SUFENTANIL SOLID DOSAGE FORMS COMPRISING OXYGEN SCAVENGERS AND METHODS OF USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit United States Application Serial No. 12/275,485, filed November 21, 2008, incorporated by reference in its entirety.

Field of the Invention

[0002] The present invention relates to compositions, methods and systems effective to minimize or eliminate the presence of oxidative degradation products in solid dosage forms comprising sufentanil. The solid dosage forms comprising sufentanil are packaged in a substantially oxygen impermeable container which includes at least one oxygen scavenging material.

Background of the Technology

[0003] Many pharmaceutical formulations and reagents used in diagnostic evaluations are sensitive to oxygen and/or moisture. Exposure of such pharmaceutical formulations and reagents to oxygen or moisture may interfere with the stability and efficacy of the pharmaceutical agent or reagent.

[0004] Oxidative degradation of sufentanil has not been reported for liquid (Sufenta) or dry powder forms of sufentanil (Janssen Pharmaceuticals, Johnson Matthey, Inc., Covidien).

[0005] Moisture resistant packaging has been shown to be a critical requirement for Fentora, a fentanyl buccal tablet (Cephalon application for Marketing Authorisation of Fentora to the European Medicines Agency (EMEA); February 21, 2007, p4). Similarly, the summary of product characteristics for Abstral (a sublingual fentanyl tablet previously known as "Rapinyl", and approved by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) in June, 2008), states that tablets should be stored in the original blister package in order to protect them from moisture (Electronic Medicines Compendium (eMC) for UK licensed medicines, last updated August 1, 2009).

[0006] Oxidative degradation of the sufentanil congener, fentanyl, has not been reported for dry powder forms of the drug or for solid fentanyl dosage forms.

[0007] The inventors, have developed solid sufentanil dosage forms (tablets), and were surprised to observe that degradation occurred following formulation, tabulating and storage. The inventors were also surprised to find that inclusion of an anti-oxidant, such as butylated hydroxytoluene (BHT), in the formulation and/or use of a desiccant in the packaging of low dose solid sufentanil dosage forms did not stop the degradation. Degradation of sufentanil was observed in solid sufentanil dosage forms prepared using aqueous and/or organic solvents following formulation, tableting and storage under various conditions.

[0008] There remains a need for development of specific pharmaceutical formulations and packaging systems to ensure that drugs, such as sufentanil, can be formulated and stored in low dose solid dosage forms in a manner where degradation is minimized and the integrity of the active drug is maintained.

Brief Summary Of The Invention.

[0009] Solid sufentanil drug dosage forms are provided in a primary package containing an oxygen scavenger, wherein the percentage of sufentanil oxidative degradation products is minimized or eliminated in solid sufentanil drug dosage forms packaged with an oxygen scavenger relative to solid sufentanil drug dosage forms packaged in the absence of an oxygen scavenger.

[0010] The packaged solid sufentanil drug dosage forms may be stored for at least 6 months under conditions selected from the group consisting of 5°C and ambient humidity, 25°C, 60% relative humidity and 40°C, 75% relative humidity, wherein following storage the percentage of sufentanil oxidative degradation products is minimized or eliminated in the solid sufentanil drug dosage forms packaged with an oxygen scavenger relative to the solid sufentanil drug dosage forms packaged in the absence of an oxygen scavenger.

[0011] The packaged solid sufentanil drug dosage forms have a mass of from about 5mg to about 25mg, a volume of from about 5mcl to about 25mcl, a mass of from about 2mg to about 10mg or a volume of from about 2mcl to about 10mcl.

[0012] The packaged solid sufentanil drug dosage forms have a thickness of from about 0.7mm to about 1.0mm or from about 0.75mm to about 0.95mm and may comprise 5 mcg, 10 mcg, 15 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 70 mcg, 80 mcg or 100 mcg of sufentanil.

[0013] The packaged solid sufentanil drug dosage forms may be housed in a drug delivery dispenser such as a cartridge or a single dose applicator and the primary package may be a foil pouch.

[0014] Methods for preventing oxidative degradation of solid sufentanil drug dosage forms are also provided.

Brief Description Of The Drawings.

[0015] Figure 1 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2 and 3 months), for 5 mcg sufentanil dosage forms made using a standard formulation following storage at 5°C and ambient humidity in HDPE bottles alone (5ug) or in HDPE bottles containing an oxygen scavenger (Stabilox®; Multisorb Technologies; 5ug-R). The designation "% Total RS" (% total related substances) is used interchangeably herein with the term "% SDP (percent sufentanil degradation products). Both terms are used to describe the percentage of the peak area for "related substances" (sufentanil degradation products) relative to the total peak area for sufentanil, e.g., following HPLC (high performance liquid chromatography) analysis.

[0016] Figure 2 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2 and 3 months), for 5mcg sufentanil dosage forms made using a standard formulation following storage at 25°C and 60% relative humidity in HDPE bottles alone (5ug) or in HDPE bottles containing an oxygen scavenger (5ug-R_Stabilox in HDPE).

[0017] Figure 3 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2 and 3 months), for 5mcg sufentanil dosage forms made using a standard formulation following storage at 40°C and 75% relative humidity in HDPE bottles alone (5ug) or in HDPE bottles containing an oxygen scavenger (5ug-R_Stabilox in HDPE).

[0018] Figure 4 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2, 3 and 6 months) for 5mcg sufentanil dosage forms made using a standard formulation following storage at 5°C and ambient humidity in HDPE bottles containing desiccant (5ug – Desiccant in HDPE) or in HDPE bottles containing an oxygen scavenger (5ug-R_Stabilox in HDPE).

[0019] Figure 5 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2, 3 and 6 months) for 5mcg sufentanil dosage forms made using a standard formulation following storage at 25°C and 60% relative humidity in HDPE bottles containing desiccant (5ug – Desiccant in HDPE) or in HDPE bottles containing an oxygen scavenger (5ug-R_Stabilox in HDPE).

[0020] Figure 6 provides a graphic depiction of % Total RS versus time (0, 0.5, 1, 2, 3 and 6 months) for 5mcg sufentanil dosage forms made using a standard formulation following storage at 40°C and 75% relative humidity in HDPE bottles containing desiccant (5ug – Desiccant in HDPE) or in HDPE bottles containing an oxygen scavenger (5ug-R_Stabilox in HDPE).

Detailed Description Of The Invention.

I. Introduction

[0021] Provided herein are compositions, methods and systems effective to minimize or eliminate the presence of oxidative degradation products in solid dosage forms comprising sufentanil.

[0022] The following disclosure describes the compositions, methods and systems which constitute the invention. The invention is not limited to the specific dosage forms, devices, methodology, systems, kits or medical conditions described herein, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention.

[0023] It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a drug formulation" includes a plurality of such formulations and reference to "a drug delivery device" includes systems comprising drug dosage forms and delivery devices for containment, storage and delivery of such dosage forms.

[0024] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

[0025] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such a disclosure by virtue of prior invention.

[0026] As used herein, the term "analgesic", is used with reference to any of a number of drugs used to relieve pain (achieve analgesia).

[0027] The term "analgesic drug" is used herein with reference to a drug which results in analgesia following administration to a subject, for example, sufentanil, or a sufentanil congener, such as alfentanil, fentanyl, lofentanil, carfentanil, remifentanil, trefentanil, or mirfentanil. The phrase " analgesic drug " is not limited to sufentanil, a sufentanil congener, or formulations comprising sufentanil or a sufentanil congener.

[0028] The term "antioxidant" as used herein refers to a molecule or combination of molecules capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. Antioxidants typically terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves.

[0029] The term "cartridge" is used herein with reference to a replaceable, single use disposable cartridge configured to hold one or more drug dosage forms, typically a 1 to 5 day supply. In one exemplary embodiment, a cartridge holds sufficient drug dosage forms for 1-5 days of treatment, e.g., 40 tablets useful for 48 to 72 hours of treatment.

[0030] . The cartridge may comprise a smart cartridge recognition system with a physical keyed feature on the cartridge, a bar code on the cartridge, a magnetic tag on the cartridge, an RFID tag on the cartridge, an electronic microchip on the cartridge, or a combination thereof. The cartridge may comprise one or more shipping tablets, wherein at least one shipping tablet is dispensed prior to dispensing of a drug dosage form.

[0031] The term "replaceable cartridge" or "disposable cartridge" is used with reference to a cartridge for housing drug dosage forms and is typically configured to hold a 1 to 5 day supply of drug dosage forms, wherein the cartridge is designed to be used in a dispensing device and discarded after use.

[0032] As used herein, the term "degradation" refers to any change in a "drug", "medication", or "pharmacologically active agent" (such as the sufentanil in a sufentanil-containing solid dosage form) during storage, for example by hydrolysis and/or oxidation of the drug or other components/excipients contained in the formulation.

[0033] As used herein, the term "degradation agent" refers to an agent, e.g., an oxidizing agent or moisture (water), which is exposed to a "drug", "medication", or

"pharmacologically active agent" (such as the sufentanil in a sufentanil-containing solid dosage form) and causes an undesirable by-product.

[0034] As used herein, the term "degradation protectant" refers to any material which protects against degradation of a "drug", "medication", or "pharmacologically active agent" (such as the sufentanil in a sufentanil-containing solid dosage form), e.g., an oxygen scavenger, a desiccant, an anti-oxidant or a combination thereof.

[0035] The term "desiccant" is used herein with reference to a sorbant, in the form of a solid, liquid, or gel which has an affinity for water, and absorbs or adsorbs moisture from it's surrounding, thus controlling the moisture in the immediate environment.

[0036] The term "drug", "medication", "pharmacologically active agent", "therapeutic agent" and the like are used interchangeably herein and generally refer to any substance that alters the physiology of an animal and can be effectively administered by the oral transmucosal route.

[0037] The terms "formulation" and "drug formulation" as used herein refer to a physical composition containing at least one pharmaceutically active substance, which may be provided in any of a number of dosage forms for delivery to a subject. The dosage form may be provided to the patient as a lozenge, pill, capsule, membrane, strip, liquid, patch, film, gum, gel, spray or other form.

[0038] The term "hydrogel-forming preparation", means a solid formulation largely devoid of water which upon contact with an aqueous solution, e.g., a bodily fluid, and in particular that of the oral mucosa, absorbs water in such a way that it forms a hydrated gel in situ. The formation of the gel follows unique disintegration (or erosion) kinetics while allowing for release of the therapeutic agent over time. Additionally, the term "hydrogel-forming preparation" describes a solid formulation largely devoid of water which upon contact with bodily fluids, and in particular those in the oral cavity, transforms into a film that releases the drug. Such films increase the surface area available for drug release and absorption thus enabling faster absorption of the drug.

[0039] As used herein, the term "oxygen scavenger" refers to a chemical substance that is added to a drug formulation or reagent in order to reduce or eliminate the generation of unwanted oxidation products. In general, an "oxygen scavenger" is effective to absorb oxygen. The term "oxygen scavenger" may be used interchangeably with the terms "oxygen scavenging element" and "oxygen absorber".

[0040] As used herein, the term "drug delivery dispenser" means the container which directly houses a drug, medication, or pharmacologically active agent. Examples include,

a cartridge, a single dose applicator, a multiple dose applicator, a thermoplastic tray, a blister pack, a flexible container, and a rigid container.

[0041] As used herein, the term "drug dosage form" refers to a physical entity containing at least one drug, medication, or pharmacologically active agent for delivery to a subject. It may be in the form of a lozenge, pill, tablet, capsule, membrane, strip, powder, patch, film, gel, spray, gum or other form.

[0042] As used herein, the term "primary packaging" means the container which directly houses a drug, medication, or pharmacologically active agent. Examples include a foil pouch, a plastic container, a plastic film container, a blister pack, a glass container, and the like.

[0043] An exemplary foil pouch comprises one of more of aluminum, zinc, nickel, tin, iron, copper, chromium, cobalt, silver, gold, magnesium, manganese, lead, galvanized iron, and metal oxides.

[0044] The term "small volume sufentanil-containing drug dosage form" is used herein with reference to a small volume dosage form that contains an amount of sufentanil from about 2 micrograms (mcg) to about 200 mcg of sufentanil, e.g., 5 mcg, 10 mcg, 15 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 70 mcg, 80 mcg, 90 mcg, or 100 mcg or more of sufentanil.

[0045] The term "solid dosage form" or "solid drug dosage form" is used herein with reference to a dosage form that is a solid, e.g., a lozenge, a pill, a tablet, a membrane or a strip.

[0046] The term "subject" includes any subject, generally a mammal (e.g., human, canine, feline, equine, bovine, ungulate etc.), adult or child, in which treatment with a sufentanil-containing solid dosage form is desired. The terms "subject" and "patient" may be used interchangeably herein.

[0047] The term "substantially oxygen impermeable material" is used herein with reference to a material that allows the passage of little or no oxygen through the material.

Inhibition of Oxidative Degradation

[0048] Many drugs are susceptible to oxidative degradation. In particular, this can be a problem when the drug is present as a low percentage of the overall drug formulation. In order to minimize or eliminate the presence of impurities in a drug formulation comprising an oxidation-susceptible active drug, and a dosage form made from such a

formulation, e.g., a solid sufentanil dosage form, preservatives and antioxidants are often employed in the formulation to address this problem. In most cases, this is sufficient to minimize or eliminate the generation of oxidative degradation products.

[0049] Given that oxidative degradation of sufentanil has not been reported for liquid (Sufenta), dry powder forms of sufentanil (Janssen Pharmaceuticals, Johnson Matthey, Inc., Covidien) or for oral transmucosal forms of fentanyl, the inventors were surprised to discover that degradation occurred in solid sufentanil dosage forms, following formulation, tabulating and storage. The inventors were also surprised to find that inclusion of an anti-oxidant such as BHT in the formulation, and/or use of a desiccant in the packaging did not stop the degradation. Degradation of sufentanil was observed in low dose solid sufentanil dosage forms prepared using aqueous and/or organic solvents following formulation, tableting and storage under various conditions.

[0050] Methods and compositions for protecting an oxidation-susceptible active drug, such as sufentanil, in a solid drug dosage form from oxidative degradation are disclosed. In some cases, the methods involve inclusion of an oxygen scavenger in the packaging for the drug dosage form. In this manner, drug dosage forms, e.g., sufentanil tablets, are produced and stored under conditions wherein the active drug is protected from oxidative degradation, thus facilitating storage of the drug dosage form over extended periods of time.

[0051] Additional protection against oxygen exposure may be afforded by employment of packaging techniques designed to minimize exposure of the active drug to oxygen and/or moisture. Exemplary packaging techniques include use of primary packaging wherein more than one oxygen scavenging material is employed alone or in combination with use of a desiccant.

[0052] In one exemplary approach, an anti-oxidant such as BHT is included in the drug formulation, a drug delivery dispenser (e.g., a cartridge) houses the drug dosage form(s), and an oxygen scavenger is included in the primary packaging for the drug delivery dispenser, wherein gas exchange is possible between the drug delivery dispenser and the oxygen scavenger in the primary package.

[0053] In another exemplary approach, an anti-oxidant such as BHT is included in the drug formulation, a desiccant is included in the drug delivery dispenser (e.g., a cartridge) which houses the drug dosage form(s), and an oxygen scavenger is included in the primary packaging wherein gas exchange is possible between the drug delivery dispenser and primary package.

[0054] In a related approach, the oxidative degradation of a drug such as sufentanil is reduced or eliminated by providing the drug in an oxygen impermeable primary package, such as a foil pouch, which comprises at least one oxygen scavenging material.

[0055] In yet another embodiment, the antioxidant and/or the desiccant is incorporated into the material that is used to make the drug delivery dispenser or primary packaging. In another embodiment, the drug delivery dispenser or primary packaging material is comprised of an antioxidant packaging material.

[0056] In a preferred embodiment, the drug delivery dispenser is comprised of a material that does not generate degradation products upon exposure to a solid dosage form containing a pharmaceutically active agent, such as sufentanil. Exemplary materials for use in packaging include, glass, polypropylene, polyethylene (e.g., high density polyethylene (HDPE) or low density polyethylene (LDPE), polyester, polystyrene, polyamide, fluoro polymers such as ACLAR®, ethylene covinyl alcohol (EVOH), , polycarbonate, polyurethane, polyvinylidene chloride (PVDC), polyvinyl alcohol (PVA) copolymers thereof, or blends thereof.

[0057] Exemplary materials for use in manufacture of single dose applicators, include but are not limited to TecoFlex EG 80A, Polyisoprene, Zylar 220; NAS 30 (NEOS NOVA), Versaflex, CL2242 (GLS Corp), KR01 (Chevron Phillips), Housing Polymer, Delrin® acetal (DuPont), Polyester (Valox; Celanex), Polypropylene, Pro Fax PD702 (Basell) and the like.

Antioxidants

[0058] Antioxidants commonly employed in pharmaceutical formulations include, but are not limited to, vitamin E, ascorbic acid, BHT (butylated hydroxytoluene), BHA (butylated hydroxyanisole), propyl gallate, ascorbyl palmitate, biflavonoids and the like. An antioxidant may be included in the formulation of an oxidation-susceptible drug, such as sufentanil, in particular, when provided in low dose solid dosage forms.

Oxygen Scavengers

[0059] Suitable oxygen scavengers include any organic or inorganic material that can absorb oxygen, for example, iron oxide powders, ferrous salts such as ferrous sulfate or ferrous chloride, sulfites, bisulfites, reducing sulfur compounds such as dithionite, ascorbic acid and/or their salts, erythorbic acid and/or their salts, reducing organic compounds such as catechol and hydroquinone, butylated hydroxytoluene (BHT),

butylated hydroxyanisole (BHA). See, e.g. U.S. Patent Publication Nos. 20060076536, 20070084144, 20060260967.

[0060] A number of oxygen scavengers and moisture absorbents are commercially available and may be purchased alone or in packages, e.g., StabilOx® (Multisorb Technologies), cyclohexene methyl acrylated (EMCM) polymer (Chevron-Phillips Chemical Company) or Ciba's Specialty Chemical's SHELFPLUS.TM.).

[0061] An oxygen scavenger may be included in the packaging in the form of pellets, canisters, packets, capsules, powders, solid materials, tablets, or as part of the packaging material itself.

Desiccants

[0062] Any commercial desiccant may be used, e.g., in the packaging of a solid sufentanil dosage form. Desiccants may be provided as pellets, canisters, packets, capsules, powders, solid materials, papers, boards, tablets, adhesive patches and films, and can be formed for specific applications, including injection moldable plastics. Exemplary solid desiccants include, silica gel (sodium silicate), alumino-silicate, activated alumina, zeolite, molecular sieves, montmorillonite clay, calcium oxide and calcium sulfate.

[0063] In some embodiments, one or more desiccants may be employed in a drug delivery dispenser, e.g., within a cartridge or single dose applicator containing drug dosage forms, or inside the primary packaging for the drug-containing drug delivery dispenser, as a means for protecting solid drug dosage forms from moisture. Exemplary locations include, in or adjacent the dosage form or delivery pathway, in or adjacent a tablet magazine or cartridge, in or adjacent other components of a dispensing device, formed as an injection molded component of a dispensing device, and any other location within or without the device wherein the desiccant is in sufficiently close proximity to the drug dosage form to pick up moisture.

Solid Dosage Forms

[0064] In general, small volume solid dosage forms containing from about 2 mcg to about 200 mcg of sufentanil are provided. In one exemplary embodiment, each dosage form contains from about 2mcg to about 100mcg of sufentanil, from about 4mcg to about 50mcg of sufentanil, from about 6mcg to about 40mcg of sufentanil, from about 8mcg to about 30mcg of sufentanil, or from about 10mcg to about 20mcg of sufentanil.

The dosage form contains sufentanil, alone, or in combination with another drug, e.g., a benzodiazepine, such as triazolam.

[0065] The process for manufacture of solid dosage forms, e.g., tablets, pills, capsules, strips, films, powders, lozenges, membranes, patches, film or other forms, comprising sufentanil, typically involves the use of an aqueous and/or organic solvent.

[0066] The sufentanil-containing solid dosage forms have a mass of from about 1mg to about 100mg or a volume of from about 1mcL to about 100mcL. More specifically, the dosage forms have a mass of from about 1mg to about: 100mg, 90mg, 80mg, 70mg, 60mg, 50mg, 40mg, 30mg, 29mg, 28mg, 27mg, 26mg, 25mg, 24mg, 23mg, 22mg, 21mg, 20mg, 19mg, 18mg, 17mg, 16mg, 15mg, 14mg, 13mg, 12mg, 11mg, 10mg, 9mg, 8mg, 7mg, 6mg or 5mg; or a volume of from about 1mcL to about: 100 mcL, 90 mcL, 80 mcL, 70 mcL, 60 mcL, 50 mcL, 40 mcL, 30 mcL, 29 mcL, 28 mcL, 27 mcL, 26 mcL, 25 mcL, 24 mcL, 23 mcL, 22 mcL, 21 mcL, 20 mcL, 19 mcL, 18 mcL, 17 mcL, 16 mcL, 15 mcL, 14 mcL, 13 mcL, 12 mcL, 11 mcL, 10 mcL, 9 mcL, 8 mcL, 7 mcL, 6 mcL or 5 mcL.

[0067] More specifically, the sufentanil-containing solid dosage forms have a mass of from about 1 to about 8mg, from about 2 to about 10mg, from about 3 to about 15mg, from about 4 to about 20mg, from about 5 to about 25mg, or a volume of from about 1 to about 8mcl, from about 2 to about 10 mcl, from about 3 to about 15mcl; from about 4 to about 20mcl, or from about 5 to about 25 mcl. In one exemplary embodiment, the tablets have a mass of 5.85 mg.

[0068] The sufentanil-containing solid dosage forms, tablets or NanoTabs™ have a thickness of from about 0.25 to about 5.0mm; from about 0.5 to about 2.5mm, from about 0.6 to about 2.0mm, from about 0.7 to about 1.0mm, from about 0.75 to about 0.95mm, e.g., about 0.85mm; and a diameter of from about 1.0 to about 10.0mm, from about 2.0 to about 5.0mm, from about 2.5 to about 4.0mm, from about 3.0 to about 3.5mm, e.g., about 3.0mm.

[0069] Tablets for oral transmucosal delivery of the combination of an opioid, such as sufentanil, typically have an erosion time of from about 2 minutes to about 40 minutes, from about 3 minutes to about 30 minutes, from about 4 minutes to about 25 minutes, from about 5 minutes to about 20 minutes, from about 5 minutes to about 15 minutes, from about 30 seconds to about 15 minutes, from about 1 minute to about 15 minutes, or from about 6 minutes to about 12 minutes.

[0070] The solid dosage forms may have essentially any shape, examples of which include a round disc with a flat, concave, or convex face, an ellipsoid shape, a spherical shape, a polygon with three or more edges and flat, concave, or convex faces. The solid dosage forms may be symmetrical or asymmetrical, and may have features or geometries that allow for controlled, convenient, and easy storage, handling, packaging or dosing.

[0071] The dosage forms typically have bioadhesive characteristics and may form a hydrogel upon contact with an aqueous solution.

[0072] Typical formulations for preparation of sufentanil-containing solid dosage forms and methods of making them are described in US Patent Publication Serial Nos. 20080166404 and 20070207207. An exemplary formulation is bioadhesive and comprises from about 0.04% to about 4% sufentanil, from about 0.08% to about 1.7% sufentanil or from abut 0.1% to about 2.0% sufentanil, e.g., about 0.04%, 0.08%, 0.1%, 0.2%, 2.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.2%, 2.2%, 2.4%, 2.5%, 2.6%, 2.8%, 3.0%, 3.2%, 3.5% or 4% sufentanil. In general, the formulation is provided as a substantially homogeneous composition which comprises sufentanil, one or more of bioadhesives, binders, hydrogel-forming excipients, bulking agents, lubricants, and other excipients and factors that affect dissolution time and/or drug stability. The drug formulations and solid dosage forms are neither effervescent nor do they comprise an ordered mixture of microparticles of drug adhered to the surface of carrier particles, where the carrier particles are substantially larger than the microparticles of drug.

[0073] Dissolution of a dosage form comprising the formulation is generally independent of pH, e.g., over a pH range of about 4 to 8.

[0074] Numerous suitable nontoxic pharmaceutically acceptable carriers for use in sufentanil-containing solid dosage forms can be found in Remington's Pharmaceutical Sciences, 17th Edition, 1985.

[0075] It will be understood that a sufentanil-containing formulation is converted into sufentanil-containing solid dosage forms for delivery to a subject using procedures routinely employed by those of skill in the art, such as direct compression, wet granulation, etc. The process for preparation of sufentanil-containing solid dosage forms typically involves use of aqueous and/or organic solvents and is optimized for each formulation in order to achieve high dose content uniformity.

Cartridges and Single Dose Applicators

[0076] The cartridge for housing drug dosage forms may be cylindrical, disk-shaped, helical, rectilinear, non-ordered, or may take the form of any assemblage of drug dosage forms that allows a drug dispensing device to dispense them in a controlled manner.

[0077] In one embodiment of the invention, a cartridge may hold sufficient drug dosage forms for 1-5 days of treatment, e.g., 40 tablets useful for 48 to 72 hours of treatment.

[0078] To prevent unused drug dosage forms from absorbing moisture or otherwise becoming exposed to moisture prior to use, a cartridge or other drug dispensing device may provide a means of sealing the drug dosage forms from exposure to moisture. This may accomplished by use of a cartridge that contains a desiccant or other absorbent or adsorbent material to absorb or adsorb moisture that penetrates the cartridge either prior to use or during normal use.

[0079] The desiccant is a sorbant, in the form of a solid, liquid, or gel that has an affinity for water, and absorbs or adsorbs moisture from the surrounding, thus controlling the moisture in the immediate environment. Any commercial desiccant may be used. Such commercial desiccants typically take the form of pellets, canisters, packets, capsules, powders, solid materials, papers, boards, tablets, adhesive patches, and films, and can be formed for specific applications, including injection moldable plastics. There are many types of solid desiccants, including silica gel (sodium silicate, which is a solid, not a gel), alumino-silicate, activated alumina, zeolite, molecular sieves, montmorillonite clay, calcium oxide and calcium sulfate, or others, any of which may be used in practicing the present invention.

[0080] In one embodiment, a single dose applicator (SDA) is used as the drug delivery dispenser for a solid sufentanil drug dosage form. In this embodiment, the SDA is contained in a primary package which is not oxygen permeable. In another embodiment, the SDA is contained in a primary package which is oxygen permeable. In yet another embodiment, the primary package is contained in a secondary package which is not oxygen permeable.

[0081] The SDA may contain the dosage form within, may have the drug dosage form attached or affixed to it, and/or may afford a seal against moisture, humidity, and light. The single dose applicator may be manually manipulated by a patient, healthcare provider, or other user to place the dosage form in the proper location for drug delivery.

[0082] The SDA may be provided as a pair of forceps, a syringe, a stick or rod, a straw, a pad, a capsule, a cup, a spoon, a strip, a tube, an applicator, a dropper, a patch, an adhesive pad, an adhesive film, a sprayer, an atomizer, or any other form suitable for the application of a single drug dosage form to the oral mucosa of a subject, e.g., the oral mucosa in the sublingual space. As will be understood by those of skill in the art, the SDA design may vary, so long as it is effective to place a drug dosage form, such as a tablet, in the desired location, e.g., in the sublingual space, in a manner that preserves integrity of the drug dosage form in the dispensing process. After use, the SDA is disposed of.

[0083] The dosage form may be provided in a drug delivery dispenser that consists of molded plastic or laminate that has indentations ("blisters") into which a dosage form is placed, referred to herein as a "blister pack". A blister pack may or may not have pre-formed or molded parts and may be used to package an SDA of any type.

[0084] SDAs may be provided in a child resistant multiple drug dispenser (MDD), which may serve to dispense the dosage forms housed therein or may be used for storage of a plurality of SDAs.

[0085] In one embodiment, an SDA serves as the drug delivery dispenser and an MDD serves as the primary package.

[0086] The dosage forms inside the SDA and MDD remain dry prior to dispensing a drug dosage form.

[0087] A desiccant may or may not be included in the drug delivery dispenser and an oxygen scavenger is typically included in the primary package.

Utility.

[0088] The presence of impurities in a pharmaceutical formulation that remain with the active pharmaceutical ingredient (API), develop during formulation, or develop upon aging of either API or formulated drug dosage forms can be problematic. The presence of such impurities even in small amounts may influence the efficacy and safety of a pharmaceutical product. Impurities in pharmaceutical products must be analyzed and identified. It is preferable that the total amount of active drug (e.g., sufentanil) degradation products not exceed 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1% or less of the amount of the active drug substance in a given drug dosage form. The International Conference on Harmonization (ICH) provides guidelines regarding the control of impurities.

[0089] The reduction or elimination of oxidative degradation products in drug dosage forms, e.g., solid dosage forms comprising sufentanil, can be achieved by inclusion of oxygen scavengers in the packaging for the drug dosage forms.

[0090] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof, both currently known equivalents and equivalents developed in the future. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein.

EXAMPLES

Example 1: Stability Studies with Solid Sufentanil Dosage Forms in the Presence and Absence of Oxygen Scavengers.

[0091] A study was carried out to evaluate the stability of tablets comprising 5mcg of sufentanil, having a mass of 5.85 mg following storage in high density polyethylene (HDPE) bottles for 0.5 months, 1 month, 2 months and 3 months under different environmental conditions with or without oxygen scavengers.

[0092] The storage conditions were the following:

(1) 5°C at ambient humidity

(2) 25°C and 60% relative humidity (RH)

(3) 40°C and 75% relative humidity (RH)

[0093] The 5mcg sufentanil formulation included 0.128% sufentanil citrate in a matrix of mannitol, hydroxypropylmethyl cellulose, stearic acid, magnesium stearate, dicalcium phosphate and butylated hydroxyl toluene (BHT), as follows.

Component	Amount Per Tablet (mg)	% in the Formulation
Sufentanil Citrate	0.0075	0.128
Mannitol SD100	4.131	70.62
Di-Calcium Phosphate di-hydrate	1.170	20.00
HPMC K4M Premium CR	0.176	3.00
Stearic Acid	0.293	5.00
Mg Stearate	0.059	1.00
BHT	0.015	0.25
Total	5.850	100.00

[0094] The HPLC profile of solid sufentanil dosage forms stored with or without oxygen scavengers (StabilOx®; Multisorb) was evaluated following storage in HDPE bottles at T=0 and at 2 weeks, 1 month, 2 months, 3 months and 6 months. The stability of sufentanil was evaluated by HPLC analysis under the conditions set forth below. As will be understood by those of skill in the art, the conditions set forth below are exemplary conditions for HPLC analysis and are not intended to be limiting as to other possible methods of analysis.

[0095] Chromatographic System and Conditions

Column	Waters XTerra RP18, 5µm, 250 mm x 4.6 mm
Detection	235 nm
Column Temperature	30 °C
Injection Volume	100 µL
Flow Rate	1.0 mL/min
Mobile Phase	MP A: 20 mM Ammonium Phosphate Buffer (pH 7.2) MP B: Acetonitrile
Run Time	55 min

[0096] Gradient Conditions

Time (min)	Mobile Phase A	Mobile Phase B
0	75	25
5	75	25
35	30	70
49	30	70
50	75	25
55	75	25

[0097] Samples analyzed for sufentanil degradation products were a composite of NanoTabs™ that provided about 50ug/mL (of sufentanil) in solution. In carrying out the method, the number of NanoTabs™ and the volume needed to achieve a nominal concentration of about 50 µg/mL was calculated, then an amount of extraction solution equivalent to approximately 30% of the sample volume was pipetted into the container, the mixture was sonicated for 15 minutes, followed by dilution to volume with 20mM ammonium phosphate buffer and thorough mixing. A glass syringe was used to filter the supernatant solution through a 0.45µm Millipore Millex Nylon syringe filter. The first mL of filtrate was discarded, then the remainder was used to fill HPLC 9 mm TFE/SIL/TFE blue cap containers, followed by HPLC analysis.

[0098]

[0099] Table 1A shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 5°C and ambient humidity,

as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50 and 0.56 following storage in HDPE bottles for 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00100] Table 1A. Stability Evaluation of 5 mcg Sufentanil Tablets at 5°C and ambient humidity.

~RRT	T=0	2 wks 5°C	1 mo 5°C	2 mo 5°C	3 mo 5°C	6 mo 5°C
0.37						
0.50	0.39%	0.53%	0.59%	0.68%	0.84%	1.10%
0.56	0.19%	0.24%	0.25%	0.32%	0.39%	0.50%
% Total Deg	0.58%	0.77%	0.84%	1.00%	1.23%	1.60%

Total Deg. = Total degradation is reported as a percentage (%) of total sufentanil peak area.

[00101] Table 1B shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 5°C and ambient humidity, as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50 and 0.56 following storage in HDPE bottles containing an oxygen scavenger at T=0, 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00102] Table 1B. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 5°C/ambient humidity in HDPE Bottles Containing Oxygen Scavengers.

~RRT	T=0	2 wks 5°C	1 mo 5°C	2 mo 5°C	3 mo 5°C	6 mo 5°C
0.37		< 0.1	< 0.1			
0.50	0.16%	< 0.1	0.22%	0.21%	0.18%	0.14%
0.56		< 0.1	0.13%	0.11%	0.10%	
% Total Deg	0.16%	0.00%	0.35%	0.32%	0.28%	0.14%

[00103] Figure 1 shows the % Total RS versus time (0, 0.5, 1, 2 and 3 months), for 5 mcg sufentanil dosage forms made using a standard formulation following storage at 5°C and ambient humidity in HDPE bottles alone (5ug) or containing an oxygen scavenger (Stabilox®; Multisorb Technologies; 5ug-R). The designation "% Total RS" (% total related substances) means the same thing and is used interchangeably herein with the term "% SDP (percent sufentanil degradation products) which is the percentage of the peak area for "related substances" (sufentanil degradation products) relative to the total peak area for sufentanil.

[00104] Table 2A shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 25°C and 60% RH, as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50, 0.54 and 0.56

following storage in HDPE bottles, at T=0, 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00105] Table 2A. Stability Evaluation of 5 mcg Sufentanil Tablets at 25°C and 60%RH in HDPE Bottles.

~RRT	T=0	2 wks 25°C/60% RH	1 mo 25°C/60% RH	2 mo 25°C/60% RH	3 mo 25°C/60% RH	6 mo 25°C/60% RH
0.37				0.11%	0.11%	0.19%
0.50	0.39%	0.86%	0.95%	1.28%	1.46%	1.69%
0.54						<0.1%
0.56	0.19%	0.40%	0.44%	0.61%	0.68%	0.76%
% Total Deg	0.58%	1.26%	1.39%	2.00%	2.25%	2.64%

[00106] Table 2B shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 25°C and 60% RH, as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50 and 0.56 following storage in HDPE bottles containing an oxygen scavenger (Stabilox®), at T=0, 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00107] Table 2B. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 25°C and 60% RH in HDPE Bottles Containing Oxygen Scavengers.

~RRT	T=0	2 wks 25°C/60% RH	1 mo 25°C/60% RH	2 mo 25°C/60% RH	3 mo 25°C/60% RH	6 mo 25°C/60% RH
0.37		< 0.1	< 0.1	< 0.1		
0.50	0.16%	< 0.1	< 0.1	< 0.1	0.10%	0.13%
0.56		< 0.1	< 0.1	< 0.1		
% Total Deg	0.16%	0.00%	0.00%	0.00%	0.10%	0.13%

[00108] Figure 2 shows the % Total RS versus time (0, 0.5, 1, 2 and 3 months) for 5mcg sufentanil dosage forms made using a standard formulation following storage at 25°C and 60% humidity in HDPE bottles alone (5ug) or containing an oxygen scavenger (5ug-R).

[00109] Table 3A shows the results of analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 40°C and 75% RH, as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50, 0.54 and 0.56 following storage in HDPE bottles at T=0, 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00110] Table 3A. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 40°C and 75% RH in HDPE Bottles.

~RRT	T=0	2 wks 40°C/75% RH	1 mo 40°C/75% RH	2 mo 40°C/75% RH	3 mo 40°C/75% RH	6 mo 40°C/75% RH
0.37		0.11%	0.22%	0.38%	0.43%	0.42%
0.50	0.39%	0.86%	0.92%	1.09%	1.12%	1.00%
0.54						0.29%
0.56	0.19%	0.46%	0.52%	0.67%	0.64%	0.46%
% Total Deg	0.58%	1.43%	1.66%	2.14%	2.19%	2.17%

[00111] Table 3B shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 40°C and 75% RH, as evidenced by peaks at relative retention times (RRT) of 0.37, 0.50 and 0.56 following storage in HDPE bottles containing an oxygen scavenger (Stabilox®), at T=0, 2 weeks, 1 month, 2 months, 3 months and 6 months.

[00112] Table 3B. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 40°C and 75% RH in HDPE Bottles Containing Oxygen Scavengers.

~RRT	T=0	2 wks 40°C/75 % RH	1 mo 40°C/75 % RH	2 mo 40°C/75 % RH	3 mo 40°C/75 % RH	6 mo 40°C/7 5% RH
0.37		< 0.1	< 0.1	< 0.1		
0.50	0.16%	< 0.1	< 0.1	< 0.1		0.56%
0.56		0.14%	0.28%	0.39%	0.32%	
% Total Deg	0.16%	0.14%	0.28%	0.39%	0.32%	0.56%

[00113] Figure 3 shows the % Total RS versus time (0, 0.5, 1, 2 and 3 months) for 5mcg sufentanil dosage forms made using a standard formulation following storage at 40°C and 75% humidity in HDPE bottles alone (5ug) or containing an oxygen scavenger (5ug-R).

[00114] Table 4 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products, following storage at 5°C and ambient humidity in HDPE bottles with or without an oxygen scavenger, reported as % Total RS versus time.

[00115] Table 4. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 5°C and Ambient Humidity in HDPE Bottles With or Without Oxygen Scavengers.

Time (months)	% Total RS (+ oxygen scavenger)	% Total RS (without oxygen scavenger)

0	0.16	0.58
0.5		0.77
1	0.35	0.84
2	0.32	1.00
3	0.28	1.23
6	0.14	1.6

[00116] Table 5 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 25°C and 60% RH in HDPE bottles for 0, 0.5, 1, 2, 3 and 6 months in HDPE bottles with or without an oxygen scavenger, reported as % Total RS versus time.

[00117] Table 5. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 25°C and 60% RH in HDPE Bottles with or without Oxygen Scavengers.

time (months)	% Total RS (+ oxygen scavenger)	% Total RS (without oxygen scavenger)
0	0.16	0.58
0.5	0	1.26
1	0	1.39
2	0	2.15
3	0.1	2.15
6	0.13	2.64

[00118] Table 6 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage at 40°C and 70%RH, in HDPE bottles +Stabilox® or without Stabilox®, reported as % Total RS versus time.

Table 6. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 40°C and 75% RH in HDPE Bottles with or without Oxygen Scavengers.

time (months)	% Total RS (+ oxygen scavenger)	% Total RS (without oxygen scavenger)
0	0.16	0.58
0.5	0.14	1.43
1	0.28	1.66
2	0.39	2.14
3	0.51	2.19
6	0.77	2.17

[00119] The results presented in Example 1 show that the generation of sufentanil degradation products following storage of solid sufentanil dosage forms is reduced or

eliminated by storing the solid sufentanil drug dosage forms (e.g., tablets) in the presence of an oxygen scavenger.

Example 2: Stability Studies with Solid Sufentanil Dosage Forms in the Presence of Desiccant or Oxygen Scavengers.

[00120] A study was carried out to evaluate the stability of tablets comprising 5mcg of sufentanil, having a mass of 5.85mg following storage in high density polyethylene (HDPE) bottles for 0.5 months, 1 month, 2 months, 3 months and 6 months under different environmental conditions in the presence of oxygen scavengers or desiccant. The desiccant used was 1g silica gel sachet®.

[00121] The storage conditions were the following:

5°C at ambient humidity;

25°C and 60% relative humidity (RH); and

40°C and 75% relative humidity (RH).

[00122] The sufentanil formulation and details of the HPLC procedure are provided in Example 1, above.

[00123] The HPLC profile of solid sufentanil dosage forms stored with StabilOx® or desiccant was evaluated following storage in HDPE bottles for 0.5 months, 1 month, 2 months, 3 months and 6 months.

[00124] Table 7 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in HDPE bottles at 5°C and ambient humidity, reported as % total SDP at T=0 and at 0.5 months, 1 month, 2 months, 3 months and 6 months in the presence of an oxygen scavenger (5ug-R_Stabilox®), or desiccant (5ug – Desiccant).

[00125] Table 7. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at 5°C in HDPE Bottles With Oxygen Scavengers or Desiccant.

Time (months)	5ug-R (+ oxygen scavenger) in HDPE	5ug – (+ desiccant) in HDPE
0	0.16	0.58
0.5		0.77
1	0.35	0.84
2	0.32	1.00
3	0.28	1.23
6	0.14	1.6

[00126] Table 8 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in HDPE bottles at 25°C and 60% RH, reported as % total SDP at T=0 and at 0.5 months, 1 month, 2 months, 3 months and 6 months in the presence of an oxygen scavenger (5ug-R), or desiccant (5ug – Desiccant).

[00127] Table 8. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at Stored at 25°C and 60% RH in HDPE Bottles With Oxygen Scavengers or Desiccant.

Time (months)	5ug-R (+ oxygen scavenger) in HDPE	5ug (+ desiccant in HDPE)
0	0.16	0.58
0.5	0	1.26
1	0	1.39
2	0	2.15
3	0.1	2.15
6	0.13	2.64

[00128] Table 9 shows the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in HDPE bottles at 40°C and 75% RH, reported as % total SDP at T=0 and at 0.5 months, 1 month, 2 months, 3 months and 6 months in the presence of an oxygen scavenger (5ug-R_Stabilox®), or desiccant (5ug – Desiccant).

[00129] Table 9. Stability Evaluation of 5 mcg Sufentanil Tablets Stored at Stored at 40°C and 75% RH in HDPE Bottles With Oxygen Scavengers or Desiccant.

Time (months)	5ug-R (+ oxygen scavenger) in HDPE	5ug (+ desiccant in HDPE)
0	0.16	0.58
0.5	0.14	1.43
1	0.28	1.66
2	0.39	2.14
3	0.51	2.19
6	0.77	2.17

Example 3: Stability Studies with Solid Sufentanil Dosage Forms in Cartridges in the Presence of Oxygen Scavengers.

[00130] Further studies were carried out on stability of solid sufentanil dosage forms following storage in cartridges comprising 40 tablets and StabilOx®. A study was carried out to evaluate the stability of tablets comprising 10mcg of sufentanil, having a

mass of 5.85mg, following storage in cartridges for 1 month, 2 months, and 3 months under different storage conditions in the presence of an oxygen scavenger (Stabilox®).

[00131] The storage conditions were the following:

25°C and 60% relative humidity (RH); and

40°C and 75% relative humidity (RH).

[00132] The sufentanil formulation was the following: 0.256% sufentanil citrate in matrix of mannitol, hydroxypropylmethyl cellulose, stearic acid, magnesium stearate, dicalcium phosphate and butylated hydroxyl toluene (BHT).

[00133] The HPLC profile of solid sufentanil dosage forms stored with oxygen scavengers (an (Stabilox®) was evaluated following storage in cartridges for T=0, 1 month, 2 months and 3 months, using the conditions provided in Example 1, above.

[00134] Tables 10A and B show the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in HDPE bottles or cartridges made of various materials and containing an oxygen scavenger, at 25°C and 60% RH, as evidenced by peaks at relative retention times (RRT) of 0.36, 0.49/0.50 and 0.54/0.55 at T=0, 1 month, 2 months and 3 months.

[00135] Table 10A. Stability Evaluation of 10 mcg Sufentanil Tablets Stored at 25°C and 60% RH in HDPE Bottles or Cartridges With Oxygen Scavengers.

		"Control" HDPE Bottle			**Polycarbonate Lexan HP2 Resin PC - HP2NR - Cartridge**		
~RRT	T=0	T=1 mo	T=2 mo	T=3 mo	T=1 mo	T=2 mo	T=3 mo
0.36		<QL*	<QL	<QL	<QL	<QL	<QL
0.49/0.5	0.28	<QL	<QL	<QL	0.25	0.15	0.12
0.54/0.55	0.11	<QL	<QL	<QL	0.11	<QL	<QL
TOTAL	0.39	<QL			0.36		

<QL means less than quantitation limit.

[00136] Table 10B. Stability Evaluation of 10 mcg Sufentanil Tablets Stored at 25°C and 60% RH in Cartridges With Oxygen Scavengers.

		K-Resin - Cartridge			**PCHP2R - Cartridge**		
~RRT	T=0	T=1 mo	T=2 mo	T=3 mo	T=1 mo	T=2 mo	T=3 mo
0.36		<QL	<QL	<QL	<QL	<QL	
0.49/0.5	0.28	0.30	0.22	0.22	0.48	<QL	<QL
0.54/0.55	0.11	0.13	0.11	0.11	0.23	<QL	<QL
TOTALS	0.39	0.43	0.33	<QL	0.71	<QL	<QL

[00137] Tables 11A and B show the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in HDPE bottles or cartridges made of various materials and containing an oxygen scavenger, at 40°C and

75% RH, as evidenced by peaks at relative retention times (RRT) of 0.36, 0.49/0.50 and 0.54/0.55 at T=0, 1 month, 2 months and 3 months.

[00138] Table 11A. Stability Evaluation of 10 mcg Sufentanil Tablets Stored at 40°C and 75% RH in Cartridges With Oxygen Scavengers.

		"Control" – HDPE Bottle			**PC - HP2NR - Cartridge**		
	T=0	T=1 mo	T=2 mo	T=3 mo	T=1 mo	T=2 mo	T=3 mo
0.36		<QL	<QL	<QL	0.1	<QL	0.11
0.49/0.5	0.28	<QL	<QL	<QL	<QL	<QL	<QL
0.54/0.55	0.11	0.13	0.2	0.15	<QL	<QL	<QL
TOTALS	0.39	0.13	0.2	0.15	0.1	<QL	0.11

[00139] Table 11B. Stability Evaluation of 10 mcg Sufentanil Tablets Stored at 40°C and 75% RH in Cartridges With Oxygen Scavengers.

		K-Resin- Cartridge			**PCHP2R - Cartridge**		
	T=0	T=1 mo	T=2 mo	T=3 mo	T=1 mo	T=2 mo	T=3 mo
0.36		I<QL	<QL	<QL	<QL	<QL	0.11
0.49/0.5	0.28	<QL	<QL	<QL	<QL	<QL	<QL
0.54/0.55	0.11	<QL	<QL	<QL	<QL	<QL	<QL
TOTALS	0.39	<QL	<QL	<QL	<QL	<QL	<QL

Example 4: Stability Studies with Solid Sufentanil Dosage Forms in Single Dose Applicators (SDAs) in the Presence of Oxygen Scavengers.

[00140] Further studies were carried out on the stability of sufentanil in solid sufentanil dosage forms following storage in SDAs. A study was carried out to evaluate the stability of tablets comprising 20mcg of sufentanil, having a mass of 5.85mg following storage in SDAs for 1 month, 2 months, 3 months and 6 months under different storage conditions in the presence of an oxygen scavenger.

[00141] The storage conditions were the following:

5°C at ambient humidity;

25°C and 60% relative humidity (RH); and

40°C and 75% relative humidity (RH).

[00142] The sufentanil formulation is provided in Example 3, above. The HPLC profile of solid sufentanil dosage forms stored in the presence of oxygen scavengers was evaluated following storage in SDAs for 1 month, 2 months, 3 months and 6 months, using the conditions provided in Example 1, above.

[00143] Tables 12A and B show the results of HPLC analysis of solid sufentanil dosage forms for the presence of degradation products following storage in SDAs and packaging

containing oxygen scavengers, at 25°C and 60% RH, as evidenced by peaks at relative retention times (RRT) of 0.36, 0.49/0.50 and 0.54/0.55 at T=0, 1 month, 2 months and 3 months.

[00144] Table 12A. Stability Evaluation of 20 mcg Sufentanil Tablets Stored at 2-8°C and Ambient Humidity in SDAs Packaged With Oxygen Scavengers.

Time	Individual Unspecified Sufentanil Related Impurities (RS%)	Total (%)
T=0	No Impurity was detected	N/A
T=1mo	No Impurity was detected	N/A
T=2mo	No Impurity was detected	N/A
T=3mo	No Impurity was detected	N/A

[00145] Table 12B. Stability Evaluation of 20 mcg Sufentanil Tablets Stored at 25°C and 60% RH in SDAs Packaged With Oxygen Scavengers.

Time	Individual Unspecified Sufentanil Related Impurities (RS%)	Total (%)
T=0	No Impurity was detected	N/A
T=1 mo	No Impurity was detected	N/A
T=2 mo	No Impurity was detected	N/A
T=3 mo	No Impurity was detected	N/A

[00146] Table 12C. Stability Evaluation of 20 mcg Sufentanil Tablets Stored at 40°C and 75% RH in SDAs Packaged With Oxygen Scavengers.

Time	Individual Unspecified Sufentanil Related Impurities (RS%)	Total (%)
T=0	No Impurity was detected	N/A
T=1 mo	No Impurity was detected	N/A
T=2 mo	No Impurity was detected	N/A
T=3 mo	No Impurity was detected	N/A

WHAT IS CLAIMED IS:

1. A packaged solid sufentanil drug dosage form comprising:

(a) a solid sufentanil drug dosage form having a mass of from about 5mg to about 25mg or a volume of from about 5mcl to about 25mcl, said tablet comprising;

(b) a primary package containing said solid sufentanil drug dosage form and an oxygen scavenger, wherein the percentage of sufentanil oxidative degradation products is minimized or eliminated in a solid sufentanil drug dosage form packaged with said oxygen scavenger relative to a solid sufentanil drug dosage form packaged in the absence of an oxygen scavenger.

2. The packaged solid sufentanil drug dosage form according to Claim 1, wherein said drug dosage form has a mass of from about 2mg to about 10mg or a volume of from about 2mcl to about 10mcl.

3. The packaged solid sufentanil drug dosage form according to Claim 1, wherein said drug dosage form has a thickness of from about 0.7mm to about 1.0mm or from about 0.75mm to about 0.95mm.

4. The packaged solid sufentanil drug dosage form according to Claim 1, wherein the amount of sufentanil in said solid sufentanil drug dosage form is selected from the group consisting of 5 mcg, 10 mcg, 15 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 70 mcg, 80 mcg and 100 mcg of sufentanil.

5. The packaged solid sufentanil drug dosage form according to Claim 2, wherein the amount of sufentanil in said solid sufentanil drug dosage form is selected from the group consisting of 5 mcg, 10 mcg, 15 mcg, 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 70 mcg, 80 mcg and 100 mcg of sufentanil.

6. The packaged solid sufentanil drug dosage form according to Claim 3, wherein the amount of sufentanil in said solid sufentanil drug dosage form is selected from the group consisting of 5mcg, 10mcg, 15mcg, 20mcg, 30mcg, 40mcg, 50mcg, 60mcg, 70mcg, 80mcg and 100mcg of sufentanil.

7. The packaged solid sufentanil drug dosage form according to Claim 4, wherein the percentage of sufentanil oxidative degradation products is minimized or eliminated in a solid sufentanil drug dosage form packaged with said oxygen scavenger relative to a solid sufentanil drug dosage form packaged in the absence of an oxygen scavenger when said solid sufentanil drug dosage form is stored for at least 6 months under conditions selected from the group consisting of 5°C and ambient humidity, 25°C and 60% relative humidity and 40°C and 75% relative humidity.

8. The packaged solid sufentanil drug dosage form according to Claim 5, wherein the percentage of sufentanil oxidative degradation products is minimized or eliminated in a solid sufentanil drug dosage form packaged with said oxygen scavenger relative to a solid sufentanil drug dosage form packaged in the absence of an oxygen scavenger when said solid sufentanil drug dosage form is stored for at least 6 months under conditions selected from the group consisting of 5°C and ambient humidity, 25°C and 60% relative humidity and 40°C and 75% relative humidity.

9. The packaged solid sufentanil drug dosage form according to Claim 4, further comprising a drug delivery dispenser for housing said solid sufentanil drug dosage form.

10. The packaged solid sufentanil drug dosage form according to Claim 9, wherein the drug delivery dispenser is a cartridge.

11. The packaged solid sufentanil drug dosage form according to Claim 9, wherein the drug delivery dispenser is a single dose applicator.

12. The packaged solid sufentanil drug dosage form according to Claim 9, wherein the primary package is a foil pouch.

13. The packaged solid sufentanil drug dosage form according to Claim 5, further comprising a drug delivery dispenser for housing said solid sufentanil drug dosage form.

14. The packaged solid sufentanil drug dosage form according to Claim 13, wherein the drug delivery dispenser is a cartridge.

15. The packaged solid sufentanil drug dosage form according to Claim 13, wherein the drug delivery dispenser is a single dose applicator.

16. The packaged solid sufentanil drug dosage form according to Claim 13, wherein the primary package is a foil pouch.

17. A method for preventing oxidative degradation of a solid sufentanil drug dosage form comprising:

(a) providing a solid sufentanil drug dosage form having a mass of from about 5mg to about 25mg or a volume of from about 5mcl to about 25mcl, in a drug delivery dispenser;

(b) further providing an oxygen scavenger;

(c) placing the drug delivery dispenser and said oxygen scavenger in a primary package made of a substantially oxygen impermeable material, wherein the percentage of sufentanil oxidative degradation products is minimized or eliminated in said solid sufentanil drug dosage form following storage, when packaged in the presence of an oxygen scavenger relative to the percentage of sufentanil oxidative degradation products

in a solid sufentanil drug dosage form following storage, when packaged in the absence of an oxygen scavenger.

18. The method according to Claim 17, wherein said solid drug dosage form has a mass of from about 2mg to about 10mg or a volume of from about 2mcl to about 10mcl.

19. The method according to Claim 17, wherein said solid drug dosage form has a thickness of from about 0.7mm to about 1.0mm or from about 0.75mm to about 0.95mm.

20. The method according to Claim 17, wherein the amount of sufentanil in said solid drug dosage form is selected from the group consisting of 5mcg, 10mcg, 15mcg, 20mcg, 30mcg, 40mcg, 50mcg, 60mcg, 70mcg, 80mcg and 100mcg of sufentanil.

21. The method according to Claim 20, wherein the solid sufentanil drug dosage form is stored for at least 6 months under conditions selected from the group consisting of 5°C and ambient humidity, 25°C and 60% relative humidity and 40°C and 75% relative humidity.

22. The method according to Claim 20, wherein said drug delivery dispenser is a cartridge.

23. The method according to Claim 22, wherein the cartridge comprises a desiccant.

24. The method according to Claim 20, wherein the drug delivery dispenser is a single dose applicator.

25. The method according to Claim 20, wherein the primary package is a foil pouch.