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(54) Title: TOPICAL COMPOSITIONS FOR TREATMENT OF RESPIRATORY DISORDERS

(57) Abstract: The present invention relates to compositions for the treatment or prevention of asthma or other respiratory disorders by transdermal administration of a therapeutic agent. In particular, the invention relates to compositions for treating mammalian patients, including human neonates, infants or young children.



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Topical Compositions for Treatment of Respiratory Disorders

The present invention relates to compositions for treating or preventing respiratory disorders, such as asthma and bronchitis, by transdermal administration of a
5 therapeutic agent.

It is common for therapeutic compositions for treating respiratory disorders such as asthma to be administered directly to the lung by inhalation for a local therapeutic effect. Compositions to be administered by pulmonary inhalation are dispensed
10 using nebulizers, pressurized metered dose inhalers (MDIs) or dry powder inhalers (DPIs).

MDIs require co-ordination and good timing between activation of the inhaler and inhalation in order to ensure that a reasonable amount of the dose dispersed is
15 actually inhaled and reaches the deep or lower lung. The young and the elderly in particular can have difficulty with this co-ordination. To aid co-ordination, a spacer may be used. However, use of an MDI with or without a spacer can still be difficult, especially for patients whose breathing is impaired (due to their respiratory disorder, for example), or for the young, the elderly or people with poor strength in their
20 hands.

Dry powder inhalers frequently require the patient to take a deep breath in order to activate the device. It is important that exhalation into the mouthpiece prior to inhalation does not occur as moisture from the breath can prevent the inhaler from
25 functioning correctly. The use of a DPI therefore also requires coordination, and again can be difficult, especially for children.

Due to the need for the above discussed co-ordination, MDIs and DPIs are not recommended for various groups of patients, including geriatrics, neonates, infants
30 and young children. Accordingly, treatment of asthma and other respiratory disorders in neonates, infants and young children focuses on the use of a specialised inhalation device, such as the BabyhalerTM spacer device (Glaxo Ltd., UK) which involves the use of an MDI in conjunction with a face mask.

However, the use of inhalation devices for neonates, infants and young children has several disadvantages. Neonates, infants and young children can be frightened by such devices and this can lead to difficulty in fitting the inhalation apparatus and
5 maintaining it in place. Uptake of the drug through a facemask also inevitably results in the drug escaping around the sides of the mask. Accordingly, the child will not receive an optimal dose of the drug to the lungs. This results in significant and costly waste of the drug, uncertainty as to the amount of drug that has actually been administered, and can present a significant risk when the drug is being administered
10 as a rescue therapy.

Thus, alternative routes of administration must be considered. Possibly the most common route of administering pharmaceutically active agents is the oral route. However, this route of administration also has drawbacks. Tablets can be difficult
15 for certain patients to swallow and can have a delayed onset of action. As such, tablets are not recommended for rescue situations, for example, where relief from bronchoconstriction and other symptoms of asthma and respiratory disorders is required quickly. Tablets are also not ideal for the treatment of asthma and other respiratory disorders in neonates, infants and young children. In particular,
20 administering tablets to neonates or infants is difficult and there is a real risk of choking.

It is therefore an object of the present invention to provide alternative pharmaceutical compositions comprising one or more therapeutic agents for the
25 treatment of asthma and/or other respiratory disorder suitable for alternative routes of administration.

In particular, an object of the present invention is to provide a pharmaceutical composition that could be administered either as a rescue therapy to relieve
30 respiratory distress or as a preventative therapy in order to prevent triggering of respiratory distress, for example, asthma attacks associated with the well recognized circadian "dips" in respiratory function, which are exaggerated in asthma sufferers and can lead to asthma attacks.

Transdermal absorption is a well recognized, although not particularly widely used, means of drug administration. Although it benefits from being a non-invasive and convenient way of medicating a patient, delivery of drugs across the skin is difficult.

5 This is because the outer layer of the skin, the stratum corneum, forms a very effective barrier membrane that prevents most molecules from entering the body through the skin. The stratum corneum is composed of dead keratin-rich cells (corneocytes) and a lipid matrix. In adults, the stratum corneum is 10-15 μm thick, and because of its thickness, structure and composition, it is almost impermeable
10 without a penetration enhancer. As a result, the stratum corneum is the rate-determining barrier to transdermal absorption of most compounds, particularly in adults. However, in neonates, infants and young children the stratum corneum is much thinner. This means that drug absorption through the skin is increased in neonates, infants and young children, making transdermal absorption a potentially
15 effective means of administering medication. Furthermore, the clothing of neonates, infants and young children is easily and frequently removed to expose the skin, providing opportunity for, and ease of application of a topical preparation. Accordingly, the present invention is of particular use for neonates, infants and young children.

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The term "neonates" as used herein refers to a child from birth to the age of about 3 months. The term "infant" as used herein refers to a child from the age of about 3 months to about 1 year. The term "young child" as used herein refers to a child between the ages of about 1 and 7 years.

25

Transdermal administration of medicaments for treating respiratory disorders is known. US Patent No. 6,211,425 describes use of a patch designed for sustained transdermal absorption of formoterol. The aim of the invention described in the patent is to provide treatment over a prolonged period of time (6 hours or longer).

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This aim is achieved by the provision of an adhesive patch containing formoterol, which is affixed to the skin. Such means of topically applying drugs suffers from several disadvantages. Firstly, the adhesive used on the plasters has to be compatible with the therapeutic agent and other constituents of the composition

used. This means that such plasters can be expensive and that not all therapeutic agents are suitable for inclusion in them. Secondly, the application of a plaster, particularly for long periods of time, can be both impractical and undesirable, especially for a neonate, infant or young child. A neonate, infant or child's skin is delicate and can be irritated or damaged by the application or removal of an adhesive plaster, especially if the plaster is attached to the skin for a prolonged period of time. Finally, asthma sufferers frequently require rescue therapy in order to relieve respiratory distress. Sustained release of an active agent over a prolonged period will not impart the immediate levels of therapeutic agent necessary to provide relief in such situations.

US Patent No. 5,602,165 relates to a transdermal absorptive drug composition containing ibudilast for bronchial asthma and cerebrovascular disorders. This patent also discloses the use of a plaster to administer the composition which, as discussed above, is undesirable, especially in neonates, infants and young children. Once again, the object of the compositions is to provide a sustained and lasting therapeutic effect.

Neither US Patent No. 6,211,425 nor US Patent No. 5,602,165 specify compositions for treating respiratory disorders in neonates, infants and young children. What is more, neither patent provides a rapid onset of the therapeutic effect.

Thus, it is an aim of the present invention to provide pharmaceutical compositions suitable for transdermal administration of one or more therapeutic agents for the treatment of respiratory disorders, such as asthma, in a mammalian patient. The present invention also provides pharmaceutical products containing the pharmaceutical compositions, processes for preparing such pharmaceutical compositions and products, and methods of treating a mammalian patient employing such pharmaceutical compositions and products.

The present invention seeks to avoid the difficulties of inhalation and tablet therapies for treatment of respiratory disorders, by providing a topical treatment.

According to a first aspect of the present invention a pharmaceutical composition is provided, comprising a therapeutic agent for treating a respiratory disorder and a pharmaceutically acceptable carrier, the composition being suitable for topical application resulting in transdermal administration of the therapeutic agent.

5

The compositions should be capable of being absorbed by the skin with relative ease, and absorption may be aided by rubbing the composition into the skin. The compositions are therefore particularly suitable for application to and treatment of neonates, infants or young children.

10

In one embodiment, the compositions of the present invention are used to treat infants and young children, but not neonates.

Herein, the term "topical" means that the compositions are applied directly to the skin. Due to the nature of the compositions and the therapeutic agents, the therapeutic agents are absorbed transdermally into the bloodstream.

15

Preferably, the compositions are for topical administration to a mammal. The mammal may be a human and is preferably a neonate, infant or young child.

20

The compositions may be for use in therapy or prophylaxis and, in particular, for treating respiratory disorders such as asthma and bronchitis.

Therapeutic agents which may advantageously be included in the compositions include those which are usually administered orally by inhalation for the treatment of respiratory diseases, for example, β -agonists.

25

The therapeutic agent may be, in particular, a β_2 -agonist. The therapeutic agent may be either a long-acting β_2 -agonist or a short-acting β_2 -agonist. Preferred β_2 -agonists include, for example, salbutamol, terbutaline, salmeterol, bambuterol, fenoterol and formoterol. In one embodiment, the therapeutic agent is not formoterol or is not ibudilast. Preferably, the therapeutic agent is salbutamol, and more preferably it is salbutamol base. Alternatively, the therapeutic agent may be an

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anti-muscarinic agent, for example, atropine, glycopyrronium or glycopyrronium bromide, tiotropium or tiotropium bromide, ipratropium or ipratropium bromide or oxitropium.

5 In further embodiments, the therapeutic agent may be a steroid, which may be beclomethasone dipropionate, budesonide, flunisolide, prednisolone or fluticasone. The therapeutic agent may include a cromone, which may be sodium cromoglycate or nedocromil. The therapeutic agent may include theophylline, aminophylline, epinephrine, ephedrine or a leukotriene receptor antagonist, such as montelukast or
10 zafirlukast. Alternatively, the therapeutic agent may be a carbohydrate, for example heparin.

References herein to any therapeutic agent is to be understood to include any physiologically acceptable derivative. In the case of the β_2 -agonists mentioned
15 above, physiologically acceptable derivatives include salts, sulphates and especially bases.

If desired, the compositions of the present invention may comprise more than one therapeutic agent, provided that the combined agents are compatible with one
20 another under conditions of storage and use.

In preferred embodiments, the pharmaceutical composition is spreadable, such as a cream, ointment or gel. Such spreadable compositions have the advantage that they are easily applied and rubbed in to the skin.

25 Where the composition is provided as a cream, ointment or gel, it is possible to accurately control the dose to be applied to the skin of the patient by providing one or more unit or measured doses of the spreadable composition. This helps to ensure that the patient receives an accurate, predetermined dose of therapeutic
30 agent. In the present invention, such unit or measured doses may be packaged individually, for example in containers such as tubes or sachets. Alternatively, the compositions of the present invention may be dispensed by a device which is capable of dispensing an accurate, predetermined amount.

Thus, in certain embodiments the pharmaceutical composition is provided as a unit or measured dose of a therapeutically effective amount of a therapeutic agent for treating a respiratory disorder and a pharmaceutically acceptable carrier.

5

Compositions of the present invention should be stored at temperatures of about 25°C or less, in accordance with storage conditions for most pharmaceutical compositions and formulations.

10 In one embodiment of the invention, the compositions have a substantially solid form at a temperature of about 25°C or less, and a softening point of not higher than the skin temperature of the intended subject, preferably a mammalian patient.

More particularly, the pharmaceutical composition is a substantially solid dosage
15 form which is softenable on application thereof to an area of skin of a mammalian patient whereby, following application to the area of skin, the solid dosage form is softened to a consistency that can be substantially absorbed by the area of skin so as to effect administration of the unit dose of the therapeutic agent to the, preferably mammalian, patient.

20

Typically, the substantially solid dosage form is provided in the form of a tablet or of a rolled preparation, for example, a pill or the like.

In one embodiment of the invention, the pharmaceutical composition is solid at a
25 temperature of about 25°C or less and has a softening point of not higher than 35°C, such that when the composition is placed in continuous contact with the skin of a mammalian patient, it is softened to a consistency to effect substantial application of the therapeutic agent onto a desired skin area of the mammalian patient within a time period of less than 10 minutes.

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This allows for substantially complete absorption of the composition over the area of skin, so as to effect substantially complete administration of the therapeutic agent to the mammalian patient.

In such embodiments, the solid pharmaceutical composition may be provided as a unit or measured dose of a therapeutically effective amount of a therapeutic agent for treating a respiratory disorder and a pharmaceutically acceptable carrier. The
5 unit or measured dose is preferably provided as a solid tablet, and such tablets may be packaged individually.

The term "softening point" as used herein refers to a temperature at which a substantially solid dosage form starts to soften to a consistency that can be
10 absorbed by the skin of a patient, so as to allow transdermal absorption of the therapeutic agent present in the composition.

The softening point of a substantially solid dosage form of a pharmaceutical composition according to the first aspect of the present invention can be
15 determined visibly as the temperature at which the substantially solid dosage form starts to soften to a consistency that can be absorbed by the skin of a patient and as such can advantageously be substantially completely absorbed by the skin of the patient so as to leave little or no undesirable residue on the skin of a patient.

20 Alternatively, the softening point of a substantially solid dosage form of a pharmaceutical composition according to the first aspect of the present invention can be determined using a TA-XT2 texture analyser (Stable MicroSystems Ltd., UK), suitably equipped with a 5 kg load cell. The equipment is enclosed in a temperature controlled chamber (capable of operating in the region of 60°C to
25 200°C). A tablet or other substantially solid dosage form according to the present invention may be enclosed in the chamber at the specified temperature for a time of at least 10 minutes. A 3 mm flat faced probe is pushed into the tablet or other substantially solid dosage form according to the present invention for a distance of 1 mm at a speed of 0.1 mm/sec. Measurements can be repeated at temperature
30 increments of 1°C and, at the temperature at which the peak force of resistance recorded (as measured by Texture Exceed software) falls to below 50% of that for a "solid" tablet or other substantially solid dosage form according to the present invention, the tablet or other dosage form is deemed to have "softened".

The term "spreading point" as used herein refers to a temperature at which the composition has a spreading consistency. For example, the composition may flow under its own weight or at least can be spread upon the skin of a mammalian patient, for example, using finger pressure.

The mobility of a spreading composition may promote the absorption of the therapeutic agent into the skin by allowing movement of the therapeutic agent towards the skin, for example, by diffusion. The spreading point of a preparation may be measured using the TA-XT2 texture analyser mentioned above in relation to measurement of softening point and with this analyser the spreading point of a composition is the temperature at which outward flow of the composition is first observed on advance of the flat faced probe into the preparation.

In another embodiment, the pharmaceutical composition suitable for topical administration, preferably to a mammal, comprises one or more therapeutic agents and a carrier medium, wherein said preparation has a softening point of not higher than skin temperature of a mammalian patient, said composition having an aspect ratio (wall:face) of less than 1:1.

In another embodiment, the pharmaceutical composition for topical administration, preferably to a mammal, comprises a compacted granulate including one or more therapeutic agents and a pharmaceutically acceptable carrier, said compacted granulate having a softening point of not higher than skin temperature of the intended subject, preferably a mammalian patient.

In certain embodiments, the composition, which is solid prior to administration by application to the skin, has a shape to facilitate the topical application. For example, the composition can have: at least one flat surface; at least one concave surface; at least one convex surface; two flat surfaces; two concave surfaces; or two convex surfaces. The composition may be in the form of a standard tablet, spherical or half-spherical. Bullet shaped and conical shaped compositions are not preferred in the present invention.

In preferred embodiments, the compositions of the present invention have a total weight of from about 50 mg to less than 1 g, preferably from about 100 mg to about 900 mg and more preferably from about 250 mg to about 750 mg. The compositions
5 of the present invention can have a total weight of 1 g or greater, if desired.

In compositions which are prepared for human patients, the dosage form has a softening point not higher than the normal external temperature (skin temperature) of a human. This temperature is typically not higher than about 35°C. In certain
10 embodiments, the composition has a softening point from about 30°C to not higher than 35°C.

In an alternative embodiment, the pharmaceutical composition contains a dose of at least one therapeutic agent for topical application to a mammalian patient, said
15 composition being a solid during final manufacture and prior to application to an area of skin of said mammalian patient, but having a spreading consistency suitable for application to said area of skin upon exposure to (and/or contact with) the skin, said composition being individually contained in a plastic container having a removable or breakable enclosure for dispensing said unit dose.

20 In certain embodiments, the dosage form can be a plurality of substantially discrete substantially solid particles comprising one or more therapeutic agents admixed with a pharmaceutically acceptable carrier, said particles having a softening point of about 30°C to about 35°C. The particles can be enclosed in a sachet, a capsule or a
25 device suitable to dispense an individual dose of the particles.

In embodiments of the present invention wherein the pharmaceutical composition is provided as a spreadable composition (that is, in the form of a cream, ointment or gel, etc.), the carrier medium should allow the therapeutic agent to be carried in a
30 stable manner. The carrier medium may have favourable organoleptic properties, for example, the composition may be water-based so as to have a non-oily feel upon application to the skin.

The carrier medium used in the spreadable compositions according to the invention should preferably allow substantially complete absorption of the therapeutic agent through the skin of the mammalian patient, so as to effect what is preferably substantially complete administration of the therapeutic agent to the patient within a
5 time period of less than about 10 minutes, preferably less than about 5 minutes, more preferably less than about 3 minutes and most preferably less than about 1 minute following application to an area of skin.

Any component commonly used as a base for creams, ointments or gels can be used
10 as a carrier medium in the abovedescribed spreadable embodiments of the present invention. These components include: water; hydrocarbon oils and waxes; silicone oils; vegetable, animal or marine fats or oils; glycerides (such as, for example, or more glycerol esters of saturated fatty acids or polyglycolysed glycerides, cocoa butter, theobroma or the like) or glyceride derivatives; high molecular weight
15 polyethylene glycol, polyoxyethylene, lanolin and derivatives thereof; fatty acids, fatty alcohols or fatty esters (including, for example, caprylic acid, caprylic triglyceride or the like); lecithin; polyhydric alcohols or esters; wax esters; sterols; phospholipids and the like. Thickening agents such as gums or other forms of hydrophilic colloids may be included. The carrier medium may comprise more than
20 one base component.

Where the pharmaceutical composition is a cream, the carrier medium may comprise substantially more oil based components than water. Where the pharmaceutical composition is an ointment, the carrier medium may comprise substantially more
25 water than oil based components. Where the pharmaceutical composition is a gel, the carrier medium may substantially comprise water.

A carrier medium should be selected which is compatible with the therapeutic agent. The therapeutic agent should be chemically stable and the composition should be
30 designed to encourage the flux of the drug from the composition through the stratum corneum.

Delivery of agents through the skin is related to Fick's law of diffusion. In this regard, the rate of flux of an agent through the skin will be governed by factors including the surface area that the composition is spread over, and the thickness of the layer applied to the skin. The rate of delivery of an agent is therefore affected
5 by the ease with which the composition containing the agent can be spread over the surface in question.

In the present invention, rapid delivery of the drug through the skin can be achieved by selecting carrier materials which spread easily and/or are readily
10 absorbed. In compositions according to the present invention that have a substantially solid form at a temperature of about 25°C or less, and a softening point of not higher than the skin temperature of the intended subject, the softening time of the composition, and spreadability of the softened composition will contribute to the rate at which, and surface area of the skin over which, the
15 composition can be spread. Rapid delivery of the drug through the skin can be achieved by use of a carrier medium which softens rapidly at temperatures not higher than skin temperature, and which spreads easily once softened.

Another factor that controls the rate of flux of the agent across the skin is the
20 extent to which the drug is soluble in the carrier medium. Flux from the carrier through the skin is encouraged in circumstances wherein the drug is more soluble in components of the stratum corneum and other elements found on the skin, such as sweat and sebum, than it is in the carrier.

25 Preferably, the carrier medium constitutes not less than about 60%, more preferably not less than about 80% and even more preferably not less than about 90%, by weight based on the weight of the pharmaceutical composition.

In the embodiments discussed above where the compositions soften upon
30 application to the skin, the carrier medium used is preferably substantially solid at a temperature of about 25°C or less and softens to a consistency that allows for substantially complete absorption of the one or more therapeutic agents by the skin of the patient, so as to effect (preferably substantially complete) administration of

the therapeutic agents to the patient, within a time period of less than about 10 minutes, preferably less than about 5 minutes, more preferably less than about 3 minutes and most preferably less than about 1 minute following application to the area of skin.

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Typically, it is preferred that the carrier medium included in the substantially solid dosage form of the present invention may soften, and advantageously may be converted to a spreading consistency, at a temperature in the range of 30 to 35°C.

- 10 In its substantially solid form, the composition of the invention preferably has a size and shape suitable for application to a selected area of skin.

More particularly, it is preferred that the shape and configuration of the substantially solid dosage form is determined by the softening point of the composition and/or the carrier medium. It may be preferred that a substantially solid dosage form according to the present invention comprises a substantially unitary form; alternatively, it may comprise a plurality of discrete particles (such as a plurality of granules or the like) that can be absorbed by the skin of a mammalian patient. Preferably, the plurality of substantially discrete particles are provided in a sealed member (such as a capsule, sachet, blister package or the like) from which they are dispensed and applied to the skin of a patient.

Any component commonly used for suppositories can be used as carriers in the compositions of the present invention which soften upon application to the skin. These components include those derived from mammalian, vegetable or mineral origins, and materials partially or totally synthesized. Specific examples of such carriers include oils and fats of mammalian or vegetable origin, such as olive oil, corn oil, castor oil, cottonseed oil, wheat germ oil, cacao butter, hydrogenated oils, etc.; hydrocarbons, such as squalane, petrolatum, solid paraffin, liquid paraffin, etc.; and waxes, such as jojoba oil, carnauba wax, bees wax, lanolin, etc. Examples of partially or totally synthesized fatty acid esters include glycerol, mono-, di-, or triglycerides of medium or higher fatty acid, such as saturated linear fatty acid, for example lauric acid, myristic acid, palmitic acid, stearic acid, etc., or unsaturated

linear fatty acids, for example oleic acid, linoleic acid, linolenic acid, etc.

Commercially available carriers which are suitable include Witepsol (manufactured by Dynamit Nobel), Pharmasol (manufactured by Nippon Oil and Fats Co.), Isocacao (manufactured by Kao Corp.), SB (manufactured by Taiyo Oil and Fats Co.), Novata (manufactured by Henkel), Suppocire (manufactured by Gattefosse Co.), and the like. Examples of other synthetic products include polyethylene glycol, for example, macrogole, setomacrogole, etc., as well as derivatives thereof, for example, setomacrogol.

10 In order to obtain the desired softening point of the compositions of the present invention, different carriers can, if necessary, be combined in order to increase or decrease the softening point to obtain a suitable product. For example, in order to decrease the softening point, a plasticizer can be added, e.g., glyceryl monostearate, myristyl alcohol, polysorbate 80, propylene glycol or combinations thereof. In order
15 to increase the softening point, a hardener can be added, e. g., beeswax, cetyl alcohol, stearic acid, stearyl alcohol, aluminium monostearate, aluminium distearate, aluminium tristearate, bentonite, magnesium stearate, colloidal silicon dioxide or combinations thereof.

20 A carrier for use according to the present invention may comprise any ingredient suitable for use in a pharmaceutical composition and possessing the desired properties for enabling topical administration of a dose of at least one therapeutic agent, provided that it is suitable for topical application and transdermal administration. For example, the carrier may include a cellulose or one or more
25 ingredients selected from the group consisting of ingredients of the type suitable for use in suppositories including, for example, one or more glycerides (such as, for example, one or more glycerol esters of saturated fatty acids or one or more polyglycolysed glycerides, cocoa butter, theobroma or the like), one or more high molecular weight polyethylene glycol, one or more polyoxyethylene, lanolin and
30 derivatives thereof, and one or more fatty acids, fatty alcohols, fatty acid esters (including, for example, caprylic acid, caprylic triglyceride or the like), and any of the preceding ingredients can be optionally mixed with one or more organic oils (including, for example hydrogenated vegetable oils) or the like.

It is often preferred that a carrier employed in a pharmaceutical composition according to the present invention comprises, and more preferably consists essentially of, one or more glycerides, including, in particular, one or more glycerol esters of C8-C18 fatty acids or one or more polyglycolysed glycerides.

Suitably, the carrier of a pharmaceutical composition according to the present invention comprises, or consists essentially of, a mixture of glycerides, where the glycerides can be one or more mono-, di- or tri-glycerides, optionally wherein the glycerides comprise glycerol esters of C12-C18 fatty acids. In one embodiment, the glyceride mixture is a Witepsol grade product. More particularly, the carrier may comprise, or consist essentially of, a Witepsol grade product available under any of the trade marks Witepsol H5, Witepsol H15, Witepsol H32, Witepsol S51, Witepsol S55, Witepsol S58, Witepsol W25 and Witepsol W32. In a particularly preferred embodiment, the pharmaceutical compositions according to the present invention include carriers which are Witepsol grade products available under any of the following trade marks Witepsol H5, Witepsol H15, Witepsol S51 and Witepsol S55. The Witepsol grade product available under the trade mark Witepsol H15 is particularly suitable.

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In a particular embodiment of the present invention, the carrier employed in the compositions consists essentially of a Witepsol grade product substantially as described above.

Alternatively, the carrier comprises, or consists essentially of, a mixture of glycerides, where the glycerides can be selected from the group consisting of mono-, di- and tri-glycerides, the glycerides comprising glycerol esters of C_g-C_{ie} fatty acids or one or more polyglycolysed glycerides. In one embodiment, glyceride mixtures available under the trade marks Gelucire or Suppocire are used, such as any of the following: Gelucire 33/01, Gelucire 39/01, Gelucire 43/01, Gelucire 44/14, or any of the Suppocire Standard type, Suppocire N type or Suppocire P type products.

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Alternatively, the carrier used in a pharmaceutical composition according to the present invention comprises, or consists essentially of, cocoa butter.

Pharmaceutical compositions according to the present invention may further
5 comprise, where appropriate, additional ingredients such as one or more penetration enhancers (which may be surfactants, alcohols, esters, glycols or the like or any other suitable penetration enhancer), humectants, surfactants (which may be cationic, non-ionic, anionic or polymeric), emulsifiers, antioxidants, preservatives, clays, antifoaming agents, spreading agents, emollients, barriers, solubilising agents
10 for the therapeutic agent and the like.

Pharmaceutical compositions according to the present invention may also comprise solvents, such as ethanol, menthol, thymol, eucalyptol, eucalyptus oil, benzyl alcohol, isopropyl alcohol, propylene glycol, methylated spirit, phenol,
15 cyclodextrins, ethyl oleate, eugenol, glycerol, levomenol, monoethanolamine oleate, myristyl alcohol, octyldodecanol, methyl alcohol, coconut oil or silicone oil.

The presence of solvents in compositions according to the present invention aids systemic administration of the therapeutic agent. The extent to which, and speed
20 with which systemic administration of a therapeutic agent from a topically applied composition occurs is associated with the depth and rate of penetration of the therapeutic agent through the skin. The presence of solvents in compositions according to the present invention aids solubilization of the drug within the composition. Solvents for use in the present invention are also chosen in
25 accordance with their ability to cross or bridge the stratum corneum, and in particular, the tight junctions between the corneocytes within the stratum corneum. The presence of solvents in the present invention thus enhances the rate of transdermal absorption, and the depth of penetration of the therapeutic agent, by solubilizing the agent and effecting diffusion of the agent through the stratum
30 corneum.

Pharmaceutical compositions according to the present invention may further comprise organoleptic agents to improve the organoleptic properties of the

composition. Such agents include almond oil, glycerol, linseed oil, monoethanolamine oleate, grape oil, mace oil, isopropyl myristate, isopropyl palmitate, palm kernel oil, theobroma oil, wool alcohols. The inclusion of organoleptic agents can be used, for example, to enhance the feel of the composition, which can improve patient compliance.

Pharmaceutical compositions according to the present invention may further comprise sensory cues, such as anise oil, citronella oil, clove oil, eucalyptol, eucalyptus oil, eugenol, juniper oil, lemon grass oil, lemon oil, terpeneless lemon oil, melaleuca oil, neroli oil, nutmeg oil, olive oil, orange oil, terpeneless orange oil, poppy seed oil, pine oil, rose oil, sage oil, spearmint oil, lavender oil, thyme oil, vanillin.

The inclusion of such cues in the composition can provide the patient with pleasant sensory feedback upon use, allows the patient and/or person applying the formulation to recognize that administration has occurred, and may aid recollection of administration. Such factors can improve patient compliance and provide a positive psychological effect.

Pharmaceutical compositions according to the present invention may further comprise insect repellents such as citronella or lemon grass.

In some embodiments of the present invention, the compositions are substantially free of penetration enhancers. In such embodiments, the compositions are preferably prepared using a process carried out under aseptic conditions.

The use of preservatives can be undesirable, as they may provoke allergic reactions in susceptible patients, and the present invention may be advantageous in avoiding or reducing the risk of such allergic reactions. Preservatives that have been associated with allergic reactions include chlorocresol, hydroxybenzoates (parabens), polysorbates, sorbic acid and the like, and these preservatives are included in a large number of known topical compositions, including, for example, compositions available under any of the following trade marks: Drapolene, Medicaid, Siopel,

Sprilon, Eurax, Efcortelan, Mildison, Fucidin H, Nystaform, Quinocort, Terra-Cortril Nystatin, Timodine, Locoid, Locoid Crelo, Modrasone, Propaderm, Betnovate, Betnovate RD, Diprosone, Dermovate, Eumovate, Trimovate, Nerisone, Haelan, Synalar, Ultralanum Plain, Zorac, Carbo-Dome, Exorex, Differin and
5 Exelderm.

In a particularly preferred embodiment of the present invention, the pharmaceutical compositions are substantially free of the types of preservative generally included in compositions intended for dermal or transdermal administration, or at least they
10 include such preservatives in amounts that are less than those generally required in compositions intended for dermal or transdermal administration, or they include such preservatives in amounts that generally do not provoke substantial allergic reactions in susceptible patients, substantially as hereinafter described.

15 The preservatives generally employed in compositions intended for dermal or transdermal administration are included to prevent or reduce contamination of such compositions. Contamination is a particular problem where a composition is repeatedly exposed to the atmosphere or is repeatedly handled. Preservatives may not be required in compositions of the present invention where the compositions
20 are in the form of unit doses, especially if these doses are individually packaged.

Pharmaceutical compositions according to the present invention may, however, comprise one or more preservatives, such as phenoxyethanol or the like, that are included typically to substantially prevent contamination of the compositions
25 according to the present invention during manufacture but are not generally of the type employed to prevent infection due to manual application as hereinbefore described.

In further embodiments of the present invention, the compositions are substantially
30 free of antioxidants. In such cases, it is preferred that the compositions are packaged in a substantially inert atmosphere, such as nitrogen or the like.

The use of antioxidants can provoke allergic reactions in susceptible patients and the present invention may be advantageous in avoiding or reducing the risk of such allergic reactions in susceptible patients. Antioxidants that have been associated with allergic reactions include butylated hydroxyanisole, butylated hydroxytoluene
5 and the like, and are known to be available in prior art topical compositions, such as those compositions available under any of the trade marks Imuderm, Siopel and the like.

In a particularly preferred embodiment of the present invention, the pharmaceutical
10 compositions are substantially free of antioxidants of the type generally included in compositions for dermal or transdermal administration, or at least they include such antioxidants in amounts less than generally required in compositions intended for dermal or transdermal administration, or at least they include such antioxidants in amounts that generally do not provoke substantial allergic reactions in susceptible
15 patients substantially as hereinafter described.

Antioxidants are generally employed in compositions intended for dermal or transdermal administration in order to prevent the fats present in such compositions becoming rancid and to prevent oxidation of the composition following opening of
20 the packaging within which the composition is kept. Antioxidants may not be required in compositions of the present invention where the compositions are in the form of unit doses, especially if these doses are individually packaged.

Methods of preparing the softening compositions referred to above are disclosed in
25 WO 02/002 03 A1, the entire disclosure of which is hereby incorporated by reference.

Tablets of the compositions may be made by normal tableting processes. For example, tablets may be compressed on a 10-station tablet press at a
30 room/equipment temperature of 2-4°C using either stainless steel tooling or punches suitably tipped with low adhesion materials, for example, chrome.

According to a second aspect of the present invention, an applicator is provided for applying the compositions of the first aspect of the invention.

In one embodiment, the applicator is a pad, sponge, bar, brush, cotton ball or glove.

5

In another embodiment, the applicator comprises a receiving means for receiving and carrying a pharmaceutical composition and a grip for enabling a user to hold and manipulate the applicator. The grip and receiving means may be arranged such that a user holding the applicator by the grip is protected from inadvertent contact with the composition. The composition is preferably in the form of a unit or measured dose.

10

In further embodiments, the applicator also includes an intermediate member attached to the composition, and the receiving means of the applicator may be configured to be removably attachable to the intermediate member.

15

In alternative embodiments, the applicator comprises a pharmaceutical composition as substantially hereinbefore described, together with a covering member that can be arranged to substantially cover the pharmaceutical composition when the latter is applied to an area of skin of the mammalian patient, and means for adhering the covering member to an area of skin of the mammalian patient.

20

According to a third aspect of the present invention, a kit is provided comprising a composition of the first aspect of the present invention and an applicator.

25 Preferably, the kit comprises at least one dose of the pharmaceutical composition.

In one embodiment, the applicator included in the kit is an applicator according to the second aspect of the present invention.

30 According to a fourth aspect of the present invention, a composition according to the first aspect of the present invention is provided for treating a respiratory disorder in a mammalian patient wherein said composition is to be administered transdermally by topical administration of the composition to the skin of the

patient. Methods of treating or preventing respiratory disorders, such as asthma and bronchitis, by administering the compositions according to the first aspect of the invention are also provided.

- 5 According to a fifth aspect of the invention, there is provided the use of a therapeutically active agent in the manufacture of a medicament for transdermal administration of the therapeutic agent, wherein the therapeutic agent is for treating or preventing a respiratory disorder. Preferably, a mammalian patient is to be treated.

10

The present invention will now be further illustrated by the following Examples, which do not limit the invention in any way.

Example 1

15	Ingredients:	<u>% w/w</u>
	Salbutamol	2
	Softisan 133	81
	Dry Flo AF Pure	8
	Migylol 812N	5
20	Isopropyl Myristate	2.5
	Fitoderm	1.5

Example 2

	Ingredients:	<u>% w/w</u>
25	Theophylline	5
	Softisan 133	90
	Dry Flo AF Pure	5

Example 3

30	Ingredients:	<u>% w/w</u>
	Beclomethasone Dipropionate	1
	Witepsol H15	94
	Migylol 812N	5

Example 4

	Ingredients:	<u>% w/w</u>
	Ipratropium Bromide	0.2
5	Softisan 133	89.8
	Dry Flo AF Pure	5
	Migylol 812N	5

Percentages are by weight based on the total weight of the combined ingredients

10

Method of Preparation for Examples 1-4

In each case, all ingredients excluding the drug and dry flo were melted down until molten, and the temperature of the bulk was then maintained at 60°C. The drug and dry flo were carefully sheared into the bulk using a Silverson mixer. The bulk was
15 then solidified by exposure to a low temperature, for example, below 15°C, preferably below 10°C and most preferably below 4°C. The solidified bulk was then milled down and granulated, also at low temperature, for example, below 15°C, preferably below 10°C and most preferably below 4°C.

20 Example 5

	Ingredients:	<u>% w/w</u>
	Salbutamol	2
	Dry Flo	8
	Migylol 812N	5
25	Isopropyl Myristate	2.5
	Fitoderm (vegetable squalene)	1.5
	Ethanol	1
	Softisan 133	80

30 Example 6

	Ingredients:	<u>% w/w</u>
	Salbutamol	2
	Dry Flo	8

	Migylol 812N	5
	Isopropyl Myristate	2.5
	Fitoderm	1.5
	Propylene Glycol	1
5	Softisan 133	80

Example 7

	Ingredients:	<u>% w/w</u>
	Salbutamol	2
10	Dry Flo	8
	Migylol 812N	5
	Isopropyl Myristate	2.5
	Fitoderm	1.5
	Propylene Glycol	1
15	Ethanol	1
	Softisan 133	79

Percentages are by weight based on the total weight of the combined ingredients.

20 Method of Preparation for Examples 5-7

All ingredients excluding the salbutamol, dry flo and ethanol were melted down until molten, and the temperature of the bulk was then maintained at 60°C. The salbutamol and dry flo were carefully sheared into the bulk using a Silverson mixer. Once the temperature of the bulk had reduced to a suitably low temperature (for
 25 example less than 20°C), the ethanol was mixed in. The bulk was solidified by exposing to low temperature, for example, 4°C. The solidified bulk was milled down and granulated also at low temperature, for example, 4°C.

Example 8

30	Ingredients:	<u>% w/w</u>
	Salmeterol	0.5
	Softisan 133	89.5
	Dry Flo AF Pure	5

Migylol 812N	2
Isopropyl Myristate	2
Menthol	1

- 5 Percentages are by weight based on the total weight of the combined ingredients.

Method of Preparation for Example 8

All ingredients excluding the drug, dry flo and menthol were melted down until molten, and the temperature of the bulk was then maintained at 60°C. The drug and
10 dry flo were carefully sheared into the bulk using a Silverson mixer. The bulk temperature was reduced to 40-50°C. A sufficient amount of ethanol was added to the menthol in order to effect dissolution, and this was then added to the molten bulk. The ethanol was evaporated off and the resultant bulk was solidified by exposure to a low temperature, for example, below 15°C, preferably below 10°C and
15 most preferably below 4°C. The solidified bulk was then milled down and granulated, also at low temperature, for example, below 15°C, preferably below 10°C and most preferably below 4°C.

Claims

1. A pharmaceutical composition comprising a therapeutic agent for treating a respiratory disorder and a pharmaceutically acceptable carrier, the composition
5 being suitable for topical application resulting in transdermal administration of the therapeutic agent.
2. A pharmaceutical composition as claimed in claim 1, wherein the composition is for topical application to a mammal.
10
3. A pharmaceutical composition as claimed in claim 2, wherein said mammal is a human, preferably a neonate, infant or young child.
4. A pharmaceutical composition as claimed in any of claims 1-3, wherein the
15 therapeutic agent is a β -agonist.
5. A pharmaceutical composition as claimed in any one of claims 1-3, wherein the therapeutic agent is an anti-muscarinic agent.
- 20 6. A pharmaceutical composition as claimed in any one of claims 1-3, wherein the therapeutic agent is beclomethasone dipropionate, budesonide, flunisolide, prednisolone, fluticasone, sodium cromoglycate, nedocromil, theophylline, aminophylline, epinephrine, ephedrine, heparin or a leukotriene receptor antagonist.
- 25 7. A pharmaceutical composition as claimed in any one of claims 1- 6, which further comprises one or more solvents.
8. A pharmaceutical composition as claimed in claim 7, wherein at least one of the solvents is ethanol, menthol, thymol, eucalyptol, eucalyptus oil, benzyl alcohol,
30 isopropyl alcohol, propylene glycol, methylated spirit, phenol, cyclodextrins, ethyl oleate, eugenol, glycerol, levomenol, monoethanolamine oleate, myristyl alcohol, octyldodecanol, methyl alcohol, coconut oil or silicone oil.

9. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition is spreadable.
10. A pharmaceutical composition as claimed in claim 9, wherein the
5 composition is in the form of an ointment, cream or gel.
11. A pharmaceutical composition as claimed in any one of claims 1-9, wherein the composition is a substantially solid dosage form at a temperature of about 25°C or less and, upon contact with the skin, softens to a consistency that allows
10 transdermal absorption of the therapeutic agent.
12. A pharmaceutical composition as claimed in claim 11, wherein the composition is in the form of a solid tablet, said tablet comprising a therapeutically effective amount of the therapeutic agent.
15
13. A pharmaceutical composition as claimed in either of claims 11 or 12, wherein the composition has a total weight from about 50 mg to less than 1 g, from about 100 mg to about 900 mg or from about 250 mg to about 750 mg.
- 20 14. A pharmaceutical composition as claimed in any one of claims 11-13, wherein the composition has a softening point of not higher than 35°C.
15. A pharmaceutical composition as claimed in claim 14, wherein the composition is softened to a consistency to allow transdermal absorption of the
25 therapeutic agent within a time period of less than 10 minutes when the composition is placed in continuous contact with the skin of a patient.
16. A pharmaceutical composition as claimed in any one of claims 1-8, comprising a compacted granulate of the therapeutic agent and the pharmaceutically
30 acceptable carrier, said compacted granulate having a softening point of not higher than skin temperature of a mammalian patient.

17. A pharmaceutical composition as claimed in any one of claims 1-8, wherein the composition comprises a plurality of substantially discrete substantially solid particles comprising the therapeutic agent admixed with a pharmaceutically acceptable carrier medium, said particles having a softening point of about 30°C to
5 about 35°C.

18. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the carrier medium is one or more glycerides, cocoa butter, theobroma, one or more high molecular weight polyethylene glycol, one or more polyoxyethylene,
10 lanolin and derivatives thereof, and one or more fatty acids, fatty alcohols and fatty esters, one or more organic oil, and one or more glycerides, or combinations thereof.

19. A pharmaceutical composition as claimed in any one of the preceding claims,
15 wherein the composition is free of preservatives.

20. A pharmaceutical composition as claimed in any one of claims 1-18, which further comprises one or more preservatives to prevent or reduce contamination of the composition during preparation.
20

21. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition is substantially free of antioxidants.

22. A pharmaceutical composition as claimed in any one of the preceding claims,
25 wherein the composition comprises not less than about 60% by weight carrier based on the weight of the pharmaceutical composition, not less than about 80% by weight or not less than about 90% by weight.

23. A pharmaceutical composition as claimed in any one of the preceding claims,
30 wherein the composition is for treating a respiratory disorder by topical administration of the composition.

24. A pharmaceutical composition as claimed in claim 23, wherein the respiratory disorder is asthma or bronchitis.

25. Use of a therapeutic agent in the manufacture of a medicament for topical
5 application providing transdermal administration of the therapeutic agent for treating a respiratory disorder.

26. A use as claimed in claim 25, wherein the therapeutic agent is salbutamol.

10 27. An applicator for applying a pharmaceutical composition as claimed in any one of claims 1-22.

28. A pharmaceutical product comprising a pharmaceutical composition as claimed in any one of claims 1-22, together with a covering member that can be
15 arranged to substantially cover the pharmaceutical composition when the latter is to be applied to an area of skin of the mammalian patient, and a means for adhering the covering member to an area of skin of the mammalian patient.

29. A kit comprising a composition as claimed in any one of claims 1-22, and an
20 applicator as claimed in claim 27.

30. A pharmaceutical composition or product substantially as herein described in any one of the Examples.