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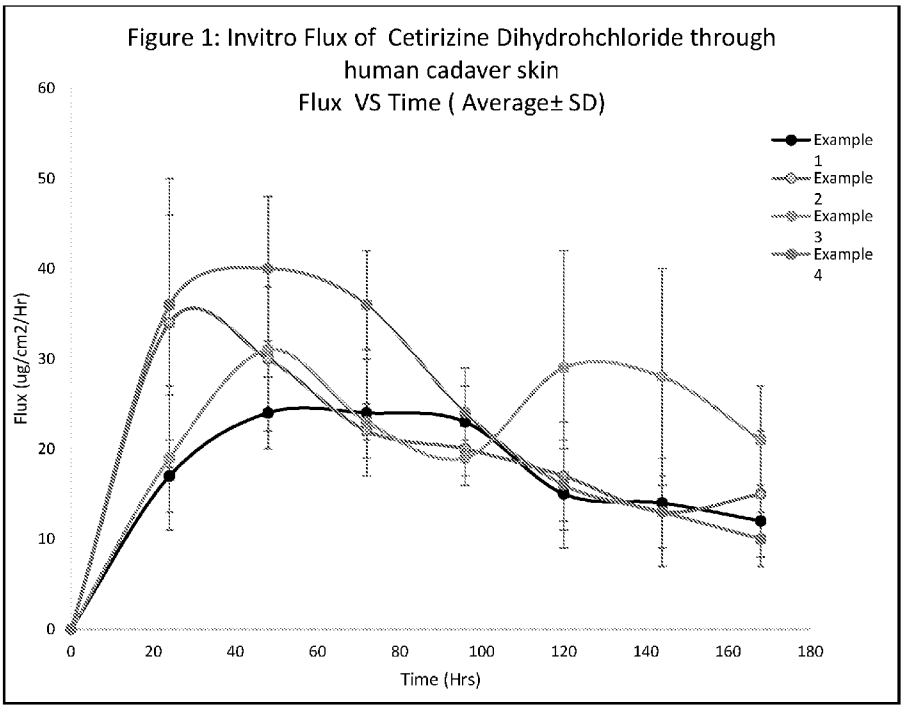

(57) Abstract: A transdermal semisolid formulation preferably transdermal gel formulation comprising cetirizine dihydrochloride and carrier system comprising excipients such as but not limited to solvents, penetration enhancers, gelling agents or polymers, pH adjusting agents either alone or in combinations thereof. The transdermal gel formulation provides continuous in vitro delivery of cetirizine dihydrochloride for a period of up to seven days. The transdermal gel formulation can be added to a reservoir patch. For the treatment and/or prevention and/or relief of symptoms associated with allergic rhinitis and/or urticaria and/or upper respiratory allergies, by topical application of transdermal gel formulation to skin for up to one day or by topical application of reservoir patch to skin for a duration selected from the group comprising for one day, two days, three days, four days, five days, six days, or seven days, reducing the dosing frequency

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Transdermal and/or Topical Delivery Systems Comprising Cetirizine Dihydrochloride

CROSS-REFERENCE TO RELATED APPLICATIONS

This PCT application claims the benefit under 35 U.S.C. §119(e) of Application Serial No. 62/402,037 filed on September 30, 2016 entitled TRANSDERMAL AND/OR TOPICAL DELIVERY SYSTEM COMPOSED OF CETIRIZINE HYDROCHLORIDE and whose entire disclosure is incorporated by reference herein.

Field of Invention

The invention relates to in vitro transdermal delivery of cetirizine dihydrochloride (Synonym: cetirizine hydrochloride[19]) for a period of up to, for example, 7 days from a semisolid transdermal formulation preferably transdermal gel formulation. Further, invention suggest transdermal delivery of cetirizine dihydrochloride by topical application of transdermal gel formulation to skin and/or by incorporation of transdermal gel formulation into a transdermal delivery system particularly reservoir patch which can be topically applied to skin for the treatment and/or prevention and/or relief of symptoms associated with allergic rhinitis and/or urticaria and/or upper respiratory allergies wherein duration of topical application of transdermal gel is for up to one day and/or duration of topical application of reservoir patch can be selected from the group comprising for one day, two days, three days, four days, five days, six days, seven days. Topical application of reservoir patch to skin for more than one day can reduce the dosing frequency of cetirizine dihydrochloride.

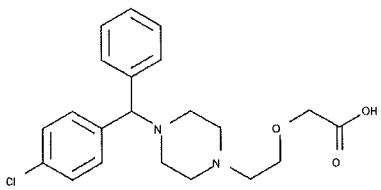
Background

Worldwide 10-30% population and in America 40-60 million people are affected with allergic rhinitis[4]. Allergic rhinitis is caused by the reaction of the immune system to allergens. Symptoms of allergic rhinitis may develop when people inhale an allergen or consume a food to which they are allergic[3]. Symptoms of allergic rhinitis includes such as sneezing, watery eyes, runny nose, stuffy nose, itchy eyes, itchy mouth, itchy skin, fatigue[2,3], etc. Allergic rhinitis can be seasonal and

perennial. In seasonal allergic rhinitis symptoms can appear in spring, summer and early fall. Allergens for seasonal allergic rhinitis are such as grass, trees and weeds pollen. In perennial allergic rhinitis symptoms are occurring throughout the year. Allergens for perennial allergic rhinitis are such as dander, dust mites, mold or cockroach, pet hair[2], etc.

Urticaria occurs in more than 20% people worldwide at some point in their lifetime[4,5]. Urticaria or hives affects the skin and symptoms includes such as red or skin colored raised itchy bumps, blanching, welts[5,6]. Hives can vary in size and shape, appear and disappear anywhere on the body[5,6]. Usually each hive disappear within 24 hours and does not leave scar or bruise. Urticaria can be acute or chronic. Acute urticaria is short lived and last for few weeks. Urticaria is chronic or long term if symptoms appear daily for more than six weeks [5,6]. Hives can be triggered by factors such as pollen, some plants, some food, some medicines, bacterial or viral infections, physical stimuli, pet dander, blood transfusion, insect bites, latex[5], etc. Urticaria can also be idiopathic.

Cetirizine ((+/-)- [2-[4-[(4-chlorophenyl) phenylmethyl] -1-piperazinyl] ethoxy] acetic acid), has the structure



It is practically insoluble in water at 25°C, with solubility of 100 microgram/ml (µg/ml). Cetirizine has molecular weight of 388.89 gm/mole with log P value of 2.98. To increase the solubility of cetirizine, it usually sold in its dihydrochloride salt form. Cetirizine hydrochloride can treat the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. Zyrtec label states, "Cetirizine hydrochloride treats uncomplicated skin manifestations of chronic idiopathic urticaria and reduces the occurrence, duration and severity of hives and decreases pruritus. It is also indicated for the relief of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis. Symptoms treated effectively includes nasal pruritus, sneezing, ocular pruritus, rhinorrhea, tearing, postnasal discharge, redness

of the eyes. Allergens for seasonal allergic rhinitis include for example ragweed, grass and tree pollens. Allergens for perennial allergic rhinitis include for example animal dander, dust mites, molds"[1]. For the relief of symptoms cetirizine hydrochloride is administered once daily. Commercially cetirizine hydrochloride is available as syrup, tablet, orally disintegrating tablet, chewable tablet, capsule and ophthalmic solution or drops.

In day to day life allergic rhinitis symptoms can be troublesome. Symptoms like nasal congestion, runny nose, sneezing, itching, watery eyes, fatigue can make the person irritable, tired, affect the sleep and work output[7,9]. A cross sectional study was conducted with 683 adult allergic rhinitis patients and reported for employed patients and student patient loss of productivity was around 21%, and impact on daily activities was around 22%[8]. If left untreated allergic rhinitis symptoms can affect the quality and comfort of life. Similarly, chronic urticaria can also undermines the quality of life due to itching, raised bumps on the skin. Visible hives accompanied with itching on the skin can impact the social life and emotions of the patient[10].

Symptoms of seasonal allergic rhinitis last from day to few weeks and for perennial allergic rhinitis symptoms can occur anytime throughout year. Similarly, urticaria can last up to a day to few weeks to six weeks and more. To get relief from the symptoms of allergic rhinitis and urticaria, patients need to administer cetirizine hydrochloride everyday till the rhinitis and urticaria goes way. This everyday drug administration can be inconvenient for the patients. Therefore, for the treatment and/or prevention of symptoms associated with allergic rhinitis and urticaria there is a requirement for a better drug delivery system which can decrease the dosing frequency. The transdermal delivery of cetirizine dihydrochloride can reduce the frequency of drug administration.

In transdermal drug delivery, drug is delivered through the skin. The transdermal formulation or transdermal delivery system is topically applied to the intact skin surface. Drug is released from topically applied transdermal formulation or transdermal delivery system and delivered to systemic circulation through the intact skin via different routes such as intercellular routes, transcellular route,

transappendageal route to attain pharmacologic effect. Drug is continuously released and delivered to systemic circulation during the entire period of application of transdermal formulation or transdermal delivery system to skin. With transdermal delivery dosing frequency of drug administration can be reduced as drug can be delivered for the entire period of application of transdermal formulation or transdermal delivery system to skin wherein period of application is variable and can be for one day, two days, three days, four days, five days, six days, seven days or more.

Transdermal delivery of cetirizine dihydrochloride can overcome its current dosage administration of orally every day. The Cetirizine dihydrochloride transdermal formulation or cetirizine dihydrochloride transdermal delivery system as set forth herein can be applied topically to skin and can deliver cetirizine dihydrochloride into systemic circulation during the entire period of its application wherein period of application can be selected from the group such as for one day, for two days, for three days, for four days, for five days, for six days, for seven days, or more. Therefore, transdermal delivery of cetirizine dihydrochloride can overcome every day dose regimen of oral delivery by continuously delivering the drug for longer time period.
In general, at times in oral drug delivery side effects are associated with peak plasma drug concentration. Transdermal delivery can overcome such side effects as the same amount of drug is delivered slowly, therefore the drug plasma concentration is always less than peak plasma drug concentration.

Transdermal delivery of the drug can be stopped anytime (in any emergency, side effects, adverse effects) by removing the transdermal formulation or transdermal delivery system from the patient's skin.

As per above mentioned reason for the treatment and/or prevention of symptoms associated with allergic rhinitis and urticaria transdermal delivery can reduce the dosing frequency of cetirizine dihydrochloride for the patients. Based on the requirement and severity of symptoms, cetirizine dihydrochloride transdermal delivery system of the invention can be applied and left on skin for a period of time, for example, selected from the group 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7

days, or more. Similarly, the transdermal gel formulation of cetirizine dihydrochloride of the invention can be topically applied and left on the skin for up to one day. Transdermal delivery of cetirizine dihydrochloride can provide convenient and patient friendly dosing regimen to patients with allergic rhinitis and chronic urticaria.

In transdermal and topical drug delivery, formulations or systems are applied to the patient's skin surface but there is a difference in both the drug delivery. In transdermal drug delivery, drug penetrates through the skin and reaches systemic circulation to have pharmacologic effect[11]. Therefore, in transdermal drug delivery drug plasma concentration is in therapeutic range. On the other hand, in topical drug delivery, drug either does not or minimally penetrate through the skin and exert localized effect or exert effect at its site of application[11]. Therefore, there is insignificant drug plasma concentration.

There are patents known in the art which have mentioned about the cetirizine hydrochloride formulations for example Patent application US20120027876A1 discloses the treatment of dermatitis by topical application of formulation comprising one or more antihistamine, one or more polysaccharide and one or more group 1, 2 or 13 metal hydroxides. Topical formulations are disclosed comprising antihistamine drugs such as diphenhydramine hydrochloride, loratadine, cetirizine hydrochloride. A topical gel–type dispersion formulation comprising cetirizine hydrochloride is prepared by using equate children's allergy relief cetirizine hydrochloride oral medicine, equate max strength liquid antacid, xanthan gum powder and corn starch. This patent application is about the topical treatment in which composition is applied to affected area with dermatitis which gives shield from external environment by leaving a light film. Furthermore, formulation decreases the span of rash by drying out the irritants.

Patent application US20140079791A1 discloses a transdermal composition, prepared by first coating the active pharmaceutical ingredient particles with highly volatile silicones or mixtures of highly volatile silicones and later dispersing the coated active pharmaceutical particles in a cream or gel base. Silicone compound evaporates after application of gel to skin surface. Example and method of

preparation of cetirizine gel composition is disclosed. The patent application mentions about the cetirizine but does not teach or inform about the salt of cetirizine such as cetirizine dihydrochloride.

US Patent number 6790847B2 discloses antihistamine gel formulations for topical application to the skin. The patent states that the "object of the invention is to provide a fast and locally acting pharmaceutical form of the preferred antihistamines cetirizine and loratadine for the treatment of disorders or diseases of the skin resulting from excessive release of histamine which permits a rapid onset of the effect". Examples of cetirizine hydrochloride gel formulations are disclosed. One of the cetirizine hydrochloride gel formulation was applied to the skin of 20 volunteers and relieved sunburn, redness and itching caused by insect bites or sunburn.

US Patent number 6258816B1discloses "sulfonanilide NSAIDs e.g. Nimesulide and thereof when combined with cetirizine forms an excellent synergistic antileukotriene, antihistaminic, anti-allergy and anti-inflammatory composition". Examples of different dosage form are disclosed such as tablets, topical gel, transdermal gel, capsules, sustained release bilayer tablets, metered dose inhaler, injection. Topical gel example contains both nimesulide and cetirizine (suitable pharmaceutical form).

US patent number 6277387B1 relates to the addition of a histamine antagonist, an interleukin-1 antagonist and/or a TNF alpha antagonist to compositions wherein compositions are cosmetic, pharmaceutical or dermatological. The patent relates to the treatment of sensitive skin, irritable skin, inhibiting manifestations of irritable skin and preventing or decreasing the irritant side effects of dermatological, cosmetic or pharmaceutical active agents. In the disclosed composition examples, cetirizine is incorporated in very small percentage that is, make up removal lotion for the face contains 0.001% cetirizine, antiwrinkle skin care cream for the face contains 0.15% cetirizine, pain relief gel contains 0.03% cetirizine.

US Patent number 5627183A discloses "Methods are disclosed utilizing optically pure (+) cetirizine for the treatment of urticaria in humans while avoiding the concomitant liability of adverse effects associated with the racemic mixture of

cetirizine". Patent talks about different routes of administration for example parenteral, oral, rectal, transdermal and like forms of administration. Only oral formulation examples of capsules and tablets are disclosed.

The references as set forth above disclose about once a day delivery of cetirizine dihydrochloride through topical and/or transdermal route. In contrast, the invention as disclosed herein can deliver cetirizine dihydrochloride to the systematic circulation through patch technology for up to 7 days or more. This invention will help to improve patient compliance by reducing dosing frequency and also deliver uniform amount of cetirizine dihydrochloride to the patients for up to 7 days or more.

Brief Summary of the Invention

In one aspect, the invention provides continuous in vitro transdermal delivery of cetirizine dihydrochloride from transdermal gel formulation for 7 days.

In another aspect invention provides the method for reducing the dosing frequency of cetirizine dihydrochloride.

In yet another aspect, for transdermal delivery of cetirizine dihydrochloride semisolid transdermal formulation is a transdermal gel formulation. In yet another aspect, transdermal formulation is composed of cetirizine dihydrochloride and carrier system. In yet another aspect, carrier system is composed of excipients selected from the group of solvents, penetration enhancers, gelling agents or polymers, pH adjusting agents either alone or in combinations thereof.

In yet another aspect, transdermal semisolid formulation comprises cetirizine dihydrochloride in an amount between 2%- 30% w/w and carrier system in an amount between 70%- 98% w/w. More preferably, cetirizine dihydrochloride in an amount between 3%- 20%w/w and carrier system in an amount between 80%- 97% w/w. Most preferably, cetirizine dihydrochloride in an amount between 6% - 15% w/w and carrier system in an amount between 85%- 94% w/w.

In one aspect, transdermal gel formulation comprises cetirizine dihydrochloride in an amount between 2%- 30% w/w and carrier system in an amount between 70%- 98% w/w. More preferably, cetirizine dihydrochloride in an amount between 3%- 20%w/w and carrier system in an amount between 80%- 97% w/w. Most preferably, cetirizine dihydrochloride in an amount between 6% - 15% w/w and carrier system in an amount between 85%- 94% w/w.

In one aspect a transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 0.1%- 40%w/w, dimethyl sulfoxide in an amount between 1%- 80%w/w, hexylene glycol in an amount between 1%- 80%w/w, diethylene glycol monoethyl ether (Transcutol P) in an amount between 1%- 80%w/w, lactic acid in an amount between 1%- 80%w/w, oleyl alcohol (kollicream OA) in an amount between 0.5%- 50%w/w, ethanol in an amount between 1%- 80%w/w, glycerin in an amount between 0.5%- 70%w/w , propylene glycol monolaurate type II (lauroglycol 90) in an amount between 0.5%- 70%w/w, water in an amount between 0.5%- 85%w/w, sodium hydroxide 50% w/w in an amount between 0.05%- 30%w/w , hydroxypropyl cellulose (Klucel HF) in an amount between 0.25%- 20%w/w. In another aspect transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 0.1%- 40%w/w, dimethyl sulfoxide in an amount between 5%- 60% w/w, hexylene glycol in an amount between 1%- 50%w/w, diethylene glycol monoethyl ether (Transcutol P) in an amount between 2% - 50%w/w, lactic acid in an amount between 1%- 30%w/w , oleyl alcohol (kollicream OA) in an amount between 1%- 30% w/w, ethanol in an amount between 1%- 50%w/w, glycerin in an amount between 1%- 30%w/w , propylene glycol monolaurate type II (lauroglycol 90) in an amount between 1%- 30% w/w, water in an amount between 1%- 60%w/w, sodium hydroxide 50% w/w in an amount between 0.5%- 15%w/w, hydroxypropyl cellulose (Klucel HF) in an amount between 1%- 15%w/w.

Further, the semisolid transdermal formulation comprising cetirizine dihydrochloride and carrier system can be added to transdermal delivery system wherein, transdermal delivery system is a reservoir system. Without limiting in scope semisolid transdermal formulation is transdermal gel formulation comprising cetirizine dihydrochloride and carrier system which can be added to transdermal delivery system wherein, transdermal delivery system is a reservoir system.

Method of treatment and/or prevention and/or relief of symptoms associated with allergic rhinitis and/or urticaria includes either the topical application of transdermal formulation or topical application of reservoir system containing transdermal formulation to the skin wherein duration of topical application of transdermal formulation is for up to 1 day and, wherein duration of topical application of reservoir patch containing transdermal formulation is selected from the group for

one day, for two days, for three days, for four days, for five days, for six days, for seven days. Preferably, method of treatment and/or prevention and/or relief of symptoms of allergic rhinitis and/or urticaria includes either the topical application of transdermal gel formulation or topical application of reservoir system incorporated with transdermal gel formulation to the skin wherein duration of topical application of transdermal gel is for up to 1 day and, wherein duration of topical application of reservoir patch containing transdermal gel formulation is selected from the group for one day, for two days, for three days, for four days, for five days, for six days, for seven days thereby reducing the dosing frequency.

The invention provides a semisolid transdermal formulation for transdermal delivery of cetirizine dihydrochloride. The invention provides a semisolid transdermal formulation for transdermal delivery of cetirizine dihydrochloride wherein the formulation is a transdermal gel formulation. The invention provides a transdermal gel formulation comprising cetirizine dihydrochloride and a carrier system. The invention provides a transdermal gel formulation wherein the carrier system comprises excipients selected from the group consisting of solvents, penetration enhancers, gelling agents, thickening agents, polymers, pH adjusting agents, stabilizing agents, skin irritation reducing agents either alone and combinations thereof. The invention provides a transdermal gel formulation wherein the carrier system comprises excipients selected from the group consisting of solvents, penetration enhancers, gelling agents, polymers, pH adjusting agents, and combinations thereof. The invention provides a transdermal gel formulation wherein the solvent is present and selected from the group consisting of cosolvents, sulfoxide, alcohol, polyhydric alcohol, glycol, acid, glycol ether, water, polar solvents, semi polar solvents, nonpolar solvents, pyrrolidone, dimethylisosorbide, and combinations thereof. The invention provides a transdermal gel formulation wherein the penetration enhancer is present and is selected from the group consisting of fatty alcohol, propylene glycol mono-and diesters of fats and fatty acids, solubilizers, surfactants, fatty acid, esters, terpene and terpenoids, sulfoxide, alcohol, amide, triglycerides, and combinations thereof. The invention provides a transdermal gel formulation wherein the penetration enhancer is present and is selected from the group consisting of fatty alcohol, propylene glycol mono- and diesters of fats and fatty acids (such as propylene glycol monolaurate type II), esters, terpene and terpenoids, and combinations thereof. The invention provides a

transdermal gel formulation wherein the gelling agents is present and is selected from the group consisting of cellulose, cellulose derivatives, , carboxyvinyl polymers, natural polymers and derivatives, synthetic polymers and derivatives, semisynthetic polymers and derivatives, polysaccharides and derivatives, water swellable, organic solvent swellable polymers, and combinations thereof. The invention provides a transdermal gel formulation wherein the pH adjusting agent is present and is selected from the group consisting of acids, bases, buffer, and combinations thereof. The invention provides a transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 1%- 40% w/w and carrier system in an amount between 99%-60% w/w. The invention provides a transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 3%- 30% w/w and carrier system in an amount between 97%-70% w/w. The invention provides a transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 5%- 20% w/w and carrier system in an amount between 95%-80% w/w. The invention provides a transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 6%- 18% w/w and carrier system in an amount between 94%-82% w/w.

The invention provides a transdermal gel formulation comprising: cetirizine dihydrochloride in an amount between 6%- 18%w/w, dimethyl sulfoxide in an amount between 5%- 60% w/w, hexylene glycol in an amount between 1%- 50%w/w, diethylene glycol monoethyl ether in an amount between 2% - 50%w/w, lactic acid in an amount between 1%- 30%w/w, oleyl alcohol) in an amount between 1%- 30% w/w, ethanol in an amount between 1%- 50%w/w, glycerin in an amount between 1%- 30%w/w, propylene glycol monolaurate type II in an amount between 1%- 30% w/w, water in an amount between 1%- 60%w/w, sodium hydroxide 50% w/w in an amount between 0.5%- 15%w/w, and hydroxypropyl cellulose (Klucel HF) in an amount between 1%- 15%w/w.

The invention provides a semisolid transdermal formulation wherein the duration of transdermal delivery of cetirizine dihydrochloride is selected from the group of 1day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, and more than 7 days. The invention provides a semisolid transdermal formulation wherein the duration of transdermal delivery of cetirizine dihydrochloride is 7 days. The invention provides a semisolid transdermal formulation wherein the duration of transdermal delivery of cetirizine dihydrochloride is 3 days. The invention provides a method of treatment

and/or prevention and/or reduction and/or relief of one or more symptoms of allergic rhinitis comprising topical application of a transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergic rhinitis comprising topical application of a reservoir patch comprising a transdermal gel formulation of the invention to a patient in need thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of skin manifestations and/or one or more symptoms of urticaria comprising topical application of a transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of skin manifestations and/or one or more symptoms of urticaria comprising topical application of a reservoir patch comprising a transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergies comprising topical application of a transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergies comprising topical application of a reservoir patch comprising the transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of upper respiratory allergies comprising topical application of the transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction and/or relief of one or more of symptoms of upper respiratory allergies comprising topical application of a reservoir patch comprising the transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction of one or more symptoms due to release of extra histamines in the body of a patient comprising topical application of the transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of treatment and/or prevention and/or reduction of one or more symptoms due to release of extra histamines in the body of a patient comprising topical application of a reservoir patch comprising the transdermal gel formulation of the invention to a patient in need of thereof. The invention provides a method of

the invention wherein the duration of topical application is for one day or up to one day. The invention provides a method of the invention wherein the duration of topical application is selected from the group consisting of one day, for two days, for three days, for four days, for five days, for six days, and for seven days. The invention provides a method of the invention wherein the duration of topical application is for one day or up to one day. The invention provides a method of the invention wherein the duration of topical application is selected from the group consisting of one day, for two days, for three days, for four days, for five days, for six days, and for seven days. The invention provides a method of the invention wherein the duration of topical application is for one day or up to one day. The invention provides a method of the invention wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days. The invention provides a method of the invention wherein the duration of topical application is for one day or up to one day. The invention provides a method of the invention wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days. The invention provides a method of the invention wherein the duration of topical application is for one day or up to one day. The invention provides a method of the invention wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

Brief Description of the Drawing

The invention will be described in conjunction with the following drawings wherein: Figure 1 is is a graph of Flux ($\mu g/cm^2/hr$) VS Time (hour), presenting in vitro transdermal delivery of cetirizine dihydrochloride through human cadaver skin continuously for seven days from transdermal gel formulation.

Detailed Description of the Invention

Cetirizine dihydrochloride refers to all pharmaceutically acceptable forms of cetirizine either alone or in combinations thereof, for example in following forms but not limited to such as salt or racemic form of salt or base or racemic form of

base, solid solution or isomer or crystalline or co crystalline or amorphous or prodrug or metabolites or derivatives or analogs.

The term active substance or active agent refers to Cetirizine dihydrochloride.

The terms cetirizine dihydrochloride and cetirizine hydrochloride are used interchangeably.

The terms penetration enhancers and permeation enhancers are used interchangeably

As used herein, the phrase "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

The term "derivative" or "derivatized" as used herein includes chemical modification of a compound of the invention, or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a "derivative" may be a functional equivalent of a compound of the invention, which is capable of inducing the improved pharmacological functional activity in a given subject. Illustrative of such chemical modifications would be replacement of hydrogen by a halo group, an alkyl group, an acyl group or an amino group.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of a compound of the invention is also meant to include within its scope all the possible isomers , racemic form and their mixtures, and any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, such as, for example, a compound which has a structural formula different from the one of the compounds of the invention, and yet is directly or indirectly converted in vivo into a compound of the invention, upon administration to a subject, such as a mammal, particularly a human being.

The compound may be in the form of a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate,

nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

The terms formulation and composition are used interchangeably.

The terms reservoir patch and reservoir system are used interchangeably.

The term semisolid includes without any limitation such as gels, creams, ointments, lotion, emulsion, suspension, paste, balms, wherein gels are preferred.

Without limiting in scope, solvents, penetration enhancers, gelling agents, polymers, thickening agents, pH adjusting agents, suspending agents, stabilizing agents, surfactants, emulsifying agents, skin irritation reducing agents, humectants, emollients alone or in combinations thereof can be used in semisolid formulations.

Abbreviations: μg stands for microgram, cm stands for centimeter, hr stands for hour, g stands for gram, hrs stands for hours

All the pharmaceutical compositions or formulations are weight by weight percent.

The term "about" and the use of ranges in general, whether or not qualified by the term about, means that the number comprehended is not limited to the exact number set forth herein, and is intended to refer to ranges substantially within the quoted range while not departing from the scope of the invention. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 50% of the particular term.

Topical administration includes administration to the skin or mucosa for transdermal delivery. Administration of the compositions according to the present invention may be via any common topical route so long as the target tissue is available via that

route. This includes direct topical administration to an affect area of, for example, the skin or mucosal surface or scalp or genital area. The term topical application refers to application to skin.

As used herein, the term "transdermal" refers to delivery, administration or application of a drug by means of direct contact with skin or mucosa. Such delivery, administration or application is also known as dermal, percutaneous, transmucosal and buccal. As used herein, "dermal" includes skin and mucosa, which includes oral, buccal, nasal, rectal and vaginal mucosa.

The terms transdermal delivery system refers to transdermal patch, patch, reservoir patch, and systems which can be topically applied to skin, patches known to those skilled in the art, comprising a transdermal formulation according to the invention.

As used herein, "transdermal drug delivery system" refers to a system (e.g., a device) comprising a formulation that releases drug upon application to the skin. In some embodiments, the transdermal drug delivery system is a substantially non-aqueous, solid form, capable of conforming to the surface with which it comes into contact, and capable of maintaining such contact so as to facilitate topical application without adverse physiological response, and without being appreciably decomposed by aqueous contact during topical application to a subject. Many such systems are known in the art and commercially available, such as transdermal drug delivery patches. Typically, transdermal drug delivery systems are classified into one of two categories: matrix-type systems and reservoir-type systems.

A transdermal drug delivery system may be packaged or provided in a package, such as a pouchstock material used in the prior art for transdermal drug delivery systems in general. For example, DuPont's SURLYN® can be used in a pouchstock material. Alternatively, a pouchstock comprising a coextruded ethylene acrylic acid/low-density polyethylene (EAA/LDPE) material, or BAREX® from INEOS (acrylonitrile-methyl acrylate) may be used.

The term allergic rhinitis refers to seasonal allergic rhinitis and/or perennial allergic rhinitis.

The term urticaria refers to acute urticaria and/or chronic urticaria and/or chronic idiopathic urticaria.

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is an elderly human. In another embodiment, the subject is a human adult. In another embodiment, the subject is a human child. In yet another embodiment, the subject is a human infant.

As used herein, the term "agent" refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management of a disease or disease symptoms or condition. As used herein, the term "effective amount" refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

As used herein, the terms "therapies" and "therapy" can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to small molecule therapy.

As used herein, the terms "treat," "treatment," and "treating" in the context of the administration of a therapy to a subject refer to the reduction or inhibition of the progression and/or duration of a disease or condition, the reduction or amelioration of the severity of a disease or condition, and/or the amelioration of one or more symptoms thereof.

As used herein, the terms "prevent," "preventing" and/or "prevention" in the context of the administration of a therapy to a subject refer to the prevention or inhibition of the recurrence, onset, and/or development of a disease or condition, or a symptom thereof in a subject resulting from the administration of a therapy (e.g., a prophylactic or therapeutic agent), or a combination of therapies (e.g., a combination of prophylactic or therapeutic agents).

The invention provides a semisolid transdermal formulation for transdermal delivery of cetirizine dihydrochloride. In one aspect, the semisolid transdermal formulation of cetirizine dihydrochloride is a transdermal gel. In another aspect, transdermal gel formulation of the invention gives continuous in vitro transdermal delivery of cetirizine dihydrochloride for a duration of 7 days. In yet another aspect, the transdermal gel formulation of the invention can be added into a transdermal delivery system, wherein transdermal delivery system is a reservoir patch. In yet another aspect invention provides method for reducing dosing frequency of cetirizine dihydrochloride.

Carrier system plays an important role in semisolid transdermal formulation. The carrier system can have multiple functions in the formulation without any limitation such as it determines drug solubility, governs permeation of the drug, influence the release rate of drug, determines formulation stability, etc. For a good transdermal formulation carrier system composition is highly important. To get the required transdermal delivery of drug appropriate selection, combination and concentration of carrier system excipients are very important.

In one aspect, the semisolid transdermal formulation comprises cetirizine dihydrochloride and a carrier system. In the semisolid transdermal formulation cetirizine dihydrochloride can be dissolved and/or suspended in the carrier system. In another aspect, carrier system is comprised of excipients selected from the group of components such as but not limited to solvents, penetration enhancers, pH adjusting agents, polymers or gelling agents or thickening agents, stabilizing agents either alone or in combinations thereof. In another aspect, carrier system is comprised of excipients selected from the group of components such as solvents, penetration enhancers, pH adjusting agents, gelling agents or polymers alone or in

combinations thereof. Without any limitation, preferred semisolid transdermal formulation is a transdermal gel formulation.

In one aspect, semisolid transdermal formulation comprises cetirizine dihydrochloride in an amount between 1%- 49% w/w and carrier system in an amount between 51%- 99% w/w. Preferably, cetirizine dihydrochloride in an amount between 2%- 30% w/w and carrier system in an amount between 70%- 98% w/w. More preferably, cetirizine dihydrochloride in an amount between 3%- 20%w/w and carrier system in an amount between 80%- 97% w/w. Most preferably, cetirizine dihydrochloride in an amount between 6% - 15% w/w and carrier system in an amount between 85%- 94% w/w.

In another aspect, semisolid transdermal formulation is a transdermal gel formulation and comprises cetirizine dihydrochloride in an amount between 1%- 49% w/w and carrier system in an amount between 51%- 99% w/w. Preferably, cetirizine dihydrochloride in an amount between 2%- 30% w/w and carrier system in an amount between 70%- 98% w/w. More preferably, cetirizine dihydrochloride in an amount between 3%- 20%w/w and carrier system in an amount between 80%- 97% w/w. Most preferably, cetirizine dihydrochloride in an amount between 6% - 15% w/w and carrier system in an amount between 85%- 94% w/w.

To get the target transdermal delivery of cetirizine dihydrochloride different experiments were designed. Experiment were conducted using human cadaver skin to see the effect of formulation variables on the in vitro flux of cetirizine dihydrochloride. Different formulation variables were such as different concentration of cetirizine dihydrochloride, different solvents, different combination of solvents, different permeation enhancers, combinations of permeation enhancers, different gelling agents, different formulation pH etc.

Drug amount or concentration plays an important role in formulation. Required transdermal delivery of drug or dose cannot be achieved if the amount of drug in the formulation is less. In one aspect, cetirizine dihydrochloride is present in the formulation in an amount between 1%- 49% w/w. Preferably, cetirizine dihydrochloride is present in the formulation in an amount between 2%- 30% w/w.

More preferably, cetirizine dihydrochloride is present in the formulation in an amount between 3%- 20%w/w. More preferably, cetirizine dihydrochloride is present in the formulation in an amount between 5%- 20%w/w. Most preferably, cetirizine dihydrochloride is present in the formulation in an amount between 6% - 15% w/w.

Solvents solubilize drug in the formulation. Required amount of drug cannot be added to the formulation if solubility of the drug is low in the solvent system which may result into failure of adequate transdermal delivery. At the same time if the solubility of drug is too high in the formulation, drug may not leave the formulation. Therefore, selection of solvent system having optimum drug solubility is very significant. In certain embodiments, cosolvents may be added in the formulation which further helps to achieve the drug solubility. If required, solvents and cosolvents are also added to make up the weight of the formulations. Depending on the physicochemical properties of drug, at times there are limited solvents which can solubilize the drug. In the present invention excipients of solvents and cosolvents known to those skilled in the art are selected from the group such as but not limited to sulfoxide (such as but not limited to decylmethylsulfoxide, dimethyl sulfoxide, etc.), glycol ethers (such as but not limited to ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, etc.), acids (such as but not limited to ascorbic acid, levulinic acid, alginic acid, lactic acid, adipic acid, etc.), polyhydric alcohols (such as but not limited to glycerin, sorbitol, mannitol, etc.), pyrrolidone (such as but not limited to N-methyl 2-pyrrolidone, etc), glycols (such as but not limited to propylene glycol, butylene glycol, hexylene glycol, dipropylene glycol, polyethylene glycol, polypropylene glycol, etc.), volatile solvents (such as but not limited to methanol, ethanol, propanol, isopropyl alcohol, ethyl acetate, acetone, etc.), alcohol and alcohol derivatives(such as but not limited to C_1-C_{20} alcohol, etc.), polar solvents (such as but limited to water, etc.), non-polar solvents, semi polar solvents, oils, dimethylisosorbide, medium chain triglycerides, cyclodextrin, derivative of glycols and others either alone or in combinations thereof. Without any limitation preferred solvents are dimethyl sulfoxide, diethylene glycol monoethyl ether, lactic acid, glycerin, propylene glycol, hexylene glycol, dipropylene glycol, polyethylene glycol, ethanol, water, dimethylisosorbide.

Penetration enhancers are pharmacologically inactive chemicals. Their main function is to interact with the skin and increases the drug permeation or flux. Although lot of penetration enhancers are commercially available but there are very few penetration enhancers which facilitates or increases the permeation of a particular drug. For example, penetration enhancer for drug A may not act as penetration enhancer for drug B. Similarly, penetration enhancer may work as an enhancer with excipient combination of carrier system A and may not achieve its full effect with excipients combination carrier system B. The invention may comprise excipients which are penetration enhancers known to those skilled in the art are selected from the group such as but not limited to fatty acids (such as but not limited to butyric acid, valeric acid, caprylic acid, capric acid, oleic acid, lauric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, etc.), fatty alcohol (such as but not limited to butyl alcohol, cetyl alcohol, myristyl alcohol, oleyl alcohol, stearyl alcohol, lauryl alcohol, etc.), glycol (such as but not limited to propylene glycol, polyethylene glycol, etc.), terpene and terpinoids (such as but not limited to limonene, terpineol, carvone, nerolidol, thymol, cineole, etc.), sulfoxide (such as but not limited to dimethylsulfoxide, decylmethylsulfoxide, etc.), pyrrolidones (such as but not limited to N-methyl-2-pyrrolidone, etc.), amides (such as but not limited to urea, azone, dimethylacetamide, dimethylformamide ,etc.), triglycerides (such as but not limited to triacetin, etc.), phospholipids (such as but not limited to lecithine, etc.), hydrocarbons (such as but not limited to squalene, alkanes, etc.), propylene glycol mono- and diesters of fats and fatty acids (such as propylene glycol monolaurate type II, propylene glycol monolaurate type I, propylene glycol monocaprylate type I, etc.), esters, fatty alcohol esters, fatty acid esters, (such as but not limited to lauryl lactate, methyl oleate, ethyl oleate, decyl oleate, oleyl oleate, isopropyl myristate, sorbitan monoleate, glyceryl monolaurate, isopropyl palmitate, glyceryl monoelate, etc.), polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, nanocarriers (such as but not limited to surfactant based vesicles, lipid based vesicles, etc.), surfactant or solubilizer or cosurfactants (such as but not limited to caprylocaprroyl polyoxyl-8 glycerides, propylene glycol dicaprolate/dicaprate, propylene glycol monocaprylate (type II), etc.) and other either alone or in combinations thereof.

Gelling agents, thickening agents, and/or polymers may impart viscosity to the formulation. Viscosity gives body to the formulation and affects the release of the drug from the formulation. Generally due to viscosity, release of drug from the gel is always lower than from the solution. In the present invention excipients of gelling agents or thickening agents or polymers known to those skilled in the art are selected from the group such as but not limited to natural polymers, semisynthetic polymers, synthetic polymers, cellulose and its derivatives (such as but not limited to hydroxypropyl methyl cellulose, methyl cellulose, methylhydoxyethyl cellulose, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, etc.), natural polymers, polysaccharides and its derivatives (such as but not limited to acacia, chitosan, agar, xanthum gum, alginic acid and derivatives, tragacanth, potassium or sodium carrageenan, guar gum, cassia tora, collagen, pectin, gelatin, gellum gum, gum copal, resin, starch, etc.), carboxyvinyl polymers or carbomers (such as but not limited to carbopol 934 NF, carbopol 71G NF, carbopol 972P NF, carbopol 980 NF, pemulen TR-1 NF, carbopol ultrez 10 NF, carbopol 971 P NF, etc.), clays (such as but not limited to bentonite , magnesium aluminum silicate, hectorites, etc.), polyethylene and its co-polymers, polyacrylamide, polyvinyl alcohol, polyvinylpyrrolidone homopolymer and polyvinyl pyrrolidone copolymers (such as but not limited to PVP, poloxamer, etc.), water and/or organic solvent swellable polymers, eudragit, acrylic acid ester, etc. either alone or in combinations thereof. Without any limitation preferred are gelling agents. More preferably hydroxypropyl cellulose.

In the present invention pH adjusting agents known to those skilled in the art are selected from the group such as but not limited to base and its derivatives (such as but not limited to triethylamine, sodium hydroxide, ammonium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, sodium carbonate, etc.), acids and its derivatives (such as but not limited to acetic acid, ascorbic acid, hydrochloric acid, citric acid, fumaric acid, phosphoric acid, carboxylic acids, etc.), pH stabilizers, buffers (such as but not limited to phosphate buffer, citrate buffer, acetate buffer, etc.) either alone or in combinations thereof. Without any limitation, preferred are hydrochloric acid and sodium hydroxide.

Without any limitation, the preferable transdermal formulation of the invention comprises cetirizine dihydrochloride, solvents, penetration enhancers, gelling agents or polymers, pH adjusting agents.

Apart from these components other components known to those skilled in the art without any limitation such as stabilizing agents, emulsifying agents, surfactants, emollients, humectants, skin irritation reducing agents, suspending agents are also within the scope of this patent application. Stabilizing agents known to those skilled in the art includes such as but not limited to complexing agents, antioxidants, oxidizing agents, chelating agents, preservatives, and excipients which helps to get stable formulation (such as but not limited to butylated hydroxyanisole, butylated hydroxytoulene, sodium metabisulfite, ascorbic acid, boric acid, citric acid, sorbic acid, ascorbyl palmitate, vitamin E, EDTA, benzyl alcohol, sodium benzoate, propylparaben, methylparaben, phenol, chlorocresol, etc.), surfactants and emulsifying agents (such as but not limited to nonionic surfactants, amphoteric surfactants, anionic surfactants, cationic surfactants, sodium lauryl sulfate, tween, span, tween 20, tween 40, tween 80, span 20, span 40, span 80, peg 400 monooleate, linoleoyl polyoxyl – 6- glycerides, oleyl polyoxyl-6 glycerides, sodium dioctyl sulfosuccinate, glyceryl esters, etc.), emollients, humectants, skin irritation reducing agents (such as but not limited to petrolatum, glycerol, lecithin, mineral oil, propylene glycol, lanolin, dimethicone, zinc oxide, etc.), either alone or in combinations thereof.

It is well known to those skilled in the art that few excipients can have multiple functions or uses. Such as depending on the formulation they can function as solvents, penetration enhancers, surfactants or all.

While the disclosure has mentioned excipients herein, this is not meant to be limiting, and other suitable excipients for the transdermal formulation are mentioned in, for example, the "Handbook of Pharmaceutical Excipients, Sixth Edition," published by the Pharmaceutical Press and the American Pharmacists Association, London, USA and "Remington's the science and practice of pharmacy, 21st edition", published by the Wolter's Kluwer Company, PA, and penetration or permeation enhancers are set forth in "Percutaneous Penetration Enhancers" (Eric W. Smith,

Howard I. Maibach, 2005. November, CRC press), and are also within the scope of the invention.

The invention provides transdermal gel formulation comprising cetirizine dihydrochloride and carrier system wherein components of carrier system are selected from the group such as solvents, penetration enhancers, gelling agents or polymers, pH adjusting agents either alone or in combinations thereof. Further, cetirizine dihydrochloride is present in an amount between 1%- 49% w/w and carrier system is present in an amount between 51%-99% w/w. Preferably, cetirizine dihydrochloride is present in an amount between 2%- 30% w/w and carrier system is present in an amount between 70%- 98% w/w. More preferably, cetirizine dihydrochloride is present in an amount between 3%- 20%w/w and carrier system is present in an amount between 80%- 97% w/w. Most preferably, cetirizine dihydrochloride is present in an amount between 6% - 15% w/w and carrier system is present in an amount between 85%- 94% w/w.

The invention provides an exemplary transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 1%- 40%w/w, dimethyl sulfoxide in an amount between 1%- 80%w/w, hexylene glycol in an amount between 1%- 80%w/w, diethylene glycol monoethyl ether (Transcutol P) in an amount between 1%- 80%w/w, lactic acid in an amount between 1%- 80%w/w, oleyl alcohol (kollicream OA) in an amount between 0.5%- 50%w/w, ethanol in an amount between 1%- 80%w/w, glycerin in an amount between 0.5%- 70%w/w , propylene glycol monolaurate type II (lauroglycol 90) in an amount between 0.5%- 70%w/w, water in an amount between 0.5%- 85%w/w, sodium hydroxide 50% w/w in an amount between 0.05%- 30%w/w , hydroxypropyl cellulose (Klucel HF) in an amount between 0.25%- 20%w/w. Preferably, cetirizine dihydrochloride in an amount between 3%- 20%w/w, dimethyl sulfoxide in an amount between 5%- 60% w/w, hexylene glycol in an amount between 2%-50%w/w, diethylene glycol monoethyl ether (Transcutol P) in an amount between 2% - 50%w/w, lactic acid in an amount between 2%- 30%w/w , oleyl alcohol (kollicream OA) in an amount between 1%- 30% w/w, ethanol in an amount between 2%- 50%w/w, glycerin in an amount between 1%- 30%w/w , propylene glycol monolaurate type II (lauroglycol 90) in an amount between 1%- 30% w/w, water in an amount between 2%-

60%w/w, sodium hydroxide 50% w/w in an amount between 0.5%- 15%w/w, hydroxypropyl cellulose (Klucel HF) in an amount between 1%- 15%w/w. Without any limitation, an exemplary transdermal gel formulation in this range is provided in Example 4 as formulation 045.

In another aspect transdermal gel formulation comprising cetirizine dihydrochloride in an amount between 0.1%- 40%w/w, dimethyl sulfoxide in an amount between 5%- 60% w/w, hexylene glycol in an amount between 1%-50%w/w, diethylene glycol monoethyl ether (Transcutol P) in an amount between 2% - 50%w/w, lactic acid in an amount between 1%- 30%w/w , oleyl alcohol (kollicream OA) in an amount between 1%- 30% w/w, ethanol in an amount between 1%- 50%w/w, glycerin in an amount between 1%- 30%w/w , propylene glycol monolaurate type II (lauroglycol 90) in an amount between 1%- 30% w/w, water in an amount between 1%- 60%w/w, sodium hydroxide 50% w/w in an amount between 0.5%- 15%w/w, hydroxypropyl cellulose (Klucel HF) in an amount between 1%- 15%w/w.

Examples

Example 1

Formulation 039 (%w/w)	
Cetirizine Dihydrochloride	5.00%
Dimethyl sulfoxide	32.30%
Hexylene Glycol	9.00%
Propylene glycol monolaurate type II (Lauroglycol 90)	3.90%
Diethylene glycol monoethyl Ether (Transcutol P)	22.00%
Water	5.00%
Glycerin	2.90%
Ethanol	5.00%
Propylene Glycol	5.00%
Dimethyl Isosorbide	5.00%
Sodium Hydroxide 50% w/w	1.50%
Hydroxypropyl Cellulose (Klucel HF)	3.40%

Example 1: Formulation 039

In vitro experiment was conducted in semi-automatic Logan FDC -6T diffusion cell drive system using human cadaver skin with an average flux of 18ug/cm2/hr for upto 168 hrs.

Example 2

Formulation 051 (%w/w)	
Cetirizine Dihydrochloride	7.21%
Dimethyl sulfoxide	31.93%
Hexylene Glycol	6.70%
Propylene glycol monolaurate type II (Lauroglycol 90)	4.00%
Diethylene glycol monoethyl ether (Transcutol P)	18.00%
Water	9.27%
Ethanol	6.70%
Lactic Acid	6.20%
Oleyl Alcohol (Kollicream OA)	3.09%
Sodium Hydroxide 50% w/w	3.40%
Hydroxypropyl cellulose (Klucel HF)	3.50%

Example 2: Formulation 051

In vitro experiment was conducted in semi-automatic Logan FDC -6T diffusion cell drive system using human cadaver skin with an average flux of 21 ug/cm2/hr for upto 168 hrs.

Example 3

Formulation 054 (%w/w)	
Cetirizine Dihydrochloride	7.00%
Dimethyl sulfoxide	34.00%
Hexylene Glycol	7.10%
Diethylene glycol monoethyl ether (Transcutol P)	17.50%
Water	12.00%
Propylene glycol monolaurate type II (Lauroglycol	3.90%

90)	
Ethanol	6.50%
Oleyl Alcohol (Kollicream OA)	3.60%
Glycerin	2.90%
Sodium hydroxide 50% w/w	2.10%
Hydroxypropyl cellulose (Klucel HF)	3.40%

Example 3: Formulation 054

In vitro experiment was conducted in semi-automatic Logan FDC -6T diffusion cell drive system using human cadaver skin with an average flux of 24 ug/cm2/hr for upto 168 hrs.

Example 4

Formulation 045 (%w/w)	
Cetirizine Dihydrochloride	7.00%
Dimethyl sulfoxide	31.00%
Hexylene Glycol	6.50%
Diethylene glycol monoethyl ether (Transcutol P)	17.50%
Water	9.00%
Propylene glycol monolaurate type II (Lauroglycol 90)	3.90%
Ethanol	6.50%
Oleyl Alcohol (Kollicream OA)	3.00%
Glycerin	2.90%
Lactic acid	6.00%
Sodium hydroxide 50% w/w	3.30%
Hydroxypropyl cellulose (Klucel HF)	3.40%

Method of preparation (Example 4 – Formulation 045)

Quantity:10g gel

In a beaker accurately weigh the required quantities of dimethyl sulfoxide, hexylene glycol, diethylene glycol monoethyl ether (Transcutol P), lactic acid, oleyl alcohol

(kollicream OA), ethanol, glycerin, propylene glycol monolaurate type II (lauroglycol 90), water. Mix all the weighed ingredients on the magnetic stirrer to obtain clear solution. Add accurately weighed cetirizine dihydrochloride to the solution and stir on magnetic stirrer until fully dissolve. Now add accurately weighed sodium hydroxide 50%w/w to the drug solution and mix it by stirring on the magnetic stirrer. Slowly add the accurately weighed gelling agent hydroxypropyl cellulose (klucel HF) while stirring on the magnetic stirrer and stir overnight on magnetic stirrer to get clear gel.

Example 4: Formulation 045
In vitro experiment was conducted in semi-automatic Logan FDC -6T diffusion cell drive system using human cadaver skin with an average flux of 25 ug/cm2/hr for upto 168 hrs.

Example 4 is an exemplary optimized formulation and Example 1-3 are representative graphs indicating that by small changes in the concentration of the ingredients or changes in the ingredients changes in the individual flux are observed; however, all release the active for 7 days. This suggests that by using formulation 045 ingredients, the steady state profile of cetirizine dihydrochloride can be achieved.

Figure 1 shows the in vitro transdermal flux of cetirizine dihydrochloride from formulation through human cadaver skin for a continuous period of 7 days.

In one aspect, transdermal gel formulation of the invention can be added into a transdermal delivery system wherein transdermal delivery system is a reservoir patch. It is well known to those skilled in the art that there are different designs of reservoir patches. In general, components of reservoir patch well known in the art includes backing layer, release membrane, adhesive, protective liner or release liner. Outermost layer of the reservoir patch is backing layer. Usually backing layer and release membrane are sealed to form a cavity in which formulation is filled and act as a reservoir. Next to release membrane is the adhesive. To attach the reservoir patch to skin there can be a peripheral adhesive layer which is outside the cavity or

there can be adhesive layer covering the cavity. Next to adhesive is the protective liner which is removed prior to application of reservoir patch to skin. Upon application of reservoir patch adhesive and/or release membrane is in the contact with the skin. Reservoir patch is sealed or prepared in a way to avoid the formulation leakage during storage or in use. It is well known to those skilled in the art that there are other ways to attach the reservoir patch to the skin such as by adhesive overlays, in- line adhesive layer, other fastening means such as elastic armbands, belts, tapes, buckles. Although the well-known design of reservoir patch in the art has been described but it is well known to those skilled in the art that there can be several modifications in the design of the reservoir patch such as active substance and/or other excipients can be mixed with the adhesive and this adhesive can be coated on the release membrane. The modifications in the design of reservoir patch are also within the scope of this patent application without departing from the spirit and scope thereof.

Backing layer may be thin, flexible, robust and should not react with active substance or formulation excipients. It keeps the formulation safe during storage and use, it prevents the loss of active substance or drug substance and excipients from the formulation, provides appropriate occlusitivity. Backing film known to those skilled in the art includes such as but not limited to films of ethylene/vinyl acetate copolymers, polyester, polyurethane, polyethylene, polyvinyl chloride, vinyl acetate resins, aluminized films, metal foils, non-woven fabric etc. Without any limitation example of well-known backing layer includes 3M Scotchpak™ 1012 backing polyester film laminate, 3M Scotchpak™ 9723 backing tan polyester film laminate, 3M Scotchpak™ 9730 backing tan polyester film laminate, 3M Scotchpak™ 9733 backing polyester film laminate, 3M Scotchpak™ 9754 polyester film, 3M Scotchpak™ 9757 polyester film, 3M Scotchpak™ 9758 polyester film, 3M CoTran™ 9700 backing melt-blown polyurethane nonwoven backing, 3M CoTran™ 9701 backing polyurethane monolayer film, 3M CoTran™ 9719 backing polyethylene monolayer film, 3M CoTran™ 9722 backing polyethylene monolayer film, DOW BLF 2050 backing layer, etc. Apart from mentioned backing films, other backing films which are well known to those skilled in the art also within the scope of this patent application.

Release membrane allows the diffusion of the drug and other formulation components from formulation reservoir to the skin. Without limiting in scope release membrane are permeable microporous or rate controlling membrane. Rate controlling release membrane controls the rate of diffusion of drug. Without any limitation well known microporous release membrane includes such as microporous polypropylene membrane, microporous polyethylene membrane, etc. Without any limitation well known rate controlling release membrane includes such as ethylene vinyl acetate copolymer membrane, etc. Apart from mentioned release membranes, other release membranes which are well known to those skilled in the art also within the scope of this patent application.

Upon the application of transdermal delivery system to skin, adhesives or adhesive layer helps the transdermal system to fix or adhere to the skin firmly during its period of use. Pressure sensitive adhesives known to those skilled in the art includes such as but not limited to silicone polymers, acrylic polymers, acrylic copolymers, rubber based adhesives, crosslinked polymers such as styrene- butadiene copolymers, polyisobutylene, polybutylene, hot melt adhesive etc. Without any limitation well known examples of pressure sensitive adhesive includes amine compatible BIO PSA- 7-4202, amine compatible BIO-PSA 7- 4301, BIO-PSA hot melt 7-4560, BIO PSA- 7-4602, BIO PSA- 7-4601, DURO-TAK 387-2054, DURO-TAK 387-2156, DURO-TAK 87-9301, DURO-TAK 387-2287, DURO-TAK 87-235A, polyisobutylene medium molecular weight, polyisobutylene low molecular weight, polyisobutylene 55000 mw, polyisobutylene 2300 mw, polyisobutylene 35000 mw, polyisobutylene 1100000, acrylic adhesive 788, etc. At times adhesives are mixed with other excipients without any limitation excipients are such as mineral oil. Apart from mentioned adhesives, other adhesives and excipients which are well known to those skilled in the art also within the scope of this patent application.

Protective liner or release liners are located next to release membrane or adhesives. Protective liners protect the adhesive, release membrane or formulation during storage. Protective liner is removed prior to application of transdermal delivery system to the skin. Protective liner or release liner known to those skilled in the art includes such as but not limited to polyester film, siliconized polyester films, siliconized polyethylene terephthalate film, fluoropolymer coated polyester film, etc.

Without any limitation well known examples of protective liner or release liner includes such as 3M SCOTCHPAK™ 1022 release liner fluoropolymer coated polyester Film, 3M SCOTCHPAK™ 9741 release liner fluoropolymer coated polypropylene film, 3M SCOTCHPAK™ 9742 release liner fluoropolymer coated polyester film, 3M SCOTCHPAK™ 9744 release liner fluoropolymer coated polyester film, 3M SCOTCHPAK™ 9755 release liner fluoropolymer coated polyester film, 3M SCOTCHPAK™ 1022W release liner fluoropolymer coated polyester film – white, 3M SCOTCHPAK™ 9755W release liner fluoropolymer coated polyester film – white, 3M™ SCOTCHPAK™ 9709 release liner fluorosilicone coated polyester film, etc. Apart from mentioned protective liner, other protective liners which are well known to those skilled in the art also within the scope of this patent application.

Optionally tapes can also be used in the transdermal delivery systems. Without any limitation tapes well known in the art includes such as 3M CoTran™ 9695 nonwoven polyester tape, 3M CoTran™ 9698 nonwoven polyurethane tape, 3M CoTran™ 9766 double coated polyethylene tape, 3M CoTran™ 9722L polyvinyl chloride foam tape, 3M CoTran™ 9773 polyethylene foam tape, etc.

In one aspect, transdermal gel formulation of the invention can be applied topically to the skin. In another transdermal gel formulation of the invention can be incorporated into a reservoir patch, wherein reservoir patch can be applied to the skin.

For transdermal delivery of cetirizine dihydrochloride, period of topical application of transdermal gel formulation of the invention can be for up to one day. For transdermal delivery of cetirizine dihydrochloride, period of topical application of reservoir patch comprising transdermal gel formulation of the invention can be selected from the group such as for one day, for two days, for three days, for four days, for five days, for six days, for seven days or more thereby reducing the dosing frequency. To treat and/or prevent and/or relief of the symptoms of urticaria and/or allergic rhinitis those skilled in the art can choose the period of application of transdermal gel formulation or reservoir patch to the skin of the patient based on the factors like type, severity and symptoms of allergic rhinitis and/or urticaria such as

perennial allergic rhinitis, seasonal allergic rhinitis, chronic idiopathic urticaria, acute urticaria, etc.

Cetirizine dihydrochloride is an antihistamine. It has potential to treat and/or prevent and/or alleviate symptoms associated with allergies, treat and/or prevent and/or alleviate symptoms associated with upper respiratory allergy, treat and/or prevent and/or alleviate symptoms and/or symptoms of diseases caused by extra release of histamines in the body. Those skilled in the art can choose the period of application of transdermal gel formulation or reservoir patch (comprising transdermal gel formulation) to the skin to treat and/or prevent and/or alleviate symptoms of allergies, treat and/or prevent and/or alleviate symptoms of upper respiratory allergy, treat and/or prevent and/or alleviate symptoms and/or symptoms of diseases caused by extra release of histamines in the body. Period of continuous patch application can be selected from the group comprising one day, two days, three days, four days, five days, six days, seven days, or more.

As illustrated by the in vitro flux data of cetirizine dihyrochloride in figure 1, formulation of the invention can transdermally deliver cetirizine dihydrochloride continuously for 7 days. Furthermore, it can be proposed that formulation of the invention may have the potential to transdermally deliver therapeutically effective amount of cetirizine dihydrochloride to treat and/or prevent and/or relief of the symptoms of allergic rhinitis and/or urticaria by applying formulation of the invention on the appropriate surface area of the skin and/or by applying transdermal reservoir patch of appropriate surface area containing transdermal gel formulation of the invention to the skin wherein, duration of the application of formulation can be for up to one day, duration of topical application of reservoir patch can be selected from the group such as for one day, for two days, for three days, for four days, for five days, for six days, for seven days. Moreover, if needed flux of the formulation can be altered by changing the parameters without any limitation such as surface area of the patch, cetirizine dihydrochloride concentration, composition of the carrier system, pH of the formulation, type and/or concentration of penetration enhancers and/or solvents and/or gelling agents, etc. without departing from the teachings of present invention.

If reservoir patch is left on the skin for more than 7 days and has drug, it can deliver drug for more than 7 days. Topical application of reservoir patch to skin for more than 7 days is also within the scope of this patent application.

In conclusion, transdermal gel formulation has continuous in vitro transdermal delivery of cetirizine dihydrochloride for a period of 7 days. Therefore, dosing frequency of cetirizine dihydrochloride for the treatment and/or prevention and/or relief of symptoms associated with allergic rhinitis and/or urticaria and/or upper respiratory allergies can be reduced by continuous topical application of reservoir patch wherein duration of topical application is selected from the group comprising for one day, two days, three days, four days, five days, six days, seven days.

While the invention has described in detail and with reference to specific example thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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CLAIMS

WHAT IS CLAIMED IS:

1. A semisolid transdermal formulation for transdermal delivery of cetirizine dihydrochloride.

2. The semisolid transdermal formulation of claim 1 for transdermal delivery of cetirizine dihydrochloride wherein the formulation is a transdermal gel formulation.

3. The transdermal gel formulation of claim 2 comprising cetirizine dihydrochloride and a carrier system.

4. The transdermal gel formulation of claim 3 wherein the carrier system comprises excipients selected from the group consisting of solvents, penetration enhancers, gelling agents, thickening agents, polymers, pH adjusting agents, stabilizing agents, skin irritation reducing agents either alone and combinations thereof.

5. The transdermal gel formulation of claim 3 wherein the carrier system comprises excipients selected from the group consisting of solvents, penetration enhancers, gelling agents, polymers, pH adjusting agents, and combinations thereof.

6. The transdermal gel formulation of claim 5 wherein the solvent is present and selected from the group consisting of cosolvents, sulfoxide, alcohol, polyhydric alcohol, glycol, acid, glycol ether, water, polar solvents, semi polar solvents, nonpolar solvents, pyrrolidone, dimethylisosorbide, and combinations thereof.

7. The transdermal gel formulation of claim 5 wherein the penetration enhancer is present and is selected from the group consisting of fatty alcohol, propylene glycol mono-and diesters of fats and fatty acids, solubilizers, surfactants, fatty acid, esters, terpene and terpenoids, sulfoxide, alcohol, amide, triglycerides, and combinations thereof.

8. The transdermal gel formulation of claim 5 wherein the penetration enhancer is present and is selected from the group consisting of fatty alcohol, propylene glycol mono- and diesters of fats and fatty acids (such as propylene glycol monolaurate type II), esters, terpene and terpenoids, and combinations thereof.

9. The transdermal gel formulation of claim 5 wherein the gelling agents is present and is selected from the group consisting of cellulose, cellulose derivatives, , carboxyvinyl polymers, natural polymers and derivatives, synthetic polymers and derivatives, semisynthetic polymers and derivatives, polysaccharides and derivatives, water swellable, organic solvent swellable polymers, and combinations thereof.

10. The transdermal gel formulation of claim 5 wherein the pH adjusting agent is present and is selected from the group consisting of acids, bases, buffer, and combinations thereof.

11. The transdermal gel formulation of claim 3 comprising cetirizine dihydrochloride in an amount between 1%- 40% w/w and carrier system in an amount between 99%-60% w/w.

12. The transdermal gel formulation of claim 3 comprising cetirizine dihydrochloride in an amount between 3%- 30% w/w and carrier system in an amount between 97%-70% w/w.

13. The transdermal gel formulation of claim 3 comprising cetirizine dihydrochloride in an amount between 5%- 20% w/w and carrier system in an amount between 95%-80% w/w.

14. The transdermal gel formulation of claim 3 comprising cetirizine dihydrochloride in an amount between 6%- 18% w/w and carrier system in an amount between 94%-82% w/w.

15. The transdermal gel formulation of claim 3 comprising:

cetirizine dihydrochloride in an amount between 6%- 18%w/w,
dimethyl sulfoxide in an amount between 5%- 60% w/w,
hexylene glycol in an amount between 1%-50%w/w,
diethylene glycol monoethyl ether in an amount between 2% - 50%w/w,
lactic acid in an amount between 1%- 30%w/w,
oleyl alcohol) in an amount between 1%- 30% w/w,
ethanol in an amount between 1%- 50%w/w,
glycerin in an amount between 1%- 30%w/w,
propylene glycol monolaurate type II in an amount between 1%- 30% w/w,

water in an amount between 1%- 60%w/w,
sodium hydroxide 50% w/w in an amount between 0.5%- 15%w/w, and
hydroxypropyl cellulose (Klucel HF) in an amount between 1%- 15%w/w.

16. The semisolid transdermal formulation of claim 2 wherein the duration of transdermal delivery of cetirizine dihydrochloride is selected from the group of 1day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, and more than 7 days.

17. The semisolid transdermal formulation of claim 2 wherein the duration of transdermal delivery of cetirizine dihydrochloride is 7 days.

18. The semisolid transdermal formulation of claim 2 wherein the duration of transdermal delivery of cetirizine dihydrochloride is 3 days.

19. A method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergic rhinitis comprising topical application of the transdermal gel formulation of claim 2 to a patient in need of thereof.

20. A method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergic rhinitis comprising topical application of a reservoir patch comprising the transdermal gel formulation of claim 2 to a patient in need thereof.

21. A method of treatment and/or prevention and/or reduction and/or relief of skin manifestations and/or one or more symptoms of urticaria comprising topical application of the transdermal gel formulation of claim 2 to a patient in need of thereof.

22. A method of treatment and/or prevention and/or reduction and/or relief of skin manifestations and/or one or more symptoms of urticaria comprising topical application of a reservoir patch comprising the transdermal gel formulation of claim 2 to a patient in need of thereof.

23. A method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergies comprising topical application of the transdermal gel formulation of claim 2 to a patient in need of thereof.

24. A method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of allergies comprising topical application of a reservoir patch comprising the transdermal gel formulation of claim 2 to a patient in need of thereof.

25. A method of treatment and/or prevention and/or reduction and/or relief of one or more symptoms of upper respiratory allergies comprising topical application of the transdermal gel formulation of claim 2 to a patient in need of thereof.

26. A method of treatment and/or prevention and/or reduction and/or relief of one or more of symptoms of upper respiratory allergies comprising topical application of a reservoir patch comprising the transdermal gel formulation of claim 2 to a patient in need of thereof.

27. A method of treatment and/or prevention and/or reduction of one or more symptoms due to release of extra histamines in the body of a patient comprising topical application of the transdermal gel formulation of claim 2 to a patient in need of thereof.

28. A method of treatment and/or prevention and/or reduction of one or more symptoms due to release of extra histamines in the body of a patient comprising topical application of a reservoir patch comprising the transdermal gel formulation of claim 2 to a patient in need of thereof.

29. The method of claim 19 wherein the duration of topical application is for one day or up to one day.

30. The method of claim 20 wherein the duration of topical application is selected from the group consisting of one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

31. The method of claim 21 wherein the duration of topical application is for one day or up to one day.

32. The method of claim 22 wherein the duration of topical application is selected from the group consisting of one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

33. The method of claim 23 wherein the duration of topical application is for one day or up to one day.

34. The method of claim 24 wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

35. The method of claim 25 wherein the duration of topical application is for one day or up to one day.

36. The method of claim 26 wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

37. The method of claim 27 wherein the duration of topical application is for one day or up to one day.

38. The method of claim 28 wherein the duration of topical application is selected from the group consisting of for one day, for two days, for three days, for four days, for five days, for six days, and for seven days.

Figure 1

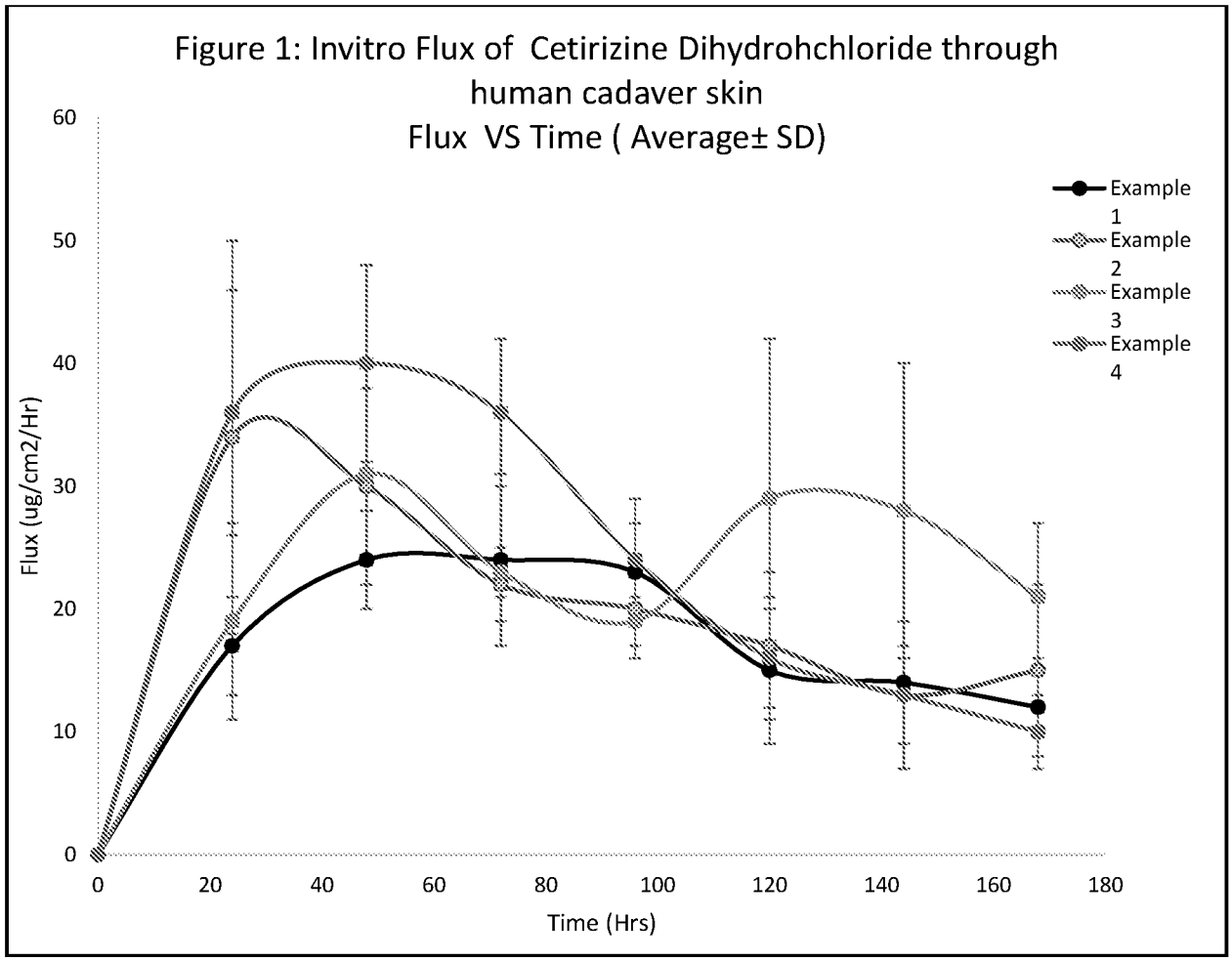
Figure 1: Invitro Flux of Cetirizine Dihydrohchloride through human cadaver skin
Flux VS Time (Average± SD)
Flux (ug/cm2/Hr)
Time (Hrs)
0
10
20
30
40
50
60
0
20
40
60
80
100
120
140
160
180
Example 1
Example 2
Example 3
Example 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/52408

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 9/06, 9/10, 31/495, 47/06, 47/10, 47/30, 47/38, 47/44; C07D 241/04 (2017.01)

CPC - A61K 9/06, 9/0012, 9/0014, 31/495, 47/06, 47/10, 47/30, 47/38, 47/44; C07D 241/04

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 6,790,847 B2 (WALCH, H) 14 September 2004; column 3, lines 48-57; column 4, lines 50-67; column 5, lines 27-32 and 41-45; column 6, lines 50-60	1-7, 9-13 --- 8, 14, 16-38
X	CIURLIZZA C, et al. "Semisolid Formulations containing Cetirizine: Human Skin Permeation and Topical Antihistaminic Evaluation in a Rabbit Model" Archives of Dermatological Research 2014, vol. 306, no. 8, pages 711-717 (abstract); abstract	1
Y	WO 98/00168 A1 (NOVARTIS CONSUMER HEALTH S.A.) 8 January 1998; page 3, second and bottom paragraphs; page 4, first-fifth paragraphs; page 6, top paragraph; page 7, bottom two paragraphs; page 8, top paragraph; page 12, example 1	8, 14, 16-18, 29-38
Y	US 2015/0374703 A1 (LEIGHTON, M) 31 December 2015; paragraphs [0027], [0030], [0040], [0042], [0057], [0067]-[0070], [0072], [0076], [0082]-[0083], [0099], [0141], [0144], [0150]	19-38
Y	WO 98/18416 A1 (THERATECH INC) 7 May 1998; page 7, lines 9-14 and 31-33	20, 22, 24, 26, 28, 30, 32, 34, 36, 38
A	CHANTASART, D et al. "Structure Enhancement Relationship of Chemical Penetration Enhancers in Drug Transport across the Stratum Corneum" Pharmaceutics 2012, vol. 4, pages	7

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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
24 October 2017 (24.10.2017)	13 NOV 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas 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/US17/52408

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/0114041 A1 (MERZ PHARMACEUTICAL, LLC; 28 April 2016; paragraphs [0009], [0081]-[0082], [0154], [0271]	15
A	US 2003/0147926 A1 (EBERT, CD et al.) 7 August 2003; paragraphs [0013], [0113], [0119], [0122]-[0123], [0127]	15