(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2013 (10.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/067346 A1

(51) International Patent Classification:
A61K 9/70 (2006.01) *A61K 31/565* (2006.01)
A61K 47/10 (2006.01) *A61K 31/57* (2006.01)

(21) International Application Number:
PCT/US2012/063314

(22) International Filing Date:
2 November 2012 (02.11.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/555,546 4 November 2011 (04.11.2011) US
61/645,778 11 May 2012 (11.05.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/067346 A1

(54) **Title**: DERMAL DELIVERY COMPOSITIONS AND METHODS

(57) **Abstract**: A composition for transdermal delivery of a progestin for progestin hormone therapy is disclosed. Also disclosed is a transdermal delivery device comprising the composition. For progestin-only hormone therapy, the composition contains an anti-oxidant and does not contain an estrogen. For therapy involving a progestin and an estrogen, the composition contains the progestin, the estrogen and an additional anti-oxidant. Methods of improving the stability of progestin-containing compositions comprising oxidative agents are also disclosed. The methods comprise including one or more anti-oxidants in the compositions.

Title

Dermal Delivery Compositions and Methods

Field of the Invention

This invention is in the field of transdermal delivery of steroid hormones.

Background of the Invention

Various adhesive matrix compositions have been developed for transdermal delivery of steroid hormones. For example, U.S. Patent No. 7,384,650 describes a transdermal hormone delivery system that utilizes an adhesive composition comprising a pressure sensitive adhesive (PSA), a humectant, a skin permeation enhancer, an estrogen and a progestin.

U.S. Patent Publications 2010/0292660 and 2010/0255072 describe transdermal delivery systems that can be used, among other ways, in conjunction with the PSA matrix described in US 7,384,650.

The above-cited patent and patent applications are incorporated by reference as though fully set forth herein.

Summary of the Invention

This invention relates to a polymeric matrix useful in a transdermal delivery system for transdermal delivery of a progestin, in the absence of an estrogen.

One aspect of the invention features composition for transdermal delivery of a progestin that comprises: (a)a carrier, (b) a progestin, (c) a skin permeation enhancer and (d) an anti-oxidant, wherein the composition comprises a component that contributes to degradation of the progestin, wherein the component is one or more of an organic solvent, polyvinyl pyrrolidone (PVP), or a PVP copolymer. In one embodiment, the carrier is a polymeric pressure sensitive adhesive. In one embodiment, the component that contributes to degradation of the progestin is one or more of PVP, polyvinyl pyrrolidone/vinyl acetate (PVP/VA), or dimethyl sulfoxide (DMSO) and the anti-oxidant is not an estrogen or is additional to an estrogen.

The progestin can be desogestrel, dihydroprogesterone, drospirenone, ethynodiol acetate, ethynodiol diacetate, etogestrel, gestodene, gestogen, 17-hydrogesterone,

hydroxyprogesterone caproate, 3-keto-desogestrel, levonorgestrel, medroxyprogesterone acetate, medroxyprogesterone diacetate, megestrol, megestrol acetate, normegesterol, norelgestromin, norethindrone (i.e., norethisterone), norethindrone acetate, norethynodrel, norgestimate, norgestrel, 19-nortestosterone, progesterone, nestorone, methoxyprogesterone, or dl-norgestrel, or any combination of two or more of said progestins. In certain embodiments, the progestin is levonorgestrel or norethindrone acetate.

The anti-oxidant is selected from Vitamins A, C, D, and E, carotenoids, flavanoids, isoflavanoids, beta-carotene, butylated hydroxytoluene ("BHT"), butylated hydroxyanisole (BHA), glutathione, lycopene, gallic acid and esters thereof, salicylic acid and esters thereof, sulfites, alcohols, amines, amides, sulfoxides, surfactants, or any combination thereof. In certain embodiments, the anti-oxidant is sodium bisulfite, sodium sulfite, isopropyl gallate, Vitamin C and E, Irganox 1010, Irgafos 168 or BHT or any combination of two or more of those anti-oxidants. In certain embodiments, the anti-oxidant comprises one or more phenolic anti-oxidants. In particular, the anti-oxidant is BHT, pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate), or tris(2,4-di-tert-butylphenyl) phosphite.

In certain embodiments, the polymeric carrier is a pressure sensitive adhesive (PSA) selected from a polyacrylate adhesive, a polyisobutylene adhesive, or a silicone adhesive. The PSA may be polymerized by free radical polymerization. For instance, the PSA can be a polyacrylate adhesive. The PSA may comprise a 2-ethylhexyl acrylate co-monomer. The polyacrylate adhesive can further comprise about 50 to 60% w/w vinyl acetate co-monomer.

In certain embodiments, the skin permeation enhancer comprises one or more of: alcohols; alkanones; amides and other nitrogenous compounds; 1-substituted azacycloheptan-2-ones; bile salts; cholesterol; cyclodextrins and substituted cyclodextrins; ethers; saturated and unsaturated fatty acids; saturated and unsaturated fatty acid esters; saturated and unsaturated fatty alcohol esters; glycerides and monoglycerides; organic acids; methyl nicotinate; pentadecalactone; polyols and esters thereof; phospholipids; sulfoxides; surfactants; terpenes; and combinations thereof. In one embodiment, the skin permeation enhancer comprises an organic solvent. In some instances, the organic solvent is DMSO. In certain embodiments, the skin permeation enhancer comprises one or more of: DMSO, a fatty (C_8-C_{20}) alcohol ester of a hydroxy acid, a lower (C_1-C_4) alkyl ester of a hydroxy acid, and a C_6-C_{18} fatty acid. In a

particular embodiment, the skin permeation enhancer comprises one or more of: DMSO, lauryl lactate, ethyl lactate, and capric acid.

The above-described composition can also include a humectant. In certain embodiments, the humectant is PVP or a PVP co-polymer, such as PVP/VA.

In various embodiments of the above-described composition, the progestin is present in a concentration based on weight of the composition of 0.1% to 3.0% or 0.2% to 2.0% or 0.5% to 1.5%. The skin permeation enhancer can present in a concentration based on weight of the composition of 1% to 50% or 2% to 40%.

In certain embodiments, the anti-oxidant in the composition includes BHT. The BHT can be present in a concentration based on weight of the hormone of 10% to 500%, 20% to 200%, or 50% to 150%.

In certain embodiments, the composition may be one that does not comprise an estrogen.

In certain embodiments, the anti-oxidant in the composition is pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) or tris (2,4-di-tert-butylphenyl) phosphite.

Another aspect of the invention features a transdermal drug delivery device that comprises: (a) a transdermal composition as summarized above, which comprises a PSA and has a skin contacting surface and a non-skin contacting surface; (b) a release liner adjacent the skin contacting surface of the transdermal composition; and (c) a backing layer adjacent the non-skin contacting surface.

Another aspect of the invention features a method of improving the stability of a progestin-only transdermal delivery composition that includes an oxidizing agent. The method comprises adding an anti-oxidant other than an estrogen to the composition. In certain embodiments, the oxidizing agent is one or more of an organic solvent, PVP, or a PVP copolymer. In certain embodiments, the composition comprises a PSA. The progestin can be desogestrel, dihydroprogesterone, drospirenone, ethynodiol acetate, ethynodiol diacetate, etogestrel, gestodene, gestogen, 17-hydrogesterone, hydroxyprogesterone caproate, 3-keto-desogestrel, levonorgestrel, medroxyprogesterone acetate, medroxyprogesterone diacetate, megestrol, megestrol acetate, normegesterol, norelgestromin, norethindrone (norethisterone), norethindrone acetate, norethynodrel, norgestimate, norgestrel, 19-nortestosterone,

progesterone, nestorone, methoxyprogesterone, and dl-norgestrel or any combination of two or more of said progestins. In particular, the progestin is levonorgestrel or norethindrone acetate.

In certain embodiments of the method, the anti-oxidant is selected from Vitamins A, C, D, and E, carotenoids, flavanoids, isoflavanoids, beta-carotene, butylated hydroxytoluene ("BHT"), butylated hydroxyanisole (BHA), glutathione, lycopene, gallic acid and esters thereof, salicylic acid and esters thereof, sulfites, alcohols, amines, amides, sulfoxides, phenolics or surfactants, or any combination of two or more of said anti-oxidants. In particular, the anti-oxidant is sodium bisulfite, sodium sulfite, isopropyl gallate, Vitamin C and E, Irganox 1010, Irgafos 168 or BHT or any combination of two or more of said anti-oxidants.

In certain embodiments of the method, the polymeric carrier is a PSA selected from a polyacrylate adhesive, a polyisobutylene adhesive, or a silicone adhesive. The PSA may be polymerized by free radical polymerization. For instance, the PSA may be a polyacrylate adhesive. The PSA can comprise a 2-ethylhexyl acrylate monomer. The polyacrylate adhesive can further comprises about 3 to 60% w/w vinyl acetate monomer.

In various embodiments of the method, the skin permeation enhancer in the composition comprises one or more of: alcohols; alkanones; amides and other nitrogenous compounds; 1-substituted azacycloheptan-2-ones; bile salts; cholesterol; cyclodextrins and substituted cyclodextrins; ethers; saturated and unsaturated fatty acids; saturated and unsaturated fatty acid esters; saturated and unsaturated fatty alcohol esters; glycerides and monoglycerides; organic acids; methyl nicotinate; pentadecalactone; polyols and esters thereof; phospholipids; sulfoxides; surfactants; terpenes; and combinations thereof. In certain embodiments, the enhancer comprises an organic solvent. In particular, the organic solvent is DMSO. In certain embodiments, the enhancer comprises one or more of: DMSO, a fatty (C_8-C_{20}) alcohol ester of a hydroxy acid, a lower (C_1-C_4) alkyl ester of a hydroxy acid, and a C_6-C_{18} fatty acid. In particular, the enhancer comprises DMSO, lauryl lactate, ethyl lactate, and capric acid.

In certain embodiments of the method, the composition further comprises a humectant. The humectant may be PVP or a PVP co-polymer, such as PVP/VA.

In various embodiments of the method, the progestin is present in the composition in a concentration based on weight of the composition of 0.1% to 3.0% or 0.2% to 2.0% or 0.5% to 1.5%. The skin permeation enhancer is present in a concentration based on weight of the composition of 1% to 50% or 2% to 40%.

In various embodiments of the method, the anti-oxidant in the composition is BHT. The BHT may present in a concentration based on weight of the hormone of 10% to 500%, 20% to 200%, or 50% to 150%.

In various embodiments of the method, the anti-oxidant in the composition is pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) or tris (2,4-di-tert-butylphenyl) phosphite.

These and other embodiments, which are more fully described below, are meant to be illustrative and not limiting of the invention.

Detailed Description of the Invention

The present invention is useful in delivering a progestin hormone to a patient that can benefit from progestin-only hormone supplementation, *i.e.,* delivery of a progestin with or without concomitant delivery of an estrogen. In an aspect of the present invention, the progestin, in particular, levonorgestrel, is stabilized, *i.e.,* protected from degradation, by incorporation of an anti-oxidant. While ethinyl estradiol itself has anti-oxidizing activity, it is contemplated in accordance with this invention that if an estrogen is present, then a further anti-oxidant that is not an active pharmaceutical ingredient, *e.g.,* that is not ethinyl estradiol or other hormone, is included in the transdermal composition.

As discussed further hereinbelow, certain components of a transdermal composition, such as the transdermal compositions described in US 7,384,650 and hereinbelow, have been found to contribute to degradation of levonorgestrel. Such components include the polyacrylate **pressure sensitive adhesive ("PSA"), the PVP humectant** (e.g., PVP/VA), and the dimethyl sulfoxide skin permeation enhancer. Incorporation of an excipient that functions as an anti-oxidant can protect the progestin from degradation, *i.e.*, it can slow degradation of the progestin, and thereby increase the shelf life of the composition.

Progestin-containing Transdermal Composition: The composition for transdermal delivery, *i.e.,* systemic delivery through the skin, comprises a progestin, an anti-oxidant, a skin permeation enhancer and a carrier. The composition does not necessarily comprise an estrogen, If it does not, it may be referred to as a "progestin-only transdermal composition". The composition optionally also comprises excipients such as gelling agents, plasticizers, humectants, buffers, and the like. The composition can be formulated and applied to the skin, for instance, as a gel, an ointment, or a spray, or it can be contained within a transdermal delivery device, such as a patch, in which the composition is contained, for example, within a reservoir by a semi-permeable membrane or as a soft polymeric matrix that is in direct contact with the skin, *i.e.,* that is firm enough that a reservoir membrane is not required.

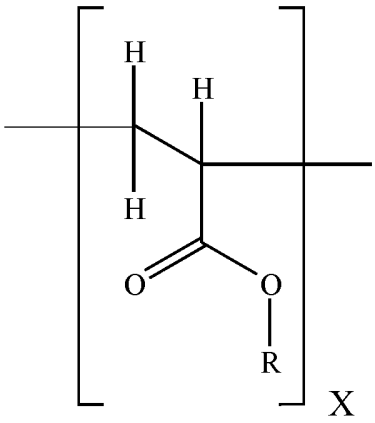
In an illustrative embodiment of the invention, the composition is a polymeric matrix comprising a polymer such as a pressure-sensitive adhesive (PSA) as a carrier, the progestin, the anti-oxidant and the skin permeation enhancer. The polymer can be a pressure sensitive adhesive ("PSA") that forms a biologically acceptable adhesive polymer matrix capable of forming adhesive active-containing thin films or coatings through which the progestin can pass into the skin. Suitable polymers are biologically and pharmaceutically compatible, nonallergenic, insoluble in and compatible with body fluids or tissues with which the device is contacted. The use of water soluble polymers is generally less preferred since dissolution or erosion of the matrix would affect the release rate of the progestin as well as the capability of the dosage unit to remain in place on the skin. So, in certain embodiments, the polymer is non-water soluble.

Suitable progestin transdermal compositions are disclosed, *e.g.,* in US 7,045,145, US 7,384,650, US 20100255072, US 2010292660, and US 20100178323, all of which are incorporated herein by reference as though fully set forth.

Polymers used to form a polymer matrix in the progestin-containing layer can have glass transition temperatures below room temperature such that they are soft and pliable at room temperature. The polymers are preferably non-crystalline but may have some crystallinity if necessary for the development of other desired properties. Cross-linkable monomeric units or sites can be incorporated into such polymers. For example, cross-linking monomers that can be incorporated into polyacrylate polymers include polymethacrylic esters of polyols such as

butylene diacrylate and dimethacrylate, trimethylol propane trimethacrylate and the like. Other monomers that provide such sites include allyl acrylate, allyl methacrylate, diallyl maleate and the like.

PSAs that can be used to form the adhesive composition are typically polyacrylate, polyisobutylene, or silicone adhesives. A useful adhesive polymer formulation comprises a polyacrylate adhesive polymer of the general formula (I):



wherein X represents the number of repeating units sufficient to provide the desired properties in the adhesive polymer and R is H or a lower (C_1-C_{10}) alkyl, such as ethyl, butyl, 2-ethylhexyl, octyl, decyl and the like. The adhesive polymer matrix can comprise, for instance, a polyacrylate adhesive copolymer having a 2-ethylhexyl acrylate monomer and approximately 50-60% w/w of vinyl acetate as a co-monomer. An example of a suitable polyacrylate adhesive copolymer for use in the present invention includes, but is not limited to, that sold under the tradename of Duro Tak® 87-4098 by Henkel Corporation , Bridgewater, N.J., which comprises vinyl acetate co-monomer.

Progestins: Progestins useful in the practice of the present invention include desogestrel, dihydroprogesterone, drospirenone, ethynodiol acetate, ethynodiol diacetate, etogestrel, gestodene, gestogen, 17-hydrogesterone, hydroxyprogesterone caproate, 3-keto-desogestrel, levonorgestrel, medroxyprogesterone acetate, medroxyprogesterone diacetate, megestrol, megestrol acetate, normegesterol, norelgestromin, norethindrone (i.e., norethisterone), norethindrone acetate, norethynodrel, norgestimate, norgestrel, 19-nortestosterone, progesterone, nestorone, methoxyprogesterone, and dl-norgestrel or any combination of two or more of said progestins. Of particular interest are levonorgestrel and norethindrone and

norethindrone salts, *e.g.*, norethindrone acetate. Levonorgestrel is a potent progestin on a weight-dose basis and may be selected for that or other reasons. The progestin is typically present in a concentration based on weight of the transdermal composition (i.e., wt%) of 0.1 to 3 % or 0.2 to 2.0 % or 0.5-1.5 %.

Estrogens: Estrogens useful in the practice of the present invention include, without limitation, ethinyl estradiol, 17-beta-estradiol, estradiol-3,17-diacetate; estradiol-3-acetate; estradiol 17-acetate; estradiol-3,17-divalerate; estradiol-3-valerate; estradiol-17-valerate; 3-mono-, 17-mono- and 3,17-dipivilate estradiol esters; 3-mono-, 17-mono- and 3,17-dipropionate estradiol esters; 3-mono-, 17-mono- and 3,17-dicyclo pentyl-propionate estradiol esters, and estrone. Of particular interest is ethinyl estradiol. The estrogen is typically present in a concentration based on weight of the transdermal composition (*i.e.*, wt%) of 0.1 to 3 % or 0.2 to 2.0 % or 0.5 to 1.5 %, e.g., 0.5 to 1 %.

Skin Permeation Enhancers: A number of skin permeation enhancers have been used to improve passage of progestins through the skin and into the blood stream. These include, *e.g.*, alcohols; alkanones; amides and other nitrogenous compounds; 1-substituted azacycloheptan-2-ones; bile salts; cholesterol; cyclodextrins and substituted cyclodextrins; ethers; saturated and unsaturated fatty acids; saturated and unsaturated fatty acid esters; saturated and unsaturated fatty alcohol esters; glycerides and monoglycerides; organic acids; methyl nicotinate; pentadecalactone; polyols and esters thereof; phospholipids; sulfoxides; surfactants; terpenes; and combinations thereof.

As specific examples, the following can be mentioned: decanol, dodecanol, 2-hexyl decanol, 2-octyl dodecanol, oleyl alcohol, undecylenic acid, lauric acid, myristic acid and oleic acid, fatty alcohol ethoxylates, esters of fatty acids with methanol, ethanol or isopropanol, methyl laurate, ethyl oleate, isopropyl myristate and isopropyl palmitate, esters of fatty alcohols with acetic acid or lactic acid, lauryl lactate, oleyl acetate, 1,2-propylene glycol, glycerol, 1,3-butanediol, dipropylene glycol and polyethylene glycols.

Of particular interest are volatile organic solvents, including, but not limited to, dimethyl sulfoxide (DMSO), C_1-C_8 branched or unbranched alcohols, such as ethanol, propanol, isopropanol, butanol, isobutanol, and the like, as well as azone (laurocapram: 1-

dodecylhexahydro-2H-azepin-2-one) and methylsulfonylmethane. Also of particular interest are fatty acids and esters thereof.

For example, a skin permeation enhancer useful in the present invention can be a mixture of (1) a pharmaceutically acceptable organic solvent, such as dimethyl sulfoxide (DMSO), (2) a fatty (C_8-C_{20}) alcohol ester of a hydroxy acid, such as lauryl lactate, (3) a lower (C_1-C_4) alkyl ester of a hydroxy acid, *e.g.*, ethyl lactate, and (4) a C_6-C_{18} fatty acid, such as capric acid. In specific embodiments, the fatty alcohol ester of lactic acid is lauryl lactate and the lower alkyl ester of lactic acid is ethyl lactate. A medium- to long-chain fatty acid in the skin permeation enhancer formulation can be employed among the skin permeation enhancers. Capric acid is preferred for use but other C_6-C_{18} saturated or unsaturated fatty acids may be used, including but not limited to caproic acid, caprylic acid, lauric acid and myristic acid, to name a few.

In a particular embodiment, the pharmaceutically acceptable organic solvent is DMSO. Other organic solvents suitable for use in the present invention include, but are not limited to, C_1-C_8 branched or unbranched alcohols, such as ethanol, propanol, isopropanol, butanol, isobutanol, and the like, as well as azone (laurocapram: 1-dodecylhexahydro-2H-azepin-2-one) and methylsulfonylmethane, to name a few.

The fatty alcohol ester of a hydroxy acid can be a fatty alcohol ester of lactic acid, such as lauryl lactate. However, other hydroxy acids and fatty alcohols may be utilized. Alternative hydroxy acids include, but are not limited to, alpha-hydroxy acids such as glycolic acid, tartaric acid, citric acid, malic acid and mandelic acid, as well as the beta-hydroxy acid, salicylic acid. Alternative fatty alcohols include any C_8-C_{20} saturated or unsaturated fatty alcohols, such as myristyl, palmityl or oleyl alcohols, to name a few.

The lower alkyl ester of hydroxy acid can also utilize lactic acid, and can be, *e.g.,* ethyl lactate. However, other hydroxy acids, such as glycolic acid, tartaric acid, citric acid, malic acid, mandelic acid and salicylic acid, may also be utilized. In addition isopropylmyristic acid (IPM) may be used as a substitute for the lower alkyl ester of hydroxy acid.

The aforementioned combination of skin permeation enhancers may be used to enhance transdermal delivery of steroid hormones from any type of transdermal delivery composition, as discussed above. An adhesive polymer matrix-type system as described in detail herein and in US 7,045,145, US 7,384,650, US 20100255072, US 2010292660, and US

20100178323 are illustrative; however, the enhancer combination may also be utilized in non-adhesive polymers, as well as in multi-layer or reservoir-type transdermal delivery systems, gels, ointments, sprays, and lotions, to name a few.

The skin permeation enhancer is typically present in a concentration of at least 1% or at least 2% by weight of the composition. It may be present in a concentration of up to 50% or up to 40% by weight of the composition. In certain embodiments, the skin permeation enhancer is present in a concentration based on weight of the composition (*i.e.*, wt%) of 1 to 50 % or 10 to 40 % or 20 to 30 % of the composition.

Optional Additional Excipients: A number of excipients are employed in transdermal delivery compositions for various purposes. Of particular interest are polymers that function as humectants and/or as plasticizers. Incorporation of a humectant in the formulation allows the dosage unit to absorb moisture from the surface of skin, which in turn helps to reduce skin irritation and to prevent the adhesive polymer matrix of the delivery system from failing to adhere for a sufficient duration. The plasticizer/humectant may be a conventional plasticizer used in the pharmaceutical industry, for example, polyvinyl pyrrolidone (PVP). In particular, PVP/vinyl acetate (PVP/VA) co-polymers, such as those having a molecular weight of from about 50,000, are suitable for use in the present invention. The PVP/VA acts as both a plasticizer, acting to control the rigidity of the polymer matrix, as well as a humectant, acting to regulate moisture content of the matrix. The PVP/VA can be, for example, Plasdone® S-630 Copovidone (International Specialty Products, Inc. (ISP), Wayne, New Jersey), which is a 60:40 PVP:VA co-polymer that has a molecular weight of 24,000 to 30,000 and a glass transition temperature of 106°C. The amount of humectant/plasticizer is directly related to the duration of adhesion of the overlay.

Anti-oxidants: Anti-oxidants function to prevent or inhibit oxidation of other molecules by themselves becoming oxidized. In a polymeric matrix comprising both a progestin and an estrogen such as ethinyl estradiol, the ethinyl estradiol functions as an anti-oxidant and thereby helps to reduce oxidative degradation of the progestin. Employment of an additional anti-oxidant further reduces oxidative degradation. In a progestin-only composition, employment of an anti-oxidant can be even more important.

For example, certain polymers, in particular, polymers formed by free radical polymerization, have been found to act as oxidizing agents in a polymeric matrix comprising a progestin, whereby the stability of the progestin is compromised. For example, it has been discovered in accordance with the present invention that polyacrylate adhesives cause oxidation of a progestin, *e.g.,* levonorgestrel.

It has also been discovered in accordance with the present invention that PVP, which is commonly used in transdermal polymeric compositions, also contributes to oxidation of a progestin. Therefore, in transdermal compositions comprising PVP, or PVP/VA, and a progestin, addition of an anti-oxidant improves the stability of the progestin.

It has also been discovered in accordance with the present invention that certain permeation enhancers, *e.g.*, DMSO, can also cause oxidation of a progestin, *e.g.*, levonorgestrel.

Thus, one aspect of the invention features a polymeric matrix comprising the progestin, the anti-oxidant, the skin permeation enhancer and a pressure sensitive adhesive ("PSA"), wherein the PSA is a polyacrylate adhesive, *e.g.*, a polyacrylate/vinyl acetate copolymer such as Duro Tak® 87-4098, and/or wherein the polymeric matrix comprises PVP or PVP/VA, and/or wherein the permeation enhancer comprises DMSO.

A number of compounds can act as anti-oxidants in the transdermal composition of the present invention. Among compounds known to act as anti-oxidants are: Vitamins A, C, D, and E, carotenoids, flavanoids, isoflavanoids, beta-carotene, butylated hydroxytoluene ("BHT"), butylated hydroxyanisole (BHA), glutathione, lycopene, gallic acid and esters thereof, salicylic acid and esters thereof, sulfites, alcohols, amines, amides, sulfoxides, surfactants, etc. Of particular interest are phenolic anti-oxidants, *e.g.*, BHT, pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate), *e.g.*, Irganox 1010, and tris(2,4-di-tert-butylphenyl) phosphite, *e.g.*, Irgafos 168, as well as sodium bisulfite, sodium sulfite, isopropyl gallate, Vitamin C and Vitamin E.

Phenolic anti-oxidants, like BHT, which are sometimes referred to as primary anti-oxidants, are particularly suitable. Larger phenolic anti-oxidants, *e.g.*, molecular weight greater than 500 (*e.g.*, tris(2,4-di-tert-butylphenyl) phosphite) or greater than 1000 (*e.g.*, pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) may be utilized to advantage.

The pH of the transdermal composition can be maintained at about pH 6 to about pH 8, *e.g.*, at about pH 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2., 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9 or 8.0. In one embodiment, the composition is maintained at about pH 6.5 to pH7.5. In another embodiment, the composition is maintained at about pH 7. Anti-oxidants that would increase pH, *e.g.,* sodium metabisulfite, are preferably avoided. BHT can be present, *e.g.,* in a concentration based on the weight of the hormone of at least 10 wt% or at least 20 wt% or at least 30 wt% of the hormone. BHT can be present, *e.g.*, in a concentration of up to 150 wt% or 200 wt% or 500 wt% of the hormone. In certain embodiments, BHT is present in a concentration based on weight of the hormone of 10 to 500 %, 20 to 200 %, or 50 to 150 % of the hormone. Suitable concentrations of other anti-oxidants are readily ascertainable. For example, suitable concentrations of tris(2,4-di-tert-butylphenyl) phosphite, *e.g.*, Irgafos 168, include concentrations that are similar to those of BHT, although lower or higher concentrations may also be employed; suitable concentrations of pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate), *e.g.*, Irganox 1010, include similar concentrations although lower or higher concentrations may be employed, *e.g.*, concentrations that are up to about 10%, 20% or 30% higher.

The following examples are set forth to describe the invention in greater detail. They are intended to illustrate, not limit, the invention.

Examples

Example 1

A master blend, utilizing the formula listed in Table 1, below, was produced. The master blend was divided and spiked with ethinyl estradiol or known anti-oxidants as shown in Table 3. Each blend was then coated on a release liner at a target coat weight of 133 g/m^2 and dried at 60°C. The sheets were laminated, cut into 15 cm^2 samples, placed between two release liners, pouched, and then stored at 80°C. Samples were evaluated at five time points as shown in Table 2.

Table 1. Master Blend Formula

Levonorgestrel	0.38%
Penetration Enhancers, PVP/VA, Ethyl Acetate	39.0%
PSA*	60.5%

* PSA = polyacrylate adhesive copolymer having a 2-ethylhexyl acrylate monomer and approximately 50-60% w/w of vinyl acetate as a co-monomer

Table 2. Sampling Plan

Sampling Time Point	Temperature	Number of Samples Tested
0 days (T_0)	80°C	3
2 days (T_2)	80°C	3
4 days (except Batch 7) (T_4)	80°C	3
6 days (Batch 7 only) (T_6)	80°C	3
8 days (T_8)	80°C	3

Table 3. Test Blends

Batch #1	Master Blend
Batch #2	Master Blend + ethinyl estradiol, 1.53 mg/15 cm^2
Batch #3	Master Blend + BHT, 1.14 mg/15 cm^2
Batch #4	Master Blend + BHT, 1.71 mg/15 cm^2
Batch #5	Master Blend + Irganox 1010, 1.11 mg/15 cm^2 + Irgafos 168, 0.57 mg/15 cm^2
Batch #6	Master Blend + Irganox 1010, 1.66 mg/15 cm^2 + Irgafos 168, 0.85 mg/15 cm^2
Batch #7	Master Blend + ethinyl estradiol, 0.97 mg/15 cm^2

The amounts of levonorgestrel in each composition at each time point are shown in Table 4 as an average of 3 samples of each batch as a percentage of the target amount of levonorgestrel ("%TL"), which is 0.868 % based on the weight of the polymeric matrix.

Table 4. Levonorgestrel Stability as % Target Levonorgestrel

Batch	T_0	T_2	T_4	T_6	T_8
Batch 1	96.9	87.1	68.5	NA	48.1
Batch 2	106.6	92.8	93.3	NA	87.3
Batch 3	106.8	102.0	98.1	NA	97.7
Batch 4	103.4	102.2	99.7	NA	95.7
Batch 5	104.3	104.3	99.4	NA	94.6
Batch 6	102.6	101.1	98.5	NA	93.1
Batch 7	105.4	97.1	NA	93.4	91.7

These results demonstrate that ethinyl estradiol functions as an anti-oxidant in the composition and that levonorgestrel stability is markedly improved by addition of an anti-oxidant to the composition.

Example 2

To six batches of a master blend of levonorgestrel, penetration enhancers, polyvinylpyrrolidone/vinyl acetate copolymer, and pressure sensitive adhesive, substantially as described in Example 1, BHT was added at different amounts ranging from 0.02 mgs per patch (each patch contains 300 mgs of master blend) to 1.7 mgs per patch (the value of 1.7 mgs represents the molar equivalent of the amount of levonorgestrel in each patch).

Each batch was heated to 80°C and analyzed at the time points of 0, 4 and 8 days. All BHT loading values had a positive effect on the stability of levonorgestrel. The amounts of LNG remaining at T = Day 0, T = Day 4, and T = Day 8 are shown in Table 5.

Table 5. Effect of BHT concentration on the degradation of levonorgestrel

BHT (mg/patch)	Day 0	Day 4	Day 8
0	98	56	56
1.7	100	95	91
0.3	102	98	91
0.15	101	94	85
0.075	98	90	69

0.040	101	74	62
0.020	100	66	66

Example 3

The following test batches were prepared and tested as described.

a) Levonorgestrel (2.6 mg) was dissolved in 412 mg Duro Tak 87-4098 (hereinbelow, "Carrier"). Drawdowns were made and heated at 80°C for 4 and 8 days. The amounts of levonorgestrel remaining and the percent of degradants for the samples heated at 4 and 8 days were determined.

b) Levonorgestrel (2.6 mg) and 60 mg of PVP/VA were dissolved in 412 mg of Carrier. Drawdowns were made and heated at 80°C for 4 and 8 days. The amounts of levonorgestrel remaining and the percent of degradants for the samples heated at 4 and 8 days were determined.

c) Levonorgestrel (2.6 mg), 1.71 mg BHT and 60 mg PVP/VA were dissolved in 412 mg Carrier. Drawdowns were made and heated at 80°C for 4 and 8 days. The amounts of levonorgestrel remaining and the percent of degradants for the samples heated at 4 and 8 days were determined.

d) The same procedure as described in c) was performed, except 1.14 mg BHT was added.

The batch formulations are summarized in Table 6.

Table 6. Summary of Batch Formulations

	Carrier (mg)	levonorgestrel(mg)	PVP/VA(mg)	BHT(mg)
a	412	2.6		
b	412	2.6	60	
c	412	2.6	60	1.71
d	412	2.6	60	1.14

HPLC analysis was conducted to identify degradants of levonorgestrel. An aliquot of approximately 200 mg and 100 mg of the sample (exact weight recorded) for 4 and 8 day

stability was used. The sample was dissolved in 5 mL of 1:1 tetrahydrofuran:methanol (THF/MeOH). 10 µL was injected for HPLC analysis.

Levonorgestrel degradants appeared after incubation in the 80°C oven for 4 days and 8 days for samples a and b. No degradant was found for samples c and d. The results are shown in Table 7.

Table 7. Peak Area Percentage of Total Degradants

Sample ID	Total degradants (%)	
	4 day	8 day
A	0.48	0.75
B	1.26	1.28
C	0.00	0.00
D	0.00	0.00

The peak area percentages of remaining levonorgestrel after incubation in 80°C oven are shown in Table 8.

Table 8. Peak Area Percentage of Remaining Substances

Sample ID	Remaining	Remaining
	4 day	8 day
a	99.52	99.25
b	98.74	98.72
c	100.00	100.00
d	100.00	100.00

Note for Table 8: Remaining levonorgestrel percentages were directly obtained from peak area percentages.

The force degradation study described above indicated that addition of BHT reduced degradation of levonorgestrel, while addition of Povidone (PVP) slightly increased the degradation.

Example 4

Transdermal delivery patches were prepared comprising penetration enhancers, polyvinylpyrrolidone/vinyl acetate copolymer, pressure sensitive adhesive, and varying amounts of levonorgestrel (LNG) and BHT, as follows:

Lot 1: LNG (2.17 mg, 0.87 wt%) - 12.5 cm^2 patch;
Lot 2: LNG (2.6 mg, 0.87 wt%) plus BHT (1.712 mg, 0.57 wt%) - 15 cm^2 patch;

Skin flux across human cadaver skin (3 donor skin samples, 3 replicates per skin donor) was compared. Data are reported in Table 9.

Table 9. Cumulative amounts of LNG permeated as a function of time.

Lot #	Cumulative amounts of LNG permeated (ug/cm^2)						
	24 h	48 h	72 h	96 h	120 h	144 h	168 h
1	5.503 +/- 1.475	12.414 +/- 2.456	18.787 +/- 3.256	24.962 +/- 3.895	30.502 +/- 4.569	35.767 +/- 5.230	40.736 +/- 5.770
2	5.187 +/- 1.900	11.336 +/- 2.755	17.092 +/- 3.578	22.650 +/- 4.286	27.795 +/- 4.969	32.689 +/- 5.551	37.355 +/- 6.110

The mean steady-state flux of levonorgestrel (ug/cm^2/h) in each batch is shown in the following table.

Table 10. Mean steady-state flux of levonorgestrel (ug/cm^2/h)

Lot 1	0.2442 +/- 0.0312
Lot 2	0.2231 +/- 0.0312

These data show that permeation of levonorgestrel was not impeded by the addition of BHT.

Example 5

As shown in Table 11, seven transdermal compositions, each comprising approximately 164.8 mg Duro Tak® 87-4098 and 2.6 mg levonorgestrel (LNG), after drying, with and without PVP/VA and DMSO, were prepared to test the oxidative effects of a polyacrylate PSA, PVP, and DMSO.

Table 11. Compositions

Composition #	PVP/VA (mg)	DMSO (mg)
1	None	none
2	60 mg PVP/VA	none
3	60 mg PVP/VA	none
4	60 mg PVP/VA	none

5	60 mg PVP/VA	none
6	None	16 mg DMSO
7	60 mg PVP/VA	16 mg DMSO

In the case of compositions 1 – 4 and 6, the PSA was pre-heated at 78°C for 8 hours prior to addition of PVP/VA and DMSO. In the case of preparations 3 and 4, the PVP/VA was pre-heated at 80°C for 48 hours in the presence of air and nitrogen, respectively.
All preparations were then placed in an oven at 80°C for 4 days and 8 days. Degradants were analyzed by HPLC. Degradant percentage data are provided in Table 12.

Table 12. Peak Area Percentage of Total Degradants

Composition #	Degradants (%) Day 4	Degradants (%) Day 8
1	0.32	0.47
2	0.76	0.94
3	0.87	0.91
4	0.78	1.16
5	1.21	1.60
6	1.12	1.67
7	1.65	1.78

As shown in Table 12, presence of PVP/VA increased degradants roughly by two-fold. Pre-treatment of PVP/VA did not show significant difference. Heating the compositions for 8 days produced slightly more degradants than for 4 days. Pre-heating the PSA reduced the amount of degradants. Addition of DMSO increased the amount of degradants.

Example 6

A master blend utilizing the formula listed in Table 13 was produced. The master blend was then divided and spiked with BHT as shown in Table 14. Each test blend was then coated on

a release liner at a target coat weight of 200 g/m^2 and dried at 60°C for 17.5 mins using a fan speed of 2300 rpm. The sheets were then laminated, cut into 15 cm^2 samples, placed between two release liners, pouched, and then stored at 80°C. Samples were evaluated on Days 0, 4, and 8..

Table 13. Master Blend Formula

Levonorgestrel	0.378%
Ethinyl estradiol	0.333%
Penetration Enhancers, PVP/VA, Ethyl Acetate	39.558%
PSA*	59.730%

* PSA = polyacrylate adhesive copolymer having a 2-ethylhexyl acrylate monomer and approximately 50-60% w/w of vinyl acetate as a co-monomer [Duro-Tak 87-4098]

Table 14. Test Blends

Batch #1	Master Blend
Batch #2	Master Blend + BHT, 1.712 mg/15 cm^2, 2.481 g/kg
Batch #3	Master Blend + BHT, 1.000 mg/15 cm^2, 1.449 g/kg
Batch #4	Master Blend + BHT, 0.428 mg/15 cm^2, 0.620 g/kg
Batch #5	Master Blend + BHT, 0.300 mg/15 cm^2, 0.435 g/kg
Batch #6	Master Blend + BHT, 0.150 mg/15 cm^2, 0.217 g/kg

The amounts of levonorgestrel and ethinyl estradiol were determined by HPLC. The results (% LC) for each test blend are shown in Table 15 as an average of 5 samples per test blend, with %-Relative Standard Deviations (%RSD).

Table 15. Results

	Day 0		Day 4		Day 8	
Test Blend	EE (% RSD)	LNG (% RSD)	EE (% RSD)	LNG (% RSD)	EE (% RSD)	LNG (% RSD)
Control	98.7 (1.9)	100.3 (2.1)	77.3 (1.0)	43.0 (3.1)	72.9 (9.1)	28.5 (57.0)
2	98.0 (2.2)	98.7 (2.2)	91.4 (1.3)	72.1 (1.5)	85.4 (2.4)	57.5 (8.1)
3	99.1 (1.8)	99.6 (2.0)	87.8 (2.6)	66.7 (2.1)	86.9 (2.6)	54.4 (22.8)
4	99.3 (3.1)	100.2 (3.0)	85.7 (3.0)	51.6 9.4)	79.8 (5.9)	33.9 (48.6)
5	97.4 (1.8)	98.2 (1.9)	81.0 (1.8)	54.7 6.4	82.6 (3.3)	41.8 (33.6)
6	98.5 (1.2)	99.6 (1.1)	80.4 (6.1)	38.9 (51.5)	81.0 (1.6)	41.5 (7.1)

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Claims:

1. A composition for transdermal delivery of a progestin that comprises:
   a) a carrier
   b) a progestin
   c) a skin permeation enhancer and
   d) an anti-oxidant
   wherein the composition comprises a component that contributes to degradation of the progestin, wherein the component is one or more of an organic solvent, polyvinyl pyrrolidone (PVP), or a PVP copolymer.

2. The composition of claim 1, wherein the carrier is a polymeric pressure sensitive adhesive.

3. The composition of claim 1 or 2, wherein the component that contributes to degradation of the progestin is one or more of PVP, polyvinyl pyrrolidone/vinyl acetate (PVP/VA), or dimethyl sulfoxide (DMSO) and wherein the anti-oxidant is not an estrogen or is additional to an estrogen.

4. The composition of any one of the preceding claims, wherein the progestin is desogestrel, dihydroprogesterone, drospirenone, ethynodiol acetate, ethynodiol diacetate, etogestrel, gestodene, gestogen, 17-hydrogesterone, hydroxyprogesterone caproate, 3-keto-desogestrel, levonorgestrel, medroxyprogesterone acetate, medroxyprogesterone diacetate, megestrol, megestrol acetate, normegesterol, norelgestromin, norethindrone (i.e., norethisterone), norethindrone acetate, norethynodrel, norgestimate, norgestrel, 19-nortestosterone, progesterone, nestorone, methoxyprogesterone, or dl-norgestrel, or any combination of two or more of said progestins.

5. The composition of any one of the preceding claims, wherein the progestin is levonorgestrel or norethindrone acetate.

6. The composition of any one of the preceding claims, wherein the anti-oxidant is selected from Vitamins A, C, D, and E, carotenoids, flavanoids, isoflavanoids, beta-carotene, butylated hydroxytoluene ("BHT"), butylated hydroxyanisole (BHA), glutathione, lycopene, gallic acid and esters thereof, salicylic acid and esters thereof, sulfites, alcohols, amines, amides, sulfoxides, surfactants, or any combination thereof.

7. The composition of any one of the preceding claims, wherein the anti-oxidant is sodium bisulfite, sodium sulfite, isopropyl gallate, Vitamin C and E, Irganox 1010, Irgafos 168 or BHT or any combination of two or more of said anti-oxidants.

8. The composition of any one of the preceding claims, wherein the anti-oxidant comprises one or more phenolic anti-oxidants.

9. The composition of any one of the preceding claims, wherein the anti-oxidant is BHT, pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate), or tris(2,4-di-tert-butylphenyl) phosphite.

10. The composition of any one of the preceding claims, wherein the polymeric carrier is a pressure sensitive adhesive (PSA) selected from a polyacrylate adhesive, a polyisobutylene adhesive, or a silicone adhesive.

11. The composition of any one of the preceding claims, wherein the PSA is polymerized by free radical polymerization.

12. The composition of claim 11, wherein the PSA is a polyacrylate adhesive.

13. The composition of claim 12, wherein the PSA comprises a 2-ethylhexyl acrylate co-monomer.

14. The composition of claim 12, wherein the polyacrylate adhesive further comprises about 50 to 60% w/w vinyl acetate co-monomer.

15. The composition of any one of the preceding claims, wherein the skin permeation enhancer comprises one or more of: alcohols; alkanones; amides and other nitrogenous compounds; 1-substituted azacycloheptan-2-ones; bile salts; cholesterol; cyclodextrins and substituted cyclodextrins; ethers; saturated and unsaturated fatty acids; saturated and unsaturated fatty acid esters; saturated and unsaturated fatty alcohol esters; glycerides and monoglycerides; organic acids; methyl nicotinate; pentadecalactone; polyols and esters thereof; phospholipids; sulfoxides; surfactants; terpenes; and combinations thereof.

16. The composition of claim 15, wherein the skin permeation enhancer comprises an organic solvent.

17. The composition of claim 16, wherein the organic solvent is DMSO.

18. The composition of claim 15, wherein the skin permeation enhancer comprises one or more of: DMSO, a fatty (C_8-C_{20}) alcohol ester of a hydroxy acid, a lower (C_1-C_4) alkyl ester of a hydroxy acid, and a C_6-C_{18} fatty acid.

19. The composition of claim 18, wherein the skin permeation enhancer comprises one or more of: DMSO, lauryl lactate, ethyl lactate, and capric acid.

20. The composition of any one of the preceding claims, further comprising a humectant.

21. The composition of claim 20, wherein the humectant is PVP or PVP/VA.

22. The composition of any one of the preceding claims, wherein the progestin is present in a concentration based on weight of the composition of 0.1% to 3.0% or 0.2% to 2.0% or 0.5% to 1.5%.

23. The composition of any one of the preceding claims, wherein the skin permeation enhancer is present in a concentration based on weight of the composition of 1% to 50% or 2% to 40%.

24. The composition of any one of the preceding claims, wherein the anti-oxidant is BHT.

25. The composition of claim 24, wherein the BHT is present in a concentration based on weight of the hormone of 10% to 500%, 20% to 200%, or 50% to 150%.

26. The composition of any one of the preceding claims, which does not comprise an estrogen.

27. The composition of any one of the preceding claims, wherein the anti-oxidant is pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) or tris (2,4-di-tert-butylphenyl) phosphite.

28. A transdermal drug delivery device that comprises:
    a) a transdermal composition of any one of the preceding claims, said composition comprising a PSA and having a skin contacting surface and a non-skin contacting surface;
    b) a release liner adjacent the skin contacting surface of the transdermal composition; and
    c) a backing layer adjacent the non-skin contacting surface.

29. A method of improving the stability of a progestin-only transdermal delivery composition, which composition comprises an oxidizing agent, the method comprising adding an anti-oxidant other than an estrogen to the composition.

30. The method of claim 29, wherein the oxidizing agent is one or more of an organic solvent, PVP, or a PVP copolymer.

31. The method of claim 30, wherein the composition comprises a PSA.

32. The method of claim 30 or 31, wherein the progestin is desogestrel, dihydroprogesterone, drospirenone, ethynodiol acetate, ethynodiol diacetate, etogestrel, gestodene, gestogen, 17-hydrogesterone, hydroxyprogesterone caproate, 3-keto-desogestrel, levonorgestrel, medroxyprogesterone acetate, medroxyprogesterone diacetate, megestrol, megestrol acetate, normegesterol, norelgestromin, norethindrone (norethisterone), norethindrone acetate, norethynodrel, norgestimate, norgestrel, 19-nortestosterone, progesterone, nestorone, methoxyprogesterone, and dl-norgestrel or any combination of two or more of said progestins.

33. The method of claim 29, 30, 31, or 32, wherein the progestin is levonorgestrel or norethindrone acetate.

34. The method of claim 29, 30, 31, 32, or 33, wherein the anti-oxidant is selected from Vitamins A, C, D, and E, carotenoids, flavanoids, isoflavanoids, beta-carotene, bu lated hydroxytoluene ("BHT"), butylated hydroxyanisole (BHA), glutathione, lycopene, gallic acid and esters thereof, salicylic acid and esters thereof, sulfites, alcohols, amines, amides, sulfoxides, phenolics or surfactants, or any combination of two or more of said anti-oxidants.

35. The method of claim 29, 30, 31, 32, or 33, wherein the anti-oxidant is sodium bisulfite, sodium sulfite, isopropyl gallate, Vitamin C and E, Irganox 1010, Irgafos 168 or BHT or any combination of two or more of said anti-oxidants.

36. The method of claim 29, 30, 31, 32, 33, 34 or 35, wherein the polymeric carrier is a PSA selected from a polyacrylate adhesive, a polyisobutylene adhesive, or a silicone adhesive.

37. The method of claim 36, wherein the PSA is polymerized by free radical polymerization.

38. The method of claim 37, wherein the PSA is a polyacrylate adhesive.

39. The method of claim 38, wherein the PSA comprises a 2-ethylhexyl acrylate monomer.

40. The method of claim 39, wherein the polyacrylate adhesive further comprises about 3 to 60% w/w vinyl acetate monomer.

41. The method of any one of claims 29 through 40, wherein the skin permeation enhancer comprises one or more of: alcohols; alkanones; amides and other nitrogenous compounds; 1-substituted azacycloheptan-2-ones; bile salts; cholesterol; cyclodextrins and substituted cyclodextrins; ethers; saturated and unsaturated fatty acids; saturated and unsaturated fatty acid esters; saturated and unsaturated fatty alcohol esters; glycerides and monoglycerides; organic acids; methyl nicotinate; pentadecalactone; polyols and esters thereof; phospholipids; sulfoxides; surfactants; terpenes; and combinations thereof.

42. The method of claim 41, wherein the enhancer comprises an organic solvent.

43. The method of claim 42, wherein the organic solvent is DMSO.

44. The method of claim 41, 42 or 43, wherein the enhancer comprises one or more of: DMSO, a fatty (C_8-C_{20}) alcohol ester of a hydroxy acid, a lower (C_1-C_4) alkyl ester of a hydroxy acid, and a C_6-C_{18} fatty acid.

45. The method of claim 44, wherein the enhancer comprises DMSO, lauryl lactate, ethyl lactate, and capric acid.

46. The method of any one of claims 29 through 45, wherein the composition further comprises a humectant.

47. The method of claim 46, wherein the humectant is PVP or PVP/VA.

48. The method of any one of claims 29 through 47, wherein the progestin is present in a concentration based on weight of the composition of 0.1% to 3.0% or 0.2% to 2.0% or 0.5% to 1.5%.

49. The method of any one of claims 29 through 48, wherein the skin permeation enhancer is present in a concentration based on weight of the composition of 1% to 50% or 2% to 40%.

50. The method of any one of claims 29 through 49, wherein the anti-oxidant is BHT.

51. The method of claim 50, wherein the BHT is present in a concentration based on weight of the hormone of 10% to 500%, 20% to 200%, or 50% to 150%.

52. The method of any one of claims 29 through 49, wherein the anti-oxidant is pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) or tris (2,4-di-tert-butylphenyl) phosphite.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/063314

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/70 A61K47/10 A61K31/565 A61K31/57
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/18603 A1 (NOVEN PHARMA [US]; MIRANDA JESUS [US]; SABLOTSKY STEVEN [US]) 13 July 1995 (1995-07-13)	1-4, 6-26, 28-32, 34-51
Y	page 28, paragraph 1 page 30, lines 14-15, 22-24 page 33, paragraph 2; examples 4,17	5,27,33, 52

X	WO 99/15156 A1 (ETHICAL PHARMACEUTICALS SOUTH [AR]; PAGET HUGH CHARLES EDWARD [GB]; BI) 1 April 1999 (1999-04-01)	1-12, 14-26, 28-51
Y	page 14, lines 10-36; example 4	5,27,33, 52

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2013	08/03/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/063314

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 103957899 A
(43)申请公布日 2014.07.30

(21)申请号 201280054080.8
(22)申请日 2012.11.02
(30)优先权数据
61/555,546 2011.11.04 US
61/645,778 2012.05.11 US
(85)PCT国际申请进入国家阶段日
2014.05.04
(86)PCT国际申请的申请数据
PCT/US2012/063314 2012.11.02
(87)PCT国际申请的公布数据
WO2013/067346 EN 2013.05.10
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(51)Int.Cl.
A61K 9/70(2006.01)
A61K 47/10(2006.01)
A61K 31/565(2006.01)
A61K 31/57(2006.01)

权利要求书3页 说明书13页

(54)发明名称

皮肤递送组合物和方法

(57)摘要

本发明公开一种用于经皮递送孕激素以进行孕激素类激素疗法的组合物。还公开包含所述组合物的经皮递送装置。对于仅有孕激素的激素疗法，该组合物含有抗氧化剂并且不含雌激素。对于涉及孕激素和雌激素的疗法，该组合物含有孕激素、雌激素和附加的抗氧化剂。还公开了提高包含氧化剂的含孕激素的组合物的稳定性的方法。所述方法包括在所述组合物中包含一种或多种抗氧化剂。

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1. 一种用于经皮递送孕激素的组合物，该组合物包含：

a) 载体，

b) 孕激素，

c) 皮肤渗透增强剂，和

d) 抗氧化剂，

其中所述组合物包含促使孕激素降解的组分，其中所述组分是有机溶剂、聚乙烯吡咯烷酮 (PVP) 或 PVP 共聚物中的一种或多种。

2. 如权利要求 1 所述的组合物，其中所述载体是聚合物压敏粘合剂。

3. 如权利要求 1 或 2 所述的组合物，其中所述促使孕激素降解的组分是 PVP、聚乙烯吡咯烷酮 / 乙酸乙烯酯 (PVP/VA) 或二甲亚砜 (DMSO) 中的一种或多种，并且其中所述抗氧化剂不是雌激素或者是除雌激素以外还有的物质。

4. 如前述权利要求中任一项所述的组合物，其中孕激素是去氧孕烯、二氢孕酮、屈螺酮、醋炔诺醇、双醋炔诺醇、依托孕烯、孕二烯酮、gestogen、17- 氢化孕酮、己酸羟孕酮、3- 酮 - 去氧孕烯、左炔诺孕酮、醋甲羟孕酮、双醋甲羟孕酮、甲地孕酮、醋甲地孕酮、诺美孕酮、诺孕曲明、炔诺酮、醋酸炔诺酮、异炔诺酮、诺孕酯、炔诺孕酮、19- 去甲睾酮、黄体酮、醋烯诺孕酮、甲氧基孕酮或 dl-18- 甲基炔诺酮，或两种或更多种孕激素的任何组合。

5. 如前述权利要求中任一项所述的组合物，其中孕激素是左炔诺孕酮或醋酸炔诺酮。

6. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂选自维生素 A、C、D 和 E、类胡萝卜素、类黄酮、异类黄酮、β 胡萝卜素、丁基化羟基甲苯（“BHT”）、丁基化羟基苯甲醚 (BHA)、谷胱甘肽、番茄红素、没食子酸及其酯、水杨酸及其酯、亚硫酸盐、醇、胺、酰胺、亚砜、表面活性剂或其任何组合。

7. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂是亚硫酸氢钠、亚硫酸钠、没食子酸异丙酯、维生素 C 和 E、Irganox1010、Irgafos168 或 BHT，或两种或更多种所述抗氧化剂的任何组合。

8. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂包含一种或多种酚类抗氧化剂。

9. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂是 BHT、四 (3-(3,5- 二叔丁基 -4- 羟基苯基）丙酸）季戊四醇酯或亚磷酸三 (2,4- 二叔丁基苯基）酯。

10. 如前述权利要求中任一项所述的组合物，其中所述聚合物载体是选自聚丙烯酸酯粘合剂、聚异丁烯粘合剂或聚硅氧烷粘合剂的压敏粘合剂 (PSA)。

11. 如前述权利要求中任一项所述的组合物，其中所述 PSA 是通过自由基聚合进行聚合的。

12. 如权利要求 11 所述的组合物，其中所述 PSA 是聚丙烯酸酯粘合剂。

13. 如权利要求 12 所述的组合物，其中所述 PSA 包含丙烯酸 -2- 乙基己基酯共聚单体。

14. 如权利要求 12 所述的组合物，其中所述聚丙烯酸酯粘合剂进一步包含约 50％ w/w 至 60％ w/w 的乙酸乙烯酯共聚单体。

15. 如前述权利要求中任一项所述的组合物，其中所述皮肤渗透增强剂包含以下一种或多种：醇；烷酮；酰胺和其它含氮化合物；1- 取代的氮杂环庚烷 -2- 酮；胆汁盐；胆固醇；环糊精和取代的环糊精；醚；饱和以及不饱和的脂肪酸；饱和以及不饱和的脂肪酸酯；饱和

以及不饱和的脂肪醇酯；甘油酯和单酸甘油酯；有机酸；烟酸甲酯；十五酸内酯；多元醇及其酯；磷脂；亚砜；表面活性剂；萜；及其组合。

16. 如权利要求 15 所述的组合物，其中所述皮肤渗透增强剂包含有机溶剂。

17. 如权利要求 16 所述的组合物，其中所述有机溶剂是 DMSO。

18. 如权利要求 15 所述的组合物，其中所述皮肤渗透增强剂包含以下一种或多种：DMSO、羟基酸的脂肪（C_8-C_{20}）醇酯、羟基酸的低级（C_1-C_4）烷基酯以及 C_6-C_{18} 脂肪酸。

19. 如权利要求 18 所述的组合物，其中所述皮肤渗透增强剂包含以下一种或多种：DMSO、乳酸月桂酯、乳酸乙酯和癸酸。

20. 如前述权利要求中任一项所述的组合物，进一步包含保湿剂。

21. 如权利要求 20 所述的组合物，其中所述保湿剂是 PVP 或 PVP/VA。

22. 如前述权利要求中任一项所述的组合物，其中基于所述组合物的重量，孕激素的存在浓度为 0.1％至 3.0％，或 0.2％至 2.0％，或 0.5％至 1.5％。

23. 如前述权利要求中任一项所述的组合物，其中基于所述组合物的重量，所述皮肤渗透增强剂的存在浓度为 1％至 50％或 2％至 40％。

24. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂是 BHT。

25. 如权利要求 24 所述的组合物，其中基于所述激素的重量，所述 BHT 的存在浓度为 10％至 500％、20％至 200％，或 50％至 150％。

26. 如前述权利要求中任一项所述的组合物，其不包含雌激素。

27. 如前述权利要求中任一项所述的组合物，其中所述抗氧化剂是四（3-(3,5- 二叔丁基 -4- 羟基苯基）丙酸）季戊四醇酯或亚磷酸三（2,4- 二叔丁基苯基）酯。

28. 一种经皮药物递送装置，其包含：

a) 如前述权利要求中任一项所述的经皮组合物，所述组合物包含 PSA 并且具有皮肤接触面和非皮肤接触面；

b) 邻接所述经皮组合物的所述皮肤接触面的脱离衬里；以及

c) 邻接所述非皮肤接触面的背衬层。

29. 一种提高仅有孕激素的经皮递送组合物的稳定性的方法，所述组合物包含氧化剂，所述方法包含向所述组合物中添加不同于雌激素的抗氧化剂。

30. 如权利要求 29 所述的方法，其中所述氧化剂是有机溶剂、PVP 或 PVP 共聚物中的一种或多种。

31. 如权利要求 30 所述的方法，其中所述组合物包含 PSA。

32. 如权利要求 30 或 31 所述的方法，其中孕激素是去氧孕烯、二氢孕酮、屈螺酮、醋炔诺醇、双醋炔诺醇、依托孕烯、孕二烯酮、gestogen、17- 氢化孕酮、己酸羟孕酮、3- 酮 - 去氧孕烯、左炔诺孕酮、醋甲羟孕酮、双醋甲羟孕酮、甲地孕酮、醋甲地孕酮、诺美孕酮、诺孕曲明、炔诺酮、醋酸炔诺酮、异炔诺酮、诺孕酯、炔诺孕酮、19- 去甲睾酮、黄体酮、醋烯诺孕酮、甲氧基孕酮和 dl-18- 甲基炔诺酮，或两种或更多种孕激素的任何组合。

33. 如权利要求 29、30、31 或 32 所述的方法，其中孕激素是左炔诺孕酮或醋酸炔诺酮。

34. 如权利要求 29、30、31、32 或 33 所述的方法，其中所述抗氧化剂选自维生素 A、C、D 和 E、类胡萝卜素、类黄酮、异类黄酮、β 胡萝卜素、丁基化羟基甲苯（“BHT”）、丁基化羟基苯甲醚（BHA）、谷胱甘肽、番茄红素、没食子酸及其酯、水杨酸及其酯、亚硫酸盐、醇、胺、酰

胺、亚砜、酚醛物质或表面活性剂，或两种或更多种所述抗氧化剂的任何组合。

35. 如权利要求 29、30、31、32 或 33 所述的方法，其中所述抗氧化剂是亚硫酸氢钠、亚硫酸钠、没食子酸异丙酯、维生素 C 和 E、Irganox1010、Irgafos168 或 BHT，或两种或更多种所述抗氧化剂的任何组合。

36. 如权利要求 29、30、31、32、33、34 或 35 所述的方法，其中所述聚合物载体是选自聚丙烯酸酯粘合剂、聚异丁烯粘合剂或聚硅氧烷粘合剂的 PSA。

37. 如权利要求 36 所述的方法，其中所述 PSA 是通过自由基聚合进行聚合的。

38. 如权利要求 37 所述的方法，其中所述 PSA 是聚丙烯酸酯粘合剂。

39. 如权利要求 38 所述的方法，其中所述 PSA 包含丙烯酸 -2- 乙基己基酯单体。

40. 如权利要求 39 所述的方法，其中所述聚丙烯酸酯粘合剂进一步包含约 3w/w 至 60％ w/w 的乙酸乙烯酯单体。

41. 如权利要求 29 至 40 中任一项所述的方法 ：其中所述皮肤渗透增强剂包含以下一种或多种 ：醇 ；烷酮 ；酰胺和其它含氮化合物 ；1- 取代的氮杂环庚烷 -2- 酮 ；胆汁盐 ；胆固醇 ；环糊精和取代的环糊精 ；醚 ；饱和以及不饱和的脂肪酸 ；饱和以及不饱和的脂肪酸酯 ；饱和以及不饱和的脂肪醇酯 ；甘油酯和单酸甘油酯 ；有机酸 ；烟酸甲酯 ；十五酸内酯 ；多元醇及其酯 ；磷脂 ；亚砜 ；表面活性剂 ；萜 ；及其组合。

42. 如权利要求 41 所述的方法，其中所述增强剂包含有机溶剂。

43. 如权利要求 42 所述的方法，其中所述有机溶剂是 DMSO。

44. 如权利要求 41、42 或 43 所述的方法，其中所述增强剂包含以下一种或多种 ：DMSO、羟基酸的脂肪 (C_8-C_{20}) 醇酯、羟基酸的低级 (C_1-C_4) 烷基酯以及 C_6-C_{18} 脂肪酸。

45. 如权利要求 44 所述的方法，其中所述增强剂包含 DMSO、乳酸月桂酯、乳酸乙酯和癸酸。

46. 如权利要求 29 至 45 中任一项所述的方法，其中所述组合物进一步包含保湿剂。

47. 如权利要求 46 所述的方法，其中所述保湿剂是 PVP 或 PVP/VA。

48. 如权利要求 29 至 47 中任一项所述的方法，其中基于所述组合物的重量，孕激素的存在浓度为 0.1％至 3.0％，或 0.2％至 2.0％，或 0.5％至 1.5％。

49. 如权利要求 29 至 48 中任一项所述的方法，其中基于所述组合物的重量，所述皮肤渗透增强剂的存在浓度为 1％至 50％，或 2％至 40％。

50. 如权利要求 29 至 49 中任一项所述的方法，其中所述抗氧化剂是 BHT。

51. 如权利要求 50 所述的方法，其中基于所述激素的重量，所述 BHT 的存在浓度为 10％至 500％、20％至 200％，或 50％至 150％。

52. 如权利要求 29 至 49 中任一项所述的方法，其中所述抗氧化剂是四 (3-(3,5- 二叔丁基 -4- 羟基苯基) 丙酸) 季戊四醇酯或亚磷酸三 (2,4- 二叔丁基苯基) 酯。

皮肤递送组合物和方法

技术领域

[0001] 本发明属于经皮递送类固醇激素的领域。

背景技术

[0002] 已经开发出各种粘合性基质组合物以经皮递送类固醇激素。例如，美国专利7,384,650号描述一种经皮激素递送系统，其利用包含压敏粘合剂(PSA)、保湿剂、皮肤渗透增强剂、雌激素和孕激素的粘合性组合物。

[0003] 美国专利公开2010/0292660和2010/0255072结合US7,384,650中所述的PSA基质尤其描述了可使用的经皮递送系统。

[0004] 将上述专利和专利申请通过参考并入，如同将其完整地阐述于本文中一样。

发明内容

[0005] 本发明涉及适用于经皮递送系统以在无雌激素存在的条件下经皮递送孕激素的聚合物基质。

[0006] 本发明的一个方面的特征在于用于经皮递送孕激素的组合物，所述组合物包含：(a)载体、(b)孕激素、(c)皮肤渗透增强剂，和(d)抗氧化剂，其中所述组合物包含促使孕激素降解的组分，其中所述组分是有机溶剂、聚乙烯吡咯烷酮(PVP)或PVP共聚物中的一种或多种。在一个实施方式中，载体是聚合物压敏粘合剂。在一个实施方式中，促使孕激素降解的组分是PVP、聚乙烯吡咯烷酮/乙酸乙烯酯(PVP/VA)或二甲亚砜(DMSO)中的一种或多种，并且抗氧化剂不是雌激素或者是除雌激素以外还有的物质。

[0007] 孕激素可为去氧孕烯、二氢孕酮、屈螺酮、醋炔诺醇、双醋炔诺醇、依托孕烯(etogestrel)、孕二烯酮、gestogen、17-氢化孕酮、己酸羟孕酮、3-酮-去氧孕烯、左炔诺孕酮、醋甲羟孕酮、双醋甲羟孕酮、甲地孕酮、醋甲地孕酮、诺美孕酮(normegesterol)、诺孕曲明、炔诺酮、醋酸炔诺酮、异炔诺酮、诺孕酯、炔诺孕酮、19-去甲睾酮、黄体酮、醋烯诺孕酮(nestorone)、甲氧基孕酮或dl-18-甲基炔诺酮，或两种或更多种孕激素的任何组合。在某些实施方式中，孕激素为左炔诺孕酮或醋酸炔诺酮。

[0008] 抗氧化剂选自维生素A、C、D和E、类胡萝卜素、类黄酮(flavanoids)、异类黄酮、β胡萝卜素、丁基化羟基甲苯(“BHT”)、丁基化羟基苯甲醚(BHA)、谷胱甘肽、番茄红素、没食子酸及其酯、水杨酸及其酯、亚硫酸盐、醇、胺、酰胺、亚砜、表面活性剂或其任何组合。在某些实施方式中，抗氧化剂是亚硫酸氢钠、亚硫酸钠、没食子酸异丙酯、维生素C和E、Irganox1010、Irgafos168或BHT或两种或更多种那些抗氧化剂的任何组合。在某些实施方式中，抗氧化剂包含一种或多种酚类抗氧化剂。特别地，抗氧化剂是BHT、四(3-(3,5-二叔丁基-4-羟基苯基)丙酸)季戊四醇酯或亚磷酸三(2,4-二叔丁基苯基)酯。

[0009] 在某些实施方式中，聚合物载体是选自聚丙烯酸酯粘合剂、聚异丁烯粘合剂或聚硅氧烷粘合剂的压敏粘合剂(PSA)。PSA可以通过自由基聚合进行聚合。例如，PSA可为聚丙烯酸酯粘合剂。PSA可以包含丙烯酸-2-乙基己基酯共聚单体。聚丙烯酸酯粘合剂可进

一步包含约 50％ w/w 至 60％ w/w 的乙酸乙烯酯共聚单体。

[0010] 在某些实施方式中，皮肤渗透增强剂包含以下一种或多种 ：醇 ；烷酮 ；酰胺和其它含氮化合物 ；1- 取代的氮杂环庚烷 -2- 酮 ；胆汁盐 ；胆固醇 ；环糊精和取代的环糊精 ；醚 ；饱和以及不饱和的脂肪酸 ；饱和以及不饱和的脂肪酸酯 ；饱和以及不饱和的脂肪醇酯 ；甘油酯和单酸甘油酯 ；有机酸 ；烟酸甲酯 ；十五酸内酯 ；多元醇及其酯 ；磷脂 ；亚砜 ；表面活性剂 ；萜 ；及其组合。在一个实施方式中，皮肤渗透增强剂包含有机溶剂。在一些情况下，有机溶剂是 DMSO。在某些实施方式中，皮肤渗透增强剂包含以下一种或多种 ：DMSO、羟基酸的脂肪 (C_8-C_{20}) 醇酯、羟基酸的低级 (C_1-C_4) 烷基酯以及 C_6-C_{18} 脂肪酸。在一个具体实施方式中，皮肤渗透增强剂包含以下一种或多种 ：DMSO、乳酸月桂酯、乳酸乙酯和癸酸。

[0011] 上述组合物还可以包含保湿剂。在某些实施方式中，保湿剂是 PVP 或 PVP 共聚物如 PVP/VA。

[0012] 在上述组合物的各个实施方式中，基于组合物的重量，孕激素的存在浓度为 0.1％至 3.0％，或 0.2％至 2.0％，或 0.5％至 1.5％。基于组合物的重量，皮肤渗透增强剂的存在浓度可为 1％至 50％或 2％至 40％。

[0013] 在某些实施方式中，组合物中的抗氧化剂包括 BHT。基于激素的重量，BHT 的存在浓度可为 10％至 500％、20％至 200％，或 50％至 150％。

[0014] 在某些实施方式中，组合物可为不包含雌激素的组合物。

[0015] 在某些实施方式中，组合物中的抗氧化剂是四 (3-(3,5- 二叔丁基 -4- 羟基苯基) 丙酸) 季戊四醇酯或亚磷酸三 (2,4- 二叔丁基苯基) 酯。

[0016] 本发明的另一方面的特征在于一种经皮药物递送装置，包含 ：(a) 如上概括的经皮组合物，其包含 PSA 并且具有皮肤接触面和非皮肤接触面 ；(b) 邻接经皮组合物的皮肤接触面的脱离衬里 ；以及 (c) 邻接非皮肤接触面的背衬层。

[0017] 本发明的另一方面的特征在于一种提高包含氧化剂的仅有孕激素的经皮递送组合物的稳定性的方法。所述方法包括向组合物中添加不同于雌激素的抗氧化剂。在某些实施方式中，氧化剂是有机溶剂、PVP 或 PVP 共聚物中的一种或多种。在某些实施方式中，组合物包含 PSA。孕激素可为去氧孕烯、二氢孕酮、屈螺酮、醋炔诺醇、双醋炔诺醇、依托孕烯、孕二烯酮、gestogen、17- 氢化孕酮、己酸羟孕酮、3- 酮 - 去氧孕烯、左炔诺孕酮、醋甲羟孕酮、双醋甲羟孕酮、甲地孕酮、醋甲地孕酮、诺美孕酮、诺孕曲明、炔诺酮、醋酸炔诺酮、异炔诺酮、诺孕酯、炔诺孕酮、19- 去甲睾酮、黄体酮、醋烯诺孕酮、甲氧基孕酮以及 dl-18- 甲基炔诺酮，或两种或更多种孕激素的任何组合。特别地，孕激素是左炔诺孕酮或醋酸炔诺酮。

[0018] 在所述方法的某些实施方式中，抗氧化剂选自维生素 A、C、D 和 E、类胡萝卜素、类黄酮、异类黄酮、β 胡萝卜素、丁基化羟基甲苯 (“BHT”)、丁基化羟基苯甲醚 (BHA)、谷胱甘肽、番茄红素、没食子酸及其酯、水杨酸及其酯、亚硫酸盐、醇、胺、酰胺、亚砜、酚醛物质或表面活性剂，或两种或更多种所述抗氧化剂的任何组合。特别地，抗氧化剂是亚硫酸氢钠、亚硫酸钠、没食子酸异丙酯、维生素 C 和 E、Irganox1010、Irgafos168 或 BHT，或两种或更多种所述抗氧化剂的任何组合。

[0019] 在所述方法的某些实施方式中，聚合物载体是选自聚丙烯酸酯粘合剂、聚异丁烯粘合剂或聚硅氧烷粘合剂的 PSA。PSA 可以通过自由基聚合进行聚合。例如，PSA 可为聚丙烯酸酯粘合剂。PSA 可包含丙烯酸 -2- 乙基己基酯单体。聚丙烯酸酯粘合剂可进一步包含

约 3％ w/w 至 60％ w/w 的乙酸乙烯酯单体。

[0020] 在所述方法的各个实施方式中，组合物中的皮肤渗透增强剂包含以下一种或多种：醇；烷酮；酰胺和其它含氮化合物；1- 取代的氮杂环庚烷 -2- 酮；胆汁盐；胆固醇；环糊精和取代的环糊精；醚；饱和以及不饱和的脂肪酸；饱和以及不饱和的脂肪酸酯；饱和以及不饱和的脂肪醇酯；甘油酯和单酸甘油酯；有机酸；烟酸甲酯；十五酸内酯；多元醇及其酯；磷脂；亚砜；表面活性剂；萜；及其组合。在某些实施方式中，所述增强剂包含有机溶剂。特别地，有机溶剂是 DMSO。在某些实施方式中，皮肤渗透增强剂包含以下一种或多种：DMSO、羟基酸的脂肪（C_8-C_{20}）醇酯、羟基酸的低级（C_1-C_4）烷基酯以及 C_6-C_{18} 脂肪酸。特别地，所述增强剂包含 DMSO、乳酸月桂酯、乳酸乙酯和癸酸。

[0021] 在所述方法的某些实施方式中，组合物进一步包含保湿剂。保湿剂可为 PVP 或 PVP 共聚物如 PVP/VA。

[0022] 在所述方法的各个实施方式中，基于组合物的重量，组合物中孕激素的存在浓度为 0.1％至 3.0％或 0.2％至 2.0％或 0.5％至 1.5％。基于组合物的重量，皮肤渗透增强剂的存在浓度为 1％至 50％或 2％至 40％。

[0023] 在所述方法的各个实施方式中，组合物中的抗氧化剂是 BHT。基于激素的重量，BHT 的存在浓度可为 10％至 500％、20％至 200％，或 50％至 150％。

[0024] 在所述方法的各个实施方式中，组合物中的抗氧化剂是四（3-(3,5- 二叔丁基 -4- 羟基苯基）丙酸）季戊四醇酯或亚磷酸三（2,4- 二叔丁基苯基）酯。

[0025] 下文更完整地描述的这些实施方式和其它实施方式意在说明而非限制本发明。

具体实施方式

[0026] 本发明适用于向可能受益于仅有孕激素的激素补充的患者递送孕激素激素，即在有或无伴随递送雌激素的条件下递送孕激素。在本发明的一个方面，通过引入抗氧化剂使孕激素稳定，特别是使左炔诺孕酮稳定，即保护其免于降解。尽管乙炔雌二醇本身具有抗氧化活性，但根据本发明预期，如果存在雌激素，那么另外的抗氧化剂被纳入经皮组合物中，所述另外的抗氧化剂不是活性药物成分，例如不是乙炔雌二醇或其它激素。

[0027] 如下文进一步讨论，已经发现经皮组合物如 US7,384,650 和下文所述的经皮组合物的某些组分促使左炔诺孕酮降解。这些组分包括聚丙烯酸酯压敏粘合剂（“PSA”）、PVP 保湿剂（例如 PVP/VA）以及二甲亚砜皮肤渗透增强剂。引入用作抗氧化剂的赋形剂能保护孕激素免于降解，即其能减缓孕激素的降解，并从而增加组合物的保质期。

[0028] 含孕激素的经皮组合物：用于经皮递送，即通过皮肤全身递送的组合物包含孕激素、抗氧化剂、皮肤渗透增强剂和载体。该组合物不必包含雌激素，如果所述组合物不包含雌激素，那么其可称为“仅有孕激素的经皮组合物”。组合物任选地还包含赋形剂如胶凝剂、增塑剂、保湿剂、缓冲剂等。该组合物可被配制并施用于皮肤，例如，作为凝胶剂、膏剂或喷雾剂，或者该组合物可被包含于经皮递送装置如贴片中，其中将组合物通过半透膜被包含于例如储器中，或作为与皮肤直接接触的软质聚合物基质，即其足够坚固而不需要储器膜。

[0029] 在本发明的一个说明性实施方式中，组合物是包含聚合物如压敏粘合剂（PSA）作为载体、孕激素、抗氧化剂和皮肤渗透增强剂的聚合物基质。聚合物可为形成生物学可接受的粘合性聚合物基质的压敏粘合剂（“PSA”），所述粘合性聚合物基质能够形成孕激素能够

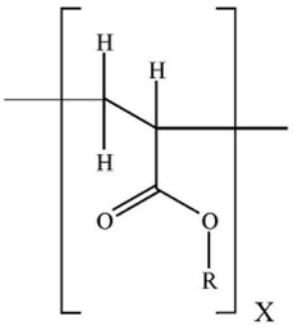
通过并进入皮肤的含活性剂的粘合性薄膜或薄层。合适的聚合物为生物学和药学相容的，不会引起过敏，不溶于装置所接触的体液或组织并与所述体液或组织相容。使用水溶性聚合物通常是不太优选的，因为基质的溶解或侵蚀将影响孕激素的释放速率以及剂量单位在皮肤上保持在位的能力。因此，在某些实施方式中，聚合物是非水溶性的。

[0030] 例如在 US7,045,145、US7,384,650、US20100255072、US2010292660 和 US20100178323 中公开了合适的孕激素经皮组合物，所有上述专利案都通过参考并入本文中，如同完整阐述一样。

[0031] 用于形成含孕激素的层中的聚合物基质的聚合物可具有低于室温的玻璃化转变温度，以使其在室温下柔软并柔韧。聚合物优选是非结晶的，但是如果对于开发其它期望的性质有必要，那么可以具有一些结晶度。可将可交联单体单元或位点引入到这些聚合物中。例如，可引入聚丙烯酸酯聚合物中的交联单体包括多元醇的聚甲基丙烯酸酯，如二丙烯酸丁二酯和二甲基丙烯酸丁二酯、三羟甲基丙烷三甲基丙烯酸酯等。提供这些位点的其它单体包括丙烯酸烯丙基酯、甲基丙烯酸烯丙基酯、马来酸二烯丙基酯等。

[0032] 可用以形成粘合性组合物的 PSA 典型地是聚丙烯酸酯、聚异丁烯或聚硅氧烷粘合剂。适用的粘合性聚合物制剂包含通式 (I) 所示的聚丙烯酸酯粘合性聚合物：

[0033]



[0034] 其中 X 表示足以在粘合性聚合物中提供期望性质的重复单元的数目，并且 R 是 H 或低级 (C_1-C_{10}) 烷基，如乙基、丁基、2- 乙基己基、辛基、癸基等。粘合性聚合物基质可包含例如具有丙烯酸 -2- 乙基己基酯单体和约 50-60％ w/w 乙酸乙烯酯作为共聚单体的聚丙烯酸酯粘合剂共聚物。适用于本发明的聚丙烯酸酯粘合剂共聚物的实例包括但不限于美国新泽西州布里奇沃特的汉高公司以商品名 Duro Tak® 87-4098 出售的共聚物，其包含乙酸乙烯酯共聚单体。

[0035] 孕激素：适用于实践本发明的孕激素包括去氧孕烯、二氢孕酮、屈螺酮、醋炔诺醇、双醋炔诺醇、依托孕烯、孕二烯酮、gestogen、17- 氢化孕酮、己酸羟孕酮、3- 酮 - 去氧孕烯、左炔诺孕酮、醋甲羟孕酮、双醋甲羟孕酮、甲地孕酮、醋甲地孕酮、诺美孕酮、诺孕曲明、炔诺酮、醋酸炔诺酮、异炔诺酮、诺孕酯、炔诺孕酮、19- 去甲睾酮、黄体酮、醋烯诺孕酮、甲氧基孕酮和 dl-18- 甲基炔诺酮，或两种或更多种孕激素的任何组合。特别感兴趣的是左炔诺孕酮和炔诺酮以及炔诺酮盐，例如醋酸炔诺酮。左炔诺孕酮是基于重量 - 剂量的强力孕激素并且可以针对那个原因或其它原因进行选择。基于经皮组合物的重量 (即重量％)，孕激素的存在浓度典型地为 0.1 至 3％或 0.2 至 2.0％或 0.5-1.5％。

[0036] 雌激素：适用于实践本发明的雌激素包括 (不限于) 乙炔雌二醇、17-β - 雌二醇、雌二醇 -3,17- 双乙酸盐；雌二醇 -3- 乙酸盐；雌二醇 17- 乙酸盐；雌二醇 -3,17- 二戊酸盐；

雌二醇 -3- 戊酸盐 ;雌二醇 -17- 戊酸盐 ;3- 单 - 新戊酸雌二醇酯、17- 单 - 新戊酸雌二醇酯和 3,17- 二新戊酸雌二醇酯 ;3- 单 - 丙酸雌二醇酯、17- 单 - 丙酸雌二醇酯和 3,17- 二丙酸雌二醇酯 ;3- 单 - 环戊基 - 丙酸雌二醇酯、17- 单 - 环戊基 - 丙酸雌二醇酯和 3,17- 双环戊基 - 丙酸雌二醇酯，以及雌激素酮。特别感兴趣的是乙炔雌二醇。基于经皮组合物的重量（即重量％），雌激素的存在浓度典型地为 0.1 至 3％，或 0.2 至 2.0％，或 0.5 至 1.5％，例如 0.5 至 1％。

[0037] 皮肤渗透增强剂 :许多皮肤渗透增强剂已被用于改善孕激素通过皮肤并进入血流。其包括例如醇 ;烷酮 ;酰胺和其它含氮化合物 ;1- 取代的氮杂环庚烷 -2- 酮 ;胆汁盐 ;胆固醇 ;环糊精和取代的环糊精 ;醚 ;饱和以及不饱和的脂肪酸 ;饱和以及不饱和的脂肪酸酯 ;饱和以及不饱和的脂肪醇酯 ;甘油酯和单酸甘油酯 ;有机酸 ;烟酸甲酯 ;十五酸内酯 ;多元醇及其酯 ;磷脂 ;亚砜 ;表面活性剂 ;萜 ;及其组合。

[0038] 可提及以下作为具体实例 :癸醇、十二烷醇、2- 己基癸醇、2- 辛基十二烷醇、油醇、十一烯酸、月桂酸、肉豆蔻酸和油酸、脂肪醇乙氧基化物、脂肪酸与甲醇、乙醇或异丙醇的酯、月桂酸甲酯、油酸乙酯、肉豆蔻酸异丙酯和棕榈酸异丙酯、脂肪醇与乙酸或乳酸的酯、乳酸月桂酯、乙酸油烯酯、1,2- 丙二醇、甘油、1,3- 丁二醇、二丙二醇和聚乙二醇。

[0039] 特别感兴趣的是挥发性有机溶剂，包括但不限于二甲亚砜 (DMSO)、C_1-C_8 支链或非支链醇如乙醇、丙醇、异丙醇、丁醇、异丁醇等，以及氮酮 (azone)（月桂氮卓酮 :1- 十二烷基六氢 -2H- 氮杂卓 -2- 酮）和甲基磺酰基甲烷。还特别感兴趣的是脂肪酸及其酯。

[0040] 例如，适用于本发明的皮肤渗透增强剂可为以下各物的混合物 :(1) 可药用的有机溶剂如二甲亚砜 (DMSO)，(2) 羟基酸的脂肪 (C_8-C_{20}) 醇酯如乳酸月桂酯，(3) 羟基酸的低级 (C_1-C_4) 烷基酯，例如乳酸乙酯，以及 (4)C_6-C_{18} 脂肪酸如癸酸。在具体实施方式中，乳酸脂肪醇酯为乳酸月桂酯以及乳酸的低级烷基酯为乳酸乙酯。在皮肤渗透增强剂中，可采用皮肤渗透增强剂制剂中的中链到长链的脂肪酸。优选使用癸酸，但是也可使用其它 C_6-C_{18} 饱和或不饱和脂肪酸，包括但不限于己酸、辛酸、月桂酸和肉豆蔻酸等。

[0041] 在一个特别实施方式中，可药用的有机溶剂为 DMSO。适用于本发明的其它有机溶剂包括但不限于 C_1-C_8 支链或非支链醇如乙醇、丙醇、异丙醇、丁醇、异丁醇等，以及氮酮（月桂氮卓酮 :1- 十二烷基六氢 -2H- 氮杂卓 -2- 酮）和甲基磺酰基甲烷等。

[0042] 羟基酸的脂肪醇酯可为乳酸的脂肪醇酯如乳酸月桂酯。然而，可以利用其它羟基酸和脂肪醇。替代性羟基酸包括但不限于 α - 羟基酸如乙醇酸、酒石酸、柠檬酸、苹果酸和杏仁酸，以及 β - 羟基酸、水杨酸。替代性脂肪醇包括任何 C_8-C_{20} 饱和或不饱和脂肪醇，如十四烷基醇、棕榈基醇或油醇等。

[0043] 羟基酸的低级烷基酯还可以利用乳酸，并且可为例如乳酸乙酯。然而，还可以利用其它羟基酸，如乙醇酸、酒石酸、柠檬酸、苹果酸、杏仁酸和水杨酸。另外可以将异丙基肉豆蔻酸 (IPM) 用作羟基酸的低级烷基酯的替代物。

[0044] 上述皮肤渗透增强剂的组合可用以增强类固醇激素从任何类型的如上所讨论的经皮递送组合物的经皮递送。如本文和 US7,045,145、US7,384,650、US20100255072、US2010292660 和 US20100178323 中详述的粘合性聚合物基质型系统是说明性的 ;然而，还可以将所述增强剂组合用于非粘合性聚合物以及多层或储器型经皮递送系统、凝胶剂、膏剂、喷雾剂和洗剂等中。

[0045] 皮肤渗透增强剂的存在浓度典型地为组合物的至少 1 重量％或至少 2 重量％。其存在浓度可以为组合物的至多 50 重量％或至多 40 重量％。在某些实施方式中，基于组合物的重量（即重量％），皮肤渗透增强剂的存在浓度为组合物的 1 至 50％，或 10 至 40％，或 20 至 30％。

[0046] 任选的附加赋形剂：出于各种目的将许多赋形剂用于经皮递送组合物。特别感兴趣的是用作保湿剂和 / 或增塑剂的聚合物。在制剂中引入保湿剂允许剂量单位从皮肤表面吸收水分，转而有助于减少皮肤刺激并且防止递送系统的粘合性聚合物基质不能胶粘足够的持续时间。增塑剂 / 保湿剂可以为制药工业中使用的常规增塑剂，例如聚乙烯吡咯烷酮 (PVP)。特别地，PVP/ 乙酸乙烯酯 (PVP/VA) 共聚物，如分子量为约 50,000 的 PVP/VA 共聚物适用于本发明。PVP/VA 充当增塑剂，用于控制聚合物基质的刚性，以及充当保湿剂，用于调控基质的水分含量。PVP/VA 可为例如 Plasdone® S-630Copovidone（新泽西州韦恩的国际特品公司 (ISP)），其为分子量为 24,000 至 30,000 并且玻璃化转变温度为 106℃的 60:40PVP:VA 共聚物。保湿剂 / 增塑剂的量与覆盖物的胶粘持续时间直接相关。

[0047] 抗氧化剂：抗氧化剂通过自身被氧化用于防止或抑制其它分子的氧化。在包含孕激素和雌激素如乙炔雌二醇两者的聚合物基质中，乙炔雌二醇用作抗氧化剂并从而有助于减少孕激素的氧化降解。采用附加的抗氧化剂会进一步减少氧化降解。在仅有孕激素的组合物中，采用抗氧化剂可能甚至更重要。

[0048] 例如，已经发现某些聚合物，特别地，通过自由基聚合形成的聚合物充当包含孕激素的聚合物基质中的氧化剂，从而使孕激素的稳定性受损。例如，根据本发明已经发现聚丙烯酸酯粘合剂导致孕激素例如左炔诺孕酮的氧化。

[0049] 根据本发明还已经发现常用于经皮聚合物组合物中的 PVP 也促使孕激素氧化。因此，在包含 PVP 或 PVP/VA 以及孕激素的经皮组合物中，添加抗氧化剂会提高孕激素的稳定性。

[0050] 根据本发明还已经发现某些渗透增强剂例如 DMSO 也可导致孕激素例如左炔诺孕酮的氧化。

[0051] 因此，本发明的一个方面的特征在于包含孕激素、抗氧化剂、皮肤渗透增强剂和压敏粘合剂（“PSA”）的聚合物基质，其中所述 PSA 为聚丙烯酸酯粘合剂，例如聚丙烯酸酯 / 乙酸乙烯酯共聚物如 Duro Tak® 87-4098，和 / 或其中所述聚合物基质包含 PVP 或 PVP/VA，和 / 或其中渗透增强剂包含 DMSO。

[0052] 许多化合物可充当本发明的经皮组合物中的抗氧化剂。已知充当抗氧化剂的化合物为：维生素 A、C、D 和 E、类胡萝卜素、类黄酮、异类黄酮、β 胡萝卜素、丁基化羟基甲苯（“BHT”）、丁基化羟基苯甲醚 (BHA)、谷胱甘肽、番茄红素、没食子酸及其酯、水杨酸及其酯、亚硫酸盐、醇、胺、酰胺、亚砜、表面活性剂等。特别感兴趣的是酚类抗氧化剂，例如 BHT、四 (3-(3,5- 二叔丁基 -4- 羟基苯基）丙酸）季戊四醇酯，例如 Irganox1010，和亚磷酸三 (2,4- 二叔丁基苯基）酯，例如 Irgafos168，以及亚硫酸氢钠、亚硫酸钠、没食子酸异丙酯、维生素 C 和维生素 E。

[0053] 有时称为主要抗氧化剂的酚类抗氧化剂如 BHT 是特别合适的。可以有利地利用较大的酚类抗氧化剂，例如分子量大于 500（例如亚磷酸三 (2,4- 二叔丁基苯基）酯）或大于

1000(例如戊四醇四(3-(3,5-二叔丁基-4-羟基苯基)丙酸酯)。

[0054] 经皮组合物的pH值可维持在约pH6至约pH8,例如约pH6.0、6.1、6.2、6.3、6.4、6.5、6.6、6.7、6.8、6.9、7.0、7.1、7.2.、7.3、7.4、7.5、7.6、7.7、7.8、7.9或8.0。在一个实施方式中,将组合物维持在约pH6.5至pH7.5。在另一实施方式中,将组合物维持在约pH7。优选地避免使用那些会提高pH值的抗氧化剂,例如焦亚硫酸钠。基于激素的重量,BHT的存在浓度可为例如激素的至少10重量%或至少20重量%或至少30重量%。BHT的存在浓度可为例如激素的至多150重量%或200重量%或500重量%。在某些实施方式中,基于激素的重量,BHT的存在浓度可为激素的10%至500%、20%至200%,或50%至150%。可容易地确定其它抗氧化剂的合适浓度。例如,亚磷酸三(2,4-二叔丁基苯基)酯,例如Irgafos168的合适浓度包括类似于BHT浓度的浓度,但也可以采用更低或更高的浓度;四(3-(3,5-二叔丁基-4-羟基苯基)丙酸)季戊四醇酯,例如Irganox1010的合适浓度包括类似浓度,但也可以采用更低或更高的浓度,例如高出至多约10%、20%或30%的浓度。

[0055] 阐述以下实施例以更详细地描述本发明。所述实施例意图说明而非限制本发明。

[0056] 具体实施方式

[0057] 实施例1

[0058] 利用下表1中所列的配方制备母共混物。分割母共混物并且掺入乙炔雌二醇或已知抗氧化剂,如表3中所示。然后将每一共混物以133g/m^2的目标涂布重量涂布在脱离衬里上并且在60℃下干燥。将薄片层压,切成15cm^2的样品,放在两个脱离衬里之间,装入袋中,并然后存放在80℃下。在如表2中所示的五个时间点评价样品。

[0059] 表1.母共混物配方

[0060]

左炔诺孕酮	0.38%
渗透增强剂、PVP/VA、乙酸乙酯	39.0%
PSA*	60.5%

[0061] *PSA=具有丙烯酸-2-乙基己基酯单体和约50-60% w/w乙酸乙烯酯作为共聚单体的聚丙烯酸酯粘合剂共聚物

[0062] 表2.取样方案

[0063]

取样时间点	温度	试验样品数
0天(T_0)	80℃	3
2天(T_2)	80℃	3
4天(除第7批以外)(T_4)	80℃	3
6天(仅第7批)(T_6)	80℃	3
8天(T_8)	80℃	3

[0064] 表 3. 试验共混物

[0065]

第 1 批	母共混物
第 2 批	母共混物 + 乙炔雌二醇,1.53mg/15cm^2
第 3 批	母共混物 +BHT,1.14mg/15cm^2
第 4 批	母共混物 +BHT,1.71mg/15cm^2
第 5 批	母共混物 +Irganox1010,1.11mg/15cm^2+Irgafos168,0.57mg/15cm^2
第 6 批	母共混物 +Irganox1010,1.66mg/15cm^2+Irgafos168,0.85mg/15cm^2
第 7 批	母共混物 + 乙炔雌二醇,0.97mg/15cm^2

[0066] 表 4 中示出在每一时间点,每一组合物中左炔诺孕酮的量,表示为每一批的 3 个样品的平均值,作为左炔诺孕酮的目标量的百分数 (“% TL”),基于聚合物基质的重量其为 0.868%。

[0067] 表 4 以目标左炔诺孕酮%表示的左炔诺孕酮稳定性

[0068]

批次	T_0	T_2	T_4	T_6	T_8
第 1 批	96.9	87.1	68.5	NA	48.1
第 2 批	106.6	92.8	93.3	NA	87.3
第 3 批	106.8	102.0	98.1	NA	97.7
第 4 批	103.4	102.2	99.7	NA	95.7
第 5 批	104.3	104.3	99.4	NA	94.6
第 6 批	102.6	101.1	98.5	NA	93.1
第 7 批	105.4	97.1	NA	93.4	91.7

[0069] 这些结果证明乙炔雌二醇用作组合物中的抗氧化剂并且通过向组合物添加抗氧化剂明显提高了左炔诺孕酮的稳定性。

[0070] 实施例 2

[0071] 向基本上如实施例 1 中所述的左炔诺孕酮、渗透增强剂、聚乙烯吡咯烷酮 / 乙酸乙烯酯共聚物和压敏粘合剂的六批母共混物中添加在每贴 0.02mg(每一贴片含有 300mg 母共混物) 至每贴 1.7mg(值 1.7mg 表示每一贴片中左炔诺孕酮的量的摩尔当量) 的范围内的不同量的 BHT。

[0072] 将每一批加热至 80℃并且在时间点 0、4 和 8 天进行分析。所有 BHT 装载值都对左

炔诺孕酮的稳定性具有积极作用。表 5 中示出在 T ＝第 0 天、T ＝第 4 天和 T ＝第 8 天剩余的 LNG 的量。

[0073] 表 5.BHT 浓度对左炔诺孕酮降解的影响

[0074]

BHT(mg/ 贴)	第 0 天	第 4 天	第 8 天
0	98	56	56
1.7	100	95	91
0.3	102	98	91
0.15	101	94	85
0.075	98	90	69
0.040	101	74	62
0.020	100	66	66

[0075] 实施例 3

[0076] 如所述对以下试验批进行制备和试验。

[0077] a) 将左炔诺孕酮 (2.6mg) 溶解于 412mg Duro Tak87-4098(下文的“载体”) 中。制得压延物 (drawdown) 并且在 80℃下加热 4 天和 8 天。测定加热 4 天和 8 天的样品的剩余左炔诺孕酮的量以及降解物的百分数。

[0078] b) 将左炔诺孕酮 (2.6mg) 和 60mg PVP/VA 溶解于 412mg 载体中。制得压延物并且在 80℃下加热 4 天和 8 天。测定加热 4 天和 8 天的样品的剩余左炔诺孕酮的量以及降解物的百分数。

[0079] c) 将左炔诺孕酮 (2.6mg)、1.71mg BHT 和 60mg PVP/VA 溶解于 412mg 载体中。制得压延物并且在 80℃下加热 4 天和 8 天。测定加热 4 天和 8 天的样品的剩余左炔诺孕酮的量以及降解物的百分数。

[0080] d) 除添加 1.14mg BHT 以外，进行与 c) 中所述相同的程序。

[0081] 将批制剂概述于表 6 中。

[0082] 表 6. 批制剂的概述

[0083]

	载体 (mg)	左炔诺孕酮 (mg)	PVP/VA(mg)	BHT(mg)
a	412	2.6		
b	412	2.6	60	
c	412	2.6	60	1.71
d	412	2.6	60	1.14

[0084] 进行 HPLC 分析以确定左炔诺孕酮的降解物。使用约 200mg 和 100mg 样品（记录的精确重量）的等分试样用于 4 天和 8 天稳定性。将样品溶解于 5mL 的 1:1 四氢呋喃：甲醇 (THF/MeOH) 中。注入 10μL 进行 HPLC 分析。

[0085] 将样品 a 和 b 在 80℃烘箱中温育 4 天和 8 天之后出现左炔诺孕酮降解物。对于样品 c 和 d，未发现降解物。表 7 中示出结果。

[0086] 表 7. 总降解物的峰面积百分数

[0087]

样品编号	总降解物(%)	
	4 天	8 天
A	0.48	0.75
B	1.26	1.28
C	0.00	0.00
D	0.00	0.00

[0088] 表 8 中示出在 80℃烘箱中温育之后剩余的左炔诺孕酮的峰面积百分数。

[0089] 表 8. 剩余物质的峰面积百分数

[0090]

样品编号	剩余	剩余
	4 天	8 天
a	99.52	99.25
b	98.74	98.72
c	100.00	100.00
d	100.00	100.00

[0091] 表 8 的注释：剩余左炔诺孕酮百分数是从峰面积百分数直接获得的。

[0092] 上述的加速降解研究表明添加 BHT 减少左炔诺孕酮的降解，而添加聚维酮 (PVP) 稍微增加降解。

[0093] 实施例 4

[0094] 制备经皮递送贴片，其包含渗透增强剂、聚乙烯吡咯烷酮 / 乙酸乙烯酯共聚物、压敏粘合剂和变化量的左炔诺孕酮 (LNG) 和 BHT，如下：

[0095] 批次 1：LNG(2.17mg，0.87 重量％)-12.5cm^2 贴片；

[0096] 批次 2：LNG(2.6mg，0.87 重量％)+BHT(1.712mg，0.57 重量％)-15cm^2 贴片；

[0097] 比较透过人尸体皮肤 (3 个供体皮肤样品，每个皮肤供体重复 3 次）的皮肤通量。表 9 中报告数据。

[0098] 表 9. 透过的 LNG 的累积量作为时间的函数

[0099]

批次编号	所透过的 LNG 的累积量(μg/cm²)						
	24 小时	48 小时	72 小时	96 小时	120 小时	144 小时	168 小时
1	5.503 +/- 1.475	12.414+/- 2.456	18.787+/- 3.256	24.962 +/- 3.895	30.502 +/- 4.569	35.767 +/- 5.230	40.736 +/- 5.770
2	5.187+/- 1.900	11.336 +/- 2.755	17.092 +/- 3.578	22.650 +/- 4.286	27.795 +/- 4.969	32.689 +/- 5.551	37.355 +/- 6.110

[0100] 下表中示出每一批中左炔诺孕酮的平均稳态通量（μg/cm²/h)。

[0101] 表 10. 左炔诺孕酮的平均稳态通量（μg/cm²/h)

[0102]

批次 1	0.2442+/-0.0312
批次 2	0.2231+/-0.0312

[0103] 这些数据显示添加 BHT 未阻碍左炔诺孕酮的穿透。

[0104] 实施例 5

[0105] 如表 11 中所示，制备七种经皮组合物以试验聚丙烯酸酯 PSA、PVP 和 DMSO 的氧化作用，所述七种经皮组合物各自包含约 164.8mg Duro Tak® 87-4098 和 2.6mg 左炔诺孕酮(LNG)，经过干燥，有和无 PVP/VA 和 DMSO。

[0106] 表 11. 组合物

[0107]

组合物编号	PVP/VA(mg)	DMSO(mg)
1	无	无
2	60mg PVP/VA	无
3	60mg PVP/VA	无
4	60mg PVP/VA	无
5	60mg PVP/VA	无
6	无	16mg DMSO
7	60mg PVP/VA	16mg DMSO

[0108] 在组合物 1-4 和 6 的情况下，在 78℃下预热 PSA8 小时，随后添加 PVP/VA 和 DMSO。在制剂 3 和 4 的情况下，分别在空气和氮气存在下在 80℃下预热 PVP/VA48 小时。

[0109] 然后将所有制剂都放到 80℃烘箱中，历时 4 天和 8 天。由 HPLC 分析降解物。在表

12 中提供降解物百分数数据。

[0110] 表 12. 总降解物的峰面积百分数

[0111]

组合物编号	降解物(%) 第 4 天	降解物(%) 第 8 天
1	0.32	0.47
2	0.76	0.94
3	0.87	0.91
4	0.78	1.16
5	1.21	1.60
6	1.12	1.67
7	1.65	1.78

[0112] 如表 12 中所示，存在 PVP/VA 使降解物增加约两倍。PVP/VA 的预处理不显示显著差异。加热组合物 8 天产生的降解物比加热 4 天稍多。预热 PSA 减少降解物的量。添加 DMSO 增加降解物的量。

[0113] 实施例 6

[0114] 利用表 13 中所列的配方制备母共混物。然后分割母共混物并且掺入 BHT，如表 14 中所示。然后将每一试验共混物以 200g/m^2 的目标涂布重量涂布在脱离衬里上并且使用风扇转速 2300rpm 在 60℃下干燥 17.5 分钟。然后将薄片层压，切成 15cm^2 的样品，放在两个脱离衬里之间，装入袋中，并然后存放在 80℃下。在第 0 天、第 4 天和第 8 天评价样品。

[0115] 表 13. 母共混物配方

[0116]

左炔诺孕酮	0.378%
乙炔雌二醇	0.333%
渗透增强剂、PVP/VA、乙酸乙酯	39.558%
PSA*	59.730%

[0117] *PSA ＝具有丙烯酸 -2- 乙基己基酯单体和约 50-60％ w/w 乙酸乙烯酯作为共聚单体的聚丙烯酸酯粘合剂共聚物 [Duro-Tak87-4098]

[0118] 表 14. 试验共混物

[0119]

第 1 批	母共混物
第 2 批	母共混物 +BHT，1.712mg/15cm^2，2.481g/kg

第 3 批	母共混物 +BHT,1.000mg/15cm^2,1.449g/kg
第 4 批	母共混物 +BHT,0.428mg/15cm^2,0.620g/kg
第 5 批	母共混物 +BHT,0.300mg/15cm^2,0.435g/kg
第 6 批	母共混物 +BHT,0.150mg/15cm^2,0.217g/kg

[0120] 通过 HPLC 测定左炔诺孕酮和乙炔雌二醇的量。表 15 中示出每一试验共混物的结果 (LC%),表示为每个试验共混物 5 个样品的平均值,具有相对标准差百分数 (RSD%)。

[0121] 表 15. 结果

[0122]

	第 0 天		第 4 天		第 8 天	
试验共混物	EE (RSD%)	LNG (RSD%)	EE (RSD%)	LNG (RSD%)	EE (RSD%)	LNG (RSD%)
对照	98.7 (1.9)	100.3 (2.1)	77.3 (1.0)	43.0 (3.1)	72.9 (9.1)	28.5 (57.0)
2	98.0 (2.2)	98.7 (2.2)	91.4 (1.3)	72.1 (1.5)	85.4 (2.4)	57.5 (8.1)
3	99.1 (1.8)	99.6 (2.0)	87.8 (2.6)	66.7 (2.1)	86.9 (2.6)	54.4 (22.8)
4	99.3 (3.1)	100.2 (3.0)	85.7 (3.0)	51.6 (9.4)	79.8 (5.9)	33.9 (48.6)
5	97.4 (1.8)	98.2 (1.9)	81.0 (1.8)	54.7 6.4	82.6 (3.3)	41.8 (33.6)
6	98.5 (1.2)	99.6 (1.1)	80.4 (6.1)	38.9 (51.5)	81.0 (1.6)	41.5 (7.1)

[0123] 应了解,本文所述的实施例和实施方式仅用于说明目的,并且鉴于其的各种修改或变化将会提示于本领域技术人员并且应包括在本申请的精神和权限以及权利要求书的范围内。

Abstract

A composition for transdermal delivery of a progestin for progestin hormone therapy is disclosed. Also disclosed is a transdermal delivery device comprising the composition. For progestin-only hormone therapy, the composition contains an anti-oxidant and does not contain an estrogen. For therapy involving a progestin and an estrogen, the composition contains the progestin, the estrogen and an additional anti-oxidant. Methods of improving the stability of progestin-containing compositions comprising oxidative agents are also disclosed. The methods comprise including one or more anti-oxidants in the compositions.