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(54) Title: TRANSDERMAL DELIVERY OF LASOFOXIFENE

(57) Abstract: The present invention to provide methods, pharmaceutical formulations, and devices for the transdermal delivery of 5-substituted-6-cyclic-5,6,7,8,-tetrahydronaphthalene2-ol compounds ("lasofoxifene" or "CP-336,156") and pharmaceutically acceptable salts thereof. The invention also provides transdermal compositions of CP-336,156 or its salts dissolved or dispersed in a suitable carrier vehicle, optionally containing permeation enhancers and other excipients. The carrier vehicle may be a pressure sensitive adhesive, polymeric reservoir, or a fluid of controlled viscosity. The carrier vehicle may be contained in a device for purposes of holding the composition against the skin surface. Such devices may be in the form of matrix patches (drug in adhesive) or reservoir patches (drug in a liquid or polymeric reservoir with peripheral, in-line, or over-layed pressure sensitive adhesive). Further provided by this invention are methods for treating pathologies associated with the binding of lasofoxifene with the human estrogen receptor-alpha. For example, the invention formulations and devices are useful to treat or prevent bone loss, obesity, breast cancer, endometriosis, cardiovascular disease and prostatic disease.

TRANSDERMAL DELIVERY OF LASOFOXIFENE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. § 119 (e) to U.S. Provisional Application Serial Nos. 60/208,789 filed June 1, 2000. The contents of this application is hereby incorporated by reference into the present disclosure.

TECHNICAL FIELD

This invention relates to the transdermal delivery of lasofoxifene (5-substituted-6-cyclic-5,6,7,8,-tetrahydronaphthalene2-ol) compounds.

BACKGROUND OF THE INVENTION

Naturally occurring estrogens and synthetic compositions demonstrating "estrogenic" activity are useful for various therapeutic applications for example, oral contraception; rclief for the symptoms of menopause; prevention of threatened or habitual abortion; relief of dysmenorrhea; relief of dysfunctional uterine bleeding; aiding in ovarian development; treating acne; diminution of excessive growth of body hair in women (hirsutism); the preventing cardiovascular disease; treating osteoporosis; treating prostatic carcinoma; and suppressing post-partum lactation [Goodman and Gilman, The Pharmacological Basis Of Therapeutics (Seventh Edition) Macmillan Publishing Company, 1985, pages 1421-1423]. Accordingly, there has been increasing interest in finding newly synthesized compositions and new uses for previously known compounds that are demonstrably estrogenic, this is, able to mimic the action of estrogen in estrogen responsive tissue. From the viewpoint of pharmacologists interested in developing new drugs useful for the treatment of human diseases and specific pathological conditions, it is most important to procure compounds with some

demonstrable estrogen-like function but which are devoid of proliferative side-effects. For example, osteoporosis, a disease in which bone becomes increasingly, more fragile, is greatly ameliorated by the use of fully active estrogens; however, due to the recognized increased risk of uterine cancer in patients chronically treated with active estrogens, it is not clinically advisable to treat osteoporosis in intact women with fully active estrogens for prolonged periods. Estrogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women; it is the only treatment which unequivocally reduces fractures. However, estrogen stimulates the uterus and is associated with an increased risk of endometrial cancer. Although the risk of endometrial cancer is thought to be reduced by a concurrent use of a progestogen, there is still concern about possible increased risk of breast cancer with the use of estrogen.

Estrogen and estrogen-like compounds have also been shown to lower plasma levels of LDL and raise those of the beneficial high density lipoproteins (HDL's). Black, et al. in EP 0605193A1. Long-term estrogen therapy, however, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer and possibly breast cancer, causing many women to avoid this treatment. Recently suggested therapeutic regimens, which seek to lessen the cancer risk, such as administering combinations of progestogen and estrogen, cause the patient to experience unacceptable bleeding. Furthermore, combining progesterone with estrogen seems to blunt the serum cholesterol lowering effects of estrogen. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for hypercholesterolemia that have the desirable effect on serum LDL but do not cause undesirable effects.

Lasofoxifene (CP-336,156) is a selective estrogen receptor modulator (agonist/antagonist). It has been shown to have similar therapeutic effects in bone and LDL levels to estradiol but without the uterine-stimulating effects associated with estradiol therapy. Ke H.Z. (1998) Endocrinology 139(4):2068-2076 and Roasti, R.L. (1998) J. Med. Chem. 41(16):2928-2931. It also has been shown to prevent bone loss in ovariectomized rats and postmenopausal women. Zhu Ke, H. (2000) Endocrinology 141(4):1338-1344. The latter study also reports that lasofoxifene decreased total serum cholesterol in female and male rats and did not affect prostate in the male rats. Thus, there is an established therapeutic benefit for the oral administration of lasofoxifene.

In certain situations, however, oral administration of drugs is unsatisfactory. For drugs with short half lives require frequent dosing (2 to 4 times daily), may lead to inadequate compliance by the patient. Second, the short plasma half life of the drug and frequent dosing regimen result in "peaks" and "valleys" in the plasma concentration profile, which increases the likelihood of adverse side effects associated with the peak concentration as well as lapse of therapeutic effectiveness toward the end of the dosing interval. Third, the potential effect of hepatic first pass metabolism associated with oral administration could lead to poor bioavailibility of the drug. Thus, an effective and consistent drug delivery system that overcomes these disadvantages would be far advantageous.

Transdermal delivery of drugs provides many advantages over conventional oral administration. Advantages of transdermal systems include convenience, uninterrupted therapy, improved patient compliance, reversibility of treatment (by removal of the system from the skin), elimination of "hepatic first pass" effect, a high degree of control over blood concentration of the drug, and improved overall therapy.

DISCLOSURE OF THE INVENTION

The present invention to provide methods, pharmaceutical formulations, and devices for the transdermal delivery of 5-substituted-6-cyclic-5,6,7,8,-tetrahydronaphthalene2-ol compounds ("lasofoxifene" or "CP-336,156") and pharmaceutically acceptable salts thereof. The invention also provides transdermal compositions of CP-336,156 or its salts dissolved or dispersed in a suitable carrier vehicle, optionally containing permeation enhancers and other excipients. The carrier vehicle may be a pressure sensitive adhesive, polymeric reservoir, or a fluid of controlled viscosity. The carrier vehicle may be contained in a device for purposes of holding the composition against the skin surface. Such devices may be in the form of matrix patches (drug in adhesive) or reservoir patches (drug in a liquid or polymeric reservoir with peripheral, in-line, or over-layed pressure sensitive adhesive). Further provided by this invention are methods for treating pathologies associated with the binding of lasofoxifene with the human estrogen receptor-alpha. For example, the invention formulations and devices are useful to treat or prevent bone loss, obesity, breast cancer, endometriosis, cardiovascular disease and prostatic disease.

MODES FOR CARRYING OUT THE INVENTION

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used in the specification and claims, the singular form "a," "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a cell" includes a plurality of cells, including mixtures thereof.

As used herein, the term "comprising" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives, and the like. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the compositions of this invention. Embodiments defined by each of these transition terms are within the scope of this invention.

As used herein, the term "lasofoxifene" is synonymous with "CP-336,156" and "5-substituted-6-cyclic-5,6,7,8,-tetrahydronaphthalene2-ol" and pharmaceutical acceptable salts thereof. The preparation of lasofoxifene and its pharmaceutical acceptable salts is disclosed in U.S. Patent No. 5,552,412, incorporated herein by reference. The term "lasofoxifene" intends the compounds and formulations disclosed in U.S. Patent No. 5,552,412.

As used herein, the terms "enhancement", "penetration enhancement" or "permeation enhancement" mean an increase in the permeability of a biological membrane (i.e. skin or mucosa) to a drug, so as to increase the rate at which the drug permeates through the membrane. "Permeation enhancer," "enhancer," "penetration enhancer," or similar term means a material that achieves such permeation enhancement, and an "effective amount" of an enhancer means an amount effective to enhance penetration through the skin or mucosa of a selected agent to a selected degree.

The enhanced permeation as effected though the use of such enhancers can be observed, for example, by measuring the rate of diffusion of the drug through animal or human skin using a diffusion cell apparatus. Such a diffusion cell is described by Merritt et al., Diffusion Apparatus for Skin Penetration, 1 J. of Controlled Release 61 (1984), incorporated herein by reference.

As used herein, "transdermal" or "percutaneous" delivery means delivery of a drug by passage into and through the skin or mucosal tissue. Hence the terms "transdermal" and "transmucosal" are used interchangeably unless specifically stated otherwise. Likewise the terms "skin," "derma," "epidermis," "mucosa," and the like shall also be used interchangeably unless specifically stated otherwise.

By "effective amount" of a drug or permeant is meant a nontoxic but sufficient amount of a compound to provide the desired local or systemic effect. An "effective amount" of permeation enhancer as used herein means an amount selected so as to provide the desired increase in membrane permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug.

By "drug delivery system," "drug/enhancer composition," or any similar terminology is meant a formulated composition containing the drug to be transdermally delivered in combination with a penetration enhancer. Other pharmaceutically acceptable materials or additives can also be contained in the drug/enhancer composition, such as a diluent, skin-irritation reducing agent, carrier or vehicle, excipient, plasticizer, emollient, or other additive and mixtures thereof provided that such additives do not materially affect the basic and novel characteristics of the matrix patch.

By the term "matrix," "matrix system," or "matrix patch" is meant an active permeant or drug dissolved or suspended in a biocompatible polymeric phase, preferably a pressure sensitive adhesive, that can also contain other ingredients or in which the enhancer is also dissolved or suspended. This definition is meant to include embodiments wherein such polymeric phase is laminated to a pressure sensitive adhesive or used with an overlay adhesive. A matrix system usually and preferably comprises an adhesive layer having an impermeable film backing laminated onto the distal surface thereof and, before transdermal application, a release liner on the proximal surface of the adhesive. The film backing protects the polymeric phase of the

matrix patch and prevents release of the drug and/or enhancer to the environment. The release liner functions similarly to the impermeable backing, but is removed from the matrix patch prior to application of the patch to an application situs. Matrix patches are known in the art of transdermal drug delivery to routinely contain such backing and release liner components, and matrix patches according to the present invention should be considered to comprise such backing and release liner or their functional equivalents. U.S. Pat. No. 5,122,383 (incorporated herein by reference) describes such backing and release liner. A matrix system therefore is a unit dosage form of a drug composition in a polymeric carrier, also containing the enhancer and other components which are formulated for maintaining the drug composition in the polymeric layer in a drug transferring relationship with the derma, i.e. the skin or mucosa. A matrix patch is distinguished from a "liquid reservoir patch," wherein an active permeant or drug is dissolved in a gelled liquid contained in an occlusive device having an impermeable back surface and an opposite surface configured appropriately with a permeable membrane and adhesive for transdermal application. e.g., U.S. Pat. No. 4,983,395, incorporated herein by reference.

As used herein, "application situs" means a site suitable for topical application with or without the means of a device, patch, or dressing, e.g. behind the ear, on the arm, back, chest, abdomen, leg, top of foot, etc.

A "composition" is intended to mean a combination of active agent and another compound or composition, inert (for example, a detectable agent or label) or active, such as an adjuvant.

A "pharmaceutical composition" is intended to include the combination of an active agent with a carrier, inert or active, making the composition suitable for diagnostic or therapeutic use *in vitro*, *in vivo* or *ex vivo*.

As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see Martin REMINGTON'S PHARM. SCI., 15th Ed. (Mack Publ. Co., Easton (1975)).

A "subject" is a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, murines, simians, humans, farm animals, sport animals, and pets.

To "treat" means to alleviate the symptoms or modify clinical manifestation of a disease or condition. To "prevent" means to delay or minimize the symptoms or clinical manifestations of a disease or condition. For the purpose of this invention, diseases or conditions suitably treated by this invention are those associated with the binding of the estrogen receptor by its natural ligand. Such conditions include, but are not limited to obesity, breast cancer, osteoporosis, endometriosis, cardiovascular disease, prostatic disease, ovulation, and blood cholesterol levels, especially LDL serum levels.

In its most basic form, this invention provides a transdermal formulation of a drug reservoir containing an effective amount of lasofoxifene and/or a pharmaceutically acceptable salt thereof. In an alternative embodiment, the formulation optionally includes an effective amount of a drug permeation enhancer and/or a cell-envelope disordering compound. Examples of cell-envelope disruptors include but are not limited to, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monooleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate or sorbitan esters. See U.S. Patent No. 5,626,866, incorporated herein by reference. In addition formulation may also contain one or more skin permeation enhancers such as triacetin. Examples of enhancers that may be used, without limitation, include saturated and unsaturated fatty acids and their esters, alcohols, monoglycerides, acetate, diethanolamides and N, N-dimethylamides, such as oleic acid, propyl oleate, isopropyl myristate, glycerol monooleate, glycerol monolaurate, methyl laurate, lauryl alcohol, lauramide diethanolamide and combinations thereof. Saturated and unsaturated sorbitan esters, such as sorbitan monooleate and sorbitan monolaurate may also be used.

In one aspect, the drug reservoir is an adhesive matrix which can be water based or solvent based. The adhesive matrix may have the additional characteristic of being pressure sensitive suitable for long-term contact with the skin. Such adhesives must be physically and chemically compatible with lasofoxifene and optionally the enhancer, and with any carriers and/or vehicles or other additives incorporated into the

drug/enhancer composition. Suitable adhesives for use in the matrix patches include acrylic adhesives including cross-linked and uncross-linked acrylic copolymers; vinyl acetate adhesives; natural and synthetic rubbers including polyisobutylenes, neoprenes, polybutadienes, and polyisoprenes; ethylenevinylacetate copolymers; polysiloxanes; polyacrylates; polyurethanes; plasticized weight polyether block amide copolymers, and plasticized styrene-rubber block copolymers

Suitable pressure sensitive adhesives include polysiloxanes, polyacrylates, polyisobutylene, and the like. These pressure sensitive adhesive polymers are very hydrophobic and are typically purchased as solutions of polymer dissolved in organic solvents. The drug and selected excipients, if any, are directly incorporated into the organic-solvent-based pressure sensitive adhesive solution, mixed, cast as a thin film, and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients. It is well known in the art that the drug has to be hydrophobic to be incorporated into the organic-solvent-based, hydrophobic adhesive. Hydrophilic salt forms of a drug are generally not compatible with such organic-solvent-based pressure sensitive adhesives and have to be converted to the more hydrophobic free acid or free base form for incorporation into the organic-solvent-based, hydrophobic adhesive.

Water-based pressure sensitive adhesives are also commercially available. These water-based adhesives are formulated as emulsions wherein the hydrophobic pressure sensitive adhesive polymer is dispersed in water with the help of surfactants. Such water-based adhesives provide inherent advantages of safety and reduced environmental problems over solvent-based pressure sensitive adhesives, because the carrier is water and not an organic solvent. The water-based adhesives are widely used in the manufacture of medical tapes and bandages, and provide excellent skin adhesion.

U.S. Patent Nos. 5,985,317; 5,783,208; 5,780,050; 5,626,866; 5,460,820 and 4,983,395 describe various polymeric transdermal matrix formulations. The disclosures of these patents are incorporated by reference to more fully describe the state of the art.

Alternatively, the drug reservoir is a liquid reservoir as described in U.S. Patent No. 5,662,925; 4,829,224 or 4,983,395, incorporated herein by references. Alternative embodiments known in the art are described in U.S. Patent No. 4, 829,224; 4,849,224 and 4,983,395, also incorporated by reference.

The matrix patch can further comprise various additives in addition to the polymer layer containing lasofoxifene, and optionally an enhancer, that are the fundamental components of the transdermal drug delivery system. These additives are generally those pharmaceutically acceptable ingredients that are known in the art of drug delivery and, more particularly, in the art of transdermal drug delivery provided that such additive ingredients do not materially alter the basic and novel characteristics of the matrix patch. For example, suitable diluents can include mineral oil, low molecular weight polymers, plasticizers, and the like. Many transdermal drug delivery formulations have a tendency to cause skin irritation after prolonged exposure to the skin, thus addition of a skin irritation reducing agent aids in achieving a composition that is better tolerated by the skin. A preferred skin irritation reducing agent is glycerin, U.S. Pat. No. 4,855,294, incorporated herein by reference. It is however notable that other so-called acceleration promoters or permeation enhancer components such as solvents and cell-envelope disordering compounds are not necessary in the present invention.

The drug reservoir containing lasofoxifene may be embodied in various types of structures known in the transdermal drug delivery art. For instance, the drug reservoir, which is the most important component of the device, may comprise a simple matrix of a subsaturated solution of lasofoxifene in the carrier or be in the form of a fibrous body impregnated with the subsaturated solution of lasofoxifene in the carrier. In addition to the reservoir, the device includes means for maintaining the reservoir in drug delivery communication with the skin. Such means include a carrier which is also an adhesive, a separate basal adhesive layer underlying the reservoir, a peripheral ring of adhesive that is interconnected to the reservoir, an adhesive overlay for the reservoir, and straps. Preferably the means is either an adhesive carrier or a separate underlying adhesive layer. Preferably the device is in the form of a laminated composite.

These devices may be manufactured by conventional techniques used in the transdermal drug delivery device art. For instance the drug and carrier may be mixed in the desired proportions to form a homogeneous mix and cast or otherwise applied to a backing layer, followed by lamination to a release liner layer. If a separate basal adhesive layer is desired, it may be cast onto the release liner layer prior to such lamination.

In use, the matrix patch may contain a distal backing laminated on the polymer layer. The distal backing defines the side of the matrix patch that faces the environment, i.e., distal to the skin or mucosa. The backing layer functions to protect the matrix polymer layer and drug/enhancer composition and to provide an impenetrable layer that prevents loss of drug to the environment. Thus, the material chosen for the backing should be compatible with the polymer layer, drug, and enhancer, and should be minimally permeable to any components of the matrix patch. Advantageously, the backing can be opaque to protect components of the matrix patch from degradation from exposure to ultraviolet light. Further, the backing should be capable of binding to and supporting the polymer layer, yet should be pliable to accommodate the movements of a person using the matrix patch. Suitable materials for the backing include metal foils, metalized polyfoils, composite foils or films containing polyester such as polyester terephthalate, polyester or aluminized polyester, polytetrafluoroethylene, polyether block amide copolymers, polyethylene methyl methacrylate block copolymers, polyurethanes, polyvinylidene chloride, nylon, silicone elastomers, rubber-based polyisobutylene, styrene, styrene-butadiene and styrene-isoprene copolymers, polyethylene, and polypropylene. A thickness of about 0.0005 to 0.01 inch is preferred. The release liner can be made of the same materials as the backing, or other suitable films coated with an appropriate release surface.

The drug reservoirs are applied to the application situs and the drug diffuses through the dermis. This invention also provides the drug reservoir, as described herein, and a means for adhering the reservoir to the application situs. Examples of such devices are described above and include an adhesive matrix containing the drug, a backing layer and a releasable liner. See also U.S. Patent Nos. 5,164,190 and 5,985,317.

For example, such a device includes a laminated composite of a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk; an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining; the reservoir therebetween that contains the formulation of this invention; the peel seal disc underlying an active agent-permeable membrane; a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer; an adhesive overlay having a central portion overlying the backing

layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

The above pharmaceutical formulations, drug reservoirs and devices are useful to treat or prevent a disorder associated with estrogen disregulation in a subject by contacting any of the pharmaceutical formulation, the drug reservoir or the device with the application situs of the subject.

This invention further provides use of an effective amount of lasofoxifene for the preparation of a transdermal medicament for the treatment or prevention of a disorder associated with estrogen disregulation.

EXPERIMENTAL METHODOLOGY

Adhesive Matrix Preparation

Pressure sensitive adhesive matrix systems prepared according to the teachings of U.S. Patent No. 5,952,000, incorporated herein by reference. First, the solids content of the adhesive solution (water or organic solvent based) was determined by placing a known weight of solution in a weighed aluminum dish and evaporating the solvents overnight in a 70. degree. C. convection oven. The solid adhesive content of the solution was calculated by dividing the adhesive solid weight after drying by the initial total solution weight. Next, a weighed quantity of adhesive solution was added to a glass bottle and the drug substance, permeation enhancer, and other excipients were weighed and added to the adhesive solution in a quantity necessary to achieve the desired dry matrix film composition. The solution containing the adhesive polymer, drug substance, and other excipients as necessary was then mixed overnight. After mixing, approximately 8 ml of the solution was dispensed on a silanized polyester release liner and film cast using a casting knife with a gap size appropriate to achieve a final dried thickness of approximately 0.05 mm. The cast film was dried in a 70.degree. C. convection oven until all solvents had evaporated to yield a dried matrix (15 minutes for organic solvent based adhesives, 30 minutes for water emulsion based adhesives). Finally, an 0.08 mm thick occlusive polyethylene backing film was laminated onto the

dried adhesive matrix, and these systems were then used to conduct in vitro skin flux experiments as described below.

Reservoir or Free Form Hydroalcoholic Gel Preparation

Hydroalcoholic gels were prepared on a 10 ml scale as follows. Ethyl alcohol (190 proof ethanol), water, glycerin, enhancer and drug were combined in the appropriate proportions and mixed for several hours. The gelling agent (hydroxypropylcellulose) was added and the solution was mixed briefly at high shear, then mixed at low shear until a gel was formed.

Skin Flux Studies

In vitro skin flux studies were conducted using human cadaver epidermal membrane in modified Franz non-jacketed diffusion cells. The epidermal membrane (stratum corneum and epidermis) was separated from whole skin (epidermal membrane and dermis) by the method of Kligman and Christopher (Arch. Dermatol. 88:702 (1963)). This method involves the exposure of the full-thickness skin to water at 60.degree C. for a time period of 60 seconds. After this period, the epidermal membrane was gently peeled off the dermis and stored for later use in aluminum foil at -5.degree. C.

Prior to each permeation experiment with a matrix system, the matrix system was cut into a circular sample of 0.7 cm.sup.2 area and the silanized release liner was removed. The adhesive was affixed to the stratum corneum side of the thawed epidermal membrane which was then cut to an appropriate size and clamped in place between the two halves of the diffusion cell with the stratum corneum facing the donor compartment. The receiver compartment was filled with water or an aqueous solution appropriate to maintain sink conditions for the drug. All receiver solutions included 0.02% (w/w) sodium azide (NaN_3) to inhibit bacterial growth. The diffusion cell was placed in a temperature controlled circulating water bath calibrated to maintain the surface temperature of the skin at 32.degree. C. The receiver compartment was constantly stirred by a magnetic stir-bar in the receiver compartment agitated by a magnetic stirring module placed under the water bath.

Permeation experiments with hydroalcoholic gels were performed using finite occluded doses. The occluded dose is an appropriate in vitro model for the application of a transdermal patch drug delivery system containing a liquid or gel reservoir.

Occluded dosing experiments were set-up according to the following procedure. Prior to skin permeation experiments, the epidermal membrane was cut to an appropriate size and placed between the two halves of the diffusion cell with the epidermal side facing the receiver compartment. The receiver compartment was filled with an appropriate solution then the diffusion cell was placed in a circulating water bath calibrated to maintain the temperature of the skin surface at 32.degree. C. and allowed to hydrate overnight. After hydration, a sample of the gel (75 .mu.l) was pipetted into a cavity created by placing a polyethylene washer over the stratum corneum surface. This cavity was covered with an occlusive backing film which was clamped in place.

Permeation experiments with aqueous solutions were performed using pre-saturated drug solutions containing excess drug solid (infinite dose). Prior to skin permeation experiments, the epidermal membrane was allowed to hydrate over night as described above. After hydration a well mixed sample of the aqueous solution (1 ml) was pipetted into the donor compartment formed by clamping a glass lid above the stratum corneum surface. The glass lid was then sealed with a Teflon.RTM. lined polypropylene cap.

The following sampling procedure was used for all dosage forms. At predetermined sampling time points, the entire contents of the receiver compartment were collected for drug quantitation and the receiver compartment was filled with fresh solution, taking care to eliminate any air bubbles at the skin/solution interface. The cumulative amount of drug permeated per unit area at any time.

The following examples are intended to illustrate, not limit the invention.

Example 1

A transdermal matrix formulation was prepared with a solvent-based acrylic pressure sensitive adhesive (TSR 58; Sekisui Chemical Co., Osaka, Japan), triacetin

(Eastman), and CP-336,156 in the proportions 84/10/6% w/w. Results of *in vitro* skin flux experiments using this matrix formulation are summarized in Table 1.

Table 1

Skin Source	No. of Diffusion Cells	Average Daily Flux of CP-336,156 over 7 Days, llg/cm2/day
Skin IA	7	5.5 ± 3.4
Skin lB	4	5.7 ± 0.8
Skin 1C	8	9.2 ± 2.9
Skin 1D	4	13.4 ± 7.8
Skin 1E	4	10.2 ± 3.4
Skin 1F	4	5.1 ± 1.1
Skin 1G	4	11.4 ± 2.4
All Skins	Mean ±SEM	8.6 ± 1.2

The results in Table 1 illustrate that CP-336,156 may be incorporated into a matrix patch containing triacetin as a skin permeation enhancer. Transdermal delivery of CP-336,156 from this formulation can be maintained for at least 7 days.

Example 2

A transdermal matrix formulation was prepared in a water-based acrylic pressure sensitive adhesive (Morstik 214, Morton, Greenville, SC) with CP-336,156 tartrate salt at a concentration of 3% w/w. A permeation enhanced formulation was prepared with 3%w/w CP-336,156 tartrate salt and 1.5%w/w sodium lauroyl glycolate (R.I.T.A. Corporation, Woodstock, IL) in the same adhesive. Results of *in vitro* skin flux experiments using these datrix formulations are summarized in Table 2.

Table 2

Skin Source	No. of Diffusion Cells	Cumulative Permeation of CP-336,156 over 24 Hours, ug/cm^2/24h		Enhancement Factor Q24 enhanced/ Q24 unenhanced
		Unenhanced	Enhanced 1.5% w/w NaLG	
Skin 2A	5	0.13 ± 0.09	0.30 ± 0.12	2.28
	5	2.70 ± 1.08	3.51 ± 0.93	1.30
	5	0.15 ± 0.09	0.46 ± 0.16	3.06
All Skins Mean ± SEM		**0.99 ± 0.85**	**1.42 ± 1.05**	**2.21 ± 0.51**

The results in Table 2 illustrate that salts of CP-336,156 may be incorporated into an adhesive matrix patch. The mean enhancement factor was 2.2 illustrating that effective amounts of a permeation enhancer may also be incorporated in these matrix systems.

Example 3

A transdermal liquid reservoir formulation was prepared with a solvent composition of USP alcohol (EtOH), water (H20), glycerin (Gly), glycerol monooleate (GMO), and methyl laurate (ML) in the proportions 50/15/30/2.5/2.5% v/v. This mixture was a clear solution. CP-336,156 tartrate salt was added at a concentration of 2 mg/ml and the formulation was gelled with 30 mg/g hydroxypropylmethylcellulose (Methocel® E10M, Dow Chemical). Results of *in vitro* skin flux experiments on this formulation are summarized in Table 3.

Table 3

Skin Source	No. of Diffusion Cells	Average Daily Flux of CP-336,156 over 7 Days, ug/cm^2/day
Skin 3A	8	17 4 ± 7.7
Skin 3B	4	15.3 ± 8.7
Skin 3C	8	23.9 ± 11.0
Skin 3D	4	27.9 ± 2.2
Skin 3E	4	21.2 ± 9.9
Skin 3F	4	15.4 ± 7.2
Skin 3G	4	30.3 ± 4.9
All Skins	Mean ±SEM	21.6 ± 2.3

The results in Table 3 illustrate that salts of CP-336,156 may be incorporated into a liquid reservoir patch containing a lower alkanol and skin permeation enhancers. Transdermal delivery of CP-336,156 from this formulation can be maintained for at least 7 days.

Example 4

A transdermal liquid reservoir formulation was prepared with a solvent composition of USP alcohol (EtOH), water (H20), glycerin (Gly), glycerol monooleate (GMO), and lauryl alcohol (LA) in the proportions 30/38/30/1/1 % v/v. This mixture is a cloudy two-phase dispersion. CP-336,156 tartrate salt was added at a concentration of 6 mg/ml and the formulation was gelled with either 30 mg/g hydrophobically-modified hydroxyethylcellulose (Natrosol® Plus 330CS, Aqualon). Results of *in vitro* skin flux experiments using this liquid reservoir formulation are summarized in Table 4.

Table 4

Skin Source	No. of Diffusion Cells	Average Daily Flux of CP-336,156 over 6 Days, ug/cm^2/day
Skin 4A	5	42.4 ± 15.5
Skin 4B	5	36.3 ± 5.2
Skin 4C	5	36.2 ± 14.9
All Skins	Mean ±SEM	38.3 ± 3.3

The results in Table 4 illustrate that transdermal delivery of CP-336,156 may be achieved from liquid reservoir formulations which are two-phase dispersions.

Example 5

Transdermal liquid reservoir formulations were prepared with a solvent composition of USP alcohol (EtOH), isopropyl alcohol (IPA), water (H20), glycerin (Gly) 26.25/8.75/35/30% v/v. Permeation enhanced formulations were prepared using glycerol monooleate at concentrations of 0.03%, 0.06%, and 0.12% v/v, with the water reduced to compensate for the added enhancer. The formulations at 0%, 0.03%, and 0.06% GMO were clear solutions, while the formulation at 0.12% GMO was a cloudy dispersion. CP-336,156 tartrate salt was added at a concentration of 6 mg/ml and the formulations were gelled with 30 mg/g hydroxypropylmethylcellulose (Methocel® EIOM, Dow Chemical). Results of *in vitro* skin flux experiments using these formulations are summarized in Table 5.

Table 5

Skin Source	Unenhanced 0% GMO	0.03% GMO		0.06% GMO		0.12% GMO	
	Average Daily flux over 7 Days, ug/cm^2/24h Mean ± SD*	**Average Daily flux over 7 Days,** ug/cm^2/24h Mean ± SD*	E	Average Daily flux over 7 Days, ug/cm^2/24h Mean ± SD*	E	Average Daily flux over 7 Days, Ug/cm^2/24h Mean ± SD*	E
Skin 5A	6.4 ± 2.3	7.1 ± 1.8	1.12	11.6 ± 4.2	1.81	16.8 ± 2.1	2.62
Skin 5B	17.4 ± 26.4	69.5 ± 23.8	3.99	74.9 ± 12.8	4.30	85.2 ± 13.0	4.89
Skin 5C	11.6 ± 4.4	22.4 ± 3.5	1.93	20.3 ± 5.4	1.74	23.6 ± 5.3	2.03
All Skins	11.8 ± 3.2	33.0 ± 18.8	2.34 ± 0.37	35.6 ± 19.8	2.62 ± 0.43	41.8 ± 21.8	3.18 ± .36

* n=2-5 diffusion cells per skin source.

E= Enhancement Factor = Average Daily Flux from Enhanced Formulation/Average Daily Flux from Unenhanced Control

The results in Table 5 Show the addition of even very small amounts of glycerol monooleate (0.03% v/v) to a liqmd reservoir vehicle containing lower alkanols substantially increases transdermal flux of CP-336,156. Thesc results also show that the permeation enhancement the permeation enhancement is roughly proportional to the concentration of glycerol monooleate in this range from 0.03% to 0.12%.

Example 6

Transdermal liquid reservoir formulations were prepared with a solvent composition of EtOH/IPA/Gly/GMO 26.25/8.75/34.94%/30.00%/0.06%% v/v. CP-336,156 tartrate salt was added at 6 mg/ml and the formulation was gelled with 30 mg/g hydroxypropylmethylcellulose (Methocel® E10M, Dow Chemical). Liquid reservoir patches with 3 cm^2 active area were manufactured with this formulation and tested for primary dermal irritation in albino rabbits.

Each of six rabbits was exposed to an active patch (3 cm^2 active area). After 24 hours, the patches were removed and the sites were scored for erythema and edema at 1 and 72 hours after patch removal. The erythema and edema scores at 1 and 72 hours after removal were then averaged to give a Primary Dermal Irritation Index (PDI). PDI values were 0.3, which would classify this formulation as a barely perceptible irritant using this widelyaccepted animal model.

The preceding discussion and examples are intended merely to illustrate the art. As is apparent to one of skill in the art, various modifications can be made to the above without departing from the spirit and scope of this invention.

CLAIMS

What is claimed is:

1. A transdermal formulation comprising a drug reservoir and an effective amount of lasofoxifene and pharmaceutically acceptable salts thereof.

2. The transdermal formulation of claim 1, further comprising an effective amount of a drug permeation enhancer.

3. A transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene and pharmaceutically acceptable salts thereof.

4. The transdermal formulation of claim 3, wherein the adhesive matrix is a solvent based pressure sensitive adhesive matrix.

5. The transdermal formulation of claim 3, wherein the adhesive matrix is a water based pressure sensitive adhesive matrix.

6. A transdermal formulation comprising a liquid reservoir drug reservoir and an effective amount of lasofoxifene and pharmaceutically acceptable salts thereof.

7. A transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene and pharmaceutically acceptable salts thereof.

8. The transdermal formulation of any of claims 3 to 7, further comprising an effective amount of a drug permeation enhancer.

9. The transdermal formulation of claim 8, wherein the drug permeation enhancer is an effective amount of cell-envelope disordering compound.

10. The transdermal formulation of claim 9, wherein the cell-envelope disordering compound comprises an effective amount of a lower alkanol.

11. The transdermal formulation of claim 8, wherein the drug permeation enhancer comprises an effective amount of a lower alkanol and an effective amount of glycerol monooleate.

12. The transdermal formulation of claim 11, wherein the effective amount of glycerol monooleate is about greater than or equal to 0.01 % w/w.

13. A transdermal device comprising a means for adhering the drug reservoir to the application situs and the pharmaceutical formulation of any of claims 3 to 7.

14. A device for administering an active agent to the skin or mucosa of an individual comprising a laminated composite of:

a. a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk;

b. an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer, and underlying the backing layer, the backing layer and membrane defining;

c. the reservoir therebetween that contains the formulation of claim 1;

d. the peel seal disc underlying an active agent-permeable membrane;

e. a heat seal about the periphery of the peel seal disc, the active agent-permeable membrane and the backing layer;

f. an adhesive overlay having a central portion overlying the backing layer and a peripheral portion that extends beyond the periphery of the peel seal disc; and

g. a removable release liner underlying the peripheral portion of the adhesive overlay and the peel seal disc.

15. A method for treating or preventing a disorder associated with estrogen deficiency or disdregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of claim 1.

16. A method for treating or preventing a disorder associated with estrogen deficicncy or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of claim 2.

17. A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of any of claims 3 to 7.

18. A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with the device of claim 14.

19. A method for treating or preventing a disorder associated with estrogen deficiency in a subject comprising contacting a dermal situs of the subject with the device of claim 14.

20. Use of an effective amount of lasofoxifene for the preparation of a transdermal medicament for the treatment or prevention of a disorder associated with estrogen deficiency.

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权利要求书 3 页 说明书 16 页

[54] 发明名称 LASOFOXIFENE 的经皮转运

[57] 摘要

本发明涉及提供经皮转运 5 - 取代 - 6 - 环 - 5，6，7，8，- 四氢萘 2 - 醇化合物（"lasofoxifene"或"CP - 336，156"）及其药学上可接受的盐的方法、药剂和装置。本发明还提供溶解或分散于适宜的载体赋形剂中的 CP - 336，156 或其盐的经皮组合物，该载体赋形剂可任选地含有渗透增强剂和其它赋形剂。该载体赋形剂可以是压敏粘合剂、聚合贮库或受控粘度的流体。该载体赋形剂可被包含在用于将该组合物保持在皮肤表面的装置中。这些装置可以是基质贴片（粘合剂中的药物）或贮库贴片（在液体或聚合贮库中的具有外周和、并行或层叠压敏粘合剂的药物）。本发明还提供了用于治疗与 lasofoxifene 和人类雌激素受体 - α 结合有关的病变的方法。例如，本发明的制剂和装置用于治疗和预防骨损失、肥胖、乳癌、子宫内膜异位、心血管疾病和前列腺疾病。

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1. 一种经皮制剂，包含药物贮库和有效量的 lasofoxifene 及其药学上可接受的盐。

2. 权利要求 1 的经皮制剂，进一步包含有效量的药物渗透增强剂。

3. 一种经皮制剂，包含粘合剂药物基质贮库和有效量的 lasofoxifene 及其药学上可接受的盐。

4. 权利要求 3 的制剂，其中该粘合剂基质为基于溶剂的压敏粘合剂基质。

5. 权利要求 3 的经皮制剂，其中该粘合剂基质为基于水的压敏粘合剂基质。

6. 一种经皮制剂，包含液体药物贮库和有效量的 lasofoxifene 及其药学上可接受的盐。

7. 一种经皮制剂，包含游离形式的水醇凝胶和有效量的 lasofoxifene 及其药学上可接受的盐。

8. 权利要求 3-7 之任一经皮制剂，进一步包含有效量的药物渗透增强剂。

9. 权利要求 8 的经皮制剂，其中该药物渗透增强剂为有效量的细胞膜扰乱化合物。

10. 权利要求 9 的经皮制剂，其中该细胞膜扰乱化合物包含有效量

的低级链烷醇。

11. 权利要求 8 的经皮制剂，其中该药物渗透增强剂包含有效量的低级链烷醇和有效量的甘油一油酸酯。

12. 权利要求 11 的经皮制剂，其中该有效量的甘油一油酸酯约大于或等于 0.01 % w/w。

13. 一种经皮装置，包括用于将药物贮库粘着到应用部位的器具和权利要求 3-7 之任一药剂。

14. 一种用于将活性剂给药于个人的皮肤或粘膜上的装置，包括如下的层压的复合物：

a. 限定贮库的上部并延伸至剥离密封圆盘外周的衬背层；

b. 活性试剂渗透膜，其延伸到该剥离密封圆盘和衬背层外周，并在该衬背层下方，衬背层和薄膜限定；

c. 其间的含有权利要求 1 制剂的贮库；

d. 在活性试剂渗透膜下方的剥离密封圆盘；

e. 在该剥离密封圆盘、该活性试剂渗透膜和该衬背层外周的热封；

f. 具有一个层叠在该衬背层上的中心部分和延伸出剥离密封圆盘外周的外周部分的粘合剂层叠物；和

g. 在该粘合剂层叠物的外周部分和剥离密封圆盘下可移去的防粘衬里。

15. 一种治疗或预防受治者的与受试者雌激素缺乏或失调有关的病症的方法，包括使受试者的应用部位与权利要求 1 的有效药剂接触。

16. 一种治疗或预防受试者的与雌激素缺乏或失调有关的病症的方法，包括使受试者的应用部位与权利要求 2 的有效药剂接触。

17. 一种治疗或预防受试者的与雌激素缺乏或失调有关的病症的方法，包括使受试者的应用部位与权利要求 3-7 之任一的有效药剂接触。

18. 一种治疗或预防受试者的与雌激素缺乏或失调有关的病症的方法，包括使受试者的应用部位与权利要求 14 的装置接触。

19. 一种治疗或预防受试者的与雌激素缺乏有关的病症的方法，包括使受试者的皮肤部位与权利要求 14 的装置接触。

20. 有效量的 lasofoxifene 用于制备治疗或预防与雌激素缺乏有关的经皮药物的用途。

LASOFOXIFENE 的经皮转运

相关申请的交叉参考

根据 35U.S.C. §119(e)本申请要求 2000 年 6 月 1 日申请的美国临时申请序列号 60/208,789 的优先权。因此将该申请的内容引用至本说明书中作为参考。

技术领域

本发明涉及 lasofoxifene(5-取代-6-环-5,6,7,8,-四氢萘-2-醇)化合物的经皮转运。

发明背景

天然存在的表现出"动情"活性的雌激素和合成组合物用于各种治疗用途，如口服避孕、缓解绝经症状、预防受惊的或习惯性流产、缓解痛经、缓解机能障碍性子宫出血、帮助卵巢发育、治疗痤疮、减少妇女体毛的过度生长(多毛症)、预防心血管疾病、治疗骨质疏松、治疗前列腺癌、和抑制产后泌乳[Goodman 和 Gilman，治疗的药理基础(第 7 版) Macmillan 出版公司，1985，第 1421-1423 页]。因此，不断增长的兴趣在于发现新合成的组合物和以前已知的表现出动情性的化合物的新用途，即在雌激素应答组织中能够模仿雌激素的作用。从兴趣在于研制用于治疗人类疾病和特定病理学的症状的药理学观点来看，获得具有某种明确的雌激素样作用但避免了增生性副作用的化合物是非常重要的。例如，使用全活性雌激素大大改善了骨质疏松，一种骨不断变得脆弱的疾病；但是，由于认识到采用活性雌激素临床治疗的受治者的子宫癌的风险增加，长期用全活性雌激素治疗未受损妇女的骨质疏松在临床上是不明智的。雌激素是在预防妇女骨质疏松或绝经后骨损失中选择的试剂；它是唯一明确地减少骨折的治疗剂。但是，雌激素刺激子宫

并与子宫内膜癌风险增大有关。虽然认为通过同时使用孕激素减少子宫内膜癌的风险，但仍然担心使用雌激素增加乳癌的风险。

雌激素和雌激素样化合物还已表现为降低 LDL 血浆水平和升高有用的高密度脂蛋白(HDL's)。Black,等人的 EP 0605193A1。但是，长期用雌激素治疗波及多种病症，包括增加子宫癌和可能的乳癌的风险，这致使许多妇女避免这种治疗。最近提倡的治疗养生法，寻求减少癌症的风险，如给予孕激素和雌激素的组合，导致受治者经受不可接受的出血。而且,孕酮与雌激素的组合似乎减少降低雌激素作用的血清胆固醇。与雌激素治疗有关的显著的不期望作用证实需要开发治疗胆甾醇过多的替代疗法，这种疗法对血清 LDL 具有期望的作用，但并不导致不期望的作用。

Lasofoxifene (CP-336,156)为选择性雌激素受体调节剂(兴奋剂/拮抗剂)。它已在骨和雌二醇中 LDL 水平的表现类似的治疗作用，但不具有与雌二醇治疗相关的子宫刺激作用。Ke H.Z. (1998) 内分泌(Endocrinology) 139(4):2068-2076 和 Roasti, PT (1998)3. Med. Chem. 41(16):2928-2931。它还已表现为预防切除卵巢的大鼠和经绝后妇女的骨损失。Thu Ke, H. (2000) Endocrinology 141(4):1338-1344。后一研究还报道 lasofoxifene 减少了雌性和雄性大鼠的总血清胆固醇而并不影响雄性大鼠的前列腺。因此，lasofoxifene 的口服给药具有确定的治疗利益。

但是，在某些情况下，口服给药并不令人满意。半衰期短的药物要求频繁地服药(2-4 次每天)，可能使受治者不能充分地遵从。其次，药物的短血浆半衰期和频繁服药法导致血浆浓度曲线上的"峰"和"谷"，它增加了与峰浓度相关的副作用和服药间隙末期失效的可能性。第三，与口服有关的肝首次通过代谢可能导致不良的药物生物利用度。因此，克服这些缺陷的有效和一致的药物转运系统是非常有利的。

药物的经皮转运提供了相对于常规口服给药的许多优点。经皮系统的优点包括方便、连续治疗，改善的受治者遵从性，治疗可逆(通过从

皮肤上除去该系统），消除“肝首次通过”效应，高度控制血药浓度，和改善全面治疗。

发明公开

本发明提供用于经皮转运 5-取代-6-环-5,6,7,8,-四氢萘 2-醇化合物("lasofoxifene"或"CP-336,156")及其药学上可接受的盐的方法、药剂和装置。本发明还提供了溶解或分散在适宜的载体赋形剂、任选含有渗透增强剂和其它赋形剂中的 CP-336,156 或其盐的经皮组合物。该载体赋形剂可以是压敏粘合剂、聚合贮库或受控粘度的液体。该载体赋形剂可以包含在用于将该组合物保持在皮肤表面的装置内。这种装置可以是基质贴片(粘合剂中的药物)或贮库贴片(在具有外周的、并行（in-line）、层叠压敏粘合剂的液体或聚合贮库中的药物)。本发明还提供了治疗与 lasofoxifene 和人雌激素受体-α结合有关的病变的方法。例如本发明制剂和装置用于治疗和预防骨损失、肥胖、乳腺癌、子宫内膜异位、心血管疾病和前列腺疾病。

实施本发明的方式

在本发明的描述和权利要求中，根据下述的定义使用以下的术语。

在说明书和权利要求中，除非上下文明确说明，单数形式的“一”、“一个”和“该”包括复数的参考物。例如，术语“细胞”包括多个细胞，包括其混合物。

本文所用的术语“包括”意指组合物和方法包括所述的成分，但不排除其它。“基本上由……组成”用于定义组合物和方法时意指排除其它任何对组合有本质意义的成分。因此，基本由本文所定义的成分组成的组合物将不排除来自分离和纯化方法的痕量污染以及药学上可接受的载体如磷酸盐缓冲盐水、防腐剂等等。“由……组成”意指排除痕量以上的其它成分和本发明组合物给药的实质性方法步骤。每一种这些变换术语定义的实施方案在本发明的范围内。

本文所用的术语"lasofoxifene"为"CP-336,156"和"5-取代-6-

环-5,6,7,8,-四氢萘 2-醇"及其药学上可接受的盐的同义词。lasofoxifene 及其药学上可接受的盐的制备公开在美国专利号5,552,412，本文引用作为参考。术语"lasofoxifene"意指在美国专利号 5,552,412 中公开的化合物和制剂。

本文所用的术语"增强"、"渗透增强"("penetration enhancement"或 "permeation enhancement")意指生物膜（即皮肤或粘膜）对药物渗透性的增加，从而增大药物渗透穿过薄膜的速率。"渗透增强剂"、"增强剂"或类似术语指实现这种渗透增强的物质，而"有效量"的增强剂意指有效增强选择的药物渗透通过皮肤或粘膜至选择程度的数量。例如使用扩散细胞仪测定药物扩散通过动物或人皮肤可以观察到使用这种增强剂引起渗透性增强。Merritt 等人，皮肤渗透的扩散仪(Diffusion Apparatus for Skin Penetration)，1 控释杂志(J. of Controlled Release)61 (1984)描述了这种扩散细胞，本文引用作为参考。

本文所用的"经皮"（"transdermal"或"percutaneous"）转运意指通过通道进入和穿透皮肤或粘膜组织的药物转运。因此，除非另外指出，术语"经皮"和"经粘膜"可互换使用。 类似地，除非另外指出，术语"皮肤"、"真皮"、"表皮"、"粘膜"等还可互换使用。

"有效量"的药物或渗透意指非毒性但足量的化合物以提供期望的局部或系统作用。本文所用的"有效量"的渗透增强剂意指选择用量以增大膜渗透性以及相应的渗透深度、给药速率和药物用量。

"药物转运系统"、"药物增强剂组合物"或任何类似术语意指与渗透增强剂组合的含有经皮转运药物的制剂组合物。其它药学上可接受的物质或添加剂还可以包含在该药物/增强剂组合物中，如稀释剂、皮肤光照还原剂、载体或赋形剂、赋形剂、增塑剂、软化剂或其它添加剂及其混合物，如果这种添加剂并不实质性影响该基质贴片的基本和新特征。

术语"基质"、"基质系统"或"基质贴片"意指一种溶解或悬浮在生物相容性聚合相中的活性渗透剂或药物，优选压敏粘合剂，它还可以含有其它成分或其中还溶解或悬浮有增强剂。这种定义意指包括聚合相层叠

至压敏粘合剂上或采用层叠粘合剂的实施方案。基质系统通常和优选包含具有层叠于其远侧表面上的不可渗透薄膜衬背和在经皮给药之前层叠在该粘合剂近中心表面的释放衬垫。薄膜衬背保护基质贴片的聚合相并防止药物和/或增强剂释放到外周。释放衬垫的功能类似于不可渗透衬背，但在应用于应用部位之前将其从基质贴片上移去。在经皮药物转运的技术中已知基质贴片通常包含这些衬背和释放衬垫组成，而考虑本发明的基质贴片应该包含这些衬背和释放衬垫或其功能等同物。美国专利号5,122,383（本文引用作为参考）描述了这种衬背和释放衬垫。因此基质系统为在聚合载体中的药物组合物单元剂型，还含有增强剂和其它制备用于将药物组合物保持在与真皮即皮肤或粘膜有关的药物转运聚合层的组分。基质贴片区别于“液体贮库贴片”，其中活性渗透剂或药物溶解于具有不可渗透底面和与渗透膜及粘合剂适宜组配以用于经皮给药的反面的封闭装置中所含的胶凝液体中。例如，美国专利号4,983,395，本文引用作为参考。

本文所用的"应用部位"意指适于采用或不采用装置、片或敷料的局部应用部位，如耳后、臂、背、胸、腹部、腿上、脚顶等。

"组合物"意指活性试剂和其它化合物或组合物的组合，这些其它化合物或组合物为惰性（例如可检测的试剂或标签）或活性的，如助剂。

“药物组合物”意指包括活性成分与载体的组合，这些载体为惰性或活性的，使该组合物适于体外、体内或离体诊断或治疗。

本文所用的术语“药学上可接受的载体”包括任何标准药学载体，如磷酸盐缓冲的盐水溶液、水和乳剂如水包油或油包水乳剂，以及各种类型的润湿剂。该组合物还可以包括稳定剂和防腐剂。载体、稳定剂和助剂的实例参见Martin雷氏制药科学(Remingtons's Pharm. SCI.)，第15版（Mack出版公司，Easton(1975)）。

“受治者”为脊椎动物，优选哺乳动物，更优选人。哺乳动物包括但不限于鼠科动物、猿、人、农场动物、运动用动物和宠物。

“治疗”意指减轻症状或改变疾病或病症的临床表现。“预防”意指延迟或最小化疾病或病症的症状和临床表现。为本发明的目的，适于

本发明治疗的疾病或病症是与通过天然配体结合的雌激素受体相关的疾病或病症。这些病症包括但不限于肥胖、乳癌、骨质疏松、子宫内膜异位、心血管疾病、前列腺疾病、排卵和血胆固醇水平，尤其是血清水平。

在最基本的形式中，本发明提供了含有有效量的 lasofoxifene 和/或其药学上可接受的盐的药物贮库经皮制剂。在一个可供选择的实施方案中，该制剂任选包含有效量的药物渗透增强剂和/或扰乱细胞膜（cell-envelope）的化合物。细胞膜破坏剂的实例包括但不限于豆蔻酸异丙酯、月桂酸甲酯、油酸、油醇、甘油一油酸酯、甘油油酸酯、甘油三烯酸酯、甘油单硬脂酸酯、甘油单月桂酸酯、丙二醇单月桂酸酯或脱水山梨醇酯。参见美国专利号 5,626,366，本文引为参考。此外，制剂还可以含有一种或多种皮肤渗透增强剂如甘油三乙酸酯。可以使用的增强剂的实例非限制性地包括饱和与不饱和脂肪酸和它们的酯、醇、甘油单酯、乙酸酯、二乙醇胺和 N, N-二甲酰胺如油酸、油酸丙酯、豆蔻酸异丙酯、甘油一油酸酯、甘油单月桂酸酯、月桂酸甲酯、月桂基醇、月桂酰胺二乙醇胺及其组合。还可以使用饱和与不饱和脱水山梨醇酯如脱水山梨醇一油酸酯和脱水山梨醇单月桂酸酯。

一方面，该药物贮库为基于水或溶剂的粘合剂基质。该粘合剂基质可以具有适于长期与皮肤接触的其它压敏特性。这种粘合剂必须是与 lasofoxifene、任选的增强剂和任何载体和/或赋形剂或加到该药物/增强剂组合物中的其它添加剂物理或化学相容的。在基质贴片中所用的适宜的粘合剂包括含交联和非交联丙烯酸共聚体的丙烯酸粘合剂；乙酸乙烯基酯粘合剂；天然和合成橡胶，包括聚异丁烯、氯丁橡胶、聚丁二烯和聚异戊二烯；乙烯乙烯基乙酸酯共聚物；聚硅氧烷；聚丙烯酸酯；聚氨酯；增塑重量聚醚嵌段酰胺共聚物和增塑苯乙烯-橡胶嵌段共聚物。

适宜的压敏粘合剂包括聚硅氧烷、聚丙烯酸酯、聚异丁烯等等。这些压敏粘合剂共聚物是非常疏水的并且一般购得作为聚合物溶于有机溶剂的溶液。将药物和任选的赋形剂直接加到基于有机溶剂的压敏粘合剂溶液中，混合，铸塑成薄膜，并干燥蒸发溶剂，留下干燥的含有药物

和赋形剂的粘合剂基质薄膜。现有技术中已知这种药物应是疏水的以将其加到基于有机溶剂的疏水粘合剂。药物的亲水盐形式一般不与基于有溶剂的压敏粘合剂相容，并且必须被转化成更疏水的游离酸或游离碱形式以加到基于有机溶剂的疏水粘合剂中。

基于水的压敏粘合剂还可商购得。将这些基于水的粘合剂制成乳剂，其中在表面活性剂的辅助下将该疏水压敏粘合剂聚合物分散在水中。这些基于水的粘合剂提供了固有的安全优点和相对于基于水的压敏粘合剂的降低的环境问题，因为该载体为水而非有溶剂。该基于水的粘合剂用于制备医学磁带和绷带，并提供了优良的皮肤粘着性。美国专利号 5,985,317、5,783,208、5,780,050、5,626,866、5,460,820 和 4,983,395 描述了各种聚合经皮基质制剂。引用这些专利作为对现有技术更为详细描述的参考。

可供选择地，该药物贮库为美国专利号 5,662,925、4,829,224 或 4,983,395 中所述的液体贮库，本文引用作为参考。现有技术中已知的可供选择的实施方案如在美国专利号 4,829,224、4,849,224 和 4,983,395 中所述，也引用作为参考。

该基质贴片可以进一步包含各种除了含有 lasofoxifene 的聚合物层之外的添加剂，和任选的增强剂，它们是经皮药物转运系统的基本组分。这些添加剂一般为药物转运技术中已知的药学上可接受的成分，更为具体地说，在添加剂成分不会实质性地改变基质贴片的基本和新的特性的经皮药物转运技术中。例如，适宜的稀释剂可以包括矿物油、低分子量聚合物、增塑剂等等。许多经皮药物转运制剂在延长与皮肤接触以后具有导致皮肤刺激的趋势，因此，加入皮肤刺激减小试剂有助于获得更好被皮肤耐受的组合物。优选的皮肤刺激减小试剂为甘油，美国专利号 4,855,294，本文引用作为参考。但是，注意到其它所谓的加速促进剂或渗透增强剂组分如溶剂和扰乱细胞膜的化合物不必需存在于本发明中。

含有 lasofoxifene 的药物贮库可以体现为经皮药物转运技术中已知的各种类型的结构。例如，作为这种装置的最重要组成的药物贮库

可以包含处在载体内的亚饱和 lasofoxifene 溶液的简单基质，或是浸渍有处在载体内的亚饱和 lasofoxifene 溶液的纤维体的形式。除了贮库，该装置包括用于使贮库与皮肤保持药物转运接触的工具。这些工具包括同时为粘合剂的载体、在该贮库下的单独的基础粘合剂层，与该贮库互连的粘合剂外周环、贮库的粘合剂层叠物和条带。优选这些工具为粘合剂载体或单独的下粘合剂层。优选该装置为层压复合物的形式。

这些装置可由经皮药物转运装置技术中所用的常规技术制备。例如，将药物和载体以期望的比例混合形成均匀的混合物和铸塑或以其它方式将其用于衬背层（**backing layer**），然后层压到防粘衬里层（**release liner layer**）。如果期望的是单独的基础粘合剂层，还可以在层压之前将其铸塑至防粘衬里层上。

在应用中，基质贴片可以含有层叠在聚合物层上的远侧衬背。该远侧衬背形成面对外界即皮肤或粘膜远侧的基质贴片的一侧。该衬背层作用在于保护基质聚合物层和药物/增强剂组合物并提供防止药物损失至外界的不可透层。因此，为该衬背选择的物质应该与聚合物层、药物和增强剂相容，并应该对基质贴片的任何组分具有最小可渗透性的。有利地，该衬背可以是不透明的，以保护基质贴片组分免于与紫外光线接触而分解。进一步，该衬背可结合到和支持聚合物层，但应该是易弯的以容许使用基质贴片的人的运动。用于该衬背的适宜物质包括金属箔、金属化聚箔、复合箔或含有聚酯如对苯二酸聚酯、聚酯或铝化聚酯的薄膜、聚四氟乙烯、聚醚嵌段酰胺共聚物、异丁烯酸聚乙烯甲酯共聚物、聚甲烷、聚亚乙烯基氯、尼龙、硅树脂高弹体、基于橡胶的聚异丁烯、苯乙烯、苯乙烯-丁二烯和苯乙烯异戊二烯共聚物、聚乙烯和聚丙烯。优选约 0.0005-0.01 英寸的厚度。防粘衬里可由与衬背相同的材料或其它适宜的包有适宜防粘表面的薄膜制成。

将该药物贮库应用于应用部位，而药物通过真皮扩散。本发明还提供了本文所述的药物贮库和将贮库粘合到应用部位的装置。这种装置的实例如上述，它包括含有药物、衬背层和可防粘的衬里的粘合剂基质。还参见美国专利号 5,164,190 和 5,985,317。

例如，这种装置包括限定贮库的上部并延伸至剥离密封圆盘外周的衬背层；活性试剂渗透膜，其延伸到该剥离密封圆盘和衬背层外周，并在该衬背层下方，衬背层和薄膜限定；两层之间的含有本发明制剂的贮库；在活性试剂渗透膜下方的剥离密封圆盘；在该剥离密封盘，活性试剂渗透膜和该衬背层外周的热封；具有一个层叠在该衬背层上的中心部分和延伸出剥离密封圆盘外周的外周部分的粘合剂层叠物；和在该粘合剂层叠物的外周部分和剥离密封圆盘下可移去的防粘衬里的层压的复合材料。

以上的药剂、药物贮库和装置用于通过使任何这种药剂、药物贮库或装置与受治者的应用部位接触而治疗和预防受治者的与雌激素失调有关的病症。

本发明进一步提供了有效量的 lasofoxifene 用于制备治疗或预防与雌激素失调有关的经皮药物的应用。

实验方法

粘合剂基质制备

根据美国专利号 5,952,000 的教导制备压敏粘合剂基质系统，本文引用作为参考。首先，将已知重量的溶液置于称重的铝盘中并在 70℃对流烘箱中蒸发溶剂过夜而测定粘合剂溶液（基于水或有机溶剂）的固含量。将干燥后的粘合剂固体重量除以最初的溶液总重而计算该溶液的固体粘合剂含量。其次，将称重的粘合剂溶液加到玻璃瓶中，称取药物、渗透增强剂、和其它赋形剂的重量，并将其加到获得目标基质薄膜组合物必需数量的粘合剂溶液中。该溶液含有必需的粘合剂聚合物、药物和其它赋形剂，然后混合过夜。混合后，将大约 8ml 的溶液分散于硅烷化聚酯释放衬垫上，并用间隙大小合适的铸塑刀进行膜铸塑以得到最终约为 0.05mm 的厚度。在 70℃的对流炉下干燥铸塑膜直到所有溶剂已

蒸发而得到干燥基质（对于基于粘合剂的有机溶剂为 15 分钟，对于基于粘合剂的水乳剂为 30 分钟）。最后，将 0.08mm 厚的闭塞聚乙烯衬背膜层叠到干燥的粘合剂基质上，然后用这些系统进行下述的体外皮肤流量实验。

贮库或游离形式水醇凝胶制备

如下在 10ml 范围内制备水醇(hydroalcoholic)凝胶。以适宜的比例合并乙醇(190 标准乙醇)、 水、甘油、增强剂和药物并混合数小时。加入胶凝剂（羟丙基纤维素）并在高剪切下简单地混合，然后在低剪切下混合直至形成凝胶。

皮肤流量研究

采用人尸表皮膜在修饰的 Franz 非夹层扩散细胞上进行体外皮肤流量研究。由 Kligman 和 Christopher (Arch. Dermatol. 88:702 (1963))法从整个皮肤中分离出表皮膜（角质层和表皮）。该方法包括将完整厚度的皮肤与水在 60℃下接触 60 分钟。然后，轻轻将表皮膜从真皮上剥落并储存以在其后于-5℃下的铝箔内应用。

在各采用基质系统的渗透实验之前，将基质系统切成 0.7 cm^2 面积的圆形试样并除去硅烷化释放衬垫。将粘合剂固定到融化的表皮膜的角质层侧，然后将其切成适宜的大小并夹在两个半份的其角质层面对供给室扩散细胞之间。收集室充满水或适于保持药物下沉条件的水溶液。所有收集器溶液包括 0.02% (w/w)叠氮化钠(NaN_3)以抑制细胞生长。将扩散细胞置于温控循环水浴中，该水浴校准至保持皮肤表面温度为 32℃。用收集室内的磁搅拌棒，通过位于水浴下的磁搅拌组件的搅动而不断地搅拌收集室。

采用有限包着剂量（occluded doses）进行水醇凝胶渗透实验。该包着剂量为适宜的用于含有液体或凝胶贮库的经皮片药物转运系统的体外模型。根据以下方法建立包着给药实验。在皮肤渗透实验之前，将

表皮膜切成适宜的大小并置于两个半份的具有面对该收集室的表皮侧面的扩散细胞之间。该收集室充满适宜的溶液，然后将扩散细胞置于调节保护皮肤表面温度在 32℃的循环水浴中，并水合过夜。水合后，将凝胶试样(75.mu.l)移液至通过将聚乙烯洗涤器置于角质层表面上方而形成的空穴。该空穴用夹在适当位置的闭合的衬背膜覆盖。

采用含有过量药物固体（无穷剂量）的预饱和的药物溶液对水溶液进行渗透实验。在皮肤渗透实验之前，使表皮膜如上述水合过夜。水合后，水合后，将良好混合的水溶液试样(1ml)滴至通过将玻璃盖夹在角质层表面上而形成的供给室。然后用 Teflon.RTM.衬里的聚乙烯盖熔封该玻璃盖。

以下的取样方法用于所有的剂型。在预定的取样时间点，收集收集室的全部内含物进行药物定量，而收集室充满新鲜的溶液，注意消除任何皮肤/溶液界面的气泡。累积量的药物在任何时间渗透每单位面积。

以下实施例意在例举，不是限定本发明。

实施例 1

用比例为 84/10/6% w/w 的基于溶剂的丙烯酸压敏粘合剂 (TSR 58; Sekisui Chemical Co., Osaka, Japan)，甘油三乙酸酯(Eastman)和 CP-336,156 制备经皮基质制剂。使用该基质制剂的体外皮肤流量实验的结果总结成表 1。

表 1

皮肤源	扩散细胞号	7 日内平均每日 CP-336,156 流量 $\mu g/cm^2$/天
皮肤 1A	7	5.5±3.4
皮肤 1B	4	5.7±0.8
皮肤 1C	8	9.2±2.9
皮肤 1D	4	13.4±7.8
皮肤 1E	4	10.2±3.4
皮肤 1F	4	5.1±1.1
皮肤 1G	4	11.4±2.4
所有皮肤	平均±SEM	8.6±12

表1的结果表明可以将CP-336,156加到含有作为渗透增强剂的甘油三乙酸酯基质贴片中。来自这种制剂的CP-336,156的经皮转运可以至少保持7天。

实施例2

在CP-336,156酒石酸盐浓度为3%w/w的基于水的丙烯酸压敏粘合剂(Morstik 214, Morton, Greenville, SC)中制备经皮基质制剂。在同样的粘合剂中用3%w/w的CP-336,156酒石酸盐和1.5%w/w的月桂酰羟乙酸钠(R.I.T.A Corporation, Woodstock, IL)制备渗透增强制剂。采用这些基质制剂的体外皮肤流量实验结果总结成表2。

表2

皮肤源	扩散细胞号	24小时内CP-336,156的累积渗透, $ug/cm^2/24h$		增强倍数 Q24增强/Q24未增强
		未增强的	增强的 1.5%w/w NaLG	
皮肤2A	5	0.13±0.09	0.30±0.12	2.28
	5	2.70±1.08	3.51±0.93	1.30
	5	0.15±0.09	0.46±0.16	3.06
所有皮肤 平均±SEM		0.99±0.85	1.42±1.05	2.21±0.51

表2的结果说明可以将CP-336,156盐加到粘合剂基质贴片中。平均增强倍数为2.2,表明还可以将有效量的渗透增强剂加到这些基质系统中。

实施例3

采用比例为 50/15/30/2.5/2.5% v/v 的 USP 醇(EtOH)、水(H_2O)、甘油(Gly)、甘油一油酸酯 (GMO)、和月桂酸甲酯(ML)的溶剂组合物制备经皮液体贮库制剂。该混合物为澄清溶液。加入浓度为 2 mg/ml 的 CP-336,156 酒石酸盐，并用 30mg/g 的羟丙基甲基纤维素(Methocel® E10M, Dow Chemical)胶凝该制剂。采用该制剂的体外皮肤流量实验结果总结成表 3。

表 3

皮肤源	扩散细胞号	7 日内平均每日的 CP-336,156 流量 μg/cm²/天
皮肤 3A	8	17.4±7.7
皮肤 3B	4	15.3±8.7
皮肤 3C	8	23.9±11.0
皮肤 3D	4	27.9±2.2
皮肤 3E	4	21.2±9.9
皮肤 3F	4	15.4±7.2
皮肤 3G	4	30.3±4.9
所有皮肤	平均±SEM	21.6±2.3

表 3 的结果表明可以将 CP-336,156 盐加到含有低级链烷醇和皮肤渗透增强剂的液体贮库贴片上。该制剂的 CP-336,156 经皮转运可以保持至少 7 天。

实施例 4

采用比例为 30/38/30/1/1% v/v 的 USP 醇(EtOH)、水(H_2O)、甘油(Gly)、甘油一油酸酯 (GMO)、和月桂酸甲酯(ML)的溶剂组合物制备经皮液体贮库制剂。该混合物为混浊的两相分散体。加入浓度为 6 mg/ml 的 CP-336,156 酒石酸盐，并用 30mg/g 疏水改性的羟乙基纤维素(Natrosol®Plus 330CS, Aqualon)胶凝该制剂。采用该液体贮库

制剂的体外皮肤流量实验结果总结成表 4。

表 3

皮肤源	扩散细胞号	6 日内平均每日的 CP-336,156 流量 $\mu g/cm^2$/天
皮肤 4A	5	42.4±15.5
皮肤 4B	5	36.3±5.2
皮肤 4C	5	36.2±14.9
所有皮肤	平均±SEM	38.3±3.3

表 4 的结果表明可以由作为两相分散体的液体贮库制剂实现 CP-336,1 56 的经皮转运。

实施例 5

采用比例为 26.25/8.75/35/30% v/v 的 USP 醇(EtOH)、异丙醇(IPA)、水(H_2O)、甘油(Gly)的溶剂组合物制备经皮液体贮库制剂。采用 0.03%、0.06%、和 0.12%v/v 浓度的甘油单油酸酯制备渗透增强制剂，同时减少水以补偿加入的增强剂。0%、0.03%和 0.06%的 GMO 制剂为澄清液体，而 0.12%GMO 的制剂为混浊的分散体。加入浓度为 6 mg/ml 的 CP-336,156 酒石酸盐，并用 30mg/g 羟丙基甲基纤维素(Methocel® E10M, Dow Chemical)胶凝该制剂。采用这些制剂的体外皮肤流量实验结果总结成表 5。

表 5

皮肤源	未增强的 0%GMO	0.03%GMO		0.06%GMO		0.12%GMO	
	7 日内的平均日流量 ug/cm²/24h 平均±SD*	7 日内的平均日流量 ug/cm²/24h 平均±SD*	E	7 日内的平均日流量 ug/cm²/24h 平均±SD*	E	7 日内的平均日流量 ug/cm²/24h 平均±SD*	E
皮肤 5A	6.4±2.3	7.1±1.8	1.12	11.6±4.2	1.81	16.8±2.1	2.62
皮肤 5B	17.4±26.4	69.5±23.8	3.99	74.9±12.8	4.30	85.2±13.0	4.89
皮肤 5C	11.6±4.4	22.4±3.5	1.93	20.3±5.4	1.74	23.6±5.3	2.03
所有皮肤	11.8±3.2	33.0±18.8	2.34±0.37	35.6±19.8	2.62±0.43	41.8±21.8	3.18±.36

*n=2-5 扩散细胞每皮肤源

E=增强倍数=增强制剂的平均日流量/未增强对照组的平均日流量

表5表明将非常少量的甘油一油酸酯(0.03% v/v)加到含有低级烷醇的液体贮库赋形剂明显地增加了CP-336,156的经皮流量。这些结果还表明渗透增强基本上与 0.03%-0.12%范围内的甘油一油酸酯的浓度成正比。

实施例6

用 26.25/8.75/34.94%/30.00%/0.06%% v/v 的 EtOH/IPA/Gly/GMO的溶剂组合物制备经皮液体贮库制剂。加入6mg/ml的CP 336,156酒石酸盐，并用 30mg/g 的羟丙基甲基纤维素(Methocel®E10M, Dow Chemical)胶凝该制剂。用该制剂制备 3cm^2 活性面积的液体贮库贴片并在白兔上测试主要皮肤刺激。

使六只兔子的每只与该活性片接触(3cm^2 活性面积)。24 小时后，移去该片并在移去该片后的1和72小时为红斑和水肿部位打分。然后算出移去1和72小时之后的红斑与水肿打分的平均数得到主要皮肤刺激指数(PDI)。PDI值为0.3，采用该广泛接受的动物模型将该制剂归类为几乎觉察不到的刺激。

上述的讨论和实例仅意在说明现有技术。对于本领域技术人员来说，显然可以在不背离本发明的构思和范围的情况下对以上作各种改动。