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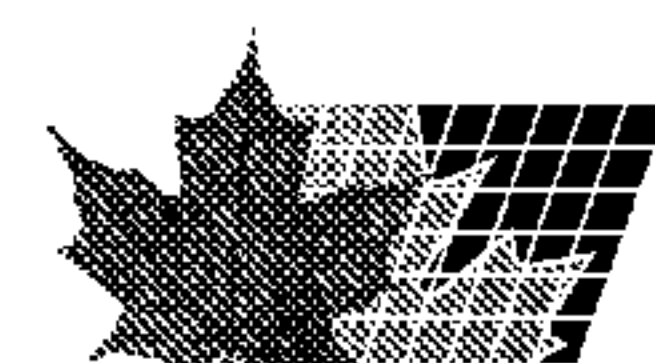
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(71) Demandeur/Applicant:
ZARS PHARMA, INC., US
(72) Inventeurs/Inventors:
ZHANG, JIE, US;
WARNER, KEVIN S., US;
SHARMA, SANJAY, US
(74) Agent: RIDOUT & MAYBEE LLP

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MEDICAMENTS

(54) Title: FLUX-ENABLING COMPOSITIONS AND METHODS FOR DERMAL DELIVERY OF DRUGS

(57) **Abrégé/Abstract:**

The present invention is drawn to adhesive solidifying formulations, methods of drug delivery, and solidified layers for dermal delivery of a drug. The formulation can include a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can include a volatile solvent system comprising at least one volatile solvent, and a non-volatile solvent system comprising at least one non-volatile solvent, wherein at least one non-volatile solvent is a flux-enabling non-volatile solvent(s) capable of facilitating the delivery of the drug at therapeutically effective rates over a sustained period of time. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvents system. When applied to the skin, the formulation can form a solidified layer after at least a portion of the volatile solvent system is evaporated.



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(74) Agents: OAKESON, Gary, P. et al.; THORPE, NORTH & WESTERN, LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).

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(71) Applicant (*for all designated States except US*): ZARS, INC. [US/US]; 1142 W. 2320 S., Salt Lake City, UT 84119 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ZHANG, Jie [US/US]; 6232 S. Loreen Dr., Salt Lake City, UT 84121 (US). WARNER, Kevin, S. [US/US]; 9224 Uinta Hills Dr., West Jordan, UT 84088 (US). SHARMA, Sanjay [IN/US]; 11633 S. Brisbane Dr., Sandy, UT 84094 (US).

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FLUX-ENABLING COMPOSITIONS AND METHODS FOR DERMAL DELIVERY OF DRUGS

FIELD OF THE INVENTION

The present invention relates generally to systems developed for dermal delivery of drugs. More particularly, the present invention relates to adhesive solidifying formulations having a viscosity suitable for application to a skin surface, and which form a sustained drug-delivering adhesive solidified layer.

BACKGROUND OF THE INVENTION

Traditional dermal drug delivery systems can generally be classified into two forms: semisolid formulations and dermal patch dosage forms. Semisolid formulations are available in a few different forms, including ointments, creams, foams, pastes, gels, or lotions and are applied topically to the skin. Dermal (including transdermal) patch dosage forms also are available in a few different forms, including matrix patch configurations and liquid reservoir patch configurations. In a matrix patch, the active drug is mixed in an adhesive that is coated on a backing film. The drug-laced adhesive layer is typically directly applied onto the skin and serves both as means for affixing the patch to the skin and as a reservoir or vehicle for facilitating delivery of the drug. Conversely, in a liquid reservoir patch, the drug is typically incorporated into a solvent system which is held by a thin bag, which can be a thin flexible container. The thin bag can include a permeable or semi-permeable membrane surface that is coated with an adhesive for affixing the membrane to the skin. The membrane is often referred to as a rate limiting membrane (although it may not actually be rate limiting in the delivery process in all cases) and can control transport of the drug from within the thin bag to the skin for dermal delivery.

While patches and semisolid formulations are widely used to deliver drugs into and through the skin, they both have significant limitations. For

example, many semisolid formulations usually contain only volatile solvent(s), such as water and ethanol, which evaporate shortly after application. The evaporation of such solvents can cause a significant decrease or even termination of dermal drug delivery, which may not be desirable in many cases.

5 Some traditional semisolid formulations may also contain some non-volatile liquid substances that are chosen or formulated for spreading the formulation or improving the aesthetics of the formulation rather than delivering the drug with sufficient flux. Drug delivery from those formulations may not be sufficient or sustainable. Additionally, semisolid formulations are often "rubbed into" the skin,
10 which does not necessarily mean the drug formulation is actually delivered into the skin. Instead, this phrase often means that a very thin layer of the drug formulation is applied onto but still outside the surface of the skin. Such thin layers of traditional semisolid formulations applied to the skin may not contain sufficient quantity of active drug to achieve sustained delivery over long periods
15 of time. Additionally, traditional semisolid formulations are often subject to unintentional removal due to contact with objects such as clothing, which may compromise the sustained delivery and/or undesirably soil clothing. Drugs present in a semisolid formulation may also be unintentionally delivered to persons who come in contact with a subject undergoing treatment with a topical
20 semisolid formulation.

With respect to matrix patches, in order to be delivered appropriately, a drug should have sufficient solubility in the adhesive, as primarily only dissolved drug contributes to the driving force required for skin permeation. Unfortunately, solubility in adhesives that is too low does not generate adequate skin
25 permeation driving force over sustained period of time. In addition, many ingredients, e.g., liquid solvents and permeation enhancers, which could be used to help dissolve the drug or increase the skin permeability, may not be able to be incorporated into many adhesive matrix systems in sufficient quantities to be effective. For example, at functional levels, most of these
30 materials may adversely alter the wear properties of the adhesive. As such, the selection and allowable quantities of additives, enhancers, excipients, or the like in adhesive-based matrix patches can be limited. To illustrate, for many drugs,

optimal transdermal flux can be achieved when the drug is dissolved in certain liquid solvent systems, but a thin layer of adhesive in a typical matrix patch often cannot hold enough appropriate drug and/or additives to be therapeutically effective. Further, the properties of the adhesives, such as coherence and tackiness, can also be significantly changed by the presence of liquid solvents or enhancers.

Regarding liquid reservoir patches, even if a drug is compatible with a particular liquid or semisolid solvent system carried by the thin bag of the patch, the solvent system still has to be compatible to the adhesive layer coated on the permeable or semi-permeable membrane; otherwise the drug may be adversely affected by the adhesive layer or the drug/solvent system may reduce the tackiness of the adhesive layer. In addition to these dosage form considerations, reservoir patches are bulkier and usually are more expensive to manufacture than matrix patches.

Another shortcoming of dermal (including transdermal) patches is that they are usually neither stretchable nor flexible, as the backing film (in matrix patches) and the thin fluid bag (in reservoir patches) are typically made of polyethylene or polyester, both of which are relatively non-stretchable materials. If the patch is applied to a skin area that is significantly stretched during body movements, such as a joint, separation between the patch and skin may occur thereby compromising the delivery of the drug. In addition, a patch present on a skin surface may hinder the expansion of the skin during body movements and cause discomfort. For these additional reasons, patches are not ideal dosage forms for skin areas subject to expansion, flexing and stretching during body movements.

In view of the shortcomings of many of the current dermal drug delivery systems, it would be desirable to provide systems, formulations, and/or methods that can i) provide sustained drug delivery over long periods of time; ii) are not vulnerable to unintentional removal by contact with clothing, other objects, or people for the duration of the application time; iii) can be applied to a skin area subject to stretching and expansion without causing discomfort or poor contact to skin; and/or iv) can be easily removed after application and use.

SUMMARY OF THE INVENTION

Although film-forming technologies have been used in cosmetic and pharmaceutical preparations, typically, the solvents used in such systems do not last very long on skin surface, and thus, are not optimal for sustained-release applications. In accordance with this, the inventors of the current invention recognized that the use of both volatile solvent as well as flux-enabling non-volatile solvent in the formulation can improve or even optimize sustained drug delivery. Thus, it would be advantageous to provide dermal delivery formulations, systems, and/or methods in the form of adhesive solidifying compositions or formulations having a viscosity suitable for application to the skin surface and which form a drug-delivering solidified layer on the skin that can be easily removed, such as by peeling or washing with a solvent. In one embodiment, the adhesive solidifying compositions or formulation, once solidified, can be cohesive.

In accordance with this, a solidifying formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system having one or more volatile solvent(s) and a non-volatile solvent system having one or more non-volatile solvent(s), wherein the non-volatile solvent system comprises at least one flux-enabling non-volatile solvent for the drug such that the drug can be delivered in therapeutically effective amounts over a period of time, even after most of the volatile solvent(s) is (are) evaporated. The formulation can have viscosity suitable for application to the skin surface prior to evaporation of at least one volatile solvent, and can further be configured such that when applied to the skin surface, the formulation forms a solidified layer after at least a portion of the volatile solvent(s) is (are) evaporated, but yet continues to deliver drug after substantially solidifying. In certain embodiments, the solidified layer can be coherent so that it is peelable from the skin, or is washable from the skin using a solvent. In one particular embodiment, the drug can be a sex hormone, and in another particular embodiment, the drug can be an anti-wart drug, though many

other drug types can be used, as described herein. The solidifying agents are typically polymers that form rigid solids without plasticizing agent (plasticizer). Therefore, the non-volatile solvent system has to be a plasticizer to the solidifying agent.

5 In an alternative embodiment, a method of dermally delivering a drug to, into, or through the skin can comprise applying a formulation to a skin surface of a subject, where the formulation comprises a drug; a solvent vehicle, and a solidifying agent. The solvent vehicle comprises a volatile solvent system including one or more volatile solvent, and a non-volatile solvent system
10 including one or more non-volatile solvent, wherein the non-volatile solvent system is flux-enabling for the drug. In this embodiment, the formulation can have a viscosity suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system, and the formulation can be applied such that the skin surface forms a solidified layer after at least partial
15 evaporation of the volatile solvent system. An additional step includes dermally delivering the drug from the solidified layer to the subject at therapeutically effective rates over a sustained period of time, wherein the drug continues to be delivered after the volatile solvent system is substantially evaporated. In some embodiments, the solidified layer can be a soft or flexible, coherent, continuous
20 solid, and can be removed by peeling.

In another embodiment, a method of preparing a formulation for dermal drug delivery can comprise steps of selecting a drug suitable for dermal delivery; selecting or formulating a non-volatile solvent or a mixture of non-volatile solvents that is flux-enabling for the selected drug, selecting a solidifying
25 agent that is compatible with the drug and the non-volatile solvent, selecting or formulating a volatile solvent system that is compatible with the drug, the non-volatile solvent and the solidifying agent; and formulating all above ingredients into a formulation. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvent system, and can be
30 applied to the skin surface where it forms a solidified layer after at least a portion of the volatile solvent system is evaporated. In this embodiment, the

drug continues to be delivered at a therapeutically effective amount after the volatile solvent system is substantially evaporated.

In still another embodiment, a solidified layer for delivering a drug can comprise a drug, a non-volatile solvent system, and a solidifying agent. The non-volatile solvent system can include at least one flux-enabling non-volatile solvent or a mixture of non-volatile solvents that is/are flux-enabling for the drug. The solidified layer can be a soft, coherent solid that is adhered to a body surface, and while dermally delivering at least a portion of the drug therefrom, the solidified layer is at least substantially devoid of water and solvents more volatile than water, and wherein the solidified layer is also flux-enabling for the drug.

Additional features and advantages of the invention will be apparent from the following detailed description and figures which illustrate, by way of example, features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical representation of the cumulative amount of diclofenac delivered transdermally across human cadaver skin over time from a formulation in accordance with embodiments of the present invention where steady-state delivery is shown over 28 hours.

FIG. 2 is a graphical representation of the cumulative amount of ropivacaine delivered transdermally across human cadaver skin over time from a formulation with similar composition in accordance with embodiments of the present invention, where steady-state delivery is shown over 30 hours.

FIG. 3 is a graphical representation of cumulative amount of testosterone delivered across a biological membrane *in vitro* over time from a solidified adhesive formulation in accordance with embodiments of the present invention, which is compared to the marketed product (AndroGel).

FIG. 4 is a graphical representation of the cumulative amount of acyclovir delivered transdermally over time from two separate formulations in accordance

with embodiments of the present invention, which is compared to the marketed product Zovirax cream.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

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Before particular embodiments of the present invention are disclosed and described, it is to be understood that this invention is not limited to the particular process and materials disclosed herein as such may vary to some degree. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and is not intended to be limiting, as the scope of the present invention will be defined only by the appended claims and equivalents thereof.

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In describing and claiming the present invention, the following terminology will be used.

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The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a drug" includes reference to one or more of such compositions.

20

"Skin" is defined to include human skin (intact, diseased, ulcerous, or broken), finger and toe nail surfaces, and mucosal surfaces that are usually at least partially exposed to air such as lips, genital and anal mucosa, and nasal and oral mucosa.

25

The term "drug(s)" refers to any bioactive agent that is applied to, into, or through the skin which is applied for achieving a therapeutic affect. This includes compositions that are traditionally identified as drugs, as well other bioactive agents that are not always considered to be "drugs" in the classic sense, e.g., peroxides, humectants, emollients, etc., but which can provide a therapeutic effect for certain conditions. When referring generally to a "drug," it is understood that there are various forms of a given drug, and those various forms are expressly included. In accordance with this, various drug forms include polymorphs, salts, hydrates, solvates, and cocrystals. For some drugs, one physical form of a drug may possess better physical-chemical properties making it more amenable for getting to, into, or through the skin, and this

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particular form is defined as the physical form favorable for dermal delivery. For example the steady state flux of diclofenac sodium from flux enabling non-volatile solvents is much higher than the steady state flux of diclofenac acid from the same flux enabling non-volatile solvents. It is therefore desirable to evaluate
5 the flux of the physical forms of a drug from non-volatile solvents to select a desirable physical form/non-volatile solvent combination.

The phrases "dermal drug delivery" or "dermal delivery of drug(s)" shall include both transdermal and topical drug delivery, and includes the delivery of drug(s) to, through, or into the skin. "Transdermal delivery" of drug can be
10 targeted to skin tissues just under the skin, regional tissues or organs under the skin, systemic circulation, and/or the central nervous system. "Topical delivery" includes delivery of a drug to a skin tissue, and subsequent absorption into deeper tissues that may occur.

The term "flux" such as in the context of "dermal flux" or "transdermal
15 flux," respectively, refers to the quantity of the drug permeated into or across skin per unit area per unit time. A typical unit of flux is microgram per square centimeter per hour. One way to measure flux is to place the formulation on a known skin area of a human volunteer and measure how much drug can permeate into or across skin within certain time constraints. Various methods
20 (*in vivo* methods) might be used for the measurements as well. The method described in Example 1 or other similar method (*in vitro* methods) can also be used to measure flux. Although an *in vitro* method uses human epidermal membrane obtained from a cadaver, or freshly separated skin tissue from hairless mice rather than measure drug flux across the skin using human
25 volunteers, it is generally accepted by those skilled in the art that results from a properly designed and executed *in vitro* test can be used to estimate or predict the results of an *in vivo* test with reasonable reliability. Therefore, "flux" values referenced in this patent application can mean that measured by either *in vivo* or *in vitro* methods.

30 The term "flux-enabling" with respect to the non-volatile solvent system (or solidified layer including the same) refers to a non-volatile solvent system (including one or more non-volatile solvents) selected or formulated specifically

to be able to provide therapeutically effective flux for a particular drug(s). For topically or regionally delivered drugs, a flux enabling non-volatile solvent system is defined as a non-volatile solvent system which, alone without the help of any other ingredients, is capable of delivering therapeutic sufficient levels of the drug across, onto or into the subject's skin when the non-volatile solvent system is saturated with the drug. For systemically targeted drugs, a flux enabling non-volatile solvent system is a non-volatile solvent system that can provide therapeutically sufficient daily doses over 24 hours when the non-volatile solvent system is saturated with the drug and is in full contact with the subject's skin with no more than 500 cm² contact area. Preferably, the contact area for the non-volatile solvent system is no more than 100 cm². Testing using this saturated drug-in-solvent state can be used to measure the maximum flux-generating ability of a non-volatile solvent system. To determine flux, the drug solvent mixture needs to be kept on the skin for a clinically sufficient amount of time. In reality, it may be difficult to keep a liquid solvent on the skin of a human volunteer for an extended period of time. Therefore, an alternative method to determine whether a solvent system is "flux-enabling" is to measure the *in vitro* drug permeation across the hairless mouse skin or human cadaver skin using the apparatus and method described in Example 1. This and similar methods are commonly used by those skilled in the art to evaluate permeability and feasibility of formulations. Alternatively, whether a non-volatile solvent system is flux-enabling can be tested on the skin of a live human subject with means to maintain the non-volatile solvent system with saturated drug on the skin, and such means may not be practical for a product. For example, the non-volatile solvent system with saturated drug can be soaked into an absorbent fabric material which is then applied on the skin and covered with a protective membrane. Such a system is not practical as a pharmaceutical product, but is appropriate for testing whether a non-volatile solvent system has the intrinsic ability to provide sufficient drug flux, or whether it is flux-enabling.

It is also noted that once the formulation forms a solidified layer, the solidified layer can also be "flux enabling" for the drug while some of the non-

volatile solvents remain in the solidified layer, even after the volatile solvents (including water) have been substantially evaporated.

The phrase "effective amount," "therapeutically effective amount," "therapeutically effective rate(s)," or the like, as it relates to a drug, refers to sufficient amounts or delivery rates of a drug which achieves any appreciable level of therapeutic results in treating a condition for which the drug is being delivered. It is understood that "appreciable level of therapeutic results" may or may not meet any government agencies' efficacy standards for approving the commercialization of a product. It is understood that various biological factors may affect the ability of a substance to perform its intended task. Therefore, an "effective amount," "therapeutically effective amount," or "therapeutically effective rate(s)" may be dependent in some instances on such biological factors to some degree. However, for each drug, there is usually a consensus among those skilled in the art on the range of doses or fluxes that are sufficient in most subjects. Further, while the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a subjective decision. The determination of a therapeutically effective amount or delivery rate is well within the ordinary skill in the art of pharmaceutical sciences and medicine.

"Therapeutically effective flux" is defined as the permeation flux of the selected drug that delivers sufficient amount of drug into or across the skin to be clinically beneficial in that some of the patient population can obtain some degree of benefit from the drug flux. It does not necessarily mean that most of the patient population can obtain some degree of benefit or the benefit is high enough to be deemed "effective" by relevant government agencies or the medical profession. More specifically, for drugs that target skin or regional tissues or organs close to the skin surface (such as joints, certain muscles, or tissues/organs that are at least partially within 5 cm of the skin surface), "therapeutically effective flux" refers to the drug flux that can deliver a sufficient amount of the drug into the target tissues within a clinically reasonable amount

of time. For drugs that target the systemic circulation, "therapeutically effective flux" refers to drug flux that, via clinically reasonable skin contact area, can deliver sufficient amounts of the selected drug to generate clinically beneficial plasma or blood drug concentrations within a clinically reasonable time.

- 5 Clinically reasonable skin contact area is defined as a size of skin application area that most subjects would accept. Typically, a skin contact area of 400 cm² or less is considered reasonable. Therefore, in order to deliver 4000 mcg of a drug to the systemic circulation via a 400 cm² skin contact area over 10 hours, the flux needs to be at least 4000 mcg/400cm²/10 hour, which equals 1
- 10 mcg/cm²/hr. By this definition, different drugs have different "therapeutically effective flux" and may be different in different subjects and or at different times for even the same subject. However, for each drug, there is usually a consensus among the skilled in the art on the range of doses or fluxes that are sufficient in most subjects at most times.

- 15 The following are estimates of flux for some drugs that are therapeutically effective or more than sufficient:

Table A - *In vitro* steady state flux values of various drugs

Drug	Indication	Estimated Therapeutically effective flux* (mcg/cm ² /h)
Ropivacaine**	Neuropathic pain	5
Lidocaine	Neuropathic pain	30
Acyclovir	Herpes simplex virus	3
Ketoprofen	Musculoskeletal pain	16
Diclofenac	Musculoskeletal pain	1
Clobetasol	Dermatitis, psoriasis, eczema	0.05
Betamethasone	Dermatitis, psoriasis, eczema	0.01
Testosterone	Hypogonadal men	0.8
Testosterone	Hormone treatment for postmenopausal women	0.25
Imiquimod	Warts, basal cell carcinoma	0.92

* Flux determined using an *in vitro* method described in Example 1.

** Estimated flux based on known potency relative to lidocaine.

The therapeutically effective flux values in Table A (with the exception of ropivacaine) represent the steady state flux values of marketed products through hairless mouse or human epidermal membrane in an *in vitro* system described in Example 1. These values are meant only to be estimates and to provide a basis of comparison for formulation development and optimization. The therapeutically effective flux for a selected drug could be very different for different diseases to be treated for, different stages of diseases, and different individual subjects. It should be noted that the flux listed may be more than therapeutically effective.

The following examples listed in Table B illustrate screening of non-volatile solvent's flux enabling ability for some of the drugs specifically studied. Experiments were carried out as described in Example 1 below and the results are further discussed in the subsequent Examples 2-9.

Table B - *In vitro* steady state flux values of various drugs from non-volatile solvent systems

Drug	Non-Volatile Solvent	Average Flux* (mcg/cm ² /hr)
Betamethasone Dipropionate	Oleic acid	0.009 ± 0.003
	Sorbitan Monolaurate	0.03 ± 0.02
Clobetasol Propionate	Propylene Glycol (PG)	0.0038 ± 0.0004
	Light Mineral Oil	0.031 ± 0.003
	Isostearic acid (ISA)	0.019 ± 0.003
Ropivacaine	Glycerol	1.2 ± 0.7
	Mineral Oil	8.9 ± 0.6
Ketoprofen	Polyethylene glycol 400	5 ± 2
	Span 20	15 ± 3
Acyclovir	Polyethylene glycol 400	0
	Isostearic acid + 10% trolamine	2.7 ± 0.6

* Each value represents the mean and st. dev of three determinations.

The *in vitro* steady state flux values in Table B from non-volatile solvents show surprising flux-enabling and non flux-enabling solvents. This information can be used to guide formulation development.

The term "plasticizing" in relation to flux-enabling non-volatile solvent(s) is defined as a flux-enabling non-volatile solvent that acts as a plasticizer for the solidifying agent. A "plasticizer" is an agent which is capable of increasing the percentage elongation of the formulation after the volatile solvent system has at least substantially evaporated. Plasticizers also have the capability to reduce the brittleness of solidified formulation by making it more flexible and/or elastic. For example, propylene glycol is a "flux-enabling, plasticizing non-volatile solvent" for the drug ketoprofen with polyvinyl alcohol as the selected solidifying agent. However, propylene glycol in a formulation of ketoprofen with Gantrez S-97 or Avalure UR 405 as solidifying agents does not provide the same plasticizing effect. The combination of propylene glycol and Gantrez S-97 or Avalure UR 405 is less compatible and results in less desirable formulation for topical applications. Therefore, whether a given non-volatile solvent is "plasticizing" depends on which solidifying agent(s) is selected.

Different drugs often have different matching flux-enabling non-volatile solvent systems which provide particularly good results. Examples of such are noted in Table C. Experiments were carried out as described in Example 1 below and the results are further discussed in the subsequent Examples 2-9.

Table C - *In vitro* steady state flux values of various drugs from particularly high flux-enabling non-volatile solvent systems

Drug	High flux-enabling non-volatile solvent	Avg. Flux* (mcg/cm ² /h)
Ropivacaine	ISA Span 20	11 ± 2 26 ± 8
Ketoprofen	Propylene glycol (PG)	90 ± 50
Acyclovir	ISA + 30% trolamine	7 ± 2
Betamethasone Dipropionate	Propylene Glycol	0.20 ± 0.07
Clobetasol propionate	PG+ISA (Ratio of PG:ISA ranging from 200:1 to 1:1)	0.8 ± 0.2

* Each value represents the mean and st. dev of three determinations.

It should be noted that "flux-enabling non-volatile solvent," "flux-enabling, plasticizing non-volatile solvent," or "high flux-enabling non-volatile solvent" can

be a single chemical substance or a mixture of two or more chemical substances. For example, the steady state flux value for clobetasol propionate in Table C is a 9:1 for propylene glycol:isostearic acid mixture that generated much higher clobetasol flux than propylene glycol or ISA alone (see Table B).

5 Therefore, the 9:1 propylene glycol:isostearic acid mixture is a "high flux-enabling non-volatile solvent" but propylene glycol or isostearic acid alone is not.

The term "adhesion" when referring to a solidified layer herein refers to sufficient adhesion between the solidified layer and the skin so that the layer
10 does not fall off the skin during intended use on most subjects.

"Adhesive" when used to describe the solidified layer means the solidified layer is adhesive to the body surface to which the initial formulation layer was originally applied (before the evaporation of the volatile solvent(s)). In one embodiment, it does not mean the solidified layer is adhesive on the opposing
15 side. In addition, it should be noted that whether a solidified layer can adhere to a human body surface for the desired extended period of time partially depends on the condition of the body surface. For example, excessively sweating or oily skin, or oily substances on the skin surface may make the solidified layer less adhesive to the skin. Therefore, the adhesive solidified layer of the current
20 invention may not be able to maintain perfect contact with the body surface and deliver the drug over a sustained period of time for every subject under any conditions on the body surface. A standard is that it maintains good contact with most of the body surface, e.g. 70% of the total area, over the specified period of time for most subjects under normal conditions of the body surface and external
25 environment.

The terms "flexible," "elastic," "elasticity," or the like, as used herein refer to sufficient elasticity of the solidified layer so that it is not broken if it is stretched in at least one direction by up to about 5%, and often to about 10% or even greater. For example, a solidified layer that exhibits acceptably elasticity
30 and adhesion to skin can be attached to human skin over a flexible skin location, e.g., elbow, finger, wrist, neck, lower back, lips, knee, etc., and will remain substantially intact on the skin upon stretching of the skin. It should be

noted that the solidified layers of the present invention do not necessarily have to have any elasticity in some embodiments.

The term "peelable," when used to describe the solidified layer, means the solidified layer can be lifted from the skin surface in one large piece or
5 several large pieces, as opposed to many small pieces or crumbs.

The term "sustained" relates to therapeutically effective rates of dermal drug delivery for a continuous period of time of at least 30 minutes, and in some embodiments, periods of time of at least about 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, or longer.

10 The use of the term "substantially" when referring to the evaporation of the volatile solvents means that a majority of the volatile solvents which were included in the initial formulation have evaporated. Similarly, when a solidified layer is said to be "substantially devoid" of volatile solvents, including water, the solidified layer has less than 10 wt%, and preferably less than 5 wt%, of the
15 volatile solvents in the solidified layer as a whole.

"Volatile solvent system" can be a single solvent or a mixture of solvents that are volatile, including water and solvents that are more volatile than water. Non-limiting examples of volatile solvents that can be used in the present invention include iso-amyl acetate, denatured alcohol, methanol, ethanol,
20 isopropyl alcohol, water, propanol, C4-C6 hydrocarbons, butane, isobutene, pentane, hexane, acetone, chlorobutanol, ethyl acetate, fluoro-chloro-hydrocarbons, turpentine, methyl ethyl ketone, methyl ether, hydrofluorocarbons, ethyl ether, 1,1,1,2 tetrafluorethane 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, or
25 combinations thereof.

"Non-volatile solvent system" can be a single solvent or mixture of solvents that are less volatile than water. It can also contain substances that are solid or liquid at room temperatures, such as pH or ion-pairing agents. After evaporation of the volatile solvent system, most of the non-volatile solvent
30 system should remain in the solidified layer for an amount of time sufficient to dermally delivery a given drug to, into, or through the skin of a subject at a sufficient flux for a period of time to provide a therapeutic effect. In some

embodiments, in order to obtain desired permeability for an active drug and/or compatibility with solidifying agents or other ingredients of the formulation, a mixture of two or more non-volatile solvents can be used to form the non-volatile solvent system. In one embodiment, the combination of two or more non-volatile solvents to form a solvent system provides a higher transdermal flux for a drug than the flux provided for the drug by each of the non-volatile solvents individually. The non-volatile solvent system may also serve as a plasticizer of the solidified layer, so that the solidified layer is elastic and flexible.

The term "solvent vehicle" describes compositions that include both a volatile solvent system and non-volatile solvent system. The volatile solvent system is chosen so as to evaporate from the adhesive peelable formulation quickly to form a solidified layer, and the non-volatile solvent system is formulated or chosen to substantially remain as part of the solidified layer after volatile solvent system evaporation so as to provide continued delivery of the drug. Typically, the drug can be partially or completely dissolved in the solvent vehicle or formulation as a whole. Likewise, the drug can also be partially or completely solubilizable in the non-volatile solvent system once the volatile solvent system is evaporated. Formulations in which the drug is only partially dissolved in the non-volatile solvent system after the evaporation of the volatile solvent system have the potential to maintain longer duration of sustained delivery, as the undissolved drug can dissolve into the non-volatile solvent system as the dissolved drug is being depleted from the solidified layer during drug delivery.

The term "adhesive" in relation to the solidified layer means it is adhesive to the skin on which the original formulation was applied, and not necessarily, and preferably not, adhesive on the other side to other objects.

"Adhesive solidifying formulation," "solidifying formulation" or "formulation" in some embodiments refers to a composition that has a viscosity suitable for application to a skin surface prior to evaporation of its volatile solvent(s), and which can become a solidified layer after evaporation of at least a portion of the volatile solvent(s). The solidified layer, once formed, can be very durable. In one embodiment, once solidified on a skin surface, the

formulation can form a peel. Such a peel can be a soft, coherent solid that can be removed by peeling large pieces from the skin relative to the size of the applied formulation, and often, can be peeled from the skin as a single piece. The application viscosity is typically more viscous than a water-like liquid, but
5 less viscous than a soft solid. Examples of preferred viscosities include materials that have consistencies similar to pastes, gels, ointments, and the like, e.g., viscous liquids that flow but are not subject to spilling. Thus, when a composition is said to have a viscosity "suitable for application" to a skin surface, this means the composition has a viscosity that is high enough so that
10 the composition does not substantially run off the skin after being applied to skin, but also has a low enough viscosity so that it can be easily spread onto the skin. A viscosity range that meets this definition can be from about 100 cP to about 3,000,000 cP (centipoises), and more preferably from about 1,000 cP to about 1,000,000 cP.

15 In some embodiments of the present invention it may be desirable to add an additional agent or substance to the formulation so as to provide enhanced or increased adhesive characteristics. The additional adhesive agent or substance can be an additional non-volatile solvent or an additional solidifying agent. Non-limiting examples of substances which might be used as additional
20 adhesion enhancing agents include copolymers of methylvinyl ether and maleic anhydride (Gantrez polymers), polyethylene glycol and polyvinyl pyrrolidone, gelatin, low molecular weight polyisobutylene rubber, copolymer of acrylsan alkyl/octylacrylamido (Dermacryl 79), and various aliphatic resins and aromatic resins.

25 The terms "washable," "washing" or "removed by washing" when used with respect to the adhesive formulations of the present invention refers to the ability of the adhesive formulation to be removed by the application of a washing solvent using a normal or medium amount of washing force. The required force to remove the formulations by washing should not cause significant skin
30 irritation or abrasion. Generally, gentle washing force accompanied by the application of an appropriate washing solvent is sufficient to remove the adhesive formulations disclosed herein. The solvents which can be used for

removing by washing the formulations of the present invention are numerous, but preferably are chosen from commonly acceptable solvents including the volatile solvents listed herein. Preferred washing solvents do not significantly irritate human skin and are generally available to the average subject.

5 Examples of washing solvents include but are not limited to water, ethanol, methanol, isopropyl alcohol, acetone, ethyl acetate, propanol, or combinations thereof. In aspect of the invention the washing solvents can be selected from the group consisting of water, ethanol, isopropyl alcohol or combinations thereof. Surfactants can also be used in some embodiments.

10 An acceptable length of time as it relates to "drying time" refers to the time it takes for the formulation to form a non-messy solidified surface after application on skin under standard skin and ambient conditions, and with standard testing procedure. It is noted that the word "drying time" in this application does not mean the time it takes to completely evaporate off the
15 volatile solvent(s). Instead, it means the time it takes to form the non-messy solidified surface as described above.

"Standard skin" is defined as dry, healthy human skin with a surface temperature of between about 30 °C to about 36 °C. Standard ambient conditions are defined by the temperature range of from 20°C to 25°C and a
20 relative humidity range of from 20% to 80%. The term "standard skin" in no way limits the types of skin or skin conditions on which the formulations of the present invention can be used. The formulations of the present invention can be used to treat all types of "skin," including undamaged (standard skin), diseased skin, or damaged skin. Although skin conditions having different
25 characteristics can be treated using the formulations of the present invention, the use of the term "standard skin" is used merely as a standard to test the compositions of the varying embodiments of the present invention. As a practical matter, formulations that perform well (e.g., solidify, provide therapeutically effective flux, etc.) on standard skin can also perform well
30 diseased or damaged skin.

The "standard testing procedure" or "standard testing condition" is as follows: To standard skin at standard ambient conditions is applied an

approximately 0.1 mm layer of the adhesive solidifying formulation and the drying time is measured. The drying time is defined as the time it takes for the formulation to form a non-messy surface such that the formulation does not lose mass by adhesion to a piece of 100% cotton cloth pressed onto the formulation surface with a pressure of between about 5 and about 10 g/cm² for 5 seconds.

“Solidified layer” describes the solidified or dried layer of an adhesive solidifying formulation after at least a portion of the volatile solvent system has evaporated. The solidified layer remains adhered to the skin, and is preferably capable of maintaining good contact with the subject’s skin for substantially the entire duration of application under standard skin and ambient conditions. The solidified layer also preferably exhibits sufficient tensile strength so that it can be peeled off the skin at the end of the application in one piece or several large pieces (as opposed to a layer with weak tensile strength that breaks into many small pieces or crumbles when removed from the skin).

As used herein, a plurality of drugs, compounds, and/or solvents may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of “about 0.01 to 2.0 mm” should be interpreted to include not only the explicitly recited values of about 0.01 mm to about 2.0 mm, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 0.5, 0.7, and 1.5, and sub-ranges such as from 0.5 to

1.7, 0.7 to 1.5, and from 1.0 to 1.5, etc. This same principle applies to ranges reciting only one numerical value. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

5 With these definitions in mind, in accordance with this, a formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system having one or more volatile solvent(s) and a non-volatile solvent system having one or more non-volatile solvent(s), wherein the non-volatile solvent system is
10 flux-enabling for the drug such that the drug can be delivered in therapeutically effective amounts over a period of time, even after most of the volatile solvent(s) is (are) evaporated. The formulation can have viscosity suitable for application to the skin surface prior to evaporation of at least one volatile solvent, and can further be configured such that when applied to the skin surface, the formulation
15 forms a solidified layer after at least a portion of the volatile solvent(s) is (are) evaporated, but yet continues to deliver drug after substantially solidifying. In certain embodiments, the solidified layer can be coherent so that it can be peeled from the skin in one piece or several large pieces, or is washable from the skin using a solvent. In one particular embodiment, the drug can be a sex
20 hormone, and in another particular embodiment, the drug can be an anti-wart drug, though many other drug types can be used, as described herein.

 In an alternative embodiment, a method of dermally delivering a drug to, into, or through the skin can comprise applying a formulation to a skin surface of a subject, where the formulation comprises a drug; a solvent vehicle, and a
25 solidifying agent. The solvent vehicle comprises a volatile solvent system including one or more volatile solvent, and a non-volatile solvent system that is flux-enabling for the drug. In this embodiment, the formulation can have a viscosity suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system, and the formulation can be applied
30 such that the skin surface forms a solidified layer adhered to the skin after at least partial evaporation of the volatile solvent system. An additional step includes dermally delivering the drug from the solidified layer to the subject at

therapeutically effective rates over a sustained period of time, wherein the drug continues to be delivered after the volatile solvent system is substantially evaporated. In some embodiments, the solidified layer can be a soft or flexible, coherent, continuous solid, and can be removed by peeling. The thickness of the formulation layer applied on the skin should also be appropriate for a given formulation and desired drug delivery considerations. If the layer is too thin, the amount of the drug may not be sufficient to support sustained delivery over the desired length of time. If the layer is too thick, it may take too long to form a non-messy outer surface of the solidified layer. If the drug is very potent and the solidified layer has very high tensile strength, a layer as thin as 0.01 mm may be sufficient. If the drug has rather low potency and the solidified layer has low tensile strength, a layer as thick as 2-3 mm may be desirable. Thus, for most drugs and formulations, the appropriate thickness can be from about 0.01 mm to about 3 mm, but more typically, from about 0.05 mm to about 1 mm.

In another embodiment, a method of preparing a formulation for dermal drug delivery can comprise steps of selecting a drug suitable for dermal delivery; selecting or formulating a non-volatile solvent or a mixture of non-volatile solvents that is flux-enabling for the selected drug, selecting a solidifying agent that is compatible with the drug and the non-volatile solvent, selecting or formulating a volatile solvent system that is compatible with the drug, the non-volatile solvent and the solidifying agent; and formulating all above ingredients into a formulation. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvent system, and can be applied to the skin surface where it forms a solidified layer after at least a portion of the volatile solvent system is evaporated. In this embodiment, the drug continues to be delivered at a therapeutically effective rate after the volatile solvent system is substantially evaporated.

In still another embodiment, a solidified layer for delivering a drug can comprise a drug, a non-volatile solvent system, and a solidifying agent. The non-volatile solvent system is flux-enabling for the drug. The solidified layer can be a soft, coherent solid that is adhered to a body surface, and while dermally delivering at least a portion of the drug therefrom, the solidified layer is at least

substantially devoid of water and solvents more volatile than water, e.g., the solidified layer can be considered substantially devoid of water and solvents more volatile than water when the solidified layer contains no more than 10 wt% or even 5 wt% of water and solvents more volatile than water. Additionally, the solidified layer is also flux-enabling for the drug. In one embodiment, the solidified layer can be so coherent and elastic that it can be stretched in at least one direction by 5%, or even 10% without breaking, cracking, or separation from a skin surface to which the solidified layer is applied, and/or can be peelable from the skin.

In some applications, reducing the moisture vapor loss from the skin surface can be desirable, and a solidified layer with a selected or formulated non-volatile solvent system that is hydrophobic can help achieve this goal. Therefore, another embodiment of the current invention is related to a solidifying formulation whose solidified layer is capable of providing significant occlusion effect (defined as decreasing the moisture vapor loss from body surfaces by at least about 20%, preferably at least about 40%).

These embodiments exemplify the present invention which is related to formulations, methods, and solidified layers that are typically in the initial form of semi-solids (including creams, gels, pastes, ointments, and other viscous liquids), which can be easily applied onto the skin as a layer, and can quickly (from 15 seconds to about 4 minutes under standard skin and ambient conditions) to moderately quickly (from about 4 to about 15 minutes under standard skin and ambient conditions) change into a solidified layer, e.g., a coherent and soft solid layer, for drug delivery. The solidified layer is optionally peelable. A solidified layer thus formed is capable of delivering drug to the skin, into the skin, across the skin, etc., over an sustained period of time, e.g., hours to tens of hours, so that most of the drug delivery occurs after the solidified layer is formed.

Additionally, the solidified layer typically adheres to the skin, but has a solidified, minimally or non-adhering, outer surface which is formed relatively soon after application and which does not substantially transfer to or otherwise soil clothing or other objects that a subject is wearing or that the solidified layer

may inadvertently contact. The solidified layer can also be formulated such that it is highly flexible and stretchable, and thus capable of maintaining good contact with a skin surface, even if the skin is stretched during body movement, such as at a knee, finger, elbow, or other joints.

5 In selecting the various components that can be used, e.g., drug, solvent vehicle of volatile solvent system and non-volatile solvent system, solidifying agent(s), etc., various considerations can occur. For example, the volatile solvent system can be selected from pharmaceutically or cosmetically acceptable solvents known in the art. In one embodiment of the present invention the volatile solvent system can include ethanol, isopropyl alcohol, 10 water, dimethyl ether, diethyl ether, butane, propane, isobutene, 1,1, difluoroethane, 1,1,1,2 tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, ethyl acetate, acetone or combinations thereof. In another embodiment of the present invention, the volatile solvent system can include iso-amyl acetate, denatured alcohol, methanol, propanol, isobutene, 15 pentane, hexane, chlorobutanol, turpentine, cytopentasiloxane, cyclomethicone, methyl ethyl ketone, or combinations thereof. The volatile solvent system can include a mixture or combination of any of the volatile solvents set forth in the embodiments above.

20 Additionally, these volatile solvents should be chosen to be compatible with the rest of the formulation. It is desirable to use an appropriate weight percentage of the volatile solvent(s) in the formulation. Too much of the volatile solvent system prolongs the drying time. Too little of the volatile solvent system can make it difficult to spread the formulation on the skin. For most formulations, the weight percentage of the volatile solvent(s) can be from about 25 10 wt% to about 85 wt%, from about 20 wt% to about 50 wt%, and in a preferred embodiment, at least 20 wt%.

The volatile solvent system can also be chosen to be compatible with the non-volatile solvent, solidifying agent, drug, and any other excipients that may be present. For example, polyvinyl alcohol (PVA) is not soluble in ethanol. 30 Therefore, a volatile solvent which can dissolve PVA needs to be formulated in the solidified layer. For instance, water can dissolve PVA and can be utilized as

a volatile solvent in a solidifying formulation; however the drying time in a formulation in which water is the only volatile solvent may be too long to certain applications. Therefore, a second volatile solvent (e.g., ethanol) can be formulated into the formulation to reduce the water content but maintain a sufficient amount of water to keep PVA in solution and thereby reduce the drying time for the formulation.

The non-volatile solvent system can also be chosen or formulated to be compatible with the solidifying agent, the drug, the volatile solvent, and any other ingredients that may be present. Most non-volatile solvent systems and solvent vehicles as a whole will be formulated appropriately after experimentation. For instance, certain drugs have good solubility in polyethylene glycol (PEG) having a molecular weight of 400 (PEG 400, non-volatile solvent) but poor solubility in glycerol (non-volatile solvent) and water (volatile solvent). However, PEG 400 cannot effectively dissolve poly vinyl alcohol (PVA), and thus, is not very compatible alone with PVA, a solidifying agent. In order to dissolve sufficient amount of an active drug and use PVA as a solidifying agent at the same time, a non-solvent system including PEG 400 and glycerol (compatible with PVA) in an appropriate ratio can be formulated, achieving a compatibility compromise. As a further example of compatibility, non-volatile solvent/solidifying agent incompatibility is observed when Span 20 is formulated into a formulation containing PVA. With this combination, Span 20 can separate out of the formulation and form an oily layer on the surface of the solidified layer after the evaporation of the volatile solvent. Thus, appropriate solidifying agent/non-volatile solvent selections are desirable in developing a viable formulation.

In further detail, non-volatile solvent(s) that can be used alone or in combination to form non-volatile solvent systems can be selected from a variety of pharmaceutically acceptable liquids, including but not limited to In one embodiment of the present invention the non-volatile solvent system can include glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine, tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, or combinations thereof. In another

embodiment the non-volatile solvent system can include benzoic acid, butyl alcohol, dibutyl sebacate, diglycerides, dipropylene glycol, eugenol, fatty acids such as coconut oil, fish oil, palm oil, grape seed oil, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid surfactants, triethyl

5 citrate, or combinations thereof. In a further embodiment the non-volatile solvent system can include 1,2,6-hexanetriol, alkyltriols, alkylidiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil,

10 castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, diethylene glycol monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugars ginger extract, glycerin, high fructose

15 corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol, pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil, vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-

20 (octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, cetareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG Fatty acid esters such as PEG-stearate, PEG - oleate, PEG- laurate, PEG fatty acid diesters such as PEG-

25 dioleate, PEG- distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid esters such as PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate, hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil, PEG-octyl phenyl ether, PEG -alkyl ethers such as PEG-cetyl ether,

30 PEG-stearyl ether, PEG- sorbitan fatty acid esters such as PEG-sorbitan diisostearate, PEG-sorbitan monostearate, propylene glycol fatty acid esters such as propylene glycol stearate, propylene glycol, caprylate/caprates, sodium

pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolized C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl sulfoxide, azone and related compounds, dimethylformamide, N-methyl formamide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2 myreth 10-adipate, honeyquat, sodium pyroglutamic acid, abyssinica oil, dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol, PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone, hydrolyzed wheat protein, or combinations thereof. In yet a further embodiment the non-volatile solvent system can include a combination or mixture of non-volatile solvents set forth in the any of the above discussed embodiments.

In addition to these and other considerations, the non-volatile solvent system can, and preferably should, also serve as plasticizer in the formulations of the current invention so that when the solidified layer is formed, the layer is flexible, stretchable, and/or otherwise "skin friendly."

Certain volatile and/or nonvolatile solvent(s) are irritating to the skin but are desirable to use to achieve the desired solubility and/or permeability of the drug. It is also desirable to add compounds that are both capable of preventing or reducing skin irritation and are compatible with the formulation. For example, in a formulation where the volatile solvent is capable of irritating the skin, it would be helpful to use a non-volatile solvent that is capable of reducing skin irritation. Examples of solvents that are known to be capable of preventing or reducing skin irritation include, but are not limited to, glycerin, honey, and propylene glycol.

The formulations of the current invention may also contain two or more non-volatile solvents that independently cannot generate as high flux for a drug as when formulated together according to a certain and often experimentally determined ratio. One possible reason for these initially non or less flux-enabling

non-volatile solvents to become more flux-enabling when formulated together may be due to the optimization of the ionization state of the drug to a physical form which has higher flux or the non-volatile solvents act in some other synergistic manner. One further benefit of the mixing of the non-volatile solvents is that it may optimize the pH of the formulation or the skin tissues under the formulation layer to minimize irritation. Examples of suitable combinations of non-volatile solvents that result in non-volatile solvent system that might be more flux-enabling include but are not limited to isostearic acid /trolamine, isostearic acid /diisopropyl amine, oleic acid/trolamine, and propylene glycol /isostearic acid.

The selection of the solidifying agent can also be carried out in consideration of the other components present in the adhesive formulation. The solidifying agent can be selected or formulated to be compatible to the drug and the solvent vehicle (including the volatile solvent(s) and the non-volatile solvent system), as well as to provide desired physical properties to the solidified layer once it is formed. Depending on the drug, solvent vehicle, and/or other components that may be present, the solidifying agent can be selected from a variety of agents. In one embodiment, the solidifying agent can include polyvinyl alcohol with a MW range of 20,000-70,000 (Amresco), esters of polyvinylmethylether/maleic anhydride copolymer (ISP Gantrez ES-425 and Gantrez ES-225) with a MW range of 80,000-160,000, neutral copolymer of butyl methacrylate and methyl methacrylate (Degussa Plastoid B) with a MW range of 120,000-180,000, dimethylaminoethyl methacrylate-butyl methacrylate-methyl methacrylate copolymer (Degussa Eudragit E100) with a MW range of 100,000-200,000, ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer with a MW greater than 5,000 or similar MW to Eudragit RLPO (Degussa), Zein (prolamine) with a MW greater than 5,000 such as Zein with a MW around 35,000 (Freeman industries), pregelatinized starch having a MW similar to Instant Pure-Cote B793 (Grain Processing Corporation), ethyl cellulose MW greater than 5,000 or MW similar to Aqualon EC N7, N10, N14, N22, N50 , or N100 (Hercules), fish gelatin having a MW 20,000-250,000 (Norland Products), gelatin, other animal sources with MW greater than 5,000,

acrylates/octylacrylamide copolymer MW greater than 5,000 or MW similar to National Starch, and Chemical Dermacryl 79.

In another embodiment the solidifying agent can include ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, polyether amides, corn starch, pregelatinized corn starch, polyether amides, shellac, polyvinyl pyrrolidone, polyisobutylene rubber, polyvinyl acetate phthalate or combinations thereof. In a further embodiment the solidifying agent can include ammonia methacrylate, carrageenan, cellulose acetate phthalate aqueous such as CAPNF from Eastman, carboxy polymethylene, cellulose acetate (microcrystalline), cellulose polymers, divinyl benzene styrene, ethylene vinyl acetate, silicone, guar gum, guar rosin, gluten, casein, calcium caseinate, ammonium caseinate, sodium caseinate, potassium caseinate, methyl acrylate, microcrystalline wax, polyvinyl acetate, PVP ethyl cellulose, acrylate, PEG/PVP, xantham gum, trimethyl siloxysilicate, maleic acid/anhydride copolymers, polacrilin, poloxamer, polyethylene oxide, poly lactic acid/poly-L-lactic acid, turpene resin, locust bean gum, acrylic copolymers, polyurethane dispersions, dextrin, polyvinyl alcohol-polyethylene glycol co-polymers, methacrylic acid-ethyl acrylate copolymers such as BASF's Kollicoat polymers, methacrylic acid and methacrylate based polymers such as poly(methacrylic acid), or combinations thereof. In another embodiment, the solidifying agent can include a combination of solidifying agents set forth in any of the above discussed embodiments. Other polymers may also be suitable as the solidifying agent, depending on the solvent vehicle components, the drug, and the specific functional requirements of the given formulation. Other polymers may also be suitable as the solidifying agent, depending on the solvent vehicle components, the drug, and the specific functional requirements of the given formulation.

In one embodiment, the non-volatile solvent system and the solidifying agent(s) should be compatible with each other. Compatibility can be defined as i) the solidifying agent does not substantially negatively influence the function of the non-volatile solvent system, except for some reduction of flux; ii) the solidifying agent can hold the non-volatile solvent system in the solidified layer

so that substantially no non-volatile solvent oozes out of the layer, and/or iii) the solidified layer formed with the selected non-volatile solvent system and the solidifying agent has acceptable flexibility, rigidity, tensile strength, elasticity, and adhesiveness to skin. The weight ratio of the non-volatile solvent system to the solidifying agent(s) can be from about 0.1:1 to about 10:1. In another aspect, the weight ratio of the non-volatile solvent system to the solidifying agent can be from about 0.2:1 to about 4:1, and more preferably from about 0.5:1 to about 2:1.

The flexibility and stretchability of a solidified layer, which is optionally also a peel, can be desirable in some applications. For instance, certain non-steroidal anti-inflammatory agents (NSAIDs) can be applied directly over joints and muscles for transdermal delivery into joints and muscles. However, skin areas over joints and certain muscle groups are often significantly stretched during body movements. Such movement prevents non-stretchable patches from maintaining good skin contact. Lotions, ointments, creams, gels, foams, pastes, or the like also may not be suitable for use for the reasons cited above. As such, in transdermal delivery of NSAIDs into joints and/or muscles, the solidifying formulations of the present invention can offer unique advantages and benefits. It should be pointed out that although good stretchability can be desirable in some applications, the solidifying formulations of the present invention do not always need to be stretchable, as certain applications of the present invention do not necessarily benefit from this property. For instance, if the formulation is applied on a small facial area overnight for treating acne, a subject would experience minimal discomfort and formulation-skin separation even if the solidified layer is not stretchable, as facial skin usually is not stretched very much during a sleep cycle.

A further feature of a formulation prepared in accordance with embodiments of the present invention is related to drying time. If a formulation dries too quickly, the user may not have sufficient time to spread the formulation into a thin layer on the skin surface before the formulation is solidified, leading to poor skin contact. If the formulation dries too slowly, the subject may have to wait a long time before resuming normal activities (e.g. putting clothing on) that

may remove un-solidified formulation. Thus, it is desirable for the drying time to be longer than about 15 seconds but shorter than about 15 minutes, and preferably from about 0.5 minutes to about 5 minutes.

Other benefits of the solidified layers of the present invention include the presence of a physical barrier that can be formed by the material itself. In some disease or injury situations, the skin surface is sensitive to the touch of foreign objects or vulnerable to infection if contact by foreign objects. In those situations, the solidified layer can provides physical protection to the skin surface. For instance, local anesthetic agents and other agents such as clonidine may be delivered topically for treating pain related to neuropathy, such as diabetic neuropathic pain. Since many of such subjects feel tremendous pain, even when their skin area is only gently touched, the physical barrier of the solidified layer can prevent or minimize pain caused by accidental contact with objects or others.

These and other advantage can be summarized in the following non-limiting list of benefits, as follows. The solidified layers of the present invention can be prepared in an initial form that is easy to apply as a semisolid dosage form. Additionally, upon volatile solvent system evaporation, the formulation layer applied to the skin is relatively thick and can contain much more active drug than a typical layer of traditional cream, gel, lotion, ointment, paste, etc., and further, is resistant to unintentional removal. The solidified layer comprises a non-volatile solvent system that is flux-enabling for the drug so that the drug can be delivered over sustained period of time at therapeutically effective rates. Further, as the solidified layer remains adhesive to skin and is preferably peelable, easy removal of the solidified layer can occur, may be without the aid of a solvent or surfactant. In some embodiments, the adhesion to skin and elasticity of the material is such that the solidified layer will not separate from the skin upon skin stretching at highly stretchable skin areas, such as over joints and muscles. For example, in one embodiment, the solidified layer can be stretched by 5%, or even 10% or greater, in at least one direction without cracking, breaking, and/or separating form a skin surface to which the layer is

applied. Still further, the solidified layer can be configured to advantageously deliver drug and protect sensitive skin areas without cracking or breaking.

In one embodiment of the invention, the solidified layer may be washed off with a solvent, such as water or ethanol, at the end of the desired drug
5 delivery. Other solvents which could also be used to wash off the solidified formulation include but are not limited to the volatile solvents listed herein. The ability to be removed by washing is particularly advantageous for certain applications. For example, if the solidifying formulation is applied to a body area with a lot of hair (e.g. an anti genital herpes solidifying formulation applied on
10 genital skin area with pubic hair), removal by peeling might cause discomfort and therefore be undesirable, and hence washing can be a preferred form of removal in this type of application. In another example, if the solidifying formulation is applied to a palmar surface, such as the palm of the hand or the sole of a foot, the ability for removal by peeling may be secondary consideration
15 to a formulation that will adhere to the skin surface. In these cases, a solidified layer configured to be easily washed off by water or ethanol may be more desirable. In washing embodiments, the solvent used to wash off the solidified layer may dissolve the layer or make it less adhesive to the skin so that it can be easily removed from the skin.

20 As a further note, it is a unique feature that the solidified layers of the present invention can keep a substantial amount of the non-volatile solvent system, which is optimized for delivering the drug, on the body surface. This feature can provide unique advantages over existing products. For example, Penlac is a product widely used for treating nail fungal infections. It contains the
25 drug ciclopirox, volatile solvents (ethyl acetate and isopropyl), and a polymeric substance. After being applied on the nail surface, the volatile solvents quickly evaporate and the formulation layer solidifies into a hard lacquer. The drug molecules are immobilized in the hard lacquer layer and are substantially unavailable for delivery into the nail. As a result, it is believed that the delivery
30 of the drug is not sustained over a long period of time. As a result, without being bound by any particular theory, it is believed that this is at least one of the reasons why Penlac, while widely used, has an efficacy rate of only about 10%.

Conversely, in the solidified layer of the present invention, the drug molecules are quite mobile in the non-volatile solvent system which is in contact with the skin surface, e.g., skin, nail, mucosal, etc., surface, thus ensuring sustained delivery.

5 Specific examples of applications that can benefit from the systems, formulations, and methods of the present invention are as follows. In one embodiment, a solidified layer including bupivacaine, lidocaine, or ropivacaine, can be formulated for treating diabetic and post herpetic neuralgia. Alternatively, dibucanine and an alpha-2 agonist such as clonidine can be
10 formulated in a solidifying formulation for treating the same disease. In another embodiment, retinoic acid and benzoyl peroxide can be combined in a solidified layer for treating acne, or alternatively, 1 wt% clindamycin and 5 wt% benzoyl peroxide can be combined in a solidifying formulation for treating acne. In another embodiment, a retinol solidifying formulation (OTC) can be prepared for
15 treating wrinkles, or a lidocaine solidifying formulation can be prepared for treating back pain. In another embodiment, a zinc oxide solidifying formulation (OTC) can be prepared for treating diaper rash (the physical barrier provided by the solidified layer against irritating urine and feces is believed to be beneficial), or an antihistamine solidified layer can be prepared for treating allergic rashes
20 such as that caused by poison ivy.

 Additional applications include delivering drugs for treating certain skin conditions, e.g., dermatitis, psoriasis, eczema, skin cancer, alopecia, wrinkles, viral infections such as cold sore, genital herpes, shingles, etc., particularly those that occur over joints or muscles where a transdermal patch may not be
25 practical. For example, solidifying formulations containing imiquimod can be formulated for treating skin cancer, prematurely aged skin, photo-damaged skin, common and genital warts, and actinic keratosis. Solidifying formulations containing antiviral drugs such as acyclovir, penciclovir, famciclovir, valacyclovir, steroids, behenyl alcohol can be formulated for treating herpes viral infections
30 such as cold sores on the face and genital areas. Solidifying formulations containing non-steroidal anti-inflammatory drugs (NSAIDs), capsaicin, alpha-2 agonists, and/or nerve growth factors can be formulated for treating soft tissue

injury and muscle-skeletal pains such as joint and back pain of various causes. As discussed above, patches over these skin areas typically do not have good contact over sustained period of time, especially for a physically active subject, and may cause discomfort. Likewise, traditional semi-solid formulations such as
5 creams, lotions, ointments, etc., may prematurely stop the delivery of a drug due to the evaporation of solvent and/or unintentional removal of the formulation. The solidifying formulations of the present invention address the shortcomings of both of these types of delivery systems.

One embodiment can entail a solidified layer containing a drug from the
10 class of alpha-2 antagonists which is applied topically to treat neuropathic pain. The alpha-2 agonist is gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after about 5 minutes and remains adhered to the body surface for the length of its application, typically hours to tens of hours. The solidified layer is
15 easily removed after the intended application without leaving residual formulation on the skin surface.

Another embodiment involves a solidifying formulation containing capsaicin which is applied topically to treat neuropathic pain. The capsaicin is gradually released from the formulation for treating this pain over a sustained
20 period of time. The formulation can become a coherent, soft solid after about 5 minutes and remains adhered to the body surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

Another embodiment involves a solidifying formulation containing
25 clobetasol propionate which is applied topically to treat hand dermatitis. The clobetasol propionate is gradually released from the formulation for treating dermatitis over a sustained period of time. The formulation can become a coherent, soft solid after about 7 minutes and remains adhered to the body surface for the length of its application. The physical barrier also protects the
30 compromised skin from potentially harmful substances. It is easily removed any time after drying without leaving residual formulation on the skin surface.

Another embodiment involves a solidifying formulation containing clobetasol propionate which is applied topically to treat alopecia. The clobetasol propionate is gradually released from the formulation for promoting hair growth over a sustained period of time. The formulation can become a coherent, soft solid after about 5 minutes and remains adhered to the body surface for the length of its application. It is easily removed any time after drying by peeling to showering.

Another embodiment involves solidifying formulations containing tazarac for treating stretch marks, wrinkles, sebaceous hyperplasia, or seborrheic keratosis.

In another embodiment, solidifying formulations containing glycerol can be made so as to provide a protective barrier for fissuring on finger tips.

Still another embodiment can include a solidifying formulation containing a drug selected from the local anesthetic class such lidocaine and ropivacaine or the like, or NSAID class, such as ketoprofen, piroxicam, diclofenac, indomethacin, or the like, which is applied topically to treat symptoms of back pain, muscle tension, or myofascial pain or a combination thereof. The local anesthetic and/or NSAID is/are gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after about 5-10 minutes and remains adhered to the body surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

A further embodiment involves a solidifying formulation containing at least one alpha-2 agonist drug, at least one tricyclic antidepressant agent, and/or at least one local anesthetic drug which is applied topically to treat neuropathic pain. The drug(s) are gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after 2-10 minutes and remains adhered to the body surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

A similar embodiment can include a solidifying formulation containing drugs capsaicin and a local anesthetic drug which is applied topically to the skin

to provide pain relief. Another embodiment can include a solidifying formulation containing the combination of a local anesthetic and a NSAID. In both of the above embodiments the drugs are gradually released from the formulation to provide pain relief over a sustained period of time.. The formulation can become
5 a coherent, soft solid after about 2-10 minutes and remains adhered to the body surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

In another embodiment, solidifying formulations for the delivery of drugs that treat the causes or symptoms of diseases involving joints and muscles can
10 also benefit from the systems, formulations, and methods of the present invention. Such diseases that may be applicable include, but not limited to, osteoarthritis (OA), rheumatoid arthritis (RA), joint and skeletal pain of various other causes, myofascial pain, muscular pain, and sports injuries. Drugs or drug classes that can be used for such applications include, but are not limited
15 to, non-steroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen and diclofenac, COX-2 selective NSAIDs and agents, COX-3 selective NSAIDs and agents, local anesthetics such as lidocaine, bupivacaine, ropivacaine, and tetracaine, steroids such as dexamethasone.

Delivering drugs for the treatment of acne and other skin conditions can
20 also benefit from principles of the present invention, especially when delivering drugs having low skin permeability. Currently, topical retinoids, peroxides, and antibiotics for treating acne are mostly applied as traditional semisolid gels or creams. However, due to the shortcomings as described above, sustained delivery over many hours is unlikely. For example, clindamycin, benzoyl
25 peroxide, and erythromycin may be efficacious only if sufficient quantities are delivered into hair follicles. However, a traditional semisolid formulation, such as the popular acne medicine benzaclin gel, typically loses most of its solvent (water in the case of benzaclin) within a few minutes after the application. This short period of a few minutes likely substantially compromises the sustained
30 delivery of the drug. The formulations of the present invention typically do not have this limitation.

In another embodiment, the delivery of drugs for treating neuropathic pain can also benefit from the methods, systems, and formulations of the present invention. A patch containing a local anesthetic agent, such as LidodermTM, is widely used for treating neuropathic pain, such as pain caused by post-herpetic neuralgia. Due to the limitations of the patch as discussed above, the solidified layers prepared in accordance with the present invention provide some unique benefits, as well as provide a potentially less expensive alternative to the use of a patch. Possible drugs delivered for such applications include, but are not limited to, local anesthetics such as lidocaine, prilocaine, tetracaine, bupivacaine, etidocaine; and other drugs including capsaicin and alpha-2 agonists such as clonidine, dissociative anesthetics such as ketamine, tricyclic antidepressants such as amitriptyline.

The solidifying formulations of the present invention can be formulated to treat a variety of conditions and disease such as musculoskeletal pain, neuropathic pain, alopecia, skin disease including dermatitis and psoriasis as well as skin restoration (cosmetic skin treatment), and infections including viral, bacterial, and fungal infection. As such the formulations can deliver a wide ranging number and types of drugs and active agents. In one embodiment the solidifying formulation can be formulated to include acyclovir, econazole, miconazole, terbinafine, lidocaine, bupivacaine, ropivacaine, and tetracaine, amitriptyline, ketanserin, betamethasone dipropionate, triamcinolone acetonide, clindamycin, benzoyl peroxide, tretinoin, isotretinoin, clobetasol propionate, halobetasol propionate, ketoprofen, piroxicam, diclofenac, indomethacin, imiquimod, salicylic acid, benzoic acid, or combinations thereof

In one embodiment, the formulation can include an antifungal drug such as amorolfine, butenafine, naftifine, terbinafine, fluconazole, itraconazole, ketoconazole, posaconazole, ravuconazole, voriconazole, clotrimazole, butoconazole, econazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole, caspofungin, micafungin, anidulafing, amphotericin B, AmB, nystatin, pimarin, griseofulvin, ciclopirox olamine, haloprogin, tolinaftate, and undecylenate, or combinations thereof.

In another embodiment, the formulation can include an antifungal drug such as acyclovir, penciclovir, famciclovir, valacyclovir, behenyl alcohol, trifluridine, idoxuridine, cidofovir, gancyclovir, podofilox, podophyllotoxin, ribavirin, abacavir, delavirdine, didanosine, efavirenz, lamivudine, nevirapine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, amantadine, interferon, oseltamivir, ribavirin, rimantadine, zanamivir, or combinations thereof.

When the formulation is intended to provide antibacterial treatment it can be formulated to include an antibacterial drug such as erythromycin, clindamycin, tetracycline, bacitracin, neomycin, mupirocin, polymyxin B, quinolones such as ciproflaxin, or combinations thereof.

When the formulation is intended to relieve pain, particularly neuropathic pain, the formulation can include a local anesthetic such as lidocaine, bupivacaine, ropivacaine, and tetracaine; an alpha-2 agonists such as clonidine.

When the formulation is intended to treat pain associated with inflammation it can be formulated to include an non-steroidal anti-inflammatory drug such as ketoprofen, piroxicam, diclofenac, indomethacin, COX inhibitors general COX inhibitors, COX-2 selective inhibitors, COX-3 selective inhibitors, or combinations thereof.

In another embodiment, the formulation can be formulated to treat skin disorders or blemishes by including active agents such as anti-acne drugs such as clindamycin and benzoyl peroxide, retinol, vitamin A derivatives such as tazarotene and isotretinoin, cyclosporin, anthralin, vitamin D3, cholecalciferol, calcitriol, calcipotriol, tacalcitol, calcipotriene, etc.

In yet another embodiment, the delivery of medication for treating warts and other skin conditions would also benefit from long periods of sustained drug delivery. Examples of anti-wart compounds include but are not limited to: imiquimod, resiquimod, keratolytic agents: salicylic acid, alpha hydroxy acids, sulfur, resorcinol, urea, benzoyl peroxide, allantoin, tretinoin, trichloroacetic acid, lactic acid, benzoic acid, or combinations thereof.

A further embodiment involves the use of the solidifying formulations for the delivery of sex steroids including but not limited to progestagens consisting

of progesterone, norethindrone, norethindroneacetate, desogestrel, drospirenone, ethynodiol diacetate, norelgestromin, norgestimate, levonorgestrel, dl-norgestrel, cyproterone acetate, dydrogesterone, medroxyprogesterone acetate, chlormadinone acetate, megestrol,
5 promegestone, norethisterone, lynestrenol, gestodene, tibolene, androgens consisting of testosterone, methyl testosterone, oxandrolone, androstenedione, dihydrotestosterone, estrogens consisting of estradiol, ethniyl estradiol, estiol, estrone, conjugated estrogens, esterified estrogens, estropipate, or combinations thereof.

10 Non-sex steroids can also be delivered using the formulations of the present invention. Examples of such steroids include but are not limited to betamethasone dipropionate, halobetasol propionate, diflorasone diacetate, triamcinolone acetonide, desoximethasone, fluocinonide, halcinonide, mometasone furoate, betamethasone valerate, fluocinonide, fluticasone
15 propionate, triamcinolone acetonide, fluocinolone acetonide, flurandrenolide, desonide, hydrocortisone butyrate, hydrocortisone valerate, alclometasone dipropionate, flumethasone pivate, hydrocortisone, hydrocortisone acetate, or combinations thereof.

A further embodiment involves controlled delivery of nicotine for treating
20 nicotine dependence among smokers and persons addicted to nicotine. Formulations of the present invention would be a cost effective way of delivering therapeutic amounts of nicotine transdermally.

Another embodiment involves using the formulation to deliver anti-histamine agents such as diphenhydramine and tripeleminamine. These agents
25 would reduce itching by blocking the histamine that causes the itch and also provide relief by providing topical analgesia.

Other drugs which can be delivered using the solidifying formulations of the present invention include but are not limited to tricyclic anti-depressants such as amitriptyline; anticonvulsants such as carbamazepine and alprazolam;
30 N-methyl-D-aspartate (NMDA) antagonists such as ketamine; 5-HT_{2A} receptor antagonists such as ketanserin; and immune modulators such as tacrolimus and picrolium.

A further embodiment involves the following steps: selecting a drug for dermal delivery, selecting or formulating a flux-enabling or high flux-enabling non-volatile solvent system for the selected drug, selecting a solidifying agent that is compatible with the non-volatile solvent system and volatile solvent system, selecting a volatile solvent system that meets a preferred drying time frame and is compatible with the above ingredients, and formulating above ingredients into a solidifying formulation that optionally further includes other ingredients such as viscosity modifying agent(s), pH modifying agent(s), and emollients.

Another embodiment involves a method of maintaining a liquid flux-enabling or high liquid flux-enabling non-volatile solvent on human skin (including mucosa or nail surfaces) for delivery of a drug into tissues under the surfaces, comprising selecting a drug for dermal delivery, selecting or formulating a flux-enabling or high flux-enabling non-volatile solvent system for the selected drug, selecting a solidifying agent that is compatible with the flux-enabling or high flux-enabling non-volatile solvent system and volatile solvent system, and formulating above ingredients into a solidifying formulation.

Another embodiment involves a method for keeping a liquid flux-enabling non-volatile solvent system on human skin for delivery of a drug into the human skin or tissues under the human skin. The method includes applying to a human skin a layer a formulation comprising a drug, a flux enabling non-volatile solvent system, a solidifying agent capable of gelling the liquid flux-enabling non-volatile solvent system into a soft solid, and a volatile solvent system that is compatible with the rest of components of the formulation. The formulation layer is such that the evaporation of at least some of the volatile solvent system transforms the formulation from an initial less than solid state into a soft-coherent solid layer. The drug in the soft-coherent solid layer is delivered at therapeutically effective rates for a sustained period of time.

One use of the present invention can be for delivering sex hormones. In one embodiment, a formulation for dermal delivery of a sex hormone can include a sex hormone, a solvent vehicle, and a solidifying agent that contributes to solidification of the formulation applied as a layer on a skin

surface upon at least partial evaporation of the volatile solvent system. The solvent vehicle can include a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. The sex hormone continues to be delivered therapeutically sufficient rates even after the volatile solvent system is at least substantially evaporated.

The formulations of the present inventions can also be used in the treatment and elimination of warts. An antiwart formulation can include an antiwart drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can include a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. The antiwart hormone continues to be delivered therapeutically sufficient rates even after the volatile solvent system is at least substantially evaporated.

In an additional embodiment, a formulation for delivering clobetasol propionate can include clobetasol propionate, a solvent vehicle, and a solidifying agent. The solvent vehicle includes a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system. The non-volatile solvent system can include propylene glycol and/or a fatty acid. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. The clobetasol propionate continues to be delivered therapeutically sufficient rates even after the volatile solvent system is at least substantially evaporated. The solidifying agent can be a protein based solidifying agent.

In another embodiment, a solidifying formulation for delivering ropivacaine can include ropivacaine, a solvent vehicle, and a solidifying agent. The volatile solvent system including at least one volatile solvent and the non-volatile solvent system which can comprise solvents such as isostearic acid span 20, and triacetin. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. Even after the at least a portion of the partial evaporation of the volatile the ropivacaine continues to be delivered into or across the skin at a rate of no less than 5 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

In another embodiment, a solidifying formulation for delivering imiquimod can include imiquimod, a solvent vehicle, and a solidifying agent. The volatile solvent system including at least one volatile solvent, and the non-volatile solvent system can comprise solvents such as isostearic acid span 20, and triacetin. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. Even after the at least a portion of the partial evaporation of the volatile the ropivacaine continues to be delivered into or across the skin at a rate of no less than 5 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

In another embodiment, a solidifying formulation for delivering imiquimod can include imiquimod, a solvent vehicle, and a solidifying agent. The volatile solvent system including at least one volatile solvent and the non-volatile solvent system can comprise solvents such as isostearic acid span 20, and triacetin. The formulation can have a viscosity which is suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. Even after the at

least a portion of the partial evaporation of the volatile the imiquimod continues to be delivered into or across the skin at a rate of no less than 0.8 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

5 In another embodiment, a solidifying formulation for delivering ketoprofen can include ketoprofen, a solvent vehicle, and a solidifying agent. The volatile solvent system includes a volatile solvent system including at least one volatile solvent and a non-volatile solvent system comprising glycerol and propylene glycol. The formulation can have a viscosity which is suitable for application
10 and adhesion to a skin surface prior to evaporation of the volatile solvent system. When applied to a skin surface the formulation forms a solidified layer after at least partial evaporation of the volatile solvent system. Even after the at least a portion of the partial evaporation of the volatile the ketoprofen continues to be delivered across the skin at a rate of no less than 10 mcg/hr/cm² for at
15 least 6 hours after the volatile solvent system has at least substantially evaporated.

Other drugs that can be delivered using the formulations and methods of the current invention include humectants, emollients, and other skin care compounds.

20

EXAMPLES

The following examples illustrate the embodiments of the invention that are presently best known. However, it is to be understood that the following are only exemplary or illustrative of the application of the principles of the present
25 invention. Numerous modifications and alternative compositions, methods, and systems may be devised by those skilled in the art without departing from the spirit and scope of the present invention. The appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity, the following examples provide
30 further detail in connection with what are presently deemed to be the most practical and preferred embodiments of the invention.

Example 1

Hairless mouse skin (HMS) or human epidermal membrane (HEM) is used as the model membranes as noted for the *in vitro* flux studies described in herein. Hairless mouse skin (HMS) is used as the model membrane for the *in vitro* flux studies described in herein. Freshly separated epidermis removed from the abdomen of a hairless mouse is mounted carefully between the donor and receiver chambers of a Franz diffusion cell. The receiver chamber is filled with pH 7.4 phosphate buffered saline (PBS). The experiment is initiated by placing test formulations (of Examples 2-5) on the stratum corneum (SC) of the skin sample. Franz cells are placed in a heating block maintained at 37 °C and the HMS temperature is maintained at 35 °C. At predetermined time intervals, 800 µL aliquots are withdrawn and replaced with fresh PBS solution. Skin flux ($\mu\text{g}/\text{cm}^2/\text{h}$) is determined from the steady-state slope of a plot of the cumulative amount of permeation versus time. It is to be noted that human cadaver skin can be used as the model membrane for the *in vitro* flux studies as well. The mounting of the skin and the sampling techniques used as the same as described above for the HMS studies.

Example 2

Human cadaver skin is used as membrane to select "flux-enabling" non-volatile solvent for betamethasone dipropionate. About 200 mL of saturated solutions of BDP in various solvents are added to the donor compartment of the Franz cells. *In vitro* analysis as described in Example 1 is used to determine the steady state flux of BDP. *In vitro* methodology used is described in Example 1. Active enzymes in the skin convert betamethasone dipropionate to betamethasone. The steady state flux values reported in Table 1 are quantified using external betamethasone standards and are reported as amount of betamethasone permeating per unit area and time.

Table 1 – Non-volatile solvents for betamethasone dipropionate

Non-volatile solvent system	Skin Flux* (ng/cm ² /h)
Propylene Glycol	195.3 ± 68.5
Triacetin	4.6 ± 2.8
Light Mineral Oil	11.2 ± 3.1
Oleic Acid	8.8 ± 3.3
Sorbitan Monolaurate	30.0 ± 15.9
Labrasol	12.2 ± 6.0

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

As seen from the results, triacetin, labrasol, oleic acid, and light mineral oil have flux values close to the estimated therapeutically effective flux of 10 ng/cm²/hr. Addition of solidifying agents and other components could possible decrease the flux and hence the above mentioned non-volatile solvents may not be an ideal choice as "flux-enabling" solvents. However, sorbitan monolaurate has 3 times higher flux than one possible therapeutic level and hence has better chances to be a "flux-enabling" solvent. Its compatibility with various solidifying agents would determine the appropriate levels at which it can be used. Additionally, propylene glycol has 19 times higher flux than therapeutic level needed, and hence provides significantly higher flux than other non-volatile solvent systems tested. The ability of a non-volatile solvent to generate a flux much higher than just barely "enabling" can be advantageous as the incorporation of other necessary or desired ingredients into the formulation tends to decrease the flux, and it may allow achieving the desired therapeutic effect with relatively low drug concentrations in the formulation, which tend to make the formulation less expensive and safer.

Example 3

Formulations of clobetasol propionate in various non-volatile solvent systems are evaluated. All solvents have 0.1% (w/w) clobetasol propionate.

The permeation of clobetasol from the test formulations through HEM is presented in Table 2 below.

Table 2 - Non volatile solvents for clobetasol propionate

Non-volatile solvent system	Skin Flux* (ng/cm ² /h)
Propylene Glycol	3.8 ± 0.4
Glycerol	7.0 ± 4.1
Light Mineral Oil	31.2 ± 3.4
Isostearic Acid (ISA)	19.4 ± 3.2
Ethyl Oleate	19.4 ± 1.6
Olive Oil	13.6 ± 3.3
Propylene Glycol/ISA (9:1)	764.7 ± 193.9

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

Human cadaver skin is used as a membrane to select "flux-enabling" solvent for clobetasol propionate. *In vitro* methodology is described in Example 1. About 200 mcl of 0.1% (w/w) solution of clobetasol in various non-volatile solvents is added to the donor compartment of Franz cells. Results obtained after LC analysis are shown in Table 2. All the neat non-volatile solutions studied herein have an average flux of less than 50 ng/cm²/hr over a 30 hour time period. Propylene glycol and glycerol have the lowest permeation for clobetasol propionate. This result is surprising considering that betamethasone dipropionate which is similar in structure to clobetasol propionate has good flux with propylene glycol. The solvent system which is a mixture of propylene glycol and isostearic acid at a weight ratio of 9:1 has significantly higher flux than either of the solvents alone or the other solvents tested. The average flux is 20 times higher than light mineral oil which appears to be the best non-mixed solvent. Hence, for clobetasol propionate, the propylene glycol/isostearic acid provided the highest flux for a non-volatile solvent system. Among the non-volatile solvents listed in Table 2, only 9:1 propylene glycol:ISA is considered to be flux enabling. In this example, flux enabling non-volatile solvent system is not a pure, single substance, but rather a mixture of two or more substances at

a flux-enabling ratio. This being stated, other ratios or substance combinations may be used to generate a flux-enabling non-volatile solvent system.

Examples 4-9

- 5 Adhesive formulations containing 0.05% (w/w) clobetasol propionate with propylene glycol and isostearic acid as non volatile solutions and various solidifying agents are prepared. The formulations are prepared from the ingredients as shown in Table 3.

10

Table 3 - Solidifying formulation components

Example	Polymer	Percent Polymer	Percent Ethanol	Percent Propylene Glycol	Percent Isostearic Acid	Precent Water
4	Polyvinyl Alcohol	20	30	19.6	0.4	30
5	Shellac	50	30	19.6	0.4	0
6	Dermacryl 79	65.76	21.16	12.76	0.26	0
7	Eudragit E100	50	30	19.6	0.40	0
8	Eudragit RLPO	50	30	19.6	0.40	0
9	Gantrez S97	14.3	57.1	28	0.6	0

Each of the compositions shown above are studied for flux of clobetasol propionate as shown in Table 4 as follows:

15

Table 4 - Steady state flux of Clobetasol propionate through human cadaver skin at 35 °C

Formulation	Skin Flux* (ng/cm ² /h)
Example 4	87.8 ± 21.4
Example 5	9.7 ± 2.4
Example 6	8.9 ± 0.8
Example 7	3.2 ± 1.7
Example 8	20.2 ± 18.6
Example 9	147.5 ± 38.8

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the

experiment was continued it is anticipated the steady state would continue.

As seen from Table 4 formulation described in Example 4 that contains polyvinyl alcohol as a solidifying agent has high flux of clobetasol propionate.

Polyvinyl alcohol is known to form stretchable solidified layers and it is likely that this formulation will have acceptable wear properties. The toughness of the resulting solidified layer can be modified by adding appropriate plasticizers if needed (the non-volatile solvent system itself can serve as a plasticizer).

Tackiness can also be modified by adding appropriate amounts of tackifier or by adding appropriate amounts of another solidifying agent such as dermacryl 79.

Regarding formulation described in Example 9, a higher percentage of ethanol is needed to dissolve the polymer. However, the solidifying agent used in Example 9 provides the highest flux of clobetasol propionate among the solidifying agents studied. The wear properties of this formulation can be modified by adding appropriate levels of other ingredients including but not limited to plasticizers, tackifiers, non-volatile solvents and or solidifying agents.

Example 10

Formulations of acyclovir in various non-volatile solvent systems are evaluated. Excess acyclovir is present.

The permeation of acyclovir from the test formulations through HMS is presented in Table 5 below.

Table 5

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Isostearic Acid	0.1 ± 0.09
Isostearic Acid + 10% Trolamine	2.7 ± 0.6
Isostearic Acid + 30% Trolamine	7 ± 2
Olive Oil	0.3 ± 0.2
Olive Oil + 11% Trolamine	3 ± 3
Olive Oil + 30% Trolamine	0.3 ± 0.2
Oleic Acid	0.4 ± 0.3
Oleic Acid + 10% Trolamine	3.7 ± 0.5
Oleic Acid + 30% Trolamine	14 ± 5
Ethyl Oleate	0.2 ± 0.2

Ethyl Oleate + 10% Trolamine	0.2 ± 0.2
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* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of acyclovir from the above non-volatile solvents are obtained by placing 200 mL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. The surprising result showed the polyethylene glycol 400, span 80, ethyl oleate, or ethyl oleate plus trolamine are not flux-enabling solvents for acyclovir (e.g., steady state flux values significantly less than the steady state flux of acyclovir in the marketed product noted in Table 1, where the flux was about 3mcg/cm²/h). However, the combination of isostearic acid and trolamine or oleic acid and increasing amounts of trolamine are flux-enabling solvents for acyclovir. As can be seen, the highest flux was achieved using 30% trolamine with oleic acid as the non-volatile solvent system.

Examples 11-14

Prototype formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 6, as follows:

Table 6

Example	11	12	13	14
	% by weight			
Ethanol	21	25	28	29.5
Eudragit RL-PO	15	18	20	21.0
Isostearic Acid	31	36	39	42.0
Trolamine	30	18	10	4.7
Acyclovir	3	3	3	2.8

In Examples 11-14, the compositions in Table 6 are prepared as follows.

Eudragit RL-PO and ethanol are combined in a glass jar and heated with stirring until the RL-PO is dissolved. The isostearic acid and trolamine is added to the RL-PO/ethanol mixture and the mixture is vigorously stirred. Once a uniform

mixture is obtained, acyclovir is added to the mixture and the formulation is vigorously mixed.

Examples 15-16

- 5 Prototype formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 7, as follows:

Table 7

Example	15	16
	% by weight	
Ethanol	26	21
Eudragit RL-PO	44	15
Isostearic Acid	26	31
Diisopropanol Amine	2	--
Neutrol TE Polyol	--	30
Acyclovir	2	3

- 10 The compositions of Examples 15 and 16 as shown in Table 3 are prepared as follows. Eudragit RL-PO and ethanol are combined in a glass jar and heated with stirring until the RL-PO is dissolved. The isostearic acid and diisopropanol amine or Neutrol TE Polyol (BASF) is added to the RL-PO/ethanol mixture and the mixture is vigorously stirred. Once a uniform mixture is obtained, acyclovir
15 is added to the mixture and the formulation is vigorously mixed.

Examples 17-18

- Prototype peel formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the
20 present invention in accordance with Table 8, as follows:

Table 8

Example	17	18
	% by weight	
Ethanol	59.6	58
Ethyl Cellulose (EC) N7	19.9	--
Ethyl Cellulose (EC) N100	--	19
Trolamine	7.6	9
Isostearic Acid	7.7	9

Acyclovir	5.2	5
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In Examples 17-18 the compositions in Table 8 are prepared as follows. Ethyl cellulose (EC)N7 or EC N100 from Aqualon and ethanol are combined in a glass jar and heated with stirring until the solid cellulose is dissolved. The isostearic acid and trolamine is added to the cellulose/ethanol mixture and the mixture is vigorously stirred. Once a uniform mixture is obtained, acyclovir is added to the mixture and the formulation is vigorously mixed.

Example 19

The formulations of Examples 11-18 are tested in a hairless mouse skin (HMS) in vitro model described in Example 1. Table 9 shows data obtained using the experimental process outlined above.

Table 9 – Steady-state flux (J) of Acyclovir through HMS

Formulation	J* ($\mu\text{g}/\text{cm}^2/\text{h}$)	Ratio to Control
Example 11	12 ± 5	6
Example 12	19 ± 1	8
Example 13	8 ± 1	4
Example 14	1 ± 1	0.5
Example 15	0.7 ± 0.3	0.35
Example 16	1 ± 0.9	0.5
Example 17	2 ± 1	1
Example 18	19 ± 7	8
Zovirax Cream	2 ± 0.4	1

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

The formulations of the invention shown above generally provide for significant penetration of the active ingredient, and further, the formulations of Examples 11-13 and 18 are found to be much greater in permeability than the marketed product Zovirax Cream. The quantity of acyclovir that permeated across the HMS stratum corneum over time for Examples 11, 12, and Zovirax Cream are

shown in FIG. 4. Each value shown indicates the mean $\pm$ SD of at least three experiments.

Examples 11-14 show the impact of the trolamine to isostearic acid (ISA) ratio on acyclovir flux enhancement. The optimal ISA:trolamine ratio is 1:1 to 2:1 and ratio greater than 4:1 show a significant decrease in the acyclovir skin flux. Additions of diisopropanol amine and Neutrol in place of trolamine (Examples 15 and 16) in the formulation show a significant decrease in acyclovir flux values. This may be due to a specific chemical interaction between trolamine and ISA creating an environment within the formulation which facilitates higher skin flux. Examples 17 and 18 utilize a different solidifying agent to evaluate the impact of the solidifying agent on acyclovir flux. Surprisingly, Example 17 shows a significant decrease in acyclovir skin flux, but Example 18, which differed from Example 17 only by the molecular weight of the solidifying agent, shows no impact on acyclovir skin flux compared to a similar ISA:trolamine ratio in Example 11.

As can be seen from FIG. 4, Examples 11 and 12 show sustained delivery of acyclovir up to 8 hours, it is reasonable to assume based on the drug load and the continued presence of the non volatile solvent that the delivery of acyclovir would continue at the reported flux values for as long as the subject desires to leave the solidified formulation affixed to the skin.

Example 20

A solidifying formulation similar to Example 12 (with no acyclovir) is applied onto a human skin surface, resulting in a thin, transparent, flexible, and stretchable solidified layer. After a few minutes of evaporation of the volatile solvent (ethanol), a solidified adhesive layer that is peelable is formed. The stretchable solidified layer has good adhesion to the skin and did not separate from the skin, and could easily be peeled away from the skin. The absence of acyclovir has minimal to impact on the physical and wear properties of the formulation and soft, coherent solid because it is present at such low concentration, when present.

Example 21

Solidifying formulations of ketoprofen in various non-volatile solvent systems are evaluated. Excess ketoprofen is present.

The permeation of ketoprofen from the test formulations through HMS is presented in Table 10 below.

Table 10

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Glycerol	2 ± 1
Polyethylene Glycol 400	5 ± 2
Span 20	15 ± 3
Propylene Glycol	90 ± 50
Oleic Acid	180 ± 20

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of ketoprofen from the above non-volatile solvents are obtained by placing 200 mcL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 10, the non-volatile solvents glycerol and polyethylene glycol 400 had low steady state flux values and would not be considered "flux-enabling." Span 20 maybe considered flux-enabling, and propylene glycol or oleic acid provided the highest flux and are considered flux-enabling non-volatile solvent systems. Assessment of flux-enabling solvents is based on the estimated therapeutically effective flux of ketoprofen (16mcg/cm²/h in Table A). Steady state flux values of a drug from the non-volatile solvent that are below the therapeutically effective flux (Table A) are not considered flux-enabling while steady state flux values of a drug from a non-volatile solvent above the therapeutically effective flux value is considered flux-enabling.

Example 22

Solidifying formulations of ropivacaine in various non-volatile solvent systems are evaluated. Excess ropivacaine is present. The permeation of

ropivacaine from the test formulations through HMS is presented in Table 11 below.

Table 11

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Glycerol	1.2 ± 0.7
Tween 20	2.4 ± 0.1
Mineral Oil	8.9 ± 0.6
ISA (Isostearic Acid)	11 ± 2
Span 20	26 ± 8

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of ropivacaine base from the above non-volatile solvents are obtained by placing 200 mcL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 11, the non-volatile solvents glycerol, and Tween 20 had low steady state flux values and would not be considered "flux-enabling". However, mineral oil and isostearic acid are flux-enabling solvents and are good candidates for evaluation with solidifying agents and volatile solvents to design an acceptable solidified formulation. Surprisingly Span 20 has much higher steady state flux values and would qualify as a highly flux-enabling solvent. Steady state flux values of a drug from the non-volatile solvent that are below the therapeutically effective flux (Table A) are not considered flux-enabling while steady state flux values of a drug from a non-volatile solvent above the therapeutically effective flux value is considered flux-enabling.

Example 23

Solidifying formulations of diclofenac sodium (obtained from Spectrum) in various non-volatile solvent systems are evaluated. Excess diclofenac sodium is present. The permeation of diclofenac sodium from the test formulations through HMS is presented in Table 12 below.

Table 12

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Glycerol	1.7 ± 0.3
Isopropyl Myristate	13 ± 3
Ethyl Oleate	14 ± 4
Propylene Glycol	30 ± 30
Span 20	98 ± 20

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of diclofenac sodium from the above non-volatile solvents are obtained by placing 200 mcL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 12, the non-volatile solvent glycerol has a steady state flux value comparable to the estimated therapeutic steady state flux value and maybe considered a flux-enabling solvent. However, the steady state flux values of isopropyl myristate, ethyl oleate, propylene glycol, and Span 20 are at least 10 times the flux value reported for glycerol. These non-volatile solvents are considered flux-enabling solvents.

Example 24

Solidifying formulations of diclofenac acid in various non-volatile solvent systems are evaluated. Excess diclofenac acid is present. The permeation of diclofenac from the test formulations through HMS is presented in Table 13 below.

Table 13

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Glycerol	0
Isopropyl Myristate	8 ± 3
Ethyl Oleate	7 ± 3
Propylene Glycol	5 ± 2
Span 20	3 ± 1

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount

versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

- 5 Steady state flux of diclofenac acid from the above non-volatile solvents are obtained by placing 200 mcL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 13, the non-volatile solvent glycerol has no reported steady state flux value and is not considered a viable non-volatile solvent candidate.
- 10 However, the steady state flux values of isopropyl myristate, ethyl oleate, propylene glycol, and Span 20 are no more than 10 times the flux value reported for currently available marketed products, and as such, could be considered flux-enabling solvents. It should be noted that the steady state flux values for diclofenac acid from each of the above non-volatile solvents are much
- 15 lower than the steady state flux values obtained with diclofenac sodium. Therefore, if therapeutically effective flux values need to be increased, utilizing a flux-enabling non-volatile solvent and the salt form of diclofenac would likely yield higher steady state flux values than using the acid form of diclofenac.

20 Example 25

Solidifying formulations of testosterone in various non-volatile solvent systems are evaluated. Excess testosterone is present. The permeation of testosterone from the test formulations through HMS is presented in Table 14 below.

Table 14

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Tween 60	0
Span 20	1.4 ± 0.2
Polyethylene Glycol 400	1.2 ± 0.1
Isostearic Acid	2.6 ± 0.1
Propylene Glycol	6 ± 2

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of testosterone from the above non-volatile solvents are obtained by placing 200 mL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 14, the non-volatile solvent Tween 60 (Polyoxyethylene sorbitan mono-stearate) have no reported steady state flux value and is not considered a viable non-volatile solvent candidate. However, the steady state flux values of Span 20, polyethylene glycol 400, isostearic acid, and propylene glycol have steady state flux values comparable to currently available marketed products (Table A), and thus, could be considered flux-enabling solvents. However, although all the non-volatile solvents except for Tween 60 are flux-enabling, propylene glycol may be better for a practical formulation because the high flux generated by it means the same amount of drug can be delivered with smaller skin contact area.

Example 26

Solidifying formulations of hydromorphone HCl in various non-volatile solvent systems are evaluated. Excess hydromorphone HCl is present. The permeation of hydromorphone HCl from the test formulations through HMS is presented in Table 15 below.

Table 15

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Propylene Glycol	2 ± 0.8
Isostearic Acid	3 ± 3
Ethyl Oleate	40 ± 16

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of hydromorphone from the above non-volatile solvents are obtained by placing 200 mL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 15, the non-volatile solvents propylene glycol and isostearic acid

may qualify as flux-enabling solvents (based on an estimated therapeutically effective flux for hydromorphone is 2 mcg/cm²/h). Clearly, the steady state flux value of hydromorphone from ethyl oleate is much higher and would qualify as a high flux-enabling solvent.

5

Example 27

Solidifying formulations of hydromorphone in various non-volatile solvent systems are evaluated. Excess hydromorphone is present. The permeation of hydromorphone from the test formulations through HMS is presented in Table 16 below.

10

Table 16

Non-volatile solvent system	Skin Flux* (mcg/cm ² /h)
Propylene Glycol	1 ± 1
Isostearic Acid	7 ± 2
Ethyl Oleate	6 ± 2

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

15

Steady state flux of hydromorphone from the above non-volatile solvents are obtained by placing 200 µL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. From Table 16, the non-volatile solvent propylene glycol may qualify as flux-enabling solvents (based on an estimated therapeutically effective flux for hydromorphone is 2 µg/cm²/h). The steady state flux value of hydromorphone from isostearic acid and ethyl oleate would also qualify as flux-enabling solvents.

20

25

Examples 28-32

Prototype solidifying formulations are prepared as follows. Several formulations are prepared in accordance with embodiments of the present invention in accordance with Table 17, as follows:

30

Table 17

Example	28	29	30	31	32
% by weight					
Volatile Solvents					
Ethanol	25	21	24	18.5	43
Water		32		28	22
Solidifying agents					
Eudragit RL-PO	18		40		
Eudragit E-100				18.5	
Polyvinyl Alcohol		21		18.5	14
Non-volatile solvents					
Glycerol			12		14
Propylene Glycol		21	4		
Polyethylene Glycol					6
Isostearic Acid	36		13		
Span 20				11	
Trolamine	18		4		
Drug					
Acyclovir	3				
Ketoprofen		5			
Ropivacaine			3		
Diclofenac Na				5.5	
Testosterone					1

Solidifying formulations of Examples 28-32 are prepared in the following manner:

- 5 • The solidifying agents are dissolved in the volatile solvent (e.g., dissolve polyvinyl alcohol in water, Eudragit polymers in ethanol),
- The non-volatile solvent is mixed with the solidifying agent/volatile solvent mixture.
- The resulting solution is vigorously mixed well for several minutes.
- 10 • The drug is then added and the formulation is mixed again for several minutes.

In all the examples noted above, the flux-enabling non-volatile solvent/solidifying agent/volatile solvent combination is compatible as evidenced by a homogeneous, single phase system that exhibited appropriate drying time, and provided a stretchable solidified layer and steady state flux for the drug (see Example 33 below).

Examples 33

The formulations of the examples are tested in a hairless mouse skin (HMS) or HEM *in vitro* model described in Example 1. Table 18 shows data obtained using the experimental process outlined above.

Table 18 – Steady-state flux (J)

Formulation	J* ($\mu\text{g}/\text{cm}^2/\text{h}$)
Example 28	$19 \pm 1^{***}$
Example 29	$35 \pm 20^{***}$
Example 30	$32 \pm 2^{***}$
Example 31**	$5 \pm 2^{****}$
Example 32	$4 \pm 1^{***}$

* Skin flux measurements represent the mean and standard deviation of three determinations.

** Data gathered using human epidermal membrane.

***Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

****Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

Acyclovir, ropivacaine, and testosterone have surprisingly higher steady state flux values when the flux-enabling non-volatile solvent is incorporated into the solidifying formulations. It is speculated that the higher flux values may be the result of contributions of the volatile solvent or the solidifying agent impacting the chemical environment (e.g., increasing solubility) of the drug in the solidified formulation resulting in higher flux values. Conversely, ketoprofen and diclofenac have lower steady state flux values when the enabling non-volatile solvent is incorporated into the solidifying formulations. This could be the result of the volatile solvent system or solidifying agent having the opposite impact on the chemical environment (e.g., decreasing solubility, physical interactions between drug and formulation) resulting in lower flux values.

FIGS. 1 and 2 provide a graphical representation of the cumulative amount of diclofenac and ropivacaine, respectively, delivered transdermally across human cadaver skin. The formulations tested were similar to those

described in Examples 30 and 31. In these particularly embodiments, steady-state delivery is shown over 28 hours, and over 30 hours, respectively.

Example 34

5 A solidifying formulation with the following composition: 10.4% polyvinyl alcohol, 10.4% polyethylene glycol 400, 10.4% polyvinyl pyrrolidone K-90, 10.4% glycerol, 27.1 % water, and 31.3% ethanol was applied onto a human skin surface at an elbow joint and a finger joint, resulting in a thin, transparent, flexible, and stretchable solidified layer. After a few minutes of evaporation of
10 the volatile solvents (ethanol and water), a solidified layer that was peelable was formed. The stretchable solidified layer had good adhesion to the skin and did not separate from the skin on joints when bent, and could easily be peeled away from the skin.

15 Examples 35-37

Three formulations similar to the formulation in Example 36 (replacing ropivacaine base with ropivacaine HCl) are applied on the stratum corneum side of freshly separated hairless mouse skin. The *in vitro* flux is determined for each formulation as outlined in Example 1. The formulation compositions are
20 noted in Table 19 below.

Table 19

Example	35	36	37
% by weight			
PVA	15	15	15
Water	23	23	23
Ethylcellulose N-100	11	11	11
Ethanol	33	33	33
Span 20	11		
Polyethylene glycol 400		11	
Tween 40			11
Tromethamine	4	4	4
Ropivacaine HCl	3	3	3
Avg. Flux* (mcg/cm ² /h)	15 ± 1	4.7 ± 0.3	3.4 ± 0.7

* Flux values represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the

linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-31 hours. If the experiment was continued it is anticipated the steady state would continue.

Since all three formulations have the exact same compositions of solidifying agent, volatile solvents, and flux-enabling non-volatile solvent. The only difference is which flux-enabling non-volatile solvent is used it is reasonable to conclude that for ropivacaine HCl that Span 20, polyethylene glycol 400, and Tween 40 qualify as flux-enabling non-volatile solvents.

Examples 38-42

A solidifying formulation for dermal delivery of imiquimod is prepared which includes a specified amount of imiquimod in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulations contained the following components:

Table 20 - Imiquimod peelable formulation ingredients

Ingredients*	Example				
	38	39	40	41	42
PVA	12	21.5			
Plastoid B**			22.7	21.1	21
Pemulen TR-2	0.3	0.3			
Water	62.7	34.4	2.8		
Isopropanol			42.5	42.5	41.7
ISA (Isostearic Acid)	19	35.2	9.2	28.2	27.8
Span 20			8.5		
Trolamine	2	3.6	6.1		
Triacetin			4.2	4.2	4.2
Imiquimod	4	5	4	4	5.3

* Ingredients are noted as weight percent.

** Polymer from Degussa

These formulations are applied to HMS skin as described in Example 1, and the imiquimod flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 38-42 are listed in Table 21.

Table 21 - Steady-state flux of imiquimod through hairless mouse skin from various adhesive peel-forming formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*	Ratio to Control**
Example 38	0.7 ± 0.09	0.7

Example 39	0.52 ± 0.06	0.6
Example 40	0.40 ± 0.08	0.4
Example 41	0.5 ± 0.1	0.5
Example 42	0.8 ± 0.1	0.9
Aldara (control)	0.92 ± 0.02	

* The flux values represent the mean and SD of three determinations

** Ratio to control calculated by dividing the flux value for each example by the flux value for Aldara control flux.

5 Regarding the formulation described in Examples 38 and 39, water is used as the volatile solvent, and the ISA, trolamine mixture is used as the non-volatile solvent system. Through experimentation, it is determined that ISA and Span 20 provide the appropriate solubility for the drug, however these non-volatile solvents are hydrophobic and not compatible with the volatile solvent system

10 used to dissolve the solidifying agent PVA. An emulsifier Pemulen TR-2 was used to emulsify the non-volatile solvents into the water phase. Further, in this embodiment, ISA and trolamine act as a plasticizer in the peelable formulation after the water (volatile solvent) has evaporated. The steady state flux of formulation Examples 38 and 39 demonstrate the value of the amount of non-

15 volatile solvent in added to the formulation in dictating the flux-generating power of the entire formulation. Formulation Examples 41 and 42 utilize a different solidifying agent which is compatible in a non-aqueous volatile solvent system (isopropanol). The selection of non-volatile solvent system ISA/triacetin or ISA/Span 20/trolamine/triacetin combination showed no change in the *in vitro* flux. The increase in *in vitro* flux is shown to be influenced by an increase in the amount of imiquimod present in the formulation. At imiquimod levels above 4% the drug is saturated in the peel formulation. The increase in *in vitro* flux as a function of increased drug addition (Examples 41 and 42) may be due to the increased solubility of drug in the solidified peel formulation once the volatile

20 solvent is evaporated off.

25

Example 38 demonstrates comparable imiquimod flux to the other formulation examples, and the value of the non-volatile solvent system and solidifying agent compatibility caused by the removal of trolamine because this non-volatile solvent negatively influenced the function of the Plastoid B polymer.

Example 43-46

A solidifying formulation for dermal delivery of imiquimod is prepared which includes a specified amount of imiquimod in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The peel formulations contained the following components:

Table 22 - Imiquimod peelable formulation ingredients

Ingredients*	Example			
	43	44	45	46
PVA	10.1			
Plastoid B**		17.5		
Eudragit RL PO			16.2	24.8
Pemulen TR-2	0.3			
Water	52.9			
Isopropanol		35.1		
Ethanol			32.4	38.6
ISA (Isostearic Acid)	16.8	23.4	23.1	27.6
Salicylic Acid	15.2	16.4	16.2	
Trolamine	1.7			
Triacetin		3.5	3.5	4.1
Imiquimod	3.0	4.1	4.0	4.8

* Ingredients are noted as weight percent.

** Polymer from Degussa

These formulations are applied to HMS skin as described in Example 1, and the imiquimod flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 43-46 are listed in Table 23.

Table 23 - Steady-state flux of imiquimod through hairless mouse skin from various adhesive peelable formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*	Ratio to Control**
Example 43	1 ± 1	1.1
Example 44	4.5 ± 0.4	5
Example 45	3.8 ± 0.5	4.2
Example 46	0.8 ± 0.2	0.9
Aldara	0.9 ± 0.02	1

* The flux values represent the mean and SD of three determinations

** Ratio to control calculated by dividing the flux value for each example by the flux value for Aldara control flux.

In vitro flux of Examples 43-46 is substantially increased compared to the Aldara control. The reason for the improved in vitro flux values maybe attributed to the addition of salicylic acid. Improved in vitro flux of imiquimod in Examples 43-46 is thought to be due to an ion pair interaction between imiquimod and salicylic acid. The ion pair mechanism is thought that the lipophilicity of the counter ion (salicylic acid) improves the flux of imiquimod across the stratum corneum because it makes imiquimod less 'comfortable' in the formulation. Another reason for the improved flux due to salicylic acid is that it acts as a penetration enhancer. Comparison of the flux of Examples 43-45 shows that the selection of the polymer and/or volatile solvents will impact the flux of imiquimod.

Examples 47-48

A solidifying formulation for dermal delivery of ropivacaine is prepared which includes a specified amount of ropivacaine in an excipient mixture to form an adhesive solidifying formulation in accordance with embodiments of the present invention. The peel formulations contain the following components:

Table 24 Ropivacaine peelable formulation ingredients

Ingredients*	Examples	
	47	48
Eudragit RL-100	39.6%	39.6%
Ethanol	23.7%	23.6%
ISA (Isostearic Acid)	13.5%	13.5%
PG (Propylene Glycol)	7.9%	4.0%
Trolamine	4.0%	4.0%
Glycerol	7.9%	11.9%
Ropivacaine	3.4%	3.4%

* Ingredients are noted as weight percent.

These formulations are applied to HMS skin as described in Example 1, and the ropivacaine flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 47 and 48 is listed in Table 25.

Table 25 - Steady-state flux of ropivacaine through hairless mouse skin from various adhesive peelable formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
-------------	---

Example 47	36 ± 5
Example 48	32 ± 2

* The flux values represent the mean and SD of three determinations

Regarding the formulation described in Examples 47 and 48, ethanol is used as the volatile solvent, and the ISA, glycerol, and PG mixture is used as the non-volatile solvent system. Through experimentation, it is determined that ISA and propylene glycol used together to provide the appropriate solubility for the drug, while being compatible with the Eudragit RL-100 solidifying agent. Further, in this embodiment, ISA, PG and glycerol serve as a plasticizer in the peelable formulation after the ethanol (volatile solvent) has evaporated. The steady state flux of ropivacaine from formulation Examples 47 and 48 demonstrate the importance of the non-volatile solvent in dictating the flux-generating power of the entire formulation.

Example 49

The effect of solubility on permeation, compatibility between the non-volatile solvent system and the solidifying agent is shown in this example. Ropivacaine base solubility in isostearic acid (ISA) is experimentally determined to be slightly above 1:4, meaning 1 gram ropivacaine base can completely dissolve in 4 gram isostearic acid. In one experiment, two solutions are made: Solution A includes 1 part ropivacaine base and 4 parts isostearic acid. Solution B includes 1 part ropivacaine base, 4 parts isostearic acid, and 1 part trolamine. (all parts are in weight). All ropivacaine in Solution A is dissolved, but only a portion of ropivacaine in solution B is dissolved. The transdermal flux across hairless mouse skin generated by the solutions is measured by a typical Franz Cell system, with the following results:

Table 26 - Flux across hairless mouse skin, *in vitro*, in $\mu\text{g/hr/cm}^2$

	Cell 1	Cell 2	Cell 3	Average
Solution A	13.1	9.9	9.1	10.7
Solution B	43.2	35.0	50.0	42.7

As can be seen, the flux generated by Solution B is about 4 times that of Solution A. These results demonstrate that the addition of the ion pairing agent

trolamine significantly increases the transdermal flux. However, the attempt to incorporate this system into a poly vinyl alcohol (PVA) based peel formulation failed because the PVA in the formulation acted as a strong pH buffer that inhibited the effect of trolamine. Addition of more trolamine, in attempt to over-
5 power the pH buffer capacity of PVA, caused the loss of the desired solidifying property of PVA (in other words, a non-volatile solvent system containing ISA and too much trolamine is not compatible with PVA). When PVA is replaced by another solidifying agent, Eudragit RL 100 (Rohm & Haas), the effect of
10 trolamine is not inhibited and formulations capable of generating fluxes around $30 \mu\text{g/hr/cm}^2$ were obtained. A by product of the addition of trolamine, ISA, and Eudragit RL 100 is that a precipitate forms from the ionic interaction of the three components. The latter example produced a better formulation in terms of flux and wear properties, but the precipitation still demonstrates the need for
15 improvement. In an effort to eliminate the ionic interaction between non-volatile solvent and solidifying agent the trolamine, ISA mixture was added to Plastoid B polymer in isopropanol. However, in this instance the trolamine was found to be incompatible with the Plastoid B polymer and the base was changed to triisopropanolamine. This combination eliminated the precipitate formed when
20 the Eudragit RL 100 polymer was used and produced a clear formulation that was capable of generated flux values around $30 \mu\text{g/hr/cm}^2$. This demonstrates the importance of compatibility between the non-volatile solvent system and the solidifying agent.

Example 50

25 A solidifying formulation for dermal delivery of ropivacaine is prepared from the following ingredients:

Table 27 - Ropivacaine solidifying formulation components

Ingredients*	Example
	56
Ropivacaine HCl	0.096
Eudragit RL-100	1.0
Ethanol	0.7
Isostearic Acid	0.34
Glycerol	0.3
Propylene Glycol	0.1
Trolamine	0.15

*Ingredients are noted as parts by weight.

The ingredients listed above are combined according to the following procedure.

- 5 The Eudragit RL-100 and ethanol are combined in a glass jar and heated to about 60 °C until the Eudragit RL-100 is completely dissolved. Once the Eudragit solution cooled to room temperature, the appropriate amount of ropivacaine HCl is added and mixed thoroughly for 1 minute. To this solution, isostearic acid (ISA) is added and the mixture is stirred vigorously for 2-3
- 10 minutes. One hour later, the solution is vigorously mixed again for 2-3 minutes. To this solution, glycerol, propylene glycol, and trolamine are added in sequential order. After addition of each ingredient the solution is stirred for 1 minute.

- 15 Additionally, the formulation prepared in accordance with this examples was applied to HMS as described in Example 1, and the ropivacaine flux was measured. A summary of the results is listed in Table 28, as follows:

Table 28 - Steady-state flux of ropivacaine through hairless mouse skin from various adhesive peelable formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
Example 49	43 ± 4

- 20 * The flux values represent the mean and SD of three determinations

- The ropivacaine peel formulations prepared in accordance with Example 6 possessed acceptable application properties, e.g., ease of removal of peel from the sample tube, ease of spreading on intended skin application site, etc., and
- 25 forms a solidified film in 2-3 minutes after being applied to normal human skin surface as a thin layer with a thickness of about 0.1 mm. The solidified peelable

layer becomes more easily peelable in 2 hours, and the peel remains affixed to the skin surface without any unintended removal of the peel for at least 12 hours. At the end of intended use, the peel is easily removed in one continuous piece.

5

Example 51

A solidifying formulation for dermal delivery of lidocaine is prepared which includes a saturated amount of lidocaine in an excipient mixture to form an adhesive peelable formulation in accordance with embodiments of the present invention. The peel formulation is prepared from the ingredients as shown in Table 29.

10

Table 29 - Lidocaine solidifying formulation components

Ingredients*	Example
	51
PVA	11.7
Eudragit E-100**	11.7
PVP-K90	5.8
Glycerol	8.8
PEG-400	8.8
Water	23.8
Ethanol	23.8
Lidocaine	5.6

*Ingredients are noted as weight percent.

** from Rohm & Haas.

15

Table 30 - Steady-state flux of lidocaine through hairless mouse skin from various adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
Example 51	47 ± 3

20

The adhesive peelable formulation of lidocaine formulation in the present example has similar physical properties to the formulations in examples noted above. The transdermal flux across hairless mouse skin is acceptable and steady-state delivery is maintained over 8 hours.

25

Examples 52-55

A solidifying formulation for dermal delivery of amitriptyline and a combination of amitriptyline and ketamine is prepared which includes an excipient mixture to form an adhesive peelable formulation in accordance with
 5 embodiments of the present invention. The peel formulation is prepared from the ingredients as shown in Table 31.

Table 31 - Amitriptyline and amitriptyline/ketamine solidifying formulation components

Ingredients*	Example			
	52	53	54	55
Isopropanol	50.3	48.6	50.8	49.8
Water	2.7	2.6	2.7	2.7
Isostearic Acid	6.2	6.1	6.3	6.2
Triisopropanolamine	7.5	7.3	7.5	7.4
Triacetin	2.9	2.8	2.9	2.8
Span 20	5.7	5.5	5.8	5.6
Plastoid B**	21.7	21.1	22	21.5
Amitriptyline	2	4		
Ketamine	1	2	2	4

*Ingredients are noted as weight percent.

** from DeGussa.

10

The ingredients listed above are combined according to the following procedure. The drug(s), water, and triisopropanolamine are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20,
 15 and isopropanol are added to the formulation and mixed well. The polymer Plastoid B is added last and heated to about 60 °C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 31 are applied to HMS according to Example 1,
 20 and the flux of amitriptyline and/or ketamine was measured. The results are summarized in Table 32:

Table 32 - Steady-state flux of amitriptyline and amitriptyline/ketamine through hairless mouse skin from various adhesive solidifying formulations at 35 °C

Formulation	Average amitriptyline flux mcg/cm ² /h*	Average ketamine flux mcg/cm ² /h*
Example 52	3 ± 1	15 ± 4
Example 53	7.6 ± 0.2	38 ± 6
Example 54	3 ± 1	
Example 55	8.2 ± 0.7	

The adhesive peelable formulation of amitriptyline and amitriptyline/ketamine formulations in the present examples have similar physical properties to the formulations in examples noted above. The transdermal flux is proportional to the amount of drug added into the formulation.

10 Examples 56-59

A solidifying formulation for dermal delivery of ropivacaine is prepared which includes an excipient mixture to form an adhesive peelable formulation in accordance with embodiments of the present invention. The peel formulation is prepared from the ingredients as shown in Table 33.

Table 33 - Ropivacaine HCl solidifying formulation components

Ingredients*	Example			
	56	57	58	59
Ropivacaine HCl	0.31	0.31	0.31	0.31
Isopropanol	2	2	2.2	2
Water	0.125	0.125	0.125	0.125
Isostearic Acid	0.36	0.66	0.41	0
Triisopropanolamine	0.31	0.34	0.34	0.34
Triacetin	0.17	0.19	0	0.19
Span 20	0.34	0	0.37	0.66
Plastoid B**	1	1	1	1

*Ingredients are noted as parts by weight.

** from Degussa.

The ingredients listed above are combined according to the following procedure.

20 The ropivacaine HCl, water, and triisopropanolamine are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20, and isopropanol are added to the formulation and mixed well. The polymer

Plastoid B is added last and heated to about 60 °C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 33 are applied to HMS according to Example 1, and the flux of ropivacaine was measured. The results are summarized in Table 34:

Table 34 - Steady-state flux of ropivacaine HCl through hairless mouse skin from various adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
Example 56	56 ± 2
Example 57	39 ± 6
Example 58	31 ± 6
Example 59	37 ± 9

The flux of Examples 56-59 show the importance of the triacetin, isostearic acid, Span 20 combination in the formulation. In Examples 56-59 formulations were made without Span 20, triacetin, and isostearic acid respectively. The *in vitro* flux of ropivacaine was impacted. The synergistic combination of the non volatile solvents is an important in obtaining the maximum in vitro flux of ropivacaine.

Example 60

This solidifying formulation has the following ingredients in the indicated weight parts:

Table 35

PVA	Water	Ethyl cellulose N-7 (Aqualon)	Dermacryl 79 (National Starch)	Ethanol	Isostearic Acid (ISA)	Glycerol	Ropivacaine
1	1.5	0.25	0.35	0.85	0.8	0.35	0.3

In this formulation, polyvinyl alcohol (USP grade, from Amresco) is a solidifying agent, ethyl cellulose and Dermacryl 79 are auxiliary solidifying agents. Isostearic acid and glycerol form the non-volatile solvent system while ethanol and water form the volatile solvent system. Ropivacaine is the drug.

Procedures of making the formulation:

1. Ropivacaine is mixed with ISA.
2. Ethyl cellulose and Dermacryl 79 are dissolved in ethanol.
3. PVA is dissolved in water at temperature of about 60-70 C.
4. All of the above mixtures are combined together in one container and glycerol is added and the whole mixture is mixed well.

The resulting formulation is a viscous fluid. When a layer of about 0.1 mm thick is applied on skin, a non-tacky surface is formed in less than 2 minutes.

Examples 61-62

Anti-fungal solidifying formulations are prepared and a qualitative assessment of peel flexibility and viscosity are evaluated. The formulation components are presented in Table 36 below.

Table 36

Example	61	62
Components	Parts by Weight	
Eudragit RL-PO	3.8	4.2
Isostearic Acid	2	2.2
Ethanol	5.3	3.8
Neutrol TE Polyol	1	1
Econazole	0.09	0.1

The peel formulation in Example 61 has a low viscosity that was lower than may be desirable for application on a nail or skin surface. The time to form a solidified peel with this formulation is longer than the desired drying time. The formulation in Example 62 had an increase in the amount of solidifying agent (Eudragit RL-PO) and decrease in amount of ethanol, which improves the viscosity and drying time. Example 62 has a viscosity suitable for application and an improved drying time.

Example 63

A solidifying formulation was prepared in accordance with Table 37, as follows:

Table 37 – Peel-forming formulation for sex steroids

Ingredient	% by weight
Ethanol	43
Water	22
Polyvinyl Alcohol	14
Glycerol	14
Polyethylene Glycol	6
Testosterone	1

The ingredients of Table 37 were combined as follows:

- The solidifying agent is dissolved in the volatile solvent (i.e. dissolve polyvinyl alcohol in water).
- The flux enabling non-volatile solvent is mixed with the solidifying agent/volatile solvent mixture.
- The resulting solution is vigorously mixed well for several minutes.
- Drug is then added and the peel formulation is mixed again for several minutes.

Example 64

The formulation prepared in Example 63 was tested for skin flux, as set forth in Table 38 below.

Table 38 – Peel-forming formulation for sex steroids

System	Skin Flux* (mcg/cm ² /h)
Example 63	4 ± 1
AndroGel	6 ± 2

*Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

AndroGel, currently marketed product, is applied directly on the hairless mouse skin and the flux determinations are made as outlined in Example 1.

The steady state flux data is shown in FIG 3. It should be noted, the steady-state flux value reported in Table 38 is determined using the linear region between 2-6 hours. As can be seen from FIG. 3, the *in vitro* flux of testosterone from AndroGel substantially decreases beyond 6 hours. This may be due in part to the evaporation of the volatile solvent which may act as the main vehicle for delivery. The solidifying formulation in Example 63 will deliver a steady-state amount of testosterone for at least 9 hours.

Examples 65-68

A stretchable adhesive solidifying formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin for treating inflammation or pain of joints and muscles) is prepared which includes saturated amount of ketoprofen in an excipient mixture (more ketoprofen than that can be dissolved in the excipient mixture) to form an adhesive peelable formulation, some of which is prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 39.

Table 39 - Ketoprofen solidifying formulation components

Ingredients*	Examples			
	65	66	67	68
PVA (polyvinyl alcohol)	10.4	21.4	21.1	21.2
PEG-400 (Polyethylene Glycol)	10.4	10.8	2.9	18.6
PVP-K90 (Polyvinyl Pyrrolidone)	10.4	0.0	0.0	0.0
Glycerol	10.4	10.8	19.0	2.9
Water	27.1	57.0	57.0	57.3
Ethanol	31.3	0	0	0
Ketoprofen	saturated	saturated	saturated	saturated

* Ingredients are noted as % by weight.

Each of the compositions of Examples 65-68 were studied for flux of ketoprofen, as shown in Table 40, as follows:

Table 40 - Steady-state flux of ketoprofen through hairless mouse skin from various adhesive peelable formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
Example 72	8 ± 3
Example 73	21 ± 6
Example 74	3 ± 1
Example 75	1 ± 0.4

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

Regarding formulation described in Example 65, ethanol and water formed the volatile solvent system, while a 1:1 mixture of glycerol and PEG 400 formed the non-volatile solvent system. Through experimentation, it is determined that PEG 400 is a slightly better solvent than glycerol for ketoprofen, while glycerol is much more compatible with PVA than PEG 400. Thus, the non-volatile solvent system of glycerol and PEG 400 are used together to provide a non-volatile solvent system for the drug, while being reasonably compatible with PVA. In additional detail with respect to the formulation in Example 65, PVA and PVP act as the solidifying agents. Further, in this embodiment, glycerol and PEG 400 also serve as plasticizers in the adhesive peelable formulation formed after the evaporation of the volatile solvents. Without the presence of glycerol and PEG 400, a film formed by PVA and PVP alone would be rigid and non-stretchable.

Regarding the formulation of Example 66, the adhesive peelable formation formed has similar physical properties as that of Example 65, though the transdermal flux across hairless mouse skin is higher. This suggests that the solidifying agent, 1:1 PVA:PVP-K-90 in Example 65 and pure PVA in Example 66, have an impact on permeation.

The formulation in Example 67 delivers less ketoprofen than the formulations of Examples 65 or 66. The formulation of Example 68 delivers much less ketoprofen than the formulations in Examples 65 and 66. One possible reason for the reduced flux is believed to be the reduced permeation

driving force caused by the high concentration of PEG 400 in the non-volatile solvent system, which resulted in too high of solubility for ketoprofen.

The only significant difference among the formulations in Examples 66, 67, and 68, respectively, is with respect to the non-volatile solvent system, or more specifically, the PEG 400:glycerol weight ratio. These results reflect the impact of the non-volatile solvent system on skin flux.

Example 69

A stretchable adhesive solidifying formulation for transdermal delivery of lidocaine is prepared which includes saturated amount of lidocaine in an excipient mixture to form an adhesive solidifying formulation in accordance with embodiments of the present invention. The formulation is prepared from the ingredients as shown in Table 41.

Table 41 - Lidocaine solidifying formulation components

Ingredients*	Example
	69
PVA	1
Eudragit E-100**	1
PVP-K90	0.5
Glycerol	0.75
PEG-400	0.75
Water	2
Ethanol	2
Lidocaine	0.48

*Ingredients are noted as parts by weight.

** from Rohm & Haas.

Table 42 - Steady-state flux of lidocaine through hairless mouse skin from an adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
Example 69	47 ± 3

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

The adhesive solidifying formulation of lidocaine in the present example has similar physical properties to the formulations in Examples 65-68. The transdermal flux across hairless mouse skin is acceptable and steady-state delivery is maintained over 8 hours.

5

Example 70

A formulation similar to the formulation of Example 65 composition (with no ketoprofen) is applied onto a human skin surface at an elbow joint and a finger joint, resulting in a thin, transparent, flexible, and stretchable film. After a few minutes of evaporation of the volatile solvents (ethanol and water), a solidified peelable layer is formed. The stretchable film has good adhesion to the skin and does not separate from the skin on joints when bent, and can easily be peeled away from the skin.

10

15 Example 71-73

A stretchable adhesive solidifying formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) is prepared which includes saturated amount of ketoprofen in an excipient mixture (more ketoprofen than that can be dissolved in the excipient mixture) to form an adhesive peelable formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 43.

20

Table 43

Ingredients*	Examples		
	71	72	73
Eugragit RL-PO	28.06	27.7	27.5
Ethanol	40.07	39.5	39.5
Glycerol	27.40	13.9	
Polyethylene Glycol 400 (PEG)		13.9	28.
Ketoprofen	4.5	5	5

25

Peel formulations of Examples 71-73 are prepared in the following manner:

- The solidifying agents are dissolved in the volatile solvent (i.e., dissolve Eudragit polymers in ethanol).
- The flux adequate non-volatile solvent (glycerol, PEG) is mixed together with the solidifying agent/volatile solvent mixture.
- The resulting solution is vigorously mixed for several minutes.
- Drug is then added and the formulation is mixed again for several minutes.

Example 74

The formulations prepared in accordance with Example 71-73 are applied to HMS as described in Example 1, and the ketoprofen flux is measured. A summary of the results is listed in Table 44, as follows:

Table 44 - Steady-state flux of ketoprofen through hairless mouse skin

Formulation	Average flux mcg/cm ² /h*
Example 71	15 ± 7
Example 72	10 ± 3
Example 73	4 ± 1

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

The ketoprofen formulations prepared in accordance with Examples 71-72 possessed acceptable solidified layer properties (e.g., formed a solidified layer in 2-3 minutes). With Example 73, the ketoprofen peel does not form a solidified layer 30 minutes after application. This demonstrates that order to obtain desired flux and wear properties in a peel formulation, a delicate balance between solidifying agents, non-volatile solvents, and volatile solvents is evaluated and considered in developing a formulation.

Example 75

A stretchable adhesive solidifying formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) is

prepared which includes saturated amount of ketoprofen in an excipient mixture (more ketoprofen than that can be dissolved in the excipient mixture) to form an adhesive peelable formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a
 5 viscous and transparent fluid, is prepared using the ingredients as shown in Table 45.

Table 45

Ingredients*	FORMULATIONS		
	A	B	C
PVA (Celvol 502 MW 10,000)	24.4		
PVA (Amresco MW 31,000-50,000)		24.4	
PVA (Celvol 523 MW 125,000)			41.7
Water	33.4	33.4	58.3
Ethanol	8.9	8.9	
PG	17.8	17.8	
Glycerol	11.1	11.1	
Gantrez ES 425	4.4	4.4	

* Ingredients are noted in weight percent.

10 Formulations A and B are prepared in the following manner:

- PVA (solidifying agent) is dissolved in water.
- The flux adequate non-volatile solvent (glycerol, PG) is mixed together with the solidifying agent/volatile solvent mixture.
- Then ethanol, and Gantrez ES 425 is added to the mixture.
- The resulting solution is vigorously mixed for several minutes.

15 Preparation of the PVA in water solution in Formulation C was not feasible for this molecular weight of PVA at the percentages noted. Formulation C demonstrates that the correct polymer molecular weight for PVA is important to obtain the desired formulation properties.

20 Formulations A and B are placed on the skin of human volunteers. After a period of several hours, long enough for the volatile solvent to evaporate, the peels were removed by the volunteers and the peelability properties were evaluated. In all instances the volunteers reported that formulation example A could not be removed in one or two pieces, but was removed in numerous small
 25 pieces. Formulation example B removed in one or two pieces. The brittle

nature of formulation A is attributed to the lower molecular weight PVA sample (Celvol). Low molecular weight PVA does not possess the same cohesive strength as higher molecular weight PVA material (Amresco) due to the reduced size of the polymer chain leading to a reduction in the degree of cross linking and physical interactions between individual PVA polymer chains. The reduced PVA chain interactions lead to a weakened peel that is unable to withstand the mechanical forces the peel is subjected to upon removal.

Example 76

A stretchable adhesive solidifying formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) was evaluated which includes an excipient mixture which will form an adhesive peelable formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 46.

Table 46

Ingredients*	FORMULATIONS			
	D	E	F	G
PVA (Amresco MW 31,000-50,000)	22.1	24.4	22.1	21.1
Water	26.6	29.2	30.9	33.8
Ethanol	12.6	4.2	8.4	8.2
Butanol	0.4	0.5	0.4	0.4
PG	19.9	21.9	17.7	16.9
Glycerol	8.8	9.7	11	10.6
Gantrez ES 425	4.6	5.1	4.4	4.0
Ketoprofen	5.0	5.0	5.1	5.0

* Ingredients are noted in weight percent.

Peel formulations in formulations D-G are prepared in the following manner:

- PVA (solidifying agent) is dissolved in water.
- The flux adequate non-volatile solvent (glycerol, PG) is mixed together with the solidifying agent/volatile solvent mixture.
- Then ethanol, and Gantrez ES 425 is added to the mixture.
- The resulting solution is vigorously mixed for several minutes.

- After mixing, ketoprofen is added and the final mixture is vigorously mixed again for several minutes.

Formulations noted above were placed in laminate packaging tubes and stored at 25 C/60% RH and 40 C/ 75% RH conditions until pulled for testing.

- 5 Physical testing was performed on each formulation. Formulations D-F have been studied the longest and the resulting viscosity increase necessitated the desire to study the viscosity of formulation G. Table 47 summarizes the data generated on each formulation.

10

Table 47

Formulation Storage Cond.	Viscosity* cPs					
	T=0	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks
D 25 C/60% RH	96000	670000	>2500000	Not measured		
D 40 C/75% RH	96000	500000	587500	2320000		
E 25 C/60% RH	168500	204500	251000	>2500000		
E 40 C/75% RH	168500	215000	217500	>2500000		
F 25 C/60% RH	23000	--	25000	36250	76250	57500
F 40 C/75% RH	23000	--	31000	40000	243500	164500
G 25 C/60% RH	11250	13750				
G 40 C/75% RH	11250	17500				

* Viscosity measured using a RVDV 1+ viscometer at 0.5 rpm.

Formulations D and E of this example had the lowest water content of the four formulations and within 4 weeks of storage attained high viscosity values.

- 15 The only difference between formulations 1 and 2 is the amount of ethanol in the formulations. It was hypothesized that reducing the level of ethanol may reduce the physical thickening of the formulation due to an incompatibility between the PVA and ethanol. The viscosity data show that the higher ethanol formulation (formulation D) had lower initial viscosity, but over the 4 weeks

storage the viscosity of both formulation D and E attained viscosity values that were too high for a viable formulation. Another hypothesis for the formulation thickening is that PVA is not compatible in high concentrations when dissolved in water. Additional formulations with higher water content were prepared to determine if an optimal water amount would keep the formulation from thickening up over time. Formulation F viscosity after 16 weeks has not reached the viscosity values of the initial viscosity values of formulations 1 and 2.

Placebo versions of the formulations above were applied on study volunteers and the drying time was assessed by placing a piece of cotton to the application site and then applying a 5 gram weight on the cotton. The cotton and weight was removed after 5 seconds. This procedure was started approximately 3 – 4 minutes after application and at 10 to 60 second intervals thereafter until the cotton was removed without lifting the peel or leaving residue behind. The results of the study are summarized in Table 48 below.

Table 48

Formulation	Drying Time (min)*
D	4 min 49 sec
E	5 min 41 sec
F	4 min 27 sec
G	5 min 1 sec

* average dry time value from 12 study subjects.

The presence of ethanol as a second volatile solvent appears to significantly reduce the time to dry. In data not shown a local anesthetic formulation containing only water as the volatile solvent and a ratio of water to PVA of 2:1 has a drying time of >15 minutes. Optimizing the ratio and the presence of an additional volatile solvent in formulations containing water significantly reduce the drying time. It is hypothesized that the additional volatile solvent, in this case ethanol, will hydrogen bond with the water and water will escape with the ethanol when evaporating off the skin thereby forming a solidified peel.

Examples 77-79

Solidifying formulations for dermal delivery of ropivacaine HCl are prepared which include excipient mixtures in accordance with embodiments of the present invention. The formulations are prepared from the ingredients as shown in Table 49.

Table 49 - Ropivacaine HCl solidifying formulation components

Ingredients*	Example		
	77	78	79
Ropivacaine HCl	6.9	6.5	6.6
Isopropanol	50.7	45.8	45.9
Water	5.5	5.2	5.2
Isostearic Acid	6.3	6.6	6.6
Triethylamine			3.0
Diisopropanolamine		3.9	
Cetyl alcohol		3.3	3.9
Triacetin	2.9	2.6	2.6
Span 20	5.8	5.2	5.2
Plastoid B**	21.9	20.9	21.0

*Ingredients are noted as weight percent.

** from Degussa.

- 10 The ingredients listed above are combined according to the following procedure. The ropivacaine HCl, water, and the amine base (triethylamine or diisopropanolamine) are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20, and cetyl alcohol (Examples 78 and 79) or isopropanol (Example 77) are added to the formulation and mixed well. The polymer Plastoid B is added last and heated to about 60 °C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 49 are applied to HMS according to Example 1, and the flux of ropivacaine was measured. The results are summarized in Table

20 50:

Table 50 - Steady-state flux of ropivacaine HCl through hairless mouse skin from various adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm ² /h*
77	96 ± 14
78	61 ± 2
79	70 ± 7

5 While the invention has been described with reference to certain preferred embodiments, those skilled in the art will appreciate that various modifications, changes, omissions, and substitutions can be made without departing from the spirit of the invention. It is therefore intended that the invention be limited only by the scope of the appended claims.

CLAIMS

What Is Claimed Is:

- 5 1. A formulation for dermal delivery of a drug, comprising:
a) a drug;
b) a solvent vehicle, comprising:
 i) a volatile solvent system including at least one volatile solvent,
 and
10 ii) a non-volatile solvent system that is flux-enabling for the drug;
 and
 c) a solidifying agent which contributes to solidification of a layer of the
formulation applied on a skin surface upon at least partial evaporation of the
volatile solvent system,
15 wherein the formulation has a viscosity suitable for application and
adhesion to the skin surface prior to evaporation of the volatile solvent system,
and wherein the formulation applied to the skin surface forms an adhesive
solidified layer after at least partial evaporation of the volatile solvent system,
wherein the drug continues to be delivered after the volatile solvent system has
20 at least substantially evaporated.
2. A formulation as in claim 1, wherein the non-volatile solvent system is
a plasticizer for the solidifying agent.
- 25 3. A formulation as in claim 1, wherein the non-volatile solvent system
comprises at least two non-volatile solvents and the non-volatile solvent system
is capable of generating higher dermal flux for the drug than each of non-volatile
solvents individually.
- 30 4. A formulation as in claim 1, wherein the formulation further comprises
an additional agent which is included to increase adhesion of the formulation
when applied to the skin surface.

5. A formulation as in claim 4, wherein the additional agent includes at least one member selected from the group consisting of copolymers of methylvinyl ether and maleic anhydride, polyethylene glycol and polyvinyl pyrrolidone, gelatin, low molecular weight polyisobutylene rubber, copolymer of acrylsan alkyl and octylacrylamido, and aliphatic resins, aromatic resins, and combinations thereof.

6. A formulation as in claim 1, wherein the volatile solvent system comprises water.

7. A formulation as in claim 1, wherein the formulation is substantially free of water.

8. A formulation as in claim 1, wherein the volatile solvent system comprises at least one solvent more volatile than water, and includes at least one member selected from the group consisting of ethanol, isopropyl alcohol, water, dimethyl ether, diethyl ether, butane, propane, isobutene, 1,1, difluoroethane, 1,1,1,2 tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, ethyl acetate, acetone, and combinations thereof.

9. A formulation as in claim 1, wherein the volatile solvent system comprises at least one solvent more volatile than water, and includes at least one member selected from the group consisting of iso-amyl acetate, denatured alcohol, methanol, propanol, isobutene, pentane, hexane, chlorobutanol, turpentine, cytopentasiloxane, cyclomethicone, methyl ethyl ketone, and combinations thereof.

10. A formulation as in claim 1, wherein the volatile solvent system includes at least one member selected from the group consisting of ethanol, iso-propyl alcohol, and combinations thereof.

11. A formulation as in claim 1, wherein the flux-enabling non-volatile solvent system provides at least twice the flux for the drug when the drug is present in the non-volatile solvent system alone than is necessary to achieve a therapeutically effective flux.

12. A formulation as in claim 1, wherein the non-volatile solvent system comprises one or more solvents selected from the group consisting of glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine, tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, and combinations thereof.

13. A formulation as in claim 1, wherein the non-volatile solvent system comprises one or more solvents selected from the group consisting of benzoic acid, butyl alcohol, dibutyl sebecate, diglycerides, dipropylene glycol, eugenol, fatty acids, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid surfactants, triethyl citrate, and combinations thereof.

14. A formulation as in claim 1, wherein the non-volatile solvent system comprises one or more solvents selected from the group consisting of 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, diethylene glycol monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugars, ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol,

pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil,
 vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-
 (octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole,
 candelilla wax, carnauba wax, cetareth-20, cetyl alcohol, polyglyceryl,
 5 dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl
 sebacate, dimethicone, dimethyl phthalate, PEG fatty acid esters, PEG-
 stearate, PEG-oleate, PEG laurate, PEG fatty acid diesters, PEG- dioleate,
 PEG-distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid
 esters, PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate,
 10 hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate,
 medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil,
 PEG-octyl phenyl ether, PEG-alkyl ethers, PEG-cetyl ether, PEG-stearyl ether,
 PEG-sorbitan fatty acid esters, PEG-sorbitan diisostearate, PEG-sorbitan
 monostearate, propylene glycol fatty acid esters, propylene glycol stearate,
 15 propylene glycol, caprylate/caprate, sodium pyrrolidone carboxylate, sorbitol,
 squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols,
 polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolyzed C8-C10
 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl
 sulfoxide, azone and related compounds, dimethylformamide, N-methyl
 20 formamide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-
 dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate,
 polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol
 esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2
 myreth 10-adipate, honeyquat, sodium pyroglutamic acid, abyssinica oil,
 25 dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol,
 PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone,
 hydrolyzed wheat protein, and combinations thereof.

15. A formulation as in claim 1, wherein the solidifying agent includes at
 30 least one member selected from the group consisting of polyvinyl alcohol, esters
 of polyvinylmethylether/maleic anhydride copolymer, neutral copolymers of butyl
 methacrylate and methyl methacrylate, dimethylaminoethyl methacrylate-butyl

methacrylate-methyl methacrylate copolymers, ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymers, prolamine (Zein), pregelatinized starch, ethyl cellulose, fish gelatin, gelatin, acrylates/octylacrylamide copolymers, and combinations thereof.

5

16. A formulation as in claim 1, wherein the solidifying agents include a member selected from the group consisting of ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, polyether amides, corn starch, pregelatinized corn starch, polyether amides, shellac, polyvinyl pyrrolidone, polyisobutylene rubber, polyvinyl acetate phthalate and combinations thereof.

10

17. A formulation as in claim 1, wherein the solidifying agents includes at least one member selected from the group consisting of ammonia methacrylate, carrageenan, cellulose acetate phthalate aqueous, carboxy polymethylene, cellulose acetate (microcrystalline), cellulose polymers, divinyl benzene styrene, ethylene vinyl acetate, silicone, guar gum, guar rosin, gluten, casein, calcium caseinate, ammonium caseinate, sodium caseinate, potassium caseinate, methyl acrylate, microcrystalline wax, polyvinyl acetate, PVP ethyl cellulose, acrylate, PEG/PVP, xanthan gum, trimethyl siloxysilicate, maleic acid/anhydride polymers, polacrilin, poloxamer, polyethylene oxide, poly lactic acid/poly-L-lactic acid, turpene resin, locust bean gum, acrylic copolymers, polyurethane dispersions, dextrin, polyvinyl alcohol-polyethylene glycol copolymers, methacrylic acid-ethyl acrylate copolymers, methacrylic acid and methacrylate based polymers such as poly(methacrylic acid), and combinations thereof.

20

25

18. A formulation as in claim 1, wherein the drug includes multiple pharmaceutically active agents.

30

19. A formulation as in claim 1, wherein the drug includes at least one member selected from the group consisting of acyclovir, econazole, miconazole, terbinafine, lidocaine, bupivacaine, ropivacaine, and tetracaine, amitriptyline, ketanserin, betamethasone dipropionate, triamcinolone acetonide, clindamycin, benzoyl peroxide, tretinoin, isotretinoin, clobetasol propionate, halobetasol propionate, ketoprofen, piroxicam, diclofenac, indomethacin, imiquimod, salicylic acid, benzoic acid, and combinations thereof.

20. A formulation as in claim 1, wherein the drug includes at least one member selected from the group consisting of amorolfine, butenafine, naftifine, terbinafine, fluconazole, itraconazole, ketoconazole, posaconazole, ravuconazole, voriconazole, clotrimazole, butoconazole, econazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole, caspofungin, micafungin, anidulafingine, amphotericin B, AmB, nystatin, pimaricin, griseofulvin, ciclopirox olamine, haloprogin, tolnaftate, undecylenate, acyclovir, penciclovir, famciclovir, valacyclovir, behenyl alcohol, trifluridine, idoxuridine, cidofovir, ganciclovir, podofilox, podophyllotoxin, ribavirin, abacavir, delavirdine, didanosine, efavirenz, lamivudine, nevirapine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, amantadine, interferon, oseltamivir, ribavirin, rimantadine, zanamivir, erythromycin, clindamycin, tetracycline, bacitracin, neomycin, mupirocin, polymyxin B, quinolones such as ciprofloxacin, lidocaine, bupivacaine, ropivacaine, tetracaine, alpha-2 agonists clonidine, tricyclic anti-depressants, carbamazepine, alprazolam, N-methyl-D-aspartate (NMDA) antagonists, 5-HT_{2A} receptor antagonist, betamethasone dipropionate, halobetasol propionate, diflorasone diacetate, triamcinolone acetonide, desoximethasone, fluocinonide, halcinonide, mometasone furoate, betamethasone valerate, fluocinonide, fluticasone propionate, triamcinolone acetonide, fluocinolone acetonide, flurandrenolide, desonide, hydrocortisone butyrate, hydrocortisone valerate, alclometasone dipropionate, flumethasone pivalate, hydrocortisone, hydrocortisone acetate, tacrolimus, pimecrolimus, tazarotene, isotretinoin, cyclosporin, anthralin, vitamin D₃, cholecalciferol, calcitriol, calcipotriol, tacalcitol, calcipotriene, ketoprofen,

piroxicam, diclofenac, indomethacin, COX inhibitors general COX inhibitors, COX-2 selective inhibitors, and COX-3 selective inhibitors, imiquimod, rosiquimod, salicylic acid, alpha hydroxy acids, sulfur, resorcinol, urea, benzoyl peroxide, allantoin, tretinoin, trichloroacetic acid, lactic acid, benzoic acid, progesterone, norethindrone, norethindroneacetate, desogestrel, drospirenone, ethynodiol diacetate, norelgestromin, norgestimate, levonorgestrel, dl-norgestrel, cyproterone acetate, dydrogesterone, medroxyprogesterone acetate, chlormadinone acetate, megestrol, promegestone, norethisterone, lynestrenol, gestodene, tibolene, androgens consisting of testosterone, methyl testosterone, oxandrolone, androstenedione, dihydrotestosterone, estradiol, ethniyl estradiol, estiol, estrone, conjugated estrogens, esterified estrogens, estropipate, anti-acne drugs, and combinations thereof.

21. A formulation as in claim 1, wherein the solidified layer is sufficiently flexible and adhesive to the skin such that when applied to the skin at a human joint, the solidified layer will remain substantially intact on the skin upon bending of the joint for at least two hours.

22. A formulation as in claim 1, wherein the solidified layer is sufficiently flexible and adhesive to the skin such that when applied to a curved body surface or weight bearing surface on the body, the solidified layer will remain substantially intact on the skin upon bending or stretching of the curved body surface or weight bearing surface.

23. A formulation as in claim 1, wherein the formulation is configured to deliver the drug at a therapeutically effective rate for at least about 2 hours following the formation of the solidified layer.

24. A formulation as in claim 1, wherein the formulation is configured to deliver the drug at a therapeutically effective rate for 2 hours to 12 hours following the formation of the solidified layer.

25. A formulation as in claim 1, wherein the formulation is configured to deliver the drug at a therapeutically effective rate for at least about 12 hours following the formation of the solidified layer.

5 26. A formulation as in claim 1, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.1:1 to about 10:1.

27. A formulation as in claim 1, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.5:1 to about 2:1.

10 28. A formulation as in claim 1, wherein at least one non-volatile solvent of the non-volatile solvent system is capable of reducing skin irritation.

15 29. A formulation as in claim 28, wherein the non-volatile solvent capable of reducing skin irritation is selected from the group consisting of glycerin, propylene glycol, and honey.

20 30. A formulation as in claim 1, wherein the solidified layer is formed within about 15 minutes of application to the skin surface under standard skin conditions and ambient conditions.

31. A formulation as in claim 1, wherein the solidified layer is formed within about 5 minutes of the application to the skin surface under standard skin conditions and ambient conditions.

25 32. A formulation as in claim 1, wherein the formulation has an initial viscosity prior to skin application from about 100 cP to about 3,000,000 cP.

30 33. A formulation as in claim 1, wherein the formulation has an initial viscosity prior to skin application from about 1,000 cP to about 1,000,000 cP.

34. A formulation as in claim 1, wherein the weight percentage of the volatile solvent system is from about 10 wt% to about 85 wt%.

5 35. A formulation as in claim 1, wherein the weight percentage of the volatile solvent system is from about 20 wt% to about 50 wt%.

36. A formulation as in claim 1, wherein the weight percentage of the volatile solvent system in the formulation is at least about 20%.

10 37. A formulation as in claim 1, wherein the non-volatile solvent system includes multiple non-volatile solvents and at least one of the non-volatile solvents is capable of improving the compatibility of the non-volatile solvent system with the solidifying agent.

15 38. A formulation as in claim 1, wherein the solidified layer is coherent and peelable from the skin.

39. A formulation as in claim 1, wherein the solidified layer is coherent, flexible, and continuous.

20

40. A formulation as in claim 1, wherein the solidified layer, upon formation, is a soft, coherent solid that is peelable from a skin surface as a single piece or as only a few large pieces relative to the application size.

25 41. A formulation as in claim 1, wherein the solidified layer can be removed by washing.

42. A formulation as in claim 41, wherein the washing includes the use of a solvent selected from the group consisting of water, ethanol, methanol,
30 isopropyl alcohol, acetone, ethyl acetate, propanol, and combinations thereof.

43. A formulation as in claim 41, wherein the washing includes the use of a non-volatile solvent.

5 44. A formulation as in claim 41, wherein the washing includes the use of water, ethanol, isopropanol, or combinations thereof.

45. A formulation as in claim 1, wherein the solidified layer delivers the drug transdermally.

10 46. A method of dermally delivering a drug, comprising:
a) applying a formulation as in one of claims 1 to 45 as a layer to a skin surface of a subject;
b) solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the volatile solvent system; and
15 c) dermally delivering the drug from the solidified layer to the skin surface at a therapeutically effective rate over a sustained period of time.

20 47. A method as in claim 46, wherein the step of applying includes applying the formulation at a thickness from about 0.01 mm to about 3 mm.

48. A method as in claim 46, wherein the step of applying includes applying the formulation at a thickness from about 0.05 mm to about 1 mm.

25 49. A method as in claim 46, wherein the skin surface is a skin surface sensitive to the touch of foreign objects or vulnerable to infection if contact by foreign objects, and the solidified layer provides physical protection to the skin surface.

30 50. A method as in claim 46, wherein the solidified layer is left on the skin surface for at least two hours.

51. A method as in claim 46, wherein the solidified layer is left on the skin for at least 6 hours.

52. A method as in claim 46, wherein the solidified layer is formed within
5 about 15 minutes of application to the skin surface under standard skin and ambient conditions.

53. A method as in claim 46, further comprising the step of peeling the solidified layer from the skin in a single piece or only a few large pieces relative
10 to the size of application.

54. A method as in claim 46, further comprising removing by washing the solidified layer after the drug is delivered removed.

15 55. A method as in 54, wherein the washing includes the use of a solvent selected from the group consisting of water, ethanol, methanol, isopropyl alcohol, acetone, ethyl acetate, propanol, and combinations thereof.

56. A method as in claim 54, wherein the washing includes the use of a
20 non-volatile solvent.

57. A method as in claim 54, wherein the washing includes the use of water, ethanol, isopropanol, or combinations thereof.

25 58. A method of preparing a formulation for dermal drug delivery, comprising:

a) selecting a drug suitable for dermal delivery;

b) selecting or formulating a non-volatile solvent system that is flux-enabling for the drug;

30 c) selecting or formulating a solidifying agent that is compatible to the flux-enabling non-volatile solvent;

d) selecting or formulating a volatile solvent system comprising at least one volatile solvent that is compatible to the flux-enabling non-volatile solvent and the solidifying agent; and

5 e) formulating the drug, the non-volatile solvent system, the solidifying agent, the volatile solvent system, and optional other ingredients into a formulation having a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface as a layer forms a solidified layer after at least a portion of the volatile solvent system is evaporated, and wherein the drug continues to be
10 delivered at a therapeutically effective rate after the volatile solvent system is at least substantially evaporated.

15 59. A method as in claim 58, wherein the volatile solvent system comprises water.

60. A method as in claim 58, wherein the volatile solvent system includes at least one member selected from the group consisting of ethanol, isopropyl alcohol, water, dimethyl ether, diethyl ether, butane, propane, isobutene, 1,1, difluoroethane, 1,1,1,2 tetrafluoroethane, 1,1,1,2,3,3,3-
20 heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, ethyl acetate, acetone, and combinations thereof.

61. A method as in claim 58, wherein the volatile solvent system includes at least one member selected from the group consisting of iso-amyl
25 acetate, denatured alcohol, methanol, propanol, isobutene, pentane, hexane, chlorobutanol, turpentine, cytopentasiloxane, cyclomethicone, methyl ethyl ketone, and combinations thereof.

62. A method as in claim 58, wherein the non-volatile solvent system
30 includes at least one member selected from the group consisting of glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine,

tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, and combinations thereof.

63. A method as in claim 58, wherein the non-volatile solvent system includes at least one member selected from the group consisting of benzoic acid, butyl alcohol, dibutyl sebacate, diglycerides, dipropylene glycol, eugenol, fatty acids, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid surfactants, triethyl citrate, and combinations thereof.

64. A method as in claim 58, wherein the non-volatile solvent system includes at least one member selected from the group consisting of 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, diethylene glycol monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugars, ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol, pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil, vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-(octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, cetareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG fatty acid esters, PEG-stearate, PEG-oleate, PEG laurate, PEG fatty acid diesters, PEG-dioleate, PEG-distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid esters, PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate,

hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil, PEG-octyl phenyl ether, PEG-alkyl ethers, PEG-cetyl ether, PEG-stearyl ether, PEG-sorbitan fatty acid esters, PEG-sorbitan diisostearate, PEG-sorbitan

5 monostearate, propylene glycol fatty acid esters, propylene glycol stearate, propylene glycol, caprylate/caprates, sodium pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolized C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl

10 sulfoxide, azone and related compounds, dimethylformamide, N-methyl formamide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2

15 myreth 10-adipate, honeyquat, sodium pyroglutamic acid, abyssinica oil, dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol, PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone, hydrolyzed wheat protein, and combinations thereof.

20 65. A method as in claim 58, wherein the solidifying agent includes at least one member selected from the group consisting of polyvinyl alcohol, esters of polyvinylmethylether/maleic anhydride copolymer, neutral copolymers of butyl methacrylate and methyl methacrylate, dimethylaminoethyl methacrylate-butyl methacrylate-methyl methacrylate copolymers, ethyl acrylate-methyl

25 methacrylate-trimethylammonioethyl methacrylate chloride copolymers, prolamine (Zein), pregelatinized starch, ethyl cellulose, fish gelatin, gelatin, acrylates/octylacrylamide copolymers, and combinations thereof.

30 66. A method as in claim 58, wherein the solidifying agent includes a member selected from the group consisting of ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, polyether amides,

corn starch, pregelatinized corn starch, polyether amides, shellac, polyvinyl pyrrolidone, polyisobutylene rubber, polyvinyl acetate phthalate and combinations thereof.

5 67. A method as in claim 58, wherein the solidifying agent includes at least one member selected from the group consisting of ammonia methacrylate, carrageenan, cellulose acetate phthalate aqueous, carboxy polymethylene, cellulose acetate (microcrystalline), cellulose polymers, divinyl benzene styrene, ethylene vinyl acetate, silicone, guar gum, guar rosin, gluten, casein, calcium
10 caseinate, ammonium caseinate, sodium caseinate, potassium caseinate, methyl acrylate, microcrystalline wax, polyvinyl acetate, PVP ethyl cellulose, acrylate, PEG/PVP, xanthan gum, trimethyl siloxysilicate, maleic acid/anhydride polymers, polacrilin, poloxamer, polyethylene oxide, poly lactic acid/poly-L-lactic acid, turpene resin, locust bean gum, acrylic copolymers, polyurethane
15 dispersions, dextrin, polyvinyl alcohol-polyethylene glycol co-polymers, methacrylic acid-ethyl acrylate copolymers, methacrylic acid and methacrylate based polymers such as poly(methacrylic acid), and combinations thereof.

 68. A method as in claim 58, wherein the drug includes at least one
20 member selected from the group consisting of acyclovir, econazole, miconazole, terbinafine, lidocaine, bupivacaine, ropivacaine, and tetracaine, amitriptyline, ketanserin, betamethasone dipropionate, triamcinolone acetonide, clindamycin, benzoyl peroxide, tretinoin, isotretinoin, clobetasol propionate, halobetasol propionate, ketoprofen, piroxicam, diclofenac, indomethacin, imiquimod, salicylic
25 acid, benzoic acid, and combinations thereof.

 69. A method as in claim 58, wherein the formulation is configured to deliver the drug at a therapeutically effective rate for at least about 2 hours following the formation of the solidified layer.

30

 70. A method as in claim 58, wherein the solidifying agent is dispersed or solvated in the solvent vehicle.

71. A method as in claim 58, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.5:1 to about 2:1.

5 72. A method as in claim 58, wherein the solidified layer is formed within about 15 minutes of application to the skin surface under standard skin and ambient conditions.

10 73. A method as in claim 58, wherein the formulation has an initial viscosity prior to skin application from about 100 cP to about 3,000,000 cP.

74. A method as in claim 58, wherein the weight percentage of the volatile solvent system is from about 10 wt% to about 85 wt%.

15 75. A method as in claim 58, wherein the non-volatile solvent system includes multiple non-volatile solvents and at least one of the non-volatile solvents is capable of improving the compatibility of the non-volatile solvent system with the solidifying agent.

20 76. A method as in claim 58, wherein the non-volatile solvent system comprises a non-volatile solvents is a plasticizer for the solidifying agent.

25 77. A method as in claim 58, wherein the non-volatile solvent system comprises a non-volatile solvent that is capable of decreasing the moisture vapor loss from the skin surface.

78. A method as in claim 58, wherein the non-volatile solvent system comprises a non-volatile solvent capable of enhancing adhesion to skin.

30 79. A method as in claim 58, wherein the flux-enabling non-volatile solvent maintains delivery of the drug into human skin or tissues.

80. A solidified layer for dermally delivering a drug, comprising:

- a) a drug;
- b) a non-volatile solvent system that is a flux-enabling for the drug; and
- c) a solidifying agent,

5 wherein the solidified layer is a soft, coherent solid that is adhered to a body surface, the solidified layer is formulated to deliver most of the drug that is dermally deliverable therefrom while the solidified layer is at least substantially devoid of water and solvents more volatile than water, and the solidified layer is also flux-enabling for the drug.

10 81. A solidified layer as in claim 80, wherein the solidified layer can be stretched in at least one direction by 5% without separation from the skin surface.

15 82. A solidified layer as in claim 80, wherein the non-volatile solvent system acts as a plasticizer for the solidifying agent.

20 83. A solidified layer as in claim 80, wherein solidified layer is sufficiently adhesive and flexible to remain substantially intact on a skin surface adjacent to a joint or muscle group where regular skin stretching occurs.

84. A solidified layer as in claim 80, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.5:1 to about 2:1.

25 85. A solidified layer as in claim 80, wherein the solidified layer is washable with water, an alcohol solvent or a combination thereof.

86. A solidified layer as in claim 80, wherein the solidified layer can be removed by washing.

87. A solidified layer as in claim 80, wherein the washing includes the use of a solvent selected from the group consisting of water, ethanol, methanol, isopropyl alcohol, acetone, ethyl acetate, propanol, and combinations thereof.

5 88. A solidified layer as in claim 80, wherein the washing includes the use of a non-volatile solvent.

89. A solidified layer as in claim 80, wherein the washing includes the use of water, ethanol, isopropanol, or combinations thereof.

10

90. A solidified layer as in claim 80, wherein the solidified layer is a peel and can be removed by peeling from the skin surface as a single piece or as only a few large pieces relative to the application size.

15

91. A solidified layer as in claim 80, wherein the solidified layer substantially devoid of water and solvents more volatile than water when the solidified layer contains no more than 10 wt% of water and solvents more volatile than water.

20

92. A solidified layer as in claim 80, wherein the solidified layer substantially devoid of water and solvents more volatile than water when the solidified layer contains no more than 5 wt% of water and solvents more volatile than water.

25

93. A formulation for dermal delivery of a sex hormone, comprising:

a) a sex hormone;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent,

and

30

ii) a non-volatile solvent system including at least one non-volatile solvent; and

c) a solidifying agent which contributes to solidification of the formulation applied as a layer on a skin surface upon at least partial evaporation of the volatile solvent system,

wherein the formulation has a viscosity suitable for application and
5 adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms a solidified layer after at least partial evaporation of the volatile solvent system, wherein the sex hormone continues to be delivered at a therapeutically sufficient rate after the volatile solvent system is at least substantially evaporated.

10 94. A formulation as in claim 93, wherein the sex hormone includes at least one member selected from the group of androgens consisting of testosterone, methyl testosterone, oxandrolone, androstenedione, dihydrotestosterone, and combinations thereof.

15 95. A formulation as in claim 93, wherein the sex hormone includes at least one member selected from a group of estrogens consisting of estradiol, ethinyl estradiol, estiol, estrone, conjugated estrogens, esterified estrogens, estropipate and combinations thereof.

20 96. A formulation as in claim 93, wherein the sex hormone includes at least one member selected from a group of progestagens consisting of progesterone, norethindrone, norethindroneacetate, desogestrel, drospirenone, ethynodiol diacetate, norelgestromin, norgestimate, levonorgestrel, dl-
25 norgestrel, cyproterone acetate, dydrogesterone, medroxyprogesterone acetate, chlormadinone acetate, megestrol, promegestone, norethisterone, lynestrenol, gestodene, tibolone, and combinations thereof.

30 97. A formulation as in claim 93, wherein the formulation includes a combination of at least two steroid hormones selected from the group of progestagen, estrogen, and androgen.

98. A formulation for dermal delivery of an anti-wart drug, comprising:

a) an anti-wart drug;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent,

and

ii) a non-volatile solvent system including at least one non-volatile solvent; and

c) a solidifying agent which contributes to solidification of a layer of the formulation applied on a skin surface upon at least partial evaporation of the volatile solvent system,

wherein the formulation has a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms an adhesive solidified layer after at least partial evaporation of the volatile solvent system, wherein the drug continues to be delivered after the volatile solvent system has at least substantially evaporated.

99. A formulation as in claim 98, wherein the solidified layer is formulated to provide substantial occlusion to the skin and wart beneath the solidified layer.

100. A formulation as in claim 98, wherein the anti-wart drug includes multiple anti-wart agents.

101. A formulation as in claim 98, wherein the drug includes at least one member selected from the group consisting of immune modulators including imiquimod, keratolytic agents including salicylic acid, alpha hydroxy acids, sulfur, resorcinol, urea, benzoyl peroxide, allantoin, tretinoin, trichloroacetic acid, lactic acid, antiviral agents, and combinations thereof.

102. A solidifying formulation of clobetasol propionate, comprising:
a) clobetasol propionate;

105

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent,

and

ii) a non-volatile solvent system comprising propylene glycol and

fatty acid; and

c) a solidifying agent which contributes to solidification of a layer of the formulation applied on a skin surface upon at least partial evaporation of the volatile solvent system,

wherein the formulation has a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms an adhesive solidified layer after at least partial evaporation of the volatile solvent system, wherein the drug continues to be delivered after the volatile solvent system has at least substantially evaporated.

103. A formulation as in claim 102, wherein the solidifying agent is a protein based solidifying agent.

104. A formulation as in claim 102, wherein the non-volatile solvent system comprises propylene glycol, isostearic acid, oleic acid, or combinations thereof.

105. A solidifying formulation of ropivacaine, comprising:

a) ropivacaine;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent,

and

ii) a non-volatile solvent system comprising solvents selected from the group consisting of isostearic acid span 20, and triacetin; and

c) a solidifying agent which contributes to solidification of a layer of the formulation applied on a skin surface upon at least partial evaporation of the volatile solvent system,

wherein the formulation has a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms an adhesive solidified layer after at least partial evaporation of the volatile solvent system, wherein the ropivacaine continues to be delivered into or across the skin at a rate of no less than 5 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

106. A solidifying formulation of imiquimod, comprising:

a) imiquimod;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent, and

ii) a non-volatile solvent system comprising solvents selected from isostearic acid, span 20, and triacetin; and

c) a solidifying agent which contributes to solidification of a layer of the formulation applied on a skin surface upon at least partial evaporation of the volatile solvent system,

wherein the formulation has a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms an adhesive solidified layer after at least partial evaporation of the volatile solvent system, wherein the imiquimod continues to be delivered into or across the skin at a rate of no less than 0.8 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

107. A solidifying formulation of ketoprofen, comprising:

a) ketoprofen;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent, and

ii) a non-volatile solvent system comprising glycerol, propylene glycol; and

c) a solidifying agent which contributes to solidification of a layer of the formulation applied on a skin surface upon at least partial evaporation of the
5 volatile solvent system,

wherein the formulation has a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system, and wherein the formulation applied to the skin surface forms an adhesive solidified layer after at least partial evaporation of the volatile solvent system,

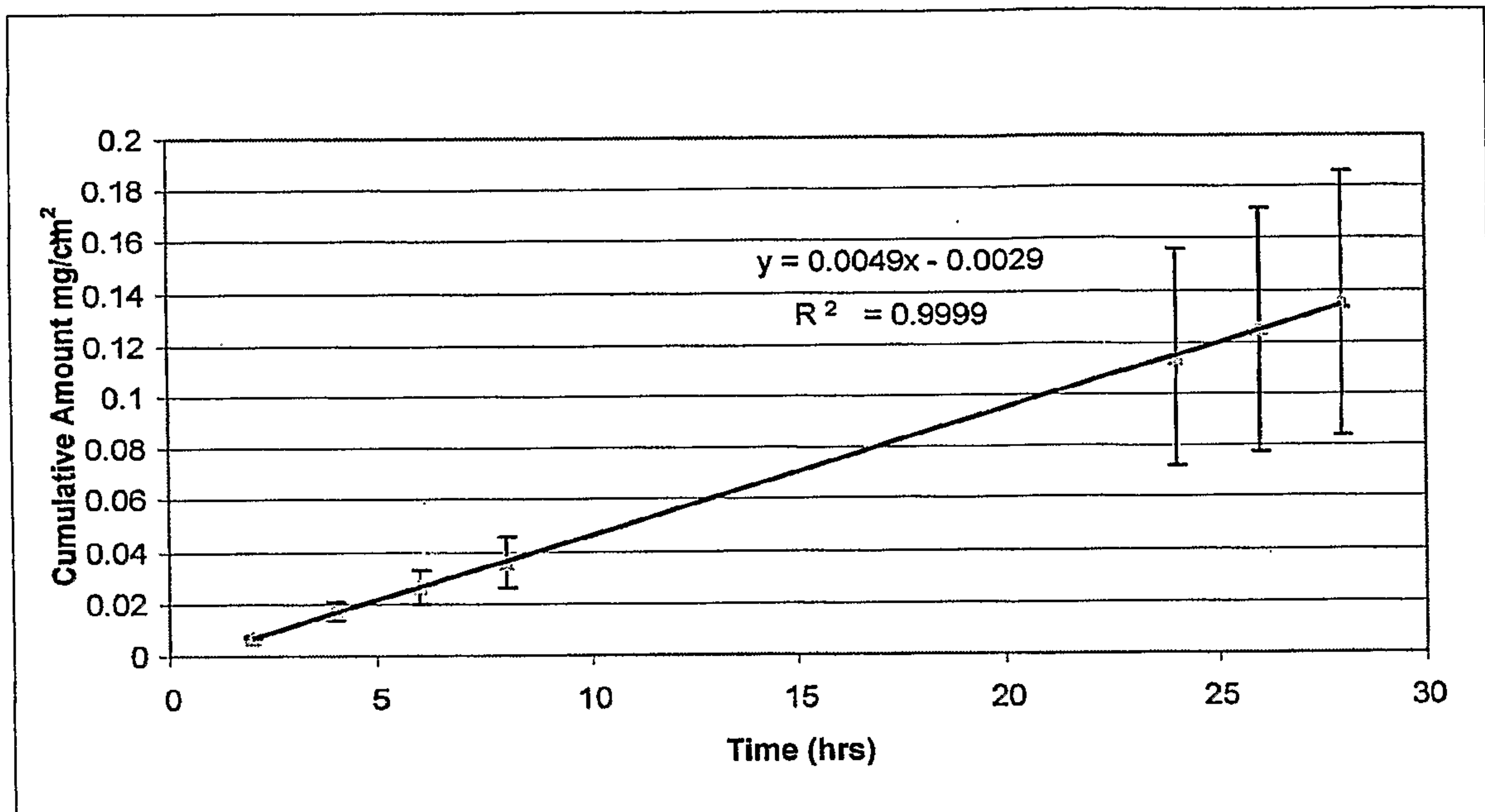
10 wherein the ketoprofen continues to be delivered across the skin at a rate of no less than 10 mcg/hr/cm² for at least 6 hours after the volatile solvent system has at least substantially evaporated.

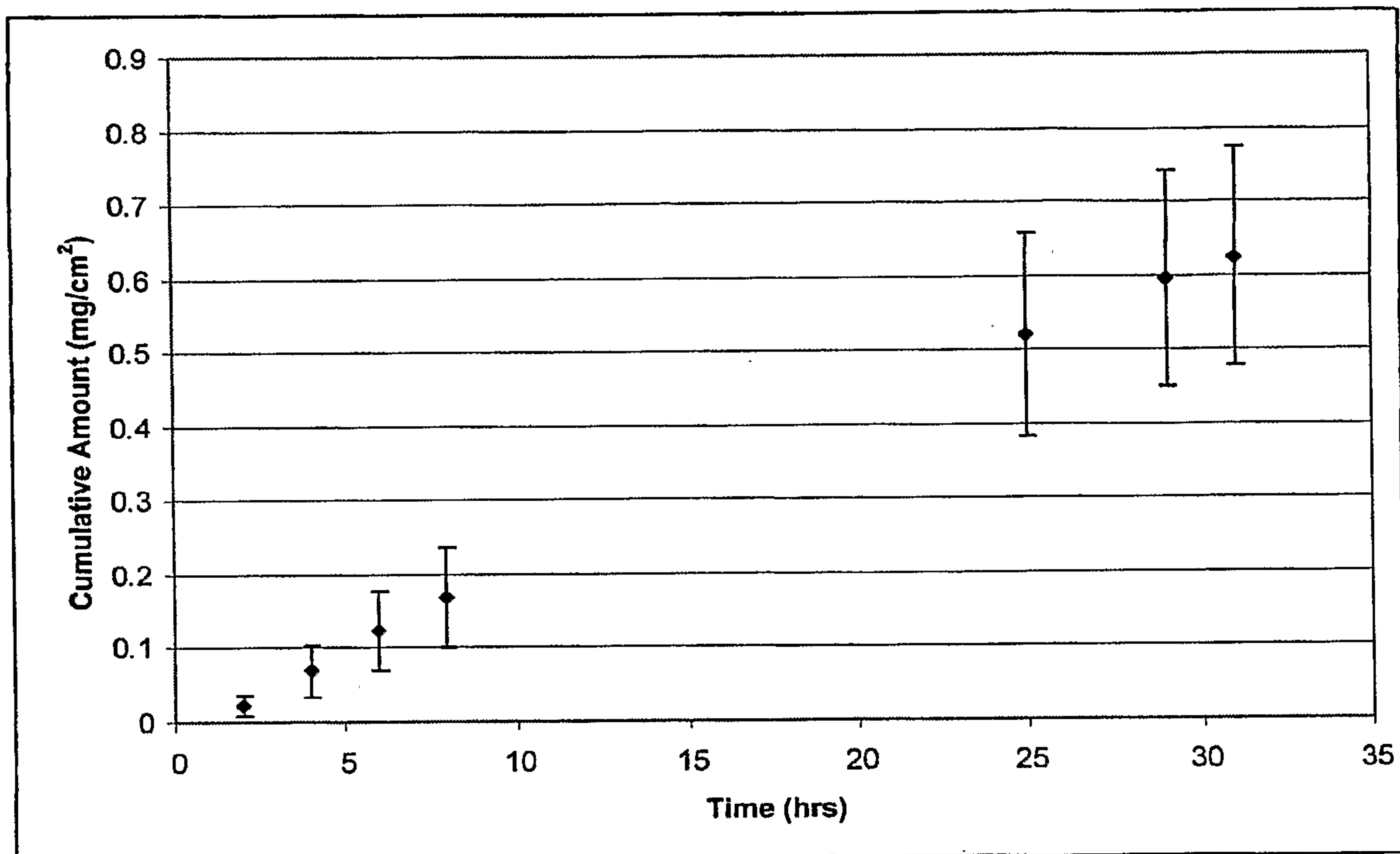
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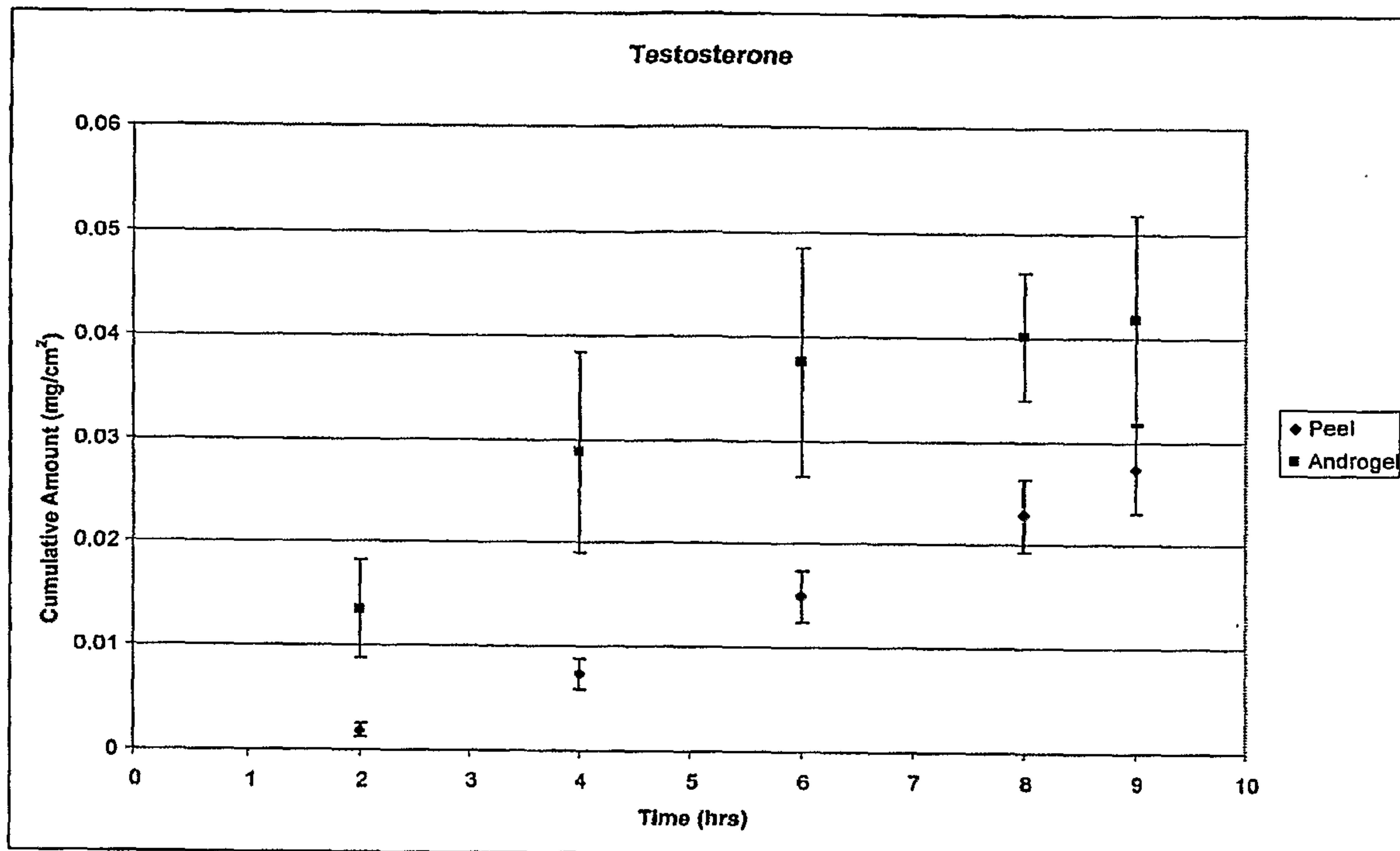
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1/4**FIG. 1**

2/4**FIG. 2**

3/4**FIG. 3**

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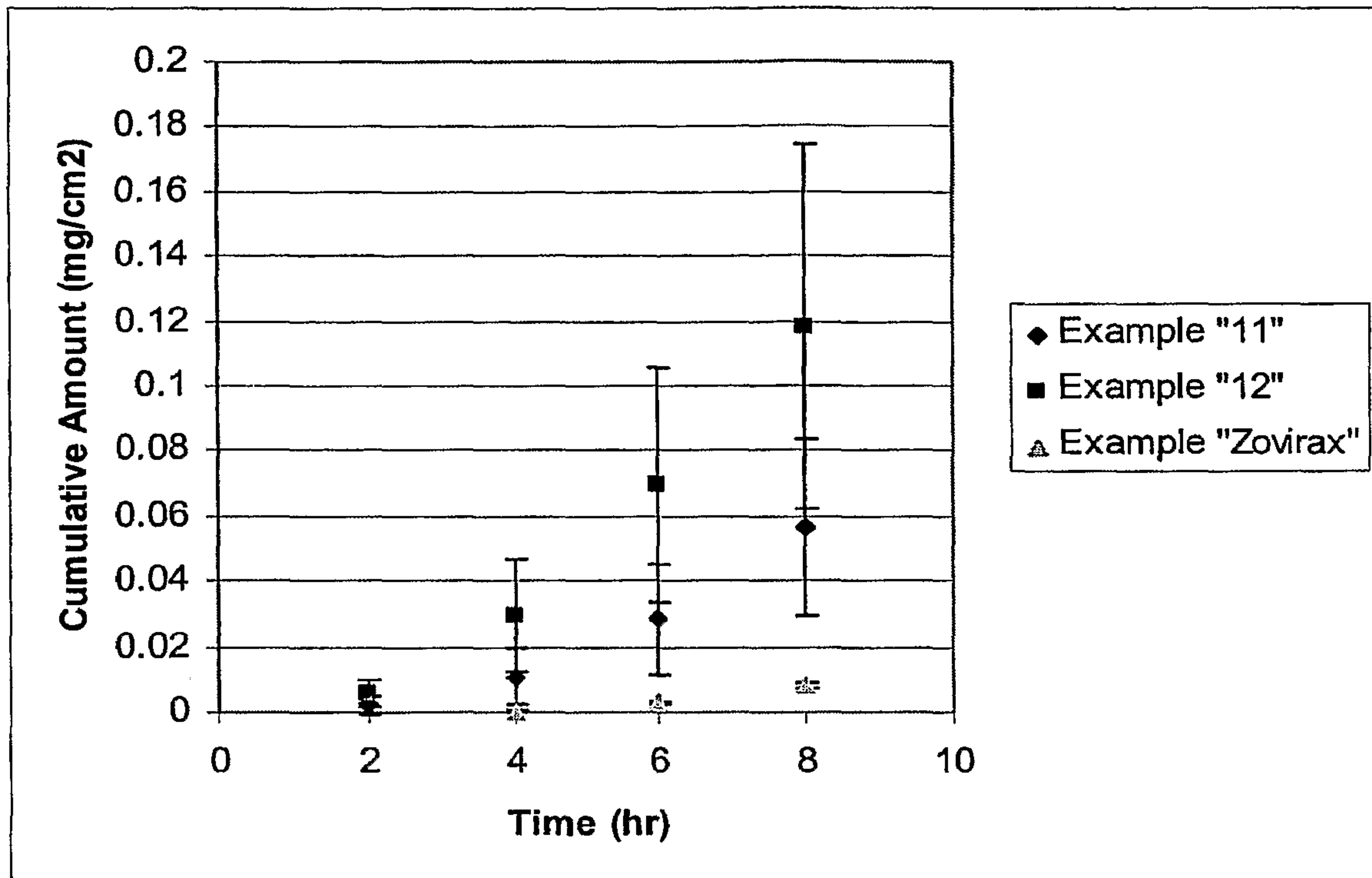


FIG. 4