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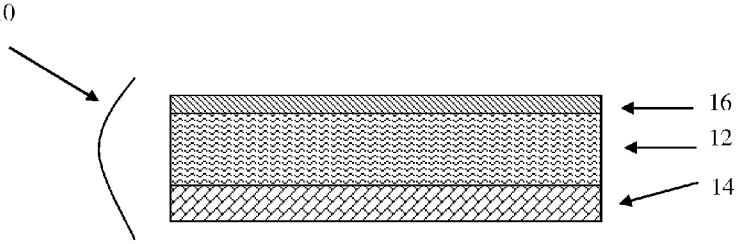
(54) **Title**: EXTENDED-RELEASE BETA AGONIST/ANTICHOLINERGIC TRANSDERMAL PATCHES AND METHODS FOR USING THE SAME

FIGURE 1



(57) **Abstract**: Extended-release beta agonist/anticholinergic transdermal patches are provided. Transdermal patches have an adhesive matrix which includes both a beta agonist, e.g., tulobuterol, and an anticholinergic, e.g., scopolamine, where the matrix is configured to be storage-stable and provide for extended release of the beta agonist and anticholinergic. Aspects of the invention further include methods of using the transdermal patches, e.g., in the treatment of pulmonary conditions, such as chronic obstructive pulmonary disease (COPD).

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EXTENDED-RELEASE BETA AGONIST/ANTICHOLINERGIC TRANSDERMAL PATCHES AND METHODS FOR USING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 U.S.C. § 119 (e), this application claims priority to the filing date of the United States Provisional Patent Application Serial No. 61/436,489, filed January 26, 2011; the disclosure of which is herein incorporated by reference.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic inflammatory process and irreversible airflow obstruction with a decline in the lung function FEV1 (i.e., forced expiratory volume in 1 second). The disease may be divided into two subgroups, namely chronic bronchitis and emphysema. Chronic bronchitis is characterized by mucus hypersecretion from the conducting airways, inflammation and eventual scarring of the bronchi (airway tubes). Emphysema is characterized by destructive changes and enlargement of the alveoli (air sacs) within the lungs. Many persons with COPD have a component of both of these conditions. COPD patients have difficulty breathing because they develop smaller, inflamed air passageways and have partially destroyed alveoli.

The presenting symptoms for COPD are typically breathlessness accompanied by a decline in FEV1. Chronic bronchitis can also be diagnosed by asking the patient whether they have a "productive cough," i.e. one that yields sputum. COPD patients are traditionally treated with bronchodilators and/or anticholinergics and evaluated by spirometry for the presence of airflow obstruction and reversibility. If airflow obstruction is present and reversibility less than 15%, particularly in a smoker, then they are often diagnosed as having COPD.

At the cellular level, COPD is characterized by an increase in the activation and/or number of alveolar macrophages, CD_8^+ T-cells and neutrophils. The neutrophil is believed to play a central role in the pathophysiology of COPD. Neutrophil activation results in the release of a number of inflammatory mediators and proteinases, most importantly neutrophil elastase which contributes to the progressive fibrosis, airway stenosis and destruction of the lung parenchyma,

leading to an accelerated decline in airway function. Neutrophil elastase also induces mucus secretion and thus may contribute to the characteristic mucus hypersecretion that characterizes COPD.

Currently, there is no known cure for COPD.

SUMMARY

Extended-release beta agonist/anticholinergic transdermal patches are provided. Transdermal patches of embodiments of the invention have an adhesive matrix which includes both a beta agonist, e.g., tulobuterol, and an anticholinergic, e.g., scopolamine, where the matrix is configured to be storage-stable and provide for extended release of the beta agonist and anticholinergic. Aspects of the invention further include methods of using the transdermal patches, e.g., in the treatment of pulmonary conditions, such as chronic obstructive pulmonary disease (COPD).

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 provides a cross-sectional view of a transdermal patch preparation according to the invention.

DETAILED DESCRIPTION

Extended-release beta agonist/anticholinergic transdermal patches are provided. Transdermal patches have an adhesive matrix which includes both a beta agonist, e.g., tulobuterol, and an anticholinergic, e.g., scopolamine, where the matrix is configured to be storage-stable and provide for extended release of the beta agonist and anticholinergic. Aspects of the invention further include methods of using the transdermal patches, e.g., in the treatment of pulmonary conditions, such as chronic obstructive pulmonary disease (COPD).

Before the present invention is described in greater detail, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are now described.

The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

It is noted that, as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

EXTENDED-RELEASE TRANSDERMAL PATCHES

As summarized above, aspects of the invention include extended-release transdermal patches, where the transdermal patches are configured to transdermally deliver (i.e., deliver across the skin into the bloodstream) a therapeutic amount of both a beta agonist, e.g., tulobuterol, and an anticholinergic, e.g., scopolamine, for an extended period of time. The therapeutic amount that is delivered by the patches may vary depending on the particular condition being treated. In some instances, the transdermal patches are configured to provide a plasma level of a beta agonist, e.g., tulobuterol, which ranges from 0.5 ng/ml to 5 ng/ml, such as 1 ng/ml to 3 ng/ml. In some instances, the transdermal patches are configured to provide a plasma level of an anticholinergic, e.g., scopolamine, which ranges from 0.1 ng/ml to 1.0 ng/ml, such as 0.2 ng/ml to 0.4 ng/ml. While the extended period of time over which the therapeutic amount is provided may vary, in some instances the extended period of time is 6 hours or longer, such as 12 hours or longer, including 24 hours or longer.

Transdermal patches of certain embodiments include an adhesive layer and a backing layer. The adhesive layer includes an amount of both a beta-agonist and an anticholinergic agent as active agents in an adhesive matrix that is formulated to provide extended release of the active agents, e.g., as described above. FIG. 1 provides a schematic of a transdermal patch according to certain embodiments of the invention. As can be seen in FIG. 1, the depicted transdermal patch 10 contains an adhesive base 12 present on a surface of a backing 14 (i.e., support).

Adhesive layers of interest include an amount of both a beta agonist and an anticholinergic present in an adhesive matrix, where the adhesive layer is a homogenous mixture of the active agents in the matrix material. The amount of the active agents present in the adhesive matrix may vary. In some instances, the total amount of active agent (i.e., the combined amount of both the beta agonist and the anticholinergic together) ranges from 0.5 to 10, such as 1 to 5 and including 1 to 3 % by weight. The weight ratio of the beta agonist to the anticholinergic in the adhesive layer may also vary, ranging in some instances from 15 to 1, such as 10 to 1 and including 3 to 1. In some instances, the amount of beta agonist in the adhesive layer ranges from 0.01 to 5, such as 0.1 to 4 and including from 0.2 to 2 % by weight.

BETA AGONISTS

A variety of different beta agonists may be employed in patches of the invention. Beta agonists of interest include, but are not limited to: amines, such as secondary amines, e.g., 2-hydroxy-phenyl-ethyl amines, e.g., salmeterol, formoterol, albuterol, bambuterol, procaterol, and tulobuterol. The beta agonist is generally present as a free base, although a pharmaceutically acceptable salt may also be employed. The total amount of beta agonist in the adhesive matrix may vary, and in some instances ranges from 1 to 5 w/w %, such as from 1 to 3 w/w %.

ANTICHOLINERGICS

A variety of different anticholinergics may be employed in patches of the invention. Anticholinergics of interest include, but are not limited to, amines, e.g., tertiary amines. The nitrogen of the tertiary amine may be part of a ring, e.g., glycopyrrolate, or acyclic, e.g., isopropamide, orphenadrine, benzalkonium chloride, etc. In some cases, the tertiary amine includes a tropane group, i.e., a bridged nitrogenous bicyclic group such as is found in a tropane alkaloid, or an N-alkylated version thereof. The tropane group may be substituted with an arylalkanoyloxy substituent such as a phenylalkanoyloxy or a thienylacetyloxy substituent. In some cases, the thienylacetyloxy substituent is a hydroxidi-2-thienylacetyloxy group. In some cases, the phenylalkanoyloxy substituent is a 2-hydroxy-phenylacetate or a 3-hydroxy-2-phenylpropanoyloxy group. Tropane containing tertiary amines of interest include Scopolamine, Atropine, Hyoscyamine, and Tiotropium. The anticholinergic of interest may be an individual isomer of any of the above or a pharmaceutically acceptable salt or hydrate of any of the above, or a combination of two or more of the above. The anticholinergic may be present as a free base or pharmaceutically acceptable salt. A given topical patch may include a single anticholinergic or two or more different anticholinergics in combination. The total amount of the one or more anticholinergics in the adhesive matrix may vary, and in some instances ranges from 0.1 to 5 w/w %, such as from 0.2 to 2 w/w %.

ADHESIVE MATRICES

As reviewed above, the adhesive layer comprises an adhesive matrix. The adhesive matrix is configured to provide for the desired extended release of the

active agents. As such, the various components of the matrix are chosen and present in amounts that provide for the desired extended release of the active agents. In some instances, the adhesive matrices include the following components: a rubber; an adhesive resin; and a higher fatty acid. Each of these components is now described in great detail below.

Rubber

Any convenient rubber may be employed in the adhesive matrix, including both natural and synthetic rubbers. Suitable synthetic rubber-type adhesives include, but are not limited to, styrene-isoprene-styrene block copolymer, polyisobutylene, isoprene rubber, styrene-butadiene-styrene block copolymer, styrene-butadiene rubber, and silicon rubber. The adhesive will, in some instances, comprise one type of synthetic rubber. In other embodiments, the adhesives will include two or more types of synthetic rubber. The total amount of the one or more rubbers in the adhesive matrix may vary, and in some instances ranges from 5 to 35 w/w %, such as from 10 to 30 w/w %, including from 15 to 25 w/w %.

Adhesive Resin

As summarized above, in addition to the rubber(s), the matrix further includes an adhesive resin. Any convenient adhesive resin may be employed. Adhesive resins of interest include, but are not limited to: petroleum resins, polyterpene resins, polyolefin resins, rosin-type resins, resin-ester-type resins, saturated alicyclic hydrocarbon resins, oil-soluble phenol type resins, etc. The adhesive will in some instances comprise one type of adhesive resin. In other embodiments, the adhesive will include two or more types of adhesive resins. The total amount of the one or more adhesive resins in the adhesive matrix may vary, and in some instances ranges from 20 to 70 w/w %, such as from 30 to 60 w/w %, including from 40 to 55 w/w %.

Higher Fatty Acid

As summarized above, the matrix further includes a higher fatty acid. Any convenient higher fatty acid may be employed. Higher fatty acids of interest include C_{11-22} fatty acids, such as C_{14-18} fatty acids. Specific higher fatty acids of interest include, but are not limited to: linolic acid, linolenic acid, oleic acid, stearic acid,

palmitic acid, lauric acid, myristic acid, isostearic acid, ricinolic acid, etc. The adhesive will, in some instances, comprise one type of higher fatty acid. In other embodiments, the adhesive will include two or more types of higher fatty acids. The total amount of the one or more higher fatty acids in the adhesive matrix may vary, and in some instances ranges from 0.1 to 3 w/w %, such as from 0.2 to 2 w/w %, including from 0.3 to 1 w/w %.

Plasticizer

Where desired, the matrix further includes a plasticizer. Any convenient plasticizer may be employed. Plasticizers of interest include, but are not limited to: oils, liquid paraffins, polybutenes, etc. The adhesive will, in some instances, comprise one type of plasticizer. In other embodiments, the adhesive will include two or more types of plasticizers. The total amount of the one or more plasticizers in the adhesive matrix may vary, and in some instances ranges from 5 to 60 w/w %, such as from 10 to 50 w/w %, including from 15 to 30 w/w %.

Anti-Oxidant

Where desired, the matrix further includes an antioxidant component. Any convenient anti-oxidant may be employed. Antioxidants of interest include, but are not limited to: ascorbic acid, tocopherol acetate, natural vitamin E, dibutylhydroxytoluene, butylhydroxyanisole and the like. The adhesive will, in some instances, comprise one type of antioxidant. In other embodiments, the adhesive will include two or more types of antioxidants. The total amount of the one or more antioxidants in the adhesive matrix may vary, and in some instances ranges from 0.25 to 5 w/w %, such as from 0.5 to 4 w/w %, including from 0.5 to 3 w/w %.

Additional components

The adhesive layer of a transdermal patch will in some embodiments include, in addition to the above-discussed components, one or more additional components. Additional components of interest include, but are not limited to, a transdermal absorption enhancer, a preservative (e.g., paraben), a stabilizing agent, a filling agent that contains a hydrophilic polymer; cross-linking agents; etc. However, in some embodiments, the transdermal patch does not include any of these additional components.

ADDITIONAL CHARACTERISTICS

As summarized above, an aspect of the subject transdermal patches is that they are storage stable. By storage-stable is meant that the compositions may be stored for extended periods of time without significant degradation and/or significant reduction in activity of the beta agonist and anticholinergic active agents. In certain embodiments, the subject compositions are stable for 3 years or longer, etc., when maintained at 25°C. In some instances, the above storage stability values are determining using the protocol described in United States Published Application Publication No. US 2009-0297590, modified to evaluate the presence of the beta agonist and anticholinergic free base (the disclosure of the storage stability assay reported in this publication is specifically incorporated by reference).

In some embodiments, the adhesive layers are self-adhesive, i.e., inherently adhesive, and thus may be fixed in a position over the skin, i.e., removably bonded to and/or about a given skin surface, without the use of additional adhesives or other means to hold the transdermal patch in place over the formulation. As the adhesive compositions are adhesive, when applied to human skin they remain stably positioned at the site of application. As such, application of force is required to remove the adhesive compositions from the site of application. While application of force is required for removal, the adhesive compositions are not so adhesive such that removal of the compositions irritates or wounds the skin site to which the compositions were applied. In certain other embodiments, a subject transdermal patch may be held in a fixed position on a skin surface using a separate adhesive such as an adhesive backing or the like or a combination of inherent adhesiveness and an additional separate adhesion means may be employed.

The shape of the patch may vary, where shapes of interest include, but are not limited to: square, rectangle, oval, circle, etc. The size of the patch may also vary, where in certain embodiments the size ranges from about 1 to 20 cm^2, such as 1 to 15 cm^2, such as 1 to 10 cm^2.

BACKING LAYER

The transdermal patch, which includes an adhesive layer, e.g., as described above, also includes a backing (i.e., support), where the adhesive layer is present on a surface of the backing. The backing may be made of a flexible material which

is capable of fitting in the movement of human body. Flexible materials of interest include, but are not limited to: various non-woven fabrics, woven fabrics, spandex, flannel, or laminates of these materials with polyethylene film, polyethylene glycol terephthalate film, polyvinyl chloride film, ethylene-vinyl acetate copolymer film, polyurethane film, and the like.

Suitable backing layer materials include, but are not limited to, polyethylene terephthalate, polyethylene, polypropylene, vinyl acetate-vinyl chloride copolymer, polyurethane, acetylcellulose, ethylcellulose, soft polyvinyl chloride, polyvinylidene chloride, polytetrafluoroethylene, polyamide, paper, a single film of metal foil such as aluminum foil or a laminated film of foil, woven or unwoven fabric made from the aforementioned materials, and combined materials with the aforementioned films.

RELEASE FILM

In addition to the adhesive layer and the backing, transdermal patches may also include a release film (shown as element 16 in FIG. 1) on the surface of the adhesive layer that is opposite the backing. The release film may provide for protection of the adhesive layer from the environment. The release film may be any convenient material, where release films include polyesters, such as PET (polyethylene terepthalate) or PP (polypropylene), and the like.

SEALED PACKAGE

In certain embodiments, transdermal patches are present in a sealed package. The sealed package may be fabricated from a packaging material that includes a hydrophilic layer to prevent the passage of oxygen, and a hydrophobic layer to prevent passage of moisture and other polar materials. Barrier materials of interest also include metallic layers, e.g., aluminum, where in certain embodiments, the barrier layer is an aluminum layer. This barrier layer has a thickness sufficient to provide for the barrier function, where the thickness may range in some instances from 5 to 15, such as 6 to 10 μm. In certain embodiments, the package is a laminate of the barrier layer in combination with one or more additional layers, e.g., polymeric layers, paper layers, etc. An aluminum containing package that may be used with the subject patch preparations is sold by Dainippon Printing Co., Ltd. (Kyoto, Japan).

EXTENDED-RELEASE TRANSDERMAL PATCH FABRICATION

Transdermal patches of the invention may be fabricated using any convenient protocol. In one protocol of interest, components of the adhesive layer, e.g., matrix components such as the rubber, adhesive resin, higher fatty acid, plasticizer and anti-oxidant are combined with the active agents using any convenient combination protocol to produce a solution; and then the solution is pasted onto backing and dried. When the adhesive base is pasted in a hot melt method, the adhesive polymer components may be first dissolved; then other components (e.g., active agents etc.,) may be added and pasted onto the backing. The opposing surface of the adhesive layer may then be conveniently covered with a release liner.

One convenient protocol for fabrication of a transdermal patch includes preparing an adhesive paste through the uniform mixing of the aforementioned ingredients and then coating the paste onto the support, followed by cutting of the resultant product to the specified size to obtain the desired transdermal patch preparation. The resultant transdermal patch preparation is then heat-sealed, one sheet to a package, using a suitable packaging material, to obtain the sealed transdermal patch.

It should be noted that the above manufacturing protocols are merely examples of fabrication protocols of interest. Any convenient protocol that is capable of producing transdermal patch, as described above, may be employed.

METHODS

The present invention provides methods of delivering a beta agonist and an anticholinergic to an individual in need thereof. Aspects of the methods include contacting a topical surface of an individual with a transdermal patch, e.g., as described above. The topical surface is generally a skin surface, such that embodiments of the invention include contacting a skin surface of an individual with a transdermal patch in a manner sufficient to deliver a therapeutic amount of the beta agonist and anticholinergic to the individual for an extended period of time.

In practicing the invention, the transdermal patch is applied to any convenient skin surface. Skin surfaces of interest include, but are not limited to: arms, leg, torso (e.g., stomach or back), head, neck, etc. The surface area that is covered by the transdermal patch following application is generally sufficient to provide for the

desired amount of active agent administration, and in certain embodiments ranges from1 cm^2 to 20 cm^2, such as from 1 cm^2 to 10 cm^2.

Following application of a topical patch, as described above, the applied patch is maintained at the target site for a period of time sufficient for delivery the desired amount of active agents. In some instances, the period of time is 6 hours or longer, such as 12 hours or longer, including 24 hours or longer.

Practice of methods according to certain embodiments results in extended release of the active agents from the transdermal patch. In some instances, practice of the methods results in a plasma level of a beta agonist, e.g., tulobuterol, which ranges from 0.5 ng/ml to 5 ng/ml, such as 1 ng/ml to 3 ng/ml. In some instances, practice of the methods provides a plasma level of an anticholinergic, e.g., scopolamine, which ranges from 0.1 ng/ml to 1.0 ng/ml, such as 0.2 ng/ml to 0.4 ng/ml. While the extended period of time over which the therapeutic amount is provided may vary, in some instances the extended period of time is 6 hours or longer, such as 12 hours or longer, including 24 hours or longer.

In some embodiments, a transdermal patch, when applied to a skin surface of an individual, will provide a relatively constant plasma level of the active agents over the extended period of time. A “relatively constant” level is a level that varies by no more than about 60%, e.g., less than about 40%, less than about 30%, or less than about 20%, over a given period of time.

In practicing the subject methods, a transdermal patch is generally applied a single time over a given time period. The dosing schedule may be daily, such that an old patch is replaced with a new patch every 24 hours. In some cases, the patch may be designed for multi-day use, such as three days.

UTILITY

Transdermal patches of the invention find use in the treatment of any condition in which it is desired to deliver a beta agonist and an anticholinergic agent to a subject. Of interest are pulmonary conditions such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, etc. Treating an individual diagnosed with COPD encompasses a method of inhibiting the progression of COPD in an individual diagnosed with COPD. By "inhibiting the progression of COPD" is intended to mean that the progressive histological and morphometric changes

associated with the clinical sequelae of COPD, including inflammation, alveolar remodeling, and lung cell death, are attenuated.

KITS

Also provided are kits, where the subject kits at least include one or more transdermal patches (e.g., as described above), as well as instructional material for using the same, e.g., in the methods of the invention. In certain embodiments, the kits include two or more transdermal patches as described above. A transdermal delivery patch in a kit may be present in a package, as described supra. The transdermal patches of the kits may be present in individual pouches or analogous containers, to preserve the composition of the patches until use.

The subject kits also may include instructions for how to use the patches, where the instructions typically include information about where to apply the patch, dosing schedules etc. The instructions may be recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e. associated with the packaging or subpackaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

Adhesive Component	(w/w %)
Tulobuterol	2
Scopolamine	2
Oleic acid	0.5
Styrene-isoprene-styrene block copolymer	20
Saturated alicyclic hydrocarbon (Petroleum resin)	46
Polybutene	10
Liquid paraffin	19
Dibutylhydroxytoluene	0.5

Weight of adhesive = 100 g/m^2. Backing = PET 10μm. Liner = PET 75 μm (Release coating on one side) .

According to the above parameters, tulobuterol, scopolamine and oleic acid are dissolved in a suitable amount of toluene (Solution A). Styrene-isoprene-styrene block copolymer, saturated alicyclic hydrocarbon resin, polybutene, liquid paraffin and dibutylhydroxytoluene are mixed with a suitable amount of toluene until being homogenous (Mixture B). The solution A and the mixture B are stirred until being homogenous, and the mixture is spread on the release coated surface of the polyethyleneterephthalate (PET) liner in the amount of 100 g/m^2 and dried. The PET backing is laminated on the adhesive side of the liner and the product is cut in a suitable size to be packed in a sealed package.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

WHAT IS CLAIMED IS:

1. A topical patch comprising:
a beta agonist; and
an anticholinergic;
wherein the topical patch is storage-stable and configured to provide extended release of a therapeutic amount the beta agonist and the anticholinergic.

2. The patch according to Claim 1, wherein the beta agonist is a secondary amine.

3. The patch according to Claim 2, wherein the secondary amine is a 2-hydroxy-phenyl-ethyl amine.

4. The patch according to Claim 3, wherein the beta agonist is present as a free base.

5. The patch according to Claim 4, wherein the beta agonist is tulobuterol.

6. The patch according to Claim 1, wherein the anticholinergic is an amine.

7. The patch according to Claim 6, wherein the anticholinergic is a tertiary amine.

8. The patch according to Claim 7, wherein the anticholinergic is scopalamine.

9. The patch according to Claim 1, wherein the patch further comprises:
a rubber;
an adhesive resin;
a higher fatty acid; and
a plasticizer.

10. The patch according to Claim 9, wherein the rubber is selected a natural rubber and a synthetic rubber.

11. The patch according to Claim 10, wherein the synthetic rubber is selected from the group consisting of styrene-butadiene rubbers, styrene-butadiene block copolymers and styrene-isoprene block copolymers; and combinations thereof.

12. The patch according to Claim 9, wherein the adhesive resin is selected from the group consisting of petroleum resins, polyterpene resins, polyolefin resins, and saturated alicyclic hydrocarbon resins; and combinations thereof.

13. The patch according to Claim 9, wherein the higher fatty acid is a C_{11-22} fatty acid.

14. The patch according to Claim 13, wherein the fatty acid is selected from the group consisting of: linolic acid, linolenic acid, oleic acid, stearic acid, palmitic acid, lauric acid, myristic acid, isostearic acid, ricinolic acid, and combinations thereof.

15. A topical patch comprising:

(a) an adhesive matrix consisting of:

(i) tulobuterol present in an amount ranging from 0.5 to 5 % by weight;

(ii) scopolamine or a pharmaceutically acceptable salt thereof present in an amount ranging from 0.1 to 5 % by weight;

(iii) a synthetic rubber in an amount ranging from 5 to 40 % by weight;

(iv) an adhesive resin present in an amount ranging from 5 to 40 % by weight;

(iv) a C_{14-18} fatty acid in an amount ranging from 2 to 20 % by weight;

(v) a plasticizer; and

(vii) an antioxidant;

(b) a backing; and

(c) a release liner;

wherein the topical patch is storage-stable and configured to provide extended release of a therapeutic amount of tulobuterol and scopolamine.

16. The patch according to Claim 15, wherein the tulobuterol and scopolamine are present as free bases.

17. The patch according to Claim 15, wherein the synthetic rubber is SIS.

18. The patch according to Claim 15, wherein the adhesive resin is saturated alicyclic hydrocarbon.

19. The patch according to Claim 15, wherein the fatty acid is oleic acid.

20. A method of treating a subject for a pulmonary condition, the method comprising applying to a topical location of the subject a topical patch according to any of Claims 1-19.

21. The method according to Claim 20, wherein the pulmonary disease is chronic obstructive pulmonary disease (COPD).

22. A kit comprising two or more topical patches according to any of Claims 1 to 19.

FIGURE 1