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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 May 2006 (04.05.2006)

PCT

(10) International Publication Number
WO 2006/047362 A2

(51) International Patent Classification:
A61K 9/70 (2006.01) *A61K 31/445* (2006.01)

(21) International Application Number:
PCT/US2005/038086

(22) International Filing Date: 21 October 2005 (21.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/621,123 21 October 2004 (21.10.2004) US

(71) Applicant *(for all designated States except US)*: **DURECT CORPORATION** [US/US]; 10240 Bubb Road, Cupertino, CA 95014 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **YUM, Su, II** [US/US]; 1021 Runnymead Ct., Los Altos, CA 94024 (US). **THEEUWES, Felix** [BE/US]; 27350 Altamont Road, Los Altos Hills, CA 94022 (US).

(74) Agent: **MCCRACKEN, Thomas, P.**; Durect Corporation, 10240 Bubb Road, Cupertino, CA 95014 (US).

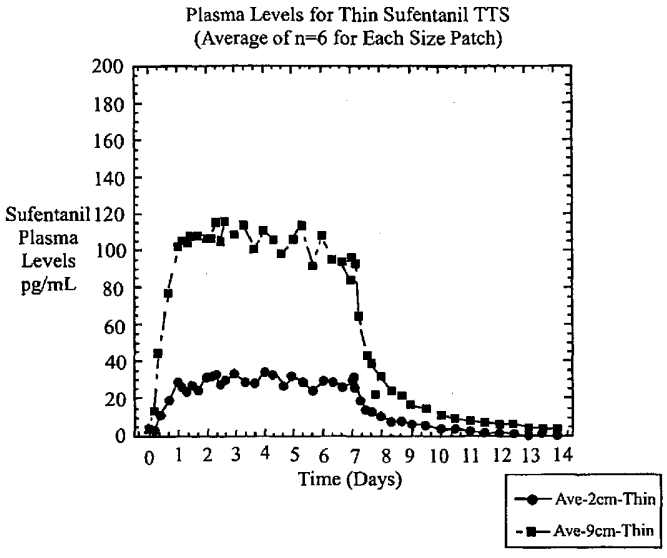
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRANSDERMAL DELIVERY SYSTEMS



(57) Abstract: Transdermal delivery systems for administering sufentanil through the skin are provided. The systems contain a sufficient amount of sufentanil to induce and maintain a constant state of analgesia when applied to a subject. The systems are characterized as having one or more features including a high degree of dosage form rate control over flux of sufentanil from the system, a high net flux of sufentanil from the system through the skin, lack of a permeation enhancer, an adhesive member demonstrating superior shear time, a low coefficient of variation in the net flux of sufentanil from the system, a high delivery efficiency, and a substantially constant steady state net flux of sufentanil from the system. Methods of using the transdermal delivery systems to administer a sufficient amount of sufentanil to induce and maintain analgesia for extended periods when applied to a subject are also provided.

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FIELD OF THE INVENTION

The invention relates generally ıl delivery systems, and more particular transdermal delivery systems for admi ıtanil through the skin. The transderma delivery systems can be used to administer sufentanil to an individual over an extended peri time to provide an analgesic effect.

BACKGROUND OF THE INVENTION

Many medications are used for the treatment of pain, ranging from well known, ove counter compounds such as aspirin, acetaminophen, ibuprofen and other non-steroidal anti-inflammatory compounds to the newly developed chemical entities such as the cyclooxyger II inhibitor compounds. Opiates in various forms, including opium, heroine and morphine t derive from the opium poppy, have very powerful analgesic properties. Opiates have been widely used for anesthesia as well for the treatment of pain, especially where the pain is ver severe. In addition to these natural opiates, many synthetic opioids have since been synthes including methadone, fentanyl and congeners of fentanyl such as sufentanil, alfentanil, lofentanil, carfentanil, remifentanil, etc. Of the opioids, morphine is still the drug of choice management of pain at least in part due to its low cost, the ability of the drug to provide reli from pain of a variety of origins, and the vast experience with this drug. Despite its therape advantages and vast experience with the drug, many pain management experts believe that morphine and other opioids are under-prescribed for patients who require long-term pain

ne reason for under prescription is the risk of the side effects associated with long- ation of opioids in general, such as development of opiate tolerance, dependence, ion, and/or other undesirable side effects (see, *e.g.*, Moulin *et al.* (1992) *Can Med.* 146:891-7). Patients who develop opioid tolerance require increased doses to achi ry analgesic effect and risk the development of further undesirable side effects suc respiratory depression, which can be life threatening. Physical dependence, which is relatec factors such as the dose administered and the length of the administration period, can gener only be resolved by discontinuing opioid administration, which in turn results in the onset o severely painful withdrawal symptoms. Other side effects that can be associated with administration of opioids include reduced cough reflex, bronchial spasms, nausea, vomiting

hormone. The

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urinary retention, changes in regulation of body temperature and sleep pattern, and release o
histamine, adrenalin, and anti-diuretic e negative effects on respiratory functio
especially impact postoperative patien ticularly susceptible to depression of
respiratory function. Even where the concerns regarding side effects might be outweighed b
serious need for pain relief as in terminally ill patients, many doctors still avoid prescribing
opioids due to concerns of abuse of surplus medication by others in contact with the patient,
even that their frequent prescription of the drug might lead to criminal investigation.

In addition to the disadvantages listed above pertaining to opioids in general, morphi
itself has also been associated with particular side effects, at times so severe as to make such
therapy intolerable, especially for patients who are on long-term pain therapy or who requir
high doses of medication to obtain relief. Some of these side effects associated with morphi
usage, particularly at high doses, include nausea and vomiting and severe constipation. In
addition, Sjorgen *et al.* (1994 *Pain* 59:313-316) have reported the phenomena of hyperalges
(increased response to certain stimulus which is not normally painful), allodynia (sensation
pain felt even when stimulus is not normally painful) and myoclonus associated with morph
use. It has thus been hypothesized that morphine and its metabolites may induce such abnor
sensitivity.

Fentanyl and its congeners were originally developed as anesthesia agents, and are
generally used in the United States for the limited purposes of intravenous administration in
balanced general anesthesia, as a primary anesthetic, or, in the case of sufentanil, for epidur
ation during labor and delivery. However, these drugs also have powerful analges
s and are several hundred- to several thousand-times more potent than morphine
g on the particular congener. A few studies have in fact suggested that fentanyl an
s be used instead of morphine due to their increased potency and decreased side eff
) morphine (see e.g., Sjorgen *et al.* (1994) *Pain* 59:313-316). Fentanyl and its
s are, however, more difficult to administer than morphine since they are not orally
absorbed, are extremely potent (requiring very precise, accurate dosing of small amounts) a
have very short half lives in the body thus requiring frequent dosing. For these reasons,
conventional methods for delivery of opioid analgesics are deemed inadequate to meet these
delivery requirements.

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duration of action and rapid recovery due to a redistribution into fat stores and a rapid decli plasma concentration. While subcutar of fentanyl and sufentanil have been th subject of experimentation on a limite(ıfusion methods are impractical as long pain therapies. For example, subcutaneous fentanyl and sufentanil delivery has been used a alternative therapy in a small number of patients who suffered significant side effects associ with administration of morphine. Paix *et al.* (1995) *Pain* 63:263-9. In these therapies, the d was infused into the subcutaneous space in relatively low drug concentrations and at relativ large volume rates (e.g., on the order of 3 mL/day to 40 mL/day) via an external syringe dri These treatment approaches have several major disadvantages that render them impractical long-term therapy. First, provision of drug from an external source adversely affects mobili the patient and is therefore inconvenient for ambulatory patients, increases the risk of infect at the subcutaneous delivery site and provides an opportunity for drug to be diverted for illi uses. Second, the infusion of large volumes of fluid may result in tissue damage or edema a site of infusion. In addition, the absorptive capacity of the subcutaneous space limits the vo of fluid that can be delivered, and this volumetric limitation can in turn limit the amount of that can be administered.

As an alternative to conventional methods for delivering opioid analgesics, transderr patch technologies, and controlled release implant technologies have been developed. For example, a fentanyl transdermal patch is commercially available (DURAGESIC®, Janssen Pharmaceutica Products, Titusville, NJ). The fentanyl patch is provided as a three-day prod nanagement applications, and is available in systems containing from 2.5 to 10 mg ıyl agent. Although the product has enjoyed significant commercial success, inher ıs in the transdermal patch technology employed by the product make it less than ic rnative to conventional systems. Most significantly, the fentanyl patch provides a ıriable rate of fentanyl delivery to the skin over the three-day application period, ar ırthermore a significant variation in the dose of fentanyl delivered among patients. DURAGESIC® Fentanyl Transdermal System Package Insert, 2004. The product is therefc dosage titrated to individual patients on the basis of a nominal flux (the average amount of fentanyl delivered to systemic circulation per hour across average skin) value.

In addition, an implantable osmotic pump sufentanil product is in late-phase clinical testing (CHRONOGESIC®, Durect Corporation, Cupertino, CA). The sufentanil pump pro

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traverse the body's skin barrier. The sufentanil pump is currently provided as a three-month product for pain management, and is b th systems containing from 9 to 40 mg sufentanil agent.

SUMMARY OF THE INVENTION

Transdermal delivery systems for administering sufentanil through the skin are prov It is thus an object of the present invention to provide a transdermal delivery system for administering sufentanil through the skin, wherein the system provides for a high delivery r sufentanil through the skin, with a concomitant low degree of variability in the delivery, wh the system provides a high degree of system control over delivery of the sufentanil agent.

It is more particularly an object of the invention to provide a transdermal delivery sy for administering sufentanil through the skin, where the system provides a dosage form rate control over flux of sufentanil from the system and a net flux from the system through the sl at least about 1 $\mu g/cm^2$/hour. The system does not contain a permeation enhancer.

In one aspect of the invention, the dosage form rate control ($\frac{J_N}{J_D}$) is at least about 5(in other systems it is at least about 60%, and in still other systems, it is at least about 65% o greater. The dosage form rate control can be provided by a number of different mechanisms/components, either alone or in combination. For example, rate control can be

at least in part by using a pharmaceutically acceptable adhesive matrix carrier ion. Alternatively, or in addition, a rate controlling membrane can be used to prov ver delivery of sufentanil from the system.

is another object of the invention to provide a transdermal delivery system for ering sufentanil through the skin. The system is a matrix-type transdermal patch sy des a pressure-sensitive adhesive matrix containing the sufentanil agent. The syste does not contain a permeation enhancer. The adhesive properties of the matrix are selected that the system has a shear time of from about 1 to 40 minutes as determined using the Shea Time Measurement Test.

In one aspect of the invention, the adhesive matrix provides dosage form rate contro flux of sufentanil from the system. In other aspects, the system is characterized by having a

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other systems provide a net flux of at least about 1.5 μg/cm /hour. In certain systems, the o size of the transdermal delivery systen nimum, such that the adhesive matrix h drug releasing interface surface area o -10 cm^2.

It is still another object of the invention to provide a transdermal delivery system for administering sufentanil through the skin. The system provides a dosage form rate control (over flux of sufentanil from the system of at least about 50% while still allowing a net flux sufentanil from the system through the skin of at least about 1 μg/cm^2/hour. The system do contain a permeation enhancer.

In one aspect of the invention, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufen from the system is even higher, for example at least about 60%, while in still other systems dosage form rate control is at least about 65%. In these systems, the dosage form rate contr can be provided by a number of different mechanisms/components, either alone or in combination. Thus, the dosage form rate control can be provided at least in part by using a pharmaceutically acceptable adhesive matrix carrier composition. Alternatively, or in addit rate controlling membrane can be used to provide control over delivery of sufentanil from th system. Despite such a high degree of system control in the present systems, certain system able to provide a net flux of sufentanil from the system through the skin of at least about 1.5 μg/cm^2/hour, while still others can provide a net flux of around 2 μg/cm^2/hour, all without th ermeation enhancer.

is a further object of the invention to provide a transdermal delivery system for ering sufentanil through the skin, where the system is able to provide high net flux l from the systems without the use of permeation enhancers and where the coeffici in the net flux ($\frac{\Delta J_N}{J_N}$) is low, being held to about 50% or less. When applied to a subject, the system provides a net flux of sufentanil from the system through the skin of at l about 1 μg/cm^2/hour with a very low degree of variability in the net flux from the system, s that the coefficient of variation in the net flux is about 50% or less. The system does not co a permeation enhancer.

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the system is even higher, for example at least about 60%, while in still other systems the dc form rate control is at least about 65%. The dosage form rate control can be provided by a number of different mechanisms/components, either alone or in combination. Thus, the dos form rate control can be provided at least in part by using a pharmaceutically acceptable adhesive matrix carrier composition and/or a rate controlling membrane. Despite such a lov degree of variability in the net flux from the present systems, certain systems are able to pro an even higher net flux of sufentanil from the system through the skin, on the order of at lea about 1.5 μg/cm^2/hour, while still others can provide a net flux of around 2 μg/cm^2/hour, all without the use of a permeation enhancer.

It is yet a further object of the invention to provide a small sized system that can be u to induce and maintain analgesia for 3 or more days when applied to a subject, where the delivery efficiency at the end of the therapeutic period is at least about 50%, more preferabl about 60%, and more preferably 70%, that is, up to about 70% of the sufentanil is delivered the subject over the course of three days. Accordingly, a transdermal delivery system for administering sufentanil through the skin is provided. The system includes a reservoir

g a sufficient amount of sufentanil to induce and maintain analgesia for 3 or more d plied to a subject. The reservoir may be an adhesive or non-adhesive matrix, and ha hydrated thickness of about 1.25 to 5 mils. The system provides a (drug) delivery / of up to at least about 70% of the sufentanil from the reservoir at the end of 3 or n pplication to a subject.

In one aspect of the invention, the reservoir contains a sufficient amount of sufentani induce and maintain analgesia for 5 or more days when applied to a subject while maintainir delivery efficiency of at least about 70% at the end of the 5 days, and still other systems incl a reservoir that contains a sufficient amount of sufentanil to induce and maintain analgesia fi or more days when applied to a subject while maintaining a delivery efficiency of at least ab 70% at the end of the 7 days. In certain other systems, the delivery efficiency is at least abo

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certain aspects of the invention, the high efficiency systems include a reservoir having a dru releasing interface surface area of fron m^2. In still further aspects, the high efficiency systems have a substantially ıir volume, for example a volume of abc 0.2 ml or less. In certain systems, the reservoir has a volume of from about 0.0025 to 0.154

It is another object of the invention to provide a monolithic transdermal delivery syst where the sufentanil is contained in an adhesive matrix adhered to a backing layer. Accordi a monolithic transdermal delivery system for administering sufentanil through the skin is provided. The system includes a pressure-sensitive adhesive matrix that contains sufentanil amount above the solubility of sufentanil in the matrix. When the system is applied to a sub the system provides a substantially constant steady state net flux of sufentanil from the syste through the skin of at least about 1 $\mu g/cm^2$/hour for at least about 24 hours. The system doe include a permeation enhancer or rate controlling membrane. It is a feature of the invention the systems are able to provide such high net flux systems that do not employ a permeation enhancer or rate controlling membrane and can still perform to such high standards, where u achieving steady state conditions, the system provides at least a first order release rate profil such that the system achieves substantially zero order release to provide a constant steady st flux of sufentanil from the system over an extended period of time. In certain systems, the system provides a substantially constant steady state net flux of sufentanil from the system through the skin of at least about 1 $\mu g/cm^2$/hour for at least about 36 hours.

In one aspect of the invention, certain systems are also able to provide an even highe ıte net flux net flux of sufentanil from the system through the skin, for example at l $\mu g/cm^2$/hour in some systems, or even around 2 $\mu g/cm^2$/hour in other systems. In stems, the overall size of the transdermal delivery system is kept to minimum, sucl ive matrix has a drug releasing interface surface area of from about 1-10 cm^2.

is a still further object of the invention to provide a monolithic transdermal deliver r administering sufentanil through the skin. The system includes a pressure-sensiti adhesive matrix that contains sufentanil in an amount above the solubility of sufentanil in th matrix. When the system is applied to a subject, the system provides a net flux of sufentanil from the system through the skin of at least about 1 $\mu g/cm^2$/hour. The system provides a do form rate control over flux of sufentanil from the system, but the system does not include a permeation enhancer or rate controlling membrane. In these systems, the sufentanil is provi

while still prov

In one aspect of the invention, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufen from the system is at least about 50% viding the substantially high rate of net from the system. In certain systems, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufenta from the system is even higher, for example at least about 60%, while in still other systems dosage form rate control is at least about 65%. The dosage form rate control can be provide a number of different mechanisms/components, either alone or in combination. Thus, the d form rate control can be provided at least in part by using a pharmaceutically acceptable adhesive matrix carrier composition and/or a rate controlling membrane. Despite not includ permeation enhancer or rate controlling membrane, certain systems are able to provide an e higher net flux of sufentanil from the system through the skin, on the order of at least about $\mu g/cm^2$/hour, while still others can provide a net flux of around 2 $\mu g/cm^2$/hour.

It is a still further object of the invention to provide a transdermal delivery system fo administering sufentanil through the skin of a living subject, wherein the system provides a substantially constant delivery rate of sufentanil over a single application administration per of at least about 48 hours and the constant delivery rate is sufficient to establish and maintai plasma sufentanil concentration having a minimum to maximum ratio of about 1.8 or less o the relevant administration period.

In one aspect of the invention, the delivery rate of sufentanil from the transdermal system is substantially zero order. In other aspects of the invention, the delivery ra l is characterized by a total decline or increase of about 5 to 6% over the administra id preferably, the delivery rate of sufentanil is characterized by substantially no tot or decrease over the administration period. The subject transdermal delivery syste o provide a delivery rate at steady state of at least about 1 μg/hr to 10 μg/hr, and th ation period is at least about 48 hours to 7 days. In certain embodiments, the net fl from the system through the skin is at least about 1 $\mu g/cm^2$/hour, and the system does not co a permeation enhancer. In other aspects of the invention, the system has a shear time of fro about 1 to 40 minutes as determined using the Shear Time Measurement test. In still further aspects, the system provides dosage form rate control (J_N / J_D) over flux of sufentanil from t system of at least about 50% and a net flux from the system through the skin of at least abou

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50% or less, of the system is a monolithic system comprising a pressure-sensitive adhesive matrix containing sufentanil in an amc solubility of sufentanil in the matrix, a subject system provides a substantially dy state net flux of sufentanil from the system through the skin of at least about 1 μg/cm²/hour for at least about 24 hours. In yet o aspects, system is a monolithic system including a pressure-sensitive adhesive matrix contai the sufentanil active agent in an amount above the solubility of sufentanil in the matrix, and system provides a net flux from the system through the skin of at least about 1 μg/cm²/hour, wherein a dosage form control over flux of sufentanil from the system is provided by the sy itself. Preferably, the above-described systems do not include a permeation enhancer or a r controlling membrane.

It is an advantage of the present invention that the transdermal delivery systems are to provide sustained analgesia in a subject for from 3 to 7 days. It is a further advantage of invention that the systems are readily constructed to provide any number of different dosag sizes, and further are able provide preferential pharmacological release characteristics and profiles. It is a still further advantage of the invention that the system control provided by t systems allows for maximum control over the plasma concentrations of the delivered sufent and therefore the therapeutic effect.

These and other objects, aspects and advantages of the present invention will readil occur to the skilled practitioner upon reading the instant disclosure and specification.

BRIEF DESCRIPTION OF THE DRAWINGS

igure 1 presents a cross-sectional view through a transdermal delivery system acco sent invention.

igure 2 presents a cross-sectional view through another transdermal delivery systen g to the present invention.

Figure 3 present a schematic representation of a manufacturing process for producin transdermal delivery system according to the present invention.

Figure 4 depicts the results from the Example 1 *in vitro* skin flux study using a transdermal delivery system according to the present invention.

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Figure 6 depicts the results from the Example 5 pharmacokinetic study using a transdermal delivery system having a (interface surface area of 1.42 cm^2.

Figure 7 depicts the measured ; ma levels from Example 4 for the test subjects wearing "thin" transdermal delivery systems.

Figure 8 depicts the measured sufentanil plasma levels from Example 4 for the test subjects wearing "thick" transdermal delivery systems.

Figure 9 depicts the average sufentanil plasma levels for all four test groups from Example 4.

Figure 10 depicts the *in vitro* cumulative release data (with breathable overlay) obtai in the Example 5 IVIVC study using the 2 and 8 cm^2 "thick" and "thin transdermal delivery systems.

Figure 11 depicts the *in vivo* input data obtained in the Example 5 IVIVC study usin 2 and 8 cm^2 "thick" and "thin transdermal delivery systems.

Figure 12 depicts the *in vitro* and *in vivo* cumulative release data obtained in the Exa 5 IVIVC study using the 2 and 8 cm^2 "thick" and "thin transdermal delivery systems.

Figure 13 depicts the *in vitro* and *in vivo* cumulative release data obtained in the Exa 5 IVIVC study using the 2 cm^2 "thick" and "thin transdermal delivery systems.

Figure 14 depicts the *in vitro* and *in vivo* cumulative release data obtained in the Exa 5 IVIVC study using the 8 cm^2 "thick" and "thin transdermal delivery systems.

DETAILED DESCRIPTION OF THE INVENTION

efore describing the present invention in detail, it is to be understood that this inve ited to particularly exemplified materials or process parameters as such may, of co s also to be understood that the terminology used herein is for the purpose of descri · embodiments of the invention only, and is not intended to be limiting.

All publications, patents and patent applications cited herein, whether supra or infra, hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the singu forms "a," "an" and "the" include plural referents unless the content clearly dictates otherwi Thus, for example, reference to "a polymer" includes a mixture of two or more such molecu reference to "a solvent" includes a mixture of two or more such compositions, reference to "

the phrase "al

applied to all values or quantities specified by that range. Thus, the phrase "about 1-12 wt%
means "about 1 to about 12 wt%", and bout 1-10 cm^2" means "about 1 to abou
cm^2", and the like.

It is an object of the present invention to provide a transdermal delivery system for administering sufentanil through the skin.

A transdermal delivery system for administering sufentanil through the skin was firs suggested 1984 in U.S. Patent No. 4,588,580 to Gale et al. The Gale et al. patent claims the transdermal patch technology employed in the commercial DURAGESIC® fentanyl transde patch product. Over the course of the next twenty years, literally thousands of other patent applications have been filed relating to a wide spectrum of transdermal delivery technologie transdermal patch design and components, and transdermal delivery techniques. A large nu of these new patent applications have, like the Gale et al. patent, included the suggestion for sufentanil patch, but these suggestions are provided by way of including the sufentanil agen long laundry list of drugs rather than by providing an enabling disclosure of how to actually design a proper sufentanil system. However, despite twenty years of such suggestions, there never been a sufentanil patch that has entered into clinical testing.

The glaring absence of sufentanil transdermal systems from the pharmaceutical rese and development and clinical landscapes, despite both the commercial success of a fentanyl patch and constant suggestions from the patent literature, can be attributed to a number of features related to transdermal delivery in general and the sufentanil agent in specific, all of

itures are well recognized in the transdermal art. Initially, all transdermal delivery nust overcome the natural barrier to percutaneous absorption of an agent, which ba is naturally provided by the skin. The physical and chemical properties of any agent affect the degree to which that agent may move across the skin barrier (the s) via percutaneous absorption, and thus agents can be characterized by their skin on or epidermal permeability. Agents exhibiting a high degree of skin permeation good candidates for transdermal delivery systems, whereas agents exhibiting a low degree o skin permeation are generally considered not to be good candidates.

There is also a very high degree of variability in the permeability of human skin to a particular agent. In fact, skin permeability is known to differ widely by region (e.g., skin fr the thigh will have different permeability than skin from the chest, and both will differ from

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a particular individual's forearm will have different permeability). Shaw et al. (1991) in *Physiology, Biochemistry, and Molecu* *the Skin*, Second Ed., pp. 1447-1479, Goldsmith, L. A. Ed., Oxford Universi ord, UK. These variances are reported t as much as 70%. Accordingly, it is not just a matter of overcoming the skin barrier, rather transdermal delivery system designs must also account for a wide variance in the degree to which an agent is able to traverse the skin.

Another inherent feature in transdermal delivery systems relates to the relationship between the skin surface area that the system releases the agent to (the target surface or drug releasing interface) and the amount agent that can be delivered from the system. Transderm delivery systems must maintain intimate contact with the target surface for the duration of treatment. Accordingly, there is a *de facto* upward limit on the size for any transdermal syst dictated by the size where a given patch will be prone to lifting and peeling from the target surface in response to normal flexing and movement by the individual. A reasonable transdermal patch size generally has a drug releasing interface surface area of around 40 cm less. However, restricting the size of a transdermal delivery system in this manner limits the amount of agent that can be delivered from that system. Accordingly, agents with poor skin permeability generally require larger patch sizes to bring agent delivery rates up to acceptab levels.

With regard to the features of the sufentanil agent itself, it is well known that sufenta has a very high potency, reported to be from 7.5 – 15 times more potent than fentanyl. See l

). 4,588,580 to Gale et al. Sufentanil also has a relatively narrow therapeutic index very high potency, will produce highly undesirable side effects upon over dosage o death. Sufentanil is also reported to have extremely poor skin permeability, for in the Gale et al. patent it was noted that fentanyl has poor skin permeability and th l has even less permeability than fentanyl, and in U.S. Patent Publication No. US 6829 to Venkatraman et al., it was noted that sufentanil is from 50 to 75% less permeable than fentanyl in skin. Accordingly, the skilled transdermal artisan is faced with conflicting choices when considering the design of a sufentanil transdermal delivery system would be expected that the amount of sufentanil that can be delivered from a given system v be exceedingly low due to the poor skin permeability of sufentanil. This in turn suggests tha techniques must be employed to increase sufentanil skin permeability, for example by using

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where the possibility of overdose would lead to design of a system that has a restricted deliv rate.

When the above-noted sufenta sign considerations are combined with considerations such as the need to reduce the affect of skin variability on transdermal delive system performance, it is no small wonder that an effective sufentanil transdermal delivery system has heretofore not been developed. The skilled artisan was left with the design conc discussed above and two suggested approaches for a transdermal sufentanil system, appeari either end of a two-decade long period and providing two similar approaches to the problem The first suggestion for a sufentanil system was provided in US Patent No. 4,588,580 to Ga al. In this document, Gale et al. noted the low skin permeability of both fentanyl and sufent The two suggestions for system design that were provided by Gale et al. were to either prov matrix type system that delivered the agent for continuous periods and had no system contr (relying instead on skin permeability to control agent input rates), or preferably to provide a system where the system itself controls the maximum rate at which the agent is delivered through the skin. In the second design that provides system control, Gale et al. taught that i necessary to substantially increase the flux of the agent (fentanyl or sufentanil) through the by use of a skin permeation enhancer. The second suggestion from Gale et al. was used to design the DURAGESIC® transdermal fentanyl system, where a reservoir of the fentanyl a is provided with a rate-limiting membrane to provide a system-controlled patch. Alcohol is added to the reservoir as a permeation enhancer, where the alcohol serves to enhance fentan igh the rate-limiting membrane and increase the permeability of the skin to fentany cted design provides a transdermal delivery system that is able to deliver the fentan cceptably high rates (due to the addition of a permeation enhancer), but net delive ly variable, particularly from an interindividual perspective (DURAGESIC® Fenta mal System Package Insert, 2004). Whereas such person-to-person variability may le in a fentanyl system, it would likely not be acceptable in a sufentanil system due safety considerations. The other alternative suggested by Gale et al., that is, a system that r solely on skin permeability to control delivery rates, would likewise have unacceptably high variability for a sufentanil system.

The second suggested approach for a sufentanil transdermal delivery system was provided almost 20 years after Gale et al. in U.S. Patent Publication No. US 2003/0026829

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permeability than fentanyl. It was also noted that the fentanyl and sufentanil agents require careful handling due to their safety prc ;tem design that is suggested for sufenta uses a subsaturated system (where the nt is present in an amount below the solubility limit of the agent in the selected system) monolithic matrix, wherein the system is rate-controlled. Accordingly, the Venkatraman et al. transdermal system would be expected administer the sufentanil agent at a decreasing rate that is proportional to the level of saturat of the agent in the system, and relies upon skin permeability to control the delivery rate. Th approach is generally the first approach suggested by Gale et al., that is, a non-rate controlle system. Venkatraman et al. teach that a saturated system (e.g., depot system) would provide a higher rate of delivery, but that their subsaturated system must nevertheless be selected. A review of *in vitro* data relating to delivery of sufentanil from the Venkatraman et al. system indicates that it provides a low net flux (for systems containing between 2-11% sufentanil, t net flux ranges from 0.1 to 0.9 $\mu g/cm^2$/hour), and further that there is substantial variability net delivery. Here again, it is believed that whereas such variability may be suitable for a fentanyl transdermal system, it would not be suitable for a sufentanil transdermal delivery system.

Applicant has taken a substantial departure from these past suggested approaches, an has now developed a transdermal delivery system for administering sufentanil through the s where the system is characterized by having a high degree of system control (dosage form r control) over delivery of sufentanil from the system in spite of also having a high total net fl system through the skin with a particularly low variability (coefficient of variation) :nt delivery systems are surprisingly able to provide these performance features wi ? permeation enhancers.

·om Shaw et al. (1985) "Transdermal Dosage Forms," in *Rate Control in Drug The* et al. eds), pp: 65-70, Churchill Livingstone, Edinburgh, it is known that in a rate l transdermal delivery system, the relation between the net flux (J_N), the flux throu skin (J_S) and flux from the dosage form (J_D) can be given by the following equation:

(Formula I): $$\frac{1}{J_N} = \frac{1}{J_S} + \frac{1}{J_D}$$

)e represented

J_N J_S

system, which is defined as $\frac{J_N}{J_D}$, can b by the following equation:

(Formula II): $\frac{\Delta J_N}{J_N} = \frac{\Delta J_S}{J_S}\left(1 - \frac{J_N}{J_D}\right)$.

As can be seen from the relationships represented by Formula I and Formula II, the ability to exert a high degree of dosage form rate control in a transdermal delivery system c substantially eliminate the effect that skin flux variability may have on the variability of net through the skin from the dosage form. The transdermal delivery systems of the present invention are designed to provide a high degree of dosage form rate control. Accordingly, i embodiment of the invention, a transdermal delivery system for administering sufentanil thr the skin is provided. The system provides a dosage form rate control over flux of sufentanil the system and a net flux from the system through the skin of at least about 1 μg/cm^2/hour. system does not contain a permeation enhancer. In particular systems of the invention, the dosage form rate control ($\frac{J_N}{J_D}$) is at least about 50%, in other systems it is at least about 60% and in still other systems, it is at least about 65% or greater. The dosage form rate control c provided by a number of different mechanisms/components, either alone or in combination. example, rate control can be provided at least in part by using a pharmaceutically acceptable

matrix carrier composition, wherein the materials used to construct the matrix are ;o as to provide control over delivery of the sufentanil agent from the transdermal ;ystem. Alternatively, or in addition, a rate controlling membrane can be used to ontrol over delivery of sufentanil from the system.

the instant transdermal delivery systems, the sufentanil agent can be present in the an amount of about 1-20 weight percent (wt%) relative to the total system, prefera in an amount of about 1-20 wt%, preferably in an amount of about 1-12 wt%. In certain sys the sufentanil is provided as a depot, and is thus present in the system in an amount above th solubility of sufentanil in the system, such that there will be both dissolved and undissolved sufentanil in the system. In any regard, the transdermal delivery systems are provided with sufficient amount of the sufentanil agent to provide for a steady state net flux sufficient to administer the sufentanil at from about 0.01 to 200 μg/hour when the system is applied to th

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the skin of a subject, while still further systems are able to provide a steady state net flux sufficient to administer sufentanil at fr 2 μg/hour.

The present transdermal delive ıtain a sufficient amount of sufentanil s they may be used to induce and maintain a suitable state of analgesia in a subject for 3 or m days when applied to the skin of that subject. Other systems contain a sufficient amount of sufentanil to induce and maintain a suitable state of analgesia in a subject for 5 or more day while still others contain enough to induce and maintain a suitable state of analgesia in a sul for 7 or more days.

The long duration intended uses of the present transdermal delivery systems impart further design considerations upon those systems. Particularly, the transdermal delivery sys must maintain intimate contact with the target surface (drug releasing interface surface) for duration of treatment. A system that has insufficient adhesive properties and/or which is to rigid and nonflexible, will be prone to displacement from the target skin surface, thereby interrupting or at least reducing the intended rate of delivery of sufentanil from the system. patch that is too large will also be prone to lifting and peeling from the target surface in resp to normal flexing and movement by the individual. In addition, the adhesive properties of t system must take into account the changes in skin hydration brought about by normal daily activity, such as bathing or showering, and perspiring due to exercise or exertion.

Accordingly, the materials used in the construction of a transdermal delivery system according to the present invention are selected to provide a patch that has suitable drape, tha / so as to maintain contact between the target skin surface and the drug releasing of the system throughout normal movement, stretching and bending of the skin site ısdermal delivery systems that are provided as a monolithic, matrix-type system (w tanil is blended with an adhesive carrier composition, such as a pressure-sensitive to provide both a carrier matrix for the sufentanil as well as the means for affixing the target skin surface), the adhesive is selected to have a shear time within a spec range of times deemed suitable for present systems.

More particularly, a Shear Time Measurement Test can be used to assess adhesive properties in a monolithic transdermal delivery system constructed according to the present invention. The Shear Time Measurement Test is conducted as follows. A bar formed from plate is provided. The bar is placed on a horizontal surface and the face of the bar is cleaned

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the cleaned surface of the bar so that the contact with the bar is ½ x ½ (the sample is appl the surface ½" from the bottom of the ond end of the sample patch hangs freel below the bar. A weight holder is atta e end of the sample patch. The bar is tl suspended at a suitable height using a support structure, such that the face of the bar with th patch adhered to it is completely vertical. Care is taken not to impart any peeling force on t sample patch during this set-up procedure. The test is then run by carefully attaching a 100 weight to the weight holder at the free end of the sample patch and recording the time that it takes for the sample patch to completely separate from the face of the vertical test bar. An appropriate shear time as determined by the Shear Time Measurement Test indicates that a sample adhesive system has suitable skin adhesion properties and suitable cold flow propert A passing test result from the Shear Time Measurement Test is between about 1 to 40 minu Patches that adhere for longer periods of time will generally adhere too tightly to the skin surface, giving rise to displacement under influence of normal movement. Patches that adh for shorter periods of time will not have suitable adherence to remain in place. In preferred embodiments, the adhesive system should have a Shear Time Measurement Test result of between about 2 and 20 minutes, and more preferably between about 5 and 15 minutes.

Accordingly, in an embodiment of the invention, a transdermal delivery system for administering sufentanil through the skin is provided. The system is a matrix-type transder patch system, and includes a pressure-sensitive adhesive matrix containing the sufentanil ag The system does not contain a permeation enhancer. The adhesive properties of the matrix such that the system has a shear time of from about 1 to 40 minutes as determined u Time Measurement Test. In the subject system, the adhesive matrix provides dos control over flux of sufentanil from the system. The systems are characterized by substantially high net flux of sufentanil from the system. In this regard, certain sys net flux of sufentanil from the system through the skin of at least about 1 $\mu g/cm^2/h$ er systems provide a net flux of at least about 1.5 $\mu g/cm^2$/hour. In certain preferre systems, the overall size of the transdermal delivery system is kept to minimum, such that th adhesive matrix has a drug releasing interface surface area of from about 1-10 cm^2. In cert systems, the sufentanil agent can be present in an amount of about 1-20 weight percent (wt% relative to the total system, preferably in an amount of about 1-12 wt%. In certain other sys the sufentanil is provided as a depot, and is thus present in the system in an amount above th

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sufentanil at from about 1 to 20 μg/hour when the system is applied to the skin of a subject, while still further systems are able to provide a steady state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour.

The present adhesive transdermal delivery systems contain a sufficient amount of sufentanil so that they may be used to induce and maintain a suitable state of analgesia in a subject for 3 or more days when applied to the skin of that subject. Other systems contain a sufficient amount of sufentanil to induce and maintain a suitable state of analgesia in a subj for 5 or more days, while still others contain enough to induce and maintain a suitable state analgesia in a subject for 7 or more days.

In one particular embodiment, the instant adhesive transdermal delivery systems are provided as a dimensionally stratified family of transdermal patches of varying doses, all ha an adhesive matrix with a drug releasing interface surface area of from about 1-10 cm^2. For example, the family can include four patches having drug releasing interface surface area of 6 and 8 cm^2, respectively, wherein the patches respectively contain 1, 2, 3 and 4 mg of the sufentanil agent. In this case, the size of the patch provides a visual clue to a health service provider, possibly avoiding accidental application of a transdermal delivery system containi incorrect dose of sufentanil. In addition, the nested doses allow for convenient dosing of an l, where step-wise incremental increases/decreases in the dose can be made with th plication/removal of one or more of the sized patches in the family. The superior properties displayed by the instant adhesive systems further allow for in-clinic dos procedures, where a particular patch (e.g., the 8 cm^2 patch containing 4 mg of l) can be divided into halves, thirds or quarters, to provide a different, fully operabl ing a reduced size and therefore a reduced dose of sufentanil (e.g., a 4 cm^2 patch w mg sufentanil, or a 2 cm^2 patch with 1 mg sufentanil). In this regard, indicia may be provid the backing of the subject patches to facilitate accurate division of a particular patch into tw more patches of smaller size and dose.

It is a surprising feature of the transdermal delivery systems of the present invention they are able to provide such high system control and high net flux of sufentanil from the

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Accordingly, in one embodiment, a tra very system for administering sufentani

through the skin is provided. The syst dosage form rate control ($\frac{J_N}{J_D}$) over flu

sufentanil from the system of at least about 50% while still allowing a net flux of sufentanil the system through the skin of at least about 1 μg/cm^2/hour. The system does not contain a permeation enhancer. In certain systems, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufentanil from the system is even higher, for example at least about 60%, while in still othe systems the dosage form rate control is at least about 65%. As with the other systems of the present invention, the dosage form rate control can be provided by a number of different mechanisms/components, either alone or in combination. Thus, the dosage form rate contro be provided at least in part by using a pharmaceutically acceptable adhesive matrix carrier composition, wherein the materials used to construct the matrix are selected so as to provide control over delivery of the sufentanil agent from the transdermal delivery system. Alternatively, or in addition, a rate controlling membrane can be used to provide control ove delivery of sufentanil from the system. Despite such a high degree of system control in the present systems, certain systems are able to provide a net flux of sufentanil from the system through the skin of at least about 1.5 μg/cm^2/hour, while still others can provide a net flux o ~~~~ μg/cm^2/hour, all without the use of a permeation enhancer.

certain high system control/high net flux systems, the sufentanil agent can be pres unt of about 1-20 weight percent (wt%) relative to the total system, preferably in a f about 1-12 wt%. In certain other systems, the sufentanil is provided as a depot, a nt in the system in an amount above the solubility of sufentanil in the system, such be both dissolved and undissolved sufentanil in the system. The transdermal deliv ~~~~ re provided with sufficient amount of the sufentanil agent to provide for a steady s net flux sufficient to administer the sufentanil at from about 0.01 to 200 μg/hour when the system is applied to the skin of a subject. Certain other systems of the present invention pro a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when system is applied to the skin of a subject, while still further systems are able to provide a ste state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour.

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of analgesia in a subject for 5 or more days when applied to the skin of that subject. Other systems contain a sufficient amount of induce and maintain a suitable state of analgesia in a subject for 5 or more da others contain enough to induce and maintain a suitable state of analgesia in a subject for 7 or more days.

It is another surprising feature of the transdermal delivery systems of the present invention that they are able to provide such high net flux of sufentanil from the systems witl the use of permeation enhancers, wherein the coefficient of variation in the net flux ($\frac{\Delta J_N}{J_N}$) low, being held to about 50% or less. It is even more surprising that transdermal delivery systems displaying such high net flux of sufentanil and such low variability in the net flux c provided in such small sizes, generally in the order of about 20% the size of previous transdermal systems. Accordingly, in one embodiment, a transdermal delivery system for administering sufentanil through the skin is provided. When applied to a subject, the systen provides a net flux of sufentanil from the system through the skin of at least about 1 $\mu g/cm^2$ with a very low degree of variability in the net flux from the system, such that the coefficier variation in the net flux ($\frac{\Delta J_N}{J_N}$) is about 50% or less. The system does not contain a perme enhancer.

In certain preferred low variability systems, the subject system further provides a do form rate control over flux of sufentanil form the system. More particularly, certain system

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the system is even higher, for example at least about 60%, while in still other systems the dc form rate control is at least about 65%. As with the other systems of the present invention, t dosage form rate control can be provided by a number of different mechanisms/components either alone or in combination. Thus, the dosage form rate control can be provided at least i part by using a pharmaceutically acceptable adhesive matrix carrier composition and/or a ra controlling membrane. Despite such a low degree of variability in the net flux from the pres

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net flux of around 2 μg/cm /hour, all without the use of a permeation enhancer.

In certain low variability/high ıs, the sufentanil agent can be present i amount of about 1-20 weight percent (to the total system, preferably in an am of about 1-12 wt%. In certain other systems, the sufentanil is provided as a depot, and is th present in the system in an amount above the solubility of sufentanil in the system, such tha there will be both dissolved and undissolved sufentanil in the system. The transdermal deli systems are provided with sufficient amount of the sufentanil agent to provide for a steady s net flux sufficient to administer the sufentanil at from about 0.01 to 200 μg/hour when the system is applied to the skin of a subject. Certain other systems of the present invention pr a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour whe system is applied to the skin of a subject, while still further systems are able to provide a ste state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour.

The present low variability/high net flux transdermal delivery systems contain a sufficient amount of sufentanil so that they may be used to induce and maintain a suitable st of analgesia in a subject for 3 or more days when applied to the skin of that subject. Other systems contain a sufficient amount of sufentanil to induce and maintain a suitable state of analgesia in a subject for 5 or more days, while still others contain enough to induce and maintain a suitable state of analgesia in a subject for 7 or more days.

It is still another surprising feature of the transdermal delivery systems of the presen invention that a very small sized system can be used to induce and maintain analgesia for 3 s when applied to a subject, wherein the delivery efficiency at the end of the therap at least about 70%, that is, at least about 70% of the sufentanil is delivered to the ver the course of three days. The delivery efficiency, or system efficiency, for a gi ıal delivery system at any point in time can be assessed by dividing the mass of l delivered from the system at substantially zero order by the total mass of sufentar provided in the system at the initiation of the administration. In addition, since the of sufentanil provided in a new system is known, the delivery efficiency for a given patch removed from a subject after, e.g., a three day administration period, can be readily determi by extracting the sufentanil remaining in the system to determine the remaining mass of sufentanil and then comparing this mass against the starting mass. In the present invention, transdermal delivery systems are designed such that the sufentanil has a very low solubility

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controls over system efficiency can be used, such as where the sufentanil is added to a syste a tightly controlled particle size distrib

Accordingly, in one embodime nal delivery system for administering sufentanil through the skin is provided. The system includes a reservoir containing a suffici amount of sufentanil to induce and maintain analgesia for 3 or more days when applied to a subject. The reservoir may be an adhesive or non-adhesive matrix, and has a dry, non-hydr thickness of about 1.25 to 5 mils. The system provides a delivery efficiency of at least abou 50% of the sufentanil from the reservoir at the end of 3 or more days of application to a subj preferably at least about 60%, and more preferably at least about 70%. In certain systems, t reservoir contains a sufficient amount of sufentanil to induce and maintain analgesia for 5 o more days when applied to a subject while maintaining a delivery efficiency of up to at leas about 70% at the end of the 5 days, and still other systems include a reservoir that contains sufficient amount of sufentanil to induce and maintain analgesia for 7 or more days when ap to a subject while maintaining a delivery efficiency of up to at least about 70% at the end of days. In certain other systems, the delivery efficiency is even greater, for example, at least 80% at the end of the application period. It is preferred that the overall system size of the in high efficiency transdermal delivery systems is minimized as much as possible. Accordingl preferred embodiments, the high efficiency systems include a reservoir having a drug releas interface surface area of from about 1-10 cm^2. In still further preferred embodiments, the hi efficiency systems have a substantially small reservoir volume, for example a volume of abo less. In certain systems, the reservoir has a volume of from about 0.0025 to 0.154 certain systems, the reservoir in the high efficiency transdermal delivery systems an adhesive matrix composition. In certain preferred systems, the subject system ovides a dosage form rate control over flux of sufentanil form the system. More ly, certain systems are further able to provide a dosage form rate control ($\frac{J_N}{J_D}$) ov flux of sufentanil from the system of at least about 50% while still providing a high delivery efficiency from the system. In certain systems, the dosage form rate control ($\frac{J_N}{J_D}$) over flux sufentanil from the system is even higher, for example at least about 60%, while in still othe systems the dosage form rate control is at least about 65%. As with the other systems of the

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be provided at least in part by using a pharmaceutically acceptable adhesive matrix carrier composition and/or a rate controlling r ldditionally, certain other high efficiency systems are also able to provide a relat flux of sufentanil from the system thro the skin, for example at least about 1 μg/cm²/hour in some systems, and at least about 1.5 μg/cm²/hour, or even around 2 μg/cm²/hour in other systems. It is notable that in these high efficiency/high flux systems, there is still no need to provide a permeation enhancer, and as certain of the instant systems do not include a permeation enhancer.

In certain of the instant high efficiency transdermal delivery systems of the present invention, the sufentanil agent can be present in an amount of about 1-20 weight percent (w relative to the total system, preferably in an amount of about 1-12 wt%. In certain other sys the sufentanil is provided as a depot, and is thus present in the system in an amount above t solubility of sufentanil in the system, such that there will be both dissolved and undissolved sufentanil in the system. The transdermal delivery systems are provided with sufficient amc of the sufentanil agent to provide for a steady state net flux sufficient to administer the sufer at from about 0.01 to 200 μg/hour when the system is applied to the skin of a subject. Still systems of the present invention provide a steady state net flux sufficient to administer sufe at from about 1 to 20 μg/hour when the system is applied to the skin of a subject, while furt systems are able to provide a steady state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour.

The transdermal delivery systems of the invention may be provided as either a liquid oir-type or a matrix-type device. Both of these configurations will naturally inclu ayer that provides a protective outer surface for the devices, as well as a release lin will cover the adhesive portion of the device that is used to affix the same to the s The release liner is removed prior to application, thereby exposing the adhesive f the device, which will typically be a pressure-sensitive adhesive. Accordingly, to Figures 1 and 2, a transdermal patch device is generally indicated at **2**. The dev includes a backing layer **4**, a reservoir **6** that contains the sufentanil agent, and a release line The reservoir **6** may be a liquid or gel reservoir, or it may be a matrix carrier that can be sel adhesive or non-adhesive. Referring specifically to Figure 2, in those devices where the reservoir is either a liquid or gel reservoir, or a non-adhesive matrix, the device **2** will furthe comprise an adhesive layer **10** that serves to adhere the device to the skin. The adhesive lay

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provide for selective movement of the sufentanil agent through the layer.

The backing layer **4**, which adl ıg-containing reservoir **6** serves as the ı layer of the device during use and func :imary structural element of the device. backing layer is thus typically a sheet or film of a preferably flexible elastomeric material th substantially impermeable to the sufentanil agent. This backing layer **4** typically has a thick of about 0.1 to 5 mils, preferably about 0.5 to 2 mils, and more preferably about 1 to 1.5 mil and is generally a material that permits the device to follow the contours of the skin such tha can be worn comfortably on any skin area including joints or other areas of flexure. Accordingly, there is a reduced likelihood of the device dislodging from the skin due to differences in the flexibility or resiliency of the skin and the device, as well as in response tc normal mechanical strain brought about by movement and the like. The backing layer may further be a monolithic (single layer) or a multi-layer (multilaminate), and may further be a breathable or occlusive material comprising fabric. Most commonly, the backing layer **4** wi a polymeric material, or a laminate of polymeric materials. Suitable materials include, but a not limited to, polyethylene, polypropylene, polyesters, polyurethanes, polyethylene vinyl acetate, polyvinylidene chloride, block copolymers such as PEBAX , polyvinyl acetate, polyvinylidene chloride, polyurethane, ethylene vinyl acetate, polyethylene terephthalate, polybutylene terephthalate, coated paper products, metal or metalized sheets and the like, an any combinations thereof.

In preferred embodiments, the backing layer **4** comprises a low-, medium- or high- olyethylene material, or a polyester material. In a particularly preferred embodime ng layer comprises a laminate of polyethylene and aluminum vapor coated polyest(OTCHPAK® 1109 Backing, available from 3M, St. Paul, MN), or a laminate of and polyethylene/ethylene vinyl acetate (e.g., SCOTCHPAK® 9733 Backing, ava).

he reservoir **6** is disposed on the backing layer. The reservoir may be formed from number of standard materials well known in the art. In those devices where the reservoir is liquid or gel-type reservoir, any suitable gelling agent may be used to form an aqueous gel system, for example cellulose materials. In those devices where the reservoir is a matrix-ty reservoir, it may be formed from any polymeric material in which sufentanil has some solub within a desired solubility range, for example, a polyurethane, ethylene/vinyl acetate copoly

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preferably a polyisobutylene, polyacrylate or a styrenic block copolymer-based adhesive.

More particularly, in those eml he invention where the transdermal deli system is provided as a monolithic, ad device, the reservoir **6** can be formed fr standard pressure sensitive adhesives known in the art. Suitable pressure sensitive adhesive use in the practice of the invention thus include, but are not limited to, polyacrylates, polysiloxanes, polyisobutylene (PIB), polyisoprene, polybutadiene, styrenic block polymers blends and combinations of the above, and the like. Suitable styrenic block copolymer-base adhesives include, but are not limited to, styrene-isoprene-styrene block copolymer (SIS), styrene-butadiene-styrene copolymer (SBS), styrene-ethylenebutene-styrene copolymers (SEBS), and di-block analogs thereof. Suitable acrylic polymers are comprised of a copoly or terpolymer comprising at least two or more exemplary components selected from acrylic acids, alkyl acrylates, methacrylates, copolymerizable secondary monomers or monomers w functional groups. Examples of monomers include, but are not limited to, acrylic acid, methacrylic acid, methoxyethyl acrylate, ethyl acrylate, butyl acrylate, butyl methacrylate, h acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acryl isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, dec methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, tridecyl methacrylat hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitri dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acryla tert-butylaminoethyl methacrylate, methoxyethyl acrylate, methoxyethyl methacrylate, and

, e.g., Satas (1989) "Acrylic Adhesives," *Handbook of Pressure-Sensitive Adhesive gy*, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, NY. In a preferr ent, the pressure-sensitive adhesive is an acrylate having no functional groups or c .g., DURO-TAK® 87-9301, available from National Starch & Chemical, Bridgew blend of acrylate-vinylacetates having –COOH and –OH functional groups (DURC 7-2051 and 87-2287, National Starch & Chemical).

In certain other preferred embodiments, the reservoir **6** is formed from a monolithic adhesive matrix containing a polyisobutylene material. The polyisobutylene preferably comprises a blend of a high molecular weight polyisobutylene (about 450,000 to 2,100,000 viscosity average molecular weight) and a low molecular weight polyisobutylene (about 1,0 450,000 viscosity average molecular weight). In the polyisobutylene compositions of the pr

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about 40:60 to about 90:10.

In a particularly preferred emb ressure-sensitive adhesive is a combina of low and high molecular weight poly IB) polymers, for example, a high molecular weight PIB having a viscosity average molecular weight of about 1,100,000 (OPANOL® B100, available from BASF, North Mount Olive, NJ) and a low molecular wei PIB having a viscosity average molecular weight of about 50,000-55,000 (OPPANOL® B 1 available from BASF). In another preferred embodiment, the pressure-sensitive adhesive is combination of a high molecular weight PIB having a viscosity average molecular weight o about 1,100,000 (VISTANEX® MM L-100, available from ExxonMobil, Houston, TX) and low molecular weight PIB having a viscosity average molecular weight of about 50,000-55, (OPPANOL® B 11 SFN, available from BASF).

In practice, the material forming the reservoir **6** has a solubility for the drug of about % to about 25 wt % of the total reservoir material; preferably about 2 wt % to about 20 wt % more preferably about 4 wt % to about 15 wt % ; and even more preferably about 6 wt % to about 12 wt %. The reservoir 3, with or without the adhesive coating 6, has a thickness of a

The reservoir **6** further includes the sufentanil agent and may also contain other optic ingredients, such as carriers, vehicles, additives, excipients, stabilizers, dyes, diluents, plasticizers, tackifying agents, crystallization inhibitors, solubility enhancers, inert fillers, antioxidants, anti-irritants, vasoconstrictors and other materials without pharmacological act that are suitable for administration in conjunction with the transdermal delivery systems of t vention. These optional materials are pharmaceutically acceptable in that they are do not interfere with delivery of sufentanil from the system, and are not for any ot iologically or otherwise undesirable. If a pressure sensitive adhesive is used in ce with the present invention, this must also be pharmaceutically acceptable. Exan itive materials include water, mineral oil, silicone, inorganic gels, aqueous emulsio gars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

Accordingly, in certain transdermal delivery systems of the invention where the rese is an adhesive matrix, the reservoir **6** comprises one or more materials capable of improving adhesive characteristics such as by reducing quick tack (tackifying agents), reducing cold-fl increasing viscosity, and/or toughening the matrix structure. Examples of suitable materials include, but are not limited to, aliphatic hydrocarbons; aromatic hydrocarbons; hydrogenate

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feedstocks of the thermal polymerization and subsequent hydrogenation of petrochemical feedstocks, rosin ester tackifiers, mine tylmethacrylate, high molecular weight acrylates, and any combinations theret

In certain systems, the reservoir **6** comprises one or more viscosity-enhancing agents improve the adhesive properties of the device, for example by allowing for removal and replacement. The viscosity-enhancing agent may further serve to reduce the abuse potential the transdermal delivery system by preferentially associating with the sufentanil agent to pr a highly viscous composition that resists extraction of the sufentanil agent under typical abu conditions (alcohol extraction). The material can be a high viscosity liquid carrier material ("HVLCM") that is non-water soluble, and has a viscosity of at least 5,000 cP, (and optiona least 10,000, 15,000; 20,000; 25,000 or even 50,000 cP) at 37°C and that does not crystalliz neat under ambient or physiological conditions. The term "non-water soluble" refers to a material that is soluble in water to a degree of less than one percent by weight under ambien conditions. A particularly preferred viscosity-enhancing agent is sucrose acetate isobutyrat (SAIB) or some other ester of a sugar alcohol moiety with one or more alkanoic acid moieti These materials have bioadhesive qualities.

In practice, a small amount of the SAIB or similar viscosity-enhancing agent is adde pressure-sensitive material such as a PIB or acrylic adhesive base. Due to the low hydrophobicity and low surface tension of the SAIB material, this enables the resultant adhesive/viscosity agent mixture to retain pressure sensitive properties even after the syster

lied and removed from the skin surface a number of times. This in turn allows the 'earing a long-duration patch to remove the device during showering or heavy exer reapply the device without losing adhesion.

i those systems where a plasticizer is utilized, the reservoir can further comprise a :r material that is typically an inert, organic, apolar, nonvolatile hydrophobic liquid ', the plasticizer may be a hydrophobic liquid. Suitable plasticizer materials thus include, but are not limited to, various long-chain aliphatic esters and alcohols, including su materials as polybutene, mineral oil, linseed oil, octyl palmitate, squalene, squalane, silicone isobutyl stearate, olive oil, isopropyl myristate, isostearyl alcohol, oleyl alcohol, and the like Particularly preferred for use herein is polybutene, for example IDOPOL® L-14 or H-100,

organic salts, s

inc oxide, mag

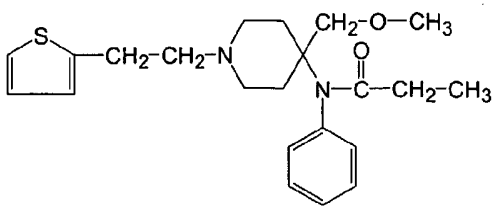
In addition, the reservoir can include one or more filler materials. Suitable fillers in
but are not limited to, metal oxides, in synthetic polymers, clays and the like.
metal oxides may be silicon dioxide, z gnesium oxide, titanium oxide, and calc
oxide. Inorganic salts can be calcium, magnesium and sodium carbonate, calcium and magnesium sulfate, calcium phosphate, and the like. Synthetic polymers can include metha resin, nylon, polyethylene, and the like. Suitable clay compounds include talc, bentonite an kaolin.

Referring again to Figures 1 and 2, the device **2** further comprises a peelable release **8**. The release liner is a disposable element that serves only to protect the device prior to application to the skin. Typically, the release liner is formed from a material impermeable tc sufentanil agent and other components of the system, and is easily removable from the reser Release liners can generally be made of the same materials as the backing layer. Suitable materials thus include a polymeric material that may be optionally metallized. Examples of polymeric materials include polyurethane, polyvinyl acetate, polyvinylidene chloride, polypropylene, polycarbonate, polystyrene, polyethylene, polyethylene terephthalate, polybutylene terephthalate, paper, and the like, and a combination thereof. In preferred embodiments, the protective layer comprises a siliconized polyester sheet, or has a fluoropolymer coating. Particularly preferred materials are SCOTCHPAK® 9744 (availabl from 3M), and MEDIRELEASE® 2249 (available from Mylan Tech., St. Paul, MN).

Referring now to Figure 2, certain transdermal delivery systems of the invention ma
n adhesive layer **10** that serves to adhere the device **2** to the skin. The adhesive lay
lly a drug-permeable pressure sensitive adhesive that is applied over the reservoir.
pressure sensitive adhesives are well known in the art. Suitable pressure sensitive
s for use in the adhesive layer **10** thus include, but are not limited to, polyacrylates,
anes, polyisobutylene (PIB), polyisoprene, polybutadiene, styrenic block polymers
d combinations of the above, and the like. These materials are disclosed in greater detail hereinabove. The adhesive layer may also serve the purpose of a rate controlling laye membrane. However, in some systems, a further layer **12** is added as a rate controlling membrane. Suitable rate controlling membrane materials are known in the art and include, are not limited to, low to high density polyethylene, ethylene vinyl acetate, polyurethane, an styrene poly-butadiene.

d it has the fol

(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N- phenylpropanamide. The molecu weight of sufentanil base is 386.56, an lowing structural formula:



The sufentanil agent is added to the reservoir in an amount of from about 0.1 mg/cm about 2 mg/cm^2, preferably in an amount of from about 0.3 mg/cm^2 to about 0.8 mg/cm^2, an even more preferably in an amount of about 0.4 mg/cm^2 to about 0.7 mg/cm^2.

Although a number of different transdermal delivery system configurations are suita for use in practicing the current invention, it is preferred that the systems are provided as a monolithic device, where the sufentanil is contained in an adhesive matrix adhered to a back layer. Accordingly, in one embodiment of the invention, a monolithic transdermal delivery system for administering sufentanil through the skin is provided. The system includes a pressure-sensitive adhesive matrix that contains sufentanil in an amount above the solubility sufentanil in the matrix. When the system is applied to a subject, the system provides a ally constant steady state net flux of sufentanil from the system through the skin of at 1 μg/cm^2/hour for at least about 24 hours. The system does not include a perme or rate controlling membrane. Here again, it is surprising that such high net flux hat do not employ a permeation enhancer or rate controlling membrane can still o such high standards, where upon achieving steady state conditions, the system at least a first order release rate profile such that the system achieves substantially order release to provide a constant steady state flux of sufentanil from the system over an extended period of time. In certain systems, the system provides a substantially constant ste state net flux of sufentanil from the system through the skin of at least about 1 μg/cm^2/hour least about 36 hours

Additionally, certain systems are also able to provide an even higher steady state net net flux of sufentanil from the system through the skin, for example at least about 1.5

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that the adhesive matrix has a drug releasing interface surface area of from about 1-10 cm².

In certain of the instant constar flux transdermal delivery systems of th present invention, the sufentanil agent t in an amount of about 1-20 weight per (wt%) relative to the total system, preferably in an amount of about 1-12 wt%. The transde delivery systems are provided with sufficient amount of the sufentanil agent to provide for a steady state net flux sufficient to administer the sufentanil at from about 0.01 to 200 μg/hou when the system is applied to the skin of a subject. Still other systems of the present inventi provide a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hc when the system is applied to the skin of a subject, while further systems are able to provide steady state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour. The pr systems contain a sufficient amount of sufentanil so that they may be used to induce and maintain a suitable state of analgesia in a subject for 3 or more days when applied to the ski that subject. Other systems contain a sufficient amount of sufentanil to induce and maintain suitable state of analgesia in a subject for 5 or more days, while still others contain enough t induce and maintain a suitable state of analgesia in a subject for 7 or more days.

In another related embodiment of the invention, a monolithic transdermal delivery s for administering sufentanil through the skin is provided. The system includes a pressure-sensitive adhesive matrix that contains sufentanil in an amount above the solubility of sufen in the matrix. When the system is applied to a subject, the system provides a net flux of sufentanil from the system through the skin of at least about 1 μg/cm²/hour. The system

a dosage form rate control over flux of sufentanil from the system, but the system de a permeation enhancer or rate controlling membrane. In these systems, the sufe ed as a depot, and is thus present in the system in an amount above the solubility of l in the system, such that there will be both dissolved and undissolved sufentanil in

In certain systems, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufentanil from system is at least about 50% while still providing the substantially high rate of net flux from system. In certain systems, the dosage form rate control ($\frac{J_N}{J_D}$) over flux of sufentanil from system is even higher, for example at least about 60%, while in still other systems the dosag form rate control is at least about 65%. As with the other systems of the present invention, t

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part by using a pharmaceutically acceptable adhesive matrix carrier composition and/or a ra

controlling membrane. Despite not in[illegible]leation enhancer or rate controlling membrane, certain systems are able to [illegible]en higher net flux of sufentanil from the system through the skin, on the order of at least about 1.5 μg/cm^2/hour, while still others can provide a net flux of around 2 μg/cm^2/hour.

In certain of the subject monolithic systems, the sufentanil agent can be present in an amount of about 1-20 weight percent (wt%) relative to the total system, preferably in an amount of about 1-12 wt%. The instant transdermal delivery systems are provided with sufficient amount of the sufentanil agent to provide for a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 μg/hour when the system is applied to the skin of a subj Certain other systems of the present invention provide a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when the system is applied to the skin o subject, while still further systems are able to provide a steady state net flux sufficient to administer sufentanil at from about 1 to 2 μg/hour. It is a surprising feature of the instant systems in that they can also provide a substantially constant steady state net flux of sufenta from the system through the skin for at least about 24 hours. Certain other systems are furth able to provide a substantially constant steady state net flux (J_N) of sufentanil of at least abo μg/cm^2/hour. Still others are able to provide a substantially constant steady state net flux (J_1 sufentanil for at least about 36 hours. In certain preferred systems, the overall size of the transdermal delivery system is kept to minimum, such that the adhesive matrix has a drug interface surface area of from about 1-10 cm^2.

he monolithic transdermal delivery systems contain a sufficient amount of sufentar may be used to induce and maintain a suitable state of analgesia in a subject for 3 s when applied to the skin of that subject. Other systems contain a sufficient amou l to induce and maintain a suitable state of analgesia in a subject for 5 or more days l others contain enough to induce and maintain a suitable state of analgesia in a sut for 7 or more days.

In yet a further related embodiment of the invention, a transdermal delivery system f administering sufentanil through the skin of a living subject is provided. The subject systen provides a substantially constant delivery rate of sufentanil over a single application administration period of at least about 48 hours and the constant delivery rate is sufficient to

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the delivery ra

sufentanil from the transdermal delivery system is substantially zero order. In others, the delivery rate of sufentanil is characteri decline or increase of about 5 to 6% ov administration period, and preferably, te of sufentanil is characterized by substantially no total increase or decrease over the administration period. The subject transdermal delivery systems are able to provide a delivery rate at steady state of at least ab μg/hr to 10 μg/hr, and the administration period extends from at least about 48 hours to 7 da Additionally, all of the above-described transdermal delivery systems of the present inventi can be engineered to provide a substantially constant delivery rate of sufentanil over a singl application administration period of at least about 48 hours, wherein the constant delivery ra sufficient to establish and maintain a plasma sufentanil concentration having a minimum to maximum ratio of about 1.8 or less over the relevant administration period.

All of the transdermal delivery systems of the present invention can be readily manufactured using known techniques. For example, to produce matrix-type systems, a sol of a suitable polymeric reservoir material can be added to a double planetary mixer, followe addition of desired amounts of the sufentanil base. Typically, the polymeric reservoir mater an adhesive polymer, which can be solubilized in an organic solvent, e.g., ethanol, ethyl ace and hexane. After mixing has taken place for a suitable period of time to achieve acceptabl uniformity of the ingredients, the resultant mixture can be feed into a casting die. In such c the matrix/sufentanil mixture is cast as a wet film onto a moving web or belt, which is draw through lines and a series of ovens are then used to evaporate the casting solvent to acceptat imits. The dried reservoir film can then be laminated to a selected backing membra und onto take-up rolls. In subsequent operations, individual transdermal patches a eparated and unit-packaged. In other processes, a reservoir can be formed using dr and thermal film-forming using equipment known in the art. Preferably, the mater ended and extruded using a slot die followed by calendering to an appropriate

When manufacturing certain preferred monolithic systems according to the inventio include a polyisobutylene/polyisobutylene blend as the matrix, it is preferable to use a solve the polyisobutylene that is a non-solvent for the sufentanil, such as low molecular weight hydrocarbon solvents like heptane, hexane, or cyclohexane. Preferably, the mixture of

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into glass ves

A preferred manufacturing process for a monolithic transdermal delivery system pre according to the invention is as follow d amounts of both high and low molecu weight PIBs and polybutene are added sels containing pre-measured amount o heptane and the containers are sealed. The PIB fractions and polybutene in the sealed conta are completely dissolved in n-heptane at room temperature using magnetic stirring equipme Mixing of the n-heptane polymer solution may continue in case when one or more of the ina ingredients needs to be added in the polybutene-PIB formulations. Typical mass ratios of th low molecular weight PIB, high molecular weight PIB, polybutene oil and n-heptane are: 1.23:1:2.1:10.1, respectively. Selective additives in small quantities can be added at the exp of all other non-solvent materials in the solution.

A pre-weighed amount of sufentanil is added to the above n-heptane solutions of polybutene-polyisobutylene and the sufentanil suspension is homogeneously mixed for approximately 2 days for complete equilibration of sufentanil and the vehicle, using magnet stirring equipment at room temperature. Then, stirring action is stopped for approximately 1 minutes, air bubbles are removed from the sufentanil suspension, which is now ready to be transferred on a piece of release liner for precision-thickness coating of the suspension using either a motorized film applicator (Elcometer, Inc.) or precision glass plates and square mul clearance applicators (Gardner PG&T Co.).

The wet suspension films on release liner section are air-dried for approximately 20 minutes at room temperature and 30 minutes at 70°C in a convection oven (Blue M Electric, ass A Oven). The oven dried sufentanil suspension films coated on the release line rvoir/release liner laminate) are cooled to room temperature and a precut piece of t ilm is laminated onto the reservoir/release liner laminate, which is still sitting on a glass plates. A aluminum roller (diameter: 1 in., length: 4 in.) or a piece of lamina it (Roll over Roll Coater, SciMac Scientific Machine) is used to aid the lamination zing and eliminating air pockets out of the reservoir/release liner laminates.

The final steps of the sufentanil transdermal delivery system fabrication include die cutting the final laminates, using steel rule dies and a punch press (Schmidt Toggle Press, Schmidt Feintechnik Corp.) into required system size (Apex Die, Inc.). Appearance of the c edges of the systems is examined. The total thickness and weight of the systems are determi using a pair of calipers (Mitutoyo Corp.) and a precision balance, respectively and recorded.

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pouches are labeled appropriately and counted and recorded.

Referring now to Figure 3, a fl ustrating the system manufacturing ste along with materials, tools and equipm quired for each unit operation for the systems is provided.

Once the transdermal delivery systems are produced, they are used to provide an extended period of analgesia in a subject using the following methods. The term "subject," used herein, is used interchangeably with "individual" and refers to any vertebrate in which desired to provide a state of analgesia. The term thus broadly refers to any animal that is to treated with the systems of the present invention, such as birds, fish and mammals including humans. In certain embodiments, the systems and methods of the present invention are suit to provide sustained analgesia in veterinary practice and animal husbandry, e.g., birds and mammals, whenever a long-term state of analgesia is convenient or desirable. In certain cas the compositions are particularly suited for used with companion animals such as dogs or ca and additionally may be used with horses. In preferred embodiments, the term "subject" int a human subject. Furthermore, the term "subject" does not denote a particular age, and the present systems are thus suited for use with subjects of any age, such as infant, adolescent, a and senior aged subjects.

A suitable transdermal delivery system containing sufentanil and prepared according the present invention is applied to a clean, dry and preferably non-hairy area of skin on a sul for example, the inner upper arm surface or upper buttock. It is intended that different skin d for subsequent system applications. Upon application to the skin, the sufentanil of the transdermal delivery system will diffuse into the skin where it is absorbed ir stream to produce a systemic analgesic effect. The onset of analgesia depends on ıctors, such as, potency of the sufentanil, the solubility and diffusivity of sufentanil the thickness of the target skin, the concentration of sufentanil in the device reserv ke. Generally, the subject will experience an adequate effect within about one to s hours of initial application. When continuous analgesia is desired, a depleted system is rem and a fresh system applied to a new location. For example, the 3 to 7 day systems of the pre invention can be sequentially removed and replaced with a fresh system at the end of the administration period to provide relief from chronic pain. Substantially uninterrupted seque system applications can thus be used to maintain plasma sufentanil levels at a substantially

EXAMPLI

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Below are examples of specific embodiments for carrying out the present invention. examples are offered for illustrative purposes only, and are not intended to limit the scope o present invention in any way.

Example 1: *In Vitro* Sufentanil Flux Through Human Skin.

In-vitro permeation sufentanil flux studies were conducted with human skin from ca donors (dermatomed full thickness). Thigh skin from sixteen different donors was used in t experiments, with a minimum of 5 replicate skin samples per donor (total n = 82). Prior to t *vitro* skin drug flux experiment, the skin tissue was examined under a magnifying glass for a defects such as pinholes. Excluding any damaged areas, the intact skin areas were cut into 1 inch circles. Monolithic adhesive matrix patches using a high molecular weight / low molec weight polyisobutylene (PIB) blend for the adhesive was prepared as described above. In th tests, a sufentanil transdermal delivery system was placed on the *stratum corneum* side of th pre-cut skin sample. Then, the assembly of system and pre-cut skin specimen was positione the top edge of the receptor side of a modified Franz cell with the dermal side of the skin tis facing the receptor chamber. The donor side of the Franz Cell was securely positioned over skin/system assembly, and the receptor chamber was filled with citrate buffer at pH 5.0

g 0.01% sodium azide. The Franz cell with the test system was equilibrated at 32°(ion of the experiment. At predetermined intervals (typically 6 hours, 1, 2, 3, 4, 5, 6 he entire receptor solution was collected from the Franz cell and refilled with fresh medium. The receptor solutions were assayed for sufentanil concentration using a romatographic method. The cumulative delivery amount and skin drug flux were d for each skin/test system assembly. Figure 3 illustrates the actual sufentanil skin over 7 days through human cadaver specimens from the 16 different donors. The overall av sufentanil skin flux was approximately 1.9 μg/cm² /hr, with a coefficient of variation of 40%

3) blend for th

1 cm² of 1.42 cm² monolithic adhesive matrix patches, using a high molecular weight / lov molecular weight polyisobutylene (PII e adhesive and containing sufentanil we prepared as described above.

In the test, the sufentanil transdermal delivery system was held adhesively on a stain steel holder, having the drug releasing surface of the patch facing up and immersable in rele medium, and positioned at the center of a USP Dissolution Apparatus II with 1 L vessels. Accurately, 600 mL of degassed 0.005N sodium phosphate, pH 5.5 buffer solution was plac the vessels and maintained at 32° C while the paddle speed was maintained at 50 rpm durin dissolution experiment.

At the preset time intervals of 1, 2, 4, 8, 12, 16, 24, 36, and 48 hours, 1 mL portions the dissolution medium was withdrawn from the vessels and dispensed into HPLC vials. Th following conditions were used for the sufentanil assay in the samples:

Mode:		Isocratic
Mobile Phase:	A - 75%	0.1% triethylamine in H_2O
	(adjusted to pH=3.0 with H_3PO_4)	
	B - 25%	100% acetonitrile
Stop Time:		4.0 minutes
Post time:		None
Column Temperature:		40°C
e:		1.0 mL/min
ction:		230 nm
Volume:		10 µL
pler Temperature:		ambient room temperature
ı time:		2 minutes

rom the sufentanil concentration, total volume of the buffer solution remaining in tl vessels and time intervals, it was possible to calculate the cumulative amounts of sufentanil dissolved or released from the patches over time, and dissolution rate or release rate of sufer from the sample transdermal delivery systems were calculated.

The results from the dissolution rate test are presented in Figures 5A and 5B, and provided below in Tables 1 and 2.

Time (hours)	Amount of Sufentanil (µg) Vessel 1	Amount of Sufentanil (µg) Vessel 2	Amount of Sufentanil (µg) Vessel 3	Amount of Sufentanil (µg) Vessel 4			% In Sufen Load Relea
0.5	59.5	59.81	58.10	49.66	56.71	4.75	6.56
1	137.48	146.58	142.16	140.91	141.78	3.76	16.39
2	236.93	251.04	242.34	243.48	243.45	5.81	28.14
3	309.37	334.27	318.36	321.13	320.78	10.30	37.08
4	371.07	399.54	387.28	386.72	386.15	11.67	44.64
6	445.24	467.06	441.88	443.05	449.31	11.92	51.94
8	469.14	503.65	486.94	486.77	486.62	14.09	56.26
12	513.76	553.54	518.40	520.91	526.66	18.17	60.88
16	533.20	578.49	544.58	546.57	550.71	19.44	63.67
24	576.36	624.70	583.73	587.56	593.09	21.58	68.57
36	622.85	673.35	621.61	632.56	637.59	24.34	73.71
48	652.20	704.98	658.56	673.27	672.25	23.53	77.72

Table 2

Midpoint Time (hour)	Rate (µg/cm²/hr) Vessel 5	Rate (µg/cm²/hr) Vessel 6	Rate (µg/cm²/hr) Vessel 7	Rate (µg/cm²/hr) Vessel 8	Average	SD
	81.31	68.65	77.09	59.42	71.62	9.68
	109.95	107.80	123.80	115.59	114.28	7.14
	73.84	70.74	74.89	70.86	72.58	2.10
	58.57	48.24	55.33	59.41	55.39	5.08
	40.21	37.21	43.66	33.42	38.62	4.35
	22.76	21.60	23.56	20.22	22.03	1.45
7	12.68	11.32	10.90	14.25	12.29	1.51
10	7.75	6.50	6.12	7.96	7.08	0.91
14	3.23	5.68	5.26	4.65	4.70	1.07
20	3.20	3.18	2.31	3.38	3.02	0.48
30	3.09	2.01	2.10	1.96	2.29	0.53

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Example 3: Pharmacokinetic E ufentanil Transdermal Delivery System Following A Single Application in Rats.

Sufentanil transdermal delivery systems having a drug releasing interface surface ar 1 cm^2 or 1.42 cm^2 (both of which contain approximately 0.67 mg sufentanil free base per cn were applied to 5 each of male and female rats of 7 to 8 weeks old (CD (Crl:CD® (SD) 1 G BR) from Charles River Labs). The systems were monolithic adhesive matrix patches, usin high molecular weight / low molecular weight polyisobutylene (PIB) blend for the adhesive were prepared as described above.

At least 16 hours before dosing, the back and shoulders of each animal was shaved a the targeted application areas washed with water. Care was taken not to abrade the skin. O the transdermal delivery systems was applied to the dorsal midline and held in contact with skin by elastic wrap placed over the system and around the animal. During the course of th study, the animals were given *ad libitum* certified rodent diet #8728C(Harlan Teklad, Inc) a water, and housed in a controlled environment, temperature of 18-26 °C, a relative humidity 50±20% and a 12 hour light/12 hour dark cycle.

Blood samples (approximately 1 ml each) were collected from each animal at time 0 (before system application) and at 24, 48, 96 and 168 hours after application of the system. Blood v collected via jugular venipuncture and transferred into tubes containing potassium EDTA

ılant.

lood samples were maintained on wet ice, in chilled Kryoracks, or at approximatel entrifugation to obtain plasma. Centrifugation was carried out within 30 minutes o ı. Plasma samples were transferred to a tube and were maintained on dry ice prior t approximately -70°C.

ufentanil in the plasma samples was assayed using HPLC. The analytical techniqu the determination of sufentanil in rat plasma was as follows. Sufentanil in rat plasma was determined using a HPLC/MS/MS method in the positive electrospray mode. The analytica column was a YMC basic (50 x 2 mm, 5u) with mass detection of the transitions 387.4/238. amu for sufentanil and 337.4/188.0 amu for the internal standard.

The results of the study are presented below in Table 3.

		Plasma (pg/mL)		
Patch Size, No. of Subjects	Sample Time	Average Conc.	Standard Deviation	% RSD
1.0 cm^2, Male + Female n = 9	0	0	0	0
	24	1232	655	53
	48	1428	930	65
	96	994	331	33
	168	856	328	38
1.42 cm^2, Male + Female n = 10	0	0	0	0
	24	1211	412	34
	48	1360	493	36
	96	1235	384	31
	168	781	332	43

The data from the 1.42 cm^2 patch study are also depicted in Figure 6. As can be seer plasma concentration of sufentanil, delivered from a single transdermal delivery system, hav drug releasing interface surface area of 1.42 cm^2, increased to establish an approximate cons level starting at approximately 24 hours after the system application and continued to maint for 168 hours (7 days). During the course of the 7-day delivery, the plasma itions of sufentanil from time 24-168 hours in male and female rats were approxim 0 pg/ml and 1,140 ±270 pg/ml, respectively. There is no statistically significant e in the sufentanil plasma concentrations between the male and female rats, suggest drug delivery rate from the system and pharmacokinetic parameters such as systen rance do not differ significantly between the two sexes of the rats used in the PK st

The variability of the sufentanil plasma concentrations is remarkably and equally lov both male and female rats (coefficient of variation of approximately 23%), confirming the fa that not only the variability of systemic clearance of the drug in different rats is low but also most importantly rate controlled drug delivery through the skin of different rats of both sexe

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Example 3: Preparation of Sufentan al Delivery Systems.

A series of 3-day and 7-day mc ;ive matrix patches, using either a high molecular weight / low molecular weight polyisobutylene (PIB) blend, or acrylic polymers 1 the adhesive are prepared as follows. The systems include from 1 to 4 mg of sufentanil and prepared to deliver in human subjects, depending on the system size, from about 90 to 360 μ sufentanil per day, from systems having a drug releasing interface surface area of from 2 to cm^2, respectively. Each system is individually packaged in an aluminum foil pouch carryin appropriate pharmaceutical label.

The components for the 7-day systems are listed in Table 4 below.

Table 4

Components	Primary material / Vendor	Regulatory Status	Secondary material / Vendor	Regulatory Status	Notes
Backing Film	Scotchpak 1109 Backing (3M)	DMF # 2610	Scotchpak 9733 Backing (3M)	DMF # 14291	1109 - laminate of polyethylene and aluminum vapor c polyester. 9733 - laminate of polyester and polyethylene/ethyl vinyl acetate.
High Molecular Weight PIB utylene	Oppanol B100 (BASF)	Conforms to 21 CFR 172.615 (chewing gum base). ISO 9001 Certified	Vistanex MM L-100 (ExxonMobil)	Conforms to 21 CFR 172.615 (chewing gum base).	Viscosity average molecular weight i approx. 1,100,000
ecular IB utylene	Oppanol B 12 SFN (BASF)	Conforms to 21 CFR 172.615 (chewing gum base). ISO 9001 Certified	Oppanol B 11 SFN (BASF)	Conforms to 21 CFR 172.615 (chewing gum base). ISO 9001 Certified	Viscosity average molecular weight i approx. 50,000-55
ıe	Indopol L-14 (BP Amoco)	DMF # 17390	Indopol H-100 (BP Amoco)	DMF # 17390	Indopol L-14 is viscosity-equivale light mineral oil, U
Release Liner	Scotchpak 9744 (3M)	DMF # 15781	Medirelease 2249 (Mylan Tech)	DMF # 14652	3M release liner h fluoropolymer coa and Mylan's relea liner has a silicone coating
Pouch	Polyester/ foil (Technipaq)	Conforms to appropriate CFR sections	Paper/ polyester/ foil (Technipaq)	Conforms to appropriate CFR sections	Approximately 2.7 x 3.25 in
Label	Paper Label	Not applicable	None	Not applicable	Product and drug

			ndial	Povic Crosp	
	(Avery)				drug content, and number
Additional Inactive Ingredients	Colloidal Silicone Dioxide (Cabot)	NF compe	lone/ povidone (BASF)	USP/NF compendial	CSD grade is M5F M5DP. Povidone grade is Kollidon 30 or crospovidone grad Kollidon CL-M.

The components for the 3-day systems are listed in Table 5 below.

Table 5

Components	Primary material / Vendor	Regulatory Status	Secondary material / Vendor	Regulatory Status	Notes
Backing Film	Scotchpak 1109 Backing (3M)	DMF # 2610	Scotchpak 9733 Backing (3M)	DMF # 14291	1109 - laminate of polyethylene and alu vapor coated polyest 9733 - laminate of p and polyethylene/eth vinyl acetate.
Acrylate	Duro-Tak 87-9301 (National Starch & Chemical)	DMF # 7477	Duro-Tak 87-2051, 87-2287 (National Starch & Chemical)	DMF # 7477 DMF # 7477	87-9301 has no funct groups and no cross l 87-2051and 87-2287 COOH and OH funct groups, respectively, acrylate-vinylacetate
Release Liner	Scotchpak 9744 (3M)	DMF # 15781	Medirelease 2249 (Mylan Tech)	DMF # 14652	3M release liner has fluoropolymer coatin Mylan's release liner silicone coating
	Polyester/ foil (Technipaq)	Conforms to appropriate CFR sections	Paper/ polyester/ foil (Technipaq)	Conforms to appropriate CFR sections	Approximately 2.75 3.25 in
	Paper Label (Avery)	Not applicable	None	Not applicable	Product and drug nar system size, drug cor and code number
	Colloidal Silicone Dioxide (Cabot)	NF compendial	Povidone/ Crospovidone (BASF)	USP/NF compendial	CSD grade is M5P o Povidone grade is K 30 or crospovidone g Kollidon CL-M.

Example 4: *In vivo* Pharmacokinetic Study with 7-day Sufentanil Transdermal Deliv Systems.

Two Sufentanil transdermal delivery systems (patches) were produced, in two sizes with active surface areas of 2 and 8 cm^2, and used in a clinical pharmacokinetic performanc

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transdermal patches was as follows (on a percentage of total dry weight): Oppanol B100 (15.
Oppanol B12 SFN (22.0%); Indopol P 4 (48.5%); CAB-O-Sil M-5P (6.4%); ar
sufentanil (7.7%); with the final patch :chpak #9744 release liner (3M) and a
Scotchpak #1109 backing material (3M). The two sizes of patches were identical in all aspe
except that the casting thicknesses were different; that is, "thin" patches were produced havi
nominal 15 mil (wet) coating thickness of the bulk matrix/drug formulation, and "thick" pat
were produced having a nominal 25 mil (wet) coating thickness of the same bulk formulatio
The amount of sufentanil present in the patches was proportional to the casting thicknesses,
therefore "thin" patches had a lower sufentanil drug content per square cm compared to the
"thick" patches. The average sufentanil content per patch determined at the time of lot relea
for the thin and thick sufentanil patch lots, 2 cm^2 and 8 cm^2 sizes, used in the present study a
summarized in Table 6. As can be seen, the thick 2 cm^2 and 8 cm^2 patches had at least abou
75% higher sufentanil content compared to the corresponding thin 2 cm^2 and 8 cm^2 patches.

Table 6

Sufentanil TTS Descriptions and Observed Sufentanil Content

Lot Number	Code Number	Patch Size (cm^2)	Formulation Nominal Casting Thickness	Observed Sufentanil (mg) per Patch at T=0 (n=10)
24A	45-01	2	15 mil, thin	0.91
25A	47-01	2	25 mil, thick	1.70
24B	45-02	8	15 mil, thin	3.84
25B	47-02	8	25 mil, thick	6.71

he study was performed in 24 healthy human volunteers, broken up into four test gr
viduals each (n=6), wherein the sufentanil patches were applied to the chest of the
subjects that had been blocked with naloxone. In order to ensure that the patches remained i
place, breathable overlay tape was used for each subject. The study was initiated with a low
dose intravenous (IV) infusion of sufentanil (48 μg/6 hours) followed by application of the 2
thick and thin patches, or a high dose IV infusion of sufentanil (192 μg/6 hours) followed by
application of the 8 cm^2 thick and thin patches. The patches were left in place for 7 days an

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ge and standar

observed for the subjects that wore the 2 cm^2 patches are reported in Table 7 below, and the individual sufentanil plasma levels obs subjects that wore the 8 cm^2 patches are reported in Table 8 below. The averag l deviation sufentanil plasma levels for four of the test groups are reported in Table 9 below, and the average plasma levels across d 1-7 of the study are reported in Table 10 below. Figure 7 depicts the measured sufentanil pl levels for the subjects that wore the thin patches, and Figure 8 depicts the measured sufentar plasma levels for the subjects that wore the thick patches. Finally, Figure 9 depicts the aver sufentanil plasma levels from all four test groups.

Sufenta

mal Volunteers after Application of Sufentanil TTS for 7 Days

Time (Hours)	Time (Days)	Lot 25A, 2 cm^2 - Thick Patches											
		Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8	Subject 9	Subject 10	Subject 11	Subj 12
0	0.00	0	0	0	2.83	3.05	2.10	0	0	0	0	2.03	0
4	0.17	4.27	5.06	0	2.66	8.12	4.28	5.71	2.15	2.82	3.07	5.52	4.3
8	0.33	13.6	13.2	5.61	4.91	26.2	5.72	14.2	11.6	15.8	8.83	15.6	14.
16	0.67	18.3	26.7	11.4	16.7	30.6	11.3	18.4	23.5	18.6	15.9	15.6	20.
24	1.00	26.4	33.6	20.7	23.5	54.3	14.4	22.8	30.0	28.5	16.9	27.0	22.
28	1.17	22.8	32.5	22.9	24.4	34.0	20.0	22.6	32.0	27.8	17.6	27.1	26.
32	1.33	20.5	26.2	20.4	32.5	33.1	13.9	19.8	31.6	31.8	19.7	27.4	23.
36	1.50	22.3	25.3	29.3	31.9	35.2	20.9	20.8	32.6	27.9	20.3	28.9	27.
40	1.67	17.6	23.1	19.0	36.5	33.5	19.6	21.8	28.8	29.4	16.7	2	5.
48	2.00	23.3	32.2	25.9	40.7	48.4	19.0	22.1	34.2	33.2	16.1	3	3.
52	2.17	18.9	32.5	25.9	42.4	47.9	24.0	32.2	35.7	37.9	20.2	3	5.
56	2.33	22.9	43.1	31.5	33.7	45.3	21.7	26.5	37.3	34.1	20.6	3	9.
60	2.50	17.8	36.5	22.8	35.8	39.9	14.2	21.6	32.5	31.8	20.5	3U.U	23.
64	2.67	22.8	36.1	25.3	43.2	34.1	18.9	21.8	33.2	26.5	20.0	29.4	18.
72	3.00	21.8	29.3	25.8	56.0	43.3	25.4	19.3	39.3	36.2	17.1	30.3	33.
80	3.33	13.7	30.3	31.1	43.3	35.3	19.2	21.3	36.5	27.4	16.0	30.0	28.
88	3.67	18.8	29.2	21.8	50.2	33.6	17.2	27.9	35.5	33.7	20.2	28.3	28.
96	4.00	13.3	31.1	37.0	54.2	39.0	32.8	16.9	37.0	33.4	21.0	33.1	30.
104	4.33	14.6	28.9	39.1	54.5	35.6	25.6	14.0	34.8	26.7	18.8	28.3	22.
112	4.67	12.0	26.3	26.8	39.4	31.4	26.2	23.4	27.4	31.2	19.8	26.9	20.
120	5.00	18.7	31.3	27.6	56.1	40.8	21.2	24.9	32.8	23.5	21.5	32.6	23.
128	5.33	11.4	36.9	28.3	44.2	35.4	16.3	21.8	33.2	23.6	19.9	30.5	18.
136	5.67	13.9	24.1	28.3	33.2	31.7	15.4	23.4	28.4	29.1	19.9	25.7	15.
144	6.00	15.5	29.0	27.1	41.8	39.2	26.8	15.1	31.9	33.2	17.8	28.3	24.
152	6.33	18.0	29.0	27.5	41.7	35.5	22.3	16.5	26.4	16.9	19.5	23.4	24.

4.0	3
3.9	2
0.3	2
0.6	1

Table 8

Sufenta

mal Volunteers after Application of Sufentanil TTS for 7 Days

Time Hours	Time Days	Subject 13	Subject 14	Subject 15	Subject 16	Subject 17	Subject 18	Subject 19	Subject 20	Subject 21	Subject 22	Subject 23	Subject 24
		atches						Lot 25B, 8 cm^2 - Thick Patches					
0	0.00	4.93	3.87	6.26	2.78	8.02	4.76	4.20	7.02	5.66	9.61	5.69	9.06
4	0.17	12.6	10.9	6.82	14.8	21.9	18.8	15.7	34.3	10.1		18.9	39.9
8	0.33	57.2	38.3	12.1	40.9	60.1	60.7	47.8	67.2	47.1	36.1	205	142
16	0.67	83.1	86.3	58.0	83.9	68.0	88.2	78.3	94.2	102	73.7	93.7	126
24	1.00	79.1	145	91.9	74.8	78.5	150	106	81.0	124	135	108	163
28	1.17	112	110	90.0	98.4	112	110	116	91.7	127	108	132	152
32	1.33	101	113	97.7	113	85.2	121	114	99.5	126	138	152	190
36	1.50	103	118	94.6	99.0	93.8	137	109	104	137	150	125	152
40	1.67	89.0	108	110	128	95.4	120	101	89.3	150	128	122	—
48	2.00	99.7	131	96.4	96.1	89.3	127	110	92.7	157	124	145	—
52	2.17	97.3	112	120	107	82.8	123	110	111	178	136	106	—
56	2.33	112	94.7	115	149	87.4	135	94.7	108	156	129	159	—
60	2.50	113	91.8	108	95.2	93.6	130	88.3	88.9	120	118	112	—
64	2.67	117	94.3	122	138	99.3	128	109	74.6	138	107	157	135
72	3.00	116	113	116	118	89.7	103	91.9	105	140	199	116	180
80	3.33	99.3	96.4	124	147	95.2	120	89.9	93.3	132	200	131	155
88	3.67	98.9	104	105	117	94.8	86.0	83.6	80.1	113	155	133	135
96	4.00	119	130	107	127	88.2	93.5	103	83.6	141	197	150	134
104	4.33	105	103	124	133	93.1	79.0	87.6	80.3	135	186	174	150
112	4.67	94.4	95.6	114	143	80.9	65.4	97.1	73.1	129	243	149	150
120	5.00	113	88.5	150	108	86.2	92.2	105	88.8	160	326	155	140
128	5.33	106	103	150	139	88.1	96.4	81.6	67.6	114	300	160	148
136	5.67	90.1	79.0	127	112	69.1	77.4	83.2	59.4	93.0	280	120	107
144	6.00	82.8	93.1	167	146	66.0	96.0	98.8	70.9	128	310	148	111
152	6.33	85.4	86.8	117	135	89.4	61.4	69.2	75.5	108	342	128	104
160	6.67	79.8	85.9	102	153	76.3	70.1	76.2	63.0	125	246	136	106

	170
	189
	158
	180
	140

erage Plasma Levels for Sufentanil TTS

Time (Hours)	Time (Days)	Lot 24A, 2 cm² Thin Patches		Lot 24A, 2 cm² Thick Patches		Lot 24B, 8 cm² Thin Patches		Lot 25B, 8 cm² Thick Patches	
		Average	SD	Average	SD	Average	SD	Average	SD
0	0.00	1.3	1.5	0.3	0.8	5.1	1.8	6.9	2.1
4	0.17	4.1	2.7	3.9	1.5	14.3	5.5	23.8	12.7
8	0.33	11.5	8.2	13.5	2.7	44.9	18.8	90.9	67.8
16	0.67	19.2	8.0	18.7	2.9	77.9	12.1	94.7	18.7
24	1.00	28.8	14.0	24.7	4.8	103.2	34.8	119.5	28.1
28	1.17	26.1	5.7	25.5	4.9	105.4	9.1	121.1	20.8
32	1.33	24.4	7.6	25.7	5.5	105.2	13.0	136.6	31.9
36	1.50	27.5	5.6	26.3	4.8	107.6	16.9	129.5	20.4
40	1.67	24.9	8.1	26.0	6.5	108.4	14.6	126.7	30.0
48	2.00	31.6	11.2	27.2	7.7	106.6	17.7	136.3	34.7
52	2.17	31.9	11.3	30.3	6.6	107.0	15.0	133.2	29.7
56	2.33	33.0	9.9	28.1	7.2	115.5	23.4	137.8	32.8
60	2.50	27.8	10.9	26.6	5.4	105.3	14.8	112.7	22.6
64	2.67	30.1	9.2	24.9	5.8	116.4	16.8	120.1	29.2
72	3.00	33.6	13.3	29.2	9.1	109.3	11.0	138.7	42.9
80	3.33	28.8	10.8	26.6	7.1	113.7	20.5	133.5	41.0
88	3.67	28.5	12.4	28.9	5.4	101.0	10.5	116.6	30.1
96	4.00	34.6	13.3	28.7	7.9	110.8	17.5	134.8	39.4
104	4.33	33.1	13.5	24.2	7.4	106.2	19.8	135.5	43.8
112	4.67	27.0	8.9	24.9	4.4	98.9	27.0	140.2	58.7
120	5.00	32.6	13.9	26.5	4.9	106.3	24.0	162.5	84.9
128	5.33	28.8	12.7	24.7	5.9	113.8	24.8	145.2	83.9
136	5.67	24.4	8.2	23.7	5.1	92.4	22.5	123.8	79.3
144	6.00	29.9	9.5	25.1	7.4	108.5	39.2	144.5	85.2
152	6.33	29.0	8.6	21.1	4.1	95.8	26.1	137.8	102.4
160	6.67	26.3	9.3	23.8	3.7	94.5	30.6	125.4	65.3

Lot Number	Lot Description	Average (pg/mL)	SD
	scription		
	cm^2, thin		
24A	2 c	29.2	10.1
25A	2 cm^2, thick	25.9	5.9
24B	8 cm^2, thin	105.0	21.1
25B	8 cm^2, thick	133.3	51.7

As can be seen by a review of the data presented in Tables 7-10, there is no significa difference in the sufentanil plasma levels achieved between the 2 cm^2 transdermal patches, e though the thick patches (Lot 25A) had about 75% greater sufentanil drug content as compa with the thin patches (Lot 24A). This same observation can be made with regard to the 8 cn transdermal patches. As can also be seen with regard to the data depicted in Figures 7-9, the *vivo* flux of sufentanil from the patches (both thick and thin) remained essentially constant a a single application administration period of at least about 7 days. Furthermore, with regard the data presented in Tables 7-10, it can be seen that the transdermal patches were able to provide a substantially constant delivery rate of sufentanil over a single application administration period of at least about 48 hours to up to 7 days, where that constant delivery was sufficient to establish and maintain a plasma sufentanil concentration having a minimur maximum ratio of about 1.8 or less over the relevant administration period.

xample 5: *In vitro/In vivo* Correlation study for 7-day Sufentanil Transdermal Deli

ı order to assess whether *in vitro* flux data obtained using the methods described in s 1 and 2 are predictive of the *in vivo* performance of the sufentanil transdermal del of the present invention as determined in Example 4 (*in vitro/in vivo* correlation, or "IVIVC"), the following modeling study was carried out. Since for many of the *in vivo* test subjects, detectable sufentanil concentrations were present at the time of the transdermal pat application (data not shown), the IVIVC model needed to account for such starting conditio determine the input from the transdermal delivery systems. A compartmental modeling approach was used. With regard to the data, there was a need in the modeling to make an

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was selected that allowed for both an initial lag and change in delivery rate over the 7 day duration of the *in vivo* studies. Thus, i enous infusion (IV)/transdermal deliver system combination, the IV and the tr very data were modeled simultaneously using a two-compartment PK model. The typical input function from the transdermal deliv system was obtained, and correlated with *in vitro* cumulative release data obtained using the methods of Examples 1 and 2 to assess the thin and thick 2 and 8 cm^2 patches used in the *in* studies described in Example 4. In order to remain consistent, the same breathable overlay used in the Example 4 studies was applied over the transdermal delivery systems placed on Franz cell apparatus. The results of the IVIVC modeling study are depicted in Figures 10-1 As can be seen by a review of Figures 10-14, the *in vitro* cadaver skin flux data obtained usi the methods of Examples 1 and 2 is representative of the *in vivo* input from the transdermal delivery systems of the present invention. In this regard, the average skin flux of sufentanil observed *in vivo* for the 2 and 8 cm^2 patches is approximately 1.1 $\mu g/cm^2$/hour.

system for adı

What is claimed is:

1. A transdermal delivery ninistering sufentanil through the skin (living subject, wherein said system provides a substantially constant delivery rate of sufenta over a single application administration period of at least about 48 hours and said constant delivery rate is sufficient to establish and maintain a plasma sufentanil concentration having minimum to maximum ratio of about 1.8 or less over the said administration period.

2. The transdermal delivery system of claim 1 wherein the delivery rate of sufei is substantially zero order.

3. The transdermal delivery system of claim 2 wherein the delivery rate of sufei is characterized by a total decline of about 5 to 6% over the administration period.

4. The transdermal delivery system of claim 2 wherein the delivery rate of sufei is characterized by a total increase of about 5 to 6% over the administration period.

5. The transdermal delivery system of claim 2 wherein the delivery rate of sufei is characterized by substantially no total increase or decrease over the administration period

The transdermal delivery system of claim 1 wherein the delivery rate at stead least about 1 μg/hr.

The transdermal delivery system of claim 1 wherein the delivery rate at stead least about 1.5 μg/hr.

8. The transdermal delivery system of claim 1 wherein the delivery rate at stead state is at least about 2 μg/hr.

9. The transdermal delivery system of claim 1 wherein the delivery rate at stead state is at least about 3 μg/hr.

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state is at least about 5 μg/hr.

11. The transdermal deliver aim 1 wherein the delivery rate at stead state is at least about 10 μg/hr.

12. The transdermal delivery system of claim 1 wherein the administration perio at least about 48 hours.

13. The transdermal delivery system of claim 1 wherein the administration perio at least about 3 days.

14. The transdermal delivery system of claim 1 wherein the administration perio at least about 7 days.

15. The transdermal delivery system of claim 1 wherein net flux from the system through the skin is at least about 1 $\mu g/cm^2$/hour.

16. The transdermal delivery system of claim 15 wherein said system does not contain a permeation enhancer.

7. The transdermal delivery system of claim 1 wherein said system has a shea bout 1 to 40 minutes as determined using the Shear Time Measurement test.

3. The transdermal delivery system of claim 1 wherein said system provides do control (J_N / J_D) over flux of sufentanil from the system of at least about 50% and the system through the skin of at least about 1 $\mu g/cm^2$/hour.

19. The transdermal delivery system of claim 18 wherein said system does not contain a permeation enhancer.

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coefficient of variation ($\Delta J_N / J_N$) of about 50% or less.

21. The transdermal delive laim 20 wherein said system does not contain a permeation enhancer.

22. The transdermal delivery system of claim 1 wherein said system is a mon system comprising a pressure-sensitive adhesive matrix containing sufentanil in an a above the solubility of sufentanil in the matrix, and further wherein said system provi substantially constant steady state net flux of sufentanil from the system through the skin least about 1 $\mu g/cm^2$/hour for at least about 24 hours.

23. The transdermal delivery system of claim 22 wherein said system do include a permeation enhancer or a rate controlling membrane.

24. The transdermal delivery system of claim 1 wherein said system is a monolit system comprising a pressure-sensitive adhesive matrix containing sufentanil in an amount above the solubility of sufentanil in the matrix, and further wherein said system provides a r flux from the system through the skin of at least about 1 $\mu g/cm^2$/hour and provides a dosage control over flux of sufentanil from the system.

5. The transdermal delivery system of claim 24 wherein said system does not permeation enhancer or a rate controlling membrane.

5. A transdermal delivery system for administering sufentanil through the skin, said system provides a dosage form rate control over flux of sufentanil from the sy flux from the system through the skin of at least about 1 $\mu g/cm^2$/hour, and further wherein said system does not contain a permeation enhancer.

27. The transdermal delivery system of claim 26, wherein the dosage form rate control (J_N / J_D) is at least about 50%.

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29. The transdermal delive laim 26, wherein the dosage form rate control comprises control provided by ically acceptable adhesive matrix carrie composition.

30. The transdermal delivery system of claim 26, wherein the dosage form rate control comprises control provided by a rate controlling membrane.

31. The transdermal delivery system of claim 26, wherein the sufentanil is prese the system in an amount of about 1-20 wt% relative to the total system.

32. The transdermal delivery system of claim 26, wherein the sufentanil is prese the system in an amount above the solubility of sufentanil in said system.

33. The transdermal delivery system of claim 26, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 μg/hour wl applied to a subject.

34. The transdermal delivery system of claim 33, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when) a subject.

5. The transdermal delivery system of claim 26 containing a sufficient amo l to induce and maintain analgesia for 3 or more days when applied to a subject.

5. The transdermal delivery system of claim 35 containing a sufficient amo sufentanil to induce and maintain analgesia for 5 or more days when applied to a subject.

37. The transdermal delivery system of claim 35 containing a sufficient amo sufentanil to induce and maintain analgesia for 7 or more days when applied to a subject.

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system does not contain a permeation enhancer, and further wherein the system has a shear of from about 1 to 40 minutes as deter ıe Shear Time Measurement test.

39. The transdermal delivery system of claim 38, wherein the adhesive matrix provides dosage form rate control over flux of sufentanil from the system.

40. The transdermal delivery system of claim 39, wherein said system provides a flux of sufentanil from the system through the skin of at least about 1 $\mu g/cm^2$/hour.

41. The transdermal delivery system of claim 38, wherein the adhesive matrix drug releasing interface surface area of from about 1-10 cm^2.

42. The transdermal delivery system of claim 38, wherein the sufentanil is preser the system in an amount of about 1-20 wt% relative to the total system.

43. The transdermal delivery system of claim 38, wherein the sufentanil is preser the system in an amount above the solubility of sufentanil in said system.

44. The transdermal delivery system of claim 38, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 µg/hour wh) a subject.

5. The transdermal delivery system of claim 44, wherein said system provides a ıte net flux sufficient to administer sufentanil at from about 1 to 20 µg/hour when) a subject.

46. The transdermal delivery system of claim 38 containing a sufficient amou sufentanil to induce and maintain analgesia for 3 or more days when applied to a subject.

47. The transdermal delivery system of claim 46 containing a sufficient amou sufentanil to induce and maintain analgesia for 5 or more days when applied to a subject.

y system for

sufentanil to induce and maintain analgesia for 7 or more days when applied to a subject.

49. A transdermal deliver administering sufentanil through the wherein said system provides dosage form rate control (J_N / J_D) over flux of sufentanil fro system of at least about 50% and a net flux from the system through the skin of at least ab $\mu g/cm^2$/hour, and further wherein said system does not contain a permeation enhancer.

50. The transdermal delivery system of claim 49, wherein the system provides d form rate control (J_N / J_D) of at least about 60%.

51. The transdermal delivery system of claim 49, wherein the net flux (J_N) fro system through the skin is at least about 1.5 $\mu g/cm^2$/hour.

52. The transdermal delivery system of claim 49, wherein the dosage form rate control comprises control provided by a pharmaceutically acceptable adhesive matrix carrie composition.

53. The transdermal delivery system of claim 49, wherein the dosage form rate control comprises control provided by a rate controlling membrane.

4. The transdermal delivery system of claim 49, wherein the sufentanil is prese n in an amount of about 1-20 wt% relative to the total system.

5. The transdermal delivery system of claim 49, wherein the sufentanil is prese n in an amount above the solubility of sufentanil in said system.

56. The transdermal delivery system of claim 49, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 µg/hour wh applied to a subject.

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applied to a subject.

58. The transdermal delive claim 49 containing a sufficient amou sufentanil to induce and maintain analgesia for 3 or more days when applied to a subject.

59. The transdermal delivery system of claim 58 containing a sufficient amou sufentanil to induce and maintain analgesia for 5 or more days when applied to a subject.

60. The transdermal delivery system of claim 58 containing a sufficient amou sufentanil to induce and maintain analgesia for 7 or more days when applied to a subject.

61. A transdermal delivery system for administering sufentanil through the wherein said system provides a net flux of sufentanil from the system through the skin of at about 1 $\mu g/cm^2$/hour with a coefficient of variation ($\Delta J_N / J_N$) of about 50% or less when ap to a subject, and further wherein said system does not contain a permeation enhancer.

62. The transdermal delivery system of claim 61, wherein said system fi provides a dosage form rate control over flux of sufentanil from the system.

63. The transdermal delivery system of claim 62, wherein the dosage form rate $_N / J_D$) is at least about 50%.

4. The transdermal delivery system of claim 62, wherein the dosage form rate $_N / J_D$) is at least about 60%.

5. The transdermal delivery system of claim 61, wherein the dosage form rate control comprises control provided by a pharmaceutically acceptable adhesive matrix carrie composition.

66. The transdermal delivery system of claim 61, wherein the dosage form rate control comprises control provided by a rate controlling membrane.

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the system in an amount of about 1-20 wt% relative to the total system.

68. The transdermal delive laim 61, wherein the sufentanil is prese the system in an amount above the saturation point of sufentanil in said system.

69. The transdermal delivery system of claim 61, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 μg/hour wl applied to a subject.

70. The transdermal delivery system of claim 69, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when applied to a subject.

71. The transdermal delivery system of claim 61 containing a sufficient amo sufentanil to induce and maintain analgesia for 3 or more days when applied to a subject.

72. The transdermal delivery system of claim 71 containing a sufficient amo sufentanil to induce and maintain analgesia for 5 or more days when applied to a subject.

73. The transdermal delivery system of claim 71 containing a sufficient amo 1 to induce and maintain analgesia for 7 or more days when applied to a subject.

4. A transdermal delivery system for administering sufentanil through the skin comprising a reservoir containing a sufficient amount of sufentanil to induc analgesia for 3 or more days when applied to a subject, wherein the reservoir has ated thickness of about 1.25 to 5 mils and the system provides a delivery efficier at least about 70% of the sufentanil from the reservoir at the end of 3 or more days of appli to a subject.

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more days of application to a subject.

76. The transdermal delive claim 74, wherein the reservoir conta sufficient amount of sufentanil to induce and maintain analgesia for 5 or more days when ap to a subject, and the system provides a delivery efficiency of at least about 70% of the sufe from the reservoir at the end of 5 or more days of application to a subject.

77. The transdermal delivery system of claim 76, wherein the reservoir conta sufficient amount of sufentanil to induce and maintain analgesia for 7 or more days when ap to a subject, and the system provides a delivery efficiency of at least about 70% of the sufe from the reservoir at the end of 7 or more days of application to a subject.

78. The transdermal delivery system of claim 74, wherein the reservoir has a releasing interface surface area of from about 1-10 cm^2.

79. The transdermal delivery system of claim 74, wherein the reservoir compris adhesive matrix.

80. The transdermal delivery system of claim 74, wherein the system provi dosage form rate control over flux of sufentanil from the system.

1. The transdermal delivery system of claim 80, wherein the dosage form rate J_N / J_D) is at least about 50%.

2. The transdermal delivery system of claim 80, wherein the dosage form rate J_N / J_D) is at least about 60%.

83. The transdermal delivery system of claim 80, wherein the dosage form control comprises control provided by a pharmaceutically acceptable adhesive matrix c composition.

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85. The transdermal deliver aim 74, wherein the sufentanil is preser the system in an amount above the solı ıtanil in said system.

86. The transdermal delivery system of claim 74, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 0.01 to 200 μg/hour wh applied to a subject.

87. The transdermal delivery system of claim 86, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when applied to a subject.

88. The transdermal delivery system of claim 74, wherein the reservoir has a vc of about 0.0025 to 0.154 ml.

89. The transdermal delivery system of claim 74, wherein the system does not cc a permeation enhancer.

90. The transdermal delivery system of claim 74, wherein the net flux (J ...l from the system is at least about 1 $\mu g/cm^2$/hour.

1. The transdermal delivery system of claim 90, wherein the net flux (J_N) is at $\mu g/cm^2$/hour.

2. A monolithic transdermal delivery system for administering sufentanil thı ..., said system comprising a pressure-sensitive adhesive matrix containing sufentanil amount above the solubility of sufentanil in the matrix, wherein when applied to a subjec system provides a substantially constant steady state net flux of sufentanil from the s through the skin of at least about 1 $\mu g/cm^2$/hour for at least about 24 hours, and further wh the system does not include a permeation enhancer or rate controlling membrane.

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flux (J_N) of su

94. The transdermal deliv claim 92, wherein said system provi substantially constant steady state net fentanil for at least about 36 hours.

95. The transdermal delivery system of claim 92, wherein said system provides a steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when applied to a subject.

96. The transdermal delivery system of claim 92 wherein the sufentanil is presen the system in an amount of about 1-20 wt% relative to the total system.

97. The transdermal delivery system of claim 96 containing a sufficient amou sufentanil to induce and maintain analgesia for 3 or more days when applied to a subject.

98. The transdermal delivery system of claim 96 containing a sufficient amou sufentanil to induce and maintain analgesia for 5 or more days when applied to a subject.

99. The transdermal delivery system of claim 96 containing a sufficient amou sufentanil to induce and maintain analgesia for 7 or more days when applied to a subject.

)0. The transdermal delivery system of claim 92, wherein the adhesive matrix asing interface surface area of from about 1-10 cm^2.

)1. A monolithic transdermal delivery system for administering sufentanil th said system comprising a pressure-sensitive adhesive matrix containing sufentanil bove the saturation point of sufentanil in the matrix, wherein when applied to a su the system provides a net flux of sufentanil from the system through the skin of at least ab μg/cm^2/hour, and further wherein the system provides a dosage form rate control over fl sufentanil from the system but does not include a permeation enhancer or rate contr membrane.

ery system of

103. The transdermal deliv claim 101, wherein the dosage form control (J_N / J_D) is at least about 60%.

104. The transdermal delivery system of claim 101, wherein said system provi substantially constant steady state net flux of sufentanil from the system through the skin least about 24 hours.

105. The transdermal delivery system of claim 101, wherein said system provi substantially constant steady state net flux (J_N) of sufentanil of at least about 1.5 $\mu g/cm^2$/hou

106. The transdermal delivery system of claim 104, wherein said system provi substantially constant steady state net flux (J_N) of sufentanil for at least about 36 hours.

107. The transdermal delivery system of claim 104, wherein said system provides steady state net flux sufficient to administer sufentanil at from about 1 to 20 μg/hour when applied to a subject.

108. The transdermal delivery system of claim 101 wherein the sufentanil is prese the system in an amount of about 1-20 wt% relative to the total system.

)9. The transdermal delivery system of claim 108 containing a sufficient amou l to induce and maintain analgesia for 3 or more days when applied to a subject.

10. The transdermal delivery system of claim 108 containing a sufficient amou l to induce and maintain analgesia for 5 or more days when applied to a subject.

111. The transdermal delivery system of claim 108 containing a sufficient amou sufentanil to induce and maintain analgesia for 7 or more days when applied to a subject.

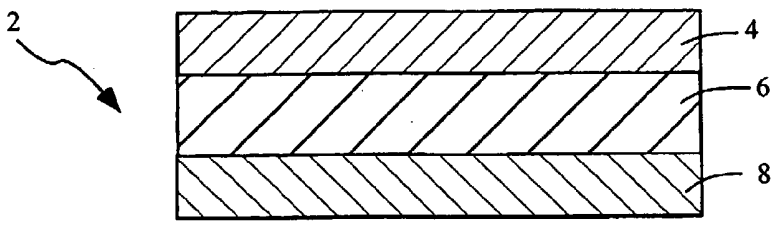

FIGURE 1

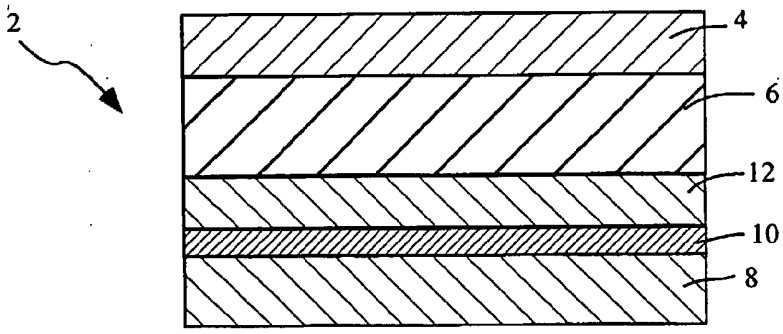

FIGURE 2

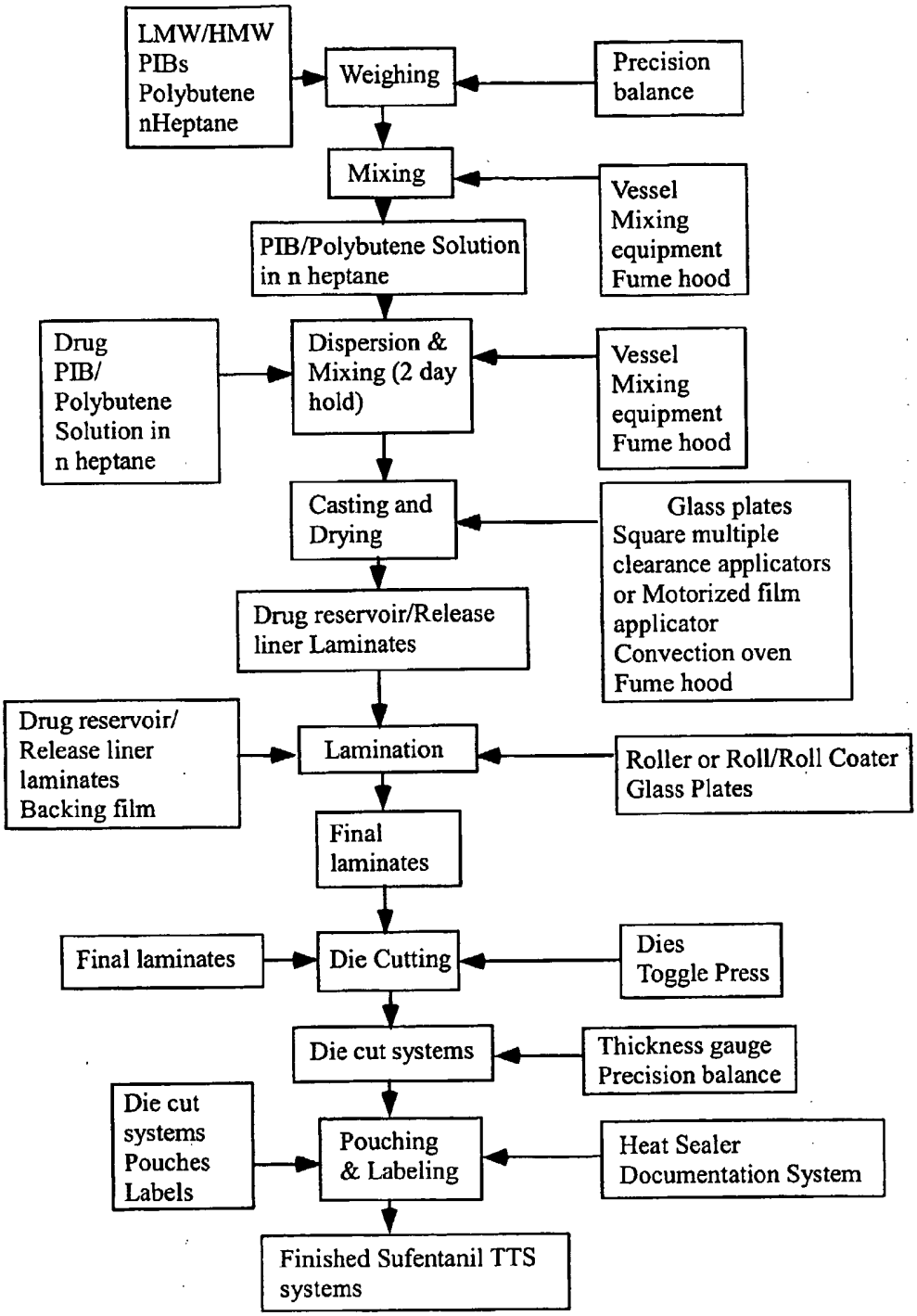
LMW/HMW PIBs Polybutene nHeptane
Weighing
Precision balance
Mixing
Vessel Mixing equipment Fume hood
PIB/Polybutene Solution in n heptane
Drug PIB/ Polybutene Solution in n heptane
Dispersion & Mixing (2 day hold)
Vessel Mixing equipment Fume hood
Casting and Drying
Glass plates Square multiple clearance applicators or Motorized film applicator Convection oven Fume hood
Drug reservoir/Release liner Laminates
Drug reservoir/ Release liner laminates Backing film
Lamination
Roller or Roll/Roll Coater Glass Plates
Final laminates
Final laminates
Die Cutting
Dies Toggle Press
Die cut systems
Thickness gauge Precision balance
Die cut systems Pouches Labels
Pouching & Labeling
Heat Sealer Documentation System
Finished Sufentanil TTS systems

FIGURE 3

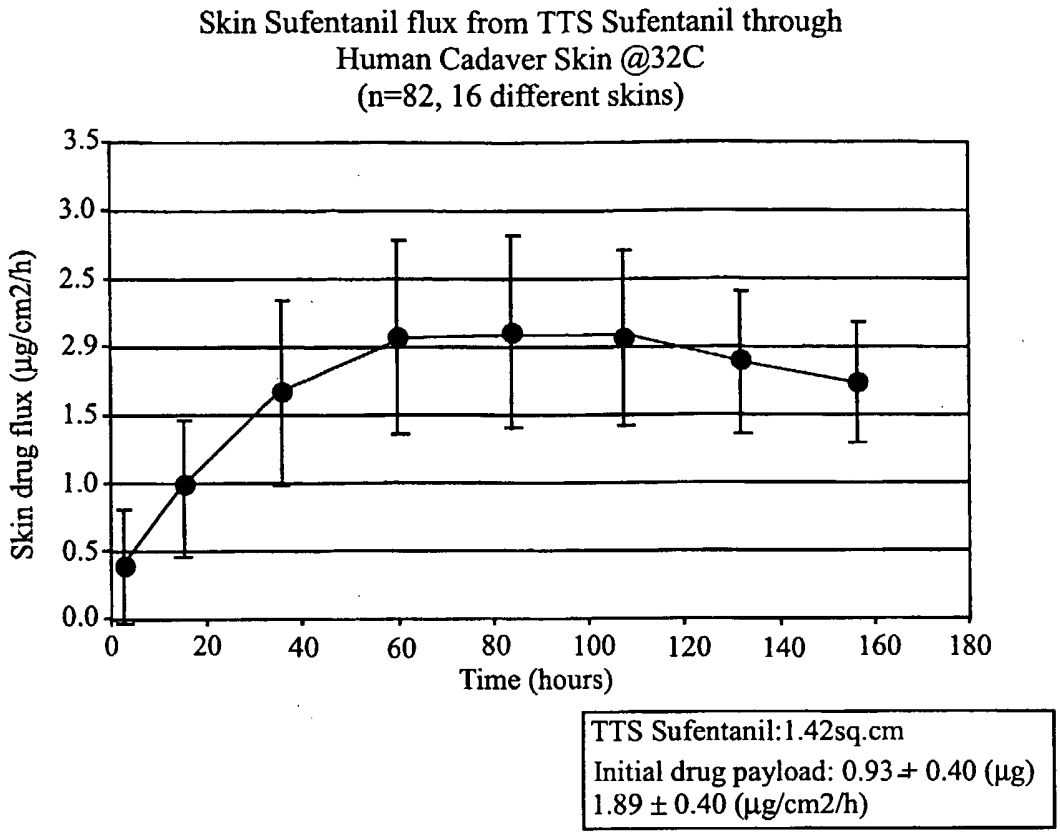

FIGURE 4

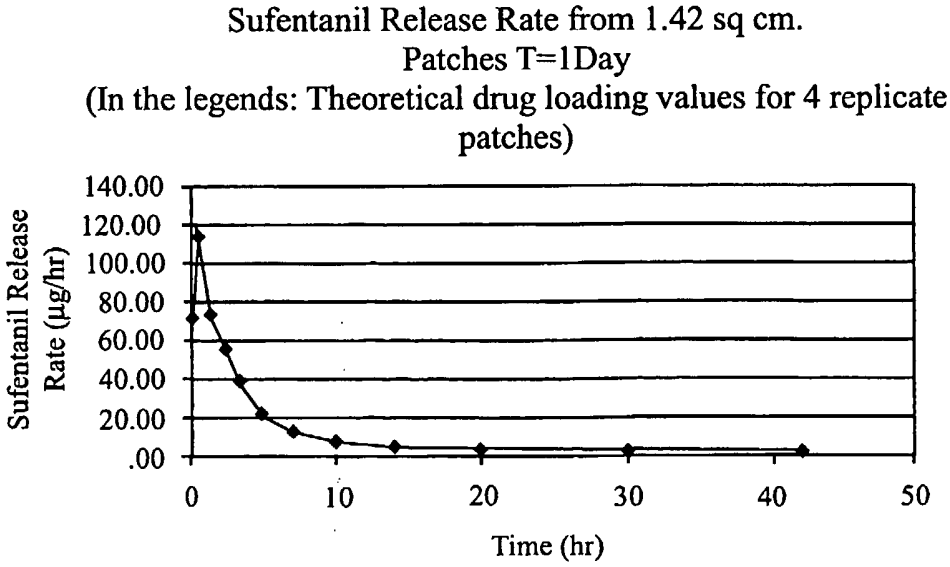

FIGURE 5A

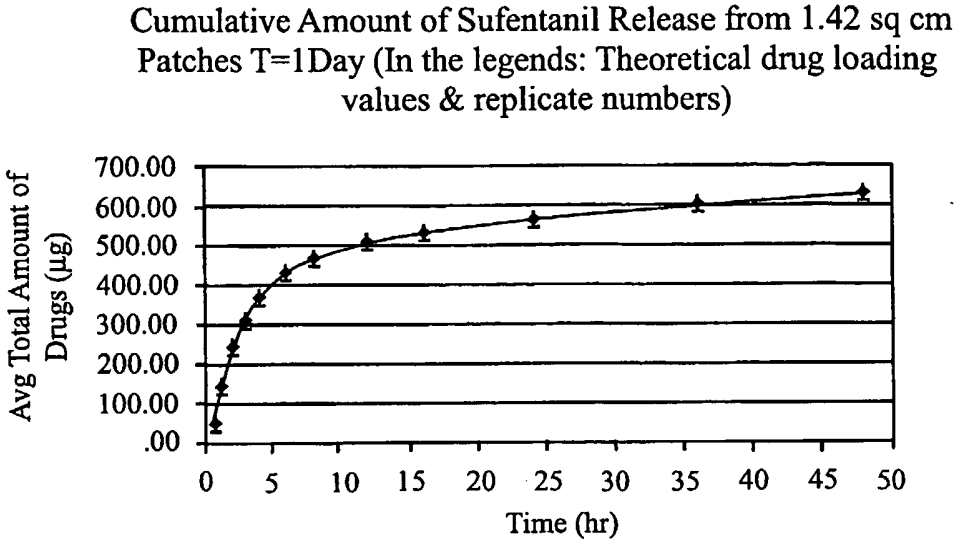

FIGURE 5B

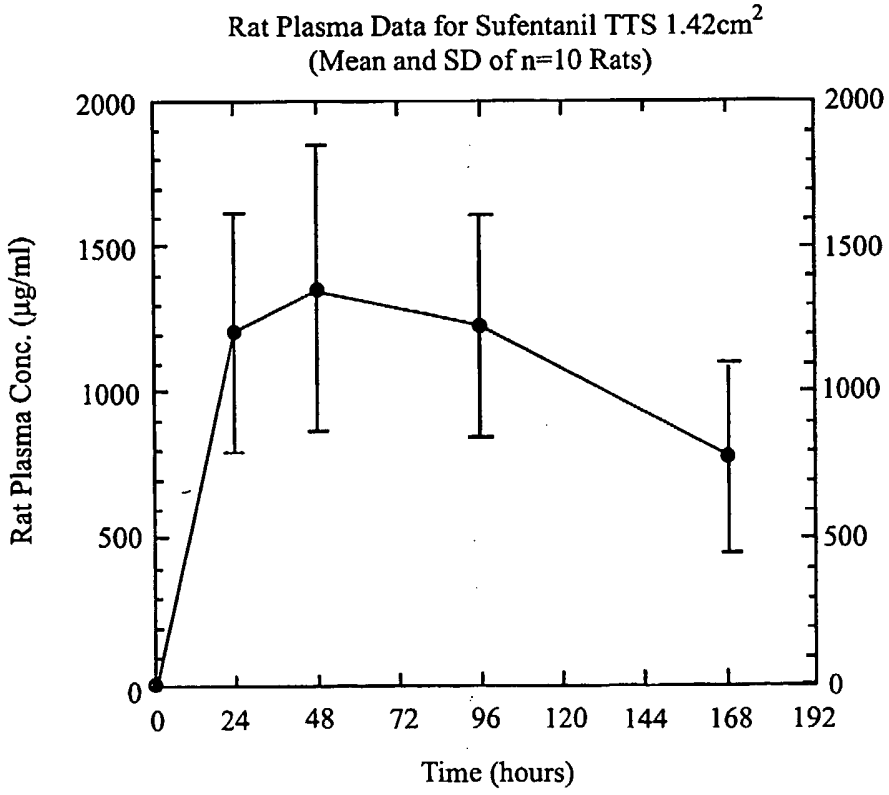

FIGURE 6

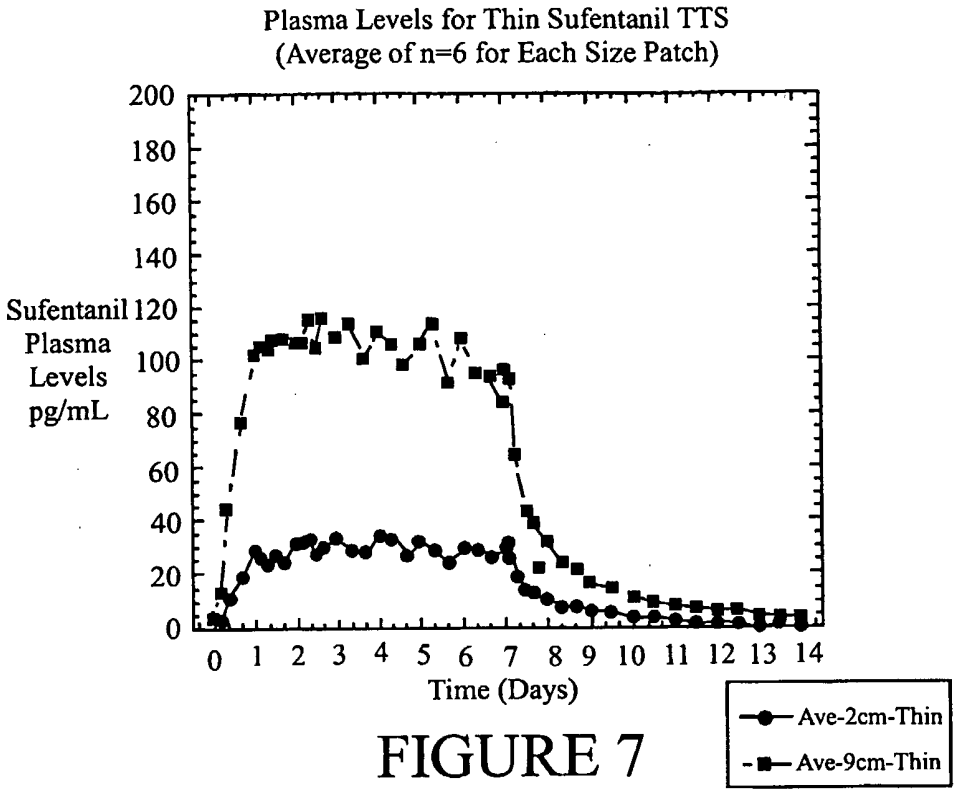

FIGURE 7

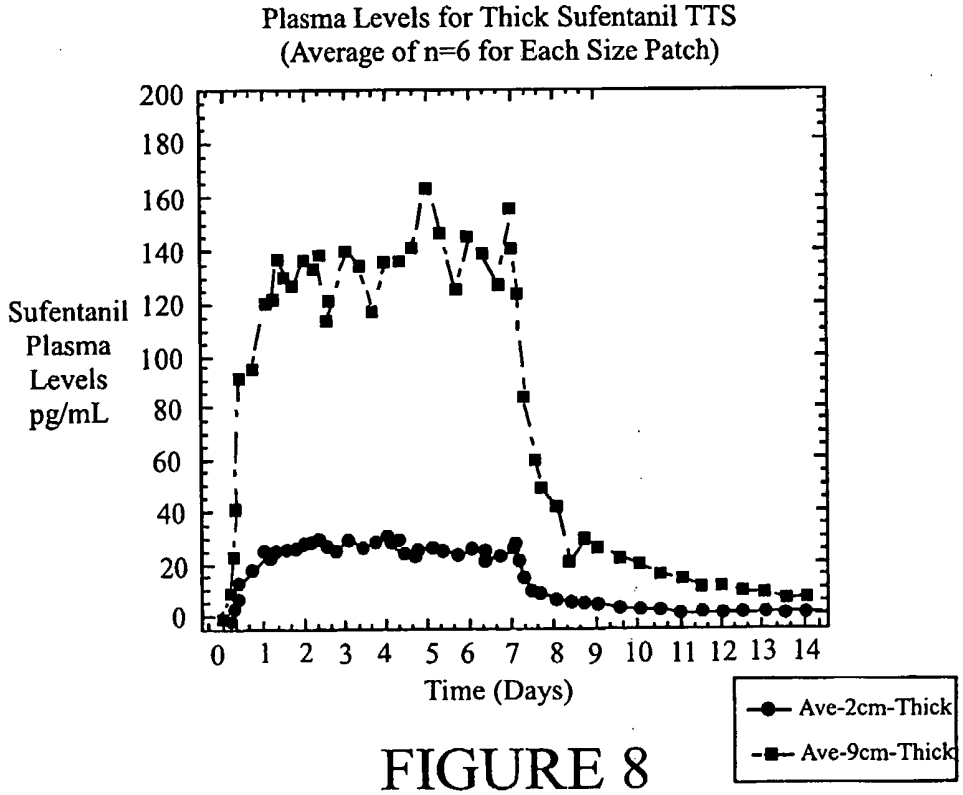

FIGURE 8

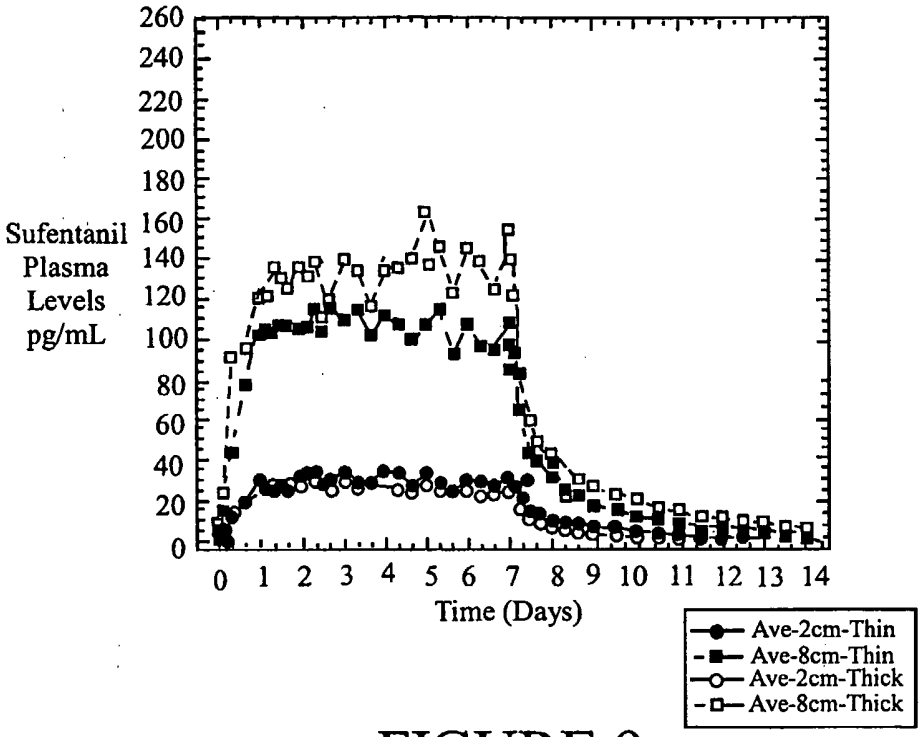
Sufentanil Plasma Levels pg/mL
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (Days)
Ave-2cm-Thin
Ave-8cm-Thin
Ave-2cm-Thick
Ave-8cm-Thick

FIGURE 9

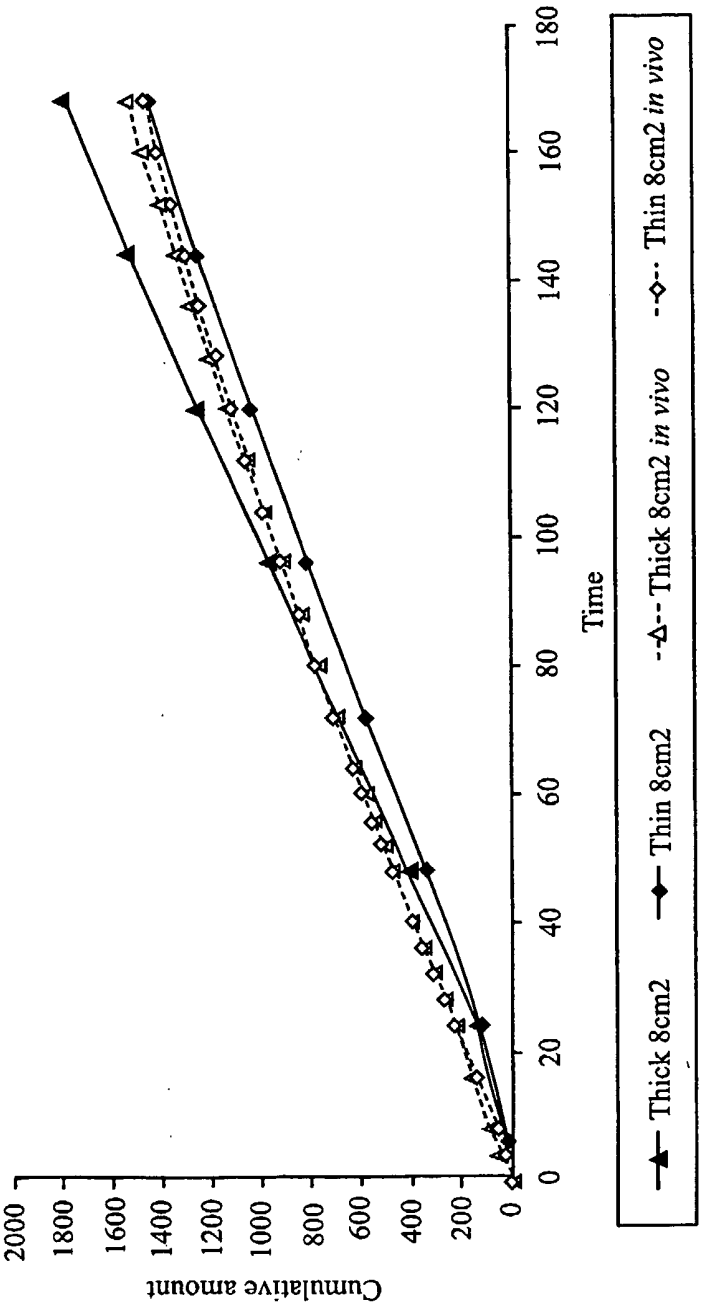
Cumulative amount
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
140
160
180
Time
Thick 8cm2
Thin 8cm2
Thick 8cm2 in vivo
Thin 8cm2 in vivo

FIGURE 10

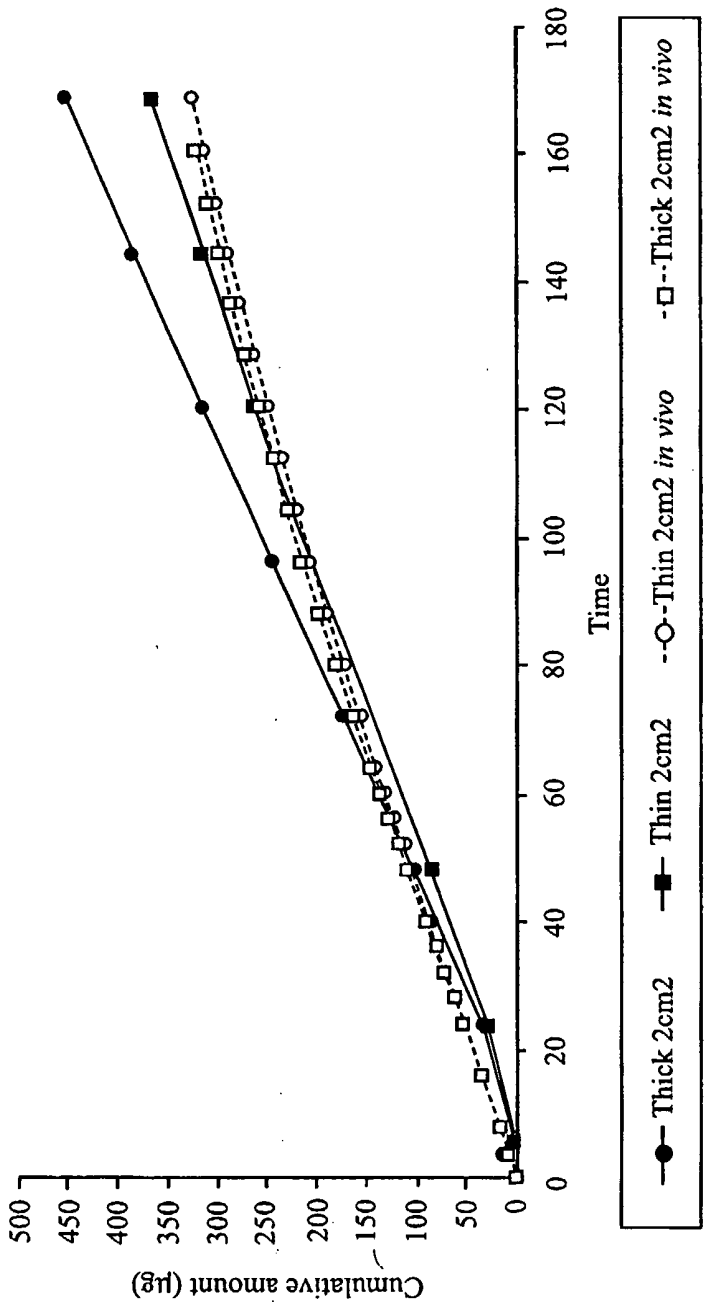
Cumulative amount (µg)
500
450
400
350
300
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180
Time
Thick 2cm2
Thin 2cm2
Thin 2cm2 in vivo
Thick 2cm2 in vivo

FIGURE 11

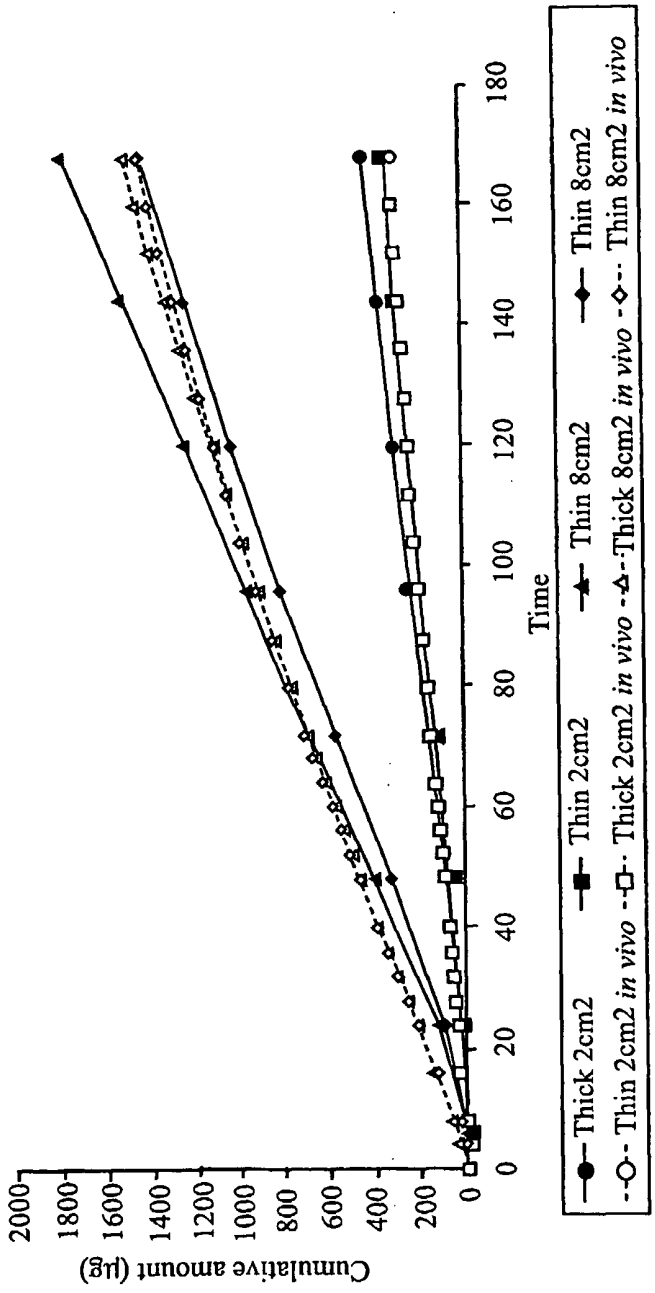
Cumulative amount (µg)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
140
160
180
Time
Thick 2cm2
Thin 2cm2
Thin 8cm2
Thin 8cm2
Thin 2cm2 in vivo
Thick 2cm2 in vivo
Thick 8cm2 in vivo
Thin 8cm2 in vivo

FIGURE 12

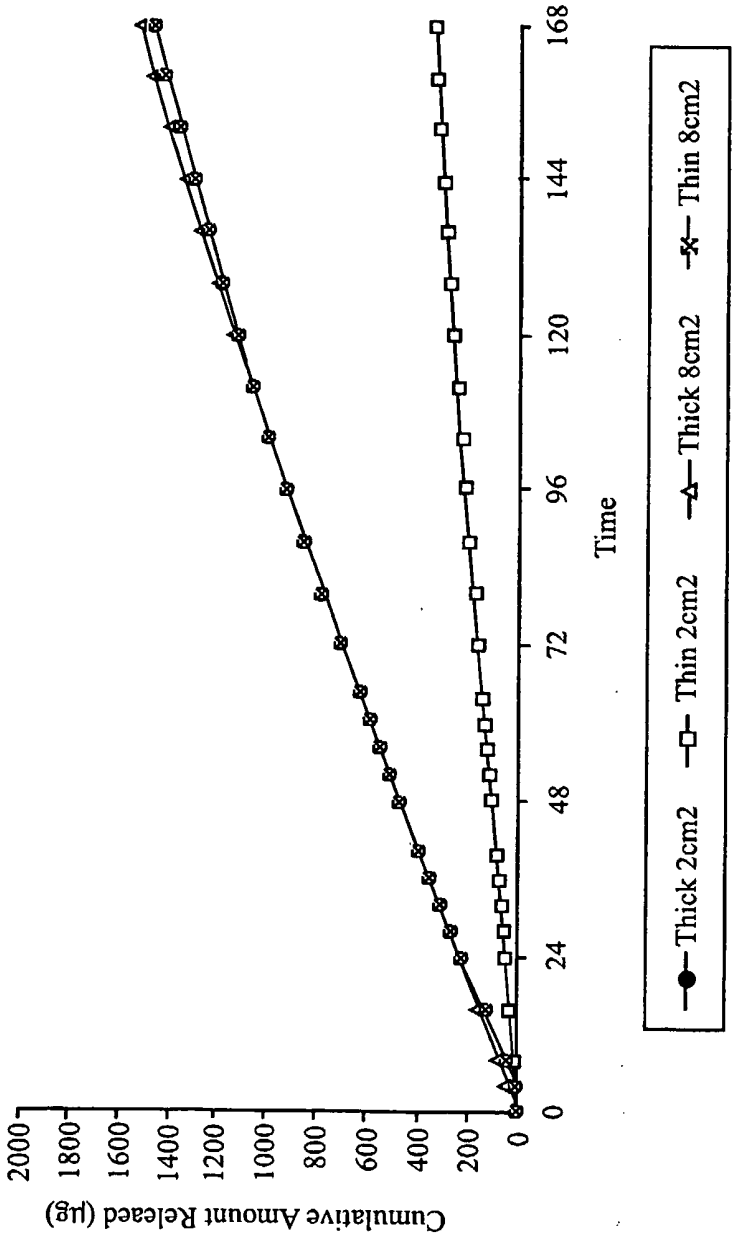
Cumulative Amount Released (µg)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
24
48
72
96
120
144
168
Time
Thick 2cm2
Thin 2cm2
Thick 8cm2
Thin 8cm2

FIGURE 13

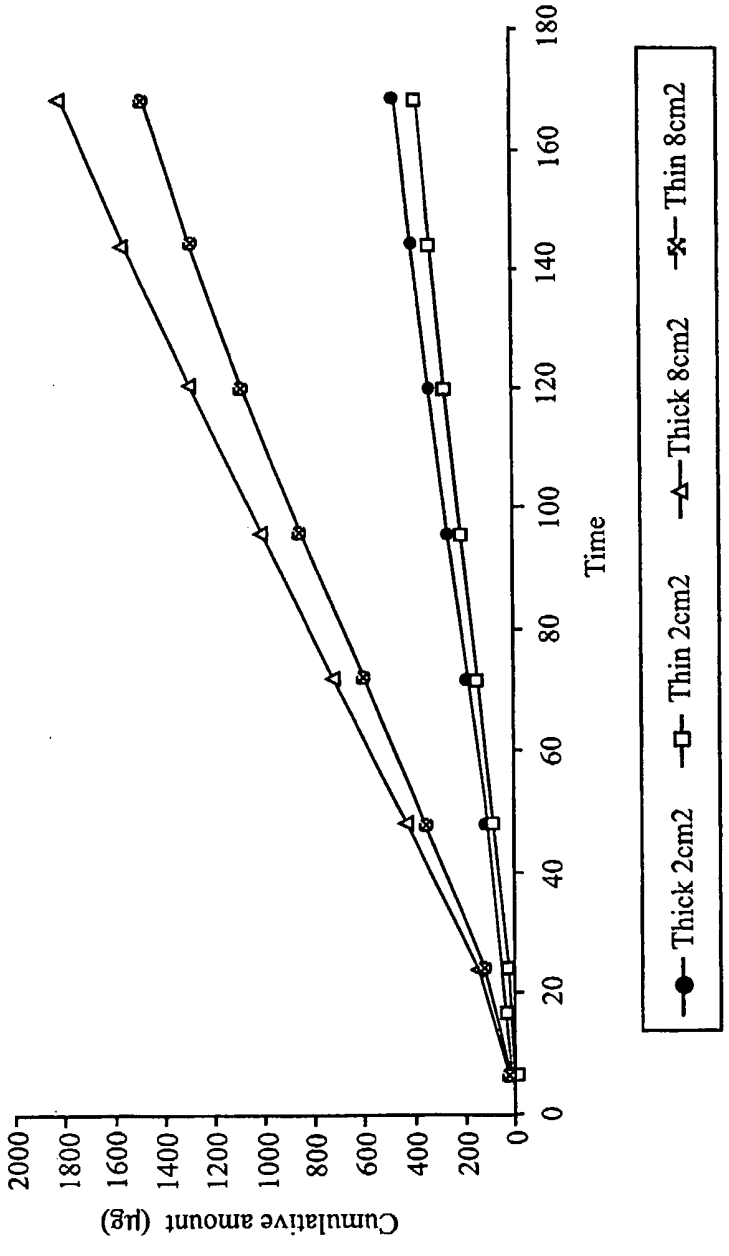
Cumulative amount (µg)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
20
40
60
80
100
120
140
160
180
Time
Thick 2cm2
Thin 2cm2
Thick 8cm2
Thin 8cm2

FIGURE 14