-19中任一项所述的组合物，用于治疗多汗症，其中所述组合物将按照每日一至四次的方案局部施用至受试者的受累皮肤区域。

25.如权利要求24所述的用途的组合物，其中所述组合物将在受试者的睡眠期之前1-2小时内局部施用至受试者的受累皮肤区域。

软性抗胆碱能药类似物的制剂

[0001] 背景

[0002] 以前已经描述了多种抗胆碱能化合物和这些化合物的制剂。毒蕈碱受体拮抗剂是经常使用的治疗剂，其通过阻断其与平滑肌、心肌和腺细胞上以及周围神经节和中枢神经系统(CNS)中的神经效应器位点处的毒蕈碱胆碱能受体的结合来抑制乙酰胆碱的作用。然而，它们的副作用(其可包括口干、畏光、视力模糊、排尿踌躇和潴留、嗜睡、头晕、烦躁不安、易怒、定向障碍、幻觉、心动过速和心律失常、恶心、便秘和严重的过敏反应)常常限制了它们的临床使用。将抗胆碱能剂局部施用至靶向区域如汗腺(在此局部阻断毒蕈碱受体将具有临床益处)将是期望的治疗策略。然而，目前使用的局部用抗胆碱能药可能表现出不想要的全身性副作用，这可能会限制可以安全施用的剂量。

[0003] 格隆溴铵(Glycopyrrolate)是一种季铵抗胆碱能药，所述季铵抗胆碱能药减少了CNS相关副作用，因为它们不能穿过血脑屏障；然而，因为格隆溴铵主要是作为未改变的药物或活性代谢物被消除，其局部施用常常与常见的不期望的抗胆碱能药全身性副作用相关。为了增加抗胆碱能药的治疗指数，在由各种先导化合物开始的许多不同的设计中已应用软性药物方法，但是还需要其他具有临床上有意义的生物学活性的新的软性抗胆碱能药。这些新型毒蕈碱拮抗剂正如所有其他软性药物一样，被设计为在涂敷部位引出它们的预期的药理学作用，但是在进入体循环后快速代谢为它们的已设计好的非活性代谢物，并迅速从体内消除，导致减少的全身性副作用和增加的治疗指数。

[0004] 软性抗胆碱能两性离子已在美国专利公开号2012/0141401(现为USP 8,568,699)及其相关专利US 8,071,693；7,538,219和7,417,147中描述过。软性抗胆碱能酯已在美国专利公开号2012/0177590(现为USP 8,628,759)及其相关专利USP 8,147,809；7,576,210和7,399,861中描述过。尽管这些公开的申请和专利确定了抗胆碱能药的两性离子或酯形式用于治疗多汗症的潜力，但是基于与已公布的散瞳数据的比较，本文中所述的针对多汗症的活性和作用持续时间出乎意料的高的事实不是已知的或以前未描述过的。

[0005] 美国专利公开号2012/0141401(USP 8,568,699)和2012/0177590(USP 8,628,759)及其相关专利USP 8,147,809；8,071,693；7,576,210；7,538,219；7,417,147和7,399,861的每一个以其整体通过引用的方式并入本文。

[0006] 多汗症是特发性病理状况，特征在于超过冷却身体所需的过量的、不可控的出汗。汗腺的功能亢进及其胆碱能刺激的紊乱已被描述为该状况可能的诱因。已知其影响大约3％的人口。多汗症不仅可能导致社交方面的强烈尴尬，甚至还可能干扰一个人的职业。

[0007] 多汗症最常涉及一个或多个区域，尤其是手、腋窝、脚或面部，尽管其甚至能涉及全身。腋窝多汗症是最常见的形式，其次是手掌多汗症。止汗药单独使用在治疗这种汗脱(excessive perspiration)中通常不是有效的。口服用药偶尔是有益的，但可能具有副作用。其他治疗替代方案包括外科手术如内窥镜胸交感神经切除术(endoscopic thoracic sympathectomy)。虽然该手术使约40％至90％的受累个体获得永久性益处，但是其是侵入性的，需要全身麻醉，并且不是没有可能的副作用。在已经历胸交感神经切除术的人中有多达50％出现躯干或大腿的代偿性和令人厌烦的出汗。阻断自主神经释放的乙酰胆碱对汗腺

的作用的A型肉毒杆菌神经毒素(BOTOX)已被证明在多汗症中是有效的。向受累个体的手掌或腋窝中注射少量BOTOX获得统计学上显著的益处。该效果持续数月,但需要重复注射,并且对于儿科患者常常并不是合适的替代方案。离子电渗疗法具有有限的疗效,并且不能用于腋窝区域。

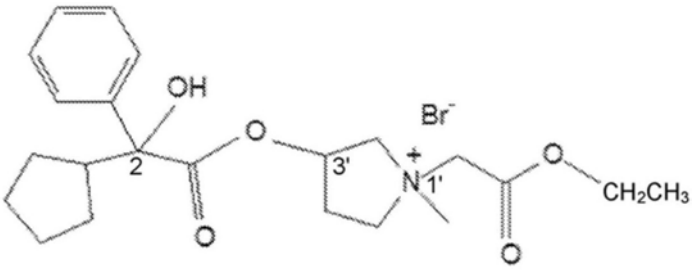
[0008] 具有高的减少出汗活性、长持续时间并具有较少的副作用的非侵入性、方便且有效的治疗将会是受欢迎的治疗多汗症的替代疗法。最近在2014年3月14日提交的共同待决的美国专利申请号14/213,242(发明人BODOR和ANGULO)中描述了一种治疗多汗症的改进方法,该申请以其整体通过引用的方式并入本文。

[0009] 以前已提出使用包含软性抗胆碱能药类似物如格隆溴铵的软性酯类似物的局部用制剂来治疗多汗症;然而,此类酯的能满足此类产品的监管要求或提供商业上可行的货架期的稳定的、药学上可接受的制剂一直是难以找到的。因此,本领域需要一种包含软性抗胆碱能药类似物的局部施用的组合物的稳定的、药学上可接受的且商业上可行的制剂。

[0010] 概述

[0011] 本申请涉及用于治疗受试者(如患有多汗症的人)的出汗过多状况的局部用制剂。本文中的组合物包含能抑制由诸如多汗症的状况引起的汗脱的有效量或浓度的至少一种软性抗胆碱能剂,该软性抗胆碱能剂为格隆溴铵的软性酯类似物。一个优选实施方案是局部用组合物,其包含:(a)至少一种具有式(1)的化合物:

[0012]

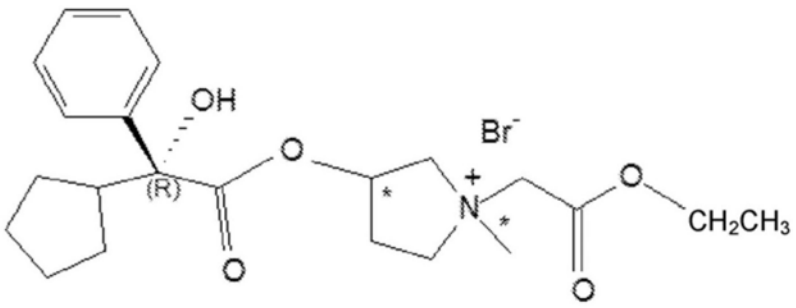


(1)

[0013] 所述化合物在2位以及1'和3'位具有R、S或RS的立体异构构型或者是其混合物,和(b)无水乙醇,条件是所述局部用组合物是无水的。

[0014] 局部用组合物的一个优选实施方案包含:(a)至少一种具有以下立体特异性式(2)的化合物:

[0015]



(2)

[0016] 所述化合物在2位具有R立体异构构型并且在1'和3'位(星号所指示的位置)具有R、S或RS的立体异构构型或者是其混合物,和(b)无水乙醇,条件是所述局部用组合物是无

水的。

[0017] 另一个实施方案提供一种局部用药物组合物，其包含(a)一种或多种前述式(2)的化合物、(b)无水乙醇和(c)一种或多种药学上可接受的载体或赋形剂，条件是所述局部用组合物是无水的。又一个实施方案提供了一种局部用药物组合物，其包含上述的(a)和(b)；(c)任选地，至少一种胶凝成分或粘度控制成分；和(d)任选地，至少一种另外的载体或赋形剂；条件是所述局部用组合物是无水的并且包含约1％至约25％的式(2)的化合物，所述组合物与包含水性溶剂或水性缓冲剂的组合物相比具有更高的储存稳定性。

[0018] 还包括使用如本文中所述的局部用组合物来治疗或抑制或缓解出汗过多(包括诸如多汗症的状况)的方法。2014年3月14日提交的共同待决的美国专利申请号14/213,242的方法在通过施用包含上述式(2)的乙酯和无水乙醇的局部用制剂(条件是所述局部用制剂是无水的)来进行时受到特别的关注并具有特别的优点。

[0019] 本申请的组合物可被配制成固体或半固体剂、粉剂、凝胶剂、乳膏、洗液、泡沫剂、溶液、悬浮液、气雾剂、贴剂、拭剂或乳剂等，并且被配制用于局部涂敷来治疗、抑制或缓解多汗症。更优选地，如上文所定义的组合物被配制成无水乙醇局部用凝胶剂，其能提供一定的优点，包括优异的组合物稳定性或增加的组合物货架期，以及使组合物中对单独的防腐剂的需要最小化或消除组合物中对单独的防腐剂的需要的益处。

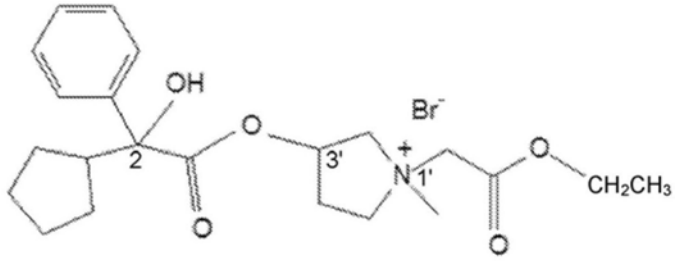
[0020] 本文中的局部用无水乙醇凝胶组合物的其他优点包括以下特性，诸如干燥时间快、在皮肤或衣服上的有限残留以及每次涂敷时便于以计量的产品量分配的能力。特定制剂还能掩盖某些软性抗胆碱能药(如本文中描述的某些化合物)可能具有的粘性。

[0021] 一种制剂包含在70-99.9％的非水性溶剂乙醇中的约0.1％至约30％的化合物。该制剂还可包括一种或多种另外的载体或赋形剂，包括胶凝赋形剂或粘度控制赋形剂，其本身是无水的，即是非水性的。

[0022] 式(1)和式(2)的化合物是乙酯。作为酯，这些化合物易发生酯交换，其是将酯的烷基与醇/烷醇的烷基交换的过程。该反应由酸或碱或甚至酶促来催化。遗憾的是，酯交换可导致大量的药物的酯基团互换成不太期望的、生物学上不太能接受的基团。例如，使用无水甲醇作为乙酯的溶剂导致不可接受地形成大量的与乙酯混合的甲酯。另一方面，使用无水乙醇导致仅形成乙酯作为酯交换的产物。此外，通过使用无水乙醇，并且通过确定组合物本身是无水的，可以避免活性成分的乙酯基团的水解。

[0023] 因此，在本文的一个方面中提供了一种用于治疗、抑制或缓解受试者的多汗症的方法，其包括：

[0024] (A)提供局部用组合物，该局部用组合物包含：(a)约1％至约25％的具有式(1)的化合物：

[0025] 

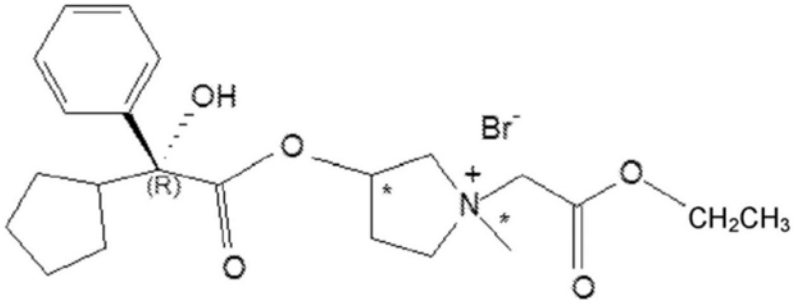
(1)

[0026] 所述化合物在2位以及1'和3'位具有R、S或RS的立体异构构型或者是其混合物；(b)无水乙醇；(c)任选地，至少一种胶凝成分或粘度控制成分；和(d)任选地，至少一种另外的载体或赋形剂；条件是所述局部用组合物是无水的；和

[0027] (B)将该组合物局部施用于患有出汗过多(如多汗症)的受试者。

[0028] 本文的另一方面还提供了一种用于治疗、抑制或缓解受试者的多汗症的方法，其包括：

[0029] (A)提供局部用组合物，该局部用组合物包含：(a)约1％至约25％的具有式(2)的化合物：

[0030] 

(2)

[0031] 所述化合物在2位具有R立体异构构型并且在1'和3'位具有R、S或RS立体异构构型或者是其混合物；(b)无水乙醇；(c)任选地，至少一种胶凝成分或粘度控制成分；和(d)任选地，至少一种另外的载体或赋形剂；条件是所述局部用组合物是无水的；和

[0032] (B)将该组合物局部施用于患有出汗过多(如多汗症)的受试者。

[0033] 有利地，该方法能提供减少出汗过多最多至约48小时。而且，令人惊讶地，该组合物的局部施用能意想不到地提供与基线状况相比持续至少约六(6)小时的汗液产生减少，其减少量基本上相当于施用包含相等浓度的格隆溴铵的组合物后同样与基线状况相比的汗液产生的减少。以前认为格隆溴铵的软性酯类似物需要多达格隆溴铵浓度的5-10倍才能提供基本上相等的活性。

[0034] 治疗有此需要的受试者的多汗症的优选方法或用于治疗、抑制或缓解其中的出汗过多的优选方法包括根据美国专利申请号14/213,242的方法施用本发明的组合物。根据该方法，在就寝前，将本文所定义的包含上述式(2)的化合物的组合物施用至受试者的患有多汗症的皮肤，使得与未处理的基线状况相比汗液产生减少至少25％持续至少六(6)小时；并使得汗液产生减少的量基本上相当于施用包含相同浓度的格隆溴铵组合物后与未处理的

基线状况相比汗液产生减少的量;并且与局部用格隆溴铵相比,其具有改善的安全性特性。具体而言,在5%药物浓度下,在'242申请中描述的测试中没有观察到软性酯的全身性抗胆碱能副作用。同样,如下文所述,在临床研究中在5%或10%的浓度下未观察到全身性抗胆碱能副作用。

[0035] 本发明的方法优选通过将组合物局部施用于人类受试者,施用至该受试者的需要减少汗液的浅表解剖学区域的皮肤。优选地,用于涂敷或施用该组合物的解剖学区域选自受试者的手掌区域、足底区域、腹股沟区域、腋窝区域和面部区域。

[0036] 本发明的方法能使汗液产生减少约25%至约99%,优选约30%至约90%,更优选至少50%,其可以是指示治疗多汗症的临床显著终点。

[0037] 如前所述,该方法能应用被配制成固体或半固体剂、粉剂、凝胶剂、乳膏、洗液、泡沫剂、溶液、悬浮液、气雾剂、贴剂、拭剂或乳剂等的组合物,并可包含约0.1%至约30%浓度的化合物,优选约1%至约25%浓度的化合物,更优选约1%至约20%浓度的化合物,并且最优选约2%至约10%浓度的化合物,所述化合物是上述式(1)的化合物,优选式(2)的化合物。

[0038] 根据本说明书的方法可包括向有需要的受试者(prn)局部施用如本文所定义的组合物。施用优选为每周至少一次,更优选每周至少三至四次(例如,每隔一天),或者可更频繁地施用,如一天一次(QD),例如在就寝前(通常,在夜间)或在受试者睡醒后(通常在早晨,并优选在沐浴或淋浴后);一天两次(BID),例如,每10-12小时;一天三次(TID),例如,每6-9小时;一天四次(QID),例如,每3-5小时;优选的上限为每天约6-8次给药或涂敷。

[0039] 令人惊讶地,本发明的方法在单次或多次涂敷后能减少汗液产生持续约4小时至约24小时的时间段,并优选持续约6小时至约12小时的时间段。

[0040] 本文中优选的组合物包含:

[0041] 作为活性成分的一种或多种式(1)或式(2)的软性格隆溴铵类似物;和

[0042] 无水乙醇(作为活性成分的非水性溶剂);

[0043] 条件是所述组合物是无水的。

[0044] 如本文中所述,本发明的制剂优选为凝胶剂。因此,更优选的组合物包含:

[0045] 作为活性成分的一种或多种式(1)或式(2)的软性格隆溴铵类似物;

[0046] 无水乙醇(作为活性成分的非水性的、药学上可接受的溶剂);和

[0047] 一种或多种胶凝剂或粘度控制剂,

[0048] 条件是所述制剂是无水的。

[0049] 式(1)或式(2)的软性格隆溴铵类似物是软性抗胆碱能乙酯。使用匹配的非水性溶剂乙醇避免了当使用诸如甲醇的醇作为乙酯的溶剂时可由酯交换产生的酯的混合物。而且,不存在水导致高得多的储存稳定性。

[0050] 有利地,无水乙醇能实现自防腐组合物,其能在无添加的防腐剂的情况下向组合物提供微生物稳定性。

[0051] 无水乙醇还能抑制细菌生长并向组合物提供除臭性质。

[0052] 根据本说明书的组合物的另一优点在于以下事实:非水性溶剂无水乙醇具有挥发性,尤其是在由体热产生的局部温度下,从而使得当将其局部涂敷于受试者时,其提供快速干燥的组合物。

[0053] 优选的胶凝剂或粘度控制剂可以是改性纤维素，例如羟丙基纤维素(HPC)，如可商购的KLUCEL™，其可优选地提供约100至约10,000cps的组合物粘度。

[0054] 详述

[0055] 在本说明书通篇中，以下定义、一般描述和例示均适用：

[0056] 本文所引用的专利、公开申请和科学文献建立了本领域技术人员的知识体系并特此通过引用的方式以其整体并入本文，如同每一篇明确地且独立地通过引用的方式并入本文。在本文中引用的任何参考文献与本说明书的具体教导之间的任何冲突应以后者为准。同样，在词语或短语在本领域中理解的定义与该词语或短语如本说明书具体教导的定义之间的任何冲突应以后者为准。

[0057] 如本文中所用，无论在过渡短语还是在权利要求主体中，术语“包含”应解释为具有开放式的含义。也就是说，该术语应解释为与短语“具有至少”或“包括至少”同义。当用于方法的内容时，术语“包括”是指该方法包括至少所述步骤，但是可以包括另外的步骤。当用于组合物的内容时，术语“包含”指的是该组合物包括至少所述特征或组分，但是还可以包括另外的特征或组分。

[0058] 术语“基本由……组成”具有部分封闭式的含义，也就是说，它们不允许包括实质上改变方法或组合物的本质特征的步骤或特征或组分；例如，显著干扰本文所述的化合物或组合物的期望性质的步骤或特征或组分，即，该方法或组合物限于指定的步骤或材料以及实质上不影响该方法或组合物的基本的和新颖的特征的那些步骤或材料。

[0059] 术语“由……组成”和“组成”是封闭式用语，仅允许包括所述的步骤或特征或组分。

[0060] 除非另有明确说明，本文中所用的单数形式“一个”、“一种”和“该”明确地还包含它们所指术语的复数形式。

[0061] 术语“约”在本文中用于表示大概、在……范围内、粗略地或在……周围。当术语“约”与数值范围结合使用时，其通过延伸所提出的数值的上下边界来修饰该范围。一般来说，术语“约”或“大概”在本文中用于修饰该数值在所述值上下20％的偏差内。

[0062] 如本文中所用，对变量的数字范围的描述意在传达该变量可以等于该范围内的任何值。因此，对于本质上不连续的变量，该变量可以等于该数值范围内的任何整数值，包括该范围的端点。类似地，对于本质上连续的变量，该变量可以等于该数值范围内的任何实数值，包括该范围的端点。例如，描述为具有0至2的值的变量，对于本质上不连续的变量来说，可以是0、1或2；而对于本质上连续的变量，可以是0.0、0.1、0.01、0.001或任何其他实数值。

[0063] 在本说明书和权利要求中，单数形式包括复数形式，除非本文另有明确规定。如本文中所用，除非另行明确说明，词语“或”以“和/或”的“包括性”意义使用，而不是以“要么/或者”的“排他性”意义使用。

[0064] 在本文中使用的技术和科学术语具有本说明书所属领域技术人员通常理解的含义，除非另行定义。本文参考了本领域技术人员已知的各种方法和材料。陈述药理学普遍原理的标准参考书包括Goodman和Gilman的The Pharmacological Basis of Therapeutics, 10th Ed.,McGraw Hill Companies Inc.,New York(2001)。

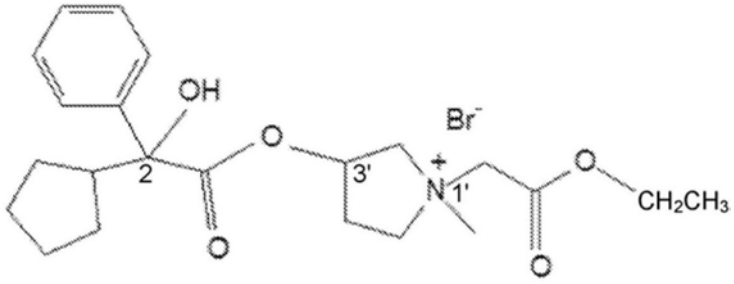
[0065] 如本文中所用，“治疗”是指与未施用化合物或组合物的个体的症状相比，在已经向其施用包含式(1)或式(2)的化合物的组合物的个体中减少、制约或抑制症状的发展，控

制、抑制、减轻和/或逆转该症状。从业者将理解，本文中描述的组合、组合物、剂型和方法伴随着熟练从业者(医师或兽医)进行的连续临床评估来使用，以确定后续治疗。这种评估有助于和报告评估是否增加、减少或继续特定的治疗剂量，和/或是否改变施用模式。

[0066] 与未施用化合物或组合物的个体的症状相比，本发明的化合物或组合物还可以在已经向其施用包含上述式(1)或式(2)的化合物的组合物的个体中预防症状或防止症状的发生。这不是绝对意义上的预防多汗症或出汗过多，它不预防该医学状况，因为它甚至不解决该状况的原因；而是它在给药剂量有效的时间段(小时)内抑制该状况的表现。

[0067] 本文中描述的方法意在用于可以体验其益处的任何受试者/患者。由此，术语“受试者”以及“患者”、“个体”和“温血动物”包括人类以及非人类受试者，如可能经历出汗过多的动物。

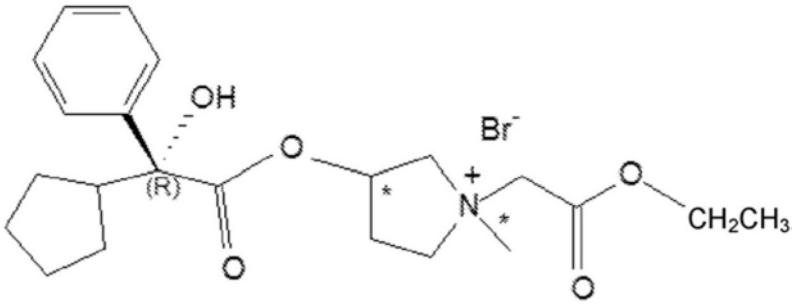
[0068] 可用于本文中的组合物中的化合物包括式(1)的那些化合物：

[0069] 

(1)

[0070] 该化合物在2位以及1’和3’位具有R、S或RS立体异构构型或者是其混合物。

[0071] 就用于本发明的组合物而言，手性中心2为R构型的化合物是特别受关注的。例如，可用于本文中的组合物的优选化合物具有立体特异性式(2)：

[0072] 

(2)

[0073] 所述化合物在2位具有R立体异构构型并且在1’和3’位(星号所指的位置)具有R、S或RS立体异构构型，或者是其混合物。

[0074] 就用于本说明书的组合物而言，以下化合物是特别受关注的：

[0075] (i)3-(2-环戊基苯基羟基乙酰氧基)-1’-甲基-1’-乙氧基羰基甲基溴化吡咯烷鎓；

[0076] (ii)3-[2(R)-环戊基苯基羟基乙酰氧基]-1’-甲基-1’-乙氧基羰基甲基溴化吡咯烷鎓；

[0077] (iii)3’(R)-[2(R)-环戊基苯基羟基乙酰氧基]-1’-甲基-1’-乙氧基羰基甲基溴

化吡咯烷鎓；

[0078] (iv)3'(S)-[2(R)-环戊基苯基羟基乙酰氧基]-1'-甲基-1'-乙氧基羰基甲基溴化吡咯烷鎓；

[0079] (v)1'(R)-3'(S)-[2(R)-环戊基苯基羟基乙酰氧基]-1'-甲基-1'-乙氧基羰基甲基溴化吡咯烷鎓；

[0080] (vi)1'(S)-3'(S)-[2(R)-环戊基苯基羟基乙酰氧基]-1'-甲基-1'-乙氧基羰基甲基溴化吡咯烷鎓；

[0081] (vii)1'(R)-3'(R)-[2(R)-环戊基苯基羟基乙酰氧基]-1'-甲基-1'-乙氧基羰基甲基溴化吡咯烷鎓；和

[0082] (viii)1'(S)-3'(R)-[2(R)-环戊基苯基羟基乙酰氧基]-1'-甲基-1'-乙氧基羰基甲基溴化吡咯烷鎓。

[0083] 注意到上述化合物与最初在2014年3月13日提交的美国临时专利申请号61/952,505中采用正确的但不同的命名方案公开的那些化合物是相同的。这些化合物以前分别被公开为：

[0084] (i)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0085] (ii)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0086] (iii)(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0087] (iv)(2R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0088] (v)(2R,1'R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0089] (vi)(2R,1'S,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0090] (vii)(2R,1'R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；和

[0091] (viii)(2R,1'S,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓。

[0092] 上述化合物(i)-(viii)可单独使用，或者上述化合物中的两种或更多种可联合用于单个组合物中。制备本发明化合物的各种方法在本领域中有描述。

[0093] 抗胆碱能有效量的此类药剂通过阻断乙酰胆碱与神经效应器位点处的毒蕈碱胆碱能受体的结合来抑制乙酰胆碱的作用。需要引发抗胆碱能响应的方法的受试者是患有对用抗胆碱能剂治疗有响应的状况的那些受试者，包括患有出汗过多或多汗症的受试者。

[0094] 式(1)或式(2)的化合物通常以药物组合物的形式施用，该药物组合物包含抗胆碱能有效量的该化合物、无水乙醇和无毒的药学上可接受的载体或赋形剂，条件是组合物本身也是无水的。药学上可接受的载体或稀释剂是本领域中公知的。该载体可以是适合施用的任何惰性材料、有机或无机的粉末、液体或气体，如：醇(如己二醇)、明胶、阿拉伯树胶、乳

糖、微晶纤维素、淀粉、羟乙酸淀粉钠、磷酸氢钙、硬脂酸镁、滑石、胶体二氧化硅等，条件是这些成分是无水的。

[0095] 已经发现，当不向该制剂添加水或水性载体时，得到具有有利性质的本发明制剂。因此，本文中的组合物是无水制剂。术语“无水的”是指该词语的普通科学含义，即不向制剂添加水或水性赋形剂。

[0096] 这样的组合物还可以含有常规添加剂，如溶剂、稳定剂、润湿剂、乳化剂、缓冲剂、粘合剂、崩解剂、芳香剂、润滑剂、助流剂、抗粘着剂、推进剂等，只要添加剂和组合物是无水的，即以避免对于组合物的储存稳定性的显著负面影响(通过酯类药物的水解)所需的程度不含水。

[0097] 将活性成分溶于作为溶剂的无水乙醇中，在无水乙醇中化合物是可溶或至少微溶的。优选组合物的表观pH为酸性(即表观pH<7)。

[0098] 本文中的组合物可以被配制成固体、半固体或液体，如为粉剂、溶液、洗液、乳膏、凝胶剂、半固体棒、泡沫剂、喷雾剂、气雾剂、溶液、混悬液或乳剂、贴剂、拭剂等形式，并且被配制用于局部施用。仅举例说明，为了治疗多汗症，被配制为无水止汗棒、凝胶剂、喷雾剂、乳膏、溶液、泡沫剂、乳剂等的局部用制剂可以是优选的。

[0099] 在制备制剂时，可能有必要在与其他成分合并之前研磨活性化合物以提供合适的粒度。活性化合物可被研磨至小于200目的粒度。

[0100] 待添加到在无水乙醇中的式(1)或式(2)的化合物的合适的局部用载体或赋形剂的一些实例包括醇，如己二醇和丙二醇；聚二甲基硅氧烷，例如聚二甲基硅氧烷350cSt；聚二甲基硅氧烷共聚醇、聚二甲基硅氧烷醇共混物20(Dimethiconol Blend 20)、聚二甲基硅氧烷醇20cSt；环甲基硅酮，例如环甲基硅酮5-NF；PGE；尿囊素；甘油；维生素A和E油；矿物油；PPG2；丙酸肉豆蔻酯；肉豆蔻酸异丙酯；乳酸C_{12-15}烷基酯；乳糖；右旋糖；蔗糖；山梨醇；甘露醇；淀粉；阿拉伯树胶；磷酸钙；藻酸盐；黄蓍胶；明胶；硅酸钙；微晶纤维素；聚乙烯吡咯烷酮；纤维素和甲基纤维素；及其混合物。制剂可另外包括：润滑剂如滑石、硬脂酸镁和矿物油；润湿剂；乳化剂和悬浮剂；和防腐剂如甲基羟基苯甲酸酯和丙基羟基苯甲酸酯。可以配制组合物以便在通过采用本领域已知的步骤施用和/或涂敷至受试者后提供活性成分的快速、改良、持续或延迟的释放或活性。可以通过明智地选择其他成分来避免使用单独的防腐剂，如下面更详细讨论的。

[0101] 该组合物可以另外含有一种或多种任选的添加剂，如着色剂、香料等。在实践中，这些任选的添加剂中的每一种都应与活性化合物相容。相容的添加剂是不会阻碍以本文所述的方式使用化合物或导致该化合物降解的那些添加剂。

[0102] 为了说明的目的，除非另有说明，否则液体制剂剂量是基于百分比溶液(g/100ml)或百分比浓度(w/v)来表示的。对于固体制剂剂量，除非另有说明，否则百分比浓度可表示为mg/mg或w/w浓度。本领域普通技术人员将容易地理解在所描述的制剂类型的上下文中的百分比浓度。

[0103] 一般而言，本文中的式(1)或式(2)的化合物的治疗有效量或抗胆碱能有效量为约1％溶液(10mg/ml)至约30％溶液(300mg/ml)。优选地，局部用组合物剂量为约1％浓度至约25％浓度，或更优选约1％浓度至约20％浓度，尤其是2％至10％，并且最优选每个治疗区域使用大概0.5至约1.0ml或2.0ml的包含约3％至约6％(例如约5％)的化合物的组合物的给

药涂敷体积。本发明组合物中化合物的确切剂量可根据其效力、施用方式、涂敷面积、受试者的年龄和体重以及待治疗的状况的严重程度而变化。每日剂量可以单次或多次施用，每天一至四次或更多次。

[0104] 就寝前施用(根据本文中治疗多汗症的优选方法)并不意味着在夜间或一天中特定的某个小时或某个时间；相反，就寝前意指该组合物优选通常在人的正常休息或睡眠(通常4至10小时)期之前约1-2小时内施用。根据在先共同待决的美国专利申请号14/213,242的方法，就寝前施用时间可提供式(1)和式(2)的活性化合物的优选的响应或活性。

[0105] 与施用含有相同浓度的格隆溴铵的组合物相比，施用如本文所述的组合物可在受试者体内提供基本上相同或相似的临床(汗液减少)响应。因此，这一发现的结果相对于以前公布的散瞳研究是令人惊讶的，所述散瞳研究表明，为显示出相似或基本上相同的临床响应，要求组合物中的所述化合物以格隆溴铵组合物浓度的5至10倍存在。

[0106] 另外，在初始剂量之后约6-10小时内施用第二剂量也可以是优选的施用方法或给药方案。

[0107] 用于治疗多汗症的局部用组合物可以是液体溶液、半固体或固体。溶液以常规方式制备，例如加入赋形剂以及无水乙醇溶剂，并且可包括防腐剂如对羟基苯甲酸酯或稳定剂如乙二胺四乙酸的碱金属盐，任选地使用乳化剂和/或分散剂，并且可以任选地使用其他有机溶剂作为溶剂化剂或溶解助剂，并将其转移到小瓶、安瓿、瓶、管、注射器等中。

[0108] 然而，无水组合物可具有以下优点：使在该制剂中包括另外的防腐剂的需要最小化或消除在该制剂中包括另外的防腐剂的需要。因此，组合物的一个优选实施方案是基本上“不含防腐剂”的组合物。“不含防腐剂”是指组合物虽然含有乙醇以及甚至可能的可以提供一些防腐性能的另一种有机溶剂，但是不具有出于其防腐性能而专门添加到组合物中的另外的防腐剂组分。

[0109] 在本文中的组合物中可以使用另外的载体或赋形剂，包括例如药学上可接受的有机溶剂如链烷烃(例如石油馏分)、植物油(例如花生油或芝麻油)、单官能醇或多官能醇(例如己二醇或甘油)；载体如天然矿物粉末(例如高岭土、粘土、滑石、白垩)、合成矿物粉末(例如高度分散的硅酸和硅酸盐)、糖(例如蔗糖、乳糖和葡萄糖)、乳化剂(例如木质素、亚硫酸盐废液、甲基纤维素、淀粉和聚乙烯吡咯烷酮)和润滑剂(例如硬脂酸镁、滑石、硬脂酸和十二烷基硫酸钠)。

[0110] 本文中的组合物可使用已知技术来配制，并且普遍接受与通常已知的赋形剂(包括防腐剂，如果需要的话)一起配制。例如，专利文献描述了软性格隆溴铵化合物是至少部分水溶性的。因此，软性格隆溴铵化合物如软性抗胆碱能药类似物(例如酯)在早期被描述为能够在缓冲(水性或基于水的)溶液中进行配制。但是，与包含软性抗胆碱能药类似物(酯)作为活性成分的无水制剂相比，发现向该制剂中添加水性组分增加在组合物中发现的水解产物，并降低活性化合物的稳定性，并因此降低产品的货架期。

[0111] 而且，对在水性或基于水的组合物中配制的软性抗胆碱能药类似物(酯)发现的稳定性降低和水解产物增加表明或甚至要求在该组合物中包括添加的防腐剂。

[0112] 除了一般偏好或需要降低被治疗的受试者对防腐剂化学品的暴露之外，某些成分如抗氧化剂/pH调节剂抗坏血酸在局部涂敷时可能具有另外的缺点。例如，发现包含抗坏血酸的水性制剂在暴露于该制剂后几小时至数小时后在个体的皮肤上产生粉色的残留物。

[0113] 因此，不含防腐剂的组合物(其也是不含抗坏血酸的组合物)可提供另一优点：在涂敷后以及在受试者皮肤上停留期间保持为无色制剂。包含柠檬酸作为抗氧化剂/pH调节剂的组合物在将该组合物涂敷于皮肤后不产生粉色的残留物；因此，本文中的组合物可包括柠檬酸作为抗氧化剂。

[0114] 实验数据证明，水性或基于水的组合物导致在组合物中存在的水解产物增加，并且导致组合物的稳定性降低，这导致包含该组合物的产品的货架期缩短。足够的货架期是注册审批以及局部用凝胶组合物商业成功的有利因素。

[0115] 下文实施例1中给出的HPLC实验数据还证明对于包含根据本说明书的无水局部用凝胶的产品，鉴定的水解产物减少并且稳定性增加。

[0116] 实施例1-概念验证

[0117] 考虑到与水相互作用以形成水凝胶的凝胶形成组分的可得性，水性或基于水的局部用制剂是最常见的。使用化合物(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓(上文列表中的化合物(iii)，为方便提及将其称为“BBI-4000”)来进行以下实验。

[0118] 制备约2％BBI-4000的各种制剂并评估它们的稳定性。溶剂体系如下：

[0119] (a)溶剂含量：100％水；

[0120] (b)溶剂含量：60％水/40％乙醇；

[0121] (c)溶剂含量：30％水/70％乙醇；

[0122] (d)溶剂含量：100％乙醇。

[0123] 对每个样品在基线下；在25℃/60％湿度下7天后；以及在40℃/75％湿度下7天后进行评估。在每种情况下对40℃7天后计算相对于基线的变化百分比。如下文实施例2所述进行HPLC分析。

[0124] 测试结论性地表明，在所测试的四种溶剂体系中，只有100％乙醇(即绝对或无水乙醇)能够提供甚至在升高的温度40℃下7天后也基本上维持BBI-4000的基线量的组合物。与含水制剂相比，无水乙醇制剂的稳定性显然存在显著不同。结果在下表I示出。

[0125] 表I

[0126]

制剂	**溶剂含量: 100%水**			
条件/时间点	基线	第 7 天@ 25°C/60%	第 7 天@ 40°C/75%	相对于基线的 变化 (40°C/75%)
BBI-4000 含量测定	1.99%	1.91%	1.80%	减少 9.5%
BBI-4000 主要水解 产物(RRT-0.79-0.84)	0	1.90%	7.42%	
制剂	**溶剂含量: 60%水，40%乙醇**			
条件/时间点	基线	第 7 天@ 25°C/60%	第 7 天@ 40°C/75%	相对于基线的 变化 (40°C/75%)
BBI-4000 含量测定	1.99%	1.94%	1.89%	减少 5%
BBI-4000 主要水解 产物(RRT-0.79-0.84)	0	0.83%	3.40%	
制剂	**溶剂含量: 30%水，70%乙醇**			
条件/时间点	基线	第 7 天@ 25°C/60%	第 7 天@ 40°C/75%	相对于基线的 变化 (40°C/75%)
BBI-4000 含量测定	1.99%	1.95%	1.89%	减少 5%
BBI-4000 主要水解 产物(RRT-0.79-0.84)	0	0.84%	3.50%	
制剂	**溶剂含量: 100%乙醇**			

[0127]

条件/时间点	基线	第 7 天@ 25°C/60%	第 7 天@ 40°C/75%	相对于基线的变化 (40°C/75%)
BBI-4000 含量测定	2.02%	2%	2.01%	减少<1%
BBI-4000 主要水解产物(RRT-0.79-0.84)	0	0	0	

[0128] 实施例2-水性制剂

[0129] 下表II显示了在制备的并经受水解和稳定性测试的包含BBI-4000(一种软性抗胆碱能乙酯)的水性制剂中包括的组分：

[0130] 表II

[0131]

材料	批号(% w/w)				
	BB-61-1	BB-62-1	BB-63-1	BB-64-1	BB-65-1
BBI-4000	2.00	2.00	2.00	2.00	2.00
羟乙基纤维素	1.00	1.00	1.00	1.00	1.00
己二醇	5.00	5.00	5.00	5.00	5.00
苯甲醇	1.00	1.00	1.00	1.00	1.00
95%乙醇	26.31	26.32	26.32	26.32	26.32
聚山梨醇酯80	1.00	1.00	1.00	1.00	1.00
聚二甲基硅氧烷醇共混物20	2.50	2.50	2.50	2.50	2.50
磷酸氢二钠，干燥的		0.09	0.09	0.09	
磷酸二氢钠，无水的		0.53	0.53	0.53	

[0132]

柠檬酸，无水的					0.20
柠檬酸三钠二水合物					1.16
水	61.19	60.56	60.56	60.56	59.83
2N HCl	至pH 5	至pH 4.5	至pH 5	至pH 5.5	至pH 5
2N NaOH	至pH 5	至pH 4.5	至pH 5	至pH 5.5	至pH 5

[0133] 在商业实验室开发了一种HPLC方法以分析软性抗胆碱能药类似物及相关物质(包括水解产物)：

[0134] 装置：

[0135] • 高效液相色谱仪(HPLC)系统色谱数据系统

[0136] • XBridge Shield RP18,4.6×150mm,3.5μm HPLC柱

[0137] • 能够称量至0.00001g的分析天平

[0138] • 超声波浴

[0139] • 容量瓶,1mL,5mL

[0140] • 注射器式滤器:25mm,0.45μm,HPF Millex-HV,Millipore或合适的替代物

[0141] 试剂、供应品、介质和溶液：

[0142] • BBI-4000标准品

[0143] • 水,HPLC级

[0144] • 乙腈(罐),最优级

[0145] • 三氟乙酸(TFA),Fisher

[0146] • 流动相“A”:含0.1％TFA的水

[0147] • 流动相“B”:含0.1％TFA的乙腈

[0148] • 自动采样器冲洗:1:1的水:乙腈

[0149] • 稀释剂:乙腈

[0150] BBI-4000标准品制备(在稀释剂中为2mg/mL)：

[0151] 一式两份地通过如下步骤制备标准品:称量2.0±0.1mg的BBI-4000至1mL容量瓶中。用乙腈溶解并稀释至刻度,并通过倒转进行混合。

[0152] 样品制备(BBI-4000凝胶)：

[0153] 在5-mL容量瓶中一式两份地制备目标浓度为2mg/mL的凝胶样品。添加1.5ml H_2O并混合以分散该样品。用乙腈稀释至刻度,并通过注射器式滤器过滤等份样品。

[0154] HPLC条件：

[0155] 如下所示设置液相色谱系统：

[0156] HPLC柱:XBridge Shield RP18,4.6×150mm,3.5μm

[0157] 柱温:25±1℃

[0158] 样品温度:环境温度

[0159] 流速:1.5mL/min

[0160] 进样量:10μL

[0161] UV检测:220nm

[0162] 运行时间:20分钟

[0163] 在不同的pH值下对制剂进行HPLC含量测定,并且评述“零时间”以及在40℃下7天时的结果:

[0164] 测定BBI-4000的含量。到第7天,含量测定数降低,表明BBI-4000水解,并且一些水解降解产物明显增加(两种两性离子立体异构体,通过RRT 0.84和RRT 0.80鉴定),表明这种制剂体系缺乏稳定性。单独调节pH,尽管在缓冲制剂中提供较低的水解降解百分比,但是不能解决该问题。

[0165] 使用包含在水性缓冲体系中的2%软性格隆溴铵乙酯(SGE)的制剂进行第二实验,其在冷藏、25℃(RT)和40℃下测试7天的稳定性,并显示相同的趋势或类似的结果。

[0166] 因此,不依赖于pH,当存在水或水性缓冲剂时,SGE通过水解相对快速地降解,并且在不到一周的时间内大幅减少。

[0167] 实施例3-无水制剂

[0168] 为了制备无水制剂,注意向制剂中不添加水或水性溶液。

[0169] 无水制剂是基于:不同量或比例的乙醇(溶剂)、己二醇(保湿剂)和羟丙基纤维素(HPC,胶凝剂)。如下所示给予每种制剂一个标识号:

[0170] 69-1=无抗氧化剂

[0171] 73-2=无抗氧化剂但含聚山梨醇酯80

[0172] 72-2=添加丙二醇和聚山梨醇酯80

[0173] 78-1和78-2=不同量的HPC

[0174] 79-1=含抗坏血酸作为抗氧化剂/酸化剂

[0175] 79-2=含维生素E作为抗氧化剂

[0176] 84-1=含柠檬酸作为抗氧化剂/酸化剂

[0177] 直至14天的重复给药研究

[0178] 在Göttingen小型猪中使用基于上文所述的制剂79-1和84-1的制剂(但具有相对高浓度的活性药物用于测试耐受性)进行和完成为期14天的皮肤和全身性毒性和毒代动力学研究。具体地,在该研究中使用的制剂的组成包括作为活性成分的BBI-4000(除了在仅有溶媒的对照中)、作为胶凝剂的羟丙基纤维素、作为软化剂的己二醇、作为抗氧化剂/pH调节剂的抗坏血酸或柠檬酸和作为无水溶媒的乙醇。

[0179] 在主研究中包括三组动物,每组具有1只雄性和1只雌性动物,组1接受溶媒,组2接受10%浓度的BBI-4000凝胶,组3接受20%浓度的BBI-4000凝胶。所有组接受2mL凝胶制剂,一天一次,连续14天,涂敷于其背部上大约10%的体表区域。

[0180] 研究包括每天观察涂敷部位、红斑和水肿(如果存在)评分、每天一般检查(包括心率)以及在第1、2、3、5、7、10和14天进行的瞳孔大小评估。经常观察心率和瞳孔大小旨在用于识别任何潜在的全身性抗胆碱能效应。在尸检过程中评价主要器官,并对于经过治疗和未经治疗的皮肤完成组织病理学评价。收集用于化学和血液学分析的血液样品以及PK样

品。

[0181] 结果显示该组合物被良好地耐受,在任何动物的经过治疗的皮肤中没有红斑或水肿的迹象。每天观察报告心率或任何其他参数没有任何异常。在所有动物中在所有时间下瞳孔大小评估被报告为正常。血液化学和血液学参数被报告在正常范围内。尸检揭示任何动物没有任何异常。

[0182] 对于用包含BBI-4000的无水组合物治疗的皮肤的组织病理学分析是不显著的并且与未经治疗的和溶媒治疗的皮肤相同。来自不同组的所有皮肤样品是相似的,具有较小的似乎与治疗无关的非特异性变化。报告的在来自所有组以及来自未治疗区域的大多数皮肤样品的真皮中有轻度、浅表炎症表明这一发现与药物或组合物无关,但与动物的关进笼子相关。

[0183] 在该研究中涂敷于皮肤的BBI-4000的预估剂量为:组3为40mg/kg/天,组2为20mg/kg/天。

[0184] PK分析揭示BBI-4000的可变的、剂量相关的全身性暴露。在接受20%BBI-4000浓度的小型猪中在第14天给药后2小时观察到最高浓度。羧酸代谢物的大多数PK值低于最低定量限(对于该含量测定,LLOQ=4.75ng/mL),与该代谢物的短半衰期一致。组1(溶媒)未报告任何高于LLOQ的值,如预期的那样。

[0185] 在该研究期间注意到在接受含抗坏血酸的制剂的所有动物的皮肤中观察到淡红色的制剂残留物。尽管通过擦拭皮肤可以除去该残留物,这种类型的残留物对人类受试者而言是不可接受的;因此,对另外的制剂进行评价。在两只新猪中采用除去抗坏血酸而代替添加柠檬酸的新制剂进行新实验。含柠檬酸的制剂的测试也被良好耐受,并且未观察到淡红色或粉色残留物。

[0186] 测试以下在表III中示出的制剂的稳定性:

[0187] 表III

[0188]

组分	A 84-1 % (w/w)	B 84-2 % (w/w)	C 84-3 % (w/w)
BBI-4000	10	10	10
KLUCEL™ MF (羟丙基纤维素)	1.25	1.25	1.25
己二醇	10	10	10
聚二甲基硅氧烷醇共混物 20	2.5	2.5	2.5
BHT	--	0.1	--
没食子酸丙酯	--	--	0.05
柠檬酸，无水的	0.1	0.1	0.1
乙醇(标准酒精度 200) (无水乙醇)	76.15	76.05	76.1

[0189] KLUCEL™ MF羟丙基纤维素(HPC)可从各种来源商购获得。DOWCORNING®聚二甲基硅氧烷醇共混物20是硅氧烷胶(6%)在聚二甲基硅氧烷中的独特共混物。BHT是丁基化的羟基甲苯,也称为二丁基羟基甲苯。

[0190] 在时间“零”时测定的BBI-4000和非-BBI-4000的水平显示在下表IV中：

[0191] 表IV

[0192]

第零天的结果		BB-84-1		BB-84-2		BB-84-3	
BBI-4000	含量测定 (Wt %)	9.81%		9.89%		9.72%	
	TAN %	98.19%		95.15%		92.17%	
通过HPLC测定的非-BBI-4000 (%)		RRT	面积%	RRT	面积%	RRT	面积%
		RRT 0.80	0.67%				
		RRT 0.96	0.10%	RRT 0.80	0.62%	RRT 0.64	6.07%
		RRT 1.09	0.86%	RRT 0.96	0.07%	RRT 0.80	0.69%
		RRT 1.48	0.19%	RRT 1.09	0.79%	RRT 0.96	0.09%
				RRT 1.49	0.16%	RRT 1.09	0.81%
				RRT 2.05	0.90%	RRT 1.49	0.17%
				RRT 2.07	2.31%		
通过HPLC测定的非-BBI-4000总量(%)		1.82%		4.85%		7.83%	

[0193] 在40℃的加速条件下7天时测定的BBI-4000和非-BBI-4000水平示于下表V中：

[0194] 表V

[0195]

第7天的结果		BB-84-1		BB-84-2		BB-84-3	
BBI-4000	含量测定 (Wt %)	10.32%		10.18%		10.08%	
	TAN %	97.89%		94.75%		93.84%	
通过 HPLC 测定的非 -BBI-4000 (%)		RRT	面积%	RRT	面积%	RRT	面积%
		RRT 0.80	0.59%	RRT 0.80	0.42%	RRT 0.64	4.28%
		RRT 0.82	0.03%	RRT 0.91	0.16%		
		RRT 0.91	0.17%	RRT 0.96	0.15%	RRT 0.80	0.58%
		RRT 0.96	0.29%	RRT 1.09	0.96%	RRT 0.96	0.20%
		RRT 1.08	0.04%	RRT 1.49	0.18%	RRT 1.09	0.90%
		RRT 1.09	0.80%	RRT 1.50	0.02%	RRT 1.49	0.18%
		RRT 1.49	0.19%	RRT 2.05	0.88%	RRT 1.50	0.02%
		RRT 1.50	0.01%	RRT 2.07	2.49%		
通过 HPLC 测定的非 -BBI-4000 总量(%)		2.11%		5.25%		6.16%	

[0196] 所有制剂均显示出良好的稳定性，然而在制剂中不存在抗氧化剂没食子酸丙酯或BHT的制剂中鉴定出较少的非-BBI-4000物质。

[0197] 使用制剂编号84-1在三种温度下进行测试：加速(40℃)、室温(25℃)和冷藏(约4℃)，已完成了为期3个月的进一步稳定性测试。使用下面的制备说明专门制备制剂编号84-1：

[0198] a)在合适的容器中合并已二醇和乙醇并混合；

[0199] b)添加柠檬酸并搅拌以溶解；

[0200] c)添加活性成分(BBI-4000)并搅拌以溶解；

[0201] d)添加KLUCEL™ MF并搅拌以溶解，以增加产品的粘度；

[0202] e)最后，添加聚二甲基硅氧烷醇共混物20并简单地分散；

[0203] f)均质化步骤a)至e)的混合物。对于小批次，可通过在用微乳化针连接的两个注射器之间通过/混合来进行均质化。对于较大的批次，可能需要顶置式或内联式均质器。

[0204] 3个月的稳定性研究结果在下表VI中提供：

[0205] 表VI制剂A 84-1的稳定性

[0206]

天/温度	0	7D-40C	14D-40C	30D-40C	30D-5C	90D-5C	30D-25C	90D-25C
测定BBI-4000 (%)	9.81	10.32	10.21	10.25	9.32	10.50	10.26	10.63
通过HPLC测定的非-BBI-4000总量(%)	1.82	2.12	2.12	3.48	2.77	2.35	3.29	3.87

[0207] 具有表VII中所示配方的制剂84-1显示良好的稳定性，并进行体内测试。

[0208] 表VII

[0209]

组分	A 84-1 % (w/w)
BBI-4000	10
KLUCEL™ MF (羟丙基纤维素)	1.25
己二醇	10
聚二甲基硅氧烷醇共混物20	2.5

[0210]

柠檬酸，无水的	0.1
乙醇(标准酒精度 200) (无水乙醇)	76.15

[0211] 在下面的临床研究中，上面的A 84-1制剂略有改变。对于5％和10％的BBI-4000凝胶，分别使用0.001％的无水柠檬酸，并相应地调节乙醇的量(对于5％凝胶为81.25％，对于10％凝胶为76.25％)。

[0212] 实施例4-临床研究

[0213] 研究BBI-4000-CL-101:用于评价在多汗症受试者中局部涂敷的BBI-4000凝胶的安全性和对汗液产生的效果的一项单中心、随机、双盲、溶媒对照的研究

[0214] 研究设计和纳入标准

[0215] 研究BBI-4000-CL-101是在24名具有腋窝多汗症的受试者中进行的BBI-4000凝胶的1期、随机、双盲和溶媒对照研究。这项研究是在多米尼加共和国的一个中心进行的。这项研究不是根据US IND进行,而是完全遵守多米尼加共和国的适用规定和良好药品临床实践指南进行的。

[0216] 这项探索性研究的目的是评价局部涂敷的BBI-4000凝胶的安全性、局部耐受性以及对汗液产生的效果。在局部涂敷凝胶之后,还进行了基于BBI-4000的药代动力学对全身性暴露的初步评估。

[0217] 这项研究中使用的药物产品是具有包括BBI-4000、羟丙基纤维素、己二醇、聚二甲基硅氧烷醇共混物20、柠檬酸和乙醇的组成的无水半透明凝胶。

[0218] 该研究由2个连续队列组成,其中队列1在使单独的一组受试者入选队列2之前建立5%BBI-4000凝胶(涂敷于一个腋窝)的可接受的耐受性:

[0219] • 队列1:基于随机、分体(split-body)设计,6名受试者每天一次(在夜间)在一个腋窝接受5%BBI-4000凝胶而在另一个腋窝接受溶媒,连续14天。

[0220] • 队列2:基于平行组设计,18名受试者(每个治疗组6名)每天一次(在夜间)随机在两个腋窝接受5%BBI-4000凝胶、10%BBI-4000凝胶或溶媒(对照),连续14天。

[0221] 受试者年龄为18至45岁,一般健康状况良好,在基线时根据以下标准诊断患有原发性腋窝多汗症:

[0222] • HDSS为3或4(HDSS=多汗症疾病严重程度分数)

[0223] • 重量测定试验显示,在休息状态下(在25℃至27℃下)在5分钟内每个腋窝的汗液产生平均值至少为100mg

[0224] • 双侧且对称的多汗症

[0225] 先前腋窝使用肉毒杆菌毒素(在2年内)或接受任何抗胆碱能药物的受试者不符合参与研究的条件。要求所有有生育潜力的女性受试者在接受积极治疗的同时使用医学上可接受的避孕方法。

[0226] 在基线评估前7天以及在研究持续期间,不允许受试者使用任何止汗剂。

[0227] 研究评估和终点

[0228] 局部耐受性评估

[0229] 对局部用BBI-4000的局部耐受性由研究人员(红斑、干燥和脱屑)和研究受试者(灼热和瘙痒)进行评估。

[0230] 研究人员基于4点量表对每个腋窝进行红斑、干燥和脱屑的严重程度分级,其中“0”为不存在,“1”为最小的(几乎不可察觉),“2”为轻度的,“3”为中度的,“4”为重度的。

[0231] 受试者基于4点量表评估任何灼热或瘙痒的严重程度,其中“0”为不存在,“1”为最低程度的(可意识到,但没有不适),“2”为轻度的,“3”为中度的,“4”为重度的。

[0232] 安全性评估

[0233] 通过AE、严重AE(SAE)或非预期AE;生命体征(血压和心率);以及临床实验室测量(血液学、化学和尿分析)来评估安全性。临床相关实验室检查结果将被收集为AE(AE=不良

事件)。

[0234] 疗效评估

[0235] 通过从基线至第15天(治疗结束)重量测定测量的汗液产生的变化和多汗症疾病严重程度量表(HDSS)的变化来评估疗效。

[0236] 对于重量测定评估,通过将滤纸(预先称重)放置在腋窝上5分钟,同时让受试者处于室温下半坐卧位来测量汗液产生。在暴露于腋窝的过程中,用塑料覆盖滤纸,然后在5分钟暴露期后称重,计算产生的汗液量。

[0237] 对于HDSS,受试者基于对他们日常活动的干扰程度在4点量表(1、2、3或4)上评定他们的多汗症的严重程度。1分表示"我的出汗从不明显,并且从未干扰我的日常活动";4分表示"我的出汗是不能忍受的,并且总是干扰我的日常活动"。

[0238] 研究BBI-4000-CL-101的主要结果

[0239] 所有受试者都完成了该项研究(包括在第16天的随访),并根据研究方案接受了14天的研究治疗。所有受试者均被包括在研究评估分析中(可评价人群)。队列1(分体)中的受试者报告没有AE,并且对于5%BBI-4000凝胶和溶媒都耐受良好,在研究期间在几个受试者中报告了仅最低程度至轻度的干燥和红斑。

[0240] 在平行设计中在两个腋窝区域都接受研究药物的队列2受试者的结果被认为是来自该研究的最信息化的数据,并且集中在以下部分。

[0241] 这是一项探索性研究,不仅能实现所测量的疗效参数的统计学显著差异,而且还提供对于局部涂敷的BBI-4000的安全性、耐受性和潜在治疗效果的早期指示。

[0242] 基线人口统计数据和疾病特征

[0243] 队列2中的受试者的年龄范围为18.6至43.7岁,每个治疗组的中位年龄为≤31岁。所有受试者都是西班牙人/拉丁美洲人。在治疗组之间就性别、种族或民族没有观察到不平衡。

[0244] 基线时汗液产生的测量值在治疗组之间一般是相似的,并与腋窝多汗症一致。基于基线重量测定评估,所有治疗组在5分钟的时间内汗液产生的中位值为>200mg(两个腋窝)。所有受试者在基线时具有3或4的HDSS分数。

[0245] 局部耐受性

[0246] 基于研究者和受试者的局部耐受性评估表明,局部涂敷于腋窝区域的5%和10%的BBI-4000凝胶在14天的治疗期间内耐受性良好。1或2名受试者偶尔报告了干燥、红斑、瘙痒和灼热,它们是最低程度的,并且未导致任何个体的治疗中止。

[0247] 安全性

[0248] 在研究进行期间任何受试者均未报告AE,并且未报告死亡或严重AE。

[0249] 通过随访期(第16天)被认为是临床相关的实验室参数没有发生变化,如研究人员报告的无实验室相关的AE所表明的。

[0250] 在研究期间,对于任何一个队列中的任何治疗组,生命体征(血压和心率)没有相对于基线的临床相关的变化。

[0251] 疗效

[0252] 在与溶媒相比时,BBI-4000制剂显示出实现了重量测定测量的汗液产生的更大减少和HDSS评估的更大改善。尽管总体汗液产生减少和HDSS改善的终点表明BBI-4000 10%

凝胶的性能优于BBI-4000 5％凝胶，但是由于这一样本量较小，很难就这两个活性制剂(active arms)的效果幅度差异作出确定性的结论。此处提供了与溶媒相比达到通常与临床上有意义的改善相关的关键终点(即汗液产生减少至少50％和HDSS具有≥2点的改善)的暴露于BBI-4000的受试者的总数的结果。

[0253] 用BBI-4000治疗的在第15天汗液产生减少至少50％的受试者比例为75％(12个中的9个)，与之相比，接受溶媒的受试者比例为33％(6个中的2个)。此外，接受BBI-4000的12个受试者中有8个(67％)报告在第15天实现≥2点的HDSS改善，而在溶媒组中6个受试者中有2个(33％)报告在第15天实现≥2点的HDSS改善。对这些受试者而言，HDSS分数的这种降低代表了从不能忍受的或勉强可忍受的多汗症到可忍受的或从不明显的多汗症的有意义的改变。

[0254] 实施例5-其他无水制剂

[0255] 开发了其他制剂，如下表所示。

[0256] 表VIII

[0257]

组分	组成(% w/w)				
	凝胶 2	凝胶 3	凝胶 4	凝胶 5	凝胶 6
羟丙基纤维素	1.250	1.250	1.250	1.250	1.250
BBI-4000	5.000	5.000	5.000	5.000	5.000

[0258]

己二醇	10.000	10.000	10.000	10.000	10.000
柠檬酸，无水的	0.001	0.001	0.001	0.001	0.001
滑石	0.500	-	-	-	-
乳酸 C12-15 烷基酯	-	2.500	-	-	-
聚二甲基硅氧烷共聚醇	-	-	1.000	-	-
硬脂酸镁	-	-	-	0.001	-
肉豆蔻酸异丙酯(IPM)	-	-	-	-	2.500
乙醇，无水的	补足至100	补足至100	补足至100	补足至100	补足至100
在 t=0 时的目测外观	半透明，中等至高粘度，光滑	无色透明，低粘度，光滑	无色透明，低粘度，光滑	无色透明，低粘度，光滑	无色透明，低粘度，光滑
评估短期稳定性	√	√	√	√	√

[0259] 举例来说，BBI-4000的量可替代地为10.000、15.000或20.000(%w/w)，并且相应地调整无水乙醇的量。

[0260] 下表IX中列出了根据上述量的其他制剂。

[0261] 表IX

[0262]

组分	组成(% w/w)				
	凝胶 AA	凝胶 BB	凝胶 CC	凝胶 DD	凝胶 EE
羟丙基纤维素	1.250	1.250	1.250	1.250	1.250
BBI-4000	10.000	10.000	10.000	10.000	10.000
己二醇	10.000	10.000	10.000	10.000	10.000

[0263]

柠檬酸，无水的	0.001	0.001	0.001	0.001	0.001
聚二甲基硅氧烷，例如 350 cSt	1.000	0.500	-	1.000	1.000
环甲基硅酮，例如 5-NF	1.000	1.000	1.000	-	-
肉豆蔻酸异丙酯	-	-	2.500	-	2.500
丙酸肉豆蔻酯	-	-	-	2.500	-
乙醇，无水的	补足至 100	补足至 100	补足至 100	补足至 100	补足至 100

[0264] 举例来说，BBI-4000的量可替代地为5.000％w/w、15.000％w/w或20.000％w/w，并且相应地调整无水乙醇的量。

[0265] 以下是本发明组合物的特别优选的实施方案的一般性配方。

[0266] 配方

[0267]

组分	量
BBI-4000	1%至 20% w/w
己二醇	10% w/w
羟丙基纤维素	1.25% w/w
柠檬酸，无水的	0.001 % w/w
聚二甲基硅氧烷醇共混物 20 或肉豆蔻酸异丙酯	2.5% w/w
无水乙醇	补足至 100 % w/w

[0268] 其他优选的实施方案在上述配方中包括替代聚二甲基硅氧烷醇共混物20的单独的或组合的聚二甲基硅氧烷或环甲基硅酮，任选地与肉豆蔻酸异丙酯一起。

[0269] 在这些组合物中，出于两个原因，肉豆蔻酸异丙酯相对于聚二甲基硅氧烷醇共混物20是优选的。第一个原因与生产工艺的转移和放大有关。已经发现，当试图增加批量大小和转移生产工艺时，难以稳定制剂中的聚二甲基硅氧烷醇共混物20的液滴。随着时间的推移，少量的聚二甲基硅氧烷醇共混物20在容器底部聚结为小液滴。改变为肉豆蔻酸异丙酯(IPM)则消除了这个问题。第二个原因与FDA对聚二甲基硅氧烷醇共混物20的接受性有关。尽管聚二甲基硅氧烷醇共混物20是化妆品制剂中可接受的成分，但以前并未在药物制剂中得到批准。FDA接受其用于临床研究中，但是可能需要额外的研究来确定其有资格用于最终制剂中。改变为肉豆蔻酸异丙酯消除了进行这种额外测试的需要，因为IPM已经在其他药物制剂中得到批准，聚二甲基硅氧烷醇共混物20对制剂的功能无害；然而，肉豆蔻酸异丙酯有益于放大和商业化。在评价多种可替代物之后，基于其在干燥期间降低粘性以及提供相似的体外渗透性的能力，选择了肉豆蔻酸异丙酯。它还提供具有与聚二甲基硅氧烷醇共混物20类似的化学稳定性特性的制剂。在临床前动物研究中，将肉豆蔻酸异丙酯制剂与聚二甲基硅氧烷醇共混物20制剂进行比较。肉豆蔻酸异丙酯制剂证明相对于聚二甲基硅氧烷醇共混物20制剂在小型猪中渗透增加。计划了两项即将进行的人体研究。第一项研究将比较含有肉豆蔻酸异丙酯的5％和15％的BBI-4000凝胶与含有聚二甲基硅氧烷醇共混物20的15％的BBI-4000凝胶的药代动力学。第二项研究将评价/证实含有肉豆蔻酸异丙酯的BBI-4000凝胶的疗效。

[0270] 虽然为了公开的目的阐述了某些优选的和替代的实施方案，但是对于本领域技术人员来说，可以对所公开的实施方案进行修改。因此，本说明书旨在覆盖不偏离以下权利要求书的精神和范围的所有实施方案及其组合和修改。

Abstract

Topical formulations comprising soft glycopyrrolates are useful for treating excessive sweating conditions in subjects, such as humans suffering from hyperhidrosis. Preferably, at least one soft anticholinergic agent is provided in an effective amount or concentration in an anhydrous formulation that can inhibit excessive perspiration resulting from a condition such as hyperhidrosis.