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(54) Title: LATREPIRDINE TRANSDERMAL THERAPEUTIC DOSAGE FORMS

(57) Abstract: The present invention provides transdermal formulations comprising latrepirdine or pharmaceutically acceptable salts thereof having desirable pharmacokinetic characteristics. Also provided are novel transdermal compositions and their manufacture.

LATREPIRDINE TRANSDERMAL THERAPEUTIC DOSAGE FORMS

FIELD OF THE INVENTION

The invention provides transdermal formulations comprising latrepirdine or pharmaceutically acceptable salts thereof. The formulations have desirable pharmacokinetic characteristics for this drug substance. Examples include mean plasma latrepirdine/metabolite ratios, AUC, and C_{max}.

BACKGROUND OF THE INVENTION

The present invention relates to therapeutic transdermal formulations of latrepirdine for the treatment of neurodegenerative diseases, and especially Alzheimer's disease (AD) and Huntingtons Disease (HD). Latrepirdine is being commercially developed as an immediate release tablet form with doses ranging from 5 mg to 20 mg administered three times a day (TID). While the proposed commercial dosage form provides efficacious blood levels of latrepirdine to subjects, it has been observed in clinical studies that significant metabolism may occur diminishing the effective potency at a given dose. Additionally, there is a positive food effect seen in the majority of subjects. That is, the systemic absorption of the drug is enhanced when the immediate release tablets are taken with food. It is therefore desired to provide a transdermal dosage form containing latrepirdine that does not undergo the degree of metabolism as the immediate release tablet dosage form nor affected by the intake of food.

The immediate release formulation uses TID dosing to maintain the plasma concentration of latrepirdine above the desirable level over a substantial portion of the day. Compared to immediate release oral formulations, a transdermal dosage form containing a physiologically active drug allows blood concentrations of the drug to be maintained at steady state for a long time at or above the therapeutic concentration. Accordingly, by achieving a QD or longer dosing regimen of latrepirdine it may be possible to reduce the frequency of dosings while providing the same or better

therapeutic effects--potentially improving compliance. With the transdermal dosage form of latrepirdine, it may also be possible to avoid a rapid increase in blood plasma concentration levels immediately after administration of the drug, thus potentially reducing or eliminating a rapid rise of drug plasma levels. There is a need in the art for new transdermal latrepirdine formulations to treat Alzheimer's disease that overcome the dosing frequency of the immediate release oral formulations or that provide other benefits over immediate release oral formulations.

The transdermal formulation of latrepirdine is utilized as an alternative to the immediate release control tablet form while still providing about the same exposure as the immediate release control tablet dosage form. Because latrepirdine in the transdermal dosage forms of the present invention does not experience the extent of metabolism to metabolite A_{met} as in the immediate release oral dosage form the bioavailability of latrepirdine is improved. Therefore the total amount of latrepirdine required to produce efficacious blood levels is reduced. This in turn leads to another advantage, which is a reduction in patient to patient variability in blood levels of latrepirdine achieved by the dosage forms of this invention. Since the variability in the amount of latrepirdine that is systemically available is reduced, more patients achieve efficacious blood levels of latrepirdine after administration of the said invention dosage form than with the reference immediate release tablet dosage form.

Therapeutic transdermal formulations and their manufacture are generally known in the art. These formulations have valuable properties. Thus, it is an aim of the present invention to provide transdermal formulations for systemic administration of latrepirdine with improved compliance, adhesion, stability, tolerability and/or safety properties.

One objective of the present invention is to provide a transdermal patch for systemic administration of latrepirdine that has an adhesive force to ensure safe application over the entire administration period.

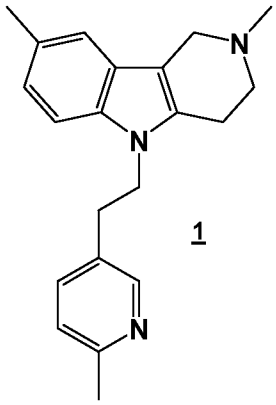
Another objective of the present invention is to provide a transdermal formulation for systemic administration of latrepirdine without having an unacceptably large surface area.

It is a further objective of the present invention to provide a transdermal formulation for systemic administration of latrepirdine that shows improved adhesive properties without changing the release profile of the active ingredient.

It is a further objective of the present invention to provide a transdermal formulation for systemic administration of latrepirdine that shows improved stability without changing the release profile of the active ingredient. It has now been found that latrepirdine is susceptible to degradation, particularly in the presence of oxygen. The present applicants have found that stable pharmaceutical compositions comprising latrepirdine can now be obtained, which show insignificant degradation of latrepirdine over a prolonged time period as indicated by standard tests. The invention is directed to these, as well as other, important ends.

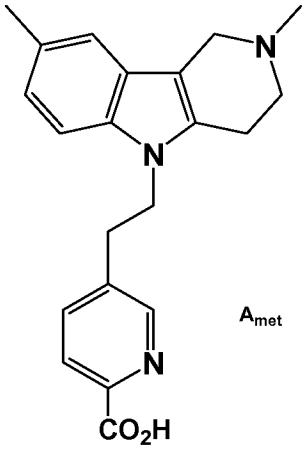
SUMMARY OF THE INVENTION

Latrepirdine, 2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1*H*-pyrido[4,3-b]indole), a known compound, has the structure **1**:



1

A metabolite of latrepirdine in humans is 5-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-b]indol-5-yl)ethyl]pyridine-2-carboxylic acid, hereinafter referred to as A_{met}, shown below:



A_{met}

The A_{met} metabolite is a metabolite produced in humans when latrepirdine is orally dosed. Its concentration in plasma is a useful indicator of the extent of latrepirdine metabolism, including first pass metabolism. A_{met} determination in human plasma samples is completed by solid phase extraction and analyzed by liquid chromatography/tandem mass spectrometry.

Latrepirdine and methods for synthesizing it are disclosed in PCT publication no. WO 2009/111540, filed March 4, 2008. Latrepirdine has utility for use in the treatment of various disorders such as Alzheimer's disease,

neurodegenerative disorders, Huntington's Disease, and schizophrenia (see, for example, U.S. Pat. No. 6,187,785; and U.S. Pat. Appl. Pub. Nos. 2007/0117835, 2007/0117834 and 2007/0225316).

In one embodiment of the invention, a pharmaceutical dosage form comprises 2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1*H*-pyrido[4,3-b]indole and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form.

In another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the plasma concentration versus time curve ($AUC_{0\text{-}inf}$) ratio of latrepirdine to its A_{met} metabolite that is greater than 0.1 but not greater than 15.

In another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the plasma concentration versus time curve ($AUC_{0\text{-}inf}$) ratio of latrepirdine to its A_{met} metabolite that is greater than 0.1 but not greater than 10.

In another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the plasma concentration versus time curve ($AUC_{0\text{-}inf}$) ratio of latrepirdine to its A_{met} metabolite that is greater than 0.1 but not greater than 5. In another embodiment, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable

carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the latrepirdine plasma concentration versus time curve for the period following administration ($AUC_{0\text{-}inf}$) of at least 8 ng-hr/mL.

In yet another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean maximum plasma concentration (C_{max}) of latrepirdine of less than about 16 ng/mL about 2 to 24 hours following application to the skin.

In yet another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, will have less than about 10 fold difference in the mean area under the latrepirdine plasma concentration versus time curve for the period following administration ($AUC_{0\text{-}inf}$) in subjects that have a CYP2D6 PM status relative to subjects that have a CYP2D6 EM status.

In another embodiment of the invention, when evaluated in a cohort of subjects having a CYP2D6 EM status, a pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier wherein said form is a transdermal dosage form and provides the same AUC_{24} as a single oral administration of 0.1 to 60 mg of immediate release latrepirdine results in a C_{max} that is less than 80% of the oral treatment with the equivalent AUC_{24}. In another embodiment, the transdermal dosage form provides the same AUC_{24} as a single oral administration of 0.1 to 60 mg of immediate

release latrepirdine results in a C_{max} that is less than 60% of the oral treatment with the equivalent AUC_{24}. In another embodiment, the transdermal dosage form provides the same AUC_{24} as a single oral administration of 0.1 to 60 mg of immediate release latrepirdine results in a C_{max} that is less than 40% of the oral treatment with the equivalent AUC_{24}. In another embodiment, the transdermal dosage form provides the same AUC_{24} as a single oral administration of 0.1 to 60 mg of immediate release latrepirdine results in a C_{max} that is less than 20% of the oral treatment with the equivalent AUC_{24}.

In another embodiment of the invention, a pharmaceutical dosage form is a transdermal dosage form and comprises a pharmaceutically acceptable carrier, and latrepirdine in an amount which releases *in vitro* from about 0.1 to 100 mg of latrepirdine following a 24 to 168 hour period when tested in a human cadaver skin flux test.

In yet another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form and provides a range of flux rates between 0.08 and 60 micro grams/hr/cm^2 when assayed in an *in vitro* human cadaver skin flux test. In another embodiment, the transdermal dosage form provides a range of flux rates between 0.8 and 60 micro grams/hr./cm^2 when assayed in an *in vitro* human cadaver skin flux test.

In another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and the daily dose of said latrepirdine ranges from 0.1 to 100 mg/day. In another embodiment, the daily dosage of latrepirdine ranges from 1 to 75 mg/day. In another embodiment, the daily dosage of latrepirdine ranges from 2 to 50 mg/day. In another embodiment, the daily dosage of latrepirdine ranges from 5 to 50 mg/day.

In another embodiment of the invention, a pharmaceutical dosage form comprises latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form and is selected from a patch, ointment, gel, cream, suspension or spray solution.

In another embodiment the present invention provides methods of treating neurological and psychiatric disorders comprising: administering to a mammal a transdermal dosage form comprising a pharmaceutically acceptable carrier and latrepirdine in an amount of latrepirdine effective in treating such disorders. Neurological and psychiatric disorders, include but are not limited to: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia, AIDS-induced dementia, vascular dementia, mixed dementias, age associated memory impairment, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, including cognitive disorders associated with schizophrenia and bipolar disorders, idiopathic and drug- induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine, migraine headache, urinary incontinence, substance tolerance, substance withdrawal, withdrawal from opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, and hypnotics, psychosis, mild cognitive impairment, amnestic cognitive impairment, multi-domain cognitive impairment, obesity, schizophrenia, anxiety, generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive compulsive disorder, mood disorders, depression, mania, bipolar disorders, trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain, acute and chronic pain states, severe pain, intractable pain, neuropathic pain, post-traumatic pain, tardive

dyskinesia, sleep disorders, narcolepsy, attention deficit/hyperactivity disorder, autism, Asperger's disease, and conduct disorder in a mammal. Accordingly, in one embodiment, the invention provides a method for treating a condition in a mammal, such as a human, selected from the conditions above, comprising administering a transdermal dosage form comprising latrepirdine and a pharmaceutically acceptable carrier in an amount of latrepirdine-effective in treating such disorders to the mammal. The mammal is preferably a mammal in need of such treatment. As examples, the invention provides a method for treating Huntington's disease, attention deficit/hyperactivity disorder, schizophrenia and Alzheimer's Disease.

A method of administering a therapeutically effective amount of latrepirdine to an individual in need thereof, such as a human, are also embraced wherein the method comprises administering a transdermal dosage form comprising latrepirdine to an area of the individual's skin and where the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 24 to about 168 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 24 to about 72 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for at least 24 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 24 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for at least 48 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 48 hours. In one aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 48 hours to about 96 hours. In one

aspect, the transdermal dosage form provides a therapeutically effective amount of latrepirdine to the individual for about 168 hours.

In another embodiment, the transdermal dosage form of the present invention is a transdermal patch comprising latrepirdine, an adhesive layer, a backing layer and a release liner.

In another embodiment, the transdermal dosage form is a transdermal patch comprising a backing layer, a reservoir layer between a backing layer and a contact adhesive layer comprising latrepirdine, at least one absorption enhancer, an antioxidant, and a hydrophilic polymer.

In another embodiment, the transdermal dosage form is a transdermal patch comprising a monolithic suspension-blend transdermal patch comprising a minimum of three layers, wherein the said layers are (a) a backing layer having inner and outer surfaces and being substantially impervious to latrepirdine; (b) a first adhesive layer having a first surface covering at least a portion of said inner surface of said backing layer, said adhesive layer comprising a 24 to 168 hour period therapeutically-effective amount of latrepirdine in a pressure sensitive adhesive; and (c) a removable release liner in contact with a second surface of said adhesive layer.

In another embodiment, the transdermal dosage form is a transdermal patch wherein the adhesive layer comprises other excipients of the formulation such as an antioxidant, one or more absorption enhancers and hydrophilic polymer. In one embodiment, latrepirdine is also contained in the adhesive layer.

In another embodiment, the transdermal dosage form is a transdermal patch comprising latrepirdine, wherein said dosage form comprises:

a. 5 wt% to 20 wt% latrepirdine;
b. 60 wt% to 90 wt% adhesive;
c. 0 wt% to 15 wt% absorption enhancer;
d. 0 wt% to 0.5 wt% antioxidant;

e. 0 wt% to 15 wt% hydrophilic polymer.

In another embodiment, the transdermal dosage form is a transdermal patch comprising latrepirdine, wherein said dosage form comprises:

a. 5 wt% to 20 wt% latrepirdine
b. 60 wt% to 90 wt% adhesive;
c. 0.1 wt% to 15 wt% absorption enhancer;
d. 0.01 wt% to 0.5 wt% antioxidant;
e. 0.1 wt% to 15 wt% hydrophilic polymer.

In another embodiment, the transdermal dosage form is a transdermal patch wherein the adhesive layer reduces active ingredient permeation from the reservoir layer through the skin by no more than 60%.

In another embodiment, the transdermal dosage form is a transdermal patch wherein the adhesive layer has a weight per unit area in the range of 5 to 60 mg/cm^2.

According to the present invention, latrepirdine may be used in the form of the free base or a pharmaceutically acceptable salt thereof. The dosage form may contain latrepirdine in a solubility-improved form. By "solubility-improved form" is meant that the latrepirdine is in a form such that it provides higher concentrations of dissolved drug in a patch formulation relative to a transdermal patch composition consisting essentially of crystalline latrepirdine.

In one embodiment, the solubility-improved form of latrepirdine is latrepirdine in amorphous form. In another embodiment, at least 90 wt% of the latrepirdine is amorphous. In another embodiment, latrepirdine is in the form of a molecular dispersion of amorphous latrepirdine in a polymer.

In one embodiment, the polymer is HPMCAS. HPMCAS is currently commercially available from Shin-Etsu Chemical (Tokyo, Japan), known by the trade name "AQOAT." Shin-Etsu manufactures three grades of AQOAT that have different combinations of substituent levels to provide enteric

protection at various pH levels. The AS-LF and AS-LG grades (the "F" standing for fine and the "G" standing for granular) provide enteric protection up to a pH of about 5.5. The AS-MF and AS-MG grades provide enteric protection up to a pH of about 6.0, while the AS-HF and AS-HG grades provide enteric protection up to a pH of about 6.8.

In another embodiment, the dispersion polymer is HPMC. HPMC is available under the trade name METHOCEL™ from Dow Chemical Co. An exemplary grade of HPMC is the E3 Prem LV grade available from Dow Chemical. This product has a methoxyl content of 28 to 30 wt%, and a hydroxypropyl content of 7 to 12 wt%. The viscosity of a 2 wt% solution of METHOCEL E3 Prem LV in water ranges from 2.4 to 3.6 cps.

The latrepirdine and polymer are collectively present in the molecular dispersion in an amount ranging from 80 wt% to 100 wt%. In one embodiment, the latrepirdine and polymer collectively constitute at least 90 wt%. In another embodiment the latrepirdine and polymer collectively constitute at least 95 wt% of the molecular dispersion. In one embodiment, the molecular dispersion consists essentially of latrepirdine and the polymer. By "consist essentially of" is meant that the molecular dispersion contains less than 1 wt% of any other excipients.

The amount of latrepirdine in the molecular dispersion may range from 0.1 wt% to 90 wt%. In one embodiment, the amount of latrepirdine in the molecular dispersion ranges from about 15 wt% to about 85 wt% In another embodiment, the amount of latrepirdine in the molecular dispersion ranges from about 25 wt% to about 75 wt%. In a further embodiment, the amount of latrepirdine in the molecular dispersion ranges from about 40 wt% to about 60 wt%.

The amount of polymer in the molecular dispersion may range from 10 wt% to 99.9 wt%. In one embodiment, the amount of polymer ranges from 15 wt% to 85 wt%. In another embodiment, the amount of polymer in the

molecular dispersion ranges from 25 wt% to 75 wt%. In a further embodiment, the amount of polymer ranges from 40 wt% to 60 wt%.

Embodiments of molecular dispersions have the following amounts of latrepirdine and polymer:

25 to 75 wt%, preferably 40 to 60 wt% latrepirdine; and

25 to 75 wt%, preferably 40 to 60 wt% polymer.

Molecular dispersions of latrepirdine and polymers may be made according to any known method. One method is a melt extrusion method, in which the latrepirdine and polymer are heated and extruded together.

In another method, the latrepirdine and polymer are dissolved in a common solvent, and the solvent is rapidly removed. Exemplary solvent methods include spray drying and spray granulating.

Preparation of Latrepirdine HPMCAS and CAP spray dried dispersions:

Latrepirdine amorphous spray dried dispersions (SDD) were prepared by spray drying, which included dissolving crystalline free base in organic solvents to form a solution. Useful solvents include those which are volatile, have a normal boiling point of about 150°C or less, exhibit relatively low toxicity, and can be removed from final product such that the level of solvent in the drug product meets the International Committee on Harmonization (ICH) guidelines for residual solvent.

In addition to solvent and latrepirdine, the solution contained various matrix-forming polymeric excipients. Latrepirdine SDDs were prepared using HPMCAS-MG (hydroxypropyl methyl cellulose acetate succinate – medium granular) and cellulose acetate phthalate CAP (1:1 w/w). Matrix-forming agents help stabilize amorphous latrepirdine, preventing or retarding formation of crystalline latrepirdine.

Preparation of latrepirdine HPMCAS spray dried dispersion:

SDD composition is reported in terms of the weight percent (wt %) drug in the dispersion. For example, a 50-wt % dispersion consists of 1 part (by weight) latrepirdine and 1 parts (by weight) HPMCAS. Dispersion was prepared by pumping a 2% w/w feed solution (latrepirdine and HPMCAS dissolved in acetone) to an atomizer inside a drying chamber. The atomizer breaks the solution up into a plume of small droplets (typically less than 100 µm in diameter). Atomization and solvent removal occur in a chamber where process conditions are controlled. The driving force for solvent removal was provided by maintaining the partial pressure of the solvent in the chamber below the vapor pressure of the solvent at the temperature of the drying droplets. Solution flow rates of 0.060 to 0.960 L/hr through the atomizer were used, and were varied depending on the type of nozzle, the size of the chamber, and the drying conditions, which include the inlet temperature and the flow rate of the drying gas through the chamber. The drying gas was introduced into the chamber at a temperature of about 75°C. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification time of latrepirdine HPMCAS dispersion was approximately 500ms. Rapid solidification helps maintain uniformity and homogeneity of amorphous drug substance within and among particles. The solid powder was collected from the gas stream using a filter system.

The particles of amorphous latrepirdine SDDs remained in the chamber for about 1200 seconds to about 3600 seconds following solidification, during which time additional solvent evaporated from the particles. Generally, the solvent level of amorphous latrepirdine SDD as it exits the chamber is less than about 10% w/w and is often less than 2% w/w. Following formation, amorphous latrepirdine SDDs were dried in vacuum oven under 30mm Hg pressure for 1 hour. After drying, residual solvent level is typically less than about 0.5% w/w.

Preparation of latrepirdine CAP spray dried dispersion:

A 50 wt% latrepirdine dispersion in CAP was prepared by pumping a 1% w/w feed solution (latrepirdine and CAP dissolved in 1:1 methanol: acetone) to an atomizer inside a drying chamber. The atomizer breaks the solution up into a plume of small droplets (typically less than 100 μm in diameter). Atomization and solvent removal occur in a chamber where process conditions are controlled. The driving force for solvent removal was provided by maintaining the partial pressure of the solvent in the chamber below the vapor pressure of the solvent at the temperature of the drying droplets. Solution flow rates of 0.060 to 0.960 L/hr through the atomizer were used, and were varied depending on the type of nozzle, the size of the chamber, and the drying conditions, which include the inlet temperature and the flow rate of the drying gas through the chamber. The drying gas was introduced into the chamber at a temperature of about 85°C. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification time of latrepirdine CAP dispersion was approximately 500ms. Rapid solidification helps maintain uniformity and homogeneity of amorphous drug substance within and among particles. The solid powder was collected from the gas stream using a filter system.

The particles of amorphous latrepirdine SDDs remained in the chamber for about 1200 seconds to about 3600 seconds following solidification, during which time additional solvent evaporated from the particles. Generally, the solvent level of amorphous latrepirdine SDD as it exits the chamber is less than about 10% w/w and is often less than 2% w/w. Following formation, amorphous latrepirdine SDDs were dried in vacuum oven under 30mm Hg pressure for 1 hour. After drying, residual solvent level is typically less than about 0.5% w/w.

Preparation of latrepirdine PVP-XL dispersion by evaporative drying:

A latrepirdine PVP dispersion was prepared by an evaporative drying process using Buchi Rotavapor. Equal amounts of crystalline latrepirdine and PVP were added to a solvent (methanol) in a round bottom flask and solubilized. The flask was moved to preheated (60°C) rotavap equipment. The flask was rotated at 45rpm and vacuum was set at 30mbar. The process continued for one hour. The sample was then transferred to a vacuum oven for secondary drying at 50mBar pressure for one hour before retrieving the sample.

Reservoirs

In another embodiment the transdermal dosage form may be comprised of a latrepirdine reservoir layer between a backing layer and a contact adhesive layer, wherein the rate controlling membrane is on the skin-proximal side of the active ingredient reservoir layer. The latrepirdine reservoir may optionally include permeation enhancers and/or other excipients. An alternate embodiment of this device has a separate permeation enhancer reservoir which is located on the skin proximal side of the backing layer and separated from the latrepirdine reservoir which is proximal to the skin by the rate-controlling membrane. Yet another embodiment of this device has the permeation enhancer contained within the contact adhesive layer. The membrane material may be selected from but not limited to the following materials: ethylene vinyl acetate copolymers, polyethylene, copolymers of ethylene, polyolefins including ethylene oxide copolymers such as Engage® (DuPont Dow Elastomers), polyamides, cellulosic materials, polyurethanes, polyether blocked amides copolymers such as PEBAX® (Elf Atochem North America, Inc.) and polyvinyl acetate.

The latrepirdine and/or permeation enhancer reservoir(s) can be a gel or a polymer and may comprise an aqueous or non-aqueous composition.

Spray solutions

Another embodiment of a transdermal dosage form of latrepirdine is a liquid formulation that is sprayable in droplets as described in US 5,958,379 which is hereby incorporated by reference. After being sprayed the composition forms a preparation within a short time, preferably within a time of less than 4 seconds, on the sprayed body surface, particularly on the sprayed skin or mucous membrane, whereby, compared to the original liquid composition, the preparation is formed to have a higher concentration of the latrepirdine and which contains the latrepirdine in a finely divided way. The composition can be applied by spraying a specific volume to achieve the desired dose. In order to achieve fast evaporation, such that the liquid composition forms the preparation on the body surface within 4 seconds.

Possible additional ingredients of the liquid formulation include a gel-forming agent. Gel-forming agents may include, but are not limited to, synthetic gel-forming agents such as polymers, particularly polyacrylates, cellulose derivatives, polyvinylalcohols and/or polyvinylacetate. The gel-forming agents can be a natural gel-forming agent, preferably phospholipids or a phospholipids mixture and particularly phospholipids and/or mixture isolated from soybeans, sunflowers and eggs. A particular phospholipid is phosphatidylcholine.

The liquid composition of latrepirdine is in the form of a dispersion, a solution and/or a suspension. The composition contains a liquid as a liquid mixture, a pharmaceutically acceptable organic solvent or solvent mixture and/or water. Preferably the liquid composition of latrepirdine contains an organic solvent, or as an organic solvent mixture, one or several alcohols which can easily be evaporated. The low molecular weight and easily evaporatable alcohols may include, but are not limited to, ethanol, propanol-1, propanol-2 and/or butanol. The liquid composition may also include propylene glycol alone or in a mixture with the afore mentioned alcohols as organic

solvents. A particular embodiment includes a dispersion containing liposomes. The liquid composition may include other ingredients such as but not limited to preservatives or buffers.

A spraying device is used which preferably operates without a blowing agent and which comprises a pump sprayer, whereby 20 to 300 µL of the liquid composition per spraying, particularly with a droplet size of between 1 µm and 1,000 µm, preferably with a droplet size of between 10 µm and 100 µm are emitted by means of a suitable spraying nozzle.

In one embodiment the transdermal dosage form of the present invention consists of a monolithic suspension-blend transdermal patch comprising a minimum of three layers, wherein the said layers are (a) a backing layer having inner and outer surfaces and being substantially impervious; (b) a first adhesive layer having a first surface covering at least a portion of said inner surface of said backing layer, said adhesive layer comprising latrepirdine in an amount sufficient to provide an effective dose of latrepirdine for 24 to 168 hours in a pressure sensitive adhesive; and (c) a removable release liner in contact with a second surface of said adhesive layer.

A combination of latrepirdine with certain organic solvents resulted in significant degradation of the latrepirdine. In particular, certain organic solvents that are good solvents for solvating pressure sensitive adhesives exhibited significant degradation of latrepirdine when combined. In particular, the said organic solvents include toluene and ethyl acetate. It is therefore apparent to those skilled in the art to avoid the usage of such solvents in the formulation and manufacture of latrepirdine-containing transdermal patches.

Latrepirdine exhibits an ability to delay crystallization in the latrepirdine-containing transdermal patch if the formulation contains latrepirdine entirely dissolved in a suitable solvent prior to coating and drying during the manufacturing process. In particular, the time to reach complete

crystallization of latrepirdine was not predictable *a priori*. It is therefore apparent to those skilled in the art to avoid a transdermal patch formulation composition that would result in variable time to reach complete crystallization of latrepirdine.

A further embodiment of the invention is a latrepirdine-containing, pressure sensitive adhesive formulation comprising a blend of latrepirdine particles essentially suspended in a solvated pressure sensitive adhesive. The selected solvent is one that can substantially or fully solvate or dissolve the adhesive while keeping the latrepirdine particles suspended in the solvated adhesive. Depending on the total therapeutically-effective amount of latrepirdine in the formulation, the final transdermal patch can either contain latrepirdine completely dissolved or essentially suspended in the pressure sensitive adhesive. The latrepirdine particles may be latrepirdine/polymer SDD particles.

The formulation of the invention can be made by blending latrepirdine particles directly with one or more solvated adhesives to form a suspension of latrepirdine particles in the solvated adhesive(s). Alternatively, the formulation can be made by first combining the latrepirdine particles with a non-solvent to wet the particles and form a slurry, which slurry then can be blended with the solvated adhesive(s) to also form a suspension of latrepirdine particles in the solvated adhesive(s). The other excipients of the formulation such as antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s) can be blended directly with the solvated adhesive(s), with the said slurry, or in parts thereof. The above formulations are useful for making monolithic devices for transdermal administration of latrepirdine.

Another embodiment of the invention is a method for making a laminate, which is useful for making a monolithic patch for transdermal administration of latrepirdine. The method comprises the steps of:

a) selecting a solvent that can substantially or fully solvate a adhesive(s) while keeping latrepirdine particles, when blended with the solvated adhesive, suspended in the solvated adhesive(s);

b) blending latrepirdine particles with one or more adhesives which are solvated with the above solvent, to form a blend formulation in which latrepirdine particles are suspended in the solvated adhesives; blending other excipients comprising antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s) into the said formulation;

c) casting the blend formulation onto a support material; and

d) removing the solvent, to produce a laminate containing the support material and a latrepirdine-containing adhesive layer. The steps may be perfomed in any order.

In another embodiment, the blend formulation formed in step (b) is further treated prior to the casting step.

The blend formulation preferably is cast onto a backing layer or release liner. The solvent can be removed during drying by evaporation from the adhesive layer. The laminate can be further processed to produce a monolithic device containing a backing layer, latrepirdine suspension-containing adhesive layer which also contains antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s), and release liner.

A further embodiment of the invention is a monolithic patch for administering latrepirdine transdermally to an individual comprising: (a) a backing layer substantially impervious to the latrepirdine to be administered transdermally; (b) a latrepirdine-containing adhesive layer in contact with at least a portion of the backing layer, the adhesive layer being cast from a formulation comprising a blend of latrepirdine particles suspended in one or more solvated adhesives which also contain antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s); and (c) a removable release liner in contact with the adhesive layer.

A further embodiment of the invention is a method for administering latrepirdine transdermally to an individual in need thereof, comprising applying a transdermal patch to an area of the individual's skin wherein the the transdermal patch comprises: (a) a backing layer substantially impervious to the latrepirdine to be administered transdermally; (b) a latrepirdine-containing adhesive layer in contact with at least a portion of the backing layer, the adhesive layer being cast from a formulation comprising a blend of latrepirdine particles suspended in one or more solvated adhesives which also contain antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s); and (c) a removable release liner in contact with the adhesive layer.

In another embodiment, the selected solvent is a solvent for the adhesive(s) but is a non-solvent for the latrepirdine, suitable for preventing high concentrations of latrepirdine particles from dissolving in the solvated adhesive, such that the solubility of latrepirdine in the solvent at 25°C is equal to or less than 5 mg/mL. In another embodiment, the solubility of latrepirdine in the solvent at 25°C equal to or less than 2 mg/mL. In a further embodiment, the solubility of latrepirdine in the solvent at 25°C is equal to or less than 1 mg/mL. Examples of such solvent include low molecular weight aliphatic hydrocarbon solvents, e.g., octane, heptane, hexane, cyclohexane and the like as long as the selected solvent exhibits the above-described latrepirdine solubility features. Heptane, or a mixture of heptane/hexane, or heptane/cyclohexane, are some preferred solvents.

The total amount of latrepirdine need not be suspended in the solvated adhesive, thus allowing for instances when a portion of the latrepirdine is dissolved in the solvated adhesive. In the discussion below, the focus will be on "suspended particles" or "suspensions" of latrepirdine, but it is to be understood that this does not exclude those embodiments in which a small proportion of the latrepirdine is dissolved in the solvated adhesive.

The formulations made in accordance with the present invention are used to manufacture improved devices for delivering latrepirdine transdermally, particularly monolithic transdermal patches. The devices may be manufactured by casting the formulation onto a support material such as a backing layer or release liner to form a latrepirdine suspension-containing adhesive layer, which can be further processed to make a transdermal patch for delivering latrepirdine. It is to be understood that the above formulations used in the manufacture of the latrepirdine transdermal patch do not exclude those embodiments in which there is an absence of suspended latrepirdine particles in the final transdermal patches.

Thus, to manufacture a device having the advantages of the present invention, one must first produce a formulation comprising a liquid blend of latrepirdine particles suspended in a solvated adhesive, which formulation then is subsequently processed to make the device. Alternative methods for producing or achieving a latrepirdine suspension-containing adhesive layer according to the invention may be apparent to persons skilled in the art, and these alternative methods thus also fall within the scope of the present invention.

In one embodiment of the formulation, one or more pressure sensitive adhesives is dissolved in heptane (or a mixture of heptane/hexane, or heptane/cyclohexane), while latrepirdine particles are blended directly with the solvated adhesive to form a suspension of latrepirdine particles in the solvated adhesive. It is understood that the solvated adhesive can comprise of additional excipients such as antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s). This suspension then is blended with the remaining heptane-solvated silicone adhesive to form the final (and more dilute) suspension. The composition then is cast onto a release liner and passed through an oven(s) to drive off the heptane. A backing film then is laminated onto the dried adhesive matrix.

In another embodiment of the formulation, the latrepirdine particles are blended in a suitable solvent such as heptane to form a slurry. The slurry of latrepirdine in heptane then is blended with a portion of the heptane-solvated adhesive and passed through a mixing device to form a uniform suspension. It is understood that the solvated adhesive can comprise of additional excipients such as antioxidant(s), absorption enhancer(s) and hydrophilic polymer(s), which are blended directly into the adhesive, or into the slurry, or in parts thereof. This suspension then is blended with the remaining heptane-solvated silicone adhesive to form the final (and more dilute) suspension. The composition then is cast onto a release liner and passed through an oven(s) to drive off the heptane. A backing film then is laminated onto the dried adhesive matrix.

The transdermal patch of the present invention contains sufficient latrepirdine to supply a daily dose of said latrepirdine ranging from 0.1 to 100 mg/day. It is understood that transdermal patches that supply 1 to 75mg/day, 2 to 50 mg/day and 5 to 50 mg/day are also within the scope of this invention.

Alternatively, the transdermal patch of the present invention contains a dose of latrepirdine that can range from 0.1 to 200 mg, 2 to 100 mg, 5 to 50 mg.

The concentration of the latrepirdine solid particles within the patch adhesive matrix surface area can vary in the range of 0.1 to 500 mg/cm^2, 0.5 to 100 mg/ cm^2 or 1 to 100mg/ cm^2.

The present invention provides non-invasive sustained delivery of latrepirdine for periods ranging from 24 hours to 168 hours. That is, the invention includes 1 day (24 hours), bi-daily (48 hours), tri-daily (72 hours) and 7 day (168 hours) transdermal patches.

The width or thickness of the adhesive layer is that width which provides at least sufficient adhesion of the device to the skin of the host. The width or thickness also may vary depending upon such factors as the amount

of latrepirdine to be delivered from the composition or adhesive layer and the desired wear period. The thickness of the adhesive layer will usually range from about 10 to 400 μm. In another embodiment, thickness of the adhesive layer will usually range from about 50 to about 300 μm. In another embodiment, the adhesive layer will be present at about 5 to about 60 mg/cm^2. In another embodiment, the adhesive layer will be present at about 5 to about 30 mg/cm^2. In another embodiment, the adhesive layer will be present at about 5 to about 15 mg/cm^2. Variations also can be determined as a matter of routine experimentation by those of ordinary skill in the art. The width also need not be uniform and may vary around the perimeter of the device, e.g., to provide a specific geometric shape or to provide a tab for removal of a protective liner.

In another embodiment, latrepirdine is administered as a free base form or its pharmaceutically acceptable salt or a prodrug form. Preferably latrepirdine is administered in the free base form. The quantity of latrepirdine contained in the adhesive layer is preferably that quantity sufficient to provide a therapeutically-effective dosage rate of the active agent to a host in need thereof.

In another embodiment, the particle size of the latrepirdine particles in suspension in the solvated adhesive has no less than 99% of volume distributed particle size of 300 μm, of 200 μm, of 150 μm, of 100 μm, but greater than 0.1 μm. It is understood that the suspended latrepirdine particles as determined by a suitable particle analysis method, known to one of skill in the art such as light diffraction based particle characterization techniques and microscopy, are free of agglomeration. A summary of appropriate microscopic techniques can be found in the literature (McCrone, W.C.; McCrone, L.B.; Delly, J.G. Polarized Light Microscopy; McCrone Research Institute: Chicago, 2002.)

In another embodiment, the suitable polymorphic forms of the suspended particles of latrepirdine are form A crystals, or form B crystals, or the amorphous form, or a mixture thereof, of latrepirdine. A preferred polymorphic form of latrepirdine is form B, which is also the thermodynamically lowest energy form of latrepirdine, and thus the most thermodynamically stable of the polymorphic forms.

In one embodiment, the present invention comprises a patch containing Form A of latrepirdine. Said latrepirdine Form A can have one or more characteristics selected from the group consisting of:

I) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 12.4, 16.1, and 17.4 ° 2θ ± 0.2 ° 2θ;

II) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.9, 12.4, 16.1, and 17.4 ° 2θ ± 0.2 ° 2θ;

III) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.9, 12.4, 16.1, 16.8, and 17.4 ° 2θ ± 0.2 ° 2θ;

IV) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 714, 1207, and 1356 cm^{-1} ± 4 cm^{-1};

V) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 714, 856, 1207, and 1356 cm^{-1} ± 4 cm^{-1};

VI) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 357, 714, 856, 1207, and 1356 cm^{-1} ± 4 cm^{-1};

VII) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 667, 897, and 1354 cm^{-1} ± 4 cm^{-1};

VIII) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 667, 778, 897, and 1354 cm^{-1} ± 4 cm^{-1};

IX) a melting point of 105 ± 5° C;

X) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 12.4 ° 2θ ± 0.2 ° 2θ, and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1207 and 1356 ± 4 cm^{-1};

XI) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 16.1 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1207 and 1356 cm^{-1} ± 4 cm^{-1};

XII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 17.4 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1207 and 1356 cm^{-1} ± 4 cm^{-1};

XIII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 12.4 ° 2θ ± 0.2 ° 2θ, and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 644 and 714 cm^{-1} ± 4 cm^{-1}; and

XIV) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 16.1 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 644 and 714 cm^{-1} ± 4 cm^{-1}.

In another embodiment, the present invention comprises a patch containing Form B of latrepirdine. Said latrepirdine Form B can have one or more characteristics selected from the group consisting of:

I) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.1, 17.5, and 19.5 ° 2θ ± 0.2 ° 2θ;

II) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.1, 17.5, 17.8, and 19.5 ° 2θ ± 0.2 ° 2θ;

III) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.1, 17.5, 17.8, 19.5, and 24.2 ° 2θ ± 0.2 ° 2θ;

IV) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 831, 851, and 1215 cm^{-1} ± 4 cm^{-1};

V) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 702, 831, 851, and 1215 cm^{-1} ± 4 cm^{-1};

VI) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 702, 831, 851, 1201 and 1215 cm^{-1} ± 4 cm^{-1};

VII) a melting point of 117 ± 5° C;

VIII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.1 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 831 and 1215 cm^{-1} ± 4 cm^{-1};

IX) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 17.5 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 831 and 1215 cm^{-1} ± 4 cm^{-1};

X) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 19.5 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 831 and 1215 cm^{-1} ± 4 cm^{-1};

XI) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 8.1 ° 2θ ± 0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 646 and 715 cm^{-1} ± 4 cm^{-1}; and

XII) an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 19.5 ° 2θ ±

0.2 ° 2θ and a Raman spectrum containing the following wavenumber (cm^{-1}) values: 646 and 715 cm^{-1} ± 4 cm^{-1}.

In another embodiment, the present invention comprises a patch containing noncrystalline latrepirdine. Said noncrystalline latrepirdine can have one or more characteristics selected from the group consisting of:

I) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 1573 cm^{-1} ± 4 cm^{-1};

II) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 646 and 715 cm^{-1} ± 4 cm^{-1};

III) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 346, 704, and 715 cm^{-1} ± 4 cm^{-1};

IV) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 346, 704, 715, and 1206 cm^{-1} ± 4 cm^{-1}; and

V) a Raman spectrum containing the following wavenumber (cm^{-1}) values: 346, 704, 715, 1206, and 1573 cm^{-1}± 4 cm^{-1}.

In another embodiment, the present invention comprises a method of preparing crystalline latrepirdine Form A for a patch formulation by one or more of the methods selected from the group consisting of:

I) crystallization from a latrepirdine free base solution;

II) crystallization from a latrepirdine free base solution by evaporation;

III) crystallization from a latrepirdine free base solution at elevated temperatures;

IV) crystallization from a latrepirdine free base solution by evaporation at elevated temperatures;

V) crystallization from a latrepirdine free base solution by evaporation of toluene;

VI) crystallization from a latrepirdine free base solution by evaporation of ethyl acetate;

VII) crystallization from a latrepirdine free base solution by evaporation of heptane; and

VIII) crystallization from a latrepirdine free base solution by evaporation of isopropyl alcohol.

In another embodiment, the present invention comprises a method of preparing crystalline latrepirdine Form B for a patch formulation by one or more of the methods selected from the group consisting of:

I) crystallization from a latrepirdine free base solution;

II) crystallization from a latrepirdine free base solution by evaporation;

III) crystallization from a latrepirdine free base solution at room temperature;

IV) crystallization from a latrepirdine free base solution by evaporation at room temperature;

V) crystallization from a latrepirdine free base solution by evaporation of toluene;

VI) crystallization from a latrepirdine free base solution by evaporation of ethyl acetate;

VII) crystallization from a latrepirdine free base solution by evaporation of heptane; and

VIII) crystallization from a latrepirdine free base solution by evaporation of isopropyl alcohol.

In another embodiment, the present invention comprises a method of preparing noncrystalline latrepirdine for a patch formulation by one or more of the methods selected from the group consisting of:

1. cooling a latrepirdine free base melt or liquid;
2. evaporating a solvent from a latrepirdine free base solution;
3. evaporating a solvent from a latrepirdine free base and polymer solution; and

4. evaporating a solvent from a latrepirdine free base solution with CAP, PVP, or HPMCAS polymers.

In another embodiment, latrepirdine is present in about 1% to about 30% w/w (dry weight). In another embodiment, latrepirdine is present in about 7% to about 15% w/w (dry weight). In another embodiment, latrepirdine is present in about 10% w/w (dry weight) of latrepirdine. In another embodiment, latrepirdine is present in about 5% to about 35% w/w (dry weight). In another embodiment, latrepirdine is present in about 10% to about 20% w/w (dry weight). In another embodiment, latrepirdine is present in about 15% w/w (dry weight).

In accordance with one embodiment of the transdermal patch of the present invention, the drug-containing adhesive layer is in direct contact with the liner layer, whereby upon removal of the liner layer and application of the transdermal patch to the skin, the adhesive layer is in direct contact with the skin. In accordance with another embodiment of the transdermal patch of the present invention, the adhesive used in the drug-containing adhesive layer is a pressure-sensitive adhesive system comprising polyisobutylene and a plasticizer. The polyisobutylene itself preferably comprises a blend of a high molecular weight polyisobutylene (about 450,000 to 4,000,000 viscosity average molecular weight) and a low molecular weight polyisobutylene (about 40,000 to 450,000 viscosity average molecular weight).

An example of a preferred high molecular weight polyisobutylene composition is a polyisobutylene composition sold under the designation Oppanol® B200 having an average molecular weight of about 4,000,000. An example of a preferred low molecular weight polyisobutylene composition is a polyisobutylene composition sold under the designation Oppanol® B12 SFN having an average molecular weight of about 55,000. In manufacturing these compositions, it is preferred to use only a solvent for the polyisobutylene which is a non-solvent for the drug, such that the solubility of the drug in the

solvent at 25°C is equal to or less than 5 mg/mL, preferably equal to or less than 2 mg/mL, most preferably equal to or less than 1 mg/mL. Examples of such solvent include low molecular weight hydrocarbon solvents, e.g., heptane, hexane, cyclohexane and the like with heptane or a mixture of heptane/hexane being particularly preferred. Preferably, the mixture of polyisobutylene compositions includes from about 65 to 90% by weight of the solvent, more preferably from about 70 to about 85% by weight of the solvent. In the polyisobutylene compositions it is preferred that the high molecular weight polyisobutylene: low molecular weight polyisobutylene in these compositions are used in a ratio of from about 20:80 to about 70:30, preferably between about 40:60 to about 50:50. The plasticizer, also functioning as a tackifier, which is utilized in conjunction with polyisobutylene to form the adhesive layer of the present invention is a generally, inert, organic, apolar, hydrophobic liquid. The term "tackifier" denotes a substance which is increasing the adhesivity/tackiness of the transdermal formulation. Preferred tackifiers are selected from the group consisting of polybutene, silicone oils, glycerine esters of hydrogenated resin acids, hydroabietyl alcohol, resin esters, hydrogenated methyl ester of wood rosin, ester of partially hydrogenated wood rosin, esters of rosin, and combinations thereof. The plasticizer/tackifier includes various long-chain aliphatic esters and alcohols, including such materials as polybutene, mineral oil, linseed oil, octyl palmitate, squalene, squalane, silicone oil, isobutyl stearate, olive oil, isopropyl palmitate, isostearyl alcohol, oleyl alcohol, and the like. An example of a preferred plasticizer/tackifier is sold under the designation Indopol H1900. Another example of a preferred plasticizer/tackifier is sold under the designation Panalane H300E. In the pressure sensitive adhesive system of polyisobutylene and a plasticizer/tackifier, it is preferred that the polyisobutylene: plasticizer/tackifier in these compositions are used in a ratio of from about 30:70 to about 80:20, preferably between about 40:60.

In accordance with another embodiment of the transdermal patch of the present invention, the adhesive used in the drug-containing adhesive layer is a pressure-sensitive polyacrylate adhesive. The polyacrylate adhesive refers to a group of pressure sensitive solvated polyacrylate adhesives made by copolymerizing one or more acrylate monomers ("acrylate" is intended to include acrylates, acrylamides and methacrylates), one or more modifying monomers, and one or more functional group-containing monomers in an organic solvent. The acrylate monomers used to make these polymers are normally alkyl acrylates of 4-17 carbon atoms, with 2-ethylhexyl acrylate, butyl acrylate, and isooctyl acrylate being preferred. Modifying monomers are typically included to alter the Tg of the polymer. Such monomers as vinyl acetate, ethyl acrylate and methacrylate, and methyl methacrylate are useful for this purpose. Such monomers may be further functionalized to provide sites for crosslinking or remained non-functionalized. Examples of functional groups of these monomers include carboxyl, hydroxy or combinations thereof. Examples of monomers that provide such functional groups are acrylic acid, methacrylic acid and hydroxy-containing monomers such as hydroxyethyl acrylate. Solvated polyacrylate pressure sensitive adhesives are commercially available under tradenames such as GELVA™ and DURO-TAK™. An example of a preferred polyacrylate adhesive is a non-functional polyacrylate under the designation Duro-Tak 87-901A or Duro-Tak 87-900A. During manufacturing, a solvent for the solvated polyacrylate which is a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or less than 5 mg/mL can be used. In another embodiment, a solvent for the solvated polyacrylate which is a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or less than 2 mg/mL can be used. In another embodiment, a solvent for the solvated polyacrylate which is a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or less than 1 mg/mL

can be used. Examples of such solvent include low molecular weight hydrocarbon solvents, e.g., heptane, hexane, cyclohexane and the like with cyclohexane or a mixture of heptane/cyclohexane being particularly preferred. Preferably, the solvated polyacrylic compositions includes from about 30 to 60%.

In accordance with another embodiment of the transdermal patch of the present invention, the adhesive used in the drug-containing adhesive layer is a pressure-sensitive silicone adhesive. Suitable silicone adhesives include pressure sensitive adhesives made from silicone polymer and resin. The polymer to resin ratio can be varied to achieve different levels of tack. Examples of useful silicone adhesives which are commercially available include the standard Bio-PSA™ series (7-4400, 7-4500 and 7-4600 series) and the amine compatible (end-capped) Bio-PSA™ series (7-4100, 7-4200 and 7-4300 series) manufactured by Dow Corning. Some preferred examples of a silicone adhesives include Bio-PSA 4301, Bio-PSA 4201, and a mixture of Bio-PSA 4301 and 4201 in a ratio ranging from 80:20 to 20:80. A plasticizer, which is utilized in conjunction with silicone adhesive(s) to form the adhesive layer of the present invention, includes various silicone fluids and mineral oils. An example of a plasticizer is high molecular weight polydimethylsiloxane silicone fluid, Dimethicone NF, commercially available as Dow Corning Silicone Medical Fluid. The viscosity of the polydimethylsiloxane silicone fluid is between 100 to 1000 cSt, preferably 350 cSt. Amounts of the polydimethylsiloxane silicone fluid are from about 0% w/w to about 20% w/w. Viscosities of the silicone fluid are from about 20 cSt to about 1000 cSt, preferably about 350 cSt. During manufacturing, the solvent for the solvated silicone should be a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or less than 5 mg/mL. The solvent for the solvated silicone may be a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or

less than 2 mg/mL. The solvent for the solvated silicone may be a non-solvent for the drug, such that the solubility of the drug in the solvent at 25°C is equal to or less than 1 mg/mL. Examples of such solvent include low molecular weight hydrocarbon solvents, e.g., heptane, hexane, cyclohexane and the like with heptane being preferred. The solvated silicone compositions include from about 20 to 50% by weight of the solvent, preferably from about 25 to about 40% by weight of the solvent.

An antioxidant to promote the stability of latrepirdine may be included in the adhesive layer. Examples of antioxidants include but are not limited to, alpha tocopherol, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, ascorbyl palmitate and combinations thereof. A preferred antioxidant is propyl gallate present in an amount of from about 0.01 to about 0.5%, e.g. 0.05% to 0.20%, more particularly 0.05% by weight based on the total weight of the pharmaceutical composition.

A skin absorption enhancer to promote the penetration of latrepirdine through the skin may be included in the adhesive layer. Suitable enhancers may be any one or more compounds with which a percutaneous absorption enhancing effect of a drug has been known. Examples include C_6-C_{20} fatty acids, fatty alcohols, fatty acid esters, alkyl ethers, aromatic organic acids, aromatic alcohols, aromatic fatty acid esters, aryl ethers, nitrated aliphatic and cycloaliphatic hydrocarbons. Furthermore, the examples include those such as lactic acid esters, acetic acid esters, monoterpene type compounds, sesquiterpene type compounds, Azone or its derivatives, glycerol fatty acid esters, sorbitan fatty acid esters, polysorbates, polyethylene glycol fatty acid esters, polyoxyethylene hardened castor oils, sucrose fatty acid esters. Examples include caprylic acid, capric acid, caproic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, lauryl alcohol, myristyl alcohol, oleyl alcohol, cetyl alcohol, methyl laurate, isopropyl myristate, myristyl myristate, octyldecyl myristate, cetyl palmitate, salicylic

acid, methyl salicylate, glycol salicylate, cinnamic acid, methyl cinnamate, cresol, cetyl lactate, ethyl acetate, propyl acetate, isopropyl palmitate, sorbitan monooleate, geraniol, thymol, eugenol, terpineol, 1-menthol, borneol, d-limonene, isoeugenol, isoborneol, nerol, dl-camphor, glycerol monolaurate, glycerol monooleate, propylene glycol monolaurate, sorbitan monolaurate, sucrose monolaurate, polysorbate 20, polyethylene glycol monolaurate, polyethylene glycol monostearate, N-methyl-2-pyrrolidone, HCO-60 (hardened caster oil), and 1-[2-(decylthio)ethyl]aza-cyclopentan-2-one (hereinafter abbreviated as pyrothiodecane), and in particular, fatty acid ester and aliphatic alcohol. Preferred absorption enhancers include but are not limited to, isopropyl palmitate, propylene glycol monolaurate, oleyl alcohol, or a combination of at least 2 of the 3 mentioned co-solvents therein in an individual amount of from about 1% to 10%, preferably from about 2% to 8%, more preferably from about 2.5% to 6%.

A hydrophilic polymer to provide a means to absorb aqueous constituents such as sweat or moisture from the skin to improve the duration of wear, and/or to improve the apparent solubility of the active in the adhesive composition, and/or to improve the thermodynamic activity (driving force) of latrepirdine, and/or to improve the physical (e.g., cold flow) or adhesive (e.g., tack, cohesive strength) properties of the adhesive composition, may be included in the adhesive layer. Examples of hydrophilic polymers include, for example, cellulose derivatives [carboxymethyl cellulose (CMC), carboxymethyl cellulose sodium (CMCNa), methyl cellulose (MC), hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose acetate sucrose (HPMC-AS), cellulose acetate phthalate (CAP), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC)], starch derivatives (pullulan), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), crosslinked polyvinylpyrrolidone (crosslinked PVP), polyvinyl acetate (VA), carboxyvinyl polymer (CVP), ethylvinyl acetate copolymer (EVA), Eudragit,

gelatin, polyacrylic acid, sodium polyacrylate, polyisobutylene-maleic anhydride copolymer, alginic acid, sodium alginate, carrageenan, Arabian gum, tragacanth gum, karaya gum and polyvinyl methacrylate. A preferred hydrophilic polymer is crosslinked PVP under the designation of Kollidon CL-M from BASF. The hydrophilic polymer may be blended in 0.01 to 20% by mass, and preferably 1 to 10% by mass based on the total mass of the pressure-sensitive adhesive layer in the patch of the invention.

The backing layer is preferably a thin film or sheet. In some instances, because of the area of skin to which the device is to be attached, the device, and therefore the backing layer, may be opaque or colored for cosmetic reasons. In one embodiment, it is a skin tone color layer with printed matter thereon. The backing layer normally provides support and a protective covering for the device. The backing layer is made of a material or combination of materials that is impermeable, or at least substantially impermeable, to the adhesive layer and the latrepirdine contained therein. Suitable materials for the backing layer include those known in the art for use with pressure sensitive adhesives. For example, the backing layer can comprise a polyolefin, including polyethylene; a polyester; multi-layer EVA film and polyester; polyurethane; or combinations thereof. Other suitable materials include, for example, cellophane, cellulose acetate, ethyl cellulose, plasticized vinyl acetate-vinyl chloride copolymers, ethylene-vinyl acetate copolymer, polyethylene terephthalate, nylon, polyethylene, polypropylene, polyvinylidene chloride (e.g., SARAN), ethylene-methacrylate copolymer (Surlyn), paper, cloth, aluminum foil and polymer-metal composites.

The material that forms the backing layer may be flexible or non-flexible. Preferably, a flexible backing layer is employed to conform to the shape of the body member to which the device is attached.

The release liner forms protective layer over the adhesive layer. The release liner is to be removed before the transdermal patch is placed on the

skin. The release liner is thus made of a material(s) that permits the liner to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. The release liner may be made of the same materials suitable for use in the backing layer as discussed above. Such material is preferably made removable or releasable from the adhesive layer, for example, by conventional treatment with silicon polymers, fluoropolymers (e.g., Teflon) or other suitable coatings on the surface thereof. Suitable release liners include those known in the art for use with pressure sensitive adhesive compositions. For example, the release liner can comprise a fluoropolymer or fluorosilicone coated polyester when the adhesive layer comprises mainly the silicone adhesive. The release liner can comprise a silicone polymer coated polyester when the adhesive layer comprises mainly the PIB or the polyacrylic adhesives. The release liner, however, can comprise various layers, including paper or paper-containing layers or laminates; various thermoplastics, such as extruded polyolefins, such as polyethylene; various polyester films; foil liners; other such layers, including fabric layers, coated or laminated to various polymers, as well as extruded polyethylene, polyethylene terephthalate, various polyamides, and the like.

In one embodiment of this invention, the patch further comprises a latrepirdine-free adhesive layer in between the backing layer and the latrepirdine-containing adhesive layer. This additional adhesive layer extends beyond at least a portion of the latrepirdine-containing adhesive layer to provide a further surface area that can adhere to the skin of the wearer, thereby enhancing the adhesive qualities of the device or patch. The size and shape of the backing layer will be essentially co-extensive with the size and shape of this additional adhesive layer. This latrepirdine-free adhesive layer can comprise any conventional pressure sensitive adhesive, namely the polyisobutylene, the polyacrylic or the silicone adhesive, as found in any of a variety of commercially available transdermal patches or tapes.

The compositions of this invention possess sufficient adhesive properties that once the release liner is removed and the composition is applied to the skin the composition can remain in place for a period of time sufficient to distribute the desired amount of the drug contained therein with a low incidence of debonding.

One skilled in the transdermal art would readily recognize the possible sizes of patches in accordance with the invention. The patch sizes preferably vary depending on the desired delivery rates of latrepirdine, preferably increasing in size as the desired delivery rate increases.

The patch, once formed, may be kept sealed in an air-tight foil pouch prior to use. The foil pouch maintains a low permeability of moisture and oxygen across the pouch once heat sealed. The interior of the foil pouch may contain an envelope of nitrogen gas to provide for improved stability of the patch. The pouch may further contain a desiccant material to maintain a low moisture environment inside the sealed pouch for improved stability. The pouch may also further contain an oxygen scavenging agent to maintain a low oxygen level environment inside the sealed pouch for improved stability.

In-vitro studies using cadaver skin

In-vitro percutaneous absorption study was used to characterize the permeation property and absorption profile of the latrepirdine-containing transdermal patches. A transdermal patch of a circular size (1.77 cm^2) was punched. The patch was adhered to the stratum corneum of a dermatomed human cadaver skin and mounted in a vertical franz diffusion cells (diffusion area of 1.77 cm^2). The receiver chamber (7 mL) was filled with a phosphate buffered saline solution with pH adjusted to 7.4 or less and 0.1% gentamicin was added to prevent microbial growth. These permeation experiments were conducted at 32°C for 24 to 168 hours and the receiver chamber was sampled on a suitable time interval. Samples were analyzed by reverse phase HPLC.

NP-HPLC method for analysis of degradants

A normal phase method was used to measure the amount of degradants in various prototype formulations of latrepirdine transdermal patches. Sample preparation was performed by extracting the drug and degradants from the patch in hexane and ethanol (80:20) with the aid of sonication to obtain a nominal concentration of about 0.1 mg latrepirdine per mL. A portion of the sample solution was filtered through a 13-mm syringe filter with a 0.22-μm nylon membrane directly into a vial for analysis by HPLC. Degradants were calculated and reported as area%.

HPLC Parameters:

Column: Zorbax Eclipse XBD-CN, 4.6- × 100-mm, 3.5-μm

Column Temperature: 30 °C

Injection Volume: 20 μL

Flow Rate: 1.0 mL/min

Detection: UV @ 225 nm

Dissolving Solvent: Hexane:EtOH (80:20)

Mobile phase:

A: Hexane:EtOH (85:15), 0.1% TFA, 0.1%TEA

B: Ethanol, 0.1% TFA, 0.1% TEA

Gradient program:

Time	%B
0	0
30	0
45	40
47	40
48	0
60	0

Retention time (latrepirdine): 21–25 minutes

DEFINITIONS

The term “latrepirdine” is interchangeable with “2,8-dimethyl-5-[2-(6-methylpyridin-3-yl)ethyl]-3,4-dihydro-1*H*-pyrido[4,3-b]indole” and should be understood herein, unless otherwise indicated herein, to include any pharmaceutically acceptable form of the compound.

By "pharmaceutically acceptable form" is meant any pharmaceutically acceptable form, including, solvates, hydrates, isomorphs, polymorphs, co-crystals, pseudomorphs, neutral forms, acid addition salt forms, and prodrugs. Latrepirdine may be present in crystalline or amorphous form. The pharmaceutically acceptable acid addition salts of latrepirdine are prepared in a conventional manner by treating a solution or suspension of the free base with about one or two chemical equivalents of a pharmaceutically acceptable acid. Conventional concentration and recrystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, mesylic, tosylic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic such as methanesulfonic, benzenesulfonic, and related acids. Preferred forms of latrepirdine include the free base and latrepirdine dihydrochloride dihydrate.

It is understood that the amount of latrepirdine that is delivered can be determined by subtracting the amount of the latrepirdine remaining (unabsorbed) in the transdermal dosage form after the time term of use is finished, from the original dose of drug loaded in the transdermal system. For instance if the transdermal system is a patch containing 20 mg latrepirdine to be worn for 24 hours, the amount of latrepirdine transdermally delivered, herein referred to as the “dose delivered” can be determined by subtracting the amount of drug remaining in the patch after 24 hours from 20 mg. The analytical method to determine the amount of latrepirdine remaining in the patch could be any method known to one skilled in the art.

By “immediate release control tablet” is meant the latrepirdine tablet for oral administration containing 20 mg crystalline latrepirdine dihydrochloride dihydrate, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate and a standard coating such as Opadry®. A control tablet with 20 mg latrepirdine dihydrochloride dihydrate is prepared as described in the Examples. Alternatively, another immediate release (IR) formulation may be used, providing that greater than about 50% of the latrepirdine is dissolved in 30 minutes when tested in a standard USP rotating paddle apparatus as disclosed in United States Pharmacopoeia (USP) Dissolution Test Chapter 711, Apparatus 2. Paddles are rotated at 50 rpm and the dissolution test is conducted in, as the test medium, 500 mL of 0.2M pH 6.8 potassium phosphate buffer at 37° C. At appropriate times following test initiation (e.g., insertion of the dosage form into the apparatus), filtered aliquots (typically 1.5 mL) from the test medium are analyzed for latrepirdine by high performance liquid chromatography (HPLC). Dissolution results are reported as the percent of the total dose of latrepirdine tested dissolved versus time.

Control tablets with different amounts of latrepirdine may be prepared by adjusting the latrepirdine dose and the relative amounts of these inert carriers. The ingredients are mixed and tableted using standard methods known to one skilled in the art. The dosing regimen for the immediate release control tablet is TID for 7 days, at which time steady state blood levels are achieved.

The “transdermal dosage form” of the present invention is a pharmaceutically-acceptable dosage form, meaning that the dosage form is safe for administration to humans and all excipients in the dosage form are pharmaceutically-acceptable, in other words safe for human transdermal use.

By “administered transdermally” is meant administration of latrepirdine through the skin.

"Cohort" refers to a standard testing population. Such testing populations are well known in the art and are designed to produce meaningful reproducible results. One common size is 20 healthy subjects, equally divided between 10 males and 10 females.

"CYP2D6 EM status" refers to subjects, preferably human, who have been determined by genotyping to be CYP2D6 Extensive metabolizers. They represent approximately 60-80% of the population and therefore enrolling sufficient EM subjects to run a single dose pharmacokinetic study is easily achievable. The importance of genotyping subjects is due to the variability that can be observed between poor metabolizers (PMs) and ultra metabolizers (UMs) for compounds which are metabolized extensively by CYP2D6. To identify Poor Metabolizers (PMs), Intermediate Metabolizers (IMs), Extensive Metabolizers (EMs), and Ultra Rapid Metabolizers (UMs), easy, reliable tests which require only a blood sample and less than a day for analysis are now available. One such example, not meant to be inclusive of all tests available, is Roche's AmpliChip CYP450 Test which was approved by the FDA in 2005. The AmpliChip test provides a predicted phenotype of the subject in one of the following four categories; Poor Metabolizers (PMs), Intermediate Metabolizers (IMs), Extensive Metabolizers (EMs) and Ultra Rapid Metabolizers.

A study to measure the concentration of latrepirdine in the plasma after initial administration may be conducted using conventional methods for making such a determination. The study should include at least 20 subjects, preferably human, which have all been genotyped to ensure that they are of the CYP2D6 EM status, in order to measure mean values for C_{max} and AUC_{0-inf}. The study should be conducted in the fasted state. Prior to the initial administration of latrepirdine, the subject has not been administered latrepirdine for a sufficient length of time (minimally 7 days) so that the subject's plasma concentration of latrepirdine prior to administration of the

dosage form is below the detectable limit. Plasma samples are taken at a sufficient number of time points to determine C_{max} and $AUC_{0\text{-}inf}$.

By "mean area under the plasma concentration versus time curve ratio of latrepirdine to its A_{met} metabolite" is meant, the individual ratio of the mean area under the plasma concentration versus time curve of latrepirdine (e.g. $AUC_{0\text{-}inf}$) to the mean area under the plasma concentration versus time curve of its A_{met} metabolite (e.g. $AUC_{0\text{-}inf}$) is first calculated, and then the corresponding individual ratios are averaged together. In this way, it is the average of each corresponding individuals ratio which is determined. The latrepirdine and A_{met} concentrations are measured by standard liquid chromatography / tandem mass spectroscopy techniques.

In vivo determinations of AUC can be made by plotting the plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis). Methods for determining the AUCs of a dosage form are well known in the art. (The calculation of an AUC is a well-known procedure in the pharmaceutical arts and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986)).

By "human cadaver skin flux test" is meant, a transdermal patch of a circular size (1.77 cm^2) is punched. The patch is adhered to the stratum corneum of a dermatomed human cadaver skin and mounted in a vertical franz diffusion cells (diffusion area of 1.77 cm^2). The receiver chamber (7 mL) is filled with a phosphate buffered saline solution with pH adjusted to 7.4 and 0.1% gentamicin is added to prevent microbial growth. These permeation experiments are conducted at 32°C for 24 to 168 hours and the receiver chamber is sampled on a suitable time interval. Receiver chamber samples are analyzed for latrepirdine by high performance liquid chromatography (HPLC).

"Dissolution Test 1" refers to the following test of dosage forms of latrepirdine. The dissolution test is conducted in a standard USP rotating paddle apparatus as disclosed in United States Pharmacopoeia (USP) Dissolution Test Chapter 711, Apparatus 2. Paddles are rotated at 50 rpm and the dosage form is added to 500 mL of 0.2M pH 6.8 potassium phosphate buffer at 37° C. At appropriate times following test initiation (i.e., insertion of the dosage form into the apparatus), filtered aliquots (typically 1.5 mL) from the test medium are analyzed for latrepirdine by high performance liquid chromatography (HPLC). Dissolution results are reported as the percent of the total dose of Latrepirdine tested dissolved versus time.

The term "characterize" as used herein means to select an appropriate set of data capable of distinguishing one solid form from another. That set of data in X-ray powder diffraction is the value of the positions of one or more reflections, reported in degrees 2θ. The selection of specific latrepirdine free base X-ray powder diffraction peaks that enable determination of a particular form is said to characterize that form.

The term "identify" as used herein means taking a selection of characteristic data for a solid form and using those data to determine whether that form is present in a sample. In X-ray powder diffraction, these data are the values that characterize the form in question as discussed above. For example, once one determines that a select number of X-ray diffraction peaks characterize a particular solid form of latrepirdine free base, one can use those peaks to determine whether that form is present in a sample containing latrepirdine free base. This sample could be composed either entirely of latrepirdine free base or of latrepirdine free base in a mixture of components (e.g., a pharmaceutical tablet or transdermal formulation). A typical variability for a peak value associated with a differential scanning calorimetry endotherm onset temperature is on the order of plus or minus 5° C.

Thermal Analysis

Differential scanning calorimetry (DSC) was performed with a Mettler-Toledo 821^e DSC instrument for Form A and a Mettler-Toledo 822^e DSC instrument for Form B. Samples of approximately 5 mg were weighed into standard aluminum pans (40µl). Each pan was crimped and vented with a pinhole with a perforated cover. Measurements were conducted at 5 °C/minute with a 60 mL/minute nitrogen purge unless otherwise noted. The temperature and heat flow were calibrated using indium and tin standards, respectively. Melting onset temperatures were determined using Mettler-Toledo STARe software Version 8.10. Melting point onset values can be reported with the modifier "about," which is standard terminology in the solid-state chemical arts and is meant to account for changes in melting point due to differences in particle size and/or chemical impurities, as well as variability introduced into melting point measurements by the analytical instrument and methodology employed. These sources introduce a variability for melting onset temperatures that is typically less than about ± 5° C. The melting onset temperatures of latrepirdine free base Forms A and B are provided in Table 1.

Table 1

Melting Onset Temperatures for Forms A and B of Latrepirdine Free Base

Latrepirdine Form	Temperature(° C)
A	105
B	117

The melting onset temperatures for Forms A and B were also measured using a hot-stage microscopy method to confirm the DSC results. Hot-stage microscopy evaluation was conducted using an Olympus BX60 optical microscope equipped with a Linkam LTS 350 hot stage and controlled with Linksys32 1.2.1 software. Solids were viewed under cross-polarized light

with a 530 nm wave plate and heated at 5 °C/minute from room temperature. Onset temperatures were determined visually, e.g., upon observation of sample melting. Melting point onset values can be reported with the modifier "about," which is standard terminology in the solid-state chemical arts and is meant to account for changes in melting point due to differences in particle size and/or chemical impurities, as well as variability introduced into melting point measurements by the analytical instrument and methodology employed. The melting onset temperatures for Forms A and B were determined in this manner were consistent with the values reported using the DSC method described for Forms A and B, e.g., about 105° C and 117° C.

Hot-stage microscopy evaluation can also be conducted to determine the solid-state form of latrepirdine free base present within a formulation as it is being developed as well as in the finished drug product. Experimental practices are similar to those described above, whereby the formulation is placed onto a microscope slide for evaluation. The melting onset temperatures determined in this manner for a patch formulation containing either Form A or Form B were also consistent with the values reported using the DSC method described for Forms A and B, e.g., about 105° C and 117°.

By "amorphous" is meant simply that the latrepirdine is in a non-crystalline state. Amounts of crystalline latrepirdine may be measured by Powder X-Ray Diffraction (PXRD), Scanning Electron Microscope (SEM) analysis, differential scanning calorimetry (DSC), or any other standard quantitative measurement. The amorphous form of latrepirdine may be in any form in which latrepirdine is amorphous. By “molecular dispersion” is meant a solid material in which the amorphous drug and the polymer are dispersed throughout one another at the molecular level. Such molecular dispersions are sometimes referred to as amorphous solid solutions. The term “molecular dispersion” is intended to include both amorphous solid solutions that are thermodynamically stable, wherein the drug is present at less than the

solubility limit of the drug in the polymer, as well as amorphous solid solutions wherein the drug is present in excess of the solubility limit of the drug in the polymer. Note that a molecular dispersion is different than a simple physical mixture, which consists of particles of amorphous or crystalline latrepirdine mixed or blended with particles of polymer.

Amorphous latrepirdine can be prepared by transferring approximately 10 mg of crystalline latrepirdine into a Mettler Toledo pan and heating to 140°C at 20°C/min in a DSC. The sample was then cooled at 100°C/min to -40°C, resulting in the formation of the amorphous latrepirdine drug substance. Alternatively, amorphous latrepirdine was prepared by transferring 500mg to a platinum crucible and heated to 140-170°C in an oven for 5-10 minutes. The sample was removed from the oven and placed in liquid nitrogen bath for 5 minutes. The sample was removed and stored with desiccant.

The polymer used in the molecular dispersion may be any pharmaceutically acceptable polymer. The term "polymer" is used conventionally, meaning a compound that is made of monomers connected together to form a larger molecule. A polymer generally consists of at least about 20 monomers connected together. Thus, the molecular weight of the polymer generally will be about 2000 daltons or more. The polymer should be inert, in the sense that it does not chemically react with the latrepirdine in an adverse manner, and should be pharmaceutically acceptable. Exemplary polymers include hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose (HPMC), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), carboxymethyl ethylcellulose (CMEC), poloxamers (also known as polyoxyethylene-polyoxypropylene block copolymers), polyvinyl pyrrolidone (PVP), and mixtures thereof.

The manufacturing of a transdermal dosage form according to the invention may be accomplished in any method known to the skilled person. In

one embodiment, the invention provides a method for manufacturing a TTS. This method comprises the steps for manufacturing a transdermal dosage form according to any of the preceding claims comprising the steps of:

a) manufacturing of the active ingredient in adhesive solution or suspension;

b) coating of the active ingredient in adhesive solution or suspension;

c) drying of the active ingredient in adhesive solution or suspension;

d) manufacturing of the skin adhesive solution;

e) coating of the skin adhesive solution;

f) laminating of the skin adhesive layer to the drug in adhesive layer; and

g) punching and pouching.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following nonlimiting examples, which refer to the accompanying Figures 1 and 2, short particulars of which are given below.

Figure 1. Schematic diagram below for the layer design of the two formulations.

Figure 2. Representative *in vitro* dissolution profiles for Latrepirdine immediate release tablets measured using Dissolution Test 1.

EXAMPLES

The following non-limiting examples illustrate the invention. The patches prepared for these studies were prepared by one of two methods: solution coating or suspension coating.

Solution coating process

In the solution coating process, which is traditionally used for preparing transdermal patches, formulation components including the solvated adhesive, active pharmaceutical ingredient (API) and excipients are dissolved in an organic solvent. The solution is then spread onto a release liner and coated into a thin film using a suitable coating knife with a known gap, such as a Gardner knife. The thin film is then dried and laminated to a backing film. Depending on the API loading and the inherent API solubility in the adhesive composition, the coated solution may become supersaturated with respect to the API during drying due to evaporation of the organic solvent. If the API loading exceeds the inherent API solubility, the API will crystallize out during the drying process and/or during storage. The resulting API attributes, including the polymorphic form, particle number, size and shape, are not controlled by design but rather largely dependant on the formulation composition, drying process and the subsequent storage condition.

Suspension coating process

In the suspension coating process, the API is not dissolved, but is instead suspended in an organic solvent containing the adhesive and other excipients. The suspension is then spread onto a release liner and coated into a thin film using a suitable coating knife with a known gap, such as a Gardner knife. The thin film is then dried and laminated to a backing film. The suspension coating process enables more direct control and specification of the API polymorphic form, particle number, size and shape in the final patch product.

The drying process used for both types of patch preparation is completed as follows. The coated patch is allowed to dry in a ventilated chemical fume hood for about 15 minutes to allow some of the solvent to evaporate. The patch is then removed from the hood and placed into a small oven with a nitrogen purge for about 10 minutes. The oven temperature is set based on the solvent used. The dried patch is then removed from the oven

and allowed to cool for about 15 minutes in the chemical fume hood prior to lamination.

Preparation A - Latrepirdine Immediate Release Core Tablets

Ingredient	Quantity(mg)/unit for 5 mg A tablet	Quantity(mg)/unit for 10 mg A tablet	Quantity(mg)/unit for 20 mg A tablet
Latrepirdine diHCl, dihydrate	5.46	10.92	21.836
Microcrystalline Cellulose[b]	60.79	55.33	110.664
Lactose Monohydrate[c]	30.00	30.00	60.000
Sodium Starch Glycolate[d]	3.00	3.00	6.000
Magnesium Stearate[e,]	0.25	0.25	0.500
Magnesium Stearate[f]	0.50	0.50	1.000
Opadry II®[g]	4.00	4.00	8.000
Purified Water[h]	(22.67)	(22.67)	(45.333)
	TOTAL 104.00	TOTAL 104.00	TOTAL 208.00

Footnotes:

[a] Note the dose and strength of the tablets is defined in terms of weight of Latrepirdine dihydrochloride (a 5mg tablet is 4.1mg of Latrepirdine free base; (a 10 mg tablet is 8.2 mg of Latrepirdine free base); (a 20 mg tablet is 16.4 mg of Latrepirdine free base) . The API has a Latrepirdine dihydrochloride theoretical factor of 91.59% (to correct for the dihydrate).

[b] weight adjusted for potency of Latrepirdine dihydrochloride. Avicel PH102, FMC Corporation

[c] Fast Flo, Foremost Farms

[d] Glycolys, Roquette

[e] Vegetable sourced; Mallinckrodt, added intragranularly

[f] Vegetable sourced; Mallinckrodt, added extragranularly

[g] Opadry II Green (85F 11805) for 5 mg tablet; Opadry II White (Y-30-18037) for 10 mg. tablet; Opadry II Pink (32K 14828)for 20 mg. tablet

[h] Removed (evaporated) during film coating/drying and does not appear in the final product.

Manufacturing Process For the preparation of the 5, 10 and 20 mg Latrepirdine tablets

The excipients from the above table (microcrystalline cellulose, lactose and sodium starch glycolate) and latrepirdine di-HCl were loaded into an appropriately sized bin, ensuring that the latrepirdine di-HCl is sandwiched between the excipients. The premix was blended for 10 minutes at 12 +/- 1 RPM and then passed through a rotary mill equipped with a 1.0mm screen, running at approximately 1000 RPM.

The sieved blend was collect in an appropriately sized bin and to this was added intragranular magnesium stearate and blend for 5 minutes at 12 +/- 1 RPM.

The lubricated blend was processed through a Gerteis roller compactor equipped with an inline oscillated mill and the granules were collected into an appropriately sized bin. The targeted ribbon solid fraction was 0.67 (0.65-0.72). The collected granules were blended in an appropriately sized bin. To this was added extragranular magnesium stearate and this mixture was blended for 5 minutes at 12 +/- 1 RPM.

Tablets were compressed on a rotary tablet press to an average target weight of 100.0mg, a target hardness of 5-9 kP, and a target thickness of 2.4-2.9 mm. The tablets were passed through a deduster. An aqueous film-

coating was applied to the tablets to a target weight gain of 4.0% using a perforated coating pan.

Example 1. Detection of Crystalline Form in a Patch Using Hot-Stage Microscopy

Formulation 1: Particles consisting entirely of latrepirdine free base Form B were added and mixed into a silicone adhesive consisting of a 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a suspension of latrepirdine free base Form B particles. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 12 mg/cm^2. The film was then exposed to ambient conditions for 15 minutes and then placed in a heated oven with temperatures of 92 – 102 °C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The resulting formulation was determined to contain latrepirdine free base Form B by evaluation of its powder X-ray diffraction pattern.

Hot-Stage Microscopy: Hot-stage microscopy evaluation was conducted using an Olympus BX60 optical microscope equipped with a Linkam LTS 350 hot stage and controlled with Linksys32 1.2.1 software. Solids were viewed under cross-polarized light with a 530 nm wave plate and heated at 5 °C/minute from room temperature. Onset temperatures were determined visually, e.g., upon observation of sample melting. Melting of crystalline material was observed within formulation 1 at approximately 120 °C.

Example 2. Preparation of latrepirdine free base Form A (Method 1):

A solution of latrepirdine free base was prepared in isopropyl alcohol at a concentration of 8 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 3. Preparation of latrepirdine free base Form A (Method 2):

A solution of latrepirdine free base was prepared in toluene at a concentration of 21 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 4. Preparation of latrepirdine free base Form A (Method 3):

A solution of latrepirdine free base was prepared in ethyl acetate at a concentration of 13 mg/mL. The solvent was fully evaporated at 50°C to produce Form A.

Example 5. Preparation of latrepirdine free base Form A (Method 4):

Form B (22 mg) was slurried in 4 mLs of heptane at room temperature for approximately one day. The slurried was filtered to produce a solution. The solution was evaporated at 50°C to produce Form A.

Example 6. Preparation of latrepirdine free base Form B (Method 1):

A solution of latrepirdine free base was prepared in toluene at a concentration of 23 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 7. Preparation of latrepirdine free base Form B (Method 2):

A solution of latrepirdine free base was prepared in ethyl acetate at a concentration of 13 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 8. Preparation of latrepirdine free base Form B (Method 3):

A solution of latrepirdine free base was prepared in isopropyl alcohol at a concentration of 8 mg/mL. The solvent was fully evaporated at room temperature to produce Form B.

Example 9. Preparation of latrepirdine free base Form B (Method 4):

Form B (21 mg) was slurried in 4 mLs of heptane at room temperature for approximately one day. The slurry was filtered to produce a solution. The solution was evaporated at room temperature to produce Form B.

Example 10: Composition Table of Patch Formulations Made with Polyisobutylene (PIB) Adhesive

			Formulation Components			Percutaneous Absorption Parameters		
Formulation	Kollidon ® CL-M (%)	Latrepirdine (%)	IPP (%)	PG ML (%)	PIB (%)	24hr permeation (ug/cm^2)	% Delivery (24hr)	Flux @ 10 hr (ug/cm^2.hr)
A	0	5	6	0	89	9	2%	0.3
B	12	5	6	0	77	17	4%	0.3
C	12	5	6	3	74	149	26%	7
D	6	10	6	1.5	76.5	197	16%	4
E	0	15	6	0	79	28	3%	1
F	0	15	6	3	76	164	10%	6
G	6	15	6	3	70	320	30%	6
H	12	15	6	1.5	65.5	303	21%	5

I	12	15	6	0	67	166	11%	3
J	12	10	6	3	69	475	53%	20

Percutaneous absorption parameters (24hr permeation, % Delivery (24hr) and Flux @ 10hr) represent averages of 2 replicates using a single cadaver skin donor (AlloSource 081124) for this study.

* Note: PIB adhesive is a blend consisting of high molecular weight polyisobutylene and a low molecular weight polyisobutylene and isobutene as a plasticizing agent.

The formulation components were added to toluene and mixed with the solvated PIB adhesive to give a slurry or viscous solution. The slurry orviscous solution was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 5 to 15 mg/cm^2. The film was then left to expose to ambient condition for 15 minutes before placed in a heated oven with oven temperature of 105°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

API: latrepirdine free base

IPP: Isopropyl palmitate

PGML: Propylene Glycol Monolaurate

Kollidon® CL-M: obtained from BASF

PIB: a blend consisting of high molecular weight polyisobutylene and a low molecular weight polyisobutylene and isobutene as a plasticizing agent.

Example 11: Composition Table of Patch Formulations Made with Silicone Adhesive

	Formulation Components				Percutaneous Absorption Parameters		
Formulation	Kollidon ®	Latrepirdine (%)	Oleyl Alcoh	Silicone	24hr permeati	% Delive	Flux @ 10 hr

	CL-M		ol (%)	adhesive * (%)	on (ug/cm^2)	ry (24hr)	(ug/cm^2. hr)
S1	0	5	0	95	122	12%	38
S2	12	5	0	83	257	24%	11
S3	12	5	6	77	528	70%	21
S4	6	10	3	81	1029	64%	51
S5	0	15	0	85	260	12%	32
S6	0	15	6	79	491	34%	17
S7	6	15	6	73	1194	58%	48
S8	12	15	3	70	758	33%	21
S9	12	15	0	73	440	39%	60
S10	12	10	6	72	878	55%	34

The percutaneous absorption parameters reported represent the averages from 2 cadaver skin donors (AlloSource 079034 and AlloSource 078362) used for this study.

* Note: The silicone adhesive is a blend consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

The formulation components were added to toluene and mixed with the solvated silicone adhesive to give a slurry or viscous solution. The slurry or viscous solution was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 7 to 22 mg/cm^2. The film was then left to expose to ambient condition for 15 minutes before placed in a heated oven with oven temperature of 95°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

API: Latrepirdine free base

Kollidon® CL-M: obtained from BASF

Oleyl Alcohol: Super-refined NOVOL NF obtained from Croda

Silicone adhesive: a blend consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

Example 12: Composition Table of Patch Formulations Made with Polyacrylate Adhesives

	Formulation Components					Percutaneous Absorption Parameters		
Formulation	DURO-TAK Adhesive	Latrpirdine (%)	DPG	Oleyl Alcohol	Kollidon ® CL-M	24hr permeation (ug/cm^2)	% Delivery (24hr)	Flux @ 10 hr (ug/cm^2. hr)
A1	87-900A	15	4	6	15	1009	61%	64
A2	87-900A	15	4	0	15	728	49%	44
A3	87-900A	15	4	6	0	632	52%	42
A4	87-900A	15	0	0	0	490	41%	30
A5	87-900A	15	0	6	15	705	51%	38
A6	87-2852	15	0	0	15	345	31%	19
A7	87-2852	15	0	6	0	366	44%	21
A8	87-	15	4	0	0	211	23%	11

	2852							
A9	87-2852	15	4	6	15	454	45%	29

The percutaneous absorption parameters reported represent the averages from 2 cadaver skin donors (NY Skin bank #65070708 and AlloSource 078098) used for this study.

The formulation components were added to toluene and mixed with the solvated polyacrylate adhesive (either Duro-Tak 87-900A or Duro-Tak 87-2852) to give a slurry or viscous solution. The slurry or viscous solution was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 5 to 11 mg/cm^2. The film was then left to expose to ambient condition for 15 minutes before placed in a heated oven with oven temperature of 95 - 100°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

API: Latrepirdine free base

DPG: Dipropylene Glycol LO+ obtained from Dow Chemical

Oleyl Alcohol: Super-refined NOVOL NF obtained from Croda

Kollidon® CL-M: obtained from BASF

DURO-TAK Adhesive: obtained from Henkel

Example 13: Comparison of Higher Energy Polymorph Form (Form A) and Lower Energy Polymorph Form (Form B) in Silicone Adhesive

	Formulation Components			Percutaneous Absorption Parameters	
Formulation	Latrepirdine (%)	Form, Particle Size	Silicone (%)	24 hr permeation (ug/cm^2)	48 hr permeation (ug/cm^2)
S78	10	B,	90	392	677

		1-5 μm			
S82	10	B, 45 - 75 μm	90	313	615
S96	10	A, < 212 μm	90	424	642

A single human cadaver skin donor (NY ID# RJ112008) was used for this study

For formulation S78, particles consisting entirely of B form of latrepirdine free base (API) were added and mixed into silicone adhesive consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a slurry with suspension of B form of latrepirdine free base (API) particles ranging from approximately 1 to 5 μm. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 12 mg/cm^2. The film was then left to expose to ambience condition for 15 minutes before placed in a heated oven with oven temperatures of 92 - 102°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

For formulation S82, particles consisting entirely of B form of latrepirdine free base (API) were added and mixed into silicone adhesive consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a slurry with suspension of B form of latrepirdine free base API particles ranging from approximately 45 to 75 μm. The suspension was then spread onto a suitable release liner or backing film

to produce a film with a coating weight of about 12 mg/cm^2. The film was then left to expose to ambience condition for 15 minutes before placed in a heated oven with oven temperatures of 94 - 100°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

For formulation S96, particles consisting entirely of A form of latrepirdine free base (API) were added and mixed into silicone adhesive consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a slurry with suspension of A form of latrepirdine free base API particles of size less than 212 µm. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 12 mg/cm^2. The film was then left to expose to ambience condition for 15 minutes before placed in a heated oven with oven temperatures of 92°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

Example 14: Comparison of Higher Energy Polymorph Form (Non-Crystalline Form) and Crystalline Form B in Silicone Adhesive

	Formulation Components			Percutaneous Absorption Parameters	
Formulation	Latrperidine (%)	API Form	Silicone (%)	24 hr permeation (ug/cm^2)	48 hr permeation (ug/cm^2)
S110	10	Non-crystalline	90	477	655
S15	10	Crystalline, Form B	90	832	943

A single human cadaver skin donor (NY ID# RJ112008) was used for this study

For formulation S110, the latrepirdine particles and silicone adhesive solvated in ethyl acetate were added to isopropyl alcohol and mixed to give a viscous solution. The viscous solution was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 8 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperature of 90 - 98°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

For formulation S15, the latrepirdine particles and silicone adhesive solvated in ethyl acetate were added to isopropyl alcohol and mixed to give a viscous solution. The viscous solution was then spread onto a suitable release liner or backing film to produce a film with a coating weight about 10 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperature of 88 - 92°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

Example 15: Inclusion of Hydrophilic Polymers in Patch Formulations Made with Silicone Adhesive

		Formulation Components			Percutaneous Absorption Parameters	
Formulation	Coating Process	Latrepirdine (%)	Hydrophilic Polymer (%)	Silicone (%)	24 hr permeation (ug/cm^2)	48 hr permeation (ug/cm^2)
S114	API in solution	10	CAP 7.3	82.7	177	254
S120	API in solution	10	HPMCAS 9.7	80.3	419	519
S116	API in solution	10	Kollidon 30 15	75	525	631
S122	API in solution	10	Kollidon CL-M 10	80	607	706
S125	API in suspension	10	CAP 7.3	82.7	241	423
S126	API in suspension	10	HPMCAS 9.7	80.3	320	600
S127	API in suspension	10	Kollidon 30 15	75	484	784

A single human cadaver skin donor (NY ID# RJ112008) was used for this study

For formulation S114, latrepirdine free base (API) was added and mixed with isopropyl alcohol until a solution was observed. CAP (cellulose acetate phthalate) is a hydrophilic polymer and is produced by a spray drying process. CAP was suspended and then mixed with silicone adhesive in ethyl acetate, forming a slurry with a solution of latrepirdine free base (API) and suspension of CAP polymer particles with the majority of the particles under 10 µm. The slurry was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 8 mg/cm^2. The film was then left to expose to ambient conditions for 25 minutes before placed in a heated oven with oven temperatures of 86-90°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

For formulation S116, latrepirdine free base (API) and BASF Kollidon® 30 (PVP) polymer were added and mixed with isopropyl alcohol until a solution was observed. Kollidon® 30 polymer or a polyvinyl pyrrolidone (PVP) polymer is a hydrophilic polymer. The solution was then mixed with the silicone adhesive in ethyl acetate, to give a slurry. The slurry was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 8 mg/cm^2. The film was then left to expose to ambient conditions for 25 minutes before placed in a heated oven with oven temperatures of 88-90°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

For formulation S120, particles consisting of latrepirdine free base (API) were added and mixed with isopropyl alcohol until a solution was observed. HPMCAS (hydroxylpropyl methylcellulose acetate succinate is a hydrophilic polymer. HPMCAS polymer was added and then mixed with silicone in ethyl acetate, forming a slurry with a solution of latrepirdine free base API and a suspension of HPMCAS polymer particles. The slurry was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 8 mg/cm^2. The film was then left to expose to ambient conditions for 25 minutes before placed in a heated oven with oven temperatures of 83-86°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

For formulation S122, particles consisting of latrepirdine free base (API) were added and mixed with isopropyl alcohol until a solution was observed. Kollidon® CL-M polymer or a crosslinked polyvinyl pyrrolidone (crosslinked-PVP) polymer is a hydrophilic polymer. BASF Kollidon® CL-M polymer was suspended and then mixed with silicone adhesive in ethyl acetate, forming a slurry with a solution of latrepirdine free base (API) and suspension of crosslinked-PVP polymer particles. The slurry was then spread onto a suitable release liner or backing film to produce a film with a coating weight of about 9 mg/cm^2. The film was then left to expose to ambient conditions for 25 minutes before placed in a heated oven with oven temperatures of 84-88°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4202 and DOW CORNING® BIO-PSA 7-4302.

For formulation S125, particles consisting entirely of B form of latrepirdine free base (API) and particles of CAP polymer were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. CAP (cellulose acetate phthalate) is a hydrophilic polymer and is produced by a spray drying process. The slurry consisted of a suspension of B form of latrepirdine free base (API) particles ranging from approximately 1 to 5 µm and CAP polymer particles with the majority of the particles under 10 µm. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film with a coating weight of about 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 99 - 101°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

For formulation S126, particles consisting entirely of B form of latrepirdine free base (API) and HPMCAS polymer were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. HPMCAS (hydroxylpropyl methylcellulose acetate succinate) is a hydrophilic polymer. The slurry consisted of a suspension of B form of latrepirdine free base (API) particles ranging from approximately 1 to 5 µm and HPMCAS polymer particles with the majority of the particles under 10 µm. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film with a coating weight of about 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 94 - 100°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a

50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

For formulation S127, particles consisting entirely of B form of latrepirdine free base (API) and BASF Kollidon ® 30 (PVP) polymer were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. Kollidon® 30 polymer or a polyvinyl pyrrolidone (PVP) polymer is a hydrophilic polymer. The slurry consisted of a suspension of B form of latrepirdine free base (API) particles ranging from approximately 1 to 5 µm and PVP polymer. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film with a coating weight of about 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 100°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The silicone adhesive comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

Example 16: Co-precipitate Particles Consisting of Latrepirdine and Hydrophilic Polymers

	Formulation Components				Percutaneous Absorption Parameters	
	Co-precipitate Particle Dispersed in Adhesive			Silicone Adhesive (%)		
Formulation	Total Particle Weight (%)	Latrepirdine (%)	Polymer (%)		24 hr permeation (ug/cm^2)	48 hr permeation (ug/cm^2)
S133	16.1	9.3	CAP 6.8	83.9	196	282

S136	17.9	9.1	HPMC AS 8.8	82.1	357	513
S138	21.7	8.7	Kollidon 30 13.0	78.3	622	885

A single human cadaver skin donor (NY ID# RJ112008) was used for this study

For formulation S133, engineered particles, produced by a spray drying process, consisting of 57.7 to 42.3 weight combination of latrepirdine free base and CAP polymer with the majority of the particles below 10 µm were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry with a suspension of the engineered particles of latrepirdine free base. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 10 to 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 92 - 102°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

For formulation S136, engineered particles, produced by a sprayed drying process, consisting of 50.9 to 49.1 weight combination of latrepirdine free base and HPMCAS polymer with the majority of the particles below 10 µm were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry with a suspension of the engineered particles of latrepirdine free base. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 10 to 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 96 - 99°C with some air flow for 10 minutes. The dried film was then laminated to a

backing film or release liner and cut to desired size using an appropriate punch.

For formulation S138, engineered particles, produced by a rotovap process, consisting of 40 to 60 weight combination of latrepirdine free base and PVP were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry with a suspension of the engineered particles of latrepirdine free base. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight of 10 to 13 mg/cm^2. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperatures of 98 - 102°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

CAP: Cellulose Acetate Phthalate

HPMCAS: Hydroxypropyl methylcellulose acetate succinate

PVP: Polyvinyl pyrrolidone

Silicone Adhesive: 50:50 mixture of DOW CORNING® BIO-PSA 7 4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive

Example 17: Improved Patch Stability with Inclusion of Antioxidant Propyl Gallate

	Formulation Components			Stability Condition (70° C for 1 week)
Formulation	Latrepirdine (%)	Duro-Tak 87-	Propyl Gallate (%)	Total Degradants (%)

		900A (%)		
A4	15	84.95	None	9.1
A4-PG	15	84.95	0.05	5.6

For formulations A4, the latrepirdine particles were dissolved in toluene and then added to polyacrylic adhesive Duro-Tak 87-900A solvated in ethyl acetate to give a viscous solution. The viscous solution was then spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperature of 100-105 °C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation A4-PG, the Latrepirdine particles and propyl gallate were dissolved in isopropyl alcohol and added to polyacrylate adhesive Duro-Tak 87-900A solvated in ethyl acetate to give a viscous solution. The viscous solution was then spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperature of 90 °C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

Example 18: Improved Patch Stability of Patches Made with Suspension Coating Process Compared to Solution Coating Process

Formulation	Coating Process	Formulation Components					Stability Condition (70° C for 1 week)
		Latrepirdine (%)	Adhesive (%)	Propyl Gallate (%)	Enhancer (%)	Kollidon CL-M (%)	Total Degradants (%)
PIB-J-PG-Sus	Suspension Coating	10	68.95% (PIB)	0.05	6% IPP 3% PGML	12	3.6
PIB-J-PG-Sol	Solution Coating	10	68.95% (PIB)	0.05	6% IPP 3% PGML	12	9.0
S7-PG-Sus	Suspension Coating	10	77.95% (silicone)	0.05	6% OA	6	0.8
S7-PG-Sol	Solution Coating	10	77.95% (silicone)	0.05	6% OA	6	1.2
A20-PG-Sus	Suspension Coating	20	79.95% (Duro-Tak 87-901A)	0.05	None	None	0.6
A4-PG-Sol	Solution Coating	15	79.95% (Duro-Tak 87-	0.05	None	None	5.6

Formulation	Coating Process	Formulation Components					Stability Condition (70° C for 1 week)
		Latrepirdine (%)	Adhesive (%)	Propyl Gallate (%)	Enhancer (%)	Kollidon CL-M (%)	Total Degradants (%)
			900A)				

IPP: Isopropyl palmitate

PGML: Propylene glycol monolaurate

OA (Oleyl Alcohol): Super-refined Novol NF obtained from Croda.

Kollidon® CL-M: crosslinked PVP obtained from BASF

PIB: an adhesive blend comprises a high molecular weight polyisobutylene and a low molecular weight polyisobutylene and isobutene as a plasticizing agent.

Silicone: an adhesive blend comprises a 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

Duro-Tak 87-901A: a polyacrylate adhesive solvated in cyclohexane obtained from Henkel.

Duro-Tak 87-900A: a polyacrylate adhesive solvated in ethyl acetate obtained from Henkel. The chemical compositions of Duro-Tak 87 901A and Duro-Tak 87-900A are similar. The adhesive is a non-reactive composition containing no functional monomers and is non-curing.

For formulation PIB-J-PG-Sus, particles consisting entirely of B form of latrepirdine free base (API), propyl gallate, absorption enhancers including

isopropyl palmitate and propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into PIB adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 100° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation PIB-J-PG-Sol, particles of latrepirdine free base (API), propyl gallate, absorption enhancers including isopropyl palmitate and propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into PIB adhesive solvated in toluene, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 110° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation S7-PG-Sus, particles consisting entirely of B form of latrepirdine free base (API), propyl gallate, oleyl alcohol, and Kollidon CL-M (crosslinked PVP) were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a

heated oven with oven temperatures of 100° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation S7-PG-Sol, particles of latrepirdine free base (API) was first dissolved in isopropyl alcohol, and this solution, together with propyl gallate, oleyl alcohol, and Kollidon CL-M (crosslinked PVP), were added and mixed into silicone adhesive solvated in ethyl acetate, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 90° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation A20-PG-Sus, particles consisting entirely of B form of latrepirdine free base (API) and propyl gallate were added and mixed into Duro-Tak 87-901A, a polyacrylate adhesive solvated in cyclohexane, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 75° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation A4-PG-Sol, the latrepirdine particles and propyl gallate were dissolved in isopropyl alcohol and added to polyacrylate adhesive Duro-Tak 87-900A solvated in ethyl acetate to give a viscous solution. The viscous solution was then spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15 minutes before placed in a heated oven with oven temperature of 90 °C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

Example 19: Improved Patch Stability of Patches Made with Inclusion of Antioxidant Propyl Gallate and Suspension Coating Process

Formulation	Coating Process	Formulation Components					Stability Condition (70° C for 1 week)
		Latrepirdine (%)	Adhesive (%)	Propyl Gallate (%)	Enhancer (%)	Kollidon CL-M (%)	Total Degradants (%)
PIB-2A	Suspension Coating	7.5	79.95 % (PIB)	0.05	2% PGML 3% IPP	7.5	2.98
PIB-2B	Suspension Coating	7.5	80% (PIB)	0	2% PGML 3% IPP	7.5	11.05

Formulation	Coating Process	Formulation Components					Stability Condition (70° C for 1 week)
		Latrepirdine (%)	Adhesive (%)	Propyl Gallate (%)	Enhancer (%)	Kollidon CL-M (%)	Total Degradants (%)
Silicone-2A	Suspension Coating	10	83.95 % (silicone)	0.05	2% PGML	4	0.53
Silicone-2B	Suspension Coating	10	84% (silicone)	0	2% PGML	4	7.61

IPP: Isopropyl palmitate

PGML: Propylene glycol monolaurate

Kollidon® CL-M: crosslinked PVP obtained from BASF

PIB: an adhesive blend comprises a high molecular weight polyisobutylene and a low molecular weight polyisobutylene and isobutene as a plasticizing agent.

Silicone: DOW CORNING® BIO-PSA 7-4301 silicone adhesive.

For formulation PIB-2A, particles consisting entirely of B form of latrepirdine free base (API), propyl gallate, isopropyl palmitate, propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into PIB adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for

15-25 minutes before placed in a heated oven with oven temperatures of 90° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation PIB-2B, particles consisting entirely of B form of latrepirdine free base (API), isopropyl palmitate, propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into PIB adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 90° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation Silicone-2A, particles consisting entirely of B form of latrepirdine free base (API), propyl gallate, propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 90° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside

was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

For formulation Silicone-2B, particles consisting entirely of B form of latrepirdine free base (API), propylene glycol monolaurate, and Kollidon CL-M (crosslinked PVP) were added and mixed into silicone adhesive in heptane as the only solvent, forming a slurry. The slurry was then mixed and spread onto a suitable release liner or backing film to produce a film. The film was then left to expose to ambient conditions for 15-25 minutes before placed in a heated oven with oven temperatures of 90° C with some air flow for 12 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch. The cut-out patch was then sealed into a foil pouch. The pouch with patch inside was then stored at 70° C for 1 week. The pouch was then opened and the patch inside was analyzed for degradants.

Example 20: Latrepirdine Containing Patches with Seven Days Release Profile

Formulation	Latrepirdine (%)	Silicone (%)	Adhesive Coat Weight (mg/cm^2)	Percutaneous Absorption Parameters				
				7 days Permeation (ug/cm^2)	% Delivery @ 1 day	% Delivery @ 3 days	% Delivery @ 5 days	% Delivery @ 7 days
S99-1	15%	85%	18.1	1937	12.7%	43.4%	60.8%	71.5%
S99-2	15%	85%	24.8	1458	11.2%	26.8%	34.3%	39.2%
S99-3	15%	85%	30.4	1469	8.2%	20.9%	27.5%	32.1%
S99-4	22%	78%	12.8	2532	23.8%	66.0%	84.3%	89.4%
S99-5	30%	70%	15.5	3347	12.9%	42.8%	60.3%	71.1%

Average of 2 human cadaver skin donors (NY ID# GR121208 and QB021709) were used for this study

For formulations S99-1 through S99-5, particles consisting entirely of B form of latrepirdine free base were added and mixed into silicone adhesive consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a slurry with suspension of B form of latrepirdine free base particles. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight ranging from about 12.8 to 30.4 mg/cm^2. The film was then left to expose to ambience condition for 15 minutes before placed in a heated oven with oven temperatures of 92 - 102°C with some air flow for 10 minutes. The dried film was then laminated to a backing film or release liner and cut to desired size using an appropriate punch.

Example 21 Inclusion of a Rate Controlled Layer in Latrepirdine Containing Patch with Seven Days Release Profile

Formulation	Latrepirdine (%)	Silicone (%)	Adhesive Coat Weight (mg/cm^2)	Skin Adhesive Layer (mg/cm^2)	Percutaneous Absorption Parameters				
					7 days Permeation (ug/cm^2)	% Delivery @ 1 day	% Delivery @ 3 days	% Delivery @ 5 days	% Delivery @ 7 days
S99-4	22%	78 %	12.8	none	2532	23.8%	66.0%	84.3 %	89.4 %
S99-6	22%	78 %	12.9	6.2	1768	10.4%	34.2%	50.5 %	62.3 %

Average of 2 human cadaver skin donors (NY ID# GR121208 and QB021709) are used for this study

For formulations S99-4 and S99-6, particles consisting entirely of B form of Latrepirdine free base (API) were added and mixed into silicone adhesive consisting of 50:50 mixture of DOW CORNING® BIO-PSA 7-4201 silicone adhesive and DOW CORNING® BIO-PSA 7-4301 silicone adhesive, in heptane as the only solvent, forming a slurry with suspension of B form of Latrepirdine free base particles. The suspension was then spread onto a suitable release liner or backing film to produce a film with a coating weight ranging from 12.8 to 12.9 mg/cm^2. The film was then left to expose to ambience condition for 15 minutes before placed in a heated oven with oven temperatures of 92 - 102°C with some air flow for 10 minutes. For formulation S99-4, the dried film was then laminated with a backing film or release liner and cut to desired size using an appropriate punch. For formulation S99-6, the dried film was further laminated with a layer of silicone containing no latrepirdine, before laminated to the backing film or release liner and cut to desired size using an appropriate punch. Inclusion of this layer reduced the permeation amount of latrepirdine but produced a more stable, pseudo zero-order absorption rate profile for seven days. See Figure 1.

Example 22: Determination of PK plasma levels of latrepirdine and it A_{met} metabolite in CD-1 mice following repeated dermal and oral administration of Latrepirdine.

Mice were dosed with dermal administration of latrepirdine free-base (n=12/sex/dose group) at the dose levels of 0, 25, 75, or 150 mg of active moiety per kg of body weight per day. Mice (n=12/sex/dose group) were also dosed with latrepirdine dihydrochloride by oral gavage at the dose level of 25 mg of nominal moiety (20.4 mg active moiety) per kg of body weight per day.

Transdermal formulation used consisted of Polypropylene Glycol 400 10% w/w and Ethyl Alcohol (200 proof) (90 % w/w) and latrepirdine free base at 150 mg/mL concentration.

Non-serial blood samples were collected from animals (n=2/sex/dose

group/time point) at the following time points 0.25, 1, 3, 6, 12, and 24 hours postdose on Study Day 7. From the control group, all of the samples were analyzed. Plasma was analyzed for Latrepirdine and A_{met} using a validated LC/MS/MS method.

Mean data were used in all analyses. The area under the plasma concentration-time curve ($AUC_{(0-24)}$) was estimated using the linear trapezoidal rule. For Day 7, the plasma concentrations of latrepirdine and A_{met} at time 0 was set to the corresponding 24-hour concentration value. Concentrations of 0 ng/mL were used for calculations for all results of Below the Limit of Quantitation (BLQ) (<1.00 ng/mL, both analytes).

Mean data for latrepirdine and its A_{met} metabolite are summarized in Table 1 and Table 2, respectively.

There were no apparent gender-related differences in exposure in this study for latrepirdine. Therefore, male and female data have been combined. The mean $AUC_{(0-24)}$ ratios of transdermally administered latrepirdine to A_{met} (25 mg/kg/day from Table 1 and Table 2) was 1.77 (1880 ng* h/mL divided by 1060 ng* h/mL). The mean $AUC_{(0-24)}$ ratios of orally administered latrepirdine to A_{met} (25 mg/kg/day from Table 1 and Table 2) was 0.43(316 ng* h/mL divided by 743 ng* h/mL).

Table 1
Mean PK Parameters for Latrepirdine in Mice after Dermal and Oral Administration of Latrepirdine on Day 7

Dose & Route (mg/kg/day)	Study Day	Gender	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng*h/mL)	t1/2 (h)	C(0) (ng/mL)
25 Dermal	7	Male	165	1.0	2340	9.69	35.3
		Female	149	1.0	1420	5.91	11.3
		Overall	157	1.0	1880	7.94	23.3
75 Dermal	7	Male	230	6.0	3080	12.0	71.5
		Female	230	1.0	3330	18.8	87.1
		Overall	223	1.0	3200	14.5	79.3
150 Dermal	7	Male	306	6.0	4990	11.6	103
		Female	243	1.0	4140	33.9	128

		Overall	274	1.0	4560	16.7	115
25 Oral	7	Male	237	0.25	346	2.28	0
		Female	282	0.25	285	0.817	0
		Overall	259	0.25	316	1.75	0

Table 2
〈 Parameters for A_{met} in Mice after Dermal and Oral Administration of Latrepirdine on Day 7

Dose & Route (mg/kg/day)	Study Day	Gender	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng*h/mL)	t1/2 (h)	C(0) (ng/mL)
25 Dermal	7	Male	76.8	1.0	765	6.09	5.49
		Female	231	1.0	1360	4.61	6.89
		Overall	154	1.0	1060	4.93	6.19
75 Dermal	7	Male	105	6.0	1400	6.54	16.1
		Female	208	3.0	2610	8.79	44.1
		Overall	155	6.0	2010	7.90	30.1
150 Dermal	7	Male	244	24	3550	NC	30.1
		Female	442	1.0	5520	7.94	77.5
		Overall	305	1.0	4530	35.0	161
25 Oral	7	Male	169	1.0	394	0.869	0
		Female	626	1.0	1080	1.46	0
		Overall	397	1.0	743	1.27	0
NC = Not calculated due to concentration vs. time profile of data.							

Abbreviations:

$AUC_{(0-24)}$: Area under the plasma drug concentration-time curve for 0-24 h

BLQ: Below the limit of quantitation

Cm_{ax}: Highest drug concentration observed in plasma

DSRD: Drug Safety Research and Development

Nominal: Not corrected for salt form

t_{max}: Time at which mean Cmax was first observed

$t_{1/2}$: Half-life

Example 23: Determination of PK plasma levels of latrepirdine in Göttingen Minipigs following application of transdermal patches of Latrepirdine.

Göttingen Minipigs were dosed once with transdermal patches of latrepirdine free-base (n=2/formulation group). The composition of the patch formulations are shown below:

Formulation	Coating Process	Formulation Components				
		Latrepirdine (%)	Adhesive (%)	Propyl Gallate (%)	Enhancer (%)	Kollidon CL-M (%)
S-102	Suspension Coating	10	73.95% (Silicone)	0.05	6% OA	10
A15-PG-Sus	Suspension Coating	15	79.95% (Duro-Tak 87-901A)	0.05	None	None

For patch formulation S-102, 20 cm^2 patches containing 20 mg of latrepiridine free base were dosed and followed by a 5-day pharmacokinetic blood collection period. For patch formulation A15-PG-Sus, 20 cm^2 patches containing 30 mg of latrepiridine free base were dosed and followed by a 10-day pharmacokinetic blood collection period. Plasma was analyzed for Latrepirdine using a validated LC/MS/MS method. The PK parameters are summarized in Table 3. The PK profiles, based on average of 2 animals, are shown in Figure 3. The PK profiles indicate that sustained plasma levels suitable for a single day application and a 7 days application are achievable by patch compositions S-120 and A15-PG-Sus respectively.

Table 3. Summary of PK Parameters Following Application of Latrepirdine Transdermal Patches on Göttingen Minipigs

Formulation	AUC (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)
5 Days of PK Blood Collection Period			
S-102			
Male (n=1)	46.2	1.85	24
Females (n=1)	12.9	0.508	24
Formulation	**AUC (ng•h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
10 Days of PK Blood Collection Period			
A15-PG-Sus			
Male (n=1)	88.0	0.794	48
Females (n=1)	80.9	0.537	72

Example 24: Determination of PK plasma levels of latrepirdine in Human following application of transdermal solutions and immediate release control tablet of Latrepirdine.

A study was conducted to evaluate the pharmacokinetics of a transdermal latrepirdine solution relative to the oral immediate release (IR) control tablet in both extensive (EM) and poor (PM) cytochrome P450 2D6 metabolizers in the fasted state. Specifically, the pharmacokinetics of a single dose of a 5 mg transdermal solution applied to the skin with occlusion over a 24 hour period was compared to a single oral 10 mg dose of the IR control tablet in EM subjects. A 125 mg/mL latrepirdine solution was applied to the skin at approximately 5 µl/cm^2. In other words, for a 5 mg transdermal dose, approximately 40 µl was applied over an 8 cm^2 surface area of skin for a 24 hour period. Following administration to the skin, the application site was occluded and remained occluded until the solution was removed from the skin approximately 24 hours following administration. The solution was removed with gentle swabbing with a gauze pad moistened only with water.

The transdermal solution comprises of 125 mg/mL of latrepirdine dissolved in a vehicle consisting of 30% by weight of ethyl alcohol, 30% by weight of polypropylene glycol 400, 30% by weight of dipropylene glycol and 10% by weight of oleyl alcohol.

This 5 mg transdermal dose was first administered to a subset (e.g., 12 EMs) of the population in order to confirm that the PK sampling scheme and exposures are adequate for determination of pharmacokinetic parameters. Following this, a second dose strength of the transdermal solution was also evaluated relative to the pharmacokinetics of a single oral 10 mg IR control tablet dose. In addition, the 5 mg transdermal dose was administered to a unique set of subjects categorized as PMs. (e.g., 7 PMs).

Both transdermal latrepirdine solution and the immediate release control tablet formulation were administered in the fasted state. The fasted state as used herein is defined as follows: the dosing state which is defined following an overnight fast (wherein zero caloric intake has occurred) of at least 10 hours. Subjects were administered the dosage form with 240 mL of water. No food were allowed for at least 4 hours post-dose. Water was allowed as desired except for one hour before and after drug administration.

Both plasma latrepirdine and its metabolite A_{met} were measured following transdermal and oral administration using conventional methods. The pharmacokinetic sampling scheme was chosen such that a sufficient number of time points are available in order to estimate peak concentrations (C_{max}) and exposures (AUC). Noncompartmental analysis of latrepirdine and A_{met} will be performed using internal software. The plasma pharmacokinetic parameters C_{max}, time of peak concentration (T_{max}), area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}), AUC_{last}(dose normalized), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}), AUC_{inf} (dose normalized), terminal half-life ($t_{1/2}$), and lag time (T_{lag}) were

summarized descriptively by analyte, treatment formulation, dose, and genotype (e.g., EM and PM). The ratio of parent to metabolite, C_{max}, AUC_{last}, and AUC_{inf} were summarized descriptively by treatment formulation, dose, and genotype.

Table 4. Summary of PK Parameters Following Application of Latrepirdine Transdermal Patches on Human EM (Effective Metabolizer) Subjects

	10 mg[b] IR (EM)	5 mg Transdermal (EM)	10 mg Transdermal (EM)
Number of Subject	12	12	12
Estimated Delivered Dose[a] (mg)	N/A	4.13	8.10
C_{max} (ng/mL)	1.65	3.83	7.33
C_{max} (dose normalized) (ng/mL)	0.20	0.77	0.73
T_{max} (hr)	2.0	9.0	9.0
AUC_{last} (ng/hr/mL)	9.93	70.67	147.1
AUC_{last}(dose normalized) (ng/hr/mL/mg)	1.22	14.13	14.71
AUC_{inf} (ng/hr/mL)	11.30	72.02	149.1
AUC_{inf} (dose normalized) (ng/hr/mL/mg)	1.39	14.41	14.91
$t_{1/2}$	6.9	24.2	26.7
T_{lag}	0.04	0.9	1.0

[a] Estimated delivered dose is calculated by subtracting the residual content of latrepirdine recovered from the applied dressing and swabbing of the application site from the initial applied dose.

[b] Contained an equivalent of 8.2 mg of latrepirdine free base.

N/A: Not applicable

Table 5. Summary of PK Parameters Following Application of Latrepirdine Transdermal Patches on Human PM (Poor Metabolizer) Subjects

	10 mg[b] IR (PM)	5 mg Transdermal (PM)
Number of Subject	7	7
Estimated Delivered Dose[a] (mg)	N/A	4.84
C_{max} (ng/mL)	16.16	6.44
C_{max} (dose normalized) (ng/mL)	1.99	1.29
T_{max} (hr)	3.1	9.0
AUC_{last} (ng/hr/mL)	240.9	199.5
AUC_{last}(dose normalized) (ng/hr/mL/mg)	29.57	39.94
AUC_{inf} (ng/hr/mL)	242.4	202.9
AUC_{inf} (dose normalized) (ng/hr/mL/mg)	29.78	40.58
$t_{1/2}$	15.5	22.2
T_{lag}	0.0	0.3

[a] Estimated delivered dose is calculated by subtracting the residual content of latrepirdine recovered from the applied dressing and swabbing of the application site from the initial applied dose.

[b] Contained an equivalent of 8.2 mg of latrepirdine free base.

N/A: Not applicable

Table 6. Summary of Plasma Metabolite A_{met} PK Parameters Following Application of Latrepirdine Transdermal Patches on Human EM (Effective Metabolizer) Subjects

	10 mg[b] IR (EM)	5 mg Transdermal (EM)	10 mg Transdermal (EM)
Number of Subject	12	12	12
Estimated Delivered Dose[a] (mg)	N/A	4.13	8.10
C_{max} (ng/mL)	95.81	9.26	18.56
T_{max} (hr)	2.0	12.0	12.0
AUC_{last} (ng/hr/mL)	491.5	229.5	486.4
AUC_{inf} (ng/hr/mL)	495.2	248.3	502.4
$t_{1/2}$	7.5	18.4	22.9
T_{lag}	0.0	2.3	2.5

[a] Estimated delivered dose is calculated by subtracting the residual content of latrepirdine recovered from the applied dressing and swabbing of the application site from the initial applied dose.

[b] Contained an equivalent of 8.2 mg of latrepirdine free base.

N/A: Not available

Table 7. Summary of Plasma Metabolite A_{met} PK Parameters Following Application of Latrepirdine Transdermal Patches on Human PM (Poor Metabolizer) Subjects

	10 mg[b] IR (PM)	5 mg Transdermal (PM)
Number of Subject	7	7
Estimated Delivered Dose[a] (mg)	N/A	4.84
C_{max} (ng/mL)	4.30	0.83
T_{max} (hr)	N/A	N/A
AUC_{last} (ng/hr/mL)	55.23	24.09
AUC_{inf} (ng/hr/mL)	63.17	N/A
$t_{1/2}$	11.1	N/A
T_{lag}	0.5	6.1

[a] Estimated delivered dose is calculated by subtracting the residual content of latrepirdine recovered from the applied dressing and swabbing of the application site from the initial applied dose.

[b] Contained an equivalent of 8.2 mg of latrepirdine free base.

N/A: Not available

Table 8. Summary of Ratio of Latrepirdine to Metabolite A_{met} Following Application of Latrepirdine Transdermal Patches on Human EM (Effective Metabolizer) Subjects

	10 mg[a] IR (EM)	5 mg Transdermal (EM)	10 mg Transdermal (EM)
Number of Subject	12	12	12
C_{max} (ng/mL)	0.01	0.46	0.44
AUC_{last} (ng/hr/mL)	0.01	0.35	0.34
AUC_{inf} (ng/hr/mL)	0.02	0.33	0.34

[a] Contained an equivalent of 8.2 mg of latrepirdine free base.

Table 9. Summary of Ratio of Latrepirdine to Metabolite A_{met} Following Application of Latrepirdine Transdermal Patches on Human PM (Poor Metabolizer) Subjects

	10 mg[a] IR (PM)	5 mg Transdermal (PM)
Number of Subject	7	7
C_{max} (ng/mL)	2.84	8.06
AUC_{last} (ng/hr/mL)	4.16	9.33
AUC_{inf} (ng/hr/mL)	3.97	N/A

[a] Contained an equivalent of 8.2 mg of latrepirdine free base.

N/A: Not available

A 125 mg/mL latrepirdine solution is applied to the skin at approximately 5 µl/cm^2. In other words, for a 5 mg transdermal dose, approximately 40 µl will be applied over an 8 cm^2 surface area of skin for a 24 hour period. Following administration to the skin, the application site is occluded and remains occluded until the solution is removed from the skin approximately 24 hours following administration. The solution is removed with gentle swabbing with a gauze pad moistened only with water. The solution consists of the following components:

Latrepirdine API	125 mg/mL
Super Refined PEG 400 EP/JPE/NF	30%
Dipropylene Glycol LO+	30%
Super Refined Novol NF	10%

Ethyl Alcohol 200 Proof USP	30%

Olympus BX60 optical microscope equipped with a Linkam LTS 350 hot stage and controlled with Linksys32 1.2.1 software. Solids were viewed under cross-polarized light with a 530 nm wave plate and heated at 5 °C/minute from room temperature. Onset temperatures were determined visually, e.g., upon observation of sample melting. Melting of crystalline material was observed within formulation 1 at approximately 120 °C.

Clinical Study with a latrepirdine transdermal patch

An additional study is conducted to evaluate the pharmacokinetics of a latrepirdine transdermal patch relative to the oral immediate release (IR) control tablet formulation in both extensive (EM) and poor (PM) cytochrome P450 2D6 metabolizers. The study design and analyses is similar to the solution study above. Specifically, the pharmacokinetics of a single dose of a latrepirdine TDS applied to the skin over a 24 hour period is compared to a single oral dose of the IR control tablet formulation. More than one dose strength of the TDS may be evaluated in order to obtain adequate pharmacokinetic concentrations.

CLAIMS

We claim:

1. A pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the plasma concentration versus time curve ($AUC_{0\text{-}inf}$) ratio of latrepirdine to its A_{met} metabolite that is greater than 0.1 but not greater than 15.

2. A pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean area under the latrepirdine plasma concentration versus time curve for the period following administration ($AUC_{0\text{-}inf}$) of at least 8 ng-hr/mL.

3. A pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when administered transdermally as a single application to a cohort of human subjects having a CYP2D6 EM status, has a mean maximum plasma concentration (C_{max}) of latrepirdine of less than about 16 ng/mL about 2 to 24 hours following application to the skin.

4. A pharmaceutical dosage form wherein said dosage form is a transdermal dosage form and comprises latrepirdine in an amount which releases *in vitro* from about 0.1 to 100 mg of latrepirdine following a 24 to 168 hour period when tested in a human cadaver skin flux test.

5. A pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is a transdermal dosage form, and when assayed in an *in vitro* human cadaver

skin flux test provides a range of flux rates between 0.08 and 60 micro grams/hr/cm^2.

6. A pharmaceutical dosage form comprising latrepirdine and a pharmaceutically acceptable carrier, wherein said dosage form is and transdermal dosage form and is selected from a patch, ointment, gel, cream or spray solution.

7. A transdermal dosage form of Claim 6 wherein said dosage form is a patch.

8. A transdermal dosage form of Claim 7 comprising a backing layer, a reservoir layer between a backing layer and a contact adhesive layer comprising latrepirdine, at least one absorption enhancer, an antioxidant, and a hydrophilic polymer.

9. The transdermal dosage form of Claim 7 comprising a monolithic suspension-blend transdermal patch comprising a minimum of three layers, wherein the said layers are (a) a backing layer having inner and outer surfaces and being substantially impervious to latrepirdine; (b) a first adhesive layer having a first surface covering at least a portion of said inner surface of said backing layer, said adhesive layer comprising a 24 to 168 hour period therapeutically-effective amount of latrepirdine in a pressure sensitive adhesive; and (c) a removable release liner in contact with a second surface of said adhesive layer.

10. The transdermal dosage form of claim 9 wherein the adhesive layer comprises other excipients of the formulation such as an antioxidant, one or more absorption enhancers and hydrophilic polymer.

11. The transdermal dosage form of claim 9 wherein said latreperdine is also contained in the adhesive layer.

12. The transdermal dosage form of claims 9 or 10 comprising latrepirdine, said dosage form comprising

a. 5 wt% to 20 wt% latrepirdine;

b. 60 wt% to 90 wt% adhesive;

c. 0 wt% to 15 wt% absorption enhancer;

d. 0 wt% to 0.5 wt% antioxidant;

e. 0 wt% to 15 wt% hydrophilic polymer.

13. A transdermal dosage form of any of Claims 9 to 11 wherein the adhesive layer polymer comprises a polymer selected from the group consisting of polydimethylsiloxanes, acrylates, methacrylates, polyisobutylenes, polybutenes and styrene-isoprene-styrene block copolymers, or mixtures thereof, respectively combined with resins selected from the group consisting of polyacrylics, silicone, or polyisobutylene.

14. A transdermal dosage form of any of claims 9 to 12 wherein the adhesive layer optionally contains antioxidants chosen from a list of alpha tocopherol, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, ascorbyl palmitate and combinations thereof.

15. A transdermal dosage form of Claim 14 wherein the adhesive layer contains propyl gallate.

16. A transdermal dosage form according to any of the preceding claims wherein the adhesive layer is produced by coating an adhesive blend containing suspension particles of latreperdine.

17. A transdermal dosage form according to any of the preceding claims wherein the adhesive layer reduces active ingredient permeation from the reservoir layer through the skin by no more than 60%.

18. A transdermal dosage form according to any of the preceding claims wherein adhesive layer has a weight per unit area in the range of 5 to 60 mg/cm^2.

19. A transdermal dosage form according to any one of the preceding claims, wherein the tackifier is selected from the group consisting of polybutene, silicone oils, glycerine esters of hydrogenated resin acids, hydroabietyl alcohol, resin esters, hydrogenated methyl ester of wood rosin,

ester of partially hydrogenated wood rosin, esters of rosin, and combinations of thereof.

20. A transdermal dosage form according to any one of the preceding claims wherein the latrepirdine is amorphous.

21. A transdermal dosage form according to any one of the preceding claims wherein the latrepirdine is crystalline.

22. A transdermal dosage form of Claim 19 where the crystalline latrepirdine is chosen from Form A or Form B or combinations thereof.

23. A transdermal dosage form of Claim 18 or 19 wherein the latrepirdine particle size is less than 300 μm.

24. A transdermal dosage form of Claim 19 or 20 wherein crystalline Form B particles are less than or equal to 5 micrometers in length.

25. A method for manufacturing a transdermal dosage form according to any of the preceding claims comprising the steps of:

a) manufacturing of the active ingredient in adhesive solution or suspension;

b) coating of the active ingredient in adhesive solution or suspension;

c) drying of the active ingredient in adhesive solution or suspension;

d) manufacturing of the skin adhesive solution;

e) coating of the skin adhesive solution;

f) laminating of the skin adhesive layer to the drug in adhesive layer; and

g) punching and pouching.

Figure 1.

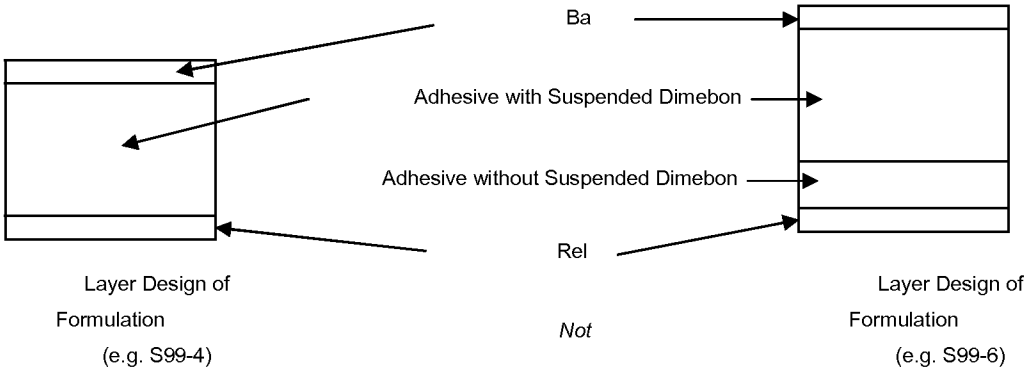


Figure 2.

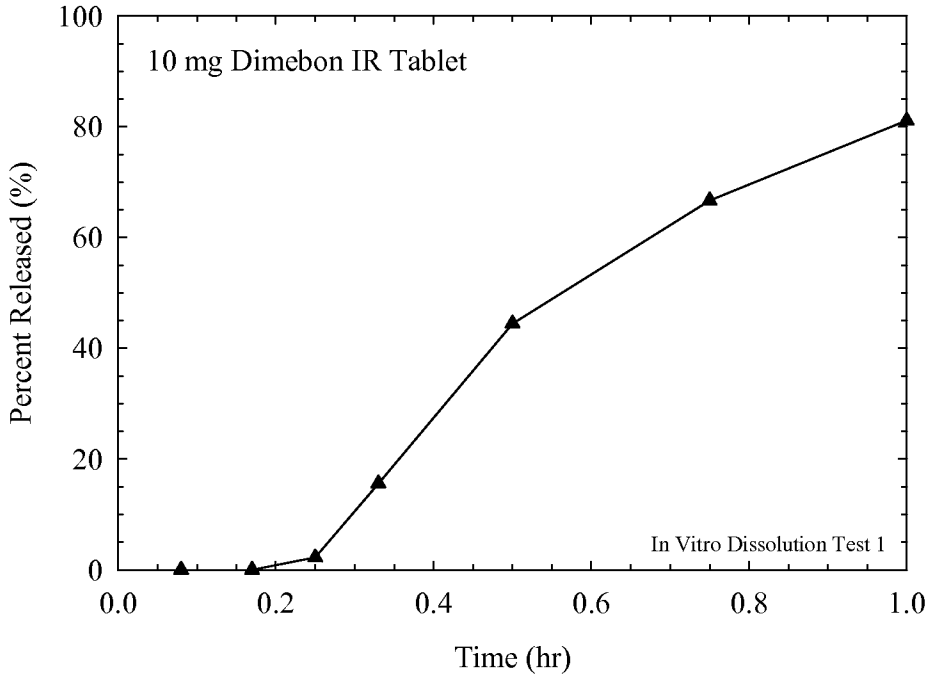
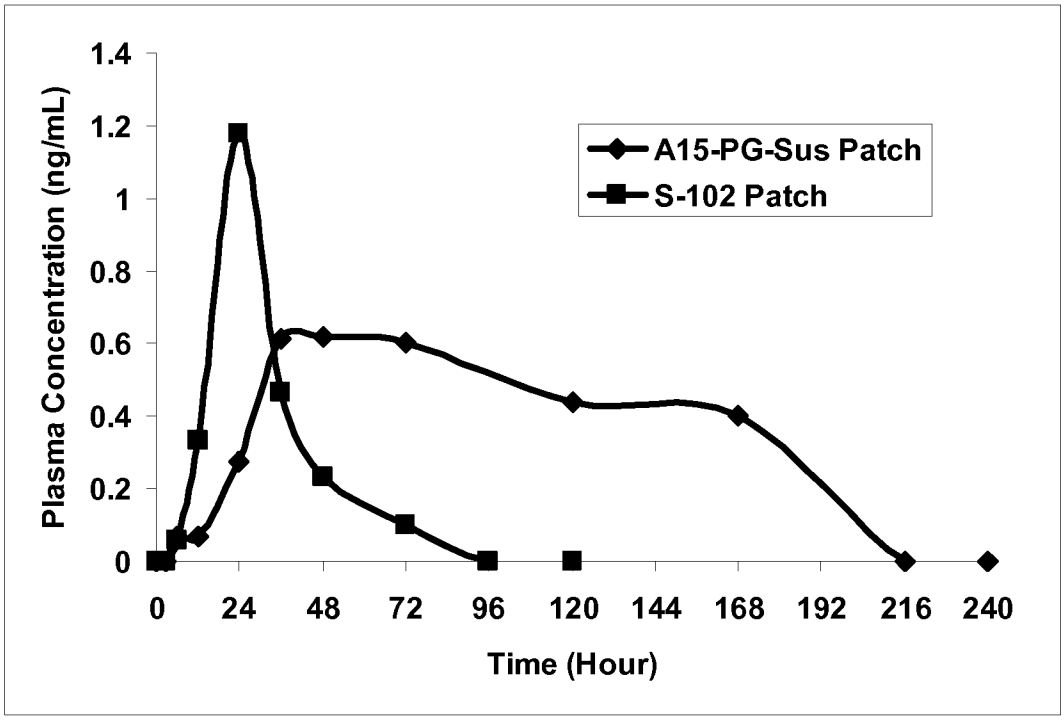


Figure 3.


Plasma Concentration (ng/mL)
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1.2
1
0.8
0.6
0.4
0.2
0
0
24
48
72
96
120
144
168
192
216
240
Time (Hour)
A15-PG-Sus Patch
S-102 Patch