



US 20070098772A1

(19) **United States**

(12) **Patent Application Publication**  
**Westcott et al.**

(10) **Pub. No.: US 2007/0098772 A1**

(43) **Pub. Date: May 3, 2007**

(54) **TRANSDERMAL NORELGESTROMIN  
DELIVERY SYSTEM**

**Related U.S. Application Data**

(76) Inventors: **Tyler D. Westcott**, San Francisco, CA  
(US); **Jane Stepic**, San Carlos, CA  
(US); **Delphine C. Imbert**, Cupertino,  
CA (US); **Jay Audett**, Mountain View,  
CA (US); **Jianye Wen**, Palo Alto, CA  
(US); **Allison Luciano**, Lebanon, NJ  
(US); **Eric N. Silverberg**, Summit, NJ  
(US); **Paul B. Foreman**, Somerville, NJ  
(US)

(60) Provisional application No. 60/720,200, filed on Sep.  
23, 2005.

**Publication Classification**

(51) **Int. Cl.**  
*A61K 9/70* (2006.01)  
*A61K 31/56* (2006.01)  
(52) **U.S. Cl.** ..... **424/449**; 514/182; 156/242

(57) **ABSTRACT**

A system for transdermal delivery of norelgestromin (NGMN) to an individual. The system has a high NGMN loading with suitable permeation enhancers to effect therapeutic flux rate. Polyacrylate drug reservoir with the NGMN and high loading of one or more of permeation enhancers and NGMN dissolved therein provides desirable adhesive characteristics and effective transdermal therapeutic properties. Estrogen can be delivered with the NGMN.

Correspondence Address:

**PHILIP S. JOHNSON**  
**JOHNSON & JOHNSON**  
**ONE JOHNSON & JOHNSON PLAZA**  
**NEW BRUNSWICK, NJ 08933-7003 (US)**

(21) Appl. No.: **11/525,684**

(22) Filed: **Sep. 22, 2006**

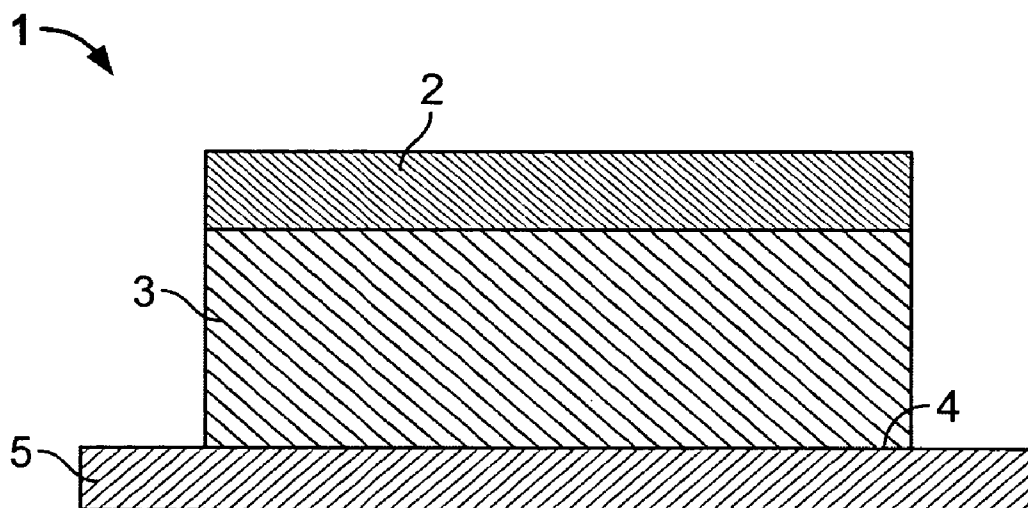


FIG. 1

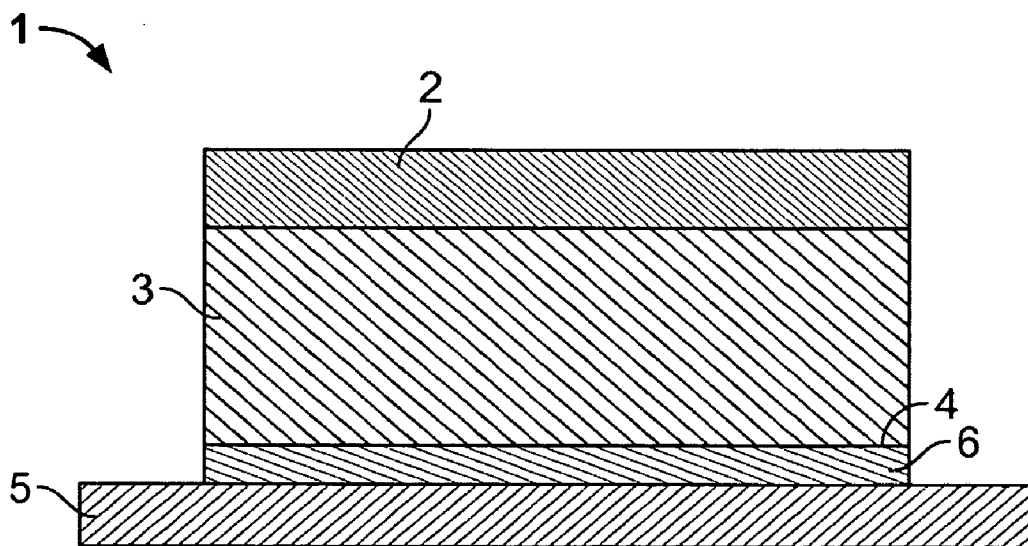


FIG. 2

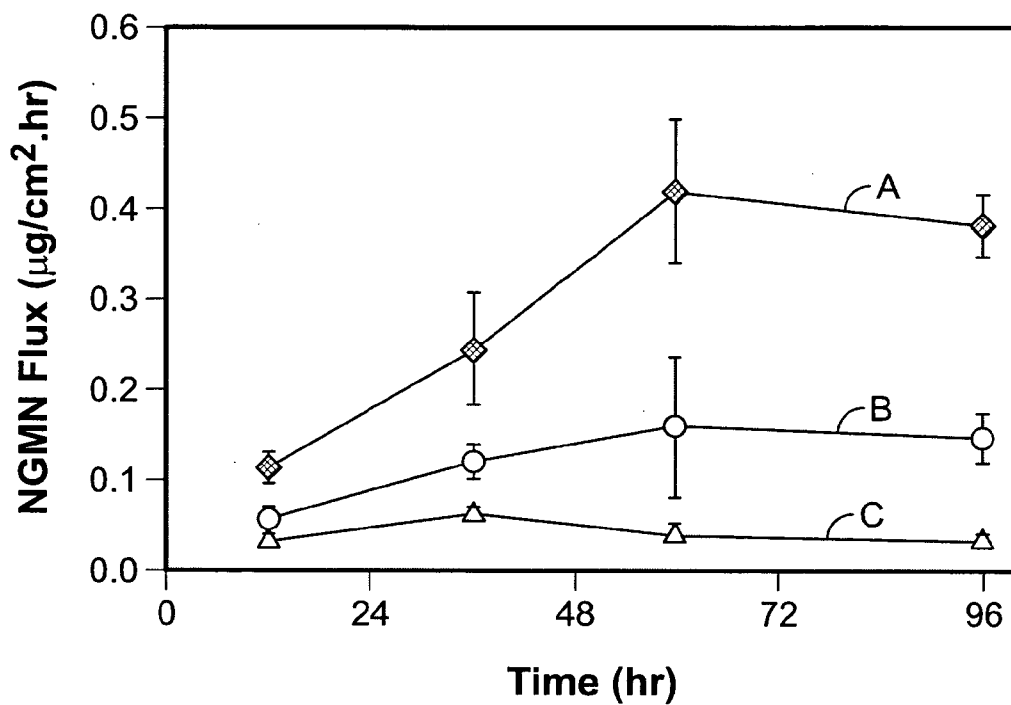


FIG. 3

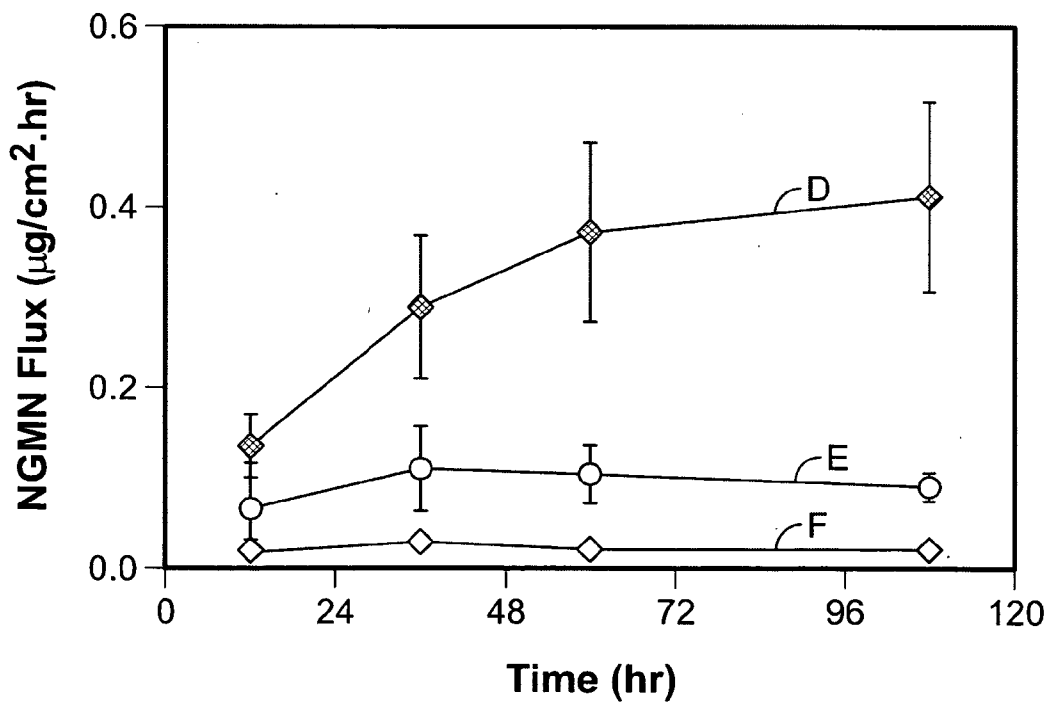


FIG. 4

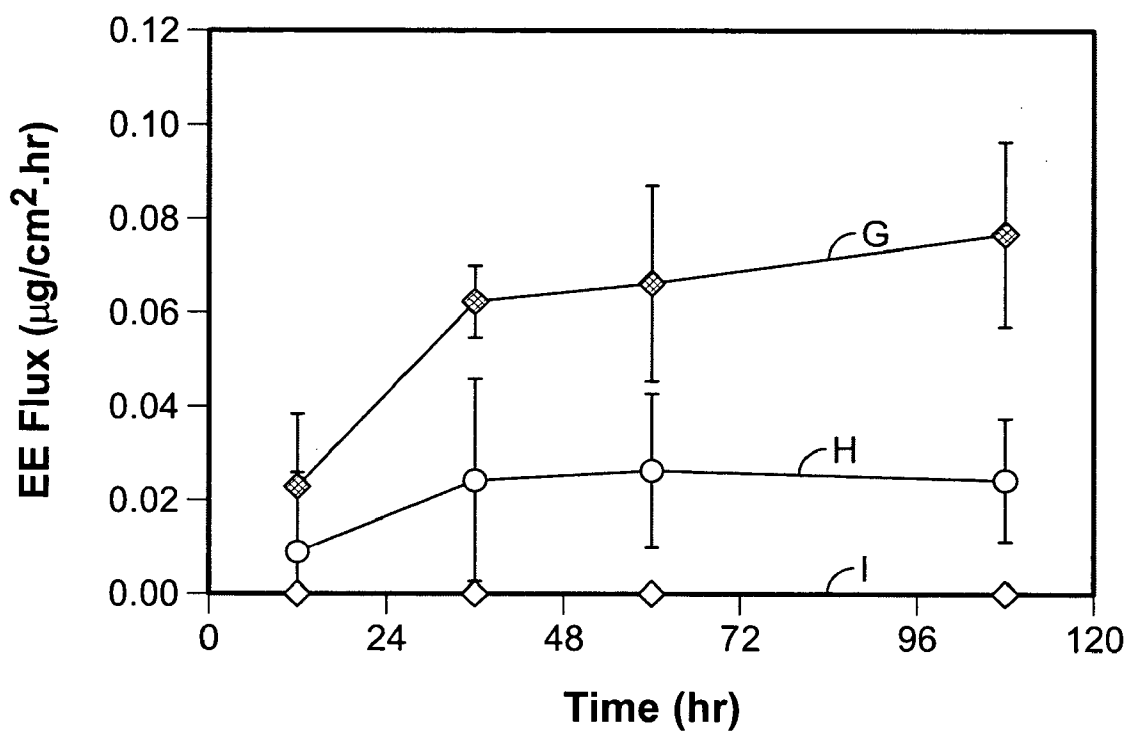


FIG. 5

## TRANSDERMAL NORELGESTROMIN DELIVERY SYSTEM

### CROSS REFERENCE TO RELATED U.S. APPLICATION DATA

[0001] The present application is derived from and claims priority to provisional application U.S. Ser. No. 60/720,200, filed Sep. 23, 2005, which is herein incorporated by reference in its entirety.

### TECHNICAL FIELD

[0002] This invention relates to a medical patch for transdermal administration of norelgestromin (NGMN) and to a method of treating a subject by administering norelgestromin (NGMN) thereto with the medical patch. In particular, the invention relates to transdermal systems for administration of NGMN preferably in combination with an estrogen with adhesive system having high enhancer tolerance when used in transdermal drug delivery.

### BACKGROUND

[0003] Transdermal devices for the delivery of biologically active agents have been used for maintaining health and therapeutically treating a wide variety of ailments. For example, analgesics, steroids, etc., have been delivered with such devices. Such transdermal devices include patches in which a biologically active agent is delivered to the body tissue passively without use of an additional energy source. Many such devices have been described, for example, in U.S. Pat. Nos. 3,598,122, 3,598,123, 4,379,454, 4,286,592, 4,314,557, 4,568,343, and U.S. Application No. 2003002682, all of which are incorporated herein by reference in their entireties.

[0004] A transdermal patch is typically a small adhesive bandage that contains the drug to be delivered. A simple type of such transdermal patches is an adhesive monolith including a drug-containing reservoir disposed on a backing. The reservoir is typically formed from a pharmaceutically acceptable pressure sensitive adhesive. In some cases, the reservoir can be formed from a non-adhesive material, the skin-contacting surface of which is provided with a thin layer of a suitable adhesive. The rate at which the drug is administered is dependent upon the rate at which drug partitions from the patch into the skin and then diffuses across the epidermis before being absorbed systemically.

[0005] Although the transdermal delivery of therapeutic agents has been the subject of intense research and development for over 30 years, only a relatively small number of drug molecules are suitable for transdermal delivery due to the fact that human skin is an excellent barrier. Various techniques have been explored to enhance the permeation of drug molecules that are not otherwise suitable for transdermal delivery. Of these techniques, chemical enhancement is the most established and is currently employed commercially. Pressure sensitive adhesives, such as acrylic adhesives, are used in most transdermal drug delivery devices as a means of providing intimate contact between the drug delivery device and the skin. The use of drugs and permeation enhancers ("enhancers"), especially at high concentrations, usually has a significant impact on the properties of pressure sensitive adhesives, such as cohesive strength, adhesive flow, tackiness and adhesion strength. Therefore,

pressure sensitive adhesives have to be designed in a way that they can provide the needed performance in the presence of enhancers.

[0006] Combinations of norelgestromin (NGMN), formerly known as 17-deacetyl norgestimate, and ethinyl estradiol (EE) have been administered orally to women as a contraceptive. These two drugs have also been described as deliverable transdermally, as mentioned, for example, in U.S. Pat. No. 5,693,335; 5,876,746; and 5,972,377. Other patents related to transdermal delivery of sex hormones are, for example, U.S. Pat. No. 4,906,169 and 5,422,119. However, delivering the sex hormones through a body surface at an adequate flux rate is a challenge.

[0007] Currently, transdermal patches for delivery of NGMN and EE (once a week ORTHO EVRA® patches from Ortho-McNeil Pharmaceutical) have three layers. The backing layer is composed of a beige flexible film with a low-density pigmented polyethylene outer layer and a polyester inner layer. The backing layer provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, micronized crospovidone (an insoluble crosslinked polyvinyl pyrrolidone), non-woven polyester fabric and lauryl lactate. The micronized crospovidone serves as a hydrophilic filler material that helps seven day wear by absorbing moisture at the skin/adhesive interface. The other components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the protective liner, which protects the adhesive layer during storage and is removed just prior to patch application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

[0008] The total amount of NGMN released from a 20 cm<sup>2</sup> ORTHO EVRA® patch over a seven-day wear period is 1.05 mg (corresponding to 17.5% of the total NGMN load and to an hourly average flux of about 0.3 µg/cm<sup>2</sup>-h. The total amount of EE released over the seven-day wear period is 0.14 mg (corresponding to 18.7% of the total EE loading) and to an hourly average flux of about 0.04 µg/cm<sup>2</sup>-h. In this current system, polyisobutylene (PIB) adhesive is highly plasticized and suffers cold-flow during storage and wear, resulting in a black-border that forms around the patch over the wear period. The inclusion of a high level (20% wt/wt) of micronized crospovidone in the current system also results in an adhesive formulation that becomes opaque white over the wear period. During the seven day wear, as moisture is absorbed, the adhesive drug layer changes from translucent to opaque and white in appearance requiring the use of an opaque backing layer to mask this phenomena during wear in the currently commercially available systems. There continues to be a need for improved delivery of sex hormones, especially sustained delivery over a period of time, and especially for NGMN, an estrogen, or NGMN in combination with an estrogen, for contraceptive effect or hormone replacement via a product with better rheology, more appealing appearance, and which is less obvious on most skin types and easier to remove. Such better products will lead to improved patient compliance.

### SUMMARY

[0009] The present invention provides a method and a device for transdermal delivery of an effective amount of

NGMN, an estrogen, or NGMN in combination with an estrogen (for contraceptive effect or for providing hormone replacement) to an individual in need thereof. In one aspect, a patch with polyacrylate reservoir suitable for multiple day delivery of NGMN is provided. In another aspect, a high loading of permeation enhancer enables high flux rate with a relatively small area, suitable for a transdermal patch that can be maintained adhesively on the body surface for an extensive period of time, such as 3, 7 days, and even longer, with acceptable rheological and adhesive properties and better appearance.

[0010] The preparation of formulations with polyacrylate for adhesion rather than PIB results in improved cold-flow resistance. This feature in turn results in an improvement in both patch aesthetics, ease of removal and improved patient compliance. The use of polyacrylate also results in formulations that are and remain translucent (versus opaque in appearance due to undissolved PVP particles and moisture uptake during 7 day wear) which, when combined with a transparent or translucent backing, have an improved translucent appearance after application and during wear. Although PVP, either dissolved, dispersed (e.g., in micronized form), or combination thereof, can be used, it is not required for the formulation of the present invention to adhere to the body surface. Further, the increased drug flux per unit area also results in a smaller patch size, again improving aesthetics and patient acceptability, and reducing the likelihood of unintentional detachment.

[0011] In the currently commercially available 7-day wear patches, the amount of NGMN and EE loaded into the adhesive drug layer resulting in adhesive layer about 0.006 inch (0.15 mm) to 0.008 inch (0.20 mm) thick. The thicker adhesive layer requires the addition of a non-woven backing for structural support during manufacturing, patch application and patch removal. The thicker adhesive layer also results in severe cold flow during storage in the pouch, and higher affinity for lint and dirt to adhere to the edge of the patch during wear. The currently available ORTHO EVRA® patches utilizes less than 20% of the NGMN and EE loaded into the patch during 7 days of wear. The effective dose of NGMN and EE in an ORTHO EVRA® contraceptive patch is 150 µg/day of NGMN and 20 µg/day of EE having a basal surface area (i.e. the area in diffusional contact with the skin) of 20 cm<sup>2</sup>. ORTHO EVRA® patches deliver the NGMN at a flux of 0.3 µg/cm<sup>2</sup>-h, and EE at a flux of 0.04 µg/cm<sup>2</sup>-h.

[0012] The use of polyacrylates results in a simpler, less complex manufacturing process as the drug/adhesive layer is thinner removing the need for a non-woven. Thus, a transdermal NGMN or NGMN and EE delivery patch can be made to have NGMN or NGMN/EE loading of higher than 5 wt %, preferably from 5 to 20 wt %, more preferably from 5 to 10 wt % of NGMN in the reservoir to deliver NGMN about 125 to about 350 µg/day, preferably from about 150 to about 300 µg/day, and more preferably from about 150 to about 250 µg/day for 7 days. With the appropriate size, patches can be made with NGMN/EE in the reservoir to deliver NGMN about 50 to about 250 µg/day and EE about 5 to 35 µg/day, preferably from about 75 to about 225 µg/day NGMN and 10 to 30 µg/day of EE, and more preferably from about 125 to about 175 µg/day of NGMN and 15 to 25 µg/day of EE for 7 days with acceptable rheology such as cold flow property.

[0013] In one aspect of the invention, a novel technique is provided for increasing adhesive enhancer tolerance. It has been discovered that by increasing the glass transition temperature of the acrylate polymer using the ratio of soft monomer and hard monomer, it is possible to load enhancer concentrations into the polymer at a high weight percent to obtain a formulation and still achieve desirable adhesive characteristics. The loading of drug and/or enhancer into the polymer composition can be, e.g., greater than 20 dry weight %, greater than 30 dry weight % (or solids wt %), even up to 40-50 wt %, and still provide adequate adhesion and rheological characteristics for pressure sensitive adhesive (PSA) application. With sufficient loadings of permeation enhancers in such formulations, sustained high rates of drug delivery can be achieved. With adequate adhesive properties, the resulting reservoir with sufficient drug loading and permeation enhancers can be used to achieve effective therapeutic results.

[0014] In one aspect of the invention, a clear multiple day patch with 3 to 7-day dermal adhesion is provided. It has been discovered that the use of a polyacrylate adhesive or proadhesive, having been plasticized with permeation enhancers to have an elastic modulus (storage modulus) of  $1 \times 10^5$  to  $2 \times 10^5$  dyn/cm<sup>2</sup>, i.e., 10,000 to 20,000 Pa (measured at 1 rad/s, 25° C.), or more preferably 10,000 to 15,000 Pa (i.e.,  $1.0 \times 10^5$  to  $1.5 \times 10^5$  dyn/cm<sup>2</sup>), either with or without PVP (e.g., up to about 6% PVP), when used with an occlusive nonporous backing, such as 0.5 mil PET/1.5 mil EVA results in superior skin adhesion for 7 days. The resultant polyacrylate formulations further result in a reduction in measured residue upon patch removal relative to existing commercial PIB-based products while providing comparable wearing performance. With the use of transparent backing such as the PET/EVA laminate, a clear patch that would not turn cloudy after multiple day use (e.g., 3 days, 7 days) can be achieved.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 illustrates a cross-section through a schematic, perspective view of one embodiment of a transdermal therapeutic system according to the present invention.

[0016] FIG. 2 illustrates a cross-section view through another embodiment of a transdermal therapeutic system of this invention.

[0017] FIG. 3 illustrates the flux profile of a NGMN formulation with permeation enhancers GMO and NLS according to the present invention compared to NGMN in other formulations.

[0018] FIG. 4 illustrates the flux profile of another NGMN formulation with EE and permeation enhancers GMO and NLS according to the present invention compared to NGMN in other formulations.

[0019] FIG. 5 illustrates the flux profile of EE with the NGMN formulation of FIG. 4.

#### DETAILED DESCRIPTION

[0020] The present invention relates to transdermal delivery of norelgestromin (NGMN), an estrogen, or NGMN in combination with an estrogen, with the help of permeation enhancers for loading adequate amount of NGMN, an estrogen, or NGMN in combination with an estrogen with

desirable flux. It is further understood that a progestin, which may be NGMN or different from NGMN (such as norgestimate) or an estrogen, which may be EE or different from EE (such as  $17\beta$  estradiol), either alone or in combination, can be made into a transdermal delivery system. The design of female sex hormone patches with polyacrylate reservoir matrix results in product attributes that are greatly improved, e.g., thinner reservoir matrix layer, smaller surface area, and better esthetics. According to the present invention, polyacrylates and polyacrylates in combination with permeation enhancers improve drug utilization resulting in patches with such improved product attributes. Using polyacrylate adhesives or proadhesives, clear patches for NGMN and EE delivery can be made. In a clear patch, the color of the skin is visible through the patch when applied to the skin, regardless of the race and color of the user. In such patches, the backing is preferably a clear pigmentless backing, e.g., EVA/PET backing known to those skilled in the art.

[0021] Traditionally a transdermal drug delivery system was formulated with a pressure sensitive adhesive that has a glass transition temperature ( $T_g$ ) in the range of  $-40^\circ\text{C}$ . to  $-10^\circ\text{C}$ . According to the present invention, a useful reservoir material is acrylate polymer. In one aspect of the present invention, one type of useful acrylate polymer for making a norelgestromin transdermal delivery patch is one that comprises, and preferably is consisted of 2-hydroxyethyl acrylate, vinyl acetate and 2-ethylhexyl acrylate. In another aspect of the present invention, a preferred starting acrylate polymeric material (which can be formulated into an adhesive material having pharmaceuticals and/or enhancers) is a stiffer material that has a glass transition temperature ( $T_g$ ) in the range of about  $-20^\circ\text{C}$ . or higher, preferably  $-15^\circ\text{C}$ . or higher, more preferably  $-15^\circ\text{C}$ . to  $0^\circ\text{C}$ ., and even more preferably  $-10^\circ\text{C}$ . to  $0^\circ\text{C}$ .; creep compliance of about  $7 \times 10^{-5}\text{ cm}^2/\text{dyn}$  (at 3600 second) or below; and modulus  $G'$  of about  $8 \times 10^5\text{ dyn/cm}^2$  or above. The polymeric material can be formulated into a transdermal reservoir matrix (including carrier structure) with a combined drug and/or enhancer concentration greater than 20 dry weight percent (wt %), greater than 30 wt %, or even greater than 40 dry weight percent. The resulting transdermal adhesive formulation with pharmaceutical agent(s) and/or enhancers will provide excellent adhesion with no cold flow, i.e., no cold flow of an amount that is noticeable by an average person when the device is removed from the pouch and would affect the normal use of the delivery system.

[0022] Some of the more preferred starting proadhesive acrylate polymers without enhancer or drug have poor adhesive properties because the glass transition temperature is too high. Once plasticized in the transdermal formulation, the glass temperatures of such formulations drop into the pressure sensitive range, about  $-10^\circ\text{C}$ . to  $-40^\circ\text{C}$ ., and the resulting creep compliance and storage modulus enable the achievement of good tack, with little or no cold flow. Creep compliance is an important parameter to evaluate cold flow behavior of a pressure sensitive adhesive (PSA). In a transdermal drug delivery system, if the creep compliance is large, the adhesive will have cold flow with time, i.e., the adhesive may lose its shape because the weight of the material in the device is under gravity.

[0023] In describing the present invention, the following terms will be employed, and are intended to be defined as

indicated below. As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the content clearly dictates otherwise.

[0024] As used herein, the term “transdermal” refers to the use of skin, mucosa, and/or other body surfaces as a portal for the administration of drugs by topical application of the drug thereto for passage into the systemic circulation.

[0025] “Biologically active agent” is to be construed in its broadest sense to mean any material that is intended to produce some biological, beneficial, therapeutic, or other intended effect, such as enhancing permeation, hormone replacement, or contraception. As used herein, the term “drug” refers to any material that is intended to produce some biological, beneficial, therapeutic, or other intended effect, such as relieving symptoms of a health disorder, but not agents (such as permeation enhancers) the primary effect of which is to aid in the delivery of another biologically active agent such as the therapeutic agent transdermally.

[0026] As used herein, the term “therapeutically effective” refers to the amount of drug or the rate of drug administration needed to produce the desired therapeutic result. As used herein, the term “permeation enhancement” intends an increase in the permeability of skin to a drug in the presence of a permeation enhancer as compared to permeability of skin to the drug in the absence of a permeation enhancer. A “permeation-enhancing amount” of a permeation-enhancer is an amount of the permeation enhancer sufficient to increase the permeability of the body surface of the drug to deliver the drug at a therapeutically effective rate.

[0027] “Acrylate”, “polyacrylate” or “acrylic polymer”, when referring to a polymer for an adhesive or “proadhesive”, refers to polymer or copolymer of acrylic acid, ester(s) thereof, acrylamide, or acrylonitrile. Unless specified otherwise, it can be a homopolymer, copolymer, or a blend of homopolymers and/or copolymers. In some embodiments, prior to incorporation of drugs and ingredients, the polymeric materials are not suitable PSAs “as is” because of the stiffness of the polymer and insufficient adhesiveness or tackiness. These polymeric materials become adhesive and have the desired PSA characteristics after incorporating drugs, permeation enhancer and optionally other ingredients in suitable quantities. Such polymeric materials, which are not suitable as a PSA as is (prior to incorporation of drugs and ingredients) but will have the desired PSA characteristics after incorporating drugs and/or other ingredients, can be called “proadhesive” herein.

[0028] As used in the present invention, “soft” monomers refer to the monomers that have a  $T_g$  of about  $-80^\circ\text{C}$ . to  $-10^\circ\text{C}$ . after polymerization into homopolymer; “hard” monomers refer to the monomers that have a  $T_g$  of about  $0$  to  $250^\circ\text{C}$ . after forming homopolymer; and “functional” monomers refer to the monomers that contain hydrogen bonding functional groups such as hydroxyl, carboxyl or amino groups (e.g., alcohols, carboxylic acid, or amines), these polar groups tend to increase the hydrophilicity of the acrylate polymer and increase polar drug solubility.

[0029] The present invention relates to transdermal delivery of NGMN, an estrogen, or NGMN in combination with an estrogen, from a polyacrylate adhesive or proadhesive and various permeation enhancers for desirable flux. A

suitable transdermal delivery patch according to the present invention can deliver NGMN, an estrogen, or NGMN in combination with an estrogen through about 5-100 cm<sup>2</sup>, preferably 5-50 cm<sup>2</sup>, and preferably about 5-25 cm<sup>2</sup>, especially about 10 to 20 cm<sup>2</sup> of intact skin over an extended period of time.

[0030] Progestins and estrogens both inhibit ovulation, albeit by separate pathways. NGMN, as a progestin, inhibits the release of luteinizing hormone (LH), whereas the predominant effect of estrogen is to inhibit the secretion of follicle-stimulating hormone (FSH). Thus, when a combination of NGMN and estrogen is administered according to the invention, ovulation is prevented by inhibiting the ovulatory stimulus and/or by inhibiting the growth of follicles. NGMN administration is believed to be advantageous relative to the parent compound (norgestimate) or its other metabolites in that NGMN inhibits little or no androgenic activity.

[0031] The transdermal patches of the invention can be used for contraception for women and they can be adapted for hormone replacement therapy. The patches can be used to deliver NGMN and, optionally an estrogen, to the skin continuously for an extended time period, typically 1-7 days and preferably for 7 days. When the patches are worn for contraception, a patch will typically be placed on the skin on the fifth day of the menstrual cycle, and replaced as needed until 21 days of wearing have elapsed. For instance, in the case of a 7-day patch, three patches will be required to deliver the drug(s) for the 21-day period. If desired, a placebo patch may be worn thereafter until the fifth day of the succeeding menstrual cycle. This regimen is repeated for each menstrual cycle.

[0032] The effective dose of NGMN for inhibiting ovulation is normally in the range of about 125 to about 350 µg/day, preferably from about 150 to about 300 µg/day, and more preferably from about 150 to about 250 µg/day. The patches of the invention will typically have a basal surface area (i.e. the area in diffusional contact with the skin) between 10 and 50 cm<sup>2</sup>. The effective dose of estrogen for inhibiting ovulation will depend upon the particular estrogen being co-administered. For instance, when the estrogen is ethinyl estradiol, the dose will normally be at least 2 µg/day, from about 2 µg/day to about 200 µg/day, and preferably from about 5 µg/day to 150 µg/day of EE, preferably from about 5 to 35 µg/day, and more preferably approximately 5 to 20 µg/day. The patches will contain sufficient amounts of NGMN and, when present, estrogen, to provide such daily doses for the intended patch wear time. Thus, the patches can deliver the NGMN at a flux of greater than 0.2 µg/cm<sup>2</sup>-h, preferably about 0.2 to 1 µg/cm<sup>2</sup>-h, more preferably about 0.2 to 0.4 µg/cm<sup>2</sup>-h and can deliver EE at a flux of greater than 0.01 µg/cm<sup>2</sup>-h, preferably about 0.01 to 0.1 µg/cm<sup>2</sup>-h, more preferably about 0.01 to 0.04 µg/cm<sup>2</sup>-h.

[0033] If a larger patch size is used, a smaller quantity of hormones per unit area would be adequate. When a prolonged therapeutic effect is desired, the patch is removed at the end of the wear period and a fresh system applied to a new location. In such cases, blood levels will remain reasonably constant.

[0034] Estrogens that may be combined with NGMN in the matrix include estradiol and esters thereof such as estradiol valerate, estradiol cypionate, estradiol acetate,

estradiol benzoate, and ethinyl estradiol (EE). EE is a preferred estrogen for use in combination with NGMN. EE/NGMN combinations may favorably affect metabolic parameters such as elevation of serum high density lipoprotein and reduction of the low density lipoprotein/high density lipoprotein ratio in serum.

[0035] The matrix may contain other additives depending upon the particular adhesive used. For instance, materials, such as polyvinyl pyrrolidone (PVP), hygroscopic agents that improve the duration of wear, or additives that improve the physical (e.g., cold flow) or adhesive (e.g., tack, cohesive strength) properties of the matrix may be included.

[0036] The patches are also useful for providing hormone replacement therapy. When used to provide hormone replacement therapy, the drug reservoir is constructed so as to provide an effective amount of NGMN, or estrogen, or a combination, for the intended purpose. Typically, the reservoir and therefore the patch is constructed to provide from about 125 to about 350 µg/day, and preferably from about 150 to about 300 µg/day NGMN co-administered with from about 5 to 45 µg/day and preferably from about 10 to 35 µg/day of EE. In an alternative embodiment, the patch will administer from about 120 to 350 µg/day, and preferably from about 150 to 300 µg/day NGMN co-administered with from about 20 to 175 µg/day and preferably from about 30 to 150 µg/day of 17-β estradiol. The patch is applied for 7 days and replaced with a new patch (for 7 days) for the duration of the therapy. Alternatively, patches for 3 days can be made and used.

[0037] Exemplary transdermal NGMN delivery systems of the present invention are illustrated by the embodiments shown in FIGS. 1 and 2. As shown in FIGS. 1 and 2, an embodiment of the transdermal monolithic patch 1 according to this invention has a backing layer 2, a drug reservoir 3 (containing NGMN, an estrogen, or NGMN in combination with an estrogen) disposed on the backing layer 2, and a peelable protective layer 5. In the reservoir 3, which can be a layer, at least the skin-contacting surface 4 is an adhesive. The reservoir is a matrix (carrier) that is suitable for carrying NGMN, an estrogen or NGMN in combination with an estrogen for transdermal delivery. Preferably, the whole matrix, with drugs and other optional ingredients, is a material that has the desired adhesive properties. The reservoir 3 can be either a single phase polymeric composition or a multiple phase polymeric composition. In a single phase polymeric composition the drug and all other components are present at concentrations no greater than, and preferably less than, their saturation concentrations in the reservoir 3. This produces a composition in which all components are dissolved. The reservoir 3 is formed using a pharmaceutically acceptable polymeric material that can provide acceptable adhesion for application to the body surface. In a multiple phase polymeric composition, at least one component, for example, the therapeutic drug NGMN, an estrogen, or NGMN in combination with an estrogen, is present in amount more than the saturation concentration. In some embodiments, more than one component, e.g., a drug and a permeation enhancer, is present in amounts above saturation concentration. In the embodiment shown in FIG. 1, the adhesive acts as the reservoir and includes NGMN and EE.

[0038] In the embodiment shown in FIG. 2, the reservoir 3 is formed from a material that does not have adequate



adhesive properties if without drug or permeation enhancer. In this embodiment of a monolithic patch **1**, the skin-contacting surface of the reservoir **4** may be formulated with a thin adhesive coating **6**. The reservoir **3** may be a single phase polymeric composition or a multiple phase polymeric composition as described earlier, except that it may not contain an adhesive with adequate adhesive bonding property for skin. The adhesive coating can contain the drug and permeation enhancer, as well as other ingredients.

[0039] The drug reservoir **3** is disposed on the backing layer **2**. At least the skin-contacting surface of the reservoir is adhesive. As mentioned, the skin-contacting surface can have the structure of a layer of adhesive. The reservoir **3** may be formed from drug (or biological active agent) reservoir materials as known in the art. For example, the drug reservoir is formed from a polymeric material in which the drug has reasonable solubility for the drug to be delivered within the desired range, such as, a polyurethane, ethylene/vinyl acetate copolymer (EVA), acrylate, styrenic block copolymer, and the like. In preferred embodiments, the reservoir **3** is formed from a pharmaceutically acceptable adhesive or proadhesive, preferably acrylate copolymer-based, as described in greater detail below. The drug reservoir or the matrix layer can have a thickness of about 1-10 mils (0.025-0.25 mm), preferably about 2-5 mils (0.05-0.12 mm), more preferably about 2-3 mils (0.05-0.075 mm).

[0040] Preferred materials for making the adhesive reservoir or adhesive coating, and for making proadhesives according to the present invention include acrylates, which can be a copolymer of various monomers ((i) "soft" monomer, (ii) "hard" monomer, and optionally (iii) "functional" monomer) or blends including such copolymers. The acrylates (acrylic polymers) can be composed of a copolymer (e.g., a terpolymer, i.e., made with three monomers; or a tetrapolymer, i.e., made with four monomers) including at least two or more exemplary components selected from the group including acrylic acids, alkyl acrylates, methacrylates, copolymerizable secondary monomers or monomers with functional groups. Functional monomers are often used to adjust drug solubility, polymer cohesive strength, or polymer hydrophilicity. Examples of functional monomers are acids, e.g., acrylic acid, methacrylic acid and hydroxy-containing monomers such as hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamides or methacrylamides that contain amino group and amino alcohols with amino group protected. Functional groups, such as acid and hydroxyl groups can also help to increase the solubility of basic ingredients (e.g., drugs) in the polymeric material. Additional useful "soft" and "hard" monomers include, but are not limited to, methoxyethyl acrylate, ethyl acrylate, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, tridecyl methacrylate, acrylonitrile, methoxyethyl acrylate, methoxyethyl methacrylate, and the like. Additional examples of acrylic adhesive monomers suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). Examples of acrylic adhesives are commercially available from National Starch and Chemical Company, Bridgewater, N.J.

[0041] The acrylate polymers can include cross-linked and non-cross-linked polymers. The polymers can be cross-linked by known methods to provide the desired polymers. However, cross-linking is hard to control and may result in polymeric materials that are too stiff or too soft. According to the present invention, it is preferred that the polymeric material for incorporation of drugs and other ingredients to be polymers without crosslinking and no cross-linking agent is used in forming the polymeric material. It is further preferred that the monomers do not self cross-link during polymerization. In the present invention, it was found that, instead of cross-linking to form a matrix adhesive with desired PSA properties for incorporating drugs and enhancers, good control of the PSA properties can be achieved by selecting polymeric materials, and in one aspect related to proadhesive, selecting materials that are too stiff prior to incorporation of drugs and other ingredients and subsequently incorporating such drugs and ingredients.

[0042] It has been found that, in the case of proadhesive, in a preferred embodiment, an acrylate polymer composition with a creep compliance (J) of  $7 \times 10^{-5}$  cm<sup>2</sup>/dyn or below and elastic modulus G' of  $8 \times 10^5$  dyn/cm<sup>2</sup> or above, although too stiff as a PSA as is, after formulating with drug or enhancer or a combination thereof at a relative high concentration will achieve the desirable adhesive properties. The plasticizing or tackifying effect of the drug(s) and/or other ingredients on the polymeric material provides a means to achieve the desired adhesive properties in the reservoir.

[0043] Acrylate polymers, when the main monomer of which has the general formula  $\text{CH}_2=\text{CH}-\text{COOR}$ , are particularly useful as proadhesives. Typical main monomers are normally alkyl acrylates of 4 to 1 carbon atoms, preferably 4-10 carbons. Useful alkyl acrylates include ethyl acrylate, butyl acrylate, amyl acrylate, hexyl acrylate, 2-ethylhexyl acrylate, octyl acrylate, isooctyl acrylate, decyl acrylate, dodecyl acrylates, with 2-ethylhexyl acrylate, butyl acrylate, and iso-octyl acrylate being preferred. Such "soft" monomers if polymerized into homopolymer generally have a T<sub>g</sub> of less than about 0° C., preferably about -10° C. to -80° C., preferably about -20° C. to -80° C. Preferably, they are present in an amount of about 10 to 70 wt % (i.e., dry weight % or solids wt %), more preferably no more than about 60% by weight, more preferably no more than about 50 wt % of the total monomer weight and more preferably about 40 to 50 wt %. As used herein, when a monomer is said to be present in the acrylate polymer at a certain percentage, it is meant that the monomer has been polymerized in the acrylate polymer at that percentage of polymerization monomer ingredients.

[0044] "Hard" modifying monomers are mainly used to modify the adhesive properties, mainly glass transition temperature (e.g., to increase the T<sub>g</sub> and to make the resulting polymer stiffer at room temperature), to meet various application requirements. A hard monomer, if polymerized into homopolymer, has a T<sub>g</sub> of about 0 to 250° C., preferably about 20 to 250° C., more preferably in the range of about 30 to 150° C. (for convenience, this is referred to as the "homopolymer T<sub>g</sub>" herein). The hard monomer component (or content in the polymer) is present in an amount of about 10 wt % or more, preferably in the range of about 30 to 60 wt %, preferably about 35 to 60 wt %, more preferably about 40 to 60 wt %, even more preferably about 40 to 50 wt % in the polymerization. Examples of hard modifying mono-

mers are methyl acrylate, vinyl acetate, methyl methacrylate, isobutyl methacrylate, vinyl pyrrolidone, substituted acrylamides or methacrylamides. Homopolymers of these monomers generally have higher glass transition temperature than homopolymers of the soft monomers.

[0045] Certain nitrogen containing monomers can be included in the polymerization to raise the  $T_g$ . These include N-substituted acrylamides or methacrylamides, e.g., N-vinyl pyrrolidone, N-vinyl caprolactam, N-tertiary octyl acrylamide(t-octyl acrylamide), dimethyl acrylamide, diacetone acrylamide, N-tertiary butyl acrylamide(t-butyl acrylamide) and N-isopropyl acrylamide(i-propyl acrylamide). Further examples of monomers that can be used in polymerization to modify and raise the  $T_g$  of the polymer include cyanoethylacrylates, N-vinyl acetamide, N-vinyl formamide, glycidyl methacrylate and allyl glycidyl ether.

[0046] Functional monomers can be used to either provide needed functionality for solubilizing agents in the polyacrylate or improve cohesive properties. Examples of functional monomers are organic acids, e.g., acrylic acid, methacrylic acid, and hydroxyl-containing monomers such as hydroxyethyl acrylate. Preferred functional monomers when incorporated into the polymer result in acid groups, i.e., —COOH, hydroxyl groups, i.e., —OH, or amino groups in the polymer for affecting the solubility of basic agents such as basic drugs. Examples of hydroxy functional monomers include hydroxyethyl acrylate, hydroxypropyl acrylate, hydroxyethyl methacrylate and hydroxypropyl methacrylate. The hydroxyl groups can be primary, secondary or tertiary hydroxyl. In some cases, the acrylate polymer can include at least one non-primary hydroxyl functional monomer component to provide orientation of the functional group in the polymer. Suitable non-primary hydroxyl functional monomers are secondary hydroxyl functional monomers such as hydroxypropyl acrylate. Useful carboxylic acid monomers to provide the functional group preferably contain from about 3 to about 6 carbon atoms and include, among others, acrylic acid, methacrylic acid, itaconic acid, and the like. Acrylic acid, methacrylic acid and mixtures thereof are particularly preferred as acids.

[0047] A functional monomer can also be a hard monomer, if its homopolymer has the high  $T_g$ . Such functional monomers that can also function as hard monomers include, e.g., hydroxyethyl acrylate, hydroxypropyl acrylate, acrylic acid, dimethylacrylamide, dimethylaminoethyl methacrylate, tert-butylaminoethyl methacrylate, methoxyethyl methacrylate, and the like.

[0048] The functional monomer(s) are preferably present in the acrylate polymer in an amount of about at least 5 wt %, preferably at least 10 wt %, preferably 10 to 40 wt %, more preferably about 10 to 30 wt %, more preferably about 10 to 20 wt %, even more preferably 10 to 15 wt %, even though some of the functional monomer(s) may be hard monomers. Examples of preferred functional monomer component include acrylic acid and hydroxyethyl acrylate, acrylamides or methacrylamides that contain amino group and amino alcohols with amino group protected. One of the applications of using functional monomers is to make a polar proadhesive having higher enhancer tolerance, in that, for example, the resulting PSA with the enhancers and/or drug will not phase separate or have excessive cold flow.

[0049] In certain embodiments, the hard monomer(s) that are not also functional monomers can constitute about 10 to

60 wt %, preferably about 40 to 60 wt % of the acrylate monomer, especially in cases in which no acidic functional hard monomer and less than about 20 wt % of hydroxyl functional hard monomer are included in the acrylate polymer. In other embodiments, the hard monomer(s) that are not also functional monomer can constitute about 5 to 15 wt %, e.g., about 10 wt % of the acrylate monomer, especially in cases in which a large amount (e.g., about 25 wt % or more) of functional hard monomer(s) are included, such as when more than about 5 wt % acidic hard functional monomers and 10 or more wt % (e.g., about 10-25 wt %) hydroxyl functional hard monomer(s) are included in the acrylate polymer.

[0050] In an embodiment, useful polyacrylates have at least about 10 wt %, preferably at least about 20 wt %, preferably at least about 30 wt % acrylic monomers having hydroxyl group, acid group, or a combination thereof. One example is a polyacrylate having about 30 wt % hydroxyl group containing (—OH) monomer and about 3 wt % acid containing (—COOH) monomer. Another contains about 26 wt % —OH monomer and about 6 wt % —COOH monomer. Another useful polar polyacrylate contains about 10 wt % —OH monomer. Yet another useful polar polyacrylate contains about 20 wt % —OH monomer. The preferred —OH monomer is hydroxyethyl acrylate and hydroxypropyl acrylate. The preferred —COOH monomer is acrylic acid. Proadhesives were made with such functional amounts.

[0051] Table 1 shows the  $T_g$  of exemplary soft and hard homopolymers the monomers of which are useful for making adhesive and proadhesive of the present invention. Some of the monomers (e.g., acrylic acid, hydroxyethyl acrylate) are also functional monomers.

TABLE 1

Examples of soft and hard homopolymers	
poly(hydroxyethyl acrylate) (hard/functional monomer)	about 100° C.
poly(acrylic acid) (hard/functional monomer)	106° C.
poly(vinyl acetate) (hard monomer)	30° C.
poly(ethylhexyl acrylate) (soft monomer)	-70° C.
poly(isopropyl acrylate) (soft monomer)	-8° C.
poly(n-propyl acrylate) (soft monomer)	-52° C.
poly(isobutyl acrylate) (soft monomer)	-40° C.
poly(n-butyl acrylate) (soft monomer)	-54° C.
poly(n-octyl acrylate) (soft monomer)	-80° C.

[0052] It has been found that the soft monomers 2-ethylhexyl acrylate and butyl acrylate are especially suitable to polymerize with functional monomers hydroxyethyl acrylate or acrylic acid either alone or in combination to form the acrylate polymer of the present invention. Further, the hard monomer vinyl acetate has been found to be very useful to polymerize with the soft monomers 2-ethylhexyl acrylate and butyl acrylate, either alone or in combination to form the proadhesive. Thus, the acrylate proadhesive polymer of the present invention is especially suitable to be made from 2-ethylhexyl acrylate or butyl acrylate copolymerized with hydroxyethyl acrylate, acrylic acid, or vinyl acetate, either alone or in combination. Another preferred hard monomer is t-octyl acrylamide, which can be used alone or in combination with other hard monomers such as acrylic acid and hydroxyethyl acrylate.

[0053] In an embodiment, the adhesive or proadhesive is made by polymerizing monomers including about 20 to 75

wt % vinyl acetate, about 5-40 wt % hydroxyl functional monomer and about 10-75 wt % soft monomer such as 2-ethylhexyl acrylate or butyl acrylate, preferably about 30 to 75 wt % vinyl acetate, about 10-40 wt % hydroxyl functional monomer and about 10-70 wt % soft monomer such as 2-ethylhexyl acrylate or butyl acrylate. In a preferred embodiment, the proadhesive is made by polymerizing monomers including about 50 to 60 wt % vinyl acetate, about 10-20 wt % hydroxyethyl acrylate, and about 20-40 wt % 2-ethylhexyl acrylate. In some cases, no carboxyl(acid) group is used. Hydroxyethyl acrylate or hydroxypropyl acrylate can be used to provide hydroxyl functionality. In certain embodiments, the adhesive or proadhesive is a terpolymer consisted of monomer components of vinyl acetate, 2-ethylhexyl acrylate and hydroxyethyl acrylate. For example, one embodiment is a proadhesive having about 50 wt % vinyl acetate, about 10 wt % hydroxyethyl acrylate, and about 40 wt % 2-ethylhexyl acrylate. As used herein, when a specific percentage is mentioned, it is contemplated there may be slight variations, e.g., of plus or minus 5% of the specific percentage (i.e., about 10 wt % may included 10 wt % $\pm$ 0.5wt %). One other embodiment is a proadhesive having about 60 wt % vinyl acetate, about 20 wt % hydroxyethyl acrylate, and about 20 wt % 2-ethylhexyl acrylate.

[0054] In another embodiment, the proadhesive is made by polymerizing monomers including both monomer with hydroxyl group and monomer with carboxyl group. For example, certain preferred monomer combination for polymerization include an alkyl acrylate, an acrylamide, a monomer with hydroxyl group and a monomer with carboxyl group, e.g., making a proadhesive by polymerizing butyl acrylate, 2-hydroxyethyl acrylate or 2 hydroxypropyl acrylate or hydroxypropyl methacrylate, t-octyl acrylamide, and acrylic acid. In an embodiment, greater than 3 wt % of a hydroxypropyl acrylate or hydroxypropyl methacrylate is used in making the acrylate polymer.

[0055] In certain cases for making a proadhesive in which both monomers with hydroxyl groups and monomer with carboxyl groups are to be polymerized with a soft monomer, e.g., butyl acrylate, the monomer proportions in the polymerization includes about 55 to 65 wt % soft monomer (e.g., butyl acrylate), about 5 to 15 wt % t-octyl acrylamide, about 20 to 30 wt % hydroxyethyl or hydroxypropyl acrylate and about 5 to 10 wt % acid monomer such as acrylic acid. In one embodiment, the acrylate polymer includes about 59 wt % butyl acrylate, about 10 wt % t-octyl acrylamide, about 25 wt % hydroxypropyl acrylate and about 6 wt % acrylic acid. In another embodiment, the hydroxypropyl acrylate is replaced with hydroxyethyl acrylate.

[0056] It is desirable that with the incorporation of a large amount of permeation enhancers, the  $T_g$  of the resulting reservoir (with the drug, permeation enhancers and other ingredients) is such that the resulting reservoir would have good PSA properties for application to the body surface of an individual. Further, the resulting reservoir should not have cold flow that affects the normal application of the transdermal delivery. In one aspect of the present invention, an acrylate polymer (or a blend of acrylate polymers) constitutes preferably about 40 wt % to 90 wt %, more preferably about 45 wt % to 80 wt % of the reservoir. It is possible to load drug and/or enhancer into the polymer composition to a high concentration, e.g., at or greater than about 20 dry weight %, at or greater than about 30 dry

weight % (or solids wt %), even up to about 40 or above, without adversely impacting the adhesion and rheological characteristics for pressure sensitive adhesive (PSA) application.

[0057] In one aspect, preferred acrylate polymers or blends thereof provide the acrylic pressure sensitive properties in the delivery system glass transition temperature of about  $-10^\circ\text{C}$ . to  $-40^\circ\text{C}$ ., preferably about  $-20^\circ\text{C}$ . to  $-30^\circ\text{C}$ . at application on a surface. The  $T_g$  of an acrylate polymer can be determined by differential scanning calorimetry (DSC) known in the art. Also, theoretical ways of calculating the  $T_g$  of acrylate polymers are also known. Thus, one having a sample of an acrylate polymer will be able to experimentally determine the  $T_g$ , for example, by DSC. One can also determine the monomer composition of the acrylate polymer and estimate theoretically the  $T_g$  by calculation. From the knowledge of the monomer composition of an acrylate polymer having drugs and enhancers, one can also make the acrylate polymer without the drug and enhancer and determine the  $T_g$ . According to the present invention, the acrylate materials, before dissolving the drug(s), permeation enhancers, etc., have  $T_g$ s that are in the range of about  $-20$  to  $10^\circ\text{C}$ ., and have rheological properties that are not quite suitable for use directly as a PSA to skin because of the stiffness of the material. The acrylate polymers preferably have a molecular weight in a range of about 200,000 to 600,000. Molecular weight of acrylate polymers can be measured by gel permeation chromatography, which is known to those skilled in the art.

[0058] To control the physical characteristics of the acrylate polymer and the polymerization, it is preferred that monomers of molecular weight of below 500, even more preferably below 200 be used in the polymerization. Further, although optionally larger molecular weight monomers (linear macromonomers such as ELVACITE™ from ICI) can be used in the polymerization, it is preferred that they are not used. Thus, preferably no monomer of molecular weight (MW) above 5000, more preferably no monomer of MW above 2000, even more preferably no monomer of MW above 500, is to be included in the polymerization to form the acrylate polymer. The adhesives and proadhesives of the present invention can be formed without such macromonomers. The adhesives and proadhesives of the present invention can be formed without such macromonomers. Thus, in an aspect of the present invention, preferably, proadhesive polymers can be formed without macromonomers, or substantially without macromonomers, to have adhesive properties too stiff for PSA as is without incorporation of a large amount of permeation enhancers and drug. However, such proadhesives will become suitable for adhering to the skin as PSA in patch application after the appropriate amount of permeation enhancers and drug are dissolved therein.

[0059] However, if desired, in certain embodiments, optionally, the reservoir can include diluent materials capable of reducing quick tack, increasing viscosity, and/or toughening the reservoir structure, such as polybutylmethacrylate (ELVACITE, manufactured by ICI Acrylics, e.g., ELVACITE 1010, ELVACITE 1020, ELVACITE 20), polyvinylpyrrolidone, high molecular weight acrylates, i.e., acrylates having an average molecular weight of at least 500,000, and the like.

[0060] The acrylate polymers of the present invention can dissolve a large amount of permeation enhancer and allow

the resulting drug and permeation enhancer-containing adhesive to have the desired adhesive and cohesive property without the drug or permeation enhancer separating out of the acrylate polymer matrix either as crystals or as oil. The resulting composition will be in the  $T_g$  and compliance range that it can be applied to a body surface without leaving an undesirable amount of residue material on the body surface upon removal of the device. The preferred acrylate polymer is not cross-linked. It is contemplated, however, that if desired, a nonsubstantial amount of cross-linking may be done, so long as it does not change substantially the  $T_g$ , creep compliance and elastic modulus of the acrylate polymer. In one aspect, it is also found that higher  $T_g$  and higher molecular weight of the acrylate are important for a preferred acrylate polymer tolerating high enhancer loading. Since the measurement of the molecular weight of an acrylate polymer is difficult, precise or definite values are often not obtainable. More readily obtainable parameters that relate to molecular weight and drug and enhancer tolerance (i.e., solubility) are creep compliance and elastic modulus.

**[0061]** Enhancers typically behave as plasticizers to acrylate adhesives. The addition of an enhancer will result in a decrease in modulus as well as an increase in creep compliance, the effect of which is significant at high enhancer loading. A high loading of enhancers will also lower the  $T_g$  of the acrylate polymer. Thus, to achieve a proadhesive that is tolerant of high enhancer loading, other than increasing the  $T_g$  by using a higher ratio of hard monomer to soft monomer and the selection of suitable monomers, it is desirable to provide suitable higher molecular weight such that chain entanglement would help to achieve the desirable rheology. As a result, selecting a higher  $T_g$  and higher molecular weight for a proadhesive will increase the elastic modulus and decrease the creep compliance of the acrylate, making the proadhesive more enhancer tolerant. The measurement of the molecular weight of an acrylate polymer is often method-dependant and is strongly affected by polymer composition, since acrylate polymers discussed here are mostly copolymers, not homopolymers. More readily obtainable parameters that relate to molecular weight and drug and enhancer tolerance (i.e., solubility) are creep compliance and elastic modulus.

**[0062]** According to the present invention, preferred useful proadhesive polymeric materials for forming drug-containing PSA are acrylate polymers that, before the incorporation of drugs, enhancers, etc., and other ingredients for transdermal formation, have creep compliance (measured at 30° C. and 3600 second) of about  $7 \times 10^{-5}$  cm<sup>2</sup>/dyn or below and storage modulus  $G'$  about  $8 \times 10^5$  dyn/cm<sup>2</sup> or above. Preferably the creep compliance is about  $6 \times 10^{-5}$  cm<sup>2</sup>/dyn to  $2 \times 10^{-6}$  cm<sup>2</sup>/dyn, more preferably about  $5 \times 10^{-5}$  cm<sup>2</sup>/dyn to  $4 \times 10^{-6}$  cm<sup>2</sup>/dyn. Preferably the storage modulus is about  $8 \times 10^5$  dyn/cm<sup>2</sup> to  $5 \times 10^6$  dyn/cm<sup>2</sup>, more preferably about  $9 \times 10^5$  dyn/cm<sup>2</sup> to  $3 \times 10^6$  dyn/cm<sup>2</sup>. Such creep compliance and modulus will render these acrylate polymers too stiff and unsuitable "as is" for dermal PSA applications. However, it was found that after formulating into a transdermal system with drugs, permeation enhancers, and the like, which produce plasticizing effect as well as tackifying effect, the acrylate polymers plasticized with permeation enhancers and/or drug would have a desirable storage modulus and creep compliance that are suitable for transdermal PSA applications. For a desirable acrylate matrix applicable to

skin with good adhesive property, the material plasticized with drug and permeation enhancers would have a resulting creep compliance that is about  $1 \times 10^{-3}$  cm<sup>2</sup>/dyn or less, preferably more than about  $7 \times 10^{-5}$  cm<sup>2</sup>/dyn, preferably from about  $7 \times 10^{-5}$  cm<sup>2</sup>/dyn to  $6 \times 10^{-4}$  cm<sup>2</sup>/dyn, more preferably about  $1 \times 10^{-4}$  cm<sup>2</sup>/dyn to  $6 \times 10^{-4}$  cm<sup>2</sup>/dyn. The preferred storage modulus of the plasticized acrylate polymer is about  $1 \times 10^5$  dyn/cm<sup>2</sup> to  $8 \times 10^5$  dyn/cm<sup>2</sup>, preferably about  $1.2 \times 10^5$  dyn/cm<sup>2</sup> to  $6 \times 10^5$  dyn/cm<sup>2</sup>, more preferably about  $1.4 \times 10^5$  dyn/cm<sup>2</sup> to  $5 \times 10^5$  dyn/cm<sup>2</sup>.

**[0063]** It was found that incorporating the proper selection of drug (including NGMN alone, an estrogen alone, and NGMN in combination with an estrogen) and other ingredients (such as permeation enhancer) and the appropriate amounts thereof into a preferred polyacrylate can change the  $T_g$ , storage modulus  $G'$ , and creep compliance the appropriate amounts to result in an effective transdermal drug delivery system with the right adhesive properties for the desirable length of time, such as 24 hours, 3 day, or even 7 day application on a body surface. Such transdermal drug delivery systems will have little or no cold flow. As used herein, "little cold flow" means that any shape change of the device caused by cold flow is not noticeable by an average person when the device is removed from the pouch and on which the device is applied over the time of use. Useful for forming adhesives incorporating an increased amount of beneficial agents (including drugs and permeation enhancers) over prior adhesives in transdermal drug delivery are the proadhesive acrylic formulations containing a relatively lower percentage of soft monomers. It has been found that increasing the molecular weight increases the modulus of elasticity and decreases the polymer chain mobility via chain entanglements. Also, increasing hard monomer content increases the glass transition temperature.

**[0064]** Acrylates are preferred materials for making the reservoir. It is contemplated that the reservoir 3 or the adhesive coating 6 can also be formed from or include other material that has pressure sensitive adhesives characteristics so that the reservoir can have drug and permeation enhancers incorporated therein. Examples of reservoir material and pressure sensitive adhesives include, but are not limited to, acrylates, polysiloxanes, polyisobutylene (PIB), polyisoprene, polybutadiene, styrenic block polymers, and the like. Examples of styrenic block copolymer-based adhesives include, but are not limited to, styrene-isoprene-styrene block copolymer (SIS), styrene-butadiene-styrene copolymer (SBS), styrene-ethylenebutene-styrene copolymers (SEBS), and di-block analogs thereof. As mentioned, a preferred reservoir material is acrylate polymer.

**[0065]** Permeation enhancers are useful for increasing the skin permeability of the drug NGMN, an estrogen or NGMN in combination with an estrogen drug combinations to achieve delivery at therapeutically effective rates. Such permeation enhancers can be applied the skin by pretreatment or delivering concurrently with the drug, for example, by incorporation in the reservoir. A permeation enhancer should have the ability to enhance the permeability of the skin for one, or more drugs or other biologically active agents. A useful permeation enhancer would enhance permeability of the desired drug or biologically active agent at a rate adequate for therapeutic level from a reasonably sized patch (e.g., about 5 to 25 cm<sup>2</sup>). Some of the useful permeation enhancers include non-ionic surfactant, one or more

can be selected from the group including glyceryl mono-oleate, glyceryl mono-laurate, sorbitan mono-oleate, glyceryl tri-oleate, and isopropyl myristate. The non-ionic surfactant can be used in the amount of 0.1 about 20 wt % solids to the total composition of the matrix layer. Examples of permeation enhancers include, but are not limited to, fatty acid esters of alcohols, including fatty acid esters of glycerin, such as capric, caprylic, dodecyl, oleic acids; fatty acid esters of isosorbide, sucrose, polyethylene glycol; caproyl lactic acid; laureth-2; laureth-2 acetate; laureth-2 benzoate; laureth-3 carboxylic acid; laureth-4; laureth-5 carboxylic acid; oleth-2; glyceryl pyroglutamate oleate; glyceryl oleate; N-myristoyl sarcosine; N-octyl-2-pyrrolidone; lauraminopropionic acid; polypropylene glycol-4-laureth-2; polypropylene glycol-4-laureth-5dimethyl-1 lauramide; lauramide diethanolamine (DEA). Preferred enhancers include, but are not limited to, N-lauroyl sarcosine, pyroglutamate (such as octyl-, ethyl-, lauryl pyroglutamate (LP)), glyceryl monolaurate (GML), glyceryl monocaprylate, glyceryl monocaprate, glyceryl monooleate (GMO) and sorbitan monolaurate. Additional examples of suitable permeation enhancers are described, for example, in U.S. Pat. Nos.: 5,785,991; 5,843,468; 5,882,676; and 6,004,578.

[0066] In some embodiments, especially some in which the reservoir does not necessarily have adequate adhesive properties and a separate adhesive layer is used, a dissolution assistant can be incorporated in the reservoir to increase the concentration of the drug or biologically active ingredient within the reservoir layer. Suitable dissolution assistants include small acids as lauric acid, oleic acid, etc. Permeation enhancers can also act as solubilization assistants. Non-ionic surfactants and dissolution assistants can be used in combination to increase the delivery rate of female sex hormones.

[0067] The permeation enhancers that are particularly useful in the transdermal delivery of progestin (e.g., NGMN) and estrogen (e.g., EE) include, fatty acid esters: ascorbyl palmitate (ASP), glyceryl caprylate (GCP), lauryl lactate (LL), ethyl myristate (EM), isopropyl Myristate (IPM), oleic acid (OA), Sorbitan Oleate (SMO), glycerol monolaurate (GMO) octyldodecanol (OYD); aromatic ester: benzyl benzoate (BB), tocopherol (TOC); alcohols: dipropylene glycol (DPG), 1,2,3-hexanetriol (HEX); amides: ethyl pyroglutamate (EPG), lauramide DEA (LDA); acid: hydroxycaprylic acid (HCP); fatty acid: N-lauroyl sarcosine (NLS); and fatty alcohol ethers: selachyl alcohol (SAL), laureth-4 (LTH) and oleth-4 (OL), oleth-2 (OL2).

[0068] In the preferred embodiments, we have found that with the appropriate permeation enhancers, no significant amount of thioglycerol, preferably no thioglycerol need to be added as permeation enhancer in the reservoir. Thus, preferably, less than 2 wt %, and more preferably less than 1 wt % of thioglycerol is to be included.

[0069] The present invention is especially suitable for transdermal delivery systems in which a large amount of permeation enhancer is needed to aid the transdermal delivery of NGMN, an estrogen, NGMN in combination with an estrogen or similar drugs. As used herein, "permeation enhancers" is meant to include dissolution assistants, unless specified otherwise in context. One or more permeation enhancers, alone or in combination, can constitute about 5 to 40 wt %, can constitute greater than 10 wt %, preferably

about 10 to 35 wt %, more preferably about 15 to 30 wt % solids of the resulting reservoir that has adequate pressure sensitive adhesive properties. Further, with a proadhesive, the permeation enhancer(s) can constitute preferably 20 to 35 wt % of the resulting reservoir.

[0070] For an adhesive that has usable adhesive property before drug and enhance addition, such as DURO-TAK® 87-4287, the enhancer(s) is preferably in the 15 to 25 wt % range. When such an adhesive is used, the adhesive before the dissolution of drug and enhancer preferably has a storage modulus of about 2 to  $5 \times 10^5$  dyn/cm<sup>2</sup>, and a creep compliance of about  $4 \times 10^{-5}$  to  $6 \times 10^{-5}$  cm<sup>2</sup>/dyn. After dissolution of drug and enhancer wherein the drug reservoir preferably has a storage modulus of  $1.0 \times 10^5$  to  $1.5 \times 10^5$  dyn/cm<sup>2</sup>. DURO-TAK® adhesives such as DURO-TAK® 87-4287 are available from National Starch & Chemicals, Bridgewater, N.J. in 2005 and at the time of the filing of the present application and their chemical and physical properties are assessable by those skilled in the art.

[0071] With the inclusion of the suitable permeation enhancer(s), a progestin preferably NGMN, an estrogen, or progestin (e.g., NGMN) in combination with an estrogen can be delivered at high flux when solubilized in the matrix of the drug reservoir to a loading of higher than 5 wt %, preferably from 5 to 20 wt %, more preferably from 5 to 10 wt %.

[0072] Other than NGMN and estrogen, it is understood that the reservoir can also contain other drugs, preferably in a single phase polymeric composition, free of undissolved components. Other drugs that can be contained in the drug reservoir include, for example, those disclosed in U.S. Pat. No. 6,004,578. One skilled in the art will be able to incorporate such drugs based on the disclosure of the present invention.

[0073] In certain embodiments, optionally, certain other plasticizer or tackifying agent is incorporated in the polyacrylate composition to improve the adhesive characteristics. Examples of suitable tackifying agents include, but are not limited to, aliphatic hydrocarbons; aromatic hydrocarbons; hydrogenated esters; polyterpenes; hydrogenated wood resins; tackifying resins such as ESCOREZ, aliphatic hydrocarbon resins made from cationic polymerization of petrochemical feedstocks or the thermal polymerization and subsequent hydrogenation of petrochemical feedstocks, rosin ester tackifiers, and the like; mineral oil and combinations thereof. The tackifying agent employed should be compatible with the polymer or blend of polymers.

[0074] The backing layer 2 may be formed from any material suitable for making transdermal delivery patches, such as a breathable or occlusive material including fabric or sheet, made of polyvinyl acetate, polyvinylidene chloride, polyethylene, polyurethane, polyester, ethylene vinyl acetate (EVA), polyethylene terephthalate (PET), polybutylene terephthalate, coated paper products, aluminum sheet and the like, or a combination thereof. In certain embodiments, the backing layer includes low density polyethylene (LDPE) materials, medium density polyethylene (MDPE) materials or high density polyethylene (HDPE) materials, e.g., SARANEX (Dow Chemical, Midland, Mich.). The backing layer may be a monolithic or a multilaminate layer. In preferred embodiments, the backing layer is a multilaminate layer including polyester/ethylene vinyl acetate (PET/EVA).

Preferably the backing layer is translucent or adequately transparent such that the color of the reservoir can be observed and device can be seen to be clear (rather than cloudy). The backing layer can have a thickness of about 0.012 mm (0.5 mil) to 0.125 mm (5 mil); preferably about 0.025 mm (1 mil) to 0.1 mm (4 mil); more preferably about 0.0625 mm (1.5 mil) to 0.0875 mm (3.5 mil).

[0075] The protective layer of the transdermal device can be made of a polymeric material that may be optionally metallized. Examples of the polymeric materials include polyurethane, polyvinyl acetate, polyvinylidene chloride, polypropylene, polycarbonate, polystyrene, polyethylene, polyethylene terephthalate, polybutylene terephthalate, paper, and the like, and a combination thereof. In preferred embodiments, the protective layer includes a siliconized polyester sheet.

[0076] A wide variety of materials that can be used for fabricating the various layers of the transdermal delivery patches according to this invention have been described above. It is contemplated that the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions is practicable.

[0077] Transdermal flux can be measured with a standard procedure using Franz cells or using an array of formulations. Flux experiments were done on isolated human cadaver epidermis. With Franz cells, in each Franz diffusion cell a disc of epidermis is placed on the receptor compartment. A transdermal delivery system is placed over the diffusion area (1.98 cm<sup>2</sup>) in the center of the receptor. The donor compartment is then added and clamped to the assembly. At time 0, receptor solution (between 21 and 24 ml, exactly measured) is added into the receptor compartment and the cell maintained at 35° C. This temperature yields a skin surface temperature of 30-32° C. Samples of the receptor compartment are taken periodically to determine the skin flux and analyzed by HPLC. In testing flux with an array of transdermal miniature patches, formulations are prepared by mixing stock solutions of each of the mixture components of formulation in organic solvents (typically 15 wt % solids), followed by a mixing process. The mixtures are then aliquoted onto arrays as 4-mm diameter drops and allowed to dry, leaving behind solid samples or "dots." (i.e., mini-patches). The array of miniature patches is then tested individually for skin flux using a permeation array, whose principle is similar to that of an array of miniature Franz cells. The test array has a plurality of cells, a piece of isolated human epidermis large enough to cover the whole array, and a multiple well plate with wells acting as the receptor compartments filled with receptor medium. The assembled permeation arrays are stored at 32° C. and 60% relative humidity for the duration of the permeation experiments. Receptor fluid is auto-sampled from each of the permeation wells at regular intervals and then measured by HPLC for flux of the drug.

Administration of the Drug(s)

[0078] On application to the skin, the drug in the drug reservoir of the transdermal patch diffuses into the skin where it is absorbed into the bloodstream to produce a systemic therapeutic effect. When the patches are worn for contraception, a patch will typically be placed on the skin on the fifth day of the menstrual cycle, and replaced as needed

until 21 days of wearing have elapsed. For instance, in the case of a 7 day patch, three patches will be required to deliver the drug(s) for the 21 day period. If desired a placebo patch may be worn thereafter until the fifth day of the succeeding menstrual cycle. This regimen is repeated for each menstrual cycle. When patches are worn for hormone replacement therapy, a patch will typically be placed on the skin once per week.

Methods of Manufacture

[0079] The transdermal devices are manufactured according to known methodology. For example, in an embodiment, a solution of the polymeric reservoir material, as described above, is added to a double planetary mixer, followed by addition of desired amounts of the drug(s), permeation enhancers, and other ingredients that may be needed. Preferably, the polymeric reservoir material is an acrylate material. The acrylate material is solubilized in an organic solvent, e.g., ethanol, ethyl acetate, hexane, and the like. The mixer is then closed and activated for a period of time to achieve acceptable uniformity of the ingredients. The mixer is attached by means of connectors to a suitable casting die located at one end of a casting/film drying line. The mixer is pressurized using nitrogen to feed solution to the casting die. Solution is cast as a wet film onto a moving siliconized polyester web. The web is drawn through the lines and a series of ovens are used to evaporate the casting solvent to acceptable residual limits. The dried reservoir film is then laminated to a selected backing membrane and the laminate is wound onto the take-up rolls. In subsequent operations, individual transdermal patches are die-cut, separated and unit-packaged using suitable pouchstock. Patches are placed in cartons using conventional equipment. In another process, the drug reservoir can be formed using dry-blending and thermal film-forming using equipment known in the art. Preferably, the materials are dry blended and extruded using a slot die followed by calendaring to an appropriate thickness.

#### EXAMPLES

[0080] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. In the following examples all percentages are by weight unless noted otherwise.  $T_g$  was determined by DSC (Differential Scanning Calorimetry) with 10° C./min heating rate. Modulus  $G'$  was storage modulus at 25° C. and 1 rad/s frequency (Frequency sweep experiment was conducted using AR-2000 rheometer from TA Instruments (TA Instruments, 109 Lukens Drive, New Castle, Del. 19720). The test conditions were: strain 1%, temperature 25° C., frequency range 0.1 to 100 rad/s, gap around 1000 micron). Creep compliance tests were conducted using AR-2000 rheometer from TA Instruments. The test conditions were: stress 1000 dyn/cm<sup>2</sup>, temperature 30° C., time 3600 seconds, gap around 1000 microns. One skilled in the art will know how to measure  $T_g$ , creep compliance, and storage modulus in view of the present disclosure.

#### Example 1

[0081] A monomer mix containing butyl acrylate, 2-hydroxyethyl acrylate, t-octyl acrylamide, acrylic acid, ethyl

acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The ratios of the monomers and initiator added totally, i.e., butyl acrylate: 2-hydroxyethyl acrylate: t-octyl acrylamide: acrylic acid: AIBN were 59: 25.5: 9.5: 6: 2. The material was then held at reflux for a suitable period of time. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around  $9 \times 10^5$  dyn/cm<sup>2</sup>, creep compliance of around  $7 \times 10^{-5}$  cm<sup>2</sup>/dyn, and glass transition temperature of  $-8^\circ$  C., and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

#### Example 2

[0082] A monomer mix containing butyl acrylate, 2-hydroxypropyl acrylate, t-octyl acrylamide, acrylic acid, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The material was held at reflux for a suitable period of time. The ratios of the monomers and initiator added totally, i.e., butyl acrylate: 2-hydroxypropyl acrylate: t-octyl acrylamide: acrylic acid: AIBN were 59: 25.5: 9.5: 6: 2. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around  $8 \times 10^5$  dyn/cm<sup>2</sup>, creep compliance of around  $4 \times 10^{-5}$  cm<sup>2</sup>/dyn, and glass transition temperature of  $-8^\circ$  C., and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

#### Example 3

[0083] A monomer mix containing vinyl acetate, 2-hydroxyethyl acrylate, 2-ethylhexyl acrylate, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The material was held at reflux for a suitable period of time. The ratios of the monomers and initiator added totally, i.e., vinyl acetate: 2-hydroxyethyl acrylate: 2-ethylhexyl acrylate: AIBN were 50: 10: 40: 1.2. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around  $2 \times 10^6$  dyn/cm<sup>2</sup>, creep compliance of around  $4 \times 10^{-6}$  cm<sup>2</sup>/dyn, and glass transition temperature of  $-14^\circ$  C., and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

#### Example 4

[0084] A monomer mix containing vinyl acetate, 2-hydroxyethyl acrylate, 2-ethylhexyl acrylate, ethyl acetate (solvent), and 2,2'-azobisisobutyronitrile (AIBN) (polymerization initiator) was prepared. A fraction was charged to an appropriate vessel and heated to reflux with stirring. The remainder was added to the vessel over time. The ratios of the monomers and initiator added totally, i.e., vinyl acetate: 2-hydroxyethyl acrylate: 2-ethylhexyl acrylate: AIBN were

60: 20: 20: 1.2. The material was held at reflux for a suitable period of time. At the end of the hold period, the contents were cooled to room temperature and the solution polymer discharged. The dry film made from this polyacrylate formulation had storage modulus of around  $4 \times 10^6$  dyn/cm<sup>2</sup>, creep compliance of around  $2 \times 10^{-6}$  cm<sup>2</sup>/dyn, and glass transition temperature of  $-8^\circ$  C., and consequently was too stiff to provide adequate adhesive properties alone. This formed a proadhesive.

#### Example 5

[0085] The combination of high capacity acrylate matrix with certain unique combinations of permeation enhancers result in a more acceptable transdermal contraceptive system with high drug and permeation enhancers loading.

[0086] Various permeation enhancers were evaluated in two adhesives (for the purpose of the Examples, the polyacrylates of Examples 1 to 4 are called adhesive for ease of reference). Various combinations of unique formulations were evaluated for flux of NGMN and EE, comprised of unary (having a single enhancer), binary (having two enhancers), and ternary (having three enhancers) combinations of enhancers.

[0087] Forty-one permeation enhancers were selected based on the evaluation of their unary, binary, and (in limited cases) ternary performance enhancement, as indicated in Table 1. Combinations were prepared by preparing mixtures of the permeation enhancers at levels up to 80% of their solubility in the neat adhesives (except where further limited due to toxicological constraints) and where their combined weight fractions exceeded a rheologically acceptable limit for each adhesive (20 wt % and 35 wt % total enhancer(s) in National Starch DURO-TAK® 87-4287 adhesive and proadhesive from Example 3 above, respectively), in which case the total combined loading was limited to the limits proportionally to their respective unary solubility limits. The NGMN solubility was then predicted based upon the unary solubility estimates, and loaded into the formulations at several fractions of saturated levels. EE was also a component of every formulation, and was maintained in a constant proportion to the NGMN level of 1:8 EE: NGMN.

TABLE 2

Evaluated Permeation Enhancers and their combinations.		
Name	Acronym	Unary (U), Binary (B), Ternary (T)
Ascorbyl Palmitate	ASP	U, B
Benzyl Benzoate	BB	U, B, T
Ceteth-20	C20	U, B
Dipropylene glycol	DPG	U, B, T
Ethyl Myristate	EM	U, B
Ethyl Palmitate	EP	U, B, T
Farnesol	FAN	U, B
Glycerol Caprylate	GCP	U, B
Glycerol-tridecanoate	GLT	U, B
Glycerol Monolaurate	GML	U, B
Glycerol Monooleate	GMO	U, B, T
Hydroxycaprylic Acid	HCP	U, B
Hexyl Decanol	HD	U, B
1,2,3-hexanetriol	HEX	U, B
Isopropyl Laurate	IPL	U, B
Isopropyl Myristate	IPM	U, B, T
Isosorbide	ISO	U, B

TABLE 2-continued

<u>Evaluated Permeation Enhancers and their combinations.</u>		
Name	Acronym	Unary (U), Binary (B), Ternary (T)
Oleth-20	L20	U, B
Laureth-2	LAU	U, B
Lauramide DEA	LDA	U, B, T
Lauryl Lactate	LL	U, B
Lauryl Laurate	LLA	U, B
Lauryl Alcohol	LOL	U, B
Lauryl Pyrrolidone	LPY	U, B
Lauric Acid	LRA	U, B, T
Laureth-4	LTH	U, B, T
N-lauroyl Sarcosine	NLS	U, B, T
Oleic Acid	OA	U, B, T
Octyl Pyroglutamate	OCP	U, B
Octyldodecyl Lactate	ODL	U, B
Oleth-4	OL	U, B
Oleth-2	OL2	U, B, T
Octyldodecanol	OYD	U, B, T
Ethyl hexyl dimethyl PABA	PAD	U, B
Polyethylene glycol 400	PEG8	U, B
PEG 200 monolaurate	PML	U, B
Selachyl Alcohol	SAL	U, B, T
Sorbitan Oleate	SMO	U, B
Stearyl Behenate	STB	U, B
Succinic Acid	SUC	U, B
Tocopheryl Acetate	TAC	U, B
Tetraethylene Glycol	TEG	U, B
Tocopherol	TOC	U, B, T

[0088] All formulations were prepared and evaluated for flux through isolated human epidermis. Formulations were prepared by mixing stock solutions of each of the mixture components in organic solvents (typically 15 wt % solid

content in ethyl acetate, methanol and/or ethanol), followed by a mixing process. The mixtures were then aliquoted onto 16x24 arrays as 4-mm diameter drops and allowed to dry, leaving behind solid samples or "dots." (i.e., mini-patches). The resulting 384 miniature patches were then tested individually for skin flux using a 384-well permeation array, whose principle is similar to that of an array of miniature Franz cells, which is a standard tool for someone one skilled in the art of transdermal formulation development. The formulations could also have been tested on conventional Franz cells and results would be expected to be similar. Each permeation array consisted of the 384 miniature patch array, a piece of isolated human epidermis large enough to cover the whole array, and a 384-well plate acting as the receptor compartment and which was filled with receptor medium. The assembled permeation arrays were stored at 32° C. and 60% relative humidity for the duration of the permeation experiments and testing was conducted just like with conventional Franz cells with standard procedure known to people skilled in the art. Receptor fluid was auto-sampled from each of the permeation wells at regular intervals and then measured by HPLC for NGMN and EE content in order to determine the flux profile and measure the flux at steady state. Every formulation was replicated at least 3 times in order to ensure accuracy.

[0089] Selected NGMN-EE/enhancers formulations with flux in the range of greater than 0.1  $\mu\text{g}/\text{cm}^2\text{h}$  were each cast into a film of 2-3 mils (0.05-0.075mm) on a siliconized polyester sheet, and backed with a conformable and translucent or transparent backing material. The examples were evaluated for transdermal flux. All samples were monitored over time for crystal formation with cross-polarizing filters under 4x magnification. Only formulations that have not crystallized are included below in Table 3 (including Tables 3-1 to 3-2).

TABLE 3-1

Example compositions of transdermal matrix formulations yielding NGMN flux of greater than 0.1 $\mu\text{g}/\text{cm}^2\text{h}$ . Compositions given as percent weight fraction.										
Example Comp.	NGMN	EE	Enhancer 1	Enhancer 2	Enhancer 3	Polyacrylate matrix	NGMN Flux ( $\mu\text{g}/\text{cm}^2\text{h}$ )			
1	5.5%	0.7%	5.0% NLS	30.0% OA	—	58.8% from Example3	0.95			
2	7.5%	0.9%	5.0% NLS	27.0% IPM	—	59.5% from Example3	0.69			
3	10.0%	1.3%	5.0% NLS	30.0% TOC	—	53.7% from Example3	0.61			
4	5.7%	0.7%	12.5% LTH	22.5% IPM	—	58.5% from Example3	0.59			
5	6.0%	0.8%	4.4% LDA	7.0% SMO	23.6% IPM	58.2% from Example3	0.59			
6	7.5%	0.9%	4.0% NLS	16.0% TOC	—	71.6% 87-4287 Adhesive	0.91			
7	9.8%	1.2%	4.0% NLS	16.0% EP	—	69.0% 87-4287 Adhesive	0.89			
8	8.3%	1.0%	5.0% NLS	14.0% SMO	—	71.7% 87-4287 Adhesive	0.86			
9	4.0%	0.5%	5.2% LDA	7.2% OL2	7.4% OA	75.7% 87-4287 Adhesive	0.84			
10	4.3%	0.5%	4.0% GMO	6.7% OA	9.3% SMO	75.2% 87-4287 Adhesive	0.72			
Control	4.0%	0.5%	none	none	none	95.5% 87-4287 Adhesive	0.05			



[0090]

TABLE 3-2

Example compositions of transdermal matrix formulations yielding NGMN flux results in the greater than 0.1 $\mu\text{g}/\text{cm}^2\text{h}$ . Compositions given as percent weight fraction.									
Example Comp.	NGMN	EE	Enhancer 1		Enhancer 2		Enhancer 3	Polyacrylate matrix	NGMN Flux ( $\mu\text{g}/\text{cm}^2\text{h}$ )
1	8.8%	1.1%	15.6%	GMO	1.1%	NLS		73.4% from Example 3	0.80
2	7.7%	0.9%	5.0%	NLS	—	—		86.4% 87-4287 Adhesive	0.51
3	10.5%	1.3%	16.2%	GMO	2.7%	SAL		69.3% from Example 3	0.50
4	10.7%	1.3%	16.5%	EP	1.0%	NLS		70.5% from Example 3	0.44
5	7.9%	1.0%	11.1%	LAU	1.5%	SAL	—	78.5% from Example 3	0.31
6	15.9%	2.0%	30%	OA	—	—		52.1% from Example 3	0.30
7	8.0%	1.0%	12.0%	SAL	—	—		79.0% 87-4287 Adhesive	0.22
8	8.9%	1.1%	29%	LPY	—	—		61.0% 87-4287 Adhesive	0.13
9	5.0%	0.6%	20.2%	LLPY	—	—	—	74.2% 87-4287 Adhesive	0.11
Control	4.0%	0.5%	none		none		none	95.5% 87-4287 Adhesive	0.05

[0091] The data in Tables 3-1 and 3-2 show that with certain novel acrylate matrix, it was able to dissolve more than 19 wt % permeation enhancers to facilitate the delivery of NGMN and EE. Such high loading of enhancers can facilitate the delivery of NGMN flux significantly higher than about 0.05  $\mu\text{g}/\text{cm}^2\text{h}$ , the unenhanced flux of NGMN from an acrylate adhesive (in some cases almost 20 times that of the unenhanced flux). The acrylate content was as low as about 54 wt %. With the DURO-TAK® 87-4287, generally for formulations with relatively high flux, the enhancer loading was slightly lower than the enhancer loading possible with the acrylate polymer from Example 3, and the acrylate content was about 69 wt % or greater. In one aspect of the present invention, one type of useful acrylate polymer for making the transdermal delivery patch is one that comprises, and preferably consists of 2-hydroxyethyl acrylate, vinyl acetate and 2-ethylhexyl acrylate. An example is DURO-TAK® 87-4287 polyacrylate adhesive, which is a

terpolymer having a monomer composition of 2-6 wt % 2-hydroxyethyl acrylate, with the rest being vinyl acetate (20-40 wt %) and 2-ethylhexyl acrylate (55-75 wt %). DURO-TAK® 87-4287 acrylate polymer has a  $T_g$  of  $-38\text{ C}$ , storage modulus of  $3.6 \times 10^5 \text{ dyn}/\text{cm}^2$  and creep compliance of about  $5 \times 10^{-5} \text{ cm}^2/\text{dyn}$ .

[0092] Tables 4-1 and 4-2 provide additional data for flux and rheological property for formulations using DURO-TAK® 87-4287 acrylate adhesive. The data in Tables 4-1 and 4-2 show that the formulations have rheological property suitable for adhesion on skin for 1 day, 2 days, 3 days, even up to 7 day delivery. The formulation examples with permeation enhancers shown in Tables 4-1 and 4-2 contain 70 to 80 wt % acrylate when no PVP was used. With the inclusion of PVP, the acrylate content can be lowered to below 65 wt %.

TABLE 4-1

Example compositions of transdermal matrix formulations yielding NGMN flux of greater than 0.1 $\mu\text{g}/\text{cm}^2\text{h}$ . Compositions given as percent weight fraction.								NGMN Flux ( $\mu\text{g}/\text{cm}^2\text{h}$ )
Example Comp.	NGMN	EE	Enhancer 1	Enhancer 2	Excipient	Polyacrylate matrix		
1	7.5%	0.75%	5% NLS	14% SMO		72.8% 87-4287 Adhesive		0.62
2	5.0%	0.05%	4% NLS	16% IPM		75.0% 87-4287 Adhesive		0.29
3	8.5%	0.85%	4% NLS	16% DPG	7% PVP	63.7% 87-4287 Adhesive		0.41
4	4.0%	0.5%	none	none	none	95.5% 87-4287 Adhesive		0.05
5	6.0%	0%	3% NLS	14% GMO		77.0% Example 3 adhesive		0.38
6	8.0%	0%	none	none	none	92.0% Example 3 adhesive		0.02

[0093]

TABLE 4-2

Rheological properties for Transdermal Formulations in Table 4-1		
Example Comp.	Modulus (dyn/cm <sup>2</sup> )	creep compliance (cm <sup>2</sup> /dyn)
1	$1.6 \times 10^5$	$1.4 \times 10^{-4}$
2	$1.1 \times 10^5$	$2.0 \times 10^{-4}$
3	$5.3 \times 10^5$	$5.8 \times 10^{-5}$
4	$3.4 \times 10^5$	$4.3 \times 10^{-5}$
5	$1.1 \times 10^6$	$1.3 \times 10^{-5}$
6	$3.0 \times 10^5$	$6.6 \times 10^{-5}$

## Example 6

[0094] Experiments were done to compare flux of formulation of the present invention with commercially available ORTHO EVRAS patches. ORTHO EVRA® patches have about 73.5 wt % polyisobutylene adhesive, 4.25 wt % lauryl lactate, 20 wt % micronized crospovidone, 2 wt % NGMN and 0.25 wt % EE similar to the formulations in the U.S. Pat. No. 5,876,746 patent. Flux experiments were done on isolated human cadaver epidermis using conventional Franz cells with standard procedure known to people skilled in the art. For each Franz diffusion cell a disc of epidermis was placed on the receptor compartment. The NGMN or NGMN/EE system was placed over the diffusion area (1.98 cm<sup>2</sup>) in the center of the receptor. The donor compartment was then added and clamped to the assembly. At time 0, receptor solution (between 21 and 24 ml, exactly measured) was added into the receptor compartment and the cell maintained at 35° C. This temperature yields a skin surface temperature of 30-32° C. Samples of the receptor compartment were taken at about 24 hour intervals for 120 hours to determine the skin flux and analyzed by HPLC. The drug flux was calculated from the HPLC data.

[0095] FIG. 3 illustrates the NGMN flux profile of a NGMN formulation with permeation enhancers GMO and NLS according to the present invention compared to NGMN in certain other formulations. The flux experiments were done using Franz cells. Curve A with the diamond data points was obtained from a formulation according to the present invention with 14.03 wt % GMO, 3.44 wt % NLS and 6.44 wt % NGMN in the polyacrylate proadhesive according to Example 3. Curve C with the triangle data points was obtained using 7.63 wt % NGMN without permeation enhancers in a polyacrylate proadhesive made according to Example 3. Curve B with the circular dot data points was obtained using the drug-containing matrix from a commercially available ORTHO EVRA® patch (Lot 62M079). The horizontal bars show the standard deviations based on replicates. The data show that the formulation of the present invention had 2 to 4 times the NGMN flux compared to that by ORTHO EVRA® patch and more than 5 times the flux without permeation enhancers.

[0096] FIG. 4 illustrates the NGMN flux profile of a NGMN formulation with EE and permeation enhancers GMO and NLS according to the present invention compared to NGMN in other formulations. The flux experiments were done using Franz cells. The upper curve D with the diamond data points was obtained from a formulation according to the present invention with 6.4 wt % NGMN, 1.0 wt % EE, 14

wt % GMO, and 3 wt % NLS and in the polyacrylate proadhesive made according to Example 3. The lower curve F with the diamond data points was obtained using 7.6 wt % NGMN without permeation enhancers in a polyacrylate proadhesive made according to Example 3. Curve E with the circular dot data points was obtained using the drug-containing matrix from an ORTHO EVRA® patch. The data show that the formulation of the present invention had 2 to 4 times the NGMN flux compared to that by ORTHO EVRA® patch and more than 5 times the flux without permeation enhancers. Thus, comparison experiments performed under the same setting showed that the present system performed significantly better than the commercially available ORTHO EVRA® patch reservoir.

[0097] FIG. 5 illustrates the EE flux profile of the formulations of FIG. 4. The upper curve G with the diamond data points was obtained from a formulation according to the present invention with 6.4 wt % NGMN, 1.0 wt % EE, 14 wt % GMO, and 3 wt % NLS and in the polyacrylate proadhesive made according to Example 3. The lower curve I with the diamond data points was obtained using 7.6 wt % NGMN without permeation enhancers in a polyacrylate proadhesive made according to Example 3. Curve H with the circular dot data points was obtained using the drug-containing matrix from an ORTHO EVRA® patch. Again the EE flux in the formulation with permeation enhancers in the polyacrylate proadhesive made according to Example 3 had an EE flux about 3 times that of the ORTHO EVRA® patch and more than 10 times higher than that from the patch without permeation enhancers.

## Example 7

[0098] Further, wearing data showed that certain clear patches without micronized PVP could be worn continuously for 3 to 7 days with adequate adhesion, without becoming opaque white, and with reduced adhesive residue upon removal. The backing used in these clear patches was transparent. These clear patches had drug reservoirs made with enhancer dissolved in either the National Starch DURO-TAK® 87-4287 or with the proadhesive from Example 3, and 0 to 8% PVP K30 (uncrosslinked). It is expected that including dissolved female sex hormones of therapeutic amounts in such drug reservoirs will also result in comparable adhesion and appearance. Comparatively, commercially available ORTHO EVRA® patches, because of the presence of micronized PVP, turned cloudy white with moisture absorption after 7 day wear. More particularly, formulations made of National Starch DURO-TAK® 87-4287, plasticized with permeation enhancers to have a modulus in the range of 10,000 to 20,000 Pa, with up to 6 wt % PVP K30, combined with a 0.5mil PET/1.5 mil EVA backing had superior wearing characteristics, left reduced levels of residue, and did not become cloudy or opaque white after 7 days.

## Example 8

[0099] NGMN-EE/enhancers formulations are made using drug and enhancer tolerant polyacrylates. These proadhesive are expected to be capable of dissolving more NGMN, EE, and enhancer(s). Using the same method as described in Example 5 above, formulation with 8 wt % NGMN, 0.8 wt % EE, 5 wt % NLS, and 30 wt % SMO are prepared and evaluated for flux through isolated human

epidermis. The polyacrylate is the polyacrylate of Example 3 (from National Starch & Chemicals, Bridgewater, N.J.). This polyacrylate was a copolymer and consisted of 10 wt % 2-hydroxyethyl acrylate, 50 wt % vinyl acetate, and 40 wt % 2-ethylhexyl acrylate. Such systems are expected to be still mono-phasic and result in transdermal flux values of around  $0.8 \mu\text{g}/\text{cm}^2\text{-hr}$ .

**[0100]** The entire disclosure of each patent, patent application, and publication cited or described in this document is hereby incorporated herein by reference. The practice of the present invention will employ, unless otherwise indicated, conventional methods used by those in pharmaceutical product development within those of skill of the art. Embodiments of the present invention have been described with specificity. The embodiments are intended to be illustrative in all respects, rather than restrictive, of the present invention. It is to be understood that various combinations and permutations of various constituents, parts and components of the schemes disclosed herein can be implemented by one skilled in the art without departing from the scope of the present invention.

What is claimed is:

1. A method of making a drug reservoir for transdermal (NGMN) delivery, comprising: providing a solution of a noncrosslinked acrylate polymer, dissolving NGMN and permeation enhancer in the solution, drying the solution to form a drug reservoir with more than 4 wt % of NGMN dissolved in the drug reservoir such that the drug reservoir has permeation enhancer and can deliver the NGMN at a flux for therapy, the polymer constitutes 45 wt % to 90 wt % of the drug reservoir, wherein the drug reservoir maintains appropriate pressure sensitive adhesive properties applicable to a body surface.

2. The method of claim 1 comprising forming the reservoir with carrier having NGMN and estrogen dissolved therein, the carrier being a polymer consist of non-crosslinked polyacrylate and wherein the NGMN flux is greater than  $0.4 \mu\text{g}/\text{cm}^2\text{-h}$ .

3. The method of claim 2 wherein the estrogen is ethinyl estradiol (EE) and the method comprising dissolving more than 15 wt % NGMN, and dissolving EE and permeation enhancer in the solution such that the NGMN together with EE (NGMN/EE) and permeation enhancer make up greater than 30 wt % dissolved solids in the drug reservoir and wherein the acrylate polymer has polar functionality.

4. The method of claim 2 wherein the estrogen is ethinyl estradiol (EE) and the acrylate polymer has at least 10 wt % functional monomer component, constitutes 45 wt % to 80 wt % of the drug reservoir and can hold the NGMN/EE together with permeation enhancer at a dissolved amount of at least 30 wt %, the acrylate polymer having a  $T_g$  of greater than  $-15^\circ\text{C}$ . if without permeation enhancer and without NGMN/EE.

5. The method of claim 2 wherein the drug reservoir can deliver the NGMN at a flux of larger than 150 mg per day at greater than  $0.4 \mu\text{g}/\text{cm}^2\text{-h}$  and the estrogen has a flux of greater than  $0.01 \mu\text{g}/\text{cm}^2\text{-h}$ .

6. The method of claim 2 wherein the NGMN flux is greater than  $0.5 \mu\text{g}/\text{cm}^2\text{-h}$  and the permeation enhancer is more than 20 wt % in the reservoir.

7. The method of claim 4 wherein the acrylate polymer has no more than 60 wt % soft monomer component, has at least 40 wt % hard monomer component at least a fraction

of which being hard functional monomer, and has 1 to 35 wt % functional monomer component.

8. The method of claim 4 wherein the drug reservoir has a glass transition temperature  $T_g$  of less than  $-10^\circ\text{C}$ . whereas the acrylate polymer has a  $T_g$  of greater than  $-15^\circ\text{C}$ . and a creep compliance of  $6 \times 10^{-5} \text{ cm}^2/\text{dyn}$  to  $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$ .

9. The method of claim 4 wherein the acrylate polymer includes (i) 40 to 50 wt % of soft alkyl acrylate monomer component, in which each soft alkyl acrylate monomer having a homopolymer  $T_g$  of  $-80^\circ\text{C}$ . to  $-20^\circ\text{C}$ ., (ii) 40 to 60 wt % of hard modifying monomer component, in which each hard modifying monomer having a homopolymer  $T_g$  of 0 to  $250^\circ\text{C}$ ., and (iii) up to 30% by weight of functional monomer component, wherein soft monomer is an alkyl acrylate monomer having 4 to 10 carbon atoms in the alkyl group.

10. The method of claim 4 wherein the acrylate polymer includes a soft acrylate monomer selected from the group consisting of butyl, hexyl, 2-ethylhexyl, octyl, and dodecyl acrylates and isomers thereof.

11. The method of claim 4 wherein the acrylate polymer includes 40 to 50 wt % of soft alkyl acrylate monomer component having a homopolymer  $T_g$  of less than  $-20^\circ\text{C}$ .

12. The method of claim 4 wherein the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ . if without NGMN and permeation enhancer, and the drug reservoir having the dissolved NGMN/EE and permeation enhancer has a  $T_g$  of  $-10^\circ\text{C}$ . to  $-20^\circ\text{C}$ ., a creep compliance of  $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$  to  $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

13. The method of claim 4 comprising incorporating permeation enhancer and NGMN/EE in the acrylate polymer to result in single phase pressure sensitive adhesive, wherein the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ ., storage modulus of  $8 \times 10^5 \text{ dyn}/\text{cm}^2$  or above if without the NGMN/EE and permeation enhancer, and the drug reservoir with the NGMN/EE and permeation enhancer has a  $T_g$  of  $-10^\circ\text{C}$ . to  $-20^\circ\text{C}$ ., a creep compliance of  $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$  to  $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

14. The method of claim 4 comprising providing the acrylate polymer having monomer components of 50 to 60 wt % vinyl acetate, 10-20 wt % hydroxyethyl acrylate, and 20-40 wt % 2-ethylhexyl acrylate.

15. The method of claim 4 comprising providing the acrylate polymer having monomer components of 55 to 65 wt % butyl acrylate, 5 to 15 wt % t-octyl acrylamide, 20 to 30 wt % hydroxyethyl or hydroxypropyl acrylate and 5 to 10 wt % acid monomer.

16. A method of making a transdermal NGMN/EE delivery drug reservoir, comprising: providing for a drug reservoir a noncrosslinked polyacrylate proadhesive containing function group and having a  $T_g$  of greater than  $-15^\circ\text{C}$ ., creep compliance of  $6 \times 10^{-5} \text{ cm}^2/\text{dyn}$  to  $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$ , and storage modulus of  $8 \times 10^5 \text{ dyn}/\text{cm}^2$  or above, dissolving NGMN and permeation enhancer in the proadhesive with a concentration of greater than 30 wt % solids of NGMN and EE together with permeation enhancer such that the resulting drug reservoir has adhesive properties appropriate for transdermal drug delivery, the resulting drug reservoir having a  $T_g$  of  $-10^\circ\text{C}$ . to  $-30^\circ\text{C}$ ., a creep compliance of  $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$  to  $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

17. A device for transdermal administration of NGMN/EE to an individual in need thereof for therapy, comprising a backing and a single phase drug reservoir comprising non-crosslinked acrylate polymer having dissolved NGMN of greater than 5 wt %, and permeation enhancer to deliver the NGMN and to deliver EE, wherein the drug reservoir is applicable as a pressure sensitive adhesive to a body surface.

18. The device of claim 17 wherein the acrylate polymer in the drug reservoir is consisted essentially of non-crosslinked polyacrylate and the reservoir has at least 30 wt % of NGMN/EE with permeation enhancer together and the NGMN flux is greater than  $0.5 \mu\text{g}/\text{cm}^2\text{-h}$  transdermally and wherein the noncrosslinked polyacrylate include polar functionality.

19. The device of claim 17 further comprising estrogen in the drug reservoir.

20. The device of claim 17 wherein the drug reservoir has 4 wt % or more of NGMN/EE and greater than 30 wt % of NGMN/EE together with permeation enhancer.

21. The device of claim 17 wherein the drug reservoir has at least 30 wt % of NGMN/EE with permeation enhancer together and the acrylate polymer comprises 50 wt % to 90 wt % of the drug reservoir, wherein the drug reservoir is applicable as a pressure sensitive adhesive to a body surface.

22. The device of claim 17 wherein the acrylate polymer has no more than 60 wt % soft monomer component, at least 40 wt % hard monomer component at least a portion of which is functional hard monomer, and 10 to 35 wt % functional monomer, the acrylate polymer constituting 45 wt % to 80 wt % of the drug reservoir and having a solubility of at least 30 wt % for the NGMN/EE together with permeation enhancer, the acrylate polymer having a  $T_g$  of greater than  $-15^\circ\text{C}$ . if without permeation enhancer and without NGMN/EE, the drug reservoir having pressure sensitive adhesive properties applicable to the body surface for transdermal delivery.

23. The device of claim 17 wherein the drug reservoir in the device includes permeation enhancer wherein the drug reservoir is of a composition having a creep compliance of  $6 \times 10^{-5} \text{ cm}^2/\text{dyn}$  to  $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$  if the drug reservoir is without NGMN/EE and without permeation enhancer.

24. The device of claim 17 wherein the acrylate polymer includes 10 to 35 wt % functional monomer component.

25. The device of claim 17 wherein the acrylate polymer includes an acrylic copolymer resulting from (i) 40 to 50 wt % of one or more soft alkyl acrylate monomers, each soft alkyl acrylate monomer having a homopolymer  $T_g$  of  $-80$  to  $-20^\circ\text{C}$ ., (ii) 5 to 15 wt % of one or more nonfunctional hard modifying monomers, each hard modifying monomer having a homopolymer  $T_g$  of 0 to  $250^\circ\text{C}$ ., and (iii) one or more functional monomers of 10 to 35 wt %.

26. The device of claim 17 wherein the acrylate polymer has (i) 40 to 50 wt % of one or more soft alkyl acrylate monomers, each soft alkyl acrylate monomer having a homopolymer  $T_g$  of  $-80$  to  $-20^\circ\text{C}$ ., (ii) 5 to 15 wt % of one or more nonfunctional hard modifying monomers, each hard modifying monomer having a homopolymer  $T_g$  of 0 to  $250^\circ\text{C}$ ., and (iii) one or more functional monomers of 10 to 35 wt %, wherein the soft monomer is an alkyl acrylate monomer having 4 to 10 carbon atoms in the alkyl group.

27. The device of claim 17 wherein the acrylate polymer includes a soft acrylate monomer selected from the group consisting of butyl, hexyl, 2-ethylhexyl, octyl, and dodecyl acrylates and isomers thereof.

28. The device of claim 17 wherein the acrylate polymer includes 40 to 50 wt % of soft alkyl acrylate monomer having a homopolymer  $T_g$  of less than  $-20^\circ\text{C}$ ..

29. The device of claim 17 wherein the acrylate polymer includes 40 to 50 wt % of soft alkyl acrylate monomer having a homopolymer  $T_g$  of less than  $-20^\circ\text{C}$ ., hard modifying monomer having a homopolymer  $T_g$  of higher than  $20^\circ\text{C}$ ., and functional monomer having acidic group.

30. The device of claim 17 wherein the acrylate polymer includes hard modifying monomer having a homopolymer  $T_g$  of 0 to  $250^\circ\text{C}$ ., wherein the permeation enhancer and the NGMN/EE are dissolved in the acrylate polymer and the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ . and a creep compliance of  $6 \times 10^{-5} \text{ cm}^2/\text{dyn}$  to  $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$  without the NGMN/EE and permeation enhancer, whereas the drug reservoir with the dissolved NGMN/EE and permeation enhancer has a creep compliance of less than  $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

31. The device of claim 17 wherein the acrylate polymer includes hard modifying monomer having a homopolymer  $T_g$  of 40 to  $100^\circ\text{C}$ ..

32. The device of claim 17 wherein the acrylate polymer includes hard modifying monomer selected from the group consisting of vinyl acetate, methyl acrylate, and methyl methacrylate.

33. The device of claim 17 wherein the acrylate polymer has acidic group and hydroxyl group therein and includes 5 to 15 wt % nonfunctional hard monomer.

34. The device of claim 17 wherein the acrylate polymer is consisted of monomer components of 50-60 wt % vinyl acetate, 10-20 wt % hydroxyethyl acrylate, and 20-40 wt % 2-ethylhexyl acrylate.

35. The device of claim 17 wherein the acrylate polymer includes functional monomer selected from the group consisting of acrylic acid, hydroxyethyl acrylate, and hydroxypropyl acrylate.

36. The device of claim 17 wherein the permeation enhancer and the NGMN/EE are dissolved in the acrylate polymer and the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ ., a creep compliance of  $6 \times 10^{-5} \text{ cm}^2/\text{dyn}$  to  $2 \times 10^{-6} \text{ cm}^2/\text{dyn}$  if without the NGMN/EE and permeation enhancer dissolved therein, whereas with the dissolved NGMN/EE and permeation enhancer the acrylate polymer is a drug reservoir with a  $T_g$  of  $-10$  to  $-20^\circ\text{C}$ ., a creep compliance of less than  $1 \times 10^{-3} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

37. The device of claim 17 wherein the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ . if without NGMN/EE and permeation enhancer, whereas the acrylate polymer with NGMN/EE and permeation enhancer at above 30 wt % in a single phase forms a drug reservoir with a  $T_g$  of  $-10$  to  $-20^\circ\text{C}$ ., a creep compliance of  $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$  to  $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

38. The device of claim 17 wherein the acrylate polymer has a  $T_g$  of 0 to  $-20^\circ\text{C}$ ., storage modulus of  $8 \times 10^5 \text{ dyn}/\text{cm}^2$  or above  $^\circ\text{C}$ . if without NGMN/EE and permeation enhancer, whereas the acrylate polymer with NGMN/EE and permeation enhancer at above 30 wt % forms a drug reservoir with a  $T_g$  of  $-10$  to  $-40^\circ\text{C}$ ., a creep compliance of  $1 \times 10^{-4} \text{ cm}^2/\text{dyn}$  to  $6 \times 10^{-4} \text{ cm}^2/\text{dyn}$  and storage modulus of  $1 \times 10^5 \text{ dyn}/\text{cm}^2$  to  $8 \times 10^5 \text{ dyn}/\text{cm}^2$ .

39. The device of claim 17 wherein the device can deliver 125 to 350  $\mu\text{g}/\text{day}$  of NGMN for 7 days and the area of the device contacting the skin is 20-50  $\text{cm}^2$ .

40. The device of claim 17 comprising permeation enhancer selected from the group consisting of N-lauroyl sarcosine, Oleth-2, selachyl alcohol, glyceryl monolaurate, ethyl palmitate, sorbitan oleate, oleic acid, isopropyl myristate, lauramide DEA, laureth-2.

41. The device of claim 17 comprising permeation enhancer selected from the group consisting of N-lauroyl sarcosine, and wherein the device contains no thioglycerol.

42. A device for transdermal administration of NGMN/EE to an individual for therapy, comprising a backing and a single phase drug reservoir comprising a matrix of acrylate polymer having polar functional group, dissolved NGMN of greater than 5 wt %, and permeation enhancer to deliver the NGMN and EE at greater flux ( $\mu\text{g}/\text{cm}^2\text{-h}$ ) than ORTHO EVRA® patch, the acrylate polymer being noncrosslinked and consisting of 5.2 wt % 2-hydroxyethyl acrylate, vinyl acetate of 20 to 40 wt % and 2-ethylhexyl acrylate of 55-75 wt %, the permeation enhancer either including N-lauroyl sarcosine or including Oleth-2 and at least one other permeation enhancing chemical, wherein the drug reservoir maintaining adhesive properties applicable to a body surface for 7 days.

43. A device for transdermal administration of NGMN/EE to an individual for therapy, comprising a rigid transparent occlusive backing and a single phase drug reservoir comprising a matrix of acrylate polymer having polar functional

group, dissolved NGMN of greater than 5 wt %, and permeation enhancer to deliver the NGMN and EE at greater flux ( $\mu\text{g}/\text{cm}^2\text{-h}$ ) than ORTHO EVRA® patch, the acrylate polymer being noncrosslinked and consisting of 5.2 wt % 2-hydroxyethyl acrylate, vinyl acetate of 20 to 40 wt % and 2-ethylhexyl acrylate of 55-75 wt %, the permeation enhancer being one of (i) including N-lauroyl sarcosine, (ii) including oleic acid and at least two other permeation enhancing chemicals, and (iii) Oleth-2 and at least one other permeation enhancing chemical, wherein skin color is visible through the device and the drug reservoir maintaining adhesive properties applicable to a body surface for 7 days without turning cloudy.

44. A device for transdermal administration of NGMN/EE to an individual for therapy, comprising a transparent occlusive backing and a single phase drug reservoir comprising a matrix of acrylate polymer, dissolved NGMN of greater than 5 wt %, EE, and permeation enhancer, the acrylate polymer being noncrosslinked and consisting of 5.2 wt % 2-hydroxyethyl acrylate, vinyl acetate of 20 to 40 wt % and 2-ethylhexyl acrylate of 55-75 wt % and having a storage modulus of 2 to  $5 \times 10^5$   $\text{dyn}/\text{cm}^2$ , wherein the drug reservoir has a storage modulus of  $1.0 \times 10^5$  to  $1.5 \times 10^5$   $\text{dyn}/\text{cm}^2$  for pressure sensitive adhesive applicable to a body surface to deliver the NGMN and EE at greater flux ( $\mu\text{g}/\text{cm}^2\text{-h}$ ) than ORTHO EVRA® patch surface for 7 days without turning cloudy.

\* \* \* \* \*