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(54) **DEVICE FOR TRANSDERMAL ADMINISTRATION OF DRUGS INCLUDING ACRYLIC POLYMERS**

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(57) **ABSTRACT**

A transdermal delivery system is provided where the drug delivery rates, onset and profiles of at least one active agent are controlled by selectively manipulating the monomeric make up of an acrylic-based polymer in the transdermal drug delivery system. The drug carrier composition may be comprised of (a) one or more acrylic-based polymers having one or more different monomers selected from the group consisting of hard and soft monomers; (b) one or more silicone-based polymers; and (c) one or more active agents where the device provides a desired solubility for the active agent and controls drug delivery rates, onset and profiles of at least one active agent.

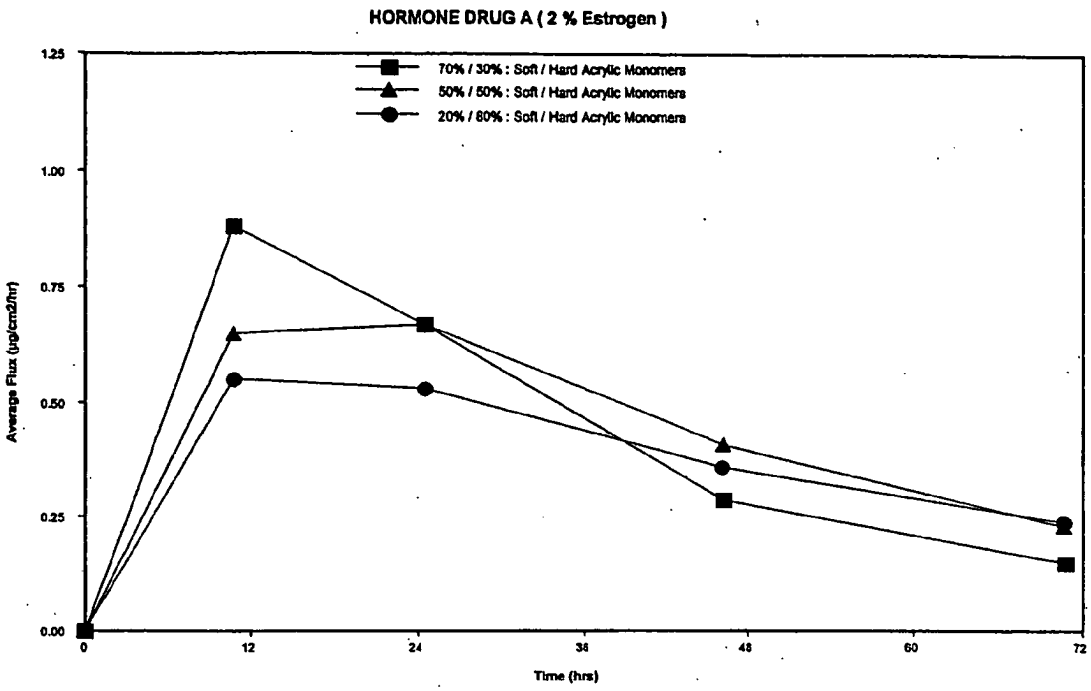

Figure 1

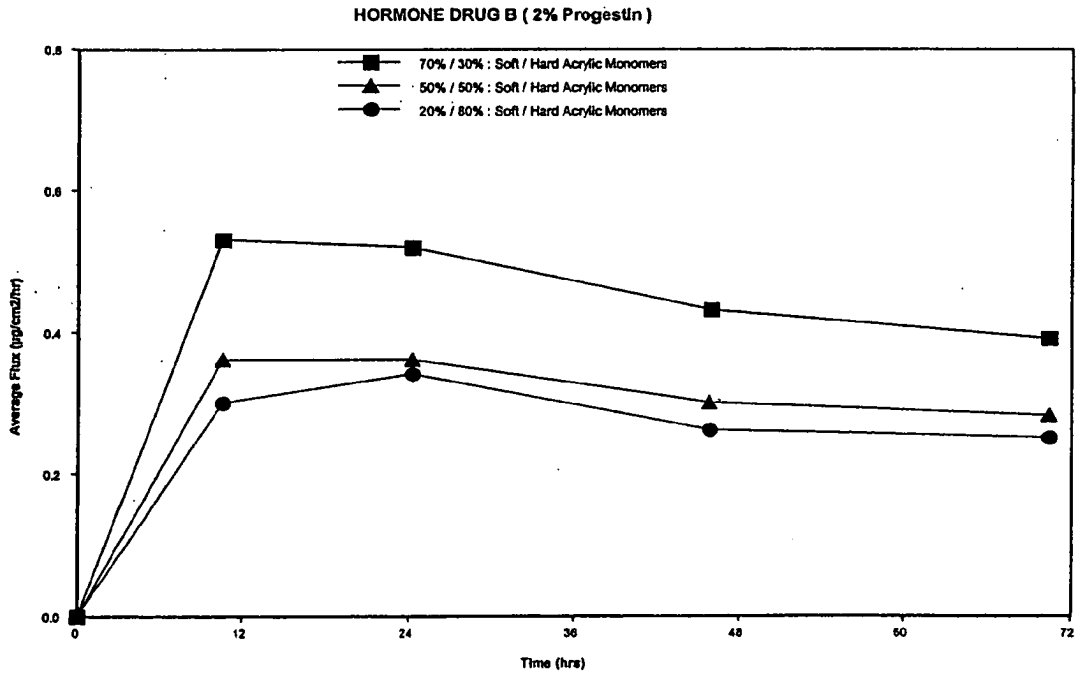

Figure 2

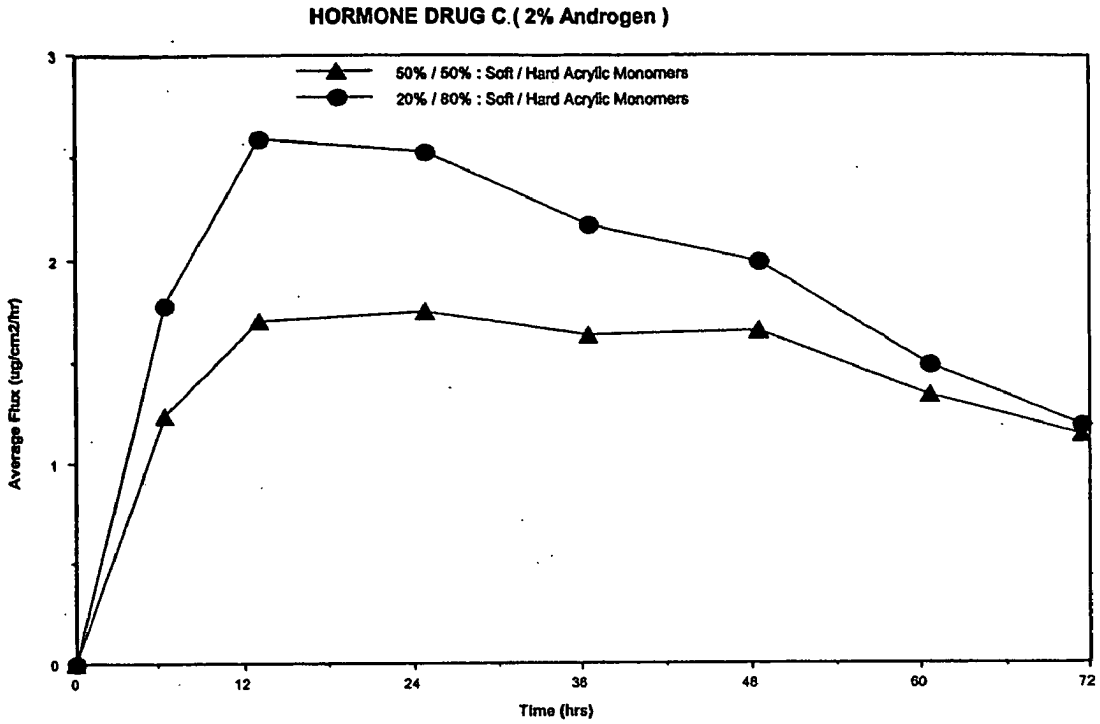

Figure 3

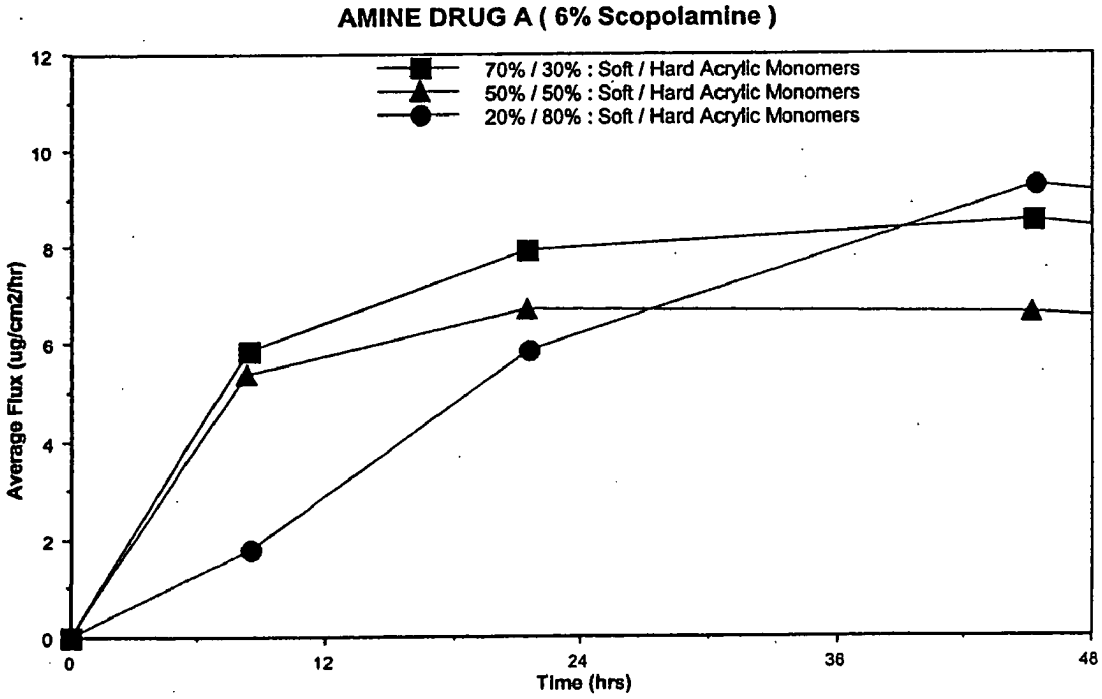

Figure 4

DEVICE FOR TRANSDERMAL ADMINISTRATION OF DRUGS INCLUDING ACRYLIC POLYMERS

[0001] This application claims the benefit of provisional application 60/616,860 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 where the drug permeation, delivery rates and profiles can be selectively modulated within the transdermal drug delivery system.

BACKGROUND OF THE INVENTION

[0003] The use of transdermal drug delivery systems to topically administer an active agent is well known. These systems incorporate the active agent into a carrier composition, such as a polymeric and/or pressure-sensitive adhesive composition, from which the active agent is delivered through the skin or mucosa of the user.

[0004] Active-ingredient-containing transdermal drug delivery systems ("patches") are essentially divided into two major technical systems: reservoir systems and matrix systems. The present invention relates to matrix systems where the active ingredient(s) are embedded in a semi-solid matrix made up of a single polymer or a blend of polymers.

[0005] Both types of devices employ a backing layer that forms the protective outer surface of the finished transdermal system and which is exposed to the environment during use. A release liner or protective layer that forms the inner surface covers the polymeric adhesive which is employed for affixing the system to the skin or mucosa of a user. The release liner or protective layer is removed prior to application, exposing the adhesive, typically a pressure-sensitive adhesive.

[0006] In the "classic" reservoir-type device, the active agent is typically dissolved or dispersed in a carrier to yield a non-finite carrier form, such as, for example, a fluid or gel. In the reservoir-type device, the active agent is generally kept separate from the adhesive. The device has a pocket or "reservoir" which physically serves to hold the active agent and carrier, and which is formed in or by a backing layer. A peripheral adhesive layer is then used to affix the device to the user.

[0007] The reservoir-type devices have a number of disadvantages including a non-uniform drug release profile where a high dose of drug is initially released upon application to the user, often described as a "burst effect." This burst or high initial release of drug then drops off after a period of time to a rate that necessary to achieve a therapeutically effective amount. Drug delivery according to this profile is generally described as first order release.

[0008] While classic reservoir-type devices are still in use today, the term reservoir is being used interchangeably herein with matrix-type devices which still rely upon a separate adhesive means used to affix the device to the user.

[0009] In a matrix-type device, the active agent is dispersed in a carrier form. The carrier form can be self-adhesive or non-adhesive. Non-adhesive matrix-type devices, that is, those which still rely on a separate adhesive means to affix the device to the user, employ a drug permeable adhesive layer (often referred to as an "in-line adhesive" since the drug must pass through this layer) applied over the drug matrix carrier layer. To better control the release rate of the drug, the non-adhesive matrix-type devices often employ one or more additional drug permeable layers such as, for example, rate controlling membranes. The non-adhesive matrix-type devices often contain excipients, such as drug delivery enhancers, to help control the release rate. These devices are often referred to as multilayer or multilaminate.

[0010] In a "monolithic" or "monolayer" matrix-type device, the active agent is typically solubilized or homogenously blended in an adhesive carrier composition, typically a pressure-sensitive adhesive or bioadhesive, which functions as both the drug carrier and the means of affixing the system to the skin or mucosa. Such devices, commonly referred to as drug-in-adhesive devices, are described, for example, in U.S. Pat. Nos. 4,994,267; 5,446,070; 5,474,783 and 5,656,286, all of which are assigned to Noven Pharmaceuticals, Inc., Miami, Fla. and herein incorporated by reference.

[0011] While matrix-type devices, especially drug-in-adhesive devices, achieve more uniform and controlled drug deliver rates over longer periods of time, most transdermal systems remain subject to a higher initial drug release than is required to achieve therapeutic efficacy. For many drugs and/or therapeutic situations, it would be advantageous to eliminate or suppress this higher initial release and achieve a "steady state" (zero order) release profile which uniformly delivers a therapeutically effective amount of drug over the extended duration of device's desired use, preferably up to 7 days or more.

[0012] The high initial blood level concentration of certain drugs may cause adverse or undesired effects, or create toxicity concerns, thereby limiting the use of transdermal administration. In other instances, the higher initial blood level concentration may reduce the amount of drug required for treatment to the point of risking under dosing, or the higher initial blood level concentration may make it impractical to increase the duration of the device's application while retaining therapeutic effectiveness. Reducing the frequency of replacing the transdermal drug delivery system would increase user compliance, reduce any lag or drop off in efficacious blood levels, and reduce the amount of drug required for treatment (also provided by reducing the higher initial blood level associated with the higher release rate).

[0013] Drug concentration in transdermal delivery systems can vary widely depending on the drug and polymers used. Low drug concentrations in the adhesive can result in difficulties in achieving an acceptable delivery rate of the medicament, preferably one approximating zero order kinetics. High drug concentrations, on the other hand, frequently affect the adhesion properties of the adhesives, and tend to promote unwanted crystallization.

[0014] Simple diffusion models for permeation of drugs through the skin suggest that permeation rates are concentration dependent, that is, dependent on both the amount and the degree of drug within the pressure sensitive adhesive

acrylate adhesives have a high affinity for many drugs and thus tend to solubilize higher concentrations of drug than do, for example, rubber adhesives. However, the use of polyacrylates alone as the adhesive is not without its drawbacks as polyacrylate adhesives, for example, may tend to cause skin irritation, especially when the transdermal device is used for extended periods of time.

[0015] Therefore, despite the existence of many different types of transdermal delivery systems in the art, there remains a continuing need for improving the selective modulation of drug permeation, delivery rates and drug profiles in transdermal delivery systems.

SUMMARY OF THE INVENTION

[0016] 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.

[0017] Another object is to provide a transdermal system, which is simple and inexpensive to manufacture. 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 which is manufactured to optimize drug loading while providing desirable adhesion to skin or mucosa as well as providing modulation of the drug delivery and profile.

[0018] 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 by selectively manipulating the monomeric make up of an acrylic-based polymer in the transdermal drug delivery system. The drug carrier composition may be comprised of (a) one or more acrylic-based polymers having one or more different monomers selected from the group consisting of hard and soft monomers; (b) one or more silicone-based polymers having one or more silanol contents (capping) and/or resin to polymer ratios and or a rubber; and (c) one or more active agents where the device provides a desired solubility for the active agent and controls drug delivery rates, onset and profiles of at least one active agent. Further manipulation of drug delivery, onset and profiles can be achieved by varying the concentrations of the drug in the drug-loaded carrier.

[0019] Further embodiments of the invention include those described in the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1** is a graphic representation of the effects on drug delivery, onset and profile of 17β-estradiol with different proportions of hard and soft acrylic-based monomers in the pressure sensitive adhesives.

[0021] **FIG. 2** is a graphic representation of the effects on drug delivery, onset and profile of norethindrone acetate with different proportions of hard and soft acrylic-based monomers in the pressure sensitive adhesives.

[0022] **FIG. 3** is a graphic representation of the effects on drug delivery, onset and profile of testosterone with different proportions of hard and soft acrylic-based monomers in the

[0023] **FIG. 4** is a graphic representation of the effects on drug delivery, onset and profile of scopolamine with different proportions of hard and soft acrylic-based monomers in the pressure sensitive adhesives.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0024] The foregoing and other objects are achieved by this invention which provides a transdermal drug delivery system to provide an adhesive matrix composition which effectively delivers drugs to a user over an extended period of time.

[0025] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

[0026] The invention relates to a pressure-sensitive adhesive composition comprising a single polymer or a blend of at least two polymers together with a drug. The blend of at least two polymers is preferred and is herein referred to as a multiple polymer adhesive system. The term "blend" is used herein to mean that there is no, or substantially no, chemical reaction or cross-linking (other than simple H-bonding) between the different polymers in the multiple polymer adhesive system.

[0027] As used herein, the term "pressure-sensitive adhesive" refers to a viscoelastic material which adheres almost instantaneously to most substrates with the application of very slight pressure and remains permanently tacky. A polymer is a pressure-sensitive adhesive within the meaning of the term as used herein if it has the properties of a pressure-sensitive adhesive per se or functions as a pressure-sensitive adhesive by admixture with tackifiers, plasticizers or other additives. The term pressure-sensitive adhesive also includes mixtures of different polymers and mixtures of polymers, such as polyisobutylenes (PIB) of different molecular weights, the resultant mixtures being a pressure-sensitive adhesive. In the last case, the polymers of lower molecular weight in the mixture are not considered to be "tackifiers," the term "tackifier" being reserved for additives which differ other than in molecular weight from the polymers to which they are added.

[0028] 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.

[0029] 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.

[0030] The term "transdermal" as used herein means passage into and/or through skin or mucosa for localized or systemic delivery of an active agent.

[0031] The term "solubilized" is intended to mean that in the carrier composition there is an intimate dispersion or dissolution of the active agent at the crystalline, molecular or ionic level. As such, the solubilized active agent is considered herein to be in "non-crystallized" form when in the compositions of the present invention.

[0032] The phrase "pharmaceutically acceptable flexible

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