(54) Title: COMPOSITIONS AND METHODS FOR MILD SEDATION, ANXIOLYSIS AND ANALGESIA IN THE PROCEDURAL SETTING

(57) Abstract: Small tablets for use in procedural sedation, anxiolysis and analgesia comprising the combination sufentanil and triazolam administered via the oral transmucosal route and methods for using the same are provided.
COMPOSITIONS AND METHODS FOR MILD SEDATION,
ANXIOLYSIS AND ANALGESIA IN THE PROCEDURAL SETTING

BACKGROUND OF THE INVENTION

Cross Reference to Other Applications

Field of the Invention
[0002] Compositions, methods and systems effective to sedate, and to provide anxiolysis and analgesia to a subject during a diagnostic or therapeutic medical or dental procedure, or prior to induction of general anesthesia are provided. The compositions, methods and systems are based on the combination of an analgesic drug, such as sufentanil, and a drug typically used to treat anxiety, for example, a drug of the benzodiazepine class, such as triazolam, delivered by the oral transmucosal route in a single, small volume, solid dosage form (e.g., a tablet).

Background of the Technology
[0003] Currently, standard regimens for treating patients during diagnostic or therapeutic medical or dental procedures are often deficient. Patients frequently are quite anxious prior to and during such procedures and often do not receive medication at all or treatment is limited to administration of a local anesthetic. Treatment options for procedural sedation, anxiolysis and analgesia have clear limitations with regard to ease of administration, onset of action, efficacy and safety. Routes of administration, formulations and dose, among other attributes contribute to these limitations.

[0004] Each class of medication has benefits and risks. Some medications are administered orally, while many are administered intravenously (IV). Some medications have slow onset, while other medications exhibit drug interactions and still others have side effects. Elderly patients and children typically require lower doses relative to adult patients and children may experience significant fear and discomfort during medication administration.

[0005] Reproducible and effective drug delivery technology represents an area of active research. Oral transmucosal drug delivery systems offer numerous advantages relative to conventional dosage forms, which include more comfortable and convenient administration,
faster onset, improved efficacy, reduced side effects, and improved patient acceptance. This is particularly relevant to procedural sedation, anxiolysis and analgesia.

[0006] Opioids are powerful sedatives as well as analgesics that are utilized to treat both acute and chronic pain of moderate to severe intensity. Opioids are also used for procedural sedation, as they provide both anxiolysis and analgesia. However, opioids can have respiratory depressive effects if not used appropriately and suffer from a high abuse potential. Opioids have a relatively rapid onset of action when administered either IV or transmucosally.

[0007] Benzodiazepines are powerful anxiolytic and amnestic agents, however, when given via the oral route, they can have a delayed and erratic onset, as well as delayed post-procedural recovery (Viitanen et al., 1999). There is no direct analgesic effect of benzodiazepines or most sedatives. As a result, anxiety and agitation can result due to under-treated pain caused by IV cannulation or other procedures. Common side effects with the use of anti-anxiety medications include dry mouth, fatigue, dizziness and headaches. More severe side effects such as memory loss, uncoordinated body movements, confusion, and irregular heartbeat may also result.

[0008] Greenblatt D.J, et al., N Engl J Med. 1991 Jun 13;324(24):1691-8, show that benzodiazepines such as triazolam caused a greater degree of sedation and greater impairment of psychomotor performance in healthy elderly persons than in young persons who received the same dose in a study where 26 healthy young subjects (average age of 30) and 21 healthy elderly subjects (average age of 69) received 125mcg and 250mcg of triazolam. On the basis of the results of this study, the authors suggest that the dose of triazolam should be reduced on average by 50 percent for elderly persons.

[0009] Procedural sedation is attempted in many clinical settings using a number of intervention scenarios, which generally include use of benzodiazepines and/or opioids via IV, oral tablets, oral liquids or transmucosal administration. These methods meet with varying degrees of success with respect to onset of action, duration of action, ease of use, level of sedation, safety and side-effects.

[0010] When IV access is not available, often either an oral or intranasal benzodiazepine, such as midazolam, or an intranasal opioid, such as sufentanil, is used for procedural sedation (Karl et al., Anesthesiology; 1992; 76:209-215). There are disadvantages to using a single agent in order to effect procedural sedation together with anxiolysis and analgesia. There is no direct analgesic effect of benzodiazepines or most sedatives, and use of opioids alone to provide procedural sedation and analgesia can result in episodes of respiratory
depression as well as post-procedural nausea and vomiting (Friesen and Lockhart, Anesthesiology, 1992; 76:46-51; Karl et al., 1992).

[0011] There is a continuing, unfilled need for compositions, methods, systems and kits for mild sedation, anxiolysis and analgesia in the procedural setting. The present invention addresses this need.

**Summary Of The Invention**

[0012] The invention provides oral transmucosal compositions and methods for procedural sedation, anxiolysis and analgesia, based on administration of a single solid tablet comprising the combination of sufentanil and triazolam, wherein upon oral transmucosal administration to an alert, awake subject, the subject is sedated and the subject’s pre-procedural anxiety level is reduced.

[0013] The tablet is bioadhesive and has a mass of from about 5mg to about 25mg or a volume of from about 5mcl to about 25mcl.

[0014] The tablet has a thickness of from about 0.7mm to about 1.0mm or from about 0.75mm to about 0.95mm and a diameter of from about 2.5mm to about 4.0mm, or from about 3.0mm to about 3.5mm.

[0011] The tablet comprises from about 4mcg to about 50mcg of sufentanil or about 10mcg to about 20mcg of sufentanil in combination with from about 100mcg to about 500mcg of triazolam or from about 150mcg to about 300mcg of triazolam.

[0012] The tablet comprises a substantially homogeneous composition and may be administered by the sublingual or buccal route.

[0013] Single dose applicators (SDAs) comprising such bioadhesive tablets are also provided, together with methods for procedural sedation, anxiolysis and analgesia of a subject during a diagnostic or therapeutic medical or dental procedure by administration of the bioadhesive tablets.

[0014] The methods include administering a sufentanil/triazolam tablet, as described herein, to a subject prior to a medical or dental procedure, wherein following administration, the cumulative RASS sedation score and the cumulative NRS anxiety score of subjects administered the sufentanil/triazolam tablet is significantly lower as compared to subjects who were administered a placebo tablet.
Brief Description of the Figures

[0015] Figures 1A and 1B are schematic depictions of an exemplary single dose applicator.

[0016] Figures 2A – C provide an illustration of one type of single dose applicator and use thereof in delivering a dosage form to a subject.

[0017] Figures 3A – F provide an illustration of six additional single dose applicators.

[0018] Figures 4A – C provide an illustration of additional single dose applicator and multiple dose applicator embodiments.

[0019] Figures 5A – B provide an illustration of two stages of use of one embodiment of a single dose applicator.

[0020] Figures 6A – D are schematic depictions of additional examples of single dose applicators (SDAs).

[0021] Figures 7A – B are a schematic depiction of an alternative embodiment of an SDA which has a pin lock 167 which must be removed before a tablet can be injected from the SDA, as well as a shroud 29 and a valve 33, which serve to protect the tablet from saliva ingress when the SDA is inserted into the mouth of a subject.

[0022] Figure 8 is a graphic depiction of least squares (LS) mean of Summed Richmond Agitation Sedation Scores (SRS) versus time, following sublingual administration of either F0315 (a tablet comprising 15mcg of sufentanil and 200mcg of triazolam plus excipients) or Placebo (a tablet comprising excipients alone), for the 4 hour study period (p<0.001). The RASS scale is described in the literature, e.g., in Sessler, et al., American Journal of Respiratory and Critical Care Medicine Vol 166. pp. 1338-1344, (2002).

[0023] Figure 9 is a graphic depiction of least squares (LS) mean of Summed Procedural Anxiety Score (SANX; NRS scale) versus time, following sublingual administration of either F0315 (a tablet comprising 15mcg of sufentanil and 200mcg of triazolam plus excipients) or Placebo (a tablet comprising excipients alone), for the 4 hour study period (p=0.004).

[0024] Figure 10 is a graphic depiction of least squares (LS) mean of Summed Pain Intensity (SPI; NRS scale) versus time, following sublingual administration of either F0315 (a tablet comprising 15mcg of sufentanil and 200mcg of triazolam plus excipients) or Placebo (a tablet comprising excipients alone), for the 4 hour study period (p=0.09).
DETAILED DESCRIPTION OF THE INVENTION

[0025] The invention provides compositions, methods, systems and kits that rely on the combination of an opioid and a benzodiazepine formulated in a single dosage form for oral transmucosal delivery. The dosage form finds use in procedural sedation, anxiolysis and analgesia.

[0026] Novel formulations are provided wherein the majority of active drug in the oral transmucosal, e.g., sublingual, dosage form or tablet is delivered across the oral mucosa. The dosage forms comprise a combination of drugs that produce a therapeutic effect and a predictable and safe pharmacokinetic profile and are delivered with or without a device.

[0027] This is important in the procedural setting, in particular in the non-hospital setting where standard anesthesia cannot be administered safely and effectively. This is also important in both inpatient and outpatient settings when difficult IV access (due to fragile veins, obesity, pediatric patients, etc) necessitates a non-invasive route to relieve the patient’s anxiety and/or pain prior to, or in place of IV cannulation.

[0028] In one embodiment, the invention provides a combination formulation comprised of a benzodiazepine, e.g., triazolam or midazolam, and an opioid, e.g., sufentanil or fentanyl.

[0029] The following disclosure describes compositions, methods, systems and kits which find utility in practicing the present invention. The invention is not limited to the specific formulations and methodology 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.

[0030] 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 formulations and devices for containment, storage and delivery of such formulations.

[0031] Unless defined otherwise, all technical and scientific terms used herein 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.
Definitions

[0032] The term “active agent” or “active” may be used interchangeably herein with the term “drug” and is used herein to refer to any therapeutically active agent.

[0033] As used herein, when a drug formulation is said to “adhere” to a surface, such as a mucosal membrane, it is meant that the formulation is in contact with the surface and retained on the surface without the application of an external force. Adhesion is not meant to imply any particular degree of sticking or bonding, nor is it meant to imply any degree of permanency.

[0034] As used herein, the term “analgesic”, is used with reference to any of a number of drugs used to relieve pain (achieve analgesia).

[0035] The term “AUC” as used herein means “area under the curve” in a plot of concentration of drug in plasma versus time. AUC is usually given for the time interval zero to infinity, however, clearly plasma drug concentrations cannot be measured to “infinity” for a patient so mathematical approaches are used to estimate the AUC from a limited number of concentration measurements.

[0036] The term “AUC_{0-inf}” as used herein means, the AUC (from zero to infinity) and represents the total amount of drug absorbed by the body, irrespective of the rate of absorption. The AUC of a transmucosal dosage form compared to that of the same drug administered intravenously serves as the basis for a measurement of bioavailability.

[0037] The term “AUC_{0-last}” is used herein with reference to the AUC (from zero to last measurement).

[0038] The term “relative AUC_{0-last}” is used herein with reference to the AUC_{0-last} of the test article following delivery via the intended route versus the AUC_{0-last} for the same drug after intravenous (sufentanil) or oral (triazolam) administration.

[0039] The term “AUC_{total}” as used herein with respect to sedation means “area under the curve” in a plot of the results from the Richmond Agitation Sedation Scale (RASS) versus time for the time period from administration of a drug dosage form (time 0) following administration to the last time-point of RASS analysis, extrapolated to infinity.

[0040] The term “anxiolytic” as used herein refers to a drug prescribed for the treatment of symptoms of anxiety.

[0041] The term “bioadhesion” as used herein refers to the process of adhesion of the dosage forms to a biological surface, e.g., a mucosal membrane.

[0042] The term “bioavailability” or "F" as used herein means “percent bioavailability” and represents the fraction of drug absorbed from a test article as compared to the same drug when administered intravenously. It is calculated from the AUC_{infty} of the test article
following delivery via the intended route versus the AUC∞ for the same drug after intravenous administration. It is calculated from the equation: Bioavailability (%) = AUC∞ (test article)/AUC∞ (intravenous route/article).

[0043] The term “congener” as used herein refers to one of many variants or configurations of a common chemical structure.

[0044] “Controlled drug delivery” refers to release or administration of a drug from a given dosage form in a controlled fashion in order to achieve the desired pharmacokinetic profile in vivo. An aspect of “controlled” drug”, “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. A dosage from comprising a formulation according to the invention may be used to deliver any drug that can be administered by the oral transmucosal delivery is the ability to manipulate the formulation and/or dosage form in order to establish the desired kinetics of drug release.

[0045] The term “disintegration” is used interchangeably herein with the term “erosion” and means the physical process by which a dosage form breaks down and pertains to the physical integrity of the dosage form alone. This can occur in a number of different ways.

[0046] The term “formulation” or “drug formulation” or “dosage form” as used herein refers to a composition containing at least one therapeutic agent or medication for delivery to a subject. The dosage form comprises a given “formulation” or “drug formulation” and may be administered to a patient in the form of a lozenge, pill, tablet, capsule, membrane, strip, liquid, patch, film, gel, spray or other form.

[0047] The terms “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. A dosage from comprising a formulation according to the invention may be used to deliver any drug that can be administered by the oral transmucosal route. “Drug” as used herein with reference to a formulation of the invention means any “drug”, “active agent”, “active”, “medication” or “therapeutically active agent” that can be effectively administered by the oral transmucosal route. It will be understood that a “drug” or formulation may include more than one therapeutic agent, wherein exemplary combinations of therapeutic agents include a combination of an opioid analog, such as sufentanil, fentanyl, alfentanil, lofentanil, carfentanil, remifentanil, trefentanil, or mirfentanil, in combination with a drug typically used for the treatment of anxiety.

[0048] The term “drug dosage form” or “dosage form” may be used interchangeably herein with the term “tablet”.

[0049] The expression "mucoadhesion" is used herein to refer to adhesion to a membrane which is covered by mucus, such as those in the oral cavity. The term "mucoadhesion" may be used interchangeably herein with the term "bioadhesion".

[0050] The term "mucosal membrane" refers generally to any of the mucus-coated biological membranes in the body. Thus, oral mucosal absorption, i.e., buccal, sublingual, gingival and palatal absorption are specifically contemplated.

[0051] The term "procedural sedation, anxiolysis and analgesia" is used herein with reference to producing a state of one or more of relaxation, sleepiness and a state of decreased pain during a diagnostic or therapeutic procedure or prior to the induction of general anesthesia in a subject or patient by administration of one or more drugs.

[0052] The term "procedural sedation" is used herein with reference to producing a state of conscious or unconscious sedation during a diagnostic or therapeutic procedure or prior to the induction of general anesthesia. Sedation may be conscious or unconscious depending on the dose of drug delivered and the age and weight of the patient or subject. Conscious sedation does not alter respiratory, cardiac, or reflex functions to the level that requires external support for these vital functions. Unconscious sedation is a controlled state of anesthesia, characterized by partial or complete loss of protective nerve reflexes, including the ability to independently breathe and respond to commands.

[0053] "Sedation" as used herein is evaluated using a number of tests, one example of which is the Richmond Agitation Sedation Scale (RASS). If the RASS score of a subject is less than 0 at a given point in time, the subject is considered to be "sedated" at that time. (Sessler, et al., American Journal of Respiratory and Critical Care Medicine Vol 166. pp. 1338-1344, (2002).

[0054] The term "mild sedation" is used herein with reference to a RASS score for a subject that is -1 or -2 at a given point in time. The term “mild sedation” may be used interchangeably with the term “Level 1 minimal sedation” according to the Joint Commission on the Accreditation of Health Care Organizations (JCAHO).

[0055] The term "anxiolysis" is used herein with reference to reducing or eliminating anxiety. Anxiety is a complex feeling of apprehension, fear, and worry often accompanied by pulmonary, cardiac, and other physical sensations. It is a common condition that can be a self-limited physiologic response to a stressor, or it can persist and result in debilitating emotions.

[0056] The term "analgesia" is used herein with reference to a reduction in or elimination of the sense of pain without loss of consciousness pain.
[0057] The term "subject" includes any subject, generally a mammal (e.g., human, canine, feline, equine, bovine, ungulate etc.), adult or child, in which treatment for a disorder is desired. The terms "subject" and "patient" may be used interchangeably herein.

[0058] The term "oral transmucosal dosage form" is used with reference to a dosage form, which comprises a drug formulation as described herein. The dosage form is used to deliver a pharmaceutically active substance to the circulation by way of the oral mucosa and is typically a "sublingual dosage form" or "buccal dosage form", for example a tablet administered by the sublingual or buccal route, however, in some cases other oral transmucosal routes may be employed. The dosage form provides for delivery of pharmaceutically active substances across the oral mucosa and by controlling the formulation the timing for release of the pharmaceutically active substance can be achieved. The dosage form comprises pharmaceutically acceptable excipients and the drug formulations which comprise the dosage form are neither effervescent nor do they comprise an essentially water-free, 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. The formulation is not a solid solution and the pharmaceutical agents and dissolution agent are combined in a manner such that a molecular mixture does not result.

[0059] The term "oral transmucosal drug delivery" as used herein refers to a dosage form wherein drug delivery occurs substantially via the oral transmucosal route and not via swallowing followed by GI absorption. The formulations and drug dosage forms are designed to provide for a drug dissolution rate and dosage form erosion rate that allows for maximal delivery via the oral mucosa, typically via placement of the dosage form within the sublingual cavity.

[0060] The term "small volume drug dosage form" or "small volume dosage form" is used herein with reference to a small volume dosage form with 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, or from about 5 to about 25mg. The "dosage form" is typically a tablet with bioadhesive characteristics and may form a hydrogel upon contact with an aqueous solution. The "small volume drug dosage form" or "small volume dosage form may be referred to as a "NanoTab™".

[0061] As used herein, "sublingual", means literally "under the tongue" and refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. Absorption occurs via highly vascularized sublingual mucosa and allows a substance more
direct access to the blood circulation, providing for direct systemic administration independent of gastro-intestinal influences.

[0062] The term "therapeutically effective amount" means an amount of a therapeutic agent, or a rate of delivery of a therapeutic agent (e.g., amount over time), effective to facilitate a desired therapeutic effect, such as pain relief. The precise desired therapeutic effect (e.g., the degree of pain relief, and source of the pain relieved, etc.) will vary according to the condition to be treated, the tolerance of the subject, the drug and/or drug formulation to be administered (e.g., the potency of the therapeutic agent (drug), the concentration of drug in the formulation, and the like), and a variety of other factors that are appreciated by those of ordinary skill in the art.

[0063] The term "T_{max}" as used herein means the time point of maximum observed plasma concentration.

[0064] The term "C_{max}" as used herein means the maximum observed plasma concentration following administration of a drug.

[0065] The term "terminal half-life" or "t\(\frac{1}{2}\) [h]" as defined herein is calculated as \(\ln(2)/\lambda z\) (defined as the first order terminal rate constant estimated by linear regression of the time versus log concentration curve) and also determined after the final dosing in repeated dose studies.

[0066] The term "T_{onset}" with respect to sedation is used herein relative to the observed "time of onset" and represents the time required for the RASS score to reach a level that is at least one point less than baseline for the first time for studies that do not include a placebo control. Alternatively "T_{onset}" is defined as the first time the sedation score for a group treated with drug first separates statistically from the sedation score for a placebo treated group (defined by p<0.05).

[0067] The term "rapid onset" with respect to sedation in the procedural setting means that onset of sedation (T_{onset}) occurs within from about 10 minutes to about 60 minutes, from about 5 minutes to about 45 minutes, from about 8 minutes to about 30 minutes, from about 5 minutes to about 20 minutes, from about 5 minutes to about 15 minutes, or from about 10 to about 12 minutes following administration of a tablet comprising the opioid/benzodiazepine combination.

[0068] The term "T_{onset}" with respect to anxiolysis is used herein relative to the observed "time of onset" using an 11-point numerical scale (NRS) where 0 = no anxiety and 10 = worst possible anxiety, and "T_{onset}" represents the time required for the anxiety score to decrease by 1 point from baseline, for the first time, for studies that do not include a placebo control. Alternatively "T_{onset}" is defined as the first time the anxiety score for a group
treated with drug first separates statistically from the anxiety score for a placebo treated
group (defined by p<0.05).

[0069] The term “rapid onset” with respect to anxiolysis in the procedural setting means
onset of anxiety relief occurs within from about 5 minutes to about 45 minutes, from about
8 minutes to about 30 minutes, from about 5 minutes to about 20 minutes, from about 5
minutes to about 15 minutes, or from about 10 to about 12 minutes following administration
of a tablet comprising the opioid/benzodiazepine combination.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0070] There is a need for a safe, non-invasive, rapid-acting medication explicitly
developed for use in relieving patients’ pain and anxiety during minor procedures performed
in the outpatient setting, where airway resuscitation expertise is minimal. The present
invention is directed to compositions, methods, systems and kits for procedural sedation,
anxiolysis and analgesia in the outpatient setting.

[0071] The invention relies on small oral transmucosal dosage forms (tablets) comprising
formulations effective for induction of sedation, anxiolysis and analgesia in the procedural
setting, for example prior to a therapeutic procedure or prior to induction of general
anesthesia. The dosage forms comprise the combination of a drug typically used to treat
anxiety, e.g., a drug of the benzodiazepine class, such as triazolam, and an analgesic drug
of the opioid class, such as sufentanil, delivered by the oral transmucosal route in a single
dosage form.

[0072] In one exemplary application, the invention finds utility both in clinics, doctor’s
offices, and in the hospital setting for use in place of oral or IV drugs in order to effect for
procedural sedation, anxiolysis and analgesia. This is particularly important for populations
such as pediatric patients, obese patients, elderly patients with fragile veins, patients with
cancer undergoing chemotherapy, and the like.

Benzodiazepines

[0073] Benzodiazepines are drugs that relieve anxiety putatively by acting on the limbic
system, an area deep inside the brain that appears to be involved in primitive emotional
responses. Exemplary drugs of the benzodiazepine class include but are not limited to
triazolam, midazolam, temazepam, estazolam, alprazolam, diazepam and lorazepam, and
are usually taken orally.

[0074] Oral benzodiazepines act fairly rapidly (within 1-2 hours), with a limited number of
side effects which can include agitation, worsened anxiety, confusion, impaired memory,
lack of coordination, speech difficulties, and others.
[0075] Some patients, in particular those who have had problems with alcohol or drug dependency, may become dependent on the chronic use of benzodiazepines, however, very short-term, acute use of benzodiazepines, for procedural sedation for example, has not been shown to lead to physical dependence and addiction. Using the sublingual route to deliver benzodiazepines pre-procedurally has resulted in effective sedation as demonstrated by the studies referenced below.

**Triazolam**

[0076] Triazolam or 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo-[4,3-alpha][1,4]benzodiazepine has a molecular weight of 343 and is marketed under brand names Halcion®, Novodorm®, Songar®). Triazolam is a benzodiazepine derivative that is generally only used as a sedative to treat insomnia.

[0077] Orally administered triazolam has a plasma half-life of 1.5 – 5.5 hours, the shortest of the clinically used benzodiazepines. Studies comparing pharmacokinetics of triazolam demonstrated a 50% increase in $C_{\text{max}}$ but no change in $T_{\text{max}}$ (0.9 hours) for elderly versus young adults. The clearance of triazolam in the elderly was approximately 40% less than young adults. Triazolam is currently approved for the short-term treatment of insomnia (generally 7 – 10 days). Triazolam is available as an oral tablet at two dosage strengths: 0.125mg and 0.250mg. A 0.2mg sublingual triazolam tablet was marketed as Dumozol®, by Dumex Ltd., Denmark, however, it is no longer commercially available.

While oral triazolam is usually used as a sleeping aid for patients with insomnia, there are also studies demonstrating the successful use of this medication for procedural anxiety. Comparison of the pharmacokinetics of sublingual triazolam with oral administration demonstrates a 28% higher bioavailability and a 20% higher peak plasma level for the sublingual route of administration. The effects of triazolam are reversed by administration of flumazenil. The initial step in triazolam metabolism is hydroxylatation catalyzed by cytochrome P450 3A (CYP 3A).

[0078] Sublingual administration of triazolam has been described as effective for preoperative sedation in a number of situations: (1) Sublingual administration of 250mcg of triazolam for preoperative sedation 60 minutes prior to oral surgery in dental outpatients resulted in significantly less anxiety and pain at 15 minutes intraoperatively than both oral triazolam and placebo. The observed decrease in pain may have been an indirect effect since benzodiazepines have been shown to not possess direct analgesic. Comparison of the pharmacokinetics of sublingual triazolam with oral administration demonstrated a 28% higher bioavailability and a higher peak plasma level for the sublingual route of administration. Tablets were the size of 325mg acetaminophen and dissolved within 90
seconds. $T_{max}$ for both oral and sublingual sufentanil was approximately 90 minutes. (Berthold CW, et al., Oral Surg Oral Med Oral Pathol Oral Radiol Endod; 1997; 84(2):119-24); (2) the PK of triazolam was evaluated in 9 healthy children, aged 6 to 9 years, who received oral triazolam (0.025mg/kg suspended in Kool-Aid) before dental treatment. The peak plasma concentration was 8.5 +/- 3.0 ng/mL (mean +/- SD). The time to peak plasma concentration was 74 +/- 25 minutes. Recovery from sedation required 180 to 240 minutes (Karl H. W, et al., Journal Clinical Psychopharmacology; 1997; 17(3):169-172); (3) the clinical effects of a 200mcg sublingual triazolam tablet were compared with those of a 10mg tablet of diazepam in a double-blind study, in 100 61-70 year old patients scheduled for ophthalmic surgery under local anesthesia. Surgery began at least 45 minutes after administration of triazolam. Authors concluded that sedation developed 60-90 minutes after administration of 200mcg sublingual triazolam, that 200mcg sublingual triazolam produced deeper sedation than 10mg oral diazepam. (Kontinen V, et al., Canadian Journal of Anesthesia, Vol 40, 829-834, 1993); (4) the relative and absolute bioavailability of triazolam was evaluated after administration by the oral and sublingual routes. The fraction absorbed relative to intravenous was 20% higher in the sublingual than in the oral treatment ($p = 0.0128$), the difference between treatments was greatest in the first 2 hours as indicated by the area under the curve from 0 to 2 hours ($p < 0.05$) describe the relative and absolute bioavailability of triazolam evaluated after administration of the marketed oral tablet (250mcg Halcion) and a sublingual prototype wafer with an IV comparator in 12 men. The fraction absorbed relative to intravenous was 20% higher in the sublingual than in the oral treatment ($p = 0.0128$); the difference between treatments was greatest in the first 2 hours as indicated by the area under the curve from 0 to 2 hours ($p < 0.05$). $T_{max}$ for sublingual triazolam was approximately 1.19 hours (71.4 minutes) (Kroboth PD et al., J Clin Psychopharmacol; 1995; 15(4):259-62); (5) eight healthy adult volunteers received 500mcg of triazolam in a commercially available tablet by sublingual and oral routes on two occasions in random sequence. The bioavailability of triazolam after sublingual administration was shown to be an average of 28% greater than for oral administration of the same dose. The mean total area under the curve for sublingual administration was significantly larger than that following oral dosage (28.9 vs 22.6 ng-hr/mL, $p < 0.025$). The peak plasma concentration after sublingual dosage was also higher than after oral administration (4.7 vs 3.9 ng/mL, $p < 0.1$). No significant differences between sublingual and oral administration were found for the elimination half-life of triazolam (4.1 vs 3.7 hr) and the time of peak concentration (1.22 vs 1.25 hr) after dose. (Scavone JM, et al., J Clin Pharmacol; 1986; 26:208-10); (6) a study on the pharmacokinetics of sublingual triazolam in
children, where nine healthy children (64-98 months old) received 250mcg or 375mcg of sublingual triazolam before dental treatment indicated a $C_{\text{max}}$ of 4.9 +/- 2.0 ng/mL (mean +/- SD) with a range of 4.0-8.2 ng/ml, a $T_{\text{max}}$ of 75 +/- 32 minutes with a range of 30-120 minutes, and an elimination half-life of 91 +/- 32 minutes with a range of 51-140 minutes. Average sublingual tablet dissolution was 4 minutes (Tweedey et al., J Clin Psychopharmacol. 2001, 21(3):268-72); (7) a review of dental literature suggests that the oral and sublingual dose range for producing sedation is 250-500mcg and that it is effective when administered 30-45 minutes before a procedure. In a study where 10 healthy adult volunteers (18-40) received sublingual triazolam (250mcg Halcion) followed by additional doses after 60 (500mcg) and 90 (250mcg) minutes, $C_{\text{max}}$ was greater than 90 minutes after the last dose and thus was not determined. Tablets dissolved in 2-3 minutes after dosing. (Jackson D, et al., Journal Clinical Psychopharmacology; 2006; 26(1):4-8).
**Midazolam**

[0079] Oral midazolam is used as a sedative before or during surgery or a medical procedure. Midazolam is very fast acting and therefore useful for anesthesia because it produces sedation, amnesia, and relief of anxiety. It has become a commonly used agent for conscious sedation of children before diagnostic or therapeutic procedures and before induction of anesthesia.

[0080] Midazolam or 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine has a molecular weight of 326. Midazolam is marketed under brand names Dormicum, Flormidal, Versed, Hypnovel and Dormonid and is a benzodiazepine derivative. It has powerful anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. It is considered a fast-acting benzodiazepine, with a short elimination half-life. Midazolam has an oral bioavailability of approximately 36% (with a broad range) and orally administered midazolam has a plasma half-life of 1.5 – 5 hours. In adults greater than 60 years, the plasma half-life of midazolam may be prolonged up to 3 times. The pharmacokinetics of midazolam is linear in the 7.5-15mg oral dose range. Midazolam is absorbed rapidly and completely after oral administration. With a dose of 15mg, maximum plasma concentrations of 70-120 ng/ml are reached within one hour. Food prolongs the time to peak plasma concentration.

[0081] Until recently, only an intravenous form of the drug was available and medical and dental practitioners typically used the intravenous form for oral administration to avoid the additional trauma of starting an IV in children. However, the liquid was bitter even with added flavoring. In November 1998, the Food and Drug Administration approved a clear, purplish-red, cherry flavored midazolam-containing liquid that contains an artificial bitterness modifier (Versed Syrup), and 2mg midazolam per 1 ml. The reported acceptance rate by children was 90%. The recommended dose for children is a single dose of 0.25 to 0.5mg/kg to a maximum dose of 20mg. The most serious side effect of midazolam is respiratory depression or arrest, which can be reversed by flumazenil (Romazicon).

[0082] The sedative effects of sublingual midazolam (Roche, Dormicum, 7.5mg) with the oral route as a premedication were compared. There were 50 patients in each group, the degree of sedation was assessed and the time for complete drug dissolution studied in the sublingual group by the inspection of tablet under the tongue every 5 minutes for 20 min. The sedation scores in the sublingual group were higher than in the oral group at 30 and 60 min after drug administration. 72% of the sublingual group had complete drug dissolution
within 10 min and 64% of the patients in the sublingual group found the tablet acceptable with regard to taste (Lim et al., Can J Anaesth; 1997; 44(7):723-6).

[0083] Transmucosal administration of midazolam has been described as effective for preoperative sedation in a number of situations: (1) midazolam was administered transmucosally in 47 children randomly assigned to 3 different groups. Group N received 0.2mg/kg nasally, group R 0.5mg/kg rectally, and group S 0.2mg/kg sublingually. 30 min after premedication the midazolam level in the sublingual group was statistically significantly higher than in the nasal group. (Geldner G, et al., Paediatric Anaesthesia; 1997 (7):103-109); (2) nasal midazolam was shown to be effective in the treatment of acute seizures (Jeannet P et al., Eur J of Paediatric Neurology, 1999, 3:73-77); (3) in a prospective, double-blind, placebo-controlled trial, children scheduled for day surgery received either injectable midazolam mixed with a thick grape syrup and placed under the tongue in one of 3 doses (0.25, 0.5, or 0.75mg/kg) or placebo and children readily accepted the mixture. None of the children receiving placebo, 28% receiving 0.25mg/kg (P = 0.02), 52% receiving 0.5mg/kg (P < 0.001), and 64% receiving 0.75mg/kg (P < 0.001) of midazolam showed satisfactory sedation at 15 min after administration (Khalil et al., Paediatric Anaesthesia, 1998; 8(8):461-465); (4) 60 children received either oral midazolam 0.5mg/kg or placebo approximately 30 min before the induction of anesthesia and the authors concluded that benzodiazepines, especially when given via the oral route, can have a delayed and erratic onset which results in delayed post-procedural recovery (Viitanen H, et al., Can J Anesth., 1999, 46(8):766-771); (5) when intranasal midazolam was compared with sufentanil as a premedicant for 60 pediatric patients, aged 1/2 to 6 years, undergoing outpatient surgery of 2 hours or less, children who had not previously cried were more likely to cry when midazolam was administered compared with sufentanil (71% versus 20%, p = 0.0031), and of 31 midazolam patients, 20 experienced nasal irritation. (Zedie N, et al., Clin Pharmacol Ther; 1996; 59:341-8); and (6) a review article by McCann and Kain (Anesthesia & Analgesia, 93:98-105, 2001) reports that although transmucosal benzodiazepines, such as midazolam, have a rapid onset of action, the intranasal route is irritating and creates crying episodes and the sublingual route results in swallowing or spitting out of the drug.

**Anxiety**

[0084] Anxiety is a complex feeling of apprehension, fear, and worry often accompanied by pulmonary, cardiac, and other physical sensations.

[0085] Anxiety may surround a specific condition or situation, such as an intense fear prior to a medical or dental diagnostic or therapeutic procedure. The fear of a subject may be so severe that they may experience physical symptoms of anxiety, and even have panic
attacks, when confronted with the situation, or even anticipating having to deal with the situation.

[0086] A subject may either avoid having a medical or dental procedure they fear or endure the situation with distress. This is particularly problematic in the pediatric situation as children often do not know that their fear of a situation is excessive or unreasonable.

[0087] Physicians and nurses are often required to perform procedures on children and adults that are perceived as painful or frightening. Children often view needle sticks as a source of pain and fear. In an effort to minimize the pain of needle sticks, the use of a mixture of lidocaine and prilocaine (EMLA) has become standard practice in many children's hospitals. Unfortunately, EMLA requires at least 60 minutes to be fully effective and reportedly may cause vasoconstriction, leading to difficult vein cannulation.

[0088] Procedural anxiety and successful sedation have been inversely correlated. It has been shown that children with low anxiety are 3.8 times more likely to be successfully sedated (Schreiber KM et al., Am J Emerg Med. 2006 Jul;24(4):397-401).

[0089] Patients scheduled for a variety of office or clinic procedures are often anxious and frightened. High levels of anxiety may result in more difficult and painful procedures. Some exemplary procedures include breast core-needle biopsy, rectal ultrasound-guided prostate biopsies, dental procedures, cosmetic procedures such as abdominal liposuction, dermatologic procedures, podiatric procedures, setting broken bones or spinal injections and the like.

[0090] A number of classes of drugs are used to treat anxiety, including but not limited to, benzodiazepines, beta blockers, miscellaneous anxiolytics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants. Certain drug classes have greater effectiveness for specific anxiety disorders than others.

[0091] For an acute anxiety attack, short-term treatment with benzodiazepines is a standard treatment. More chronic episodes of anxiety are typically treated by administration of SSRIs, SNRIs or buspirone. In other situations, tricyclic antidepressants, beta-blockers, and, rarely, monoamine oxidase inhibitors are prescribed alone or in combination with other drugs to control anxiety.

**Sufentanil and Other Opioids**

[0092] Opioids are powerful analgesics and are utilized to treat both acute and chronic pain of moderate to severe intensity. Transmucosal administration of opioids has been used to treat procedural anxiety, especially in children, however, the dose required for sedation
using an opioid alone is higher than required for analgesic purposes and may result in an increased incidence of respiratory depression and nausea and vomiting, which raises safety concerns and can delay discharge from the post-surgical recovery room (Clin. Pharmacol and Therapeutics 59:341, 1996).

[0093] Sufentanil (N-[(4-(Methoxymethyl)-1-(2-(2-thienyl)ethyl)-4-piperidinyl)]-N-phenylpropanamide), is used as a primary anesthetic, to produce balanced general anesthesia in cardiac surgery, for epidural administration during labor and delivery and has been administered experimentally in both intranasal and liquid oral formulations. A commercial form of sufentanil used for IV delivery is the SUFENTA FORTE® formulation. This liquid formulation contains 0.075mg/ml sufentanil citrate (equivalent to 0.05mg of sufentanil base) and 9.0mg/ml sodium chloride in water. It has a plasma elimination half-life of 148 minutes, and 80% of the administered dose is excreted in 24 hours. The term sufentanil, as used herein includes sufentanil base, sufentanil citrate or a pharmaceutically acceptable salt or derivative thereof.

[0094] The use of sufentanil clinically has predominantly been limited to IV administration in operating rooms or intensive care units. Intranasal sufentanil liquid has been studied in both adult and pediatric patients for procedural sedation, with doses of 5 – 20mcg or higher providing sedative effects (Vercauteran et al., 1988; Karl et al., 1992). There are some issues relating to slower onset of action and decreased bioavailability, when the medication is inadvertently swallowed. For example, Helmers et al. 1989, describes a double-blind study which compared the efficacy of 15mcg sufentanil (intranasal vs. IV) for postoperative analgesia, based upon a numeric rating scale (NRS) from 0 to 10 for pain in 16 patients. For intranasal sufentanil liquid, T_{max} was 10 minutes with a bioavailability of 78% and a peak sedation at 40 minutes. Gardner-Nix J., J Pain Symptom Management. 2001 Aug; 22(2):627-30 describes administration of liquid sublingual sufentanil to adults wherein there was an analgesic effect following administration and that the analgesic onset occurred within 6 minutes with a duration of pain relief of approximately 30 minutes. Vercauteren M et al., Anaesthesia; 1988; 43:270-273, describe effects of intranasal sufentanil liquid in both adult and pediatric patients for procedural sedation, with doses of 10 and 20mcg or higher providing sedative effects (5mcg was not sufficient). Onset of sedation was achieved in a median of 10 minutes (range 5-30 minutes) and in 5/40 patients sedation was still evident at 60 minutes. The average duration was 40.8 minutes (range 10-55 minutes).

[0095] Prior to the work of the current inventors, a solid dosage form of sufentanil had not been described and no pharmacokinetic data had been published on sublingual sufentanil in any form. Example 1 (below), United States Patent Publication Serial Nos. 20070207207;
Fentanyl (N-(1-phenethyl-4-piperidyl)-N-phenyl-propanamide) was first synthesized in Belgium in the late 1950s, and has an analgesic potency of about 80 times that of morphine. Fentanyl and its congeners are mu opioid agonists that were originally developed as anesthesia agents, and are often administered intravenously due to rapid onset of analgesia. Fentanyl and other opioid agonists, have the potential for deleterious side effects including respiratory depression, nausea, vomiting and constipation.

Alfentanil, remifentanil, lofentanil, carfentanil, trefentanil, and mirfentanil are also potent fentanyl congeners that are rapidly metabolized and may be suitable for use in a transmucosal formulation in combination with an anxiolytic, such as triazolam.

Following transbuccal administration of fentanyl using a lozenge (e.g., Actiq®), the bioavailability is 50%, however, the T\textsubscript{max} for the 200mcg dosage of Actiq® ranges from 20 – 120 minutes due to erratic GI uptake based on the fact that 75% of the fentanyl is swallowed (Actiq® package insert). More recent publications on the T\textsubscript{max} of Actiq indicate that these original times were skewed towards more rapid onset. (The Fentora package insert indicates a range of T\textsubscript{max} for Actiq extending up to 240 minutes.) Fentora (a fentanyl buccal tablet; “FBT”) exhibits a bioavailability of 65%, with reported swallowing of 50% of the drug. In contrast to the claimed dosage forms, both Actiq® and Fentora suffer from the disadvantage that substantial amounts of lozenge-administered fentanyl are swallowed by the patient. Since fentanyl has a 31% bioavailability from the GI route, this swallowed drug contributes to the C\textsubscript{max} plasma levels and results in the erratic C\textsubscript{max} and T\textsubscript{max} observed with these products.

Oral transmucosal fentanyl lozenge-on-a-stick (Oralet®) was studied for use as a procedural sedative and analgesic in pediatric patients undergoing central venous line removal (Wheeler et al., 2002). The onset of action was both delayed and erratic (T\textsubscript{max} = 53 ± 40 minutes) and it was concluded that this fentanyl lozenge was not adequate for procedural sedation in children.

There remains a need for oral transmucosal preparations that are effective sedative agents that also provide for anxiolysis and analgesia, but do not result in inadvertent swallowing of drug due to large saliva responses or nasal run-off.
Use of Opioids and Other Analgesics For Procedural Sedation, Anxiolysis and Analgesia.

[0101] Although opioids are powerful analgesics as well as sedatives, they are known to produce pruritis, respiratory depression and/or nausea and vomiting during acute use and physical dependence, possible addictive behaviors and tolerance with long-term use. Benzodiazepines are powerful anxiolytics, however they have no analgesic properties.

[0102] When IV access is not available, often either a benzodiazepine, such as oral or intranasal midazolam, or an opioid, such as intranasal sufentanil, is used for procedural sedation (Karl et al., Anesthesiology, 76:209-15, 1992). There are disadvantages of using a single agent for procedural sedation wherein the desired effect includes anxiolysis and analgesia. Benzodiazepines, in particular, when given via the oral route, can have a delayed and erratic onset which results in delayed post-procedural recovery (Viitanen et al., Anesthesia & Analgesia, 89:75-9, 1999; Viitanen et al, Canadian Journal of Anaesthesia, 46:766-71, 1999).

[0103] Sedation coupled with relief of anxiety relief (anxiolysis) and/or pain relief (analgesia) is helpful in many settings, in particular, in the outpatient setting prior to a potentially painful medical or dental diagnostic or therapeutic procedure. However, currently many potentially painful medical and dental procedures are carried out with minimal treatment a (e.g., a local anesthetic), or in some cases with no treatment at all.

[0104] There is clearly a need for a medication that has a relatively rapid onset and produces mild sedation as well as relief from anxiety and pain, and which may be used safely and conveniently in the procedural setting.

[0105] The combination of an opioid such as sufentanil and a benzodiazepine such as triazolam in a single dosage form (e.g., a tablet) for oral transmucosal administration provides a non-invasive approach to procedural sedation, anxiolysis and analgesia.

Compositions for Procedural Sedation, Anxiolysis And Analgesia

[0106] As further described herein, there is no direct analgesic effect of benzodiazepines or most sedatives, which can result in increased anxiety and agitation due to under-treated pain. Furthermore, multiple studies have demonstrated delays in post-operative discharge when large doses of oral midazolam are used as a premedication. On the other hand, treatment with opioids alone to provide procedural sedation can result in episodes of respiratory depression and post-procedural nausea and vomiting (Friesen and Lockhart, Anesthesiology, 76:46-51, 1992; Karl et al., Anesthesiology, 76:209-15, 1992). Therefore, there are significant advantages in the use of the combination of both a sedative agent,
such as a benzodiazepine, with an analgesic agent, such as an opioid, for procedural sedation, anxiolysis and analgesia in a single dosage form (e.g., a tablet) that results in high bioavailability with consistent onset and offset of action.

[0107] The novel formulations described herein are provided in a single oral transmucosal dosage form (e.g., a tablet), that is relatively undetectable due to the small size of the dosage form. The oral transmucosal administration of the combination of a fentanyl congener such as sufentanil and a benzodiazepine, such as triazolam, allows for the dose of each drug to be lowered while effectively resulting in sedation, anxiolysis and analgesia.

[0108] One exemplary use of the claimed drug dosage forms is to effect sedation, anxiolysis and analgesia prior to and during a medical or dental procedure. When the claimed compositions are individual, single drug dosage forms for use in procedural sedation, anxiolysis and analgesia, the opioid agent in the drug dosage form is sufentanil or a sufentanil congener such as alfentanil, fentanyl, lofentanil, carfentanil, remifentanil, trefentanil, or mirfentanil, provided in combination with a benzodiazepine such as triazolam or midazolam. In a preferred embodiment, sufentanil is the active agent. Sufentanil may be provided in the claimed dosage forms in any of a number of formulations and forms, e.g., as sufentanil citrate or as sufentanil base.

[0109] One preferred embodiment relies on a sufentanil congener as the active agent. Yet another preferred embodiment relies on a combination of sufentanil and at least one additional agent typical used for treatment of analgesia, e.g., a combination of sufentanil and alfentanil. Various opioid drugs have different pharmacokinetic profiles and different interactions with mu opioid receptor splice variants and, therefore, may be used in combination to enhance the therapeutic effect.

[0110] Preferred dosage forms for use in procedural sedation, anxiolysis and analgesia contain from about 2 to about 100mcg of sufentanil per tablet for oral transmucosal delivery, in combination with a benzodiazepine drug such as triazolam or midazolam. In one exemplary embodiment, each dosage form or tablet 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, in combination with from about 50mcg to about 1000mcg of triazolam, from about 75mcg to about 750mcg of triazolam, from about 100mcg to about 500mcg of triazolam or from about 125mcg to about 400mcg, from about 150mcg to about 300mcg of triazolam, or from about 175mcg to about 250mcg of triazolam.

[0111] In another exemplary embodiment, each dosage form or tablet 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, in combination with from about 0.2mg to about 5mg of midazolam, from about 0.4mg to about 8mg of midazolam, from about 0.8mg to about 6mg of midazolam, from about 1mg to about 5mg of midazolam, or from about 1.5mg to about 3mg of midazolam.

[0112] For example, a dosage form or tablet for administration to adults for procedural sedation, anxiolysis and analgesia may comprise about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100mcg of sufentanil for oral transmucosal delivery.

[0113] In one exemplary embodiment of the invention, a dosage form or tablet for use in procedural sedation, anxiolysis and analgesia contains from about 10mcg to about 1000mcg of fentanyl, from about 15mcg to about 800mcg of fentanyl, from about 20mcg to about 600mcg of fentanyl, from about 40mcg to about 400mcg of fentanyl, or from about 30mcg to about 300mcg of fentanyl, in combination with from about 50mcg to about 1000mcg of triazolam, from about 75mcg to about 750mcg of triazolam, from about 100mcg to about 500mcg of triazolam or from about 125mcg to about 400mcg or from about 150 to about 300mcg of triazolam.

[0114] In another exemplary embodiment of the invention, each dosage form or tablet contains from 10mcg to about 1000mcg of fentanyl, from about 15mcg to about 800mcg of fentanyl, from about 20mcg to about 600mcg of fentanyl, from about 40mcg to about 400mcg of fentanyl, or from about 30mcg to about 300mcg of fentanyl, in combination with from about 0.2mg to about 5mg of midazolam, from about 0.4mg to about 8mg of midazolam, from about 0.8mg to about 6mg of midazolam, from about 1mg to about 5mg of midazolam, or from about 1.5mg to about 3mg of midazolam.

[0115] For example, a dosage for administration to adults aged 18 to 60 for procedural sedation, anxiolysis and analgesia may contain about 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000mcg of fentanyl for oral transmucosal delivery.

[0116] Exemplary dosage forms or tablets for administration to children (pediatric patients) or for administration to adults over 60 years of age for use in procedural sedation, anxiolysis and analgesia contain from about 1 to about 50mcg of sufentanil per dosage form, or from about 2mcg to about 40mcg of sufentanil, from about 3mcg to about 30mcg of sufentanil, from about 4mcg to about 20mcg of sufentanil, or from about 5mcg to about 10mcg of sufentanil. For example, a formulation of the invention for administration to children or adults over 60 may comprise about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,
15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45 or 50mcg of sufentanil for oral transmucosal delivery.

[0117] Exemplary dosage forms or tablets for administration to children (pediatric patients) or for administration to adults over 60 years of age for use in procedural sedation, anxiolysis and analgesia contain from about 5 to about 500mcg of fentanyl per dosage form, from about 8mcg to about 400mcg of fentanyl, from about 10mcg to about 300mcg of fentanyl, from about 20mcg to about 200mcg of fentanyl, or from about 15mcg to about 150mcg of fentanyl.

[0118] In another exemplary embodiment, dosage forms or tablets for administration to children (pediatric patients) or for administration to adults over 60 years of age for use in procedural sedation, anxiolysis and analgesia contain from about 1 to about 50mcg of sufentanil, in combination with a benzodiazepine drug. In one exemplary embodiment, each dosage form for administration to children (pediatric patients) or for administration to adults over 60 years of age contains from about 1 to about 50mcg of sufentanil per dosage form, or from about 2mcg to about 40mcg of sufentanil, from about 3mcg to about 30mcg of sufentanil, from about 4mcg to about 20mcg of sufentanil, or from about 5mcg to about 10mcg of sufentanil, in combination with about 50mcg to about 500mcg of triazolam, from about 60mcg to about 400mcg of triazolam, from about 70mcg to about 300mcg of triazolam or from about 80mcg to about 200mcg or from about 90 to about 150mcg of triazolam, e.g., about 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, or 500mcg of triazolam.

[0119] In yet another exemplary embodiment, dosage forms or tablets for administration to children (pediatric patients) or for administration to adults over 60 years of age for use in procedural sedation, anxiolysis and analgesia contain from about 1 to about 50mcg of sufentanil per dosage form, or from about 2mcg to about 40mcg of sufentanil, from about 3mcg to about 30mcg of sufentanil, from about 4mcg to about 20mcg of sufentanil, or from about 5mcg to about 10mcg of sufentanil, in combination with from about 0.2mg to about 5mg of midazolam, from about 0.3mg to about 7mg of midazolam, from about 0.4mg to about 8mg of midazolam, from about 0.5mg to about 1mg of midazolam, or from about 0.75mg to about 0.9mg of midazolam, e.g., about 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 or 5mg of midazolam.

[0120] In another exemplary embodiment, dosage forms or tablets for administration to children (pediatric patients) or for administration to adults over 60 years of age for use in procedural sedation, anxiolysis and analgesia contain from 5 to about 500mcg of fentanyl, in combination with a benzodiazepine drug. In one exemplary embodiment, each dosage form
contains from about 5 to about 500mcg of fentanyl per dosage form, from about 8mcg to
about 400mcg of fentanyl, from about 10mcg to about 300mcg of fentanyl, from about
20mcg to about 200mcg of fentanyl, or from about 15mcg to about 150mcg of fentanyl, in
combination with from about 50mcg to about 500mcg of triazolam, from about 60mcg to
about 400mcg of triazolam, from about 70mcg to about 300mcg of triazolam or from about
80mcg to about 200mcg or from about 90 to about 150mcg of triazolam, e.g., about 50, 60,
70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, or 500mcg of triazolam.

[0121] In another exemplary embodiment of the invention, each dosage form for
administration to children (pediatric patients) or for administration to adults over 60 years of
age contains from about 5 to about 500mcg of fentanyl per dosage form, from about 8mcg
to about 400mcg of fentanyl, from about 10mcg to about 300mcg of fentanyl, from about
20mcg to about 200mcg of fentanyl, or from about 15mcg to about 150mcg of fentanyl, in
combination with from about 0.2mg to about 5mg of midazolam, from about 0.3mg to about
7mg of midazolam, from about 0.4mg to about 8mg of midazolam, from about 0.5mg to
about 1mg of midazolam, or from about 0.75mg to about 0.90mg of midazolam, e.g., about
0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 or 5mg of midazolam.

[0122] As will be understood by those of skill in the art, the dose will be on the lower end
of the range for children and adults over 60 and on the higher end of the range for adults
from 18 to 60 years of age, dependent upon body mass, in particular when administered
long-term to opioid-tolerant adults.

[0123] Congeners of sufentanil also find use in the compositions and methods of the
invention, examples of which include fentanyl, remifentanil, alfentanil, lofentanil, carfentanil,
trefentanil, and mirfentanil.

[0124] Alfentanil is a potent fentanyl congener that is rapidly metabolized and may be
used in a formulation for use in effecting procedural sedation, anxiolysis and analgesia. In
one exemplary embodiment, a dosage form for use in effecting procedural sedation,
anxiolysis and analgesia comprises from about 10mcg to about 10mg of alfentanil, from
about 50mcg to about 5mg of alfentanil, from about 100mcg to about 2mg of alfentanil, or
from about 250mcg to about 1mg of alfentanil.

[0125] Lofentanil, carfentanil, remifentanil, trefentanil and mirfentanil are also potent
fentanyl congeners that are rapidly metabolized and may be suitable for use in a dosage
form for procedural sedation and analgesia in combination with an anxiolytic, such as
triazolam.

[0126] More specifically, a dosage form for use in effecting procedural sedation,
anxiolysis and analgesia may comprise from about 0.25mcg to 99.9mg of lofentanil, from
about 0.25mcg to 99.9mg of carfentanil, from about 0.25mcg to 99.9mg of remifentanil, from about 0.25mcg to 99.9mg of trefentanil, from about 0.25mcg to 99.9mg of mirfentanil.

[0127] As will be understood by those of skill in the art, the dose will be on the lower end of the range for children and adults over 60 and on the higher end of the range for adults from 18 to 60 years of age, dependent upon body mass, in particular when administered long term to opioid-tolerant adults.

[0128] Such an exemplary dosage form for procedural sedation, anxiolysis and analgesia for administration to adults aged 18 to 60 contains remifentanil, alfentanil, lofentanil, carfentanil, trefentanil, or mirfentanil in combination with about 50 to about 1000mcg of triazolam, e.g., about 50, 60, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 600, 700, 800, 900 or 1000mcg of triazolam. In another exemplary embodiment of the invention, each dosage form for administration to adults aged 18 to 60 contains remifentanil, alfentanil, lofentanil, carfentanil, trefentanil, or mirfentanil in combination with from about 0.2 to about 5mg of midazolam, e.g. 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 or 5mg of midazolam.

[0129] In another aspect of the invention, dosage forms for administration to children (pediatric patients) or for administration to adults over 60 years of age contain remifentanil, alfentanil, lofentanil, carfentanil, trefentanil, or mirfentanil in combination with about 20 to about 1000mcg of triazolam, e.g., about 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, or 500mcg of triazolam.

[0130] In another exemplary embodiment of the invention, dosage forms for administration to children (pediatric patients) or for administration to adults over 60 years of age contain remifentanil, alfentanil, lofentanil, carfentanil, trefentanil, or mirfentanil in combination with about 0.2 to about 5mg of midazolam, e.g. 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 or 5mg of midazolam.

**Drug Dosage Forms.**

[0131] The small volume oral transmucosal drug dosage forms described herein produce a reduced saliva response as compared with conventional, larger oral dosage forms that are intended to be swallowed following administration to the oral cavity. The small volume oral transmucosal drug dosage forms described herein do not result in a substantial amount of the drug delivered via the gastrointestinal route. The NanoTabs have been designed in a disc-shaped form with flattened faces in order to provide increased surface area for adhesion and drug elution. By virtue of their small size and inclusion of a bioadhesive excipient, the NanoTabs can comfortably adhere to the sublingual mucosa within seconds.
after administration and provoke a minimal saliva response. They are intended to erode within about 6 minutes to about 12 minutes following administration.

[0132] The claimed dosage forms contain a mixture of an opioid, such as sufentanil and a benzodiazepine such as triazolam and provide for high absorption rates of the pharmaceutically active substance across the oral mucosa and reduced uptake via the gastrointestinal tract, thereby offering a more consistent and reproducible pharmacokinetic and corresponding pharmacodynamic profile.

[0133] The dosage forms are typically "sublingual dosage forms", but in some cases another oral transmucosal route, such as the buccal route may be employed. The preferred site for oral transmucosal drug delivery is the sublingual area, although in certain embodiments it may be advantageous for the dosage form to be placed inside the cheek, or to adhere to the roof of the mouth or the gum.

[0134] Typically, the dosage forms are adapted to adhere to the oral mucosa (i.e. are bioadhesive) during the period of drug delivery, and until most or all of the drug has been delivered from the dosage form to the oral mucosa.

[0135] The claimed dosage forms (also referred to herein as tablets or NanoTabs™) have a mass of less than 100mg or a volume of less than 100 mcl. More specifically, the 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, less than 100mg, less than 90mg, less than 80mg, less than 70mg, less than 60mg, less than 50mg, less than 40mg, less than 30mg, less than 29mg, less than less than 28mg, less than 27mg, less than 26mg, less than 25mg, less than 24mg, less than less than 23mg, less than 22mg, less than 21mg, less than 20mg, less than 19mg, less than 18mg, less than 17mg, less than 16mg, less than 15mg, less than 14mg, less than 13mg, less than 12mg, less than 11mg, less than 10mg, less than 9mg, less than 8mg, less than 7mg, less than 6mg or less than 5mg 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, from about 5 to about 25 mcl, less than 100mcl, less than 90mcl, less than 80mcl, less than 70mcl, less than 60 mcl, less than 50mcl, less than 40mcl, less than 30mcl, less than 29mcl, less than 28mcl, less than 27mcl, less than 26mcl, less than 25mcl, less than 24mcl, less than 23mcl, less than 22mcl, less than 21mcl, less than 20mcl, less than 19mcl, less than 18mcl, less than 17mcl, less than 16mcl, less than 15mcl, less than 14mcl, less than 13mcl, less than 12mcl, less than 11mcl, less than 10mcl, less than 9mcl, less than 8mcl, less than 7mcl, less than 6mcl or less than 5mcl. The dosage forms typically have bioadhesive characteristics and may form a hydrogel upon contact with an aqueous solution.
The claimed small-volume drug delivery 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.

Tablets for oral transmucosal delivery of the combination of an opioid, such as sufentanil and a benzodiazepine, such as triazolam 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.

In general, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% of the total amount of sufentanil in a dosage form administered to the oral mucosa of a subject is absorbed via the oral transmucosal route.

The dosage forms may be housed in a drug delivery dispenser such as a single dose applicator (SDA) and the primary package may be a foil pouch. The oxidative degradation of a drug such as sufentanil is reduced or eliminated by providing the drug dosage form in an oxygen impermeable primary package, such as a foil pouch, which comprises at least one oxygen scavenging material, e.g., a Stabilox® sachet.

Oral transmucosal drug delivery is simple, non-invasive, and can be accomplished by a caregiver or patient with minimal discomfort. A dosage form for oral transmucosal delivery may be solid or non-solid. In one preferred embodiment, the dosage form is a solid that turns into a hydrogel following contact with saliva. In another preferred embodiment, the dosage form is a solid that erodes without forming a hydrogel following contact with saliva.

Generally, oral transmucosal, e.g., sublingual, delivery of the combination of an opioid, such as sufentanil and a benzodiazepine, such as triazolam is achieved using solid dosage forms such as lozenges or tablets, however, liquids, sprays, gels, gums, powders, and films and the like may also be used.

The claimed drug dosage forms are designed and adapted to deliver a substantial amount of the drug combination to a subject via the oral mucosa.

Formulations for preparation of the claimed dosage forms and methods of making them are described in US Patent Publication Nos. 20070207207 and 20080166404. An
exemplary formulation is bioadhesive and comprises sufentanil and triazolam. In general, the formulation is (a) a non-ordered mixture of a pharmaceutically active amount of a drug, wherein the non-ordered mixture does not 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; (b) comprises a bioadhesive material which provides for adherence to the oral mucosa of the subject; and (c) is not a solid solution or a molecular mixture.

[0144] Dissolution of a dosage form comprising the formulation may be independent of pH, e.g., over a pH range of about 4 to 8.


[0146] The dosage form is a substantially homogeneous composition which comprises active ingredients, one or more of bioadhesives that provide for adherence to the mucosal tissues of the mouth of a patient, binders for binding the excipients in a single tablet, one or more hydrogel-forming excipients, one or more bulking agents, one or more lubricants, as well as other excipients and factors that affect dissolution time and/or drug stability. The drug formulations and dosage forms tablets 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.

[0147] It will be understood that the formulation is converted into a dosage form for oral transmucosal administration to a subject using procedures routinely employed by those of skill in the art, such as direct compression, wet granulation, and the like. The process for preparation of the dosage form is optimized for each formulation in order to achieve high dose content uniformity.

[0148] In a related approach, the combination of an opioid, such as a fentanyl congener and a benzodiazepine may be administered by inhalation or sublimation to sedate and provide analgesia to a subject during a diagnostic or therapeutic procedure or prior to induction of general anesthesia.

**Single Dose applicators**

[0149] The invention further provides dispensing devices and methods of using the same for oral transmucosal delivery of a tablet comprising the combination of an opioid such as sufentanil and a benzodiazepine, such as triazolam to a subject for procedural sedation, anxiolysis and analgesia.
[0150] Application of a dispensing device or single dose applicator (SDA) for oral transmucosal delivery of a dosage form for procedural sedation, anxiolysis and analgesia is not limited to any particular type of device or patient population. As such, the SDAs find utility in drug delivery to pediatric, adult and non-human mammalian subjects.

[0151] In one embodiment, a SDA is used to administer a variety of drug dosage forms, including a solid tablet, a liquid capsule, a gel capsule, a liquid, a gel, a powder, a film, a strip, a ribbon, a spray, a mist, a patch, or any other suitable drug dosage form. In a typical embodiment, the drug dosage form is a small volume a solid tablet, e.g., a NanoTab.

[0152] 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 sublingual space. As will be understood by one 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 on an oral mucosal membrane, 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, so as to eliminate the risk of contaminating the drug dispensing device with saliva, or other contaminants.

[0153] The SDA may contain the dosage form within, may have the drug dosage form attached or affixed to it, may have the dosage form dissolved in it, and may afford a seal against moisture, humidity, and light. The SDA may be manually manipulated by the patient, a healthcare provider, or other user to place the dosage form in the proper location for oral transmucosal drug delivery.

[0154] The single-dose applicator is used to deliver tablets or other dosage forms into the hand, the mouth, in the sublingual space, in the buccal space, or to other locations appropriate for specific drug delivery needs.

[0155] In one preferred embodiment, a single-dose applicator or drug dispensing device is used to deliver a dosage form to the oral mucosa, e.g., the sublingual space.

[0156] The dosage forms inside the SDA remain dry prior to dispensing, at which point a single dosage form is dispensed from the device into the mouth, e.g., the sublingual space, wherein a patient's saliva will wet the tablet and allow for tablet disintegration/erosion and drug dissolution. After use, the SDA is disposed of.

[0157] In one aspect of the invention, a sufentanil/triazolam-containing tablet is placed in the sublingual cavity, preferably under the tongue on either side of the frenulum linguae, such that it adheres upon contact.
[0158] In general, for sublingual administration, a sufentanil/triazolam-containing tablet is administered by placement under the tongue, adjacent to the frenulum using forceps, or using a syringe-type SDA, a stick or rod, a straw, a dropper, or any other device suitable for the application of the small tablet or NanoTab.

[0159] In the case of procedural sedation, anxiolysis and analgesia, the dispensing device is typically a SDA. In general, the SDAs are packaged as individual units. However, a plurality of SDAs may be provided as a series of individual SDAs attached by the backing or housed in a multiple dose dispenser or multiple dose storage unit, referred to as a multiple dose applicator (MDA) or multiple dose dispenser (MDD).

[0160] The dosage form may be provided in a package 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 cover, typically a laminated material or foil, is used to seal to the molded part. A blister pack may or may not have pre-formed or molded parts and may be used to package an SDA of any type.

[0161] Figs. 1A-B, 2A-C, Figs. 3A-F, Figs. 5A-B, Figs. 6A-D and Figs. 7A-B are schematic depictions of exemplary SDAs for use in oral transmucosal administration of a drug dosage form.

[0162] Figs. 1A and 1B show one embodiment of a SDA 123 a dispensing device for delivering drug dosage forms. The dispensing device shown in Fig. 1A depicts the SDA 123 that is ready to dispense a drug dosage form 67. In one aspect of this embodiment, a user pinches the SDA 123 which opens the applicator and a drug dosage form 67 is dispensed as shown in Fig. 1B.

[0163] Figs. 2A – C show an embodiment of a SDA 123 that is comprised of a applicator shaped as a tube 129, which has a stopper seal 127, a handle 131 (e.g., an ergonomic handle), and a single dosage form 67. Fig 2A shows the SDA 123 in its sealed configuration, prior to use. Fig 2B shows the SDA 123 with its stopper seal 127 removed, forming an opening 133, and ready for use. Fig 2C shows the SDA 123 tilted so as to dispense the dosage form 67 on the oral mucosa, e.g., in the sublingual space.

[0164] Figs. 3A – F show several alternate embodiments of the SDA 123. In all of these figures the applicator seal 127 is broken and the applicator is tilted so as to drop the drug dosage form 67 adjacent an oral mucosal membrane in the mouth of a subject, e.g., under the tongue for sublingual dosage form placement. Fig. 3A shows a tube like applicator 129 with a handle 131 located axially under the tube 129. Fig. 3B shows an applicator formed as a thermoform or blister package 151 with a foil seal 135 that is peeled so as to open the applicator package 141 prior to placing the dosage form 67. Fig. 3C shows an applicator
that is a tube 129 which is broken to break the seal prior to dosage form 67 placement.

Fig. 3D shows a blister pack tube 151 type dosage form package 141 with a handle 131 such that after the seal 135 is peeled back the blister pack 151 can be held and tilted to place the drug dosage form 67, on an oral mucosal membrane. Figs. 3E and 3F show blister pack 151 type packaging with a handle 131 shaped like a flower or an animal, respectively, to be used for a SDA 123 designed for pediatric use. Other SDA shapes could include cartoon characters, animals, super-heroes or other appropriate shapes for pediatric applications.

[0165] Figure 4A shows a flat rigid applicator 123 with a dosage form 67 adhered to one end, for example, by means of a rapidly dissolving ingestible adhesive material such that when the applicator end with the dosage form is placed under the tongue, the adhesive dissolves, the dosage form 67 is placed on an oral mucosal membrane, such as in the sublingual space, and the applicator can be removed. Fig 4B shows an applicator 123 made from a water permeable material, impregnated with drug, forming a material and dosage from matrix. When the impregnated end of this applicator 123 is placed under in the mouth on an oral mucosal membrane, the moisture in the saliva dissolves the drug and delivers it transmucosally. Figure 4C shows dissolving film dosage forms 145 and a dosage form package with a plurality of dissolving film dosage forms 143 within it. The dissolving film dosage form 143 is removed from the package 141 and placed on an oral mucosal membrane, e.g., in the sublingual space where it dissolves and delivers the drug transmucosally.

[0166] Figs. 5A – B provides an illustration of two stages of use of one embodiment of a SDA 123. Figure 5A shows the applicator 123 in its configuration prior to use, with two applicator tabs 147, two perforations 149, and a blister pack 151 containing a dosage form 67. In order to administer the dosage form 67, the two applicator tabs 147 are bent downward at the perforations 149, forming a handle 131 (Fig. 5B), and the seal 135 is peeled back to reveal the blister pack 151 and allow the dosage form 67 to be dropped on an oral mucosal membrane, e.g., in the sublingual space.

[0167] Figs. 6A – D are schematic depictions of additional examples of SDAs, including a tweezers or a reverse scissor-type SDA (6A), where a drug dosage form 67 is held between the two sides 153 of the SDA 123 such that when the latch 19 is released, the drug dosage form 67 is no longer held by the SDA and can be placed on an oral mucosal membrane by the user; a syringe-type SDA (6B) with a circular channel, where a drug dosage form 67 is pushed out of the end of the channel when a user pushes 155, the slider or plunger 159; a pusher-type SDA (6C) with a rectangular channel where a drug dosage form 67 is pushed
out of the end of the channel when a user pushes 155, the slider 159; or a slider-type SDA (6D) where drug dosage form 67 is held in a pocket 161 and the drug dosage form 67 becomes accessible when a user pulls 157 a slider 159.

[0168] Fig. 7A is a schematic depiction of an embodiment of an SDA for delivery of an oral transmucosal dosage form to a subject. The SDA is provided in child resistant packaging. The SDA has a pin lock 167 which serves as a lock-out feature and must be removed before a tablet can be injected from the SDA, as well as a pusher button 163, which is pushed by a user to eject a tablet into the mouth of the subject on a mucosal membrane, e.g., adjacent the frenulum in the sublingual space. The SDA may be disassembled and has a bottom clamshell 169 and a top clamshell 171. The SDA also has a shroud 29 and a valve 33, which serve to protect the tablet from saliva ingress when the SDA is inserted into the mouth of a subject. Fig. 7B is an exploded view of a schematic depiction of the SDA shown in Fig. 7A wherein the bottom clamshell 169 and top clamshell 171 are separated illustrating the pusher 165 and a dosage form 67, as well as the relative location of the dosage form 67, the valve 33, and the shroud 29.

Utility

[0169] Oral transmucosal drug delivery provides a simple, non-invasive means to administer a single drug dosage form in order to achieve mild sedation, anxiolysis and analgesia. For certain drugs, such as those with poor bioavailability via the GI tract, and in situations where the patient cannot ingest an oral medication, such as prior to anesthesia, oral transmucosal delivery provides a significant advantage over traditional methods of oral administration, wherein the drug is swallowed.

[0170] The oral transmucosal dosage forms described herein find utility in delivery of a combination of an opioid (such as sufentanil) and a benzodiazepine (such as triazolam) for procedural sedation, anxiolysis and analgesia. The small volume oral transmucosal dosage forms (tablets) described herein provide for a blunted Cmax, avoiding the high peak plasma levels typically observed when the IV dosage route is employed, high relative AUC, low variability in Tmax, low variability in Cmax and low variability in AUC. The sedative effect of the drug combinations described herein may be the result of an additive or synergistic pharmacodynamic effect and/or may be due to the different onset and offset times of the opioid and benzodiazepine components of the combination.

[0171] Although benzodiazepines such as triazolam and midazolam have been used for procedural sedation, studies have shown that transient residual amnesia frequently occurs when oral doses of benzodiazepines above 250mcg are administered. Triazolam is a short-
acting benzodiazepine, however, it may still cause residual impairment into the next day, with “hangover” effects such as sleepiness, impaired psychomotor and cognitive functions, any of which can impair the ability of users to drive safely, etc. (Vermeeren A., 2004, CNS Drugs. 18 (5): 297–328). It has also been shown that benzodiazepines such as triazolam cause a greater degree of sedation and greater impairment of psychomotor performance in healthy elderly persons than in young persons who received the same dose (Greenblatt et al., 1991). Therefore it is important to minimize the dose of this agent, for example by adding another agent, such as sufentanil, which can enhance the properties of triazolam in effecting procedural sedation, anxiolysis and analgesia.

[0172] The results described herein in Example 2 show that oral transmucosal administration of a single tablet containing the combination of sufentanil and triazolam was effective to sedate alert, awake subjects in an initial human clinical trial. The amount of sedation as measured by the total AUC of the RASS sedation score was greater for the combination of sufentanil and triazolam, than for the equivalent dose of sufentanil alone. Hence, the combination of sufentanil and triazolam produced a higher degree of sedation than sufentanil alone, yet the duration of analgesia was not prolonged, being approximately 4 hours for both treatments.

[0173] The results described herein in Example 3 show that oral transmucosal administration of a single tablet containing the combination of sufentanil and triazolam in a Phase 2a clinical trial was effective to provide mild sedation, anxiolysis and analgesia during an abdominal liposuction procedure. The primary endpoint was efficacy of the sufentanil/triazolam combination as compared to placebo in providing mild sedation during the procedure, assessed using the validated, objective Richmond Agitation-Sedation Scale (RASS; +4 for highly agitated to -5 for unarousable).

[0174] Key secondary endpoints included the efficacy of the sufentanil/triazolam combination in reducing anxiety compared to placebo and an assessment of analgesia.

[0175] The claimed opioid/benzodiazepine compositions find particular utility in pediatric applications, since the comfortable nature of the small, relatively flat oral transmucosal tablet will allow small children to readily accept this mode of therapy and reliably deliver drug transmucosally. Specific examples include, but are not limited to, sedation, anxiolysis and analgesia associated with a medical or dental diagnostic or therapeutic procedure or in an emergency situation, in particular, when IV access is not available or inconvenient, when a child is NPO (no oral intake allowed) or when rapid onset of drug effect is required.

[0176] The claimed opioid (e.g., sufentanil)/benzodiazepine (e.g., triazolam) containing tablets find further utility in veterinary applications. Specific examples include, but are not
limited to, treatment of any acute condition, medical or dental procedure for which IV administration is not readily available or is inconvenient, such as procedural sedation, anxiety/stress/pain relief, etc.

[0177] 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.

[0178] The following examples are provided to illustrate the invention and are not intended to limit any aspect of the invention as set forth above or in the claims below.

**EXAMPLES**

**EXAMPLE 1. Phase 1 Clinical Study of Sublingual Sufentanil**

[0179] Two different sublingual sufentanil formulations were previously evaluated in a Phase 1 clinical trial, including a slower-eroding form (erosion time of approximately 15-25 minutes), and a faster-eroding form (approximate erosion time of 6-12 minutes). Patients were blocked with a mu-opioid receptor antagonist, naltrexone (50mg orally twice per day). In a study detailed in U.S. Application Publication No. 20080268023, sufentanil plasma concentrations with respect to time were analyzed and tabulated. The maximum sufentanil concentration in plasma ($C_{max}$), time to $C_{max}$ ($T_{max}$), area under the curve (AUC$_{int}$), F and terminal t$_{1/2}$ including $C_{max}$, $T_{max}$, and t$_{1/2}$ were evaluated for each dose group. The relevant results are summarized below in Tables 1A and 1B.

[0180] **EXAMPLE 1A**: All subjects received a 10-minute IV infusion of 5mcg sufentanil. After a 1-day washout period, each subject then received a single sublingual administration of a dosage form (comprising a slow-eroding formulation) containing 2.5mcg of sufentanil. On the two subsequent study days, the dose was escalated, and each subject received a dosage form (comprising a slow-eroding formulation) containing 5 and 10mcg of sufentanil.

[0181] **EXAMPLE 1B**: All subjects received four repeated sublingual doses of a dosage form (comprising a slow-eroding formulation) containing 5mcg of sufentanil administered at 10-minute intervals.

[0182] Table 1A provides a summary of pharmacokinetic parameters including $C_{max}$, $T_{max}$, AUC$_{int}$, F and t$_{1/2}$. The $C_{max}$ after multiple sublingual dosing was 46.36 pg/mL. The mean AUC$_{int}$ increased with multiple sublingual dosing of sufentanil and was generally proportional to dose when compared to single sublingual administration.

[0183] **Table 1A. Summary of Sufentanil Pharmacokinetic Parameters**
<table>
<thead>
<tr>
<th>Parameter</th>
<th>5mcg IV</th>
<th>2.5mcg</th>
<th>5mcg</th>
<th>10mcg</th>
<th>4x5mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>81.3± 28.1</td>
<td>6.8± 2.1</td>
<td>10.9± 3.5</td>
<td>27.5± 7.7</td>
<td>46.4± 12.4</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.16± 0.03</td>
<td>0.73± 0.13</td>
<td>0.77± 0.29</td>
<td>0.68± 0.22</td>
<td>1.16± 0.23</td>
</tr>
<tr>
<td>AUC_{inf} (hr*pg/mL)</td>
<td>38.4± 8.5</td>
<td>18.0± 4.5</td>
<td>27.4± 9.1</td>
<td>71.2± 20.7</td>
<td>146.5± 39.1</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>1.66± 0.72</td>
<td>1.71± 0.51</td>
<td>1.56± 0.57</td>
<td>1.97± 0.85</td>
<td>3.29± 1.10</td>
</tr>
<tr>
<td>F (%)</td>
<td>-</td>
<td>95.3± 19.1*</td>
<td>74.5± 26.3*</td>
<td>95.5± 29.2*</td>
<td>97.2± 21.2*</td>
</tr>
</tbody>
</table>

* F% calculated using 5mcg IV AUC

**EXAMPLE 1C**: Subjects were administered a 10-minute IV infusion of 5mcg sufentanil, a single sublingual administration of a dosage form containing 10mcg of sufentanil (faster-eroding formulation) and four repeated sublingual doses of a dosage form containing 10mcg of sufentanil (faster-eroding formulation) administered at 20-minute intervals.

**EXAMPLE 1D**: Subjects were administered a 20-minute IV infusion of 50mcg sufentanil and a single sublingual administration of a dosage form containing 80mcg of sufentanil (faster-eroding formulation).

**EXAMPLE 1K**: Table 1B provides a summary of pharmacokinetic parameters including $C_{\text{max}}$, $T_{\text{max}}$, AUC_{inf}, F and $t_{1/2}$.
**Table 1B. Summary of Sufentanil Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5mcg IV</th>
<th>10mcg</th>
<th>4x10mcg</th>
<th>80mcg</th>
<th>50mcg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>63.9± 28.2</td>
<td>16.5± 6.8</td>
<td>78.7± 20.1</td>
<td>127.2± 42.3</td>
<td>561.1± 277.7</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.17± 0.0</td>
<td>0.84± 0.35</td>
<td>1.41± 0.25</td>
<td>0.89± 0.35</td>
<td>0.34± 0.11</td>
</tr>
<tr>
<td>$AUC_{\text{inf}}$ (hr*pg/mL)</td>
<td>39.4± 9.6</td>
<td>44.9± 24.6</td>
<td>253.4± 70.1</td>
<td>382.1± 88.2</td>
<td>528.0± 134.4</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>1.72± 0.47</td>
<td>1.67± 0.67</td>
<td>3.54± 1.02</td>
<td>4.23± 0.90</td>
<td>3.69± 0.78</td>
</tr>
<tr>
<td>$F$ (%)</td>
<td>-</td>
<td>60.9± 27.7*</td>
<td>87.8± 22.2*</td>
<td>70.1± 20.1*</td>
<td>-</td>
</tr>
</tbody>
</table>

* %F calculated using 5mcg IV AUC

**EXAMPLE 2. Phase 1 Clinical Study of Sublingual Sufentanil and Triazolam for Procedural Sedation and Analgesia**

[0188] The pharmacokinetics and pharmacodynamics of sufentanil and/or triazolam administered via the sublingual route using a tablet of 3 different strengths were evaluated in a Phase 1 clinical trial. The experimental design is a randomized 2 cohort, 5-arm crossover, open-label on days 1 and 2, double-blinded on days 3 to 5, single-dose, fasting design. The study involved 24 normal, healthy, non-smoking male and female subjects, divided into 2 cohorts as follows: Cohort 1: 12 male and female subjects within the age range of 18 and 60 years and Cohort 2: 12 male and female subjects within the age range of 61 and 80 years.

[0189] The study relied on a single 7-day study period for each subject and each cohort received: Day 1: Halcion® (triazolam) 125mcg tablets orally; Day 2: 5mcg sufentanil IV (slow infusion). Cohort 1 also received a sublingual tablet containing 10mcg of sufentanil and 200mcg of triazolam, 15mcg of sufentanil and 200mcg of triazolam or 10mcg of sufentanil alone on days 3-5 in a randomized, blinded design. Cohort 2 also received a sublingual tablet containing 10mcg of sufentanil and 200mcg of triazolam, 10mcg of sufentanil and 100mcg of triazolam or 10mcg of sufentanil alone on days 3-5 in a randomized, blinded design. The fractional (%) compositions of the formulation for each dosage form/tablet of sufentanil and triazolam are shown in Table 2.
[0190] **Table 2: Fractional Composition Per Tablet Of Sufentanil/Triazolam.**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>10mcg sufentanil/100mcg triazolam (%w/w)</th>
<th>10mcg sufentanil/200mcg triazolam (%w/w)</th>
<th>15mcg sufentanil/200mcg triazolam (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil Citrate, USP</td>
<td>0.256</td>
<td>0.256</td>
<td>0.385</td>
</tr>
<tr>
<td>Triazolam, (Conforms to USP)</td>
<td>1.709</td>
<td>3.419</td>
<td>3.419</td>
</tr>
<tr>
<td>Mannitol, EP/USP/JP</td>
<td>68.784</td>
<td>67.075</td>
<td>66.947</td>
</tr>
<tr>
<td>Dicalcium Phosphate Dihydrate, USP/FCC/EP</td>
<td>20.000</td>
<td>20.000</td>
<td>20.000</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose (Methocel) K4M Premium CR, EP</td>
<td>3.000</td>
<td>3.000</td>
<td>3.000</td>
</tr>
<tr>
<td>Stearic Acid, NF/EP/BP/JP</td>
<td>5.000</td>
<td>5.000</td>
<td>5.000</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Butylated Hydroxytoluene,USP</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
<td><strong>100.00</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

[0191] The mass (in mg) composition per tablet for each strength of sufentanil and triazolam tablets is shown in Table 3.

[0192] **Table 3: Mass (mg) Composition per Tablet for each Strength of Sufentanil/Triazolam Tablets.**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>10mcg sufentanil/100mcg triazolam (mg/tablet)</th>
<th>10mcg sufentanil/200mcg triazolam (mg/tablet)</th>
<th>15mcg sufentanil/200mcg triazolam (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil Citrate, USP</td>
<td>0.015</td>
<td>0.015</td>
<td>0.0225</td>
</tr>
<tr>
<td>Triazolam (conforms to USP)</td>
<td>0.1000</td>
<td>0.2000</td>
<td>0.200</td>
</tr>
<tr>
<td>Mannitol, EP/USP/JP</td>
<td>4.024</td>
<td>3.924</td>
<td>3.916</td>
</tr>
<tr>
<td>Dicalcium Phosphate Dihydrate, USP/FCC/EP</td>
<td>1.170</td>
<td>1.170</td>
<td>1.170</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose (Methocel) K4M Premium CR, EP</td>
<td>0.176</td>
<td>0.176</td>
<td>0.176</td>
</tr>
<tr>
<td>Stearic Acid, NF/EP/BP/JP</td>
<td>0.293</td>
<td>0.293</td>
<td>0.293</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>0.059</td>
<td>0.059</td>
<td>0.059</td>
</tr>
<tr>
<td>Butylated Hydroxytoluene,USP</td>
<td>0.0146</td>
<td>0.0146</td>
<td>0.0146</td>
</tr>
<tr>
<td><strong>Total (mg)</strong></td>
<td><strong>5.85</strong></td>
<td><strong>5.85</strong></td>
<td><strong>5.85</strong></td>
</tr>
</tbody>
</table>

[0193] The fractional (%) and mass (mg) composition for the 10mcg strength of sufentanil tablets are shown in Table 4.
Table 4. Fractional and Mass Composition of the 10mcg Sufentanil Tablets.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>10mcg sufentanil (g)</th>
<th>10mcg sufentanil (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil Citrate, USP</td>
<td>0.256</td>
<td>0.015</td>
</tr>
<tr>
<td>Mannitol, EP/USP/JP</td>
<td>74.9</td>
<td>4.122</td>
</tr>
<tr>
<td>Dicalcium Phosphate Dihydrate, USP/FCC/EP</td>
<td>20.000</td>
<td>1.170</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose (Methocel) K4M Premium CR, EP</td>
<td>3.000</td>
<td>0.176</td>
</tr>
<tr>
<td>Stearic Acid, NF/EP/BP/JP</td>
<td>5.000</td>
<td>0.293</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>1.000</td>
<td>0.059</td>
</tr>
<tr>
<td>Butylated Hydroxytoluene, USP</td>
<td>0.250</td>
<td>0.0146</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
<td>5.85</td>
</tr>
</tbody>
</table>

A series of blood samples were drawn during the study as exemplified by the following schedule: On days 1 to 5: One sample was drawn prior to dosing and at approximately 5, 10, 15, 20, 40, 60, 90, 120, 160, 240, 320, 480, and 640 minutes post-dosing.

Pharmacokinetic (PK) parameters, including the following, were calculated for sufentanil and triazolam: AUC0-last, Cmax, Tmax, t½ and relative AUC0-last.

Analysis of sufentanil and triazolam was carried out according to the following method. Sufentanil, triazolam and internal standards fentanyl and triazolam-D4 were extracted from 0.2 ml human plasma by solid phase extraction into an organic medium and reconstituted in 200ml of reconstitution solution. An aliquot was injected into a High Performance Liquid Chromatography system and detected using a TSQ Quantum tandem mass spectrometer and quantitated using a peak ratio method. Analyses of sufentanil and triazolam were conducted at Bioval Contract Research.

Pharmacodynamic (PD) parameters were evaluated using sedative scores [+4 to – 5 for the RASS. The RASS score was determined and recorded for each patient at a number of time-points after each dose. The RASS is used as a substantially objective assessment for sedation and includes a scale from –5 (unarousable) to +4 (combative), and includes a procedure on assessing and assigning the sedation score for a patient.

No adverse events related to nausea/vomiting or respiratory sedation occurred during this study for any subject with any dose of study medication.

The results of an analysis of onset of RASS Sedation (hours) in subjects who were less than 61 years old are shown in Table 5.
[0201] Table 5. Analysis of Onset of RASS Sedation (hours) Subjects Who Were Less Than 61 Years Old

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>12</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 15/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
</tr>
<tr>
<td>Mean</td>
<td>0.841</td>
<td>0.584</td>
<td>0.964</td>
</tr>
<tr>
<td>(SD)</td>
<td>0.69</td>
<td>0.352</td>
<td>0.908</td>
</tr>
</tbody>
</table>

[0202] The results of an analysis of total AUC of RASS sedation in subjects who were less than 61 years old are shown in Table 6.


<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>12</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 15/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
</tr>
<tr>
<td>RASS Mean</td>
<td>7.537</td>
<td>8.116</td>
<td>4.259</td>
</tr>
<tr>
<td>RASS (SD)</td>
<td>3.939</td>
<td>4.435</td>
<td>3.252</td>
</tr>
</tbody>
</table>

[0204] The results of an analysis of total duration of RASS sedation in subjects who were less than 61 years old are shown in Table 7.

[0205] Table 7. Analysis of AUCh of Total Duration of RASS Sedation: Subjects Who Were Less Than 61 Years Old

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>12</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 15/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
</tr>
<tr>
<td>Time (hours) Mean</td>
<td>4.048</td>
<td>3.972</td>
<td>2.843</td>
</tr>
<tr>
<td>Time (hours) (SD)</td>
<td>1.486</td>
<td>1.839</td>
<td>2.388</td>
</tr>
</tbody>
</table>

[0206] The results of an analysis of onset of RASS Sedation (hours) in subjects who were at least 61 years old is shown in Table 8.

[0207] Table 8. Analysis of Onset of RASS Sedation (hours) Subjects Who Were At Least 61 Years Old

<table>
<thead>
<tr>
<th></th>
<th>9</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
<td>Sufentanil 10/ Triazolam 100 (mcg)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.446</td>
<td>0.436</td>
<td>0.343</td>
</tr>
<tr>
<td>(SD)</td>
<td>0.34</td>
<td>0.129</td>
<td>0.167</td>
</tr>
</tbody>
</table>

[0208] The results of an analysis of total AUC of RASS sedation in subjects who were at least 61 years old are shown in Table 9.
[0209] Table 9. Analysis of AUC\textsubscript{total} of RASS Sedation Assessment: Subjects Who Were At Least 61 Years Old

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>12</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
<td>Sufentanil 10/ Triazolam 100 (mcg)</td>
</tr>
<tr>
<td>RASS Mean</td>
<td>9.732</td>
<td>5.203</td>
<td>6.724</td>
</tr>
<tr>
<td>RASS (SD)</td>
<td>8.501</td>
<td>4.651</td>
<td>4.866</td>
</tr>
</tbody>
</table>

[0210] The results of an analysis of total duration of RASS sedation in subjects who were at least 61 years old are shown in Table 10.

[0211] Table 10. Analysis of AUC of Total Duration of RASS Sedation: Subjects Who Were At Least 61 Years Old

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>12</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sufentanil 10/ Triazolam 200 (mcg)</td>
<td>Sufentanil 10mcg</td>
<td>Sufentanil 10/ Triazolam 100 (mcg)</td>
</tr>
<tr>
<td>Time (hours) Mean</td>
<td>4.388</td>
<td>4.618</td>
<td>5.548</td>
</tr>
<tr>
<td>Time (hours) (SD)</td>
<td>3.533</td>
<td>3.601</td>
<td>3.293</td>
</tr>
</tbody>
</table>

[0212] The results of pharmacokinetic analysis for sufentanil in subjects who were less than 61 years old are shown in Table 11.

[0213] Table 11. Summary of Sufentanil Pharmacokinetic Parameters Subjects Who Were Less Than 61 Years Old

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sufentanil 10/ Triazolam 200 (mcg)</th>
<th>Sufentanil 15/ Triazolam 200 (mcg)</th>
<th>Sufentanil 10mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max} (pg/mL)</td>
<td>21.64 +/- 6.59</td>
<td>33.00 +/- 15.17</td>
<td>20.0 +/- 5.87</td>
</tr>
<tr>
<td>T\textsubscript{max} (hr)</td>
<td>0.94 +/- 0.39</td>
<td>0.82 +/- 0.17</td>
<td>0.74 +/- 0.28</td>
</tr>
<tr>
<td>AUC\textsubscript{0-last} (hr*pg/mL)</td>
<td>43.30 +/- 19.36</td>
<td>75.88 +/- 41.35</td>
<td>35.68 +/- 10.60</td>
</tr>
<tr>
<td>t\textsubscript{1/2} (hr)</td>
<td>4.65 +/- 3.40</td>
<td>2.64 +/- 0.78</td>
<td>3.37 +/- 1.60</td>
</tr>
<tr>
<td>Relative AUC\textsubscript{0-last} (%)</td>
<td>95%</td>
<td>101%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Data reported as mean +/- SD.
Relative AUC\textsubscript{0-last} values were obtained by normalizing the doses to the 5mcg IV sufentanil comparator.

[0214] The results of pharmacokinetic analysis for triazolam in subjects who were less than 61 years old is shown in Table 12.
[0215] **Table 12. Summary of Triazolam Pharmacokinetic Parameters Subjects Who Were Less Than 61 Years Old**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Triazolam 125mcg</th>
<th>Sufentanil 10/ Triazolam 200 (mcg)</th>
<th>Sufentanil 15/ Triazolam 200 (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>1224.8 +/- 385.0</td>
<td>1528.9 +/- 520.6</td>
<td>1553.5 +/- 448.0</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.94 +/- 0.46</td>
<td>2.54 +/- 1.43</td>
<td>1.86 +/- 0.99</td>
</tr>
<tr>
<td>$AUC_{\text{0-\text{last}}}$ (hr*pg/mL)</td>
<td>5151.9 +/- 2364.7</td>
<td>9451.1 +/- 3721.4</td>
<td>9501.8 +/- 3639.3</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.10 +/- 1.27</td>
<td>3.46 +/- 1.03</td>
<td>4.08 +/- 2.45</td>
</tr>
<tr>
<td>Relative $AUC_{\text{0-\text{last}}}$ (%)</td>
<td>NA</td>
<td>120%</td>
<td>121%</td>
</tr>
</tbody>
</table>

Data reported as mean +/- SD. Relative $AUC_{\text{0-\text{last}}}$ values were obtained by normalizing the doses to the 125mcg oral triazolam comparator.

[0216] The results of pharmacokinetic analysis for sufentanil in subjects who were at least 61 years old is shown in Table 13.

[0217] **Table 13. Summary of Sufentanil Pharmacokinetic Parameters Subjects Who Were At Least 61 Years Old**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sufentanil 10/ Triazolam 200 (mcg)</th>
<th>Sufentanil 10mcg</th>
<th>Sufentanil 10/ Triazolam 100 (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>21.83 +/- 11.50</td>
<td>24.83 +/- 16.33</td>
<td>25.33 +/- 6.49</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>1.00 +/- 0.29</td>
<td>0.88 +/- 0.48</td>
<td>0.75 +/- 0.21</td>
</tr>
<tr>
<td>$AUC_{\text{0-\text{last}}}$ (hr*pg/mL)</td>
<td>53.65 +/- 49.04</td>
<td>47.65 +/- 26.84</td>
<td>52.26 +/- 17.69</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>5.32 +/- 5.20</td>
<td>5.02 +/- 6.32</td>
<td>3.65 +/- 2.44</td>
</tr>
<tr>
<td>Relative $AUC_{\text{0-\text{last}}}$ (%)</td>
<td>107%</td>
<td>87%</td>
<td>108%</td>
</tr>
</tbody>
</table>

Data reported as mean +/- SD. Relative $AUC_{\text{0-\text{last}}}$ values were obtained by normalizing the doses to the 5mcg IV sufentanil comparator.

[0218] The results of pharmacokinetic analysis for triazolam in subjects who were at least 61 years old is shown in Table 14.

[0219] **Table 14. Summary of Triazolam Pharmacokinetic Parameters Subjects Who Were At Least 61 Years Old**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Triazolam 125mcg</th>
<th>Sufentanil 10/ Triazolam 200 (mcg)</th>
<th>Sufentanil 10/ Triazolam 100 (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>1139.8 +/- 490.3</td>
<td>1599.7 +/- 554.3</td>
<td>947.2 +/- 351.6</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>0.97 +/- 0.45</td>
<td>2.53 +/- 1.19</td>
<td>2.22 +/- 1.45</td>
</tr>
<tr>
<td>$AUC_{\text{0-\text{last}}}$ (hr*pg/mL)</td>
<td>5437.2 +/- 3441.5</td>
<td>10867.1 +/- 5566.5</td>
<td>6007.2 +/- 3372.3</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.46 +/- 1.23</td>
<td>4.66 +/- 2.21</td>
<td>4.45 +/- 1.79</td>
</tr>
<tr>
<td>Relative $AUC_{\text{0-\text{last}}}$ (%)</td>
<td>NA</td>
<td>132%</td>
<td>140%</td>
</tr>
</tbody>
</table>

Data reported as mean +/- SD. Relative $AUC_{\text{0-\text{last}}}$ values were obtained by normalizing the doses to the 125mcg oral triazolam comparator.
EXAMPLE 3. Phase 2a Clinical Study of Sublingual Sufentanil and Triazolam.

[0220] A randomized, double-blind, placebo-controlled, Phase 2a study was carried out to evaluate the clinical efficacy, safety and tolerability of sublingual administration of sufentanil/triazolam NanoTabs™ in patients undergoing an elective, low-volume abdominal liposuction procedure under local anesthesia.

[0221] The objectives of the study were to evaluate the safety and efficacy of a single tablet including the combination of sufentanil and triazolam in providing Joint Commission on the Accreditation of Health Care Organizations (JCAHO) Level 1 minimal sedation during the procedure, together with anxiolyis and analgesia.

[0222] The study was carried out in patients 18 to 60 years of age who underwent an elective abdominal liposuction procedure at a single, monitored clinical research center site with a high degree of medical supervision. Patients who met all inclusion and exclusion criteria were randomly assigned to sublingual treatment with a single tablet (NanoTab™) containing 15mcg sufentanil and 200mcg triazolam or placebo.

[0223] A single tablet containing 15mcg sufentanil and 200mcg triazolam or placebo was placed directly under the tongue at the base of the frenulum using forceps by qualified medical staff. Patients were instructed that the NanoTab™ be allowed to dissolve under the tongue and not be crushed, chewed, or swallowed. Expected time for erosion after administration was 5 to 10 minutes.

[0224] The tablets containing 15mcg sufentanil and 200mcg triazolam or placebo had a volume of about 6 ml, were of uniform size for all dosage strengths, and had dimensions of approximately 3 mm in diameter and 0.7 mm in thickness.

[0225] The primary efficacy endpoint of the study was sedation, assessed by the 10-point Richmond Agitation-Sedation Scale (RASS). Secondary endpoints included: patient report of procedural anxiety, patient report of pain intensity, patient and physician global assessments of efficacy and tolerability of the study drug, and time to a modified Aldrete score of 8 (readiness for discharge measurement; Table 15).

[0226] 41 patients were randomized and 40 patients were enrolled in the study (21 treated with the sufentanil/triazolam drug combination and 19 treated with placebo).
Table 15. Components of Modified Aldrete Scoring System.

<table>
<thead>
<tr>
<th>Modified Aldrete Scoring System</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTIVITY</td>
</tr>
<tr>
<td>Able to move four extremities voluntarily on command</td>
</tr>
<tr>
<td>Able to move two extremities voluntarily on command</td>
</tr>
<tr>
<td>Unable to move</td>
</tr>
<tr>
<td>RESPIRATION</td>
</tr>
<tr>
<td>Able to deep breathe and cough freely</td>
</tr>
<tr>
<td>Dyspnea or limited breathing</td>
</tr>
<tr>
<td>Apneic</td>
</tr>
<tr>
<td>CIRCULATION</td>
</tr>
<tr>
<td>BP and HR ± 20% of preanesthetic level</td>
</tr>
<tr>
<td>BP and HR ± 20% to 50% of preanesthetic level</td>
</tr>
<tr>
<td>BP and HR ± 50% of preanesthetic level</td>
</tr>
<tr>
<td>CONSCIOUSNESS</td>
</tr>
<tr>
<td>Fully Awake (able to answer questions)</td>
</tr>
<tr>
<td>Arousable on calling (arousable only to calling)</td>
</tr>
<tr>
<td>Unresponsive</td>
</tr>
<tr>
<td>OXYGENATION</td>
</tr>
<tr>
<td>Able to maintain O₂ saturation &gt; 92% on room air</td>
</tr>
<tr>
<td>Needs O₂ inhalation to maintain saturation &gt; 90%</td>
</tr>
<tr>
<td>O₂ saturation &lt; 90%, even with O₂ supplement</td>
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</table>

[0227] A single tablet containing 15mcg sufentanil and 200mcg triazolam or placebo was administered, and 15 minutes later an initial RASS score was assessed followed by an anxiety NRS assessment. RASS, anxiety and pain intensity scores were collected every 10 minutes during the first hour after starting the procedure, every 15 minutes over the next 45 minutes, then every 30 minutes during the remaining 1.5 hours of the 4-hour study period. At the end of the 4-hour study period, the patient and physician provided global assessment of the effectiveness and tolerability of the study medication.

[0228] The Intent-to-Treat (ITT) population included randomized patients who received study medication. The analyses of the primary and secondary efficacy endpoints included data from all patients who received treatment and completed the 4-hour study period.
[0229] Safety monitoring was conducted throughout the study. Assessments of safety included measurements of heart rate, blood pressure and oxygen saturation. No adverse events were reported from the time of informed consent until the completion of the study.

[0230] The primary efficacy variable was the mean SRS-4 or the summed (cumulative) RASS score over the 4-hour study period. The RASS score was measured using the 10-point scale ranging from -5 (unarousable) to +4 (combative). The cumulative RASS scores over the 4-hour study (based on the Last Observation Carried Forward or “LOCF” method) were significantly lower for the group treated with a single tablet (NanoTab™) containing 15mcg sufentanil and 200mcg triazolam relative to those treated with placebo (p <0.001). The placebo group averaged positive cumulative (summed) RASS values once the procedure began, indicating patient anxiety and restlessness, while the patients treated with sufentanil/triazolam combination averaged negative cumulative RASS values in the mild sedation range (0 to -2) throughout the entire procedure. See Fig. 8. The sedation score for the group treated with the sufentanil/triazolam combination first separated statistically from the sedation score for the placebo treated group at 30 minutes (T_{onset}; p=0.046).

[0231] In the evaluation of procedural anxiety, a patient-reported, 11-point numerical scale (NRS) was used where 0 = no anxiety and 10 = worst possible anxiety. The summed (cumulative) anxiety score over the 4 hour study period was significantly lower for the group treated with a 15mcg sufentanil/200mcg triazolam tablet relative to the group treated with placebo (p=0.004; Fig. 9), and a separation from placebo was seen as early as 15 minutes post-dosing (p=0.034), indicating a rapid time of onset.

[0232] In the evaluation of pain intensity, a patient-reported, 11-point numerical rating scale (NRS), was used where 0 = no pain, and 10 = worst possible pain. The summed (cumulative) pain score over the 4 hour study period was lower for the group treated with a 15mcg sufentanil/200mcg triazolam tablet relative to those treated with placebo (median values of 13 versus 23 in the active and placebo groups, respectively), (p=0.09, based on non-parametric analysis; Fig. 10).

[0233] Patient and physician global assessments of efficacy and tolerability of the study drug were also evaluated in a blinded fashion. A five-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent) was used for this evaluation. The patient and physician global evaluations of efficacy and tolerability were both statistically significantly higher in the group treated with a 15mcg sufentanil/200mcg triazolam versus the group treated with placebo. A physician global efficacy and tolerability rating of very good or excellent was reported for 62% of patients treated with the sufentanil/triazolam combination as compared to 5% for the placebo group (p=<0.001). A patient global efficacy and tolerability rating of
very good or excellent was reported for 71% of patients treated with the sufentanil/triazolam combination as compared to 37% for the placebo group (p=0.028).

[0234] The time to readiness for discharge from the clinic was evaluated based on the total modified Aldrete score ≥ 8 post-procedure. The modified Aldrete score (10-point scale assessing readiness for discharge was also assessed every 30 minutes starting 2 hours after study drug dosing. The modified Aldrete score card consists of 5 items (as shown in Table 15). Each item has a score of 0, 1 or 2 and the total modified Aldrete score ranges from 0 to 10. All patients were ready for discharge from the physician’s office to home at all time points beginning at the first assessment, which was 2 hours after dosing and 1.25 hours after the start of the procedure (based on a modified Aldrete score ≥ 8).

[0235] An ANOVA model was used for the analysis of the primary and secondary efficacy measurements. The least squares mean of each treatment and its 95% confidence interval (CI) was calculated and the 95% CI of the difference between the results for patients treated with the sufentanil/triazolam combination as compared to those who received placebo treatment was used to determine if the results obtained for the respective groups were statistically significant.

[0236] Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those skilled in the art that certain changes and modifications may be practiced. Various aspects of the invention have been achieved by a series of experiments, some of which are described by way of the following non-limiting examples. Therefore, the description and examples should not be construed as limiting the scope of the invention, which is delineated by the appended description of exemplary embodiments.
IT IS CLAIMED

1. A dosage form for oral transmucosal administration to an alert, awake, subject prior to a medical or dental procedure, comprising:

   a single bioadhesive tablet having a mass of from about 5mg to about 25mg or a volume of from about 5mcl to about 25mcl, said tablet comprising the combination of sufentanil and triazolam, wherein at a specific time following said administering, the cumulative RASS sedation score is significantly lower for subjects who were administered a sufentanil/triazolam tablet as compared to subjects who were administered a placebo tablet.

2. The bioadhesive tablet according to claim 1, wherein said tablet has a mass of from about 2mg to about 10mg or a volume of from about 2mcl to about 10mcl.

3. The bioadhesive tablet according to claim 1 or 2, wherein said tablet has a thickness of from about 0.7mm to about 1.0mm or from about 0.75mm to about 0.95mm.

4. The bioadhesive tablet according to any one of claims 1 to 3, wherein said tablet has a diameter of from about 2.5mm to about 4.0mm, or from about 3.0mm to about 3.5mm.

5. The bioadhesive tablet according to any one of claims 1 to 4, wherein said tablet comprises from about 4mcg to about 50mcg of sufentanil.

6. The bioadhesive tablet according to any one of claims 1 to 4, wherein said tablet comprises from about 10mcg to about 20mcg of sufentanil.

7. The bioadhesive tablet according to any one of claims 1 to 6, wherein said tablet comprises from about 100mcg to about 500mcg of triazolam.

8. The bioadhesive tablet according to any one of claims 1 to 6, wherein said tablet comprises from about 150mcg to about 300mcg of triazolam.

9. The bioadhesive tablet according to any one of claims 1 to 8, wherein said oral transmucosal administration is sublingual administration.

10. The bioadhesive tablet according to any one of claims 1 to 9, wherein said tablet exhibits an attachment force to a porcine mucosa substrate that of from about 0.03 to 0.18 N/cm².

11. The bioadhesive tablet according to any one of claims 1 to 10, wherein said tablet does not 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.
12. A single dose applicator (SDA) comprising a bioadhesive tablet according to any one of claims 1 to 11.

13. A bioadhesive tablet according to any one of claims 1-11, for use in procedural sedation, anxiolysis and analgesia of a subject during a diagnostic or therapeutic medical or dental procedure.

14. A handheld dispensing device for placement of a tablet according to any one of Claims 1-11, in the sublingual space of a subject.

15. The use of a tablet according to any one of claims 1 to 11, for the preparation of a medicament for procedural sedation, anxiolysis and analgesia of a subject during a diagnostic or therapeutic medical or dental procedure.

16. The use according to claim 15, wherein at a specific time following said administering, the cumulative RASS sedation score is significantly lower for subjects who were administered a sufentanil/triazolam tablet as compared to subjects who were administered a placebo tablet.

17. The use according to claim 15, wherein the onset of sedation is evident 30 minutes following said administering.

18. The use according to claim 15, wherein at a specific time following said administering, the cumulative NRS anxiety score is significantly lower for subjects who were administered a sufentanil/triazolam tablet as compared to subjects who were administered a placebo tablet.

19. The use according to claim 15, wherein the onset of anxiolysis is evident 15 minutes following said administering.

20. The use according to claim 15, wherein all patients have a modified Aldrete score of greater than or equal to 8 beginning 2 hours or less following said administering.

21. The use according to claim 15, wherein the duration of sedation is 4 hours or less following said administering.

22. The use of a single dose applicator (SDA) comprising a bioadhesive tablet according to any one of claims 1 to 11, wherein said SDA is packaged in a primary package comprising an oxygen scavenger.
FIG. 7A
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/485 A61K31/5517 A61P25/04
ADD.

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)
A61K A61P

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2009/021106 A1 (ACELRX PHARMACEUTICALS INC [US]; PALMER PAMELA [US]; TZANNIS STELIS [ ] 12 February 2009 (2009-02-12) page 3 - page 38; claims 1-40</td>
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<td>X</td>
<td>US 2009/010992 A1 (PALMER PAMELA [US] ET AL) 8 January 2009 (2009-01-08) page 1 - page 8; claims 78-102; examples 3,4</td>
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1-22

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

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

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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
25 March 2011

Date of mailing of the international search report
04/04/2011

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Kling, Isabelle

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>&quot;AcelRx Pharmaceuticals Reports Positive Results from a Clinical Trial of Sublingual Sufentanil/Triazolam NanoTab™ Combination (ARX03) in Treating Procedural Pain and Anxiety&quot;, QCERLX PHARMACEUTICALS, 12 January 2009 (2009-01-12), pages 1-2, XP007914719, the whole document</td>
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