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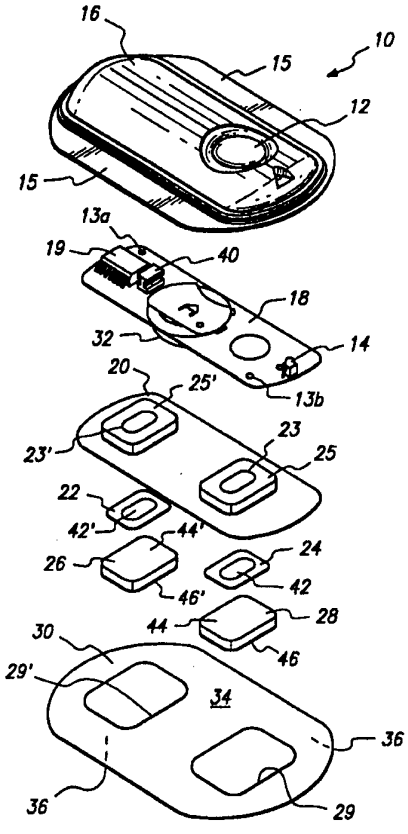
(54) Title: DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL

(57) Abstract

The invention provides an improved electrotransport drug delivery system for analgesic drugs, namely fentanyl and sufentanil. The fentanyl/sufentanil is provided as a water-soluble halide salt (e.g., fentanyl hydrochloride), preferably contained in a hydrogel formulation for use in an electrotransport device (10). In accordance with the present invention, the donor electrode (22) of the electrotransport delivery device (10) is comprised of silver and the donor reservoir (26) is substantially free of supplementary chloride ion sources and contains a predetermined "excess" loading of fentanyl/sufentanil halide to prevent silver ion migration with attendant skin discoloration.



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DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL

TECHNICAL FIELD

The invention relates generally to improved electrotransport drug delivery. Specifically, the invention relates to a device, composition and method for improved electrotransport delivery of analgesic drugs, particularly fentanyl and analogs of fentanyl.

BACKGROUND ART

The transdermal delivery of drugs, by diffusion through the epidermis, offers improvements over more traditional delivery methods, such as subcutaneous injections and oral delivery. Transdermal drug delivery avoids the hepatic first pass effect encountered with oral drug delivery. Transdermal drug delivery also eliminates patient discomfort associated with subcutaneous injections. In addition, transdermal delivery can provide more uniform concentrations of drug in the bloodstream of the patient over time due to the extended controlled delivery profiles of certain types of transdermal delivery devices. The term "transdermal" delivery, broadly encompasses the delivery of an agent through a body surface, such as the skin, mucosa, or nails of an animal.

The skin functions as the primary barrier to the transdermal penetration of materials into the body and represents the body's major resistance to the transdermal delivery of therapeutic agents such as drugs. To date, efforts have been focussed on reducing the physical resistance or enhancing the permeability of the skin for the delivery of drugs by passive diffusion. Various methods for increasing the rate of transdermal drug flux have been attempted, most notably using chemical flux enhancers.

Other approaches to increase the rates of transdermal drug delivery include use of alternative energy sources such as electrical energy and ultrasonic energy. Electrically assisted transdermal delivery is also referred to as electrotransport. The term "electrotransport" as used herein refers generally to the delivery of an agent (eg, a drug) through a membrane, such as skin, mucous membrane, or nails. The delivery is induced or aided by application of an electrical potential. For example, a beneficial therapeutic agent may be introduced into the systemic circulation of a human body by electrotransport delivery through the skin. A widely used electrotransport process, electromigration (also called iontophoresis), involves the electrically induced transport of charged ions. Another type of electrotransport, electroosmosis, involves the flow of a liquid, which liquid contains the agent to be delivered, under the influence of an electric field. Still another type of electrotransport process, electroporation, involves the formation of transiently-existing pores in a biological membrane by the application of an electric field. An agent can be delivered through the pores either passively (ie, without electrical assistance) or actively (ie, under the influence of an electric potential). However, in any given electrotransport process, more than one of these processes, including at least some "passive" diffusion, may be occurring simultaneously to a certain extent. Accordingly, the term "electrotransport", as used herein, should be given its broadest possible interpretation so that it includes the electrically induced or enhanced transport of at least one agent, which may be charged, uncharged, or a mixture thereof, whatever the specific mechanism or mechanisms by which the agent actually is transported.

Electrotransport devices use at least two electrodes that are in electrical contact with some portion of the skin, nails, mucous membrane, or other surface of the body. One electrode, commonly called the "donor"

electrode, is the electrode from which the agent is delivered into the body. The other electrode, typically termed the "counter" electrode, serves to close the electrical circuit through the body. For example, if the agent to be delivered is positively charged, ie, a cation, then the anode is the donor electrode, while the cathode is the counter electrode which serves to complete the circuit. Alternatively, if an agent is negatively charged, ie, an anion, the cathode is the donor electrode and the anode is the counter electrode. Additionally, both the anode and cathode may be considered donor electrodes if both anionic and cationic agent ions, or if uncharged dissolved agents, are to be delivered.

Furthermore, electrotransport delivery systems generally require at least one reservoir or source of the agent to be delivered to the body. Examples of such donor reservoirs include a pouch or cavity, a porous sponge or pad, and a hydrophilic polymer or a gel matrix. Such donor reservoirs are electrically connected to, and positioned between, the anode or cathode and the body surface, to provide a fixed or renewable source of one or more agents or drugs. Electrotransport devices also have an electrical power source such as one or more batteries. Typically at any one time, one pole of the power source is electrically connected to the donor electrode, while the opposite pole is electrically connected to the counter electrode. Since it has been shown that the rate of electrotransport drug delivery is approximately proportional to the electric current applied by the device, many electrotransport devices typically have an electrical controller that controls the voltage and/or current applied through the electrodes, thereby regulating the rate of drug delivery. These control circuits use a variety of electrical components to control the amplitude, polarity, timing, waveform shape, etc. of the electric current and/or voltage supplied by the power source. See, for example, McNichols et al., U.S. Patent 5,047,007.

To date, commercial transdermal electrotransport drug delivery devices (eg, the Phoresor, sold by Iomed, Inc. of Salt Lake City, UT; the Dupel Iontophoresis System sold by Empi, Inc. of St. Paul, MN; the Webster Sweat Inducer, model 3600, sold by Wescor, Inc. of Logan, UT) have generally utilized a desk-top electrical power supply unit and a pair of skin contacting electrodes. The donor electrode contains a drug solution while the counter electrode contains a solution of a biocompatible electrolyte salt. The power supply unit has electrical controls for adjusting the amount of electrical current applied through the electrodes. The "satellite" electrodes are connected to the electrical power supply unit by long (eg, 1-2 meters) electrically conductive wires or cables. The wire connections are subject to disconnection and limit the patient's movement and mobility. Wires between electrodes and controls may also be annoying or uncomfortable to the patient. Other examples of desk-top electrical power supply units which use "satellite" electrode assemblies are disclosed in Jacobsen et al., U.S. Patent 4,141,359 (see Figures 3 and 4); LaPrade, U.S. Patent 5,006,108 (see Figure 9); and Maurer et al., U.S. Patent 5,254,081.

More recently, small self-contained electrotransport delivery devices have been proposed to be worn on the skin, sometimes unobtrusively under clothing, for extended periods of time. Such small self-contained electrotransport delivery devices are disclosed for example in Tapper, U.S. Patent 5,224,927; Sibalis, et al., U.S. Patent 5,224,928; and Haynes et al., U.S. Patent 5,246,418.

There have recently been suggestions to utilize electrotransport devices having a reusable controller which is adapted for use with multiple drug-containing units. The drug-containing units are simply disconnected from the controller when the drug becomes depleted and a fresh drug-containing unit is thereafter connected to the controller. In this way, the

relatively more expensive hardware components of the device (eg, batteries, LED's, circuit hardware, etc.) can be contained within the reusable controller, and the relatively less expensive donor reservoir and counter reservoir matrices can be contained in the single use/disposable drug-containing unit, thereby bringing down the overall cost of electrotransport drug delivery. Examples of electrotransport devices comprised of a reusable controller, removably connected to a drug-containing unit are disclosed in Sage, Jr. et al., U.S. Patent 5,320,597; Sibalis, U.S. Patent 5,358,483; Sibalis et al., U.S. Patent 5,135,479 (Fig. 12); and Devane et al., UK Patent Application 2 239 803.

In further development of electrotransport devices, hydrogels have become particularly favored for use as the drug and electrolyte reservoir matrices, in part, due to the fact that water is the preferred liquid solvent for use in electrotransport drug delivery due to its excellent biocompatiblity compared with other liquid solvents such as alcohols and glycols. Hydrogels have a high equilibrium water content and can quickly absorb water. In addition, hydrogels tend to have good biocompatibility with the skin and with mucosal membranes.

Of particular interest in transdermal delivery is the delivery of analgesic drugs for the management of moderate to severe pain. Control of the rate and duration of drug delivery is particularly important for transdermal delivery of analgesic drugs to avoid the potential risk of overdose and the discomfort of an insufficient dosage.

One class of analgesics that has found application in a transdermal delivery route is the synthetic opiates, a group of 4-aniline piperidines. The synthetic opiates, eg, fentanyl and certain of its derivatives such as sufentanil, are particularly well-suited for transdermal administration. These

synthetic opiates are characterized by their rapid onset of analgesia, high potency, and short duration of action. They are estimated to be 80 and 800 times, respectively, more potent than morphine. These drugs are weak bases, ie, amines, whose major fraction is cationic in acidic media.

In an *in vivo* study to determine plasma concentration, Thysman and Preat (*Anesth. Analg.* 77 (1993) pp. 61-66) compared simple diffusion of fentanyl and sufentanil to electrotransport delivery in citrate buffer at pH 5. Simple diffusion did not produce any detectable plasma concentration. The plasma levels attainable depended on the maximum flux of the drug that can cross the skin and the drug's pharmacokinetic properties, such as clearance and volume of distribution. Electrotransport delivery was reported to have significantly reduced lag time (ie, time required to achieve peak plasma levels) as compared to passive transdermal patches (1.5 h versus 14 h). The researchers' conclusions were that electrotransport of these analgesic drugs can provide more rapid control of pain than classical patches, and a pulsed release of drug (by controlling electrical current) was comparable to the constant delivery of classical patches. See, also, eg, Thysman et al. *Int. J. Pharma.*, 101 (1994) pp. 105-113; V. Préat et al. *Int. J. Pharm.*, 96 (1993) pp. 189-196 (sufentanil); Gourlav et al. *Pain*, 37 (1989) pp. 193-202 (fentanyl); Sebel et al. *Eur. J. Clin. Pharmacol.* 32 (1987) pp. 529-531 (fentanyl and sufentanil). Passive, ie, by diffusion, and electrically-assisted transdermal delivery of narcotic analgesic drugs, such as fentanyl, to induce analgesia, have also both been described in the patent literature. See, for example, Gale et al., U.S. Patent 4,588,580, and Theeuwes et al., U.S. Patent 5,232,438.

In the last several years, management of post-operative pain has looked to delivery systems other than electrotransport delivery. Particular attention has been given to devices and systems which permit, within

predetermined limits, the patient to control the amount of analgesic the patient receives. The experience with these types of devices has generally been that patient control of the administration of analgesic has resulted in the administration of less analgesic to the patient than would have been administered were the dosage prescribed by a physician. Self-administered or patient controlled self-administration has become known (and will be referred to herein) as patient-controlled analgesia (PCA).

Known PCA devices are typically electromechanical pumps which require large capacity electrical power sources, eg, alternating current or multiple large capacity battery packs which are bulky. Due to their bulk and complexity, commercially available PCA devices generally require the patient to be confined to a bed, or some other essentially fixed location. Known PCA devices deliver drug to the patient by means of an intravenous line or a catheter which must be inserted into the intended vein, artery or other organ by a qualified medical technician. This technique requires that the skin barrier be breached in order to administer the analgesic. (See, Zdeb U.S. Patent 5,232,448). Thus, as practiced using commercially available PCA devices, PCA requires the presence of highly skilled medical technicians to initiate and supervise the operation of the PCA device along with its attendant risk of infection. Further, commercially available PCA devices themselves are somewhat painful to use by virtue of their percutaneous (ie, intravenous or subcutaneous) access.

The art has produced little in the way of transdermal electrotransport devices that can compete with the conventional PCAs in terms of the amount of drug delivered to achieve adequate analgesia and in a patient controlled manner. Further, little progress has been made to provide a hydrogel formulation for analgesic electrotransport, particularly fentanyl transdermal electrotransport delivery, that has long term stability and has performance

characteristics comparable to the patient controlled electromechanical pumps for, eg, intravenous delivery of analgesic. There is need to provide an analgesic formulation in a suitable device to take advantage of the convenience of electrotransport delivery in a small, self-contained, patient-controlled device.

DESCRIPTION OF THE INVENTION

The present invention provides a device for improved transdermal electrotransport delivery of fentanyl and analogs of fentanyl, particularly sufentanil. As such, the device of the present invention provides a greater degree of efficiency in electrotransport delivery of analgesic fentanyl or sufentanil, concomitantly providing a greater measure of patient safety and comfort in pain management. The foregoing, and other advantages of the present invention, are provided by an electrotransport delivery device for delivering fentanyl or sufentanil through a body surface (eg, intact skin) by electrotransport, the device having a anodic donor reservoir containing an at least partially aqueous solution of a fentanyl/sufentanil salt.

The invention provides a donor reservoir formulation for a transdermal electrotransport fentanyl/sufentanil delivery device having an anodic donor electrode comprised of silver, which donor reservoir formulation substantially prevents migration of silver ions into, and discoloration of, the skin of the patient. While the prior art has taught the advantage of using a halide drug salt to prevent the migration of electrochemically generated silver ions (see Untereker et al U.S. Patent 5,135,477), it has now been discovered that for halide salts of fentanyl or sufentanil which are delivered either continuously or intermittently over longer electrotransport delivery periods (eg, periods of at least several hours), the amount of fentanyl/sufentanil halide needed in the donor reservoir in order to prevent this silver migration must be well in excess

of the amount of fentanyl/sufentanil which is needed for therapeutic purposes. For fentanyl hydrochloride, the amount of drug needed to prevent silver ion migration has been determined to be at least about 3 times the amount needed for delivery into the patient at least under the specific electrotransport delivery conditions (ie, applied electrotransport current, reservoir size/weight/composition, and time of electrotransport current application) which are described in more detail hereinafter.

Other advantages and a fuller appreciation of specific adaptations, compositional variations, and physical attributes of the present invention can be learned from an examination of the following drawings, detailed description, examples, and appended claims.

BRIEF DESCRIPTION OF THE DRAWING

The present invention is hereinafter described in conjunction with the appended drawing, in which:

Figure 1 is a perspective exploded view of an electrotransport drug delivery device in accordance with the present invention.

MODES FOR CARRYING OUT THE INVENTION

The present invention relates broadly to improved devices for the transdermal electrotransport delivery of fentanyl or sufentanil, in water soluble salt form, to achieve a systemic analgesic effect. The present invention concerns a fentanyl or sufentanil halide donor reservoir composition, which is adapted to be used in an electrotransport delivery device having a silver anodic donor electrode, which formulation is effective

to prevent skin discoloration from silver ions, formed during oxidation of the silver anode, and co-delivered with the drug into the skin of the patient.

Since fentanyl and sufentanil are both bases, the salts of fentanyl and sufentanil are typically acid addition salts, eg, citrate salts, hydrochloride salts, etc. The acid addition salts of fentanyl typically have water solubilities of about 25 to 30 mg/mL. The acid addition salts of sufentanil typically have water solubilities of about 45 to 50 mg/mL. When these salts are placed in solution (eg, aqueous solution), the salts dissolve and form protonated fentanyl or sufentanil cations and counter (eg, citrate or chloride) anions. As such, the fentanyl/sufentanil cations are delivered from the anodic electrode of an electrotransport delivery device. Silver anodic electrodes have been proposed for transdermal electrotransport delivery as a way to maintain pH stability in the anodic reservoir. See for example, Untereker et al U.S. Patent 5,135,477 and Petelenz et al U.S. Patent 4,752,285. These patents also recognize one of the shortcomings of using a silver anodic electrode in an electrotransport delivery device, namely that the application of current through the silver anode causes the silver to become oxidized ($Ag \rightarrow Ag^+ + e^-$) thereby forming silver cations which compete with the cationic drug for delivery into the skin by electrotransport. Silver ion migration into the skin results in a transient epidermal discoloration (TED) of the skin. In addition to these patents, Phipps et al WO 95/27350 teaches the use of supplementary chloride ion sources in the form of high molecular weight chloride resins in the donor reservoir of a transdermal electrotransport delivery device. While these resins are highly effective at providing sufficient chloride for preventing silver ion migration, and the attendant skin discoloration, these resins can also have adverse reactions with either the drug being delivered (ie, binding of drug to the resin) and/or with the skin of the patient (ie, contributing to skin irritation reactions). Thus, for the purposes of the following discussion, the donor reservoir formulations of the

present invention will be assumed to be substantially free of such secondary chloride ion source resins. Of course during operation of a transdermal electrotranport device, chloride ions from the body of the patient will migrate from the skin into the anodic reservoir. This inherent phenomenon also takes place during the operation of the devices of the present invention, and as such, the chloride effluxing from the skin into the anodic donor reservoir is not considered to be a "supplementary source of halide/chloride ions" as that term is used herein. While the Untereker and Petelenz patents teach that providing a cationic drug in the form of a halide salt prevents the migration of silver ions (ie, by reacting the silver ions with the halide counter ion of the drug to form a water insoluble silver halide precipitate; $Ag^+ + X^- \rightarrow AgX$), it has now been determined that a significant excess (ie, an amount well in excess of the fentanyl halide salt needed to be delivered to the patient for purposes of achieving analgesia) of fentanyl halide must be provided in a donor reservoir of an electrotransport fentanyl delivery device in order to prevent silver ion migration. This is especially true for those transdermal electrotransport delivery devices which are adapted to apply electrotransport current for extended periods of time, eg, longer than about 6 hours.

In general, the "excess" amount of fentanyl halide needed to prevent silver ion migration will be highly dependent upon a number of factors including the particular halide salt used (eg, chloride, fluoride, bromide or iodide salt of the drug), the level of applied electrotransport current, the size/weight/composition of the donor reservoir, the applied current density level and the length of time over which the electrotranport current is applied. We have determined delivering fentanyl hydrochloride from polyvinyl alcohol based donor reservoirs which are used to deliver fentanyl for periods of up to about 15 hours, that the amount of fentanyl HCl needed to prevent silver ion migration during electrotransport delivery is about 2 to 3 times the amount of

fentanyl HCl needed for delivery into the patient over that same period of time for purposes of inducing and maintaining analgesia.

In the specific case of an electrotransport delivery device having a polyvinyl alcohol based donor reservoir containing fentanyl hydrochloride and having a total weight (on a hydrated basis) of about 0.3 to 0.8 g, which device (1) has an anodic donor electrode comprised of silver (eg, silver foil or silver powder-loaded polymer film) which is in electrical contact with the donor reservoir, (2) has an electrical power source which applies a DC current of about 190 μA to 230 μA to the donor and counter electrodes, (3) applies a current density, measured as the total applied current divided by the skin contact area of the donor reservoir, of less than about 0.3 mA/cm^2, and (4) is capable of applying such current for up to about eighty separate delivery intervals of about 8 to about 12 minutes duration, the fentanyl HCl loading needed to induce and maintain analgesia is about 2.5 to 3.5 mg, yet the fentanyl HCl loading needed to prevent TED is at least about 8 to 10 mg, and preferably at least about 11 to 13 mg. More specifically in the case of an electrotransport delivery device having a polyvinyl alcohol based donor reservoir containing fentanyl hydrochloride and having a total weight (on a hydrated basis) of about 0.5 to 0.8 g, which device applies a DC current of about 210 μA to the electrodes, and is capable of applying such current for up to about eighty separate delivery intervals of about 10 minutes duration, the fentanyl HCl loading needed to induce and maintain analgesia is about 3 mg, yet the fentanyl HCl loading needed to prevent TED is at least about 9 mg, and preferably at least about 12 mg.

In order to determine the loading of a halide salt of fentanyl other than fentanyl HCl, it is only necessary to supply an equivalent molar amount of halide ions to the reservoir since the silver halide salts have fairly uniformly low water solubility. For example, the loading of 8 to 10 mg of fentanyl HCl

corresponds to a molar loading of about 20 to 25 μmoles. Thus, about 20 to 25 μmoles of any of the other fentanyl halides (ie, fentanyl fluoride, fentanyl bromide or fentanyl iodide) will provide an equivalent degree of silver migration prevention as fentanyl HCl.

In addition to fentanyl, "excess" amounts of sufentanil halide salts also can be used to prevent silver ion migration. Because sufentanil is about 7 to 10 times more potent than fentanyl, only about 0.1 to 0.14 times the fentanyl dose is needed to achieve an equivalent level of analgesia. However, because the transdermal electrotransport delivery efficiency of sufentanil (ie, the rate of sufentanil delivered per unit of applied electrotransport current) is only about one-third that of fentanyl, the applied electrotransport current needed to achieve the same level of analgesia with sufentanil is about 0.3 to 0.4 times that needed for fentanyl. Thus, the "excess" amount of sufentanil chloride needed to prevent silver ion migration during electrotransport delivery of sufentanil is correspondingly reduced to about 6 to 10 μmoles or about 2.4 to 4 mg. The amount of sufentanil HCl loading needed to prevent silver ion migration, relative to the loading needed to achieve an analgesic effect in a patient, is at least about 4 times the analgesically effective loading.

As long as the reservoir matrix material has substantially no silver ion binding capacity (ie, by means of a fixed anionic (eg, COO^-) moiety as is found in cation exchange membranes), the particular matrix material chosen as the donor reservoir matrix has little if any effect on the minimum loading of halide salts of fentanyl and sufentanil which is effective to prevent silver ion migration into the patient's skin. Hydrogel matrices in particular exhibit little or no tendency to bind silver ions and so are a preferred matrix material for use with this aspect of the present invention.

Preferably, the concentration of fentanyl or sufentanil in solution in the donor reservoir is maintained at or above the level at which the transdermal electrotransport fentanyl/sufentanil flux becomes dependent on drug concentration in the donor reservoir. Transdermal electrotransport fentanyl flux begins to become dependent upon the concentration of the fentanyl salt in aqueous solution as the fentanyl salt concentration falls below about 11 to 16 mM. The 11 to 16 mM concentration is calculated based only on the volume of liquid solvent used in the donor reservoir, not on the total volume of the reservoir. In other words, the 11 to 16 mM concentration does not include the volume of the reservoir which is represented by the reservoir matrix (eg, hydrogel or other matrix) material. Furthermore, the 11 to 16 mM concentration is based upon the number of moles of fentanyl salt, not the equivalent number of moles of fentanyl free base, which is contained in the donor reservoir solution. For fentanyl HCl, the 11 to 16 mM concentration is equivalent to about 4 to 6 mg/mL. Other fentanyl halide salts will have slightly differing weight based concentration ranges based on the difference in the molecular weight of the counter ion of the particular fentanyl salt in question. As the fentanyl salt concentration falls to about 11 to 16 mM, the fentanyl transdermal electrotransport flux begins to significantly decline, even if the applied electrotransport current remains constant. Thus, to ensure a predictable fentanyl flux with a particular level of applied electrotransport current, the fentanyl salt concentration in the solution contained in the donor reservoir is preferably maintained above about 11 mM, and more preferably above about 16 mM. In addition to fentanyl, water soluble salts of sufentanil also have minimum aqueous solution concentrations below which the transdermal electrotransport flux becomes dependent on concentration of the sufentanil salt in solution. The minimum concentration for sufentanil is about 1.7 mM.

The present invention provides an electrotransport delivery device for delivering fentanyl or sufentanil through a body surface, eg, skin, to achieve an analgesic effect. The fentanyl or sufentanil salt is preferably provided in a donor reservoir of an electrotransport delivery device as an aqueous salt solution.

The dose of fentanyl delivered by transdermal electrotransport is preferably about 20 μg to about 60 μg over a delivery time of up to about 20 minutes in human patients having body weights of 35 kg or greater. More preferred is a dosage of about 35 μg to about 45 μg, and most preferred is a dosage of about 40 μg for the delivery period. The device of the invention further preferably includes means for delivering about 10 to 100, and more preferably about 20 to 80 additional like doses over a period of 24 hours in order to achieve and maintain the analgesic effect.

The dose of sufentanil delivered by transdermal electrotransport is preferably about 2.3 μg to about 7.0 μg over a delivery time of up to about 20 minutes in human patients having a body weights of 35 kg or greater. More preferred is a dosage of about 4 μg to about 5.5 μg, and most preferred is a dosage of about 4.7 μg for the delivery period. The device of the invention further preferably includes means for delivering about 10 to 100, and more preferably about 20 to 80 additional like doses over a period of 24 hours in order to achieve and maintain the analgesic effect.

The fentanyl/sufentanil salt-containing anodic reservoir formulation for transdermally delivering the above mentioned doses of fentanyl/sufentanil by electrotransport is preferably comprised of an aqueous solution of a water soluble fentanyl/sufentanil halide salt such as HCl salts. Most preferably, the aqueous solution is contained within a hydrophilic polymer matrix such as a hydrogel matrix. The fentanyl/sufentanil salt is present in an amount

sufficient to deliver the above mentioned doses transdermally by electrotransport over a delivery period of up to about 20 minutes, to achieve a systemic analgesic effect. The fentanyl/sufentanil salt typically comprises about 1 to 10 wt% of the donor reservoir formulation (including the weight of the polymeric matrix) on a fully hydrated basis, and more preferably about 1 to 5 wt% of the donor reservoir formulation on a fully hydrated basis. Although not critical to the present invention, the applied electrotransport current density is typically in the range of about 50 to 150 $\mu A/cm^2$ and the applied electrotransport current is typically in the range of about 150 to 240 μA.

The anodic fentanyl/sufentanil salt-containing hydrogel can suitably be made of a any number of materials but preferably is comprised of a hydrophilic polymeric material, preferably one that is polar in nature so as to enhance the drug stability. Suitable polar polymers for the hydrogel matrix comprise a variety of synthetic and naturally occurring polymeric materials. A preferred hydrogel formulation contains a suitable hydrophilic polymer, a buffer, a humectant, a thickener, water and a water soluble fentanyl or sufentanil salt (eg, HCl salt). A preferred hydrophilic polymer matrix is polyvinyl alcohol such as a washed and fully hydrolyzed polyvinyl alcohol (PVOH), eg, Mowiol 66-100 commercially available from Hoechst Aktiengesellschaft. A suitable buffer is an ion exchange resin which is a copolymer of methacrylic acid and divinylbenzene in both an acid and salt form. One example of such a buffer is a mixture of Polacrilin (the copolymer of methacrylic acid and divinyl benzene available from Rohm & Haas, Philadelphia, PA) and the potassium salt thereof. A mixture of the acid and potassium salt forms of Polacrilin functions as a polymeric buffer to adjust the pH of the hydrogel to about pH 6. Use of a humectant in the hydrogel formulation is beneficial to inhibit the loss of moisture from the hydrogel. An example of a suitable humectant is guar gum. Thickeners are also beneficial

in a hydrogel formulation. For example, a polyvinyl alcohol thickener such as hydroxypropylmethylcellulose (eg, Methocel K100MP available from Dow Chemical, Midland, MI) aids in modifying the rheology of a hot polymer solution as it is dispensed into a mold or cavity. The hydroxypropyl methylcellulose increases in viscosity on cooling and significantly reduces the propensity of a cooled polymer solution to overfill the mold or cavity.

In one preferred embodiment, the anodic fentanyl/sufentanil salt-containing hydrogel formulation comprises about 10 to 15 wt% polyvinyl alcohol, 0.1 to 0.4 wt% resin buffer, and about 1 to 2 wt% fentanyl or sufentanil salt, preferably the hydrochloride salt. The remainder is water and ingredients such as humectants, thickeners, etc. The polyvinyl alcohol (PVOH)-based hydrogel formulation is prepared by mixing all materials, including the fentanyl or sufentanil salt, in a single vessel at elevated temperatures of about 90°C to 95°C for at least about 0.5 hr. The hot mix is then poured into foam molds and stored at freezing temperature of about -35°C overnight to cross-link the PVOH. Upon warming to ambient temperature, a tough elastomeric gel is obtained suitable for fentanyl electrotransport.

The hydrogel formulations are used in an electrotransport device such as described hereinafter. A suitable electrotransport device includes an anodic donor electrode, preferably comprised of silver, and a cathodic counter electrode, preferably comprised of silver chloride. The donor electrode is in electrical contact with the donor reservoir containing the aqueous solution of a fentanyl/sufentanil salt. As described above, the donor reservoir is preferably a hydrogel formulation. The counter reservoir also preferably comprises a hydrogel formulation containing a (eg, aqueous) solution of a biocompatible electrolyte, such as citrate buffered saline. The anodic and cathodic hydrogel reservoirs preferably each have a skin contact

area of about 1 to 5 cm^2 and more preferably about 2 to 3 cm^2. The anodic and cathodic hydrogel reservoirs preferably have a thickness of about 0.05 to 0.25 cm, and more preferably about 0.15 cm. The applied electrotransport current is about 150 μA to about 240 μA, depending on the analgesic effect desired. Most preferably, the applied electrotransport current is substantially constant DC current during the dosing interval.

Reference is now made to FIG. 1 which depicts an exemplary electrotransport device which can be used in accordance with the present invention. FIG. 1 shows a perspective exploded view of an electrotransport device 10 having an activation switch in the form of a push button switch 12 and a display in the form of a light emitting diode (LED) 14. Device 10 comprises an upper housing 16, a circuit board assembly 18, a lower housing 20, anode electrode 22, cathode electrode 24, anode reservoir 26, cathode reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral wings 15 which assist in holding device 10 on a patient's skin. Upper housing 16 is preferably composed of an injection moldable elastomer (eg, ethylene vinyl acetate). Printed circuit board assembly 18 comprises an integrated circuit 19 coupled to discrete electrical components 40 and battery 32. Circuit board assembly 18 is attached to housing 16 by posts (not shown in FIG. 1) passing through openings 13a and 13b, the ends of the posts being heated/melted in order to heat stake the circuit board assembly 18 to the housing 16. Lower housing 20 is attached to the upper housing 16 by means of adhesive 30, the upper surface 34 of adhesive 30 being adhered to both lower housing 20 and upper housing 16 including the bottom surfaces of wings 15.

Shown (partially) on the underside of circuit board assembly 18 is a battery 32, which is preferably a button cell battery and most preferably a

lithium cell. Other types of batteries may also be employed to power device 10.

The circuit outputs (not shown in FIG. 1) of the circuit board assembly 18 make electrical contact with the electrodes 24 and 22 through openings 23,23' in the depressions 25,25' formed in lower housing, by means of electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn, are in direct mechanical and electrical contact with the top sides 44',44 of reservoirs 26 and 28. The bottom sides 46',46 of reservoirs 26,28 contact the patient's skin through the openings 29',29 in adhesive 30. Upon depression of push button switch 12, the electronic circuitry on circuit board assembly 18 delivers a predetermined DC current to the electrodes/reservoirs 22,26 and 24,28 for a delivery interval of predetermined length, eg, about 10 minutes. Preferably, the device transmits to the user a visual and/or audible confirmation of the onset of the drug delivery, or bolus, interval by means of LED 14 becoming lit and/or an audible sound signal from, eg, a "beeper". Analgesic drug, eg fentanyl, is then delivered through the patient's skin, eg, on the arm, for the predetermined (eg, 10 minute) delivery interval. In practice, a user receives feedback as to the onset of the drug delivery interval by visual (LED 14 becomes lit) and/or audible signals (a beep from the "beeper").

Anodic electrode 22 is preferably comprised of silver and cathodic electrode 24 is preferably comprised of silver chloride. Both reservoirs 26 and 28 are preferably comprised of polymer hydrogel materials as described herein. Electrodes 22, 24 and reservoirs 26, 28 are retained by lower housing 20. For fentanyl and sufentanil salts, the anodic reservoir 26 is the "donor" reservoir which contains the drug and the cathodic reservoir 28 contains a biocompatible electrolyte.

The push button switch 12, the electronic circuitry on circuit board assembly 18 and the battery 32 are adhesively "sealed" between upper housing 16 and lower housing 20. Upper housing 16 is preferably composed of rubber or other elastomeric material. Lower housing 20 is preferably composed of a plastic or elastomeric sheet material (eg, polyethylene) which can be easily molded to form depressions 25,25' and cut to form openings 23,23'. The assembled device 10 is preferably water resistant (ie, splash proof) and is most preferably waterproof. The system has a low profile that easily conforms to the body thereby allowing freedom of movement at, and around, the wearing site. The anode/drug reservoir 26 and the cathode/salt reservoir 28 are located on the skin-contacting side of device 10 and are sufficiently separated to prevent accidental electrical shorting during normal handling and use.

The device 10 adheres to the patient's body surface (eg, skin) by means of a peripheral adhesive 30 which has upper side 34 and body-contacting side 36. The adhesive side 36 has adhesive properties which assures that the device 10 remains in place on the body during normal user activity, and yet permits reasonable removal after the predetermined (eg, 24-hour) wear period. Upper adhesive side 34 adheres to lower housing 20 and retains the electrodes and drug reservoirs within housing depressions 25,25' as well as retains lower housing 20 attached to upper housing 16.

The push button switch 12 is located on the top side of device 10 and is easily actuated through clothing. A double press of the push button switch 12 within a short period of time, eg, three seconds, is preferably used to activate the device 10 for delivery of drug, thereby minimizing the likelihood of inadvertent actuation of the device 10.

Upon switch activation an audible alarm signals the start of drug delivery, at which time the circuit supplies a predetermined level of DC current to the electrodes/reservoirs for a predetermined (eg, 10 minute) delivery interval. The LED 14 remains "on" throughout the delivery interval indicating that the device 10 is in an active drug delivery mode. The battery preferably has sufficient capacity to continuously power the device 10 at the predetermined level of DC current for the entire (eg, 24 hour) wearing period.

The present invention is further explained by the following examples which are illustrative of, but do not limit the scope of, the present invention.

EXAMPLE 1

The following study was conducted to determine the amount of fentanyl hydrochloride drug loading which is necessary to prevent silver migration, resulting in transient epidermal discoloration, from a transdermal fentanyl electrotransport delivery device having a donor reservoir gel weighing about 0.6 g and having a skin contact area of about 2.8 cm^2, which device is worn for a period of up to 24 hours and which applies an electrotransport current of 240 μA (ie, a current density of 87 $\mu A/cm^2$) over a delivery interval of about 10 minutes to deliver a 40 μg dose, and which can deliver up to 80 of such doses over the 24 hour wearing period. Thus, the device has the ability to deliver up to 3.2 mg of fentanyl (80 x 40 μg = 3.2 mg) for therapeutic purposes.

Fentanyl HCl-containing polyvinyl alcohol (PVOH) hydrogel-based donor reservoirs, each reservoir having a total weight of about 0.15 g, were made with the following composition:

Material	(wt%)
Water	80.8
PVOH	15.0
Fentanyl HCl	2.0
Polacrilin	0.1
0.5 N NaOH	2.1

The materials were mixed in a jacketed beaker at 90°C and then 0.15 g aliquots of the liquid gel were dispensed into foam molds and frozen overnight at temperatures ranging from -15 to -50°C. The gels had a disk shape with an area of 1.0 cm^2 and a thickness of 1.6 mm.

A silver foil was laminated to one surface of each of the gels to form an anodic donor electrode assembly comprised of the silver foil anode and the fentanyl containing gel reservoir. Counter electrode assemblies were made using similarly sized PVOH gels which contained citrate buffered saline (pH 4). A silver chloride cathodic electrode (ie, silver chloride powder-loaded polyisobutylene film) was laminated to one surface of the counter gels. The electrodes were electrically connected to custom made power sources which applied a constant DC current of 240 μA (87 μA/cm^2).

The electrotransport systems were applied to the upper outer arms of six male volunteers and worn for a period of 15 hours, which is about 10% longer than the maximum time of current application from this system (ie, 80 x 10 minutes = 13.3 hrs). Over the 15 hour wearing period, the systems applied current continuously, after which the systems were removed and the arm of each subject was closely examined to determine if transient epidermal discoloration (TED), caused by migration of silver ions formed in the anodic electrode assembly, had occurred. The subjects were again examined one hour and again at 24 hours after system removal to confirm the initial TED

reading. In all six subjects, no TED occurred at the site of attachment of the anodic electrode assembly. This indicates that a fentanyl HCl loading of about 1.8 to 2 wt%, or about 3 mg in these gels, provides a sufficient quantity of chloride ions to prevent migration of silver ions, formed by oxidation of the silver anode, into the skin of the patient over the 15 hour wearing period. Thus, an electrotransport system which applies the same level of electrotransport current over a maximum dosing period of 13.3 hours will likewise exhibit no TED, even under conditions of maximum usage. The 2 wt% fentanyl HCl loading in these PVOH-based donor gel reservoirs can be scaled-up to larger reservoirs. Thus, for a fentanyl HCl-containing PVOH-based donor reservoir having a total weight of about 0.6 g, the reservoir containing substantially no other source of chloride ions other than the drug counter ions, the fentanyl HCl loading should be at least about 11 mg (ie, 1.8 wt% x 0.6 g = 11 mg) even though the maximum amount of fentanyl which can be delivered from the device over the 24 hour wearing period is only about 3.2 mg fentanyl. Thus, in order to prevent silver migration in this device under conditions of maximum usage, an excess amount of fentanyl HCl must be loaded into the anodic donor reservoir, which excess loading is about 3 to 4 times the amount of fentanyl needed for therapeutic purposes.

In summary, the present invention provides an improved device for the transdermal electrotransport of water soluble salts of fentanyl, and sufentanil, the device having a silver anodic donor electrode and preferably a hydrogel based donor reservoir. The electrotransport device is preferably a patient-controlled device. The hydrogel formulation contains a drug concentration which is sufficient to inhibit silver ion migration to the skin of a wearer of the electrotransport device, and thus prevent transient epidermal discoloration, and to provide an acceptable level of analgesia.

CLAIMS:

1. An electrotransport device (10) for transdermally administering an analgesic drug selected from the group consisting of fentanyl halide salts and sufentanil halide salts, the device including a silver anodic donor electrode (22) and a cathodic counter electrode (24), the donor electrode (22) being in electrical contact with a donor reservoir (26) containing the analgesic drug, the donor reservoir (26) being substantially free of sources of halide other than the analgesic drug halide, the device characterized by:

the donor reservoir (26) containing a loading amount of the analgesic drug halide salt, which loading amount is at least about 2 times greater than an amount needed for achieving an analgesic effect.

2. The device of claim 1, wherein the analgesic drug is fentanyl HCl or sufentanil HCl.

3. The device of claim 1, wherein the analgesic drug comprises fentanyl halide and the loading amount is at least about two times greater than the analgesically effective amount.

4. The device of claim 1, wherein the analgesic drug comprises a sufentanil halide and the loading amount is at least about 4 times greater than the analgesically effective amount.

5. The device of claim 1, wherein the device includes a source of electric current (32) which applies an electrotransport current to the donor and counter electrodes (22,24).

6. The device of claim 1, whereby the device causes substantially no transient epidermal skin discoloration, during or after electrotransport delivery of the fentanyl or sufentanil.

7. The device of claim 1, wherein the device is adapted to deliver the analgesic drug over a delivery period of at least about 6 hours.

8. The device of claim 7, wherein the delivery period is a cummulative period of time comprised of a plurality of analgesic drug delivery intervals.

9. The device of claim 1, wherein the donor reservoir (26) has a weight on a hydrated basis of about 0.5 g to 0.8 g, the device has an electric current source (32) which applies a DC current of about 190 μA to 230 μA to the donor and counter electrodes (22,24) over up to about 100 separate delivery intervals, each delivery interval having a duration of about 8 to 12 minutes, and the donor reservoir (26) contains at least about 9 mg of fentanyl hydrochloride.

10. The device of claim 9, wherein the donor reservoir (26) contains at least about 12 mg of fentanyl hydrochloride.

11. A method of making a device (10) for transdermally administering an analgesic drug selected from the group consisting of fentanyl halide salts and sufentanil halide salts by electrotransport, the device (10) including a silver anodic donor electrode (22) and a cathodic counter electrode (24), the donor electrode (22) being in electrical contact with a donor reservoir (26) containing the analgesic drug, the donor reservoir (26) being substantially free of sources of halide other than the analgesic drug halide, the method characterized by:

placing a loading amount of the analgesic drug halide salt in the donor reservoir (26), which loading amount is at least about 2 times greater than an analgesically effective amount.

12. The method of claim 11, wherein the analgesic drug is fentanyl HCl or sufentanil HCl.

13. The method of claim 11, wherein the analgesic drug comprises a fentanyl halide and the loading amount is at least about two times greater than the analgesically effective amount.

14. The method of claim 11, wherein the analgesic drug comprises a sufentanil halide and the loading amount is at least about 4 times greater than the analgesically effective amount.

15. The method of claim 11, wherein the device (10) includes a source of electric current (32) which applies an electrotransport current to the donor and counter electrodes (22,24).

16. The method of claim 11, whereby the device (10) causes substantially no transient epidermal skin discoloration during or after electrotransport delivery of the fentanyl or sufentanil.

17. The method of claim 11, wherein the device (10) is adapted to deliver the analgesic drug for a period of at least about 6 hours.

18. The method of claim 17, wherein the period is a cummulative period comprised of a plurality of analgesic drug delivery intervals.

19. The method of claim 11, including providing the donor reservoir (26) with a weight on a hydrated basis of about 0.5 g to 0.8 g, the device (10) has an electric current source (32) which applies a DC current of about 190 μA to 230 μA to the donor and counter electrodes (22,24) over up to about 100 separate delivery intervals, each delivery interval having a duration of about 8 to 12 minutes, and loading at least about 9 mg of fentanyl hydrochloride into the donor reservoir (26).

20. The method of claim 18, including loading at least about 12 mg of fentanyl hydrochloride into the donor reservoir (26).

21. An anodic fentanyl formulation for an electrotransport delivery device (10) having a silver anodic donor electrode (22) in contact with the formulation, a cathodic counter electrode (24) and an electrical power source (32) coupled to the donor and counter electrodes (22,24), the formulation including a hydrophilic matrix containing an aqueous solution of a fentanyl halide salt, the formulation being characterized by:

a fentanyl halide loading which is: (i) at least about 2 times greater than a minimum loading needed to achieve an analgesic effect during the period of therapy; and (ii) sufficient to substantially prevent transient epidermal skin discoloration during and after transdermal electrotransport delivery of fentanyl therefrom.

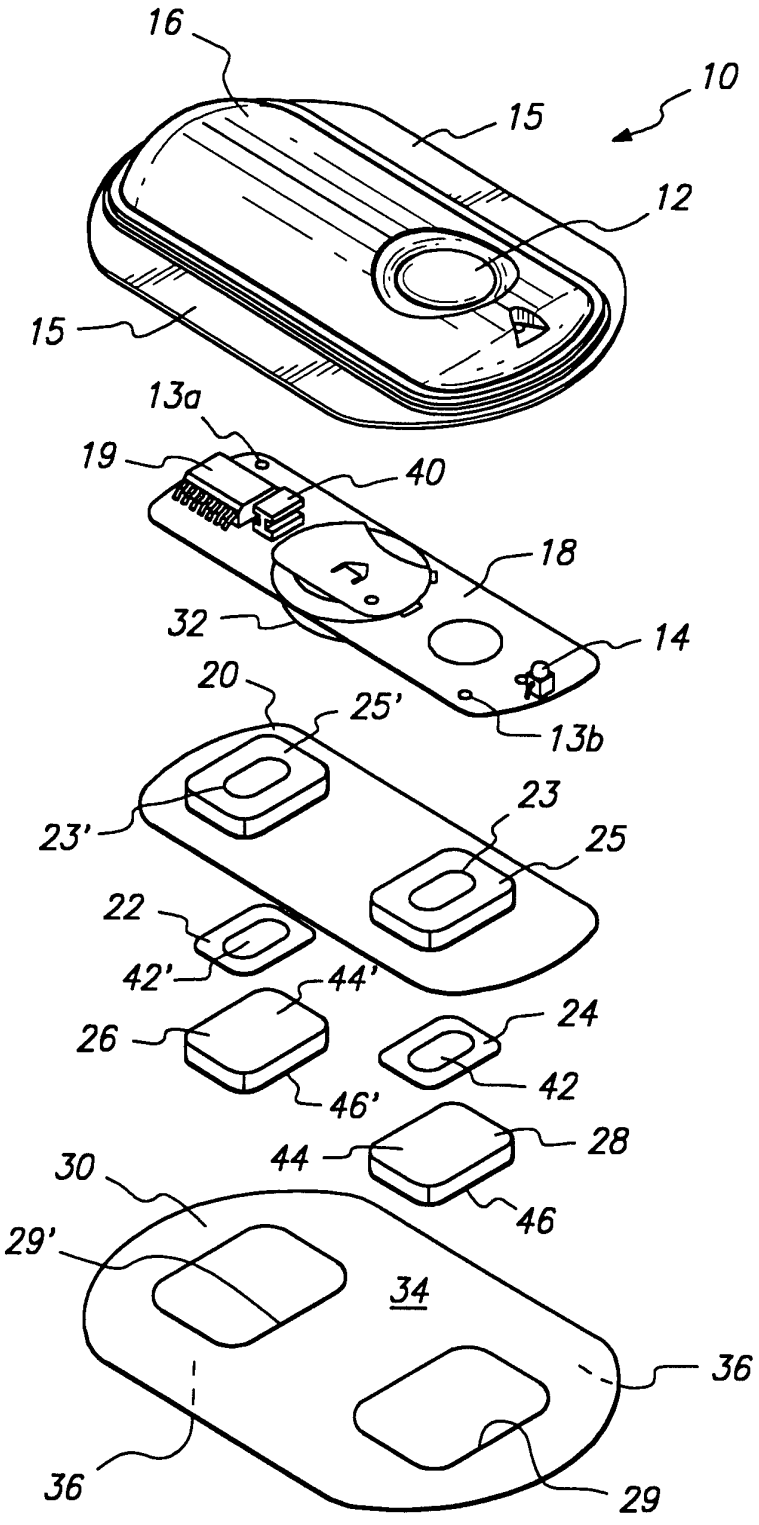
22. The formulation of claim 21, wherein the fentanyl halide salt comprises about 1.7% to 2.0 wt% of the formulation.

23. The formulation of claim 21, wherein the fentanyl halide comprises about 1.9 to 2.0 wt% of the formulation.

24. The formulation of claim 21, wherein the fentanyl halide is fentanyl hydrochloride.

25. The formulation of claim 21, wherein the hydrophilic matrix comprises polyvinyl alcohol.

FIG. 1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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 96/09264

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/30

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 01807 (ALZA CORP) 4 February 1993 see page 20, line 32 - page 24, line 9; figures ---	1-8, 10-17, 21-25
A	WO,A,91 08795 (ALZA CORP) 27 June 1991 see page 11, line 6 - page 18, line 7; figures ---	1,5-8, 11, 15-18,21
A	WO,A,90 03825 (ALZA CORP) 19 April 1990 see page 14, line 16 - page 15, line 11; claims 1-14; figures --- -/--	1,6,11, 15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 1996	20. 11. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Rakotondrajaona, C

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 96/09264

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANESTHESIA & ANALGESIA, vol. 77, no. 1, July 1993, pages 61-66, XP000576408 THYSMAN AND PRÉAT: "In vivo iontophoresis of fentanyl and sufentanil in rats: pharmacokinetics and acute antinociceptive effects" cited in the application see page 62, line 1 - page 65, line 55; figures ---	1,5-8, 11,15-17
A	US,A,5 298 017 (THEEUWES FELIX ET AL) 29 March 1994 see column 6, line 38 - column 13, line 26; figures -----	1-7, 11-17, 20-24

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/US 96/09264

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		US-A-	5169382	08-12-92
		US-A-	5147296	15-09-92
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