US 20060078601A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0078601 A1**

Kanios et al. (43) **Pub. Date: Apr. 13, 2006**

(54) **COMPOSITIONS AND METHODS FOR DELIVERING ESTRADIOL IN TRANSDERMAL DRUG DELIVERY SYSTEMS**

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(21) Appl. No.: **11/245,084**

(22) Filed: **Oct. 7, 2005**

Related U.S. Application Data

(60) Provisional application No. 60/616,862, filed on Oct. 8, 2004.

Publication Classification

(51) **Int. Cl.**
A61K 9/70 (2006.01)

(52) **U.S. Cl.** **424/449**

(57) **ABSTRACT**

A blend of at least two polymers in combination with a drug provides a pressure-sensitive adhesive composition for a transdermal drug delivery system in which the drug is delivered from the pressure-sensitive adhesive composition and through dermis when the pressure-sensitive adhesive composition is in contact with human skin.

Fig. 1

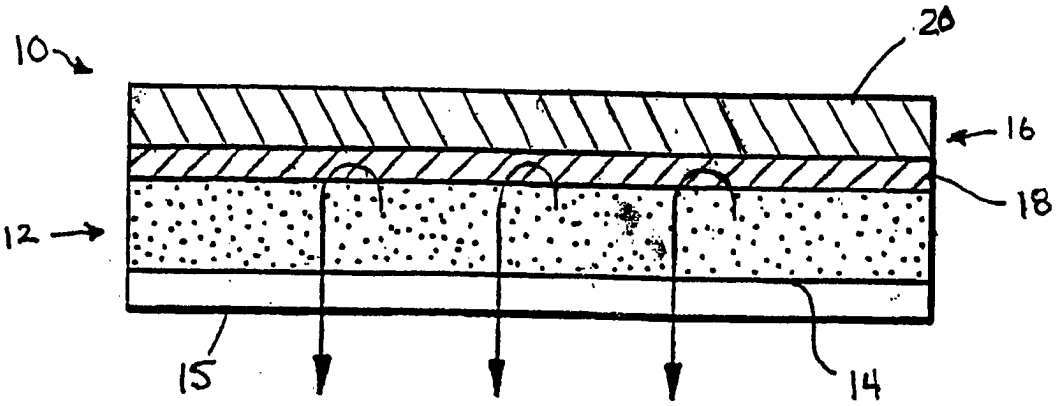


Fig. 2

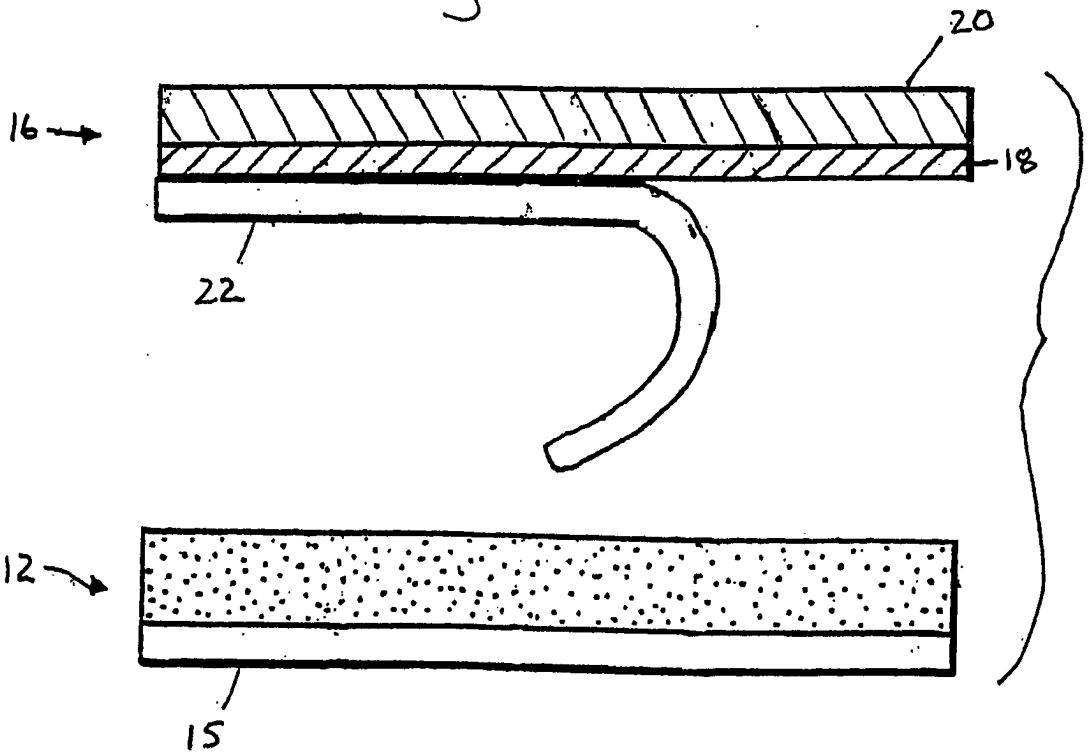


FIGURE 3

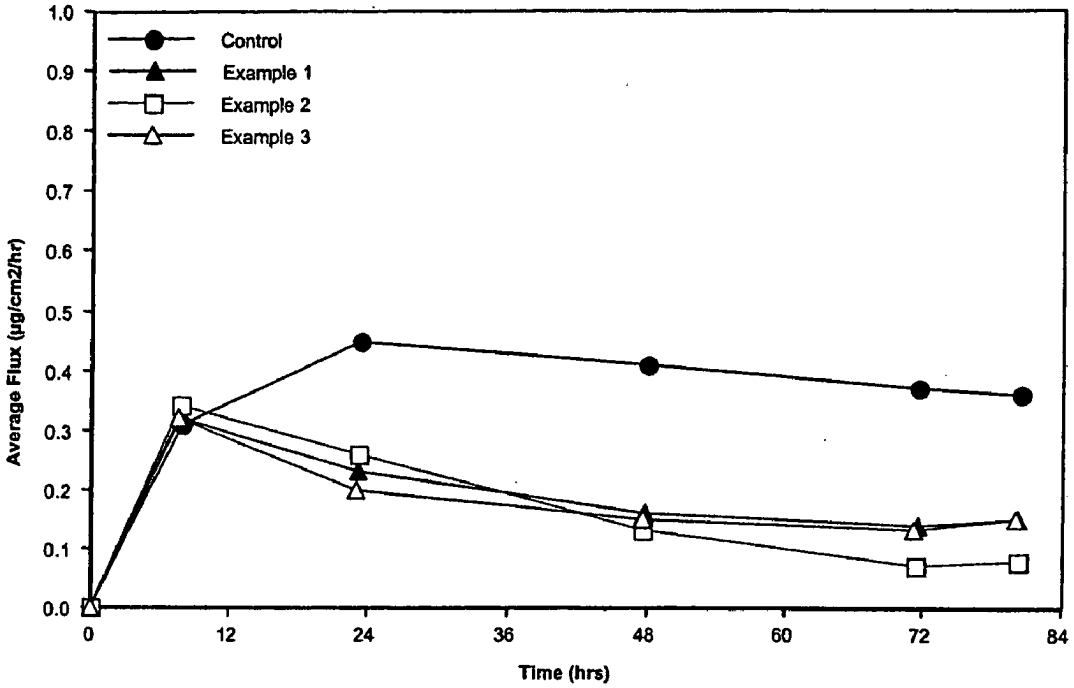
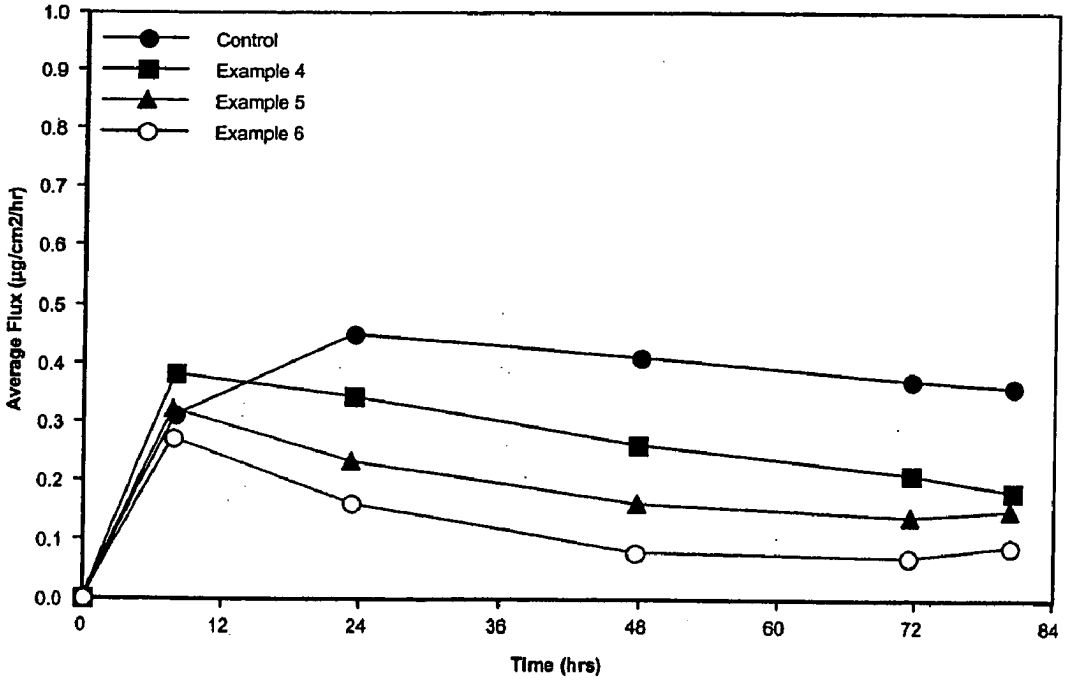


FIGURE 4



COMPOSITIONS AND METHODS FOR DELIVERING ESTRADIOL IN TRANSDERMAL DRUG DELIVERY SYSTEMS

[0001] This application claims the benefit of provisional application 60/616,862 filed Oct. 8, 2004, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates generally to transdermal drug delivery systems, and more particularly to pharmaceutically acceptable adhesive matrix compositions. The invention additionally relates to transdermal drug delivery systems providing substantially zero order drug release profiles for an extended period of time of up to seven days or longer.

BACKGROUND OF THE INVENTION

[0003] The present invention relates to transdermal delivery systems, their method of making and method of use. In particular, the present invention is directed to a transdermal drug delivery system for the topical application of one or more active agents contained in one or more polymeric and/or adhesive carrier layers, proximate to a non-drug containing polymeric and/or adhesive coating that is applied to either the transdermal system's backing or release liner. The adhesive coated backing or release liner may be processed or manufactured separately from the polymeric and/or adhesive drug carrier layers when drug loss or other system concerns are prevalent, and combined prior to topical application. The drug delivery rate and profile can be further controlled by adjusting certain characteristics of the polymers and/or adhesives themselves or of the method of making the system, relative to the active agent's properties in this transdermal system.

BACKGROUND OF THE INVENTION

[0004] The use of a transdermal drug delivery system as a means for administering therapeutically effective amounts of an active agent is well known in the art. Transdermal devices or systems can be categorized in many different ways, but those commonly called transdermal patches, incorporate the active agent into a carrier, usually a polymeric and/or a pressure-sensitive adhesive formulation.

[0005] Many factors influence the design and performance of such drug delivery devices, such as the individual drugs themselves, the physical/chemical characteristics of the system's components themselves and their performance/behavior relative to other system components once combined, external/environmental conditions during manufacturing and storage thereafter, the properties of the topical site of application, the desired rate of drug delivery and onset, the drug delivery profile, and the intended duration of delivery. Cost, appearance, size and ease of manufacturing are also important considerations. The ability to deliver a therapeutically effective amount of the drug in accordance with the intended therapy or treatment is the goal.

[0006] The simplest in design is one in which the drug is incorporated into a pressure-sensitive adhesive carrier layer, each surface of which is affixed to a polymeric film/layer—one serving as the backing (to anchor the carrier layer and control passage of environmental influences in and system removable liner (to protect the carrier layer prior to use but removed upon topical application of the carrier layer). However, when addressing all the design and performance factors and considerations to achieve the goal, this system alone cannot always provide the best method.

[0007] In this regard, a drug's delivery rate is affected by its degree of saturation and solubility in the carrier composition. Depending on the active agent itself or the dosage necessary to be therapeutically effective, the amount of drug needed to be incorporated into a single, adhesive carrier or matrix composition (i.e., drug loading) can adversely affect or be adversely affected by, such carrier or matrix.

[0008] Drug carrier compositions typically require one or more processing solvents, usually organic solvents, in which to incorporate the active agent and/or allow the polymeric/adhesive carrier to be more easily coated onto a backing or release liner. Removal of such solvents is necessary for avoiding problems associated with residual solvent amounts, such as irritation at the topical site of application, drug degradation, drug instability, loss of adhesive or cohesive properties impacting attachment of the system to the user and loss of desired delivery amount or rate. Solvent removal requires that elevated temperatures be applied to the carrier composition to evaporate such solvents. But at the same time, removal of solvents by use of elevated temperatures can also remove or evaporate other desirable components, such as the active agent and drug permeation enhancers. Their loss can even occur at temperatures below which such components may otherwise volatilize by virtue of their interaction with each other and with the other carrier components (relative volatility or reactivity).

[0009] Transdermal carrier compositions based on acrylic pressure-sensitive adhesive polymers are often preferred for their ability to incorporate or solubilize many drugs. In order to provide for adequate wear properties and drug release from the composition, acrylic-based pressure-sensitive adhesives are typically polymerized with functional monomers to provide functional groups on the acrylic-based adhesive. A problem associated with the use of such acrylic-based polymers with functional groups is that due to the generally high solubility of the drug, a large amount of drug generally must be incorporated into the composition to saturate it and provide an adequate drug release to the skin of the user. In use with low molecular weight drugs or controlled substances, the loss of the drug in the manufacturing process again can be a significant problem.

[0010] Attempts have been made to utilize rate controlling membranes and/or multiple layers, and to dissolve or suspend certain drugs in thermoplastic type carrier compositions without the use of solvents. These drug delivery devices generally do not allow a great amount of flexibility in effectively controlling the release rate of a variety of drugs, which in turn also severely limits their therapeutic application, and are expensive or burdensome to manufacture. Moreover, multiple adhesive layers are often required to affix the other layers or membranes to each other, and/or to the site of topical application.

[0011] Thus, it would therefore be desirable to provide a system for use with many types of drugs, in which the permeation rate and profile can be easily adjusted while providing an active agent containing carrier composition

SUMMARY OF THE INVENTION

[0012] Based upon the foregoing, it is an object of the present invention to overcome the limitations of the prior transdermal systems, and to provide a transdermal drug delivery system which allows selective modulation of drug permeation and delivery rates and profiles.

[0013] Another object is to provide a transdermal system, which is simple and inexpensive to manufacture, while preventing or minimizing drug loss and/or other volatile components in the composition. The present invention provides a transdermal drug delivery system for the topical application of one or more active agents contained in one or more polymeric and/or adhesive carrier layers, proximate to a non-drug containing polymeric and/or adhesive coating that is applied to either the transdermal system's backing or release liner, manufactured to optimize drug loading while providing desirable adhesion to skin or mucosa as well as providing modulation of the drug delivery and profile.

[0014] The invention is further directed to a transdermal delivery system comprising a backing composite comprising a non-drug containing polymeric and/or adhesive coating affixed or applied to a drug-impermeable layer. An active agent carrier layer comprising a pressure-sensitive adhesive composition and a drug incorporated therein, which may also contain low boiling point or volatile components such as permeation enhancers, is affixed to the backing composite. The polymeric coating is designed to provide control of permeation rate, onset and profile of the active agent from the system. The agent-carrier composition may comprise one or more layers. The agent-carrier composition may comprise at least one layer formed of a blend of at least one acrylic-based polymer and at least one silicone-based polymer, to serve as a pressure-sensitive adhesive composition for applying the system to the dermis, or a blend of acrylic-based polymers. The non-drug containing acrylic-based or other polymer coating designed to interact with the drug composition layer(s).

[0015] The invention is also directed to compositions and methods of controlling drug delivery rates, onset and profiles of at least one active agent in a transdermal delivery system, comprising the use of a non-drug containing acrylic-based polymer and/or adhesive coating one surface of which is applied to either the transdermal system's backing or release liner and the other surface is affixed to a drug containing carrier composition layer, wherein the delivery rate, onset of delivery (lag time) and delivery profile of a drug may be selectively modulated by one or more of (a) increasing or decreasing the thickness or coat weight of the acrylic-based polymer and/or adhesive coating per cm^2 as applied to the backing or release liner of the system or (b) manipulating the moiety or functionality of the acrylic-based polymer and/or adhesive coating. Either the non-drug containing coating or the carrier composition must also be a pressure-sensitive adhesive when used as area of attachment to the skin or mucosa of the user. The drug carrier composition may be comprised of (a) one or more acrylic-based polymers having one or more functionality or (b) one or more silicone-based polymers having one or more silanol contents (capping) and/or resin to polymer ratios, alone or in combination, and are present in proportions to provide a desired solubility for the drug. Further manipulation of drug

[0016] For a better understanding of the present invention, together with other and further objects thereof, reference is made to the following description, taken in conjunction with the accompanying drawings, and its scope will be pointed out in the appending claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** shows a schematic cross-sectional view of a transdermal delivery device according to an embodiment of the invention prior to use.

[0018] **FIG. 2** shows a schematic cross-section of the agent-carrier assembly and backing assembly according to the embodiment of the present invention as shown in **FIG. 1**, prior to lamination together.

[0019] **FIG. 3** is a graphic representation of the effects on drug delivery, onset and profile of estradiol with different functionalities/moieties of acrylic-based adhesives in the polymeric coating.

[0020] **FIG. 4** is a graphic representation of the effects on drug delivery, onset and profile of estradiol with varying coat weights of an acrylic-based adhesive coating.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0021] In the following description, embodiments of the invention are set forth, and terms are used in describing such embodiments, wherein:

[0022] The term "topical" or "topically" is used herein in its conventional meaning as referring to direct contact with an anatomical site or surface area on a mammal including skin, teeth, nails and mucosa.

[0023] The term "mucosa" as used herein means any moist anatomical membrane or surface on a mammal such as oral, buccal, vaginal, rectal, nasal or ophthalmic surfaces. Similarly, "skin" is meant to include mucosa, which further includes oral, buccal, nasal, rectal and vaginal mucosa.

[0024] The term "transdermal" refers to delivery, administration or application of a drug by means of direct contact with tissue, such as skin or mucosa. Such delivery, administration or application is also known as percutaneous, dermal, transmucosal and buccal.

[0025] As used herein, the terms "blend" and "mixture" are used herein to mean that there is no, or substantially no, chemical reaction or crosslinking (other than simple H-bonding) between the different polymers in the polymer matrix. However, crosslinking between a single polymer component is fully contemplated to be within the scope of the present invention.

[0026] The term "adhesive" means a substance, inorganic or organic, natural or synthetic that is capable of surface attachment at the intended topical application site by itself or functions as an adhesive by admixture with tackifiers, plasticizers, cross-linking agents or other additives. In the most preferred embodiment, the carrier of the present invention is a "pressure-sensitive adhesive" which refers to a viscoelastic material which adheres instantaneously to most substrates with the application of very slight pressure and remains

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