(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2016 (23.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/100708 A1

(51) International Patent Classification:
A61K 31/4468 (2006.01) *A61K 47/14* (2006.01)
A61K 9/70 (2006.01) *A61P 25/04* (2006.01)

(21) International Application Number:
PCT/US2015/066453

(22) International Filing Date:
17 December 2015 (17.12.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/094,659 19 December 2014 (19.12.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2016/100708 A1

(54) **Title**: TRANSDERMAL DRUG DELIVERY DEVICE INCLUDING FENTANYL

(57) **Abstract**: A transdermal drug delivery device includes a backing and an adhesive composition disposed on the backing. The adhesive composition includes a copolymer having at least 50 percent by weight C_4 to C_{10} alkyl acrylate units, based on the total weight of the copolymer, and one or more second monomer units selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone. The C_4 to C_{10} alkyl acrylate and the one or more second monomer units together make up at least 98 percent by weight of the copolymer. The adhesive composition further includes a skin permeation enhancer in a range from 5 percent to 25 percent by weight, based on the total weight of the adhesion composition, and fentanyl. The adhesive composition is substantially free of undissolved fentanyl. A method of treating a mammal including placing the transdermal drug delivery device on the mammal's skin is also disclosed.

TRANSDERMAL DRUG DELIVERY DEVICE INCLUDING FENTANYL

Cross Reference to Related Application

This application claims priority to U.S. Provisional Application No. 62/094,659, filed December 19, 2014, the disclosure of which is incorporated by reference in its entirety herein.

Background

Transdermal drug delivery devices are designed to deliver a therapeutically effective amount of drug across the skin of a patient. Transdermal drug delivery devices typically involve a carrier (such as a liquid, gel, or solid matrix, or a pressure sensitive adhesive) into which the drug to be delivered is incorporated. Devices known to the art include reservoir type devices involving membranes that control the rate of drug release to the skin and devices where the drug is dispersed or dissolved in a matrix such as a pressure sensitive adhesive.

It has long been known that fentanyl is an extremely potent and effective anesthetic and analgesic. Fentanyl is most frequently administered as the citrate salt intravenously (IV) or intramuscularly (IM) to achieve therapeutic effects. Fentanyl citrate is preferred for injection because of its aqueous solubility. Fentanyl may also be administered as a transdermal patch or as a lozenge. Additional details regarding pharmacokinetics, uses, and dosages of fentanyl may be found in the monograph "Fentanyl Citrate", AHFS 98 Drug Information, ed.: G. K. McEvoy, American Society of Health-Systems Pharmacists, p.1677-1683 (1998).

Following IV or IM administration the onset of action is very rapid but the decrease in serum fentanyl concentration is also rapid, which necessitates dosing at frequent intervals. Minimum effective analgesic serum levels of fentanyl range from 0.2 to 2 ng/mL. Furthermore, oral absorption of fentanyl is low. Lozenges that provide a combination of transmucosal and oral dosage are indicated for treatment of breakthrough cancer pain, but also have a short duration of action.

Transdermal administration of fentanyl can overcome the drawbacks of frequent dosing needed with the aforementioned routes of administration. This can also avoid the peaks and valleys obtained with pulsatile delivery, making it easier to maintain therapeutic doses without causing serious side effects that may result from peak serum levels.

A fentanyl transdermal system described in U. S. Pat. No. 4,588,580 that provides continuous systemic delivery of fentanyl for 72 hours is available under various trade designations including the terms “DURAGESIC” and “DUROGESIC”. The “DURAGESIC” reservoir transdermal fentanyl patch, sold by Johnson & Johnson, has strengths of 12.5, 25, 50, 75, and 100 μg/hr patches, which have a total content of fentanyl of 1.25, 2.5, 5.0, 7.5, and 10.0 mg per patch, respectively. The liquid reservoir contains alcohol, a gelling agent, and fentanyl. Reservoir patches are typically larger, bulkier, and more expensive to make than drug-in-adhesive patches. There is also a potential for leakage from a liquid fentanyl reservoir. Drug-in-adhesive patches having fentanyl in acrylate adhesives have been described in

U.S. Pat. Pub. Nos. 2002/0119187 (Cantor et al.), 2004/0213832 (Venkatraman et al.), 2006/0039960 (Cordes et al.), and 2004/0001882 (Tisa-Bostedt et al.), and Int. App. Pub. No. 2003/097008 (Stefano et al.). The "DURAGESIC" or "DUROGESIC" matrix transdermal fentanyl patch (also branded as DUROGESIC MAT, DUROGESIC D-TRANS, DUROGESIC SMAT), sold by Johnson & Johnson, has strengths of 12.5, 25, 50, 75, and 100 μg/hr patches, which have a total content of fentanyl of 2.1, 4.2, 8.4, 12.6, and 16.8 mg per patch, respectively.

Summary

In one aspect, the present disclosure provides a transdermal drug delivery device including a backing and an adhesive composition disposed on the backing. The adhesive composition includes a copolymer having at least 50 percent by weight C_4 to C_{10} alkyl acrylate units, based on the total weight of the copolymer, and one or more second monomer units selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone. The C_4 to C_{10} alkyl acrylate and the one or more second monomer unit together make up at least 98 percent by weight of the copolymer. The adhesive composition further includes a skin permeation enhancer in a range from 5 percent to 25 percent by weight, based on the total weight of the adhesion composition, and fentanyl. The adhesive composition is substantially free of undissolved fentanyl.

It has been found that the aforementioned transdermal drug delivery device can match, at least on an in vitro basis, the delivery profile and efficiency performance of the "DURAGESIC" or "DUROGESIC" matrix transdermal fentanyl patch.

It has further been found that a transdermal drug delivery device according to the present disclosure having lower drug content (e.g., lower coating weight or lower weight percentage of fentanyl) typically delivers fentanyl more efficiently than patches having a higher drug content. Accordingly, in some embodiments, the fentanyl is present in a range from 3 percent to 7.5 percent by weight, based on the total weight of the adhesive composition, and the adhesive composition is disposed on the backing in a layer having a coating weight in a range from 3 to 6 mg/cm^2. In some embodiments, the fentanyl content in the transdermal drug delivery device is up to 0.5 milligrams per square centimeter, and the transdermal drug delivery device has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl. Thus, the transdermal drug delivery device is capable, in some embodiments, of delivering the same amount of or more fentanyl than certain competitive products having more drug in the patch.

In another aspect, the present disclosure provides a method of treating in a mammal a condition capable of treatment by fentanyl. The method includes placing the transdermal drug delivery device as described in any of the above embodiments on the mammal's skin so that the adhesive composition is in contact with the mammal's skin. The method further includes allowing the adhesive composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of fentanyl in the mammal.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The term “acrylate” encompasses acrylates and methacrylates.

As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

Detailed Description

Several subsaturated drug-in-adhesive (DIA) patch including fentanyl have been introduced. In order to match the extended delivery of the transdermal fentanyl reservoir patch sold by Johnson & Johnson under the trade designation “DURAGESIC”, however, these patches have contained anywhere from 60% to 140% more drug for a given patch strength than the original reservoir patch. Fentanyl is an expensive drug, so it is desirable to minimize the content. In addition, the US FDA has refused to approve generic-equivalent DIA patches having significantly higher content than the reservoir patch sold by Johnson & Johnson under the trade designation “DURAGESIC” due to concerns over potential drug abuse.

A transdermal drug delivery device including an acrylate adhesive composition that typically matches, at least on an in vitro basis, the delivery profile and efficiency performance of the transdermal fentanyl reservoir patch sold by Johnson & Johnson under the trade designation “DURAGESIC” has now been found.

The adhesive composition in the transdermal drug delivery device according to the present disclosure includes a copolymer comprising at least 50 percent by weight of C_4 to C_{10} alkyl acrylate units, based on the total weight of the copolymer. In some embodiments, the adhesive composition includes a copolymer comprising at least 50 percent by weight of C_6 to C_8 alkyl acrylate units, in some embodiments, comprising at least 50 percent by weight C_8 alkyl acrylate units, based on the total weight of the copolymer. The C_4 to C_{10} alkyl acrylate units arise from one or more monomers selected from the group consisting of alkyl acrylates containing 4 to 10, 6 to 8, or 8 carbon atoms in the alkyl group and alkyl methacrylates containing 4 to 10, 6 to 8, or 8 carbon atoms in the alkyl group. Examples of suitable alkyl acrylates and methacrylates include n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isooctyl and 2-ethylhexyl acrylates and methacrylates. In some embodiments, the alkyl acrylate units comprise at least one of isooctyl acrylate, 2-ethylhexyl acrylate, n-butyl acrylate, or

cyclohexyl acrylate units. In some embodiments, the alkyl acrylate units comprise at least one of isooctyl acrylate units or 2-ethylhexyl acrylate units. In some embodiments, the alkyl acrylate units comprise isooctyl acrylate units. In some embodiments, the alkyl acrylate units comprise 2-ethylhexyl acrylate units.

Suitable copolymers for use in the adhesive composition comprise, in some embodiments, about 50 to about 97 percent by weight, in some embodiments, about 60 to about 97 percent by weight, about 50 to about 75 percent by weight, or about 60 to about 75 percent by weight of the C_4 to C_{10} alkyl acrylate units, based on the total weight of all monomer units in the copolymer.

Suitable copolymers for use in the adhesive composition comprise, in some embodiments, about 50 to about 97 percent by weight, in some embodiments, about 60 to about 97 percent by weight, about 50 to about 75 percent by weight, or about 60 to about 75 percent by weight of the C_6 to C_8 alkyl acrylate units, based on the total weight of all monomer units in the copolymer.

Suitable copolymers for use in the adhesive composition comprise, in some embodiments, about 50 to about 97 percent by weight, in some embodiments, about 60 to about 97 percent by weight, about 50 to about 75 percent by weight, or about 60 to about 75 percent by weight of the C_8 alkyl acrylate units, based on the total weight of all monomer units in the copolymer.

The acrylate copolymer further comprises second monomer units, which may be considered reinforcing monomer units by those skilled in the art. Reinforcing monomer units typically provide reinforcement to the adhesive composition to prevent it from splitting and oozing during use. Reinforcing monomers can function by increasing the glass transition temperature of the copolymer, causing intermolecular interactions between individual copolymers, covalently crosslinking the copolymer and/or physically cross-linking the copolymer. Second monomers useful for practicing the present disclosure advantageously increase the glass transition temperature of the copolymer. Suitable second monomer units comprise at least one of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone. In some embodiments, the copolymer comprises at least one of vinyl acetate or acrylamide units. In some embodiments, the copolymer comprises vinyl acetate units.

The C_4 to C_{10} alkyl acrylate units and the second monomer units together make up at least about 98% by weight of the copolymer. In some embodiments, the C_4 to C_{10} alkyl acrylate units and the second monomer units together make up at least about 98.5%, 99%, or 99.5% by weight of the copolymer. Useful individual amounts of the C_4 to C_{10} alkyl acrylate units and the second monomer units vary depending on the selection of the second monomer units.

In some embodiments, the C_6 to C_8 alkyl acrylate units and the second monomer units together make up at least about 98% by weight of the copolymer. In some embodiments, the C_6 to C_8 alkyl acrylate units and the second monomer units together make up at least about 98.5%, 99%, or 99.5% by weight of the copolymer. Useful individual amounts of the C_6 to C_8 alkyl acrylate units and the second monomer units vary depending on the selection of the second monomer units.

In some embodiments, the C_8 alkyl acrylate units and the second monomer units together make up at least about 98% by weight of the copolymer. In some embodiments, the C_8 alkyl acrylate units and the second monomer units together make up at least about 98.5%, 99%, or 99.5% by weight of the copolymer. Useful individual amounts of the C_8 alkyl acrylate units and the second monomer units vary depending on the selection of the second monomer units.

For example, in some embodiments, vinyl acetate can be useful in an amount up to 50% by weight, based on the total weight of the copolymer. In some embodiments, vinyl acetate is present in a range from 5 to 50, 5 to 30, 25 to 50, or 35 to 50 percent by weight, based on the total weight of the copolymer. In some embodiments, the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 50 to 75 percent by weight and vinyl acetate in a range from 25 to 50 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In some embodiments, the copolymer comprises the C_6 to C_8 alkyl acrylate in a range from 50 to 75 percent by weight and vinyl acetate in a range from 25 to 50 percent by weight, wherein each percent by weight is based on the total weight of the copolymer. In some embodiments, vinyl acetate is present in a range from 5 to 50, 5 to 30, 25 to 50, or 35 to 50 percent by weight, based on the total weight of the copolymer of the C_6 to C_8 alkyl acrylate and vinyl acetate. In some embodiments, vinyl acetate is present in an amount up to 50 percent by weight, based on the total weight of the copolymer of the C_6 to C_8 alkyl acrylate and vinyl acetate.

In some embodiments, the copolymer comprises the C_8 alkyl acrylate in a range from 50 to 75 percent by weight and vinyl acetate in a range from 25 to 50 percent by weight, wherein each percent by weight is based on the total weight of the copolymer. In some embodiments, vinyl acetate is present in a range from 5 to 50, 5 to 30, 25 to 50, or 35 to 50 percent by weight, based on the total weight of the copolymer of the C_8 alkyl acrylate and vinyl acetate. In some embodiments, vinyl acetate is present in an amount up to 50 percent by weight, based on the total weight of the copolymer of the C_8 alkyl acrylate and vinyl acetate.

Acrylamide and N-vinyl-2-pyrrolidone tend to stiffen the copolymer more than vinyl acetate. According, a lower amount of these reinforcing monomer units is typically useful. In some embodiments, at least one of N-vinyl-2-pyrrolidone or acrylamide is present in a range from 3 to 10, 5 to 10, or 4 to 8 percent by weight, based on the total weight of the copolymer. If at least one of N-vinyl-2-pyrrolidone or acrylamide is present in less than 3 percent by weight as the only second monomer unit, the amount is typically not enough to prevent the adhesive composition from splitting and oozing during use. If at least one of N-vinyl-2-pyrrolidone or acrylamide is present in more than 10 percent by weight, the adhesive composition is typically too stiff.

Methyl acrylate and ethyl acrylate also tend to stiffen the copolymer more than vinyl acetate. In some embodiments, at least one of ethyl acrylate or methyl acrylate is present in a range from 5 to 25, 5 to 20, 5 to 15, or 10 to 20 percent by weight, based on the total weight of the copolymer.

In some embodiments, the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 60 to 97 percent by weight, at least one of acrylamide or N-vinyl-2-pyrrolidone in a range from 3 to 10 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer. In some embodiments, the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 50 to 95 percent by weight, at least one of methyl acrylate or ethyl acrylate in a range from 5 to 20 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In some embodiments, the copolymer comprises the C_6 to C_8 alkyl acrylate in a range from 60 to 97 percent by weight, at least one of acrylamide or N-vinyl-2-pyrrolidone in a range from 3 to 10 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer. In some embodiments, the copolymer comprises the C_6 to C_8 alkyl acrylate in a range from 50 to 95 percent by weight, at least one of methyl acrylate or ethyl acrylate in a range from 5 to 20 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In some embodiments, the copolymer comprises the C_8 alkyl acrylate in a range from 60 to 97 percent by weight, at least one of acrylamide or N-vinyl-2-pyrrolidone in a range from 3 to 10 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer. In some embodiments, the copolymer comprises the C_8 alkyl acrylate in a range from 50 to 95 percent by weight, at least one of methyl acrylate or ethyl acrylate in a range from 5 to 20 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In some embodiments, the copolymer includes less than 2 (in some embodiments, less than 1) percent by weight of hydroxyl-substituted monomer units (e.g., hydroxyethyl acrylate).

Useful copolymer compositions may optionally further comprise a substantially linear macromonomer copolymerizable with the C_4 to C_{10} alkyl acrylate and reinforcing monomers and having a weight average molecular weight in the range of about 500 to about 500,000, about 2,000 to about 100,000, or about 4,000 to about 20,000 grams per mole. The macromonomer, when used, is generally present in an amount of not more than about 20% and preferably not more than about 10% by weight based on the total weight of all monomers in the copolymer. Suitable macromonomers include functionally terminated polymethylmethacrylate, styrene/acrylonitrile, polyether, and polystyrene macromonomers. Examples of useful macromonomers and their preparation are described in U.S. Patent No. 4,693,776 (Krampe et al.), the disclosure of which is incorporated herein by reference. In some embodiments, the macromonomer is a polymethylmethacrylate macromonomers.

The copolymers described above can be prepared by any suitable method, for example, that described in U.S. Patent No. RE 24,906 (Ulrich), U.S. Patent No. 4,732,808 (Krampe), and/or U.S. Patent No. 7,097,853 (Garbe), the disclosures of which are incorporated herein by reference.

The inherent viscosity of the copolymer is such as to ultimately provide a suitable pressure sensitive adhesive when used in a device according to the present disclosure. In some embodiments, the copolymer has an inherent viscosity in the range of about 0.2 dL/g to about 2.0 dL/g or about 0.3 dL/g to about 1.4 dL/g. Inherent viscosity may be measured as described in U.S. Patent No. 7,097,853 (Garbe).

Fentanyl is present in the adhesive composition in an amount between about 3% and about 7.5% by weight, based on the total weight of the adhesive composition. In some embodiments, fentanyl is present in the adhesive composition in an amount between about 3% and about 7% by weight, 4% to 7.5% by weight, or 5% to 7% by weight, based on the total weight of the composition. The adhesive composition is substantially free of undissolved fentanyl. The fentanyl is typically completely dissolved in the adhesive composition. The presence of undissolved fentanyl may be detected by examination with an optical microscope at 20x magnification. Having undissolved fentanyl in the adhesive composition may lead to physical instability of the adhesive composition over time and therefore is typically undesirable. The particular amount of fentanyl in the composition that will deliver sufficient fentanyl to achieve a desired therapeutic result varies according to the condition being treated, any drugs being coadministered with the fentanyl, desired duration of treatment, the surface area and location of the skin over which the device is to be placed, and the selection of adjuvant and other components of the transdermal delivery device.

If desired, the adhesive composition can contain components that modify the properties of the copolymer, such as plasticizers or tackifiers, in amounts readily determinable to those of skill in the art.

An adhesive composition useful in the drug delivery device according to the present disclosure includes a skin permeation enhancer. A variety of skin permeation enhancers may be useful. Examples of suitable skin permeation enhancers include materials include C_8-C_{36} fatty alcohols such as oleyl alcohol and lauryl alcohol; lower alkyl esters of C_8-C_{36} fatty acids such as ethyl oleate, isopropyl myristate, butyl stearate, and methyl laurate; tetraglycol (tetrahydrofurfuryl alcohol polyethylene glycol ether); and propylene glycol; and combinations of any of these. In some embodiments, the skin permeation enhancer comprises at least one of isopropyl myristate, tetraglycol, methyl laurate, propylene glycol, propylene glycol monolaurate, ethyl oleate, isopropyl myristate, 2-octyl-1-dodecanol, lauryl lactate, lauryl alcohol, and combinations of any of these. In some embodiments, the skin permeation enhancer is methyl laurate.

In an adhesive composition useful in the drug delivery device according to the present disclosure, the skin permeation enhancer(s) is either dispersed, typically substantially uniformly, or dissolved in the adhesive composition and is present in an amount that enhances fentanyl permeation through the skin compared to a like composition not containing a skin permeation enhancer when this phenomenon is measured using the skin permeation model described below. The amount of the skin permeation enhancer also typically affects the physical properties in a transdermal drug delivery device. For example, it is desirable to have sufficiently little cold flow that a device of the invention is stable to flow upon storage. It is also desirable that it adhere well to the skin and release cleanly from the skin. In order to achieve

resistance to cold flow, skin adhesion and clean release, the amount and structure of the comonomers in the copolymer, the inherent viscosity of the copolymer, and the amount and type of adjuvant are selected such that the adhesive layer(s) obtain the desired balance of these properties.

The total amount of skin permeation enhancer will generally be about 5% to about 25% by weight based on the total weight of the adhesive composition. If the skin permeation enhancer is present in less than 5% by weight, it may not be effective for enhancing fentanyl permeation through the skin. If the skin permeation enhancer is present in greater than 25% by weight, the adhesive composition may be too soft and leave residue on the skin. In some embodiments, the adhesive composition comprises the skin permeation enhancer in a range from 10% to 23%, 10% to 20%, 13% to 20%, or 15% to 20% by weight, based on the total weight of the adhesive composition.

In some embodiments, the adhesive composition will have a shear creep compliance (as determined by the test method below) of between about 1.0×10^{-5} and 5.0×10^{-5} cm^2/dyne. Adhesive compositions in this range have good conformance and adhesion to skin, while not being so soft as to leave excessive residue on the skin. In some embodiments, the shear creep compliance will be between 1.0×10^{-5} and 4.0×10^{-5} cm^2/dyne, 1.5×10^{-5} and 4.0×10^{-5} cm^2/dyne, or 1.5×10^{-5} and 3.0×10^{-5} cm^2/dyne.

In some embodiments, the transdermal drug delivery device is bioequivalent to a transdermal fentanyl reservoir patch obtained from Johnson & Johnson under the trade designation "DURAGESIC". That is, the drug delivery device according to the present disclosure has a delivery profile that generally matches that of the transdermal fentanyl reservoir patch obtained from Johnson & Johnson under the trade designation "DURAGESIC". In addition, in some embodiments the transdermal drug delivery device has an efficiency performance that generally matches that of the transdermal fentanyl reservoir patch obtained from Johnson & Johnson under the trade designation "DURAGESIC".

In some embodiments, the transdermal drug delivery device is bioequivalent to a transdermal fentanyl matrix patch obtained from Johnson & Johnson under the trade designation "DURAGESIC". That is, the drug delivery device according to the present disclosure has a delivery profile that generally matches that of the transdermal fentanyl reservoir patch obtained from Johnson & Johnson under the trade designation "DURAGESIC".

Comparison of delivery profile and efficiency performance may be made using two key in vitro parameters: 1) a 'shape' factor that describes the delivery profile and 2) a normalized cumulative flux that describes total flux for a given amount of drug.

The shape factor "S" is described by formula:

S=(72 hours*peak flux)/cumulative flux in a 72-hour period,

where 72 hours*peak flux is a peak flux during a 72-hour permeation study and is measured in units of micrograms per square centimeter per hour and cumulative flux is measured over the entire 72-hour time period in units of micrograms per square centimeter. If peak flux was maintained during the entire 72-hour period, then the shape factor would be 1.0. Otherwise, the shape factor will be greater than 1, since

72*(peak flux) will be greater than the cumulative flux over the 72-hour period. It is desirable that the shape factor for the drug delivery device according to the present disclosure be similar to the shape factor for the "DURAGESIC" patch (either reservoir or matrix). This similarity in shape is important, since a bioequivalence study needs to match (within an 80 to 125% confidence interval) both the C_{max} (maximum plasma level) and AUC (area under the plasma curve) of the product being compared to. Although C_{max} and AUC can generally be adjusted directly by adjusting patch size, they will change in concert with each other. If the delivery shape is either too peaked or too flat, then it becomes more difficult to simultaneously match both C_{max} and AUC. The shape factor for "DURAGESIC" reservoir was measured as 1.81, by taking averages of flux data from several permeability studies on a number of different lots of cadaver skin according the method described in the Examples, below. Thus, in some embodiments, the shape factor is in a range from 1.3 to 2.2, 1.4 to 1.9, 1.5 to 1.9, or 1.6 to 1.8. To some degree the shape factor is influenced by the relative permeability of the skin, since this will affect how quickly the patch is depleted of drug. Thus the absolute values of shape factors should generally be compared to control samples (e.g., "DURAGESIC" reservoir) tested on the same lot(s) of skin.

The normalized cumulative flux is the cumulative flux per mg fentanyl (or alternatively, per 2.5 mg fentanyl, which corresponds to the content in the 25 μg/hr "DURAGESIC" reservoir patch). If the normalized cumulative flux of the drug delivery device according to the present disclosure is greater than the normalized cumulative flux of the "DURAGESIC" reservoir patch, then the experimental patch can be expected to deliver as much or more fentanyl from a patch with equivalent total content to "DURAGESIC" reservoir patch. Other bioequivalent commercial acrylate patches have a considerably lower normalized cumulative flux than that of the "DURAGESIC" reservoir patch. That is, they need an excess of drug when compared to the "DURAGESIC" reservoir patch to match bioequivalent delivery. The normalized cumulative flux of the "DURAGESIC" reservoir patch was found to be 1681 μg/(2.5 mg fentanyl), by taking averages of flux data from several permeability studies on a number of different lots of cadaver skin according to the test method described in the Examples, below. Accordingly, the normalized cumulative flux of the "DURAGESIC" reservoir patch was found to be 672 μg/(mg fentanyl). Thus, in some embodiments, a transdermal drug delivery device according to the present disclosure has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl, in some embodiments, at least 610, 620, 650, or 675 micrograms per milligram of fentanyl.

The higher normal cumulative flux for the transdermal drug delivery device according to the present disclosure provides evidence of its efficiency. The transdermal drug delivery device according to the present disclosure can deliver the same or higher amount of fentanyl through the skin as a commercially available patch using less fentanyl in the drug delivery device. In some embodiments, the fentanyl content in the transdermal drug delivery device is up to 0.5, 0.45, 0.4, 0.35, or 0.3 milligrams per square centimeter. In some embodiments, the high efficiency can be unexpectedly achieved by lowering the coating weight of the adhesive composition on the backing. In some embodiments, the adhesive composition is disposed on the backing in a layer having a coating weight in a range from 3 mg/cm^2 to 6

mg/cm^2, 3 mg/cm^2 to 5.5 mg/cm^2, or 4 mg/cm^2 to 6 mg/cm^2. The coating weight is the weight of adhesive per unit area. It can be determined by weighing the drug delivery device or a fixed area thereof, which includes the adhesive composition, and subtracting the weight of the backing.

The transdermal delivery devices according to the present disclosure can be made in any useful form. For example, the drug delivery device can be made in the form of a tape, a patch, a sheet, or a dressing. Generally, the device will be in the form of a patch of a size suitable to deliver a preselected amount of fentanyl through the skin. In some embodiments, a 12 μg/hr strength device will have a surface area of about 3 cm^2 to about 6 cm^2 for a patch. In some embodiments, a 25 μg/hr strength device will have a surface area of about 6 cm^2 to about 15 cm^2 for a patch, in some embodiments, about 6 cm^2 to about 10 cm^2. In some embodiments, a 50 μg/hr strength device will have a surface area of about 12 cm^2 to about 30 cm^2 for a patch, in some embodiments, about 12 cm^2 to about 20 cm^2. In some embodiments, a 75 μg/hr strength device will have a surface area of about 18 cm^2 to about 45 cm^2 for a patch, in some embodiments, about 18 cm^2 to about 30 cm^2. In some embodiments, a 100 μg/hr strength device will have a surface area of about 24 cm^2 to about 60 cm^2 for a patch, in some embodiments, about 24 cm^2 to about 40 cm^2. The transdermal drug delivery device according to the present disclosure can have a total content of fentanyl selected from the group consisting of about 1.25 milligrams, about 2.5 milligrams, about 5 milligrams, about 7.5 milligrams, and about 10 milligrams, for example.

A transdermal drug delivery device according to the present disclosure also comprises a backing. The backing is typically flexible such that the device conforms to the skin. The backing may be breathable or occlusive and may comprise at least one of fabric, polymer films, coated paper products, and aluminum films. In some embodiments, the backing is an occlusive backing. Suitable backing materials include conventional flexible backing materials used for pressure sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, metallocene polyethylenes, high density polyethylene, polypropylene, polyesters such as polyethylene terephthalate, randomly oriented nylon fibers, ethylene-vinyl acetate copolymer, polyurethane, natural fibers such as rayon and the like. Backings that are multi-layered such as polyethylene terephthalate-aluminum-polyethylene composites are also suitable. The backing is typically substantially inert to the components of the adhesive layer.

Transdermal devices according to the present disclosure may be prepared by combining the copolymer, the skin permeation enhancer, and the fentanyl with an organic solvent (e.g., ethyl acetate, isopropanol, methanol, acetone, 2-butanone, ethanol, toluene, alkanes, and mixtures thereof) to provide a coating composition. The mixture can be shaken or stirred until a homogeneous coating composition is obtained. The resulting composition may then be applied to a release liner using conventional coating methods (e.g., knife coating or extrusion die coating) to provide a predetermined uniform thickness of coating composition. Suitable release liners include conventional release liners comprising a known sheet material such as a polyester web, a polyethylene web, a polystyrene web, or a polyethylene-coated paper

coated with a suitable fluoropolymer or silicone based coating. The release liner that has been coated with the composition may then be dried and laminated onto a backing using conventional methods.

A transdermal drug delivery composition of the disclosure can be used to induce an analgesic effect. The present disclosure provides a method of treating in a mammal a condition capable of treatment by fentanyl. The method includes placing the transdermal drug delivery device as described in any of the above embodiments on the mammal's skin so that the adhesive composition is in contact with the mammal's skin. The method further includes allowing the adhesive composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of fentanyl in the mammal, for example, to maintain the intended analgesic effect. The time that constitutes a sufficient time can be selected by those skilled in the art with consideration of the flux rate provided by of the device of the invention and of the condition being treated.

The amount of fentanyl that needs to be delivered and the serum concentrations that are necessary to be therapeutically effective show considerable variation between individuals. A tolerance to fentanyl generally develops with continued use, typically necessitating the need for increased dosages over time of treatment. Because of this inter- and intra- patient variation, a wide range of therapeutically effective fentanyl serum concentrations have been reported. Further details may be found in the monographs "Fentanyl Citrate", AHFS 98 Drug Information, ed.: G. K. McEvoy, American Society of Health-Systems Pharmacists, p.1677-1683 (1998) and "Fentanyl: A Review for Clinical and Analytical Toxicologists", A. Poklis, Clinical Toxicology, 33(5), 439-447 (1995).

Some Embodiments of the Invention:

In a first embodiment, the present disclosure provides a transdermal drug delivery device, comprising

a backing; and

an adhesive composition disposed on the backing, the adhesive composition comprising:
a copolymer comprising at least 50 percent by weight C_4 to C_{10} alkyl acrylate units, based on the total weight of the copolymer and one or more second monomer units selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone, wherein the C_4 to C_{10} alkyl acrylate and the one or more second monomer units together make up at least 98 percent by weight of the copolymer;

a skin permeation enhancer in a range from 5 percent to 25 percent by weight, based on the total weight of the adhesion composition; and

fentanyl in a range from 3 percent to 7.5 percent by weight, based on the total weight of the adhesive composition, wherein the adhesive composition is substantially free of undissolved fentanyl.

In a second embodiment, the present disclosure provides the transdermal drug delivery device of the first embodiment, wherein the C_4 to C_{10} alkyl acrylate units have from 6 to 8 carbon atoms.

In a third embodiment, the present disclosure provides the transdermal drug delivery device of the first or second embodiment, wherein the at least one second monomer unit is selected from the group consisting of vinyl acetate, acrylamide, and N-vinyl-2-pyrrolidone.

In a fourth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to third embodiments, the at least one second monomer unit is selected from the group consisting of vinyl acetate and acrylamide.

In a fifth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to fourth embodiments, wherein the adhesive composition is disposed on the backing in a layer having a coating weight in a range from 3 to 6 mg/cm^2.

In a sixth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to fifth embodiments, wherein the transdermal drug delivery device has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl.

In a seventh embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to sixth embodiments, wherein the fentanyl content in the transdermal drug delivery device is up to 0.5 milligrams per square centimeter.

In an eighth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to seventh embodiments, wherein the fentanyl content in the transdermal drug delivery device is up to 0.3 milligrams per square centimeter.

In a ninth embodiment, the present disclosure provides a transdermal drug delivery device, comprising

a backing; and

an adhesive composition disposed on the backing, the adhesive composition comprising:
a copolymer comprising at least 50 percent by weight C_4 to C_{10} alkyl acrylate based on the total weight of the copolymer and one or more second monomer units selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone, wherein alkyl acrylate and the one or more second monomer units together make up at least 98 percent by weight of the copolymer;

a skin permeation enhancer in a range from 5 to 25 percent by weight, based on the total weight of the adhesion composition; and

fentanyl,

wherein the fentanyl content in the transdermal drug delivery device is up to 0.5 milligrams per square centimeter, wherein the adhesive composition is substantially free of undissolved fentanyl, and wherein the transdermal drug delivery device has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl.

In a tenth embodiment, the present disclosure provides the transdermal drug delivery device of the ninth embodiment, wherein the adhesive composition comprises fentanyl in a range from 3 percent to 7.5 percent by weight, based on the total weight of the adhesive composition.

In an eleventh embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to tenth embodiments, further comprising a shape factor in a range from 1.4 to 1.9, wherein the shape factor is described by formula:

(72 hours*peak flux)/cumulative flux in a 72-hour period,

wherein the 72 hours*peak flux is a peak flux in the 72-hour period measured in units of micrograms per square centimeter per hour, and wherein cumulative flux in the 72-hour period is measured in units of micrograms per square centimeter.

In a twelfth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to eleventh embodiments, further comprising a total content of fentanyl selected from the group consisting of about 1.25 milligrams, about 2.5 milligrams, about 5 milligrams, about 7.5 milligrams, and about 10 milligrams.

In an thirteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to twelfth embodiments, wherein the transdermal drug delivery device is bioequivalent to a transdermal fentanyl matrix patch obtained from Johnson & Johnson under the trade designation "DURAGESIC" or “DUROGESIC”.

In a fourteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to thirteenth embodiments, wherein the copolymer comprises at least two of the second monomer units, and wherein the C_4 to C_{10} alkyl acrylate and the at least two of the second monomer units together make up at least 98 percent by weight of the copolymer.

In a fifteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to fourteenth embodiments, wherein the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 60 to 97 percent by weight, at least one of acrylamide or N-vinyl-2-pyrrolidone in a range from 3 to 10 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In a sixteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to fourteenth embodiments, wherein the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 50 to 95 percent by weight, at least one of methyl acrylate or ethyl acrylate in a range from 5 to 20 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In a seventeenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to thirteenth embodiments, wherein the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 50 to 75 percent by weight and vinyl acetate in a range from 25 to 50 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

In an eighteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to seventeenth embodiments, wherein the C_4 to C_{10} alkyl acrylate is isooctyl acrylate, 2-ethylhexyl acrylate, or a combination thereof.

In a nineteenth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to eighteenth embodiments, wherein the adhesive composition comprises skin permeation enhancer in a range from 13 to 20 percent by weight, based on the total weight of the adhesive composition.

In a twentieth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to eighteenth embodiments, wherein the adhesive composition comprises skin permeation enhancer in a range from 15 to 20 percent by weight, based on the total weight of the adhesive composition.

In a twenty-first embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to twentieth embodiments, wherein the skin permeation enhancer comprises at least one of isopropyl myristate, tetraglycol, methyl laurate, propylene glycol, propylene glycol monolaurate, ethyl oleate, 2-octyl-1-dodecanol, lauryl lactate, or lauryl alcohol.

In a twenty-second embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to twenty-first embodiments, wherein the skin permeation enhancer comprises at least one of isopropyl myristate, methyl laurate, propylene glycol, propylene glycol monolaurate, ethyl oleate, 2-octyl-1-dodecanol, or lauryl lactate.

In a twenty-third embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to twenty-second embodiments, wherein the skin permeation enhancer comprises methyl laurate.

In a twenty-fourth embodiment, the present disclosure provides the transdermal drug delivery device of any one of the first to twenty-third embodiments, wherein the backing is an occlusive backing.

In a twenty-fifth embodiment, the present disclosure provides a method of treating in a mammal a condition capable of treatment by fentanyl, the method comprising:

placing the transdermal drug delivery device of any one of the first to twenty-fourth embodiments on the mammal's skin so that the adhesive composition is in contact with the mammal's skin; and

allowing the adhesive composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of fentanyl in the mammal.

In a twenty-sixth embodiment, the present disclosure provides a transdermal device of the first embodiment wherein the fentanyl concentration is about 6 percent by weight, the skin permeation enhancer is methyl laurate in a concentration of about 16.5%, and the coating weight is about 4.5 mg/cm^2.

Embodiments of this invention are further illustrated by the following non-limiting examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

Fentanyl (0.8400 g) and a 40:60 blend of methanol/ethyl acetate (0.4766 g) were added together and mixed until all of the fentanyl was dissolved to form a fentanyl solution. Methyl laurate (2.6549) and solvated copolymer (28.2867 g of isooctyl acrylate/acrylamide 93:7 copolymer, 31.2% solids, in ethyl acetate/methanol 91:9) were added to the fentanyl solution and mixed until a uniform coating formulation was obtained. The coating formulation was knife coated at a wet thickness of 230 micrometers (μm) onto a release liner (SCOTCHPAK™ 9742 fluoropolymer coated release liner; available from 3M Company). The coated liner was oven dried for 2 minutes at 43°C followed by 4 minutes at 63°C. The coated liner was laminated onto a backing (SCOTCHPAK™ 9732 polyester film laminate; available from 3M Company) to form a bulk transdermal patch laminate. The nominal fentanyl and methyl laurate concentrations of the dried coating were 7.0% and 20.0%, respectively. The dried adhesive matrix coating weight was 5.5 mg/cm^2. Appropriately sized transdermal patches were punched from the bulk laminate for subsequent testing. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 1. Adhesive compliance was determined using the test method described below and the results are reported in Table 1.

Examples 2 to 12

Formulations were prepared as in Example 1 with the exception that the nominal fentanyl and methyl laurate concentrations and the nominal dried adhesive matrix coating weight were varied as shown in Table 1. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 1. Adhesive compliance (where measured) was determined using the test method described below and the results are reported in Table 1.

Examples 13 -14

Formulations were prepared as in Examples 11 and 12 with the exception that the solvated copolymer was isooctyl acrylate/acrylamide/vinyl acetate 75:5:20 copolymer, 24.0% solids, in ethyl acetate/methanol 90:10- note: confirm this ratio with JPD). The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 1. Adhesive compliance was determined using the test method described below and the results are reported in Table 1.

Example 15

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained light mineral oil NF as a replacement for methyl laurate. The nominal fentanyl and light mineral oil NF concentrations of the dried coating were 7.0% and 10.0%, respectively.

The dried adhesive matrix coating weight was 4.6 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 16

A formulation was prepared according to the general procedure of Example 15 with the exception that the nominal fentanyl and light mineral oil NF concentrations of the dried coating were 7.0% and 20.0%, respectively. The dried adhesive matrix coating weight was 5.2 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 17

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained lauryl lactate as a replacement for methyl laurate. The nominal fentanyl and lauryl lactate concentrations of the dried coating were 7.0% and 20.0%, respectively. The dried adhesive matrix coating weight was 5.6 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 18

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of light mineral oil NF and lauryl lactate as a replacement for methyl laurate. The nominal fentanyl, light mineral oil NF and lauryl lactate concentrations of the dried coating were 7.0%, 10.0% and 10.0%, respectively. The dried adhesive matrix coating weight was 5.3 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 19

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation also contained light mineral oil NF in addition to methyl laurate. The nominal fentanyl, light mineral oil NF and methyl laurate concentrations of the dried coating were 7.0%, 10.0% and 10.0%, respectively. The dried adhesive matrix coating weight was 4.8 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 20

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation also contained lauryl lactate in addition to methyl laurate. The nominal fentanyl, lauryl lactate and methyl laurate concentrations of the dried coating were 7.0%, 10.0% and 10.0%,

respectively. The dried adhesive matrix coating weight was 5.1 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 21

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation also contained 2-octyl-1-dodecanol in addition to methyl laurate. The nominal fentanyl, 2-octyl-1-dodecanol and methyl laurate concentrations of the dried coating were 6.6%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 5.1 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 22

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of ethyl oleate and propylene glycol as a replacement for methyl laurate. The nominal fentanyl, ethyl oleate and propylene glycol concentrations of the dried coating were 6.3%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 4.2 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 23

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of ethyl oleate and light mineral oil NF as a replacement for methyl laurate. The nominal fentanyl, ethyl oleate and light mineral oil NF concentrations of the dried coating were 4.7%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 4.3 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 24

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of ethyl oleate and isopropyl myristate as a replacement for methyl laurate. The nominal fentanyl, ethyl oleate and isopropyl myristate concentrations of the dried coating were 5.3%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 4.6 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 25

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of propylene glycol monolaurate and light mineral oil NF as a replacement for methyl laurate. The nominal fentanyl, propylene glycol monolaurate and light mineral oil NF concentrations of the dried coating were 7.0%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 4.6 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

Example 26

A formulation was prepared according to the general procedure of Example 1 with the exception that the formulation contained a combination of 2-octyl-1-dodecanol and light mineral oil NF as a replacement for methyl laurate. The nominal fentanyl, 2-octyl-1-dodecanol and light mineral oil NF concentrations of the dried coating were 5.4%, 12.0% and 12.0%, respectively. The dried adhesive matrix coating weight was 4.7 mg/cm^2. The permeation through human cadaver skin was determined using the test method described below and the results are reported in Table 2.

In Vitro Skin Permeation Test Method

The skin permeation data given in the examples above was obtained using the following test method. The release liner was removed from a 1.0 cm^2 patch and the patch was applied to human cadaver skin and pressed to cause uniform contact with the skin. The resulting patch/skin laminate was placed patch side up across the orifice of the lower portion of a vertical diffusion cell. The diffusion cell was assembled and the lower portion filled with 5 mL of warm (32°C) receptor fluid (0.1 M phosphate buffer, pH 6.5) so that the receptor fluid contacted the skin. The sampling port was covered except when in use.

The cells were maintained at 32 ± 2°C throughout the course of the experiment. The receptor fluid was stirred by means of a magnetic stirrer throughout the experiment to assure a uniform sample and a reduced diffusion barrier on the dermal side of the skin. The entire volume of receptor fluid was withdrawn at specified time intervals and immediately replaced with fresh fluid. The withdrawn fluid was filtered through a 0.45 μm filter. Approximately 1 to 2 mL were then analyzed for fentanyl using conventional high performance liquid chromatography methods (Column: 80A Extend C18 4.6mm x 75mm, 3.5μm particle size; Mobile phase: 35/65 25mM ammonium hydroxide/acrylonitrile. Flow Rate: 1.5 mL/min; Detector: UV at 210 nm; Injection Volume: 25 μL; Run time: 3.0 minutes). The cumulative amount of fentanyl penetrating through the skin at each time interval was calculated and reported as μg/cm^2. A "normalized" cumulative flux, CFnorm, was determined by calculating the cumulative flux at 72 hours that would be achieved from a patch sized so as to have a content of 2.5 mg of fentanyl (CFnorm = (Cum. flux at 72 hrs in μg/cm^2)*(2.5 mg)/(Content in mg/cm^2)). A shape factor, S, was determined as follows: S = (72 * Peak flux)/(Cum. flux at 72 hours). The shape factor, S, is

indicative of how much higher the peak flux is as compared to the average flux over the entire time period.

Adhesive Compliance Test Method

The release liner is removed from a sample of the material to be tested. The exposed adhesive surface is folded back on itself in the lengthwise direction to produce a "sandwich" configuration, i.e., backing/adhesive/backing. The "sandwiched" sample is passed through a laminator, or alternatively rolled with a hand-operated roller, then two 5 cm^2 test samples are cut using a circular die. One test sample is centered on a first stationary plate of a parallel plate shear-creep rheometer. The small, non-stationary plate of the shear-creep rheometer is centered over the first sample on the first stationary plate such that the string attaching the weight (500 g) is toward the front of the rheometer. The second test sample is centered on the upper surface of the small, non-stationary plate. A second stationary plate is placed over the second test sample and the entire assembly is clamped into place to prevent slippage of the stationary plates. The plates are placed in a horizontal configuration. The end of the small, non-stationary plate that is opposite the end with the string and weight is monitored by a displacement measurement mechanism. The string is extended over the front pulley of the rheometer, but the weight is initially supported so that it does not exert force on the non-stationary plate. The support for the weight is removed so that the weight hangs free and the displacement of the non-stationary plate is measured for 3 minutes. The displacement at 3 minutes is used to calculate compliance, J, using the equation:

$J = 2*A*X/(h*f)$

where A is the area of one face of the test sample, h is the thickness of the adhesive mass (i.e., two times the matrix thickness of the sample being tested), X is the displacement and f is the force due to the mass attached to the string. All testing is performed at 22 °C ± 1 °C.

Table 1.

Ex.	Fentanyl Wt. %	Methyl laurate Wt. %	Coating Weight (mg/cm^2)	Cum Flux 12 hrs (ug/cm^2)	Cum Flux 24 hrs (ug/cm^2)	Cum Flux 48 hrs (ug/cm^2)	Cum Flux 72 hrs (ug/cm^2)	CFnorm	S	Compliance [x 10^{-5} cm^2/dyne]
1	7	20	5.5	53	118	201	251	1631	1.54	3.04
2	7	10	3.5	33	72	110	140	1423	1.64	
3	7	10	5.5	32	87	155	204	1326	1.53	
4	7	15	3.5	54	109	167	199	2029	1.75	
5	7	15	5.5	48	119	201	253	1643	1.67	
6	7	20	3.5	63	118	175	205	2092	1.96	
7	7	25	3.5	61	119	171	195	1986	2.05	
8	7	25	5.5	57	119	197	243	1580	1.6	4.51
9	7.4	10	5.5	30	64	129	178	1094	1.27	
10	7.4	20	5.5	33	76	154	211	1295	1.31	
11	6	15	4.5	47	87	138	166	1537	1.9	1.43
12	6	20	4.5	43	86	144	176	1626	1.78	2.81
13	6	15	4.5	44	80	131	164	1519	2.05	2.11
14	6	20	4.5	29	54	96	129	1194	1.76	3.03

Table 2.

Ex.	Cum Flux 12 hrs (ug/cm^2)	Cum Flux 24 hrs (ug/cm^2)	Cum Flux 48 hrs (ug/cm^2)	Cum Flux 72 hrs (ug/cm^2)	CFnorm	S
15	28	68	122	155	1215	1.55
16	33	90	178	238	1635	1.42
17	38	90	162	206	1326	1.49
18	25	68	139	192	1285	1.33
19	33	88	172	229	1697	1.44
20	39	90	167	219	1545	1.51
21	39	70	115	144	1282	1.93
22	40	70	111	138	1331	2.04
23	34	58	94	116	1428	1.88
24	34	63	107	133	1367	1.79
25	45	83	140	175	1364	1.76
26	26	47	82	106	1041	1.69

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

What is claimed is:

1. A transdermal drug delivery device, comprising

a backing; and

an adhesive composition disposed on the backing, the adhesive composition comprising:

a copolymer comprising at least 50 percent by weight C_4 to C_{10} alkyl acrylate units, based on the total weight of the copolymer and one or more second monomer units selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone, wherein the C_4 to C_{10} alkyl acrylate and the one or more second monomer units together make up at least 98 percent by weight of the copolymer;

a skin permeation enhancer in a range from 5 percent to 25 percent by weight, based on the total weight of the adhesion composition; and

fentanyl in a range from 3 percent to 7.5 percent by weight, based on the total weight of the adhesive composition,

wherein the adhesive composition is substantially free of undissolved fentanyl, and wherein the adhesive composition is disposed on the backing in a layer having a coating weight in a range from 3 to 6 mg/cm^2.

2. The transdermal drug delivery device of claim 1, wherein the fentanyl content in the transdermal drug delivery device is up to 0.3 milligrams per square centimeter.

3. The transdermal drug delivery device of claim 1 or 2, wherein the transdermal drug delivery device has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl.

4. A transdermal drug delivery device, comprising

a backing; and

an adhesive composition disposed on the backing, the adhesive composition comprising:

a copolymer comprising at least 50 percent by weight C_4 to C_{10} alkyl acrylate based on the total weight of the copolymer and one or more second monomer unit selected from the group consisting of vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, and N-vinyl-2-pyrrolidone, wherein alkyl acrylate and the one or more second monomer unit together make up at least 98 percent by weight of the copolymer;

a skin permeation enhancer in a range from 5 to 25 percent by weight, based on the total weight of the adhesion composition; and

fentanyl,

wherein the fentanyl content in the transdermal drug delivery device is up to 0.5 milligrams per square centimeter, wherein the adhesive composition is substantially free of undissolved fentanyl, and wherein the transdermal drug delivery device has a normalized cumulative flux after 72 hours of at least 600 micrograms per milligram of fentanyl.

5. The transdermal drug delivery device of claim 4, wherein the adhesive composition comprises fentanyl in a range from 3 percent to 7.5 percent by weight, based on the total weight of the adhesive composition.

6. The transdermal drug delivery device of any preceding claim, further comprising a shape factor in a range from 1.4 to 1.9, wherein the shape factor is described by formula:

(72 hours*peak flux)/cumulative flux in a 72-hour period,

wherein the 72 hours*peak flux is a peak flux in the 72-hour period measured in units of micrograms per square centimeter per hour, and wherein cumulative flux in the 72-hour period is measured in units of micrograms per square centimeter.

7. The transdermal drug delivery device of any preceding claim, further comprising a total content of fentanyl selected from the group consisting of about 1.25 milligrams, about 2.5 milligrams, about 5 milligrams, about 7.5 milligrams, and about 10 milligrams.

8. The transdermal drug delivery device of any preceding claim, wherein the transdermal drug delivery device is bioequivalent to a transdermal fentanyl matrix patch obtained from Johnson & Johnson under the trade designation "DURAGESIC" or “DUROGESIC”.

9. The transdermal drug delivery device of any preceding claim, wherein the copolymer comprises at least two of the second monomer units, and wherein the C_4 to C_{10} alkyl acrylate and the at least two of the second monomer units together make up at least 98 percent by weight of the copolymer.

10. The transdermal drug delivery device of any preceding claim, wherein the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 60 to 97 percent by weight, at least one of acrylamide or N-vinyl-2-pyrrolidone in a range from 3 to 10 percent by weight, and vinyl acetate in a range from 0 to 30 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

11. The transdermal drug delivery device of any one of claims 1 to 8, wherein the copolymer comprises the C_4 to C_{10} alkyl acrylate in a range from 50 to 75 percent by weight and vinyl acetate in a range from 25 to 50 percent by weight, wherein each percent by weight is based on the total weight of the copolymer.

12. The transdermal drug delivery device of claim 10 or 11, wherein the C_4 to C_{10} alkyl acrylate is isooctyl acrylate, 2-ethylhexyl acrylate, or a combination thereof.

13. The transdermal drug delivery device of any preceding claim, wherein the adhesive composition comprises skin permeation enhancer in a range from 13 to 20 percent by weight, based on the total weight of the adhesive composition.

14. The transdermal drug delivery device of any preceding claim, wherein the skin permeation enhancer comprises at least one of isopropyl myristate, tetraglycol, methyl laurate, propylene glycol, propylene glycol monolaurate, ethyl oleate, 2-octyl-1-dodecanol, lauryl lactate, or lauryl alcohol.

15. A method of treating in a mammal a condition capable of treatment by fentanyl, the method comprising:

placing the transdermal drug delivery device of any preceding claim on the mammal's skin so that the adhesive composition is in contact with the mammal's skin; and

allowing the adhesive composition to remain on the skin for a time sufficient to establish or maintain a therapeutically effective blood level of fentanyl in the mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/066453

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/4468 (2006.01) ***A61K 9/70 (2006.01)*** ***A61K 47/14 (2006.01)*** ***A61P 25/04 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

GOOGLE PATENTS, PUBMED, PATENTSCOPE, AUSPAT, IP AUSTRALIA INTERNAL DATABASES: 3M Innovative Properties Company; Preszler Prince, Amy; Cantor, Adam; Woehrle, Stephen; Hart, John; Dizio, James; Sykora, Sarah; Husberg, Michael. **REGISTRY, CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIAP, EPODOC:** 29590-42-9/rn, 103-11-7/rn, 141-32-2/rn, 108-05-4/rn, 79-06-1/rn, 140-88-5/rn, 88-12-0/rn, 437-38-7/rn, isooctyl acrylate, ethylhexyl acrylate, n-butyl acrylate, cyclohexyl acrylate, n-pentyl acrylate, n-hexyl acrylate, n-nonyl acrylate, n-decyl acrylate, isoheptyl acrylate, isohexyl acrylate, vinyl acetate, acrylamide, ethyl acrylate, methyl acrylate, N-vinyl-2-pyrrolidone, fentanyl, fentanyl, sublimaze, actiq, durogesic, fentora, matrifen, haldid, onsolis, instanyl, abstral, lazanda, transdermal, percutaneous, topical, skin, epidermal, patch, delivery, administration, therapeutic, TDD, TDDS, drug-in-adhesive, adhesive-matrix and similar terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2016	07 March 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Thomas Case AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832656

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2015/066453**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/052204 A1 (ALZA CORPORATION) 23 April 2009 Abstract; [0031, 0061, 0067, 0071, 0074, 0077, 0097, 00101, 00104, 00105, 00111, 00129-00132,]; Claims 1, 25, 26	1-15
A	US 2014/0005617 A1 (CHOI ET AL) 02 January 2014 Abstract	
A	WO 2011/010556 A1 (NIPRO PATCH CO, LTD) 27 January 2011 & English machine translation obtained from Google.com Abstract	
X	CN 101780057 B (COSMED PHARMACEUTICAL CO LTD & CHANGZHOU NO 4 PHARMACEUTICAL FACTORY CO LTD) 05 September 2012 & English machine translation obtained from Google.com & English abstract obtained from Espacenet Abstract; [0004, 0009, 0015, 0022]; Table 3; Example 2	1-15
X	US 2014/0243765 A1 (SAMYANG BIOPHARMACEUTICALS CORPORATION & TRANSDERM INC) 28 August 2014 Abstract; , [0010-0011, 0014, 0018, 0027, 0029]; Claim 5	1-15
A	US 2011/0020407 A1 (HOSRTMANN ET AL) 27 January 2011 Abstract	
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A	WO 2012/012417 A1 (3M INNOVATIVE PROPERTIES COMPANY) 26 January 2012 Abstract	
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2015/066453**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2015/066453**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2015/066453**

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End of Annex

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