US009833419B2

(12) **United States Patent**
Mantelle

(10) **Patent No.: US 9,833,419 B2**
(45) **Date of Patent: *Dec. 5, 2017**

(54) **TRANSDERMAL ESTROGEN DEVICE AND DELIVERY**

(71) Applicant: **NOVEN PHARMACEUTICALS, INC.**, Miami, FL (US)

(72) Inventor: **Juan Mantelle**, Miami, FL (US)

(73) Assignee: **NOVEN PHARMACEUTICALS, INC.**, Miami, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/870,574**

(22) Filed: **Sep. 30, 2015**

(65) **Prior Publication Data**

US 2016/0015655 A1 Jan. 21, 2016

Related U.S. Application Data

(63) Continuation of application No. 14/738,255, filed on Jun. 12, 2015, which is a continuation of application No. 14/024,985, filed on Sep. 12, 2013, now Pat. No. 9,724,310, which is a continuation of application No. 13/553,972, filed on Jul. 20, 2012, now Pat. No. 9,730,900, which is a continuation of application No. 12/216,811, filed on Jul. 10, 2008, now Pat. No. 8,231,906.

(51) **Int. Cl.**

A61K 9/70	(2006.01)
A61K 31/565	(2006.01)
A61K 9/00	(2006.01)
A61K 47/10	(2017.01)
A61K 47/32	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/7069*** (2013.01); ***A61K 9/0014*** (2013.01); ***A61K 9/7061*** (2013.01); ***A61K 31/565*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/32*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Melissa Fisher

(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Described are transdermal drug delivery systems for the transdermal administration of estrogen, comprising a polymer matrix and estrogen. Methods of making and using such systems also are described.

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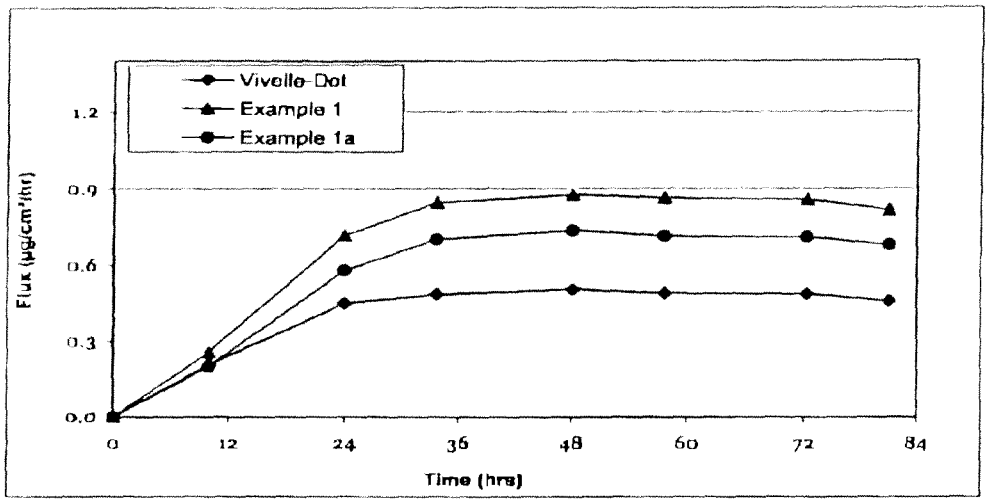

TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

FIELD OF THE INVENTION

Described herein are compositions and methods for the transdermal delivery of estrogen.

BACKGROUND

This invention relates generally to transdermal drug delivery systems, and more particularly, to transdermal drug delivery systems for the delivery of estrogen. The use of a transdermal system, for example, a patch comprising a pressure-sensitive adhesive containing a drug, as a means of delivering drug through the skin is well known. However, there remains a need for transdermal drug delivery systems designed for the delivery of specific drugs, such as estrogen, and there remains a particular need for smaller transdermal drug delivery systems that exhibit desired pharmacokinetic properties.

Transdermal delivery systems (adhesive patches) as dosage forms have been the subject of a vast number of patent applications over the last 25 years, yielding many patents but few commercial products in comparison. To those working in the field, the relatively small number of commercial products is not surprising. Although regulatory, economic, and market hurdles play a role in limiting the number of products on the market, the task of developing a transdermal delivery system that achieves desired physical and pharmacokinetic parameters to satisfy physician and patient demand is more daunting. Parameters to be considered during commercial product development may include drug solubility, drug stability (e.g., as may arise from interaction with other component materials and/or the environment), delivery of a therapeutic amount of drug at a desired delivery rate over the intended duration of use, adequate adhesion at the anatomical site of application, integrity (e.g., minimal curling, wrinkling, delaminating and slippage) with minimal discomfort, irritation and sensitization both during use and during and after removal, and minimal residual adhesive (or other components) after removal. Size also may be important from a manufacturing and patient viewpoint, and appearance may be important from a patient viewpoint. The physical manufacturing and production aspects of commercial product development (e.g., the identity and costs of materials, equipment, and labor) and supporting analytical methods required for regulatory compliance also can be significant.

Of the physical parameters that are considered when developing a commercial transdermal drug delivery system, size, e.g., surface area at the site of application, is often dictated and limited by other physical and pharmacokinetic requirements, such as desired drug delivery rates and daily dosages. In general, it is easier to develop a relatively "large" transdermal drug delivery system that will achieve drug delivery at target therapeutic levels over an intended duration of therapy, than it is to develop a smaller transdermal drug delivery system that still exhibits acceptable pharmacokinetic properties. Still, because size directly impacts costs (e.g., costs of component materials, costs of packaging materials, costs for production and manufacturing equipment, labor costs relative to product yield per run time, etc.)

surface may permit the use of less aggressive adhesives), there is a need for smaller transdermal drug delivery systems.

SUMMARY

In accordance with one embodiment, there is provided a transdermal drug delivery system comprising a drug containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area. In some embodiments, the polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP. In some embodiments, the polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol, all based on the total dry weight of the polymer matrix. In some embodiments, the polymer matrix comprises about 20% by weight acrylic adhesive, about 56.9% by weight silicone adhesive, about 7.5% by weight soluble PVP, about 6.0% by weight oleyl alcohol, about 8.0% by weight dipropylene glycol, and about 1.6% by weight estradiol. In some embodiments, the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.

In some embodiments, the penetration enhancer comprises oleyl alcohol or dipropylene glycol, or both.

In some embodiments, the polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days. In some embodiments, the polymer matrix comprises an amount of estradiol effective to deliver an amount of estradiol selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

In some embodiments, the polymer matrix has a coat weight of greater than about 10 mg/cm^2. In some embodiments, the polymer matrix has a coat weight selected from the group consisting of about 12.5 and about 15 mg/cm^2.

In accordance with some embodiments, there is provided a transdermal drug delivery system comprising a polymer matrix comprising estradiol, wherein the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

In accordance with some embodiments, there is provided a method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a transdermal drug delivery system comprising a drug-containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area. In some embodiments, the system has an active surface area that is about 60% of a size selected from the group consisting of 2.5, 3.75, 5.0, 7.5 and 10.0 cm^2 and is effective to deliver an amount of estradiol per day of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day, respectively.

In accordance with some embodiments, there is provided

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