(12) STANDARD PATENT (11) Application No. **AU 2017312811 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Liquid naloxone spray

(51) International Patent Classification(s)
A61K 31/485 (2006.01) ***A61K 47/18*** (2006.01)
A61K 9/00 (2006.01)

(21) Application No: **2017312811** (22) Date of Filing: **2017.08.10**

(87) WIPO No: **WO18/034920**

(30) Priority Data

(31) Number	(32) Date	(33) Country
15/601,331	**2017.05.22**	**US**
15/238,909	**2016.08.17**	**US**

(43) Publication Date: **2018.02.22**
(44) Accepted Journal Date: **2023.03.16**

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(56) Related Art
WO 2016/007245 A1
US 2016/0199294 A1
WO 2015/136373 A1

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2018 (22.02.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/034920 A1

(51) International Patent Classification:
A61K 31/485 (2006.01) *A61K 9/00* (2006.01)
A61K 47/18 (2017.01)

(21) International Application Number:
PCT/US2017/046198

(22) International Filing Date:
10 August 2017 (10.08.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15/238,909 17 August 2016 (17.08.2016) US
15/601,331 22 May 2017 (22.05.2017) US

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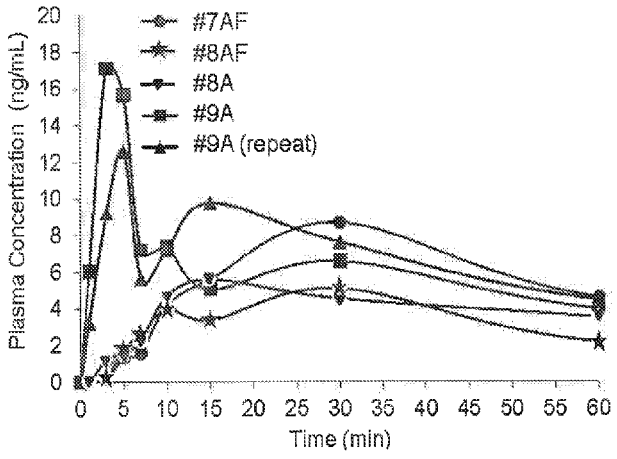
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

(54) Title: LIQUID NALOXONE SPRAY

FIG. 1



(57) Abstract: The invention provides stable liquid formulations containing naloxone, a pharmaceutically acceptable salt, or a derivative thereof. The invention further provides methods for treating opioid dependence, opioid overdose, and congenital insensitivity to pain with anhidrosis by administering the liquid formulations of the present invention intranasally to a patient in need thereof. Further, the invention provides a method of treating opioid dependence-, opioid overdose, and congenital insensitivity to pain with anhidrosis by administering intranasally the naloxone formulations of the present invention.

WO 2018/034920 A1

[Continued on next page]

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

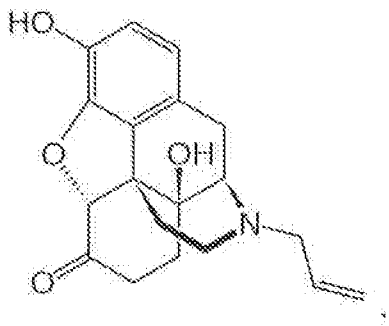
LIQUID NALOXONE SPRAY

Field of the Invention

[0001] The invention is directed to liquid spray formulations containing naloxone, a pharmaceutically acceptable salt thereof, or a derivative thereof. The invention is further directed to methods of treating opioid dependence, opioid overdose, and congenital insensitivity to pain with anhidrosis by administering liquid spray formulations containing naloxone, pharmaceutically acceptable salts thereof, or derivatives thereof to a patient in need thereof.

Background of the Invention

[0002] Naloxone has the following structure and is synthesized from thebaine:



[0003] Naloxone is most commonly used to treat patients suffering from opioid dependence or overdose because it is a competitive μ-opioid antagonist that blocks the effects of opioids. Naloxone is currently available in Suboxone® (Suboxone is a registered trademark of Reckitt Benckiser Healthcare (UK) Limited) as tablet or sublingual film strip formulations. Suboxone® contains buprenorphine and naloxone in a 4:1 ratio. Naloxone is also available as an aqueous nasal spray under the trademark Narcan® (Narcan is a registered trademark of Adapt Pharma Operations Limited LLC, "Adapt Pharma"), which contains 4.42% w/w naloxone hydrochloride dihydrate, 0.01% w/w benzalkonium chloride ("BKC") as a preservative, 0.74% w/w sodium chloride as an isotonicity agent and 0.2 % w/w edetate disodium dihydrate ("EDTA") as a stabilizing agent. Adapt Pharma has U.S. Patent Nos. 9,211,253, 9,468,747 and 9,561,117 listed in the U.S. Food and Drug Administration's Orange Book for Narcan® 4 milligram nasal spray. Each of these patents discloses and claims naloxone formulations containing an isotonicity agent. Additional Adapt Pharma also has U.S. Patent No. 9,480,644 listed in the Orange Book for a 2-milligram naloxone nasal spray, which discloses and claims naloxone formulations that also contain an isotonicity agent. U.S. Patent Nos. 9,192,570 and 9,289,425 assigned to Indivior, Inc

disclose and claim naloxone nasal sprays that contain both citric acid as a buffer and benzyl alcohol as an anti-microbial agent.

[0004] One issue with other opioid dependence treatments is that they can become addictive. Naloxone, however, does not appear to be addictive and patients do not build up a tolerance.

[0005] Naloxone has also been used as a treatment for cognitive insensitivity to pain with anhidrosis. Insensitivity to pain with cognitive anhidrosis is a disorder in which the patient cannot feel pain.

[0006] Naloxone may be administered orally, intravenously, by injection or via the nasal mucosa. Naloxone has a low mean serum half-life when administered parentally. The quick metabolism may require repeat dosing or cause patient discomfort between doses. Enteral administration has low bioavailability due to hepatic first pass metabolism.

[0007] Accordingly, while there are some naloxone formulations currently available, there is a need for safe and effective liquid spray formulations that are stable including physically and chemically stable and contain naloxone, pharmaceutically acceptable salts or a derivative thereof.

Summary of the Invention

[0008] The liquid spray formulations of the present invention are for intranasal and/or sublingual administration.

[0009] In one aspect, the invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt thereof, or a derivative thereof, water, and a chelating agent, wherein the formulation does not contain an isotonicity agent or a buffer.

[00010] In another aspect, the stable liquid spray formulations of the present invention are suitable for intranasal administration.

[00011] In another aspect, the liquid spray formulations of the present invention do not contain an isotonicity agent.

[00012] In another aspect, the liquid spray formulations of the present invention do not contain sodium chloride.

[00013] In another aspect, the liquid spray formulations of the present invention do not contain benzalkonium chloride.

[00014] In another aspect, the liquid spray formulations of the present invention do not contain a buffer.

[00015] In another aspect, the liquid spray formulations of the present invention do not contain citric acid.

[00016] In another aspect, the liquid spray formulations of the present invention do not contain an alcohol.

[00017] In yet another aspect, the invention is directed to methods for treating opioid dependence comprising administering the liquid spray formulations of the present invention to a patient in need of opioid dependence treatment, wherein administration occurs either intranasally, sublingually or intranasally and sublingually, wherein if administration occurs intranasally and sublingually administration occurs simultaneously, sequentially or concomitantly.

[00018] In a further aspect, the invention is directed to methods for treating opioid overdose comprising administering the liquid spray formulations of the present invention to a patient in need of opioid overdose treatment, wherein administration occurs either intranasally, sublingually or intranasally and sublingually, wherein if administration occurs intranasally and sublingually administration occurs simultaneously, sequentially or concomitantly.

[00019] In an additional aspect, the invention is directed to methods for treating congenital insensitivity to pain with anhidrosis comprising administering the liquid spray formulations of the present invention to a patient in need of treatment for congenital insensitivity to pain with anhidrosis, wherein administration occurs either intranasally, sublingually or intranasally and sublingually, wherein if administration occurs intranasally and sublingually administration occurs simultaneously, sequentially or concomitantly.

Brief Description of the Figures

[00020] Figure 1. Mean plasma concentration of Formulations #9A, #9A repeat #8A, #8AF and #7AF normalized to a 4-mg dosage. Values based on a geometric mean.

Detailed Description of the Invention

[00021] Applicants have created new liquid naloxone formulations that are stable and comfortable to the user despite containing no buffer or isotonicity agent. The formulations that do not contain an alcohol are especially suitable for administration to children. Further, the alcohol-free formulations may be suitable for patients in recovery from alcohol addiction.

[00022] In a preferred embodiment, the liquid naloxone formulation is a spray. In yet a more preferred embodiment, the liquid naloxone formulation is in a simple solution form. As used herein, the term "simple solution" refers to a solution in which the solute(s) has fully dissolved in the solvent.

[00023] As used herein, the term "stable" includes but is not limited physical and chemical stability.

[00024] In one embodiment, the present invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt thereof, or a derivative thereof, water, and a chelating agent, wherein the formulation does not contain an isotonicity agent or a buffer.

[00025] In another embodiment, the liquid spray formulations of the present invention is for intranasal administration.

[00026] In another embodiment, the liquid spray formulations of the present invention do not contain sodium chloride, citric acid, benzyl alcohol, or benzalkonium chloride.

[00027] In another embodiment, the present invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt thereof, or a derivative thereof, a co-solvent selected from the group consisting of an alcohol, a glycol, and a combination thereof water, and edetate disodium dihydrate as a chelating agent, wherein the formulation does not contain an isotonicity agent or a buffer.

[00028] The liquid spray formulation of claim 4, wherein the alcohol is ethanol (dehydrated alcohol) and the glycol is propylene glycol.

[00029] In another embodiment, the liquid spray formulations of the present invention have a pH from about 3.0 to about 6.0, more preferably about 4.5.

[00030] In another embodiment, the present invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt thereof, or a derivative thereof, water, a chelating agent, and an antioxidant, preferably sodium ascorbate, wherein the formulation does not contain an isotonicity agent or a buffer.

[00031] In another embodiment, the present invention is directed to liquid spray formulations comprising:

from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, preferably from about 2% to about 10% w/w;

from about 10% to about 99% w/w water;

from about 0.0001% to 0.05% w/w of a chelating agent, preferably edetate disodium dehydrate,

wherein the formulation does not contain an isotonicity agent or a buffer.

[00032] In another embodiment, the liquid spray formulations of the present invention do not contain an alcohol.

[00033] In another embodiment, the present invention is directed to liquid spray formulations comprising:

from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, preferably from about 2% to about 10% w/w;

from about 80% to about 98% w/w water;

from about 0.0001% to 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate,

wherein the formulation does not contain an isotonicity agent, a buffer or a co-solvent.

[00034] In another embodiment, the present invention is directed to liquid spray formulations comprising:

from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, preferably from about 2% to about 10% w/w;

from about 35% to about 85% w/w water;

from about 0.0001% to 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate; and

from about 2% to about 90% w/w of a co-solvent selected from the group consisting of ethanol, propylene glycol and a combination thereof, preferably ethanol at a concentration from about 2% to about 50% w/w, or a combination of propylene glycol at a concentration from about 5% to about 10% w/w and ethanol at a concentration from about 2% to about 50% w/w or a combination of ethanol at about 20 % w/w and propylene glycol at about 5 % w/w or a combination of ethanol at about 50 % w/w and propylene glycol at about 5 % w/w,

wherein the formulation does not contain an isotonicity agent or a buffer.

[00035] In another embodiment, the present invention is directed to liquid spray formulations comprising

from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, preferably from about 2% to about 10% w/w;

from about 35% to about 85% w/w water;

from about 0.0001% to 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate; and

propylene glycol as a co-solvent at a concentration from about 5% to about 10% w/w,

wherein the formulation does not contain an isotonicity agent, a buffer or an alcohol.

[00036] In another embodiment, the liquid spray formulations of the present invention comprise a preservative selected from the group consisting of butyl paraben, methyl paraben, ethyl paraben, propyl paraben, sodium benzoate, benzoic acid and a combination thereof, preferably from about 0.005% to about 0.2% w/w methyl paraben and more preferably 0.1% w/w methyl paraben.

[00037] In another embodiment, the liquid spray formulations of the present invention do not contain a preservative.

[00038] In another embodiment, the liquid spray formulations of the present invention are administered in a nasal spray device.

[00039] In another embodiment, the liquid spray formulations of the present invention are administered in a nasal spray device that is capable of producing a droplet size distribution wherein greater than 90% of the composition particles are greater than 10 microns in diameter during administration or a droplet size distribution wherein:

the mean Dv(10) is from about 5 to about 40 microns during administration;

the mean Dv(50) is from about 20 to about 80 microns during administration; and

the mean Dv(90) is from about 50 to about 700 microns during administration, or

a spray plume that has an ovality ratio of from about 1.0 to 2.5, or a spray plume width from about 25 to about 70 millimeters during administration and a spray plume angle from about 15 to about 70 degrees during administration.

[00040] In another embodiment, the liquid spray formulations of the present invention are administered in a nasal spray device that has a single reservoir comprising about 125 µl to 127 µL of the formulation.

[00041] In another embodiment, the liquid spray formulations of the present invention are administered in a nasal spray device that delivers about 100 µL of the formulation by a single actuation.

Formulations with An Alcohol

[00042] In one embodiment, the invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt or a derivative thereof, water as a solvent, a co-solvent and an antioxidant or chelating agent. In a preferred embodiment, naloxone is in salt form.

[00043] In another embodiment, the invention is directed to liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt or a derivative thereof, water as a solvent, a co-solvent and a permeation enhancer or chelating agent. In a preferred embodiment, naloxone is in salt form.

[00044] The co-solvent may be an alcohol, a glycol, or a mixture thereof. The formulations preferably contain from about 5 to about 90% w/w co-solvent. More preferably the formulations contain from about 10 % to about 70 % w/w from about 10 % to about 55% w/w or from about 40% to about 65% w/w or from about 45% to about 60 % w/w or from about 45 % to about 55 % w/w co-solvent. In a preferred embodiment, the formulations contain about 10% w/w, about 12% w/w, about 25% w/w or about 55 % w/w co-solvent. In a more preferred embodiment, the formulations contain about 10 % w/w ethanol as a co-solvent or about 2% to about 45% ethanol as a co-solvent, or about 10% to about 20% ethanol as a co-solvent, or about 10 % w/w propylene glycol and about 2% w/w ethanol as a co-solvent or about 20% w/w ethanol and about 5% w/w propylene glycol as a co-solvent or about 50% w/w ethanol and 5 % w/w propylene glycol as co-solvent.

[00045] Suitable antioxidants include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), methionine, sodium ascorbate, sodium thiosulfate, thioglycerol, ascorbic acid, ascorbyl palmitate, propyl gallate, dL-alpha-tocopherol, sodium sulfite, sodium metabisulfite, sodium bisulfite cysteine hydrochloride, glutathione and a combination thereof. Presently preferred antioxidants include BHA, BHT, sodium thiosulfate, dL alpha-tocopherol (Vitamin E) and sodium ascorbate.

[00046] In a preferred embodiment, the amount of antioxidant included in the formulation is from about 0.001% to about 0.5% w/w.

[00047] In another preferred embodiment, the amount of antioxidant is about 0.01% w/w of BHA.

[00048] In an alternative embodiment, the antioxidant is a mixture of about 0.01% w/w of BHA and about 0.005% w/w of BHT.

[00049] In yet another embodiment, the antioxidant is about 0.01% w/w of sodium thiosulfate.

[00050] In a preferred embodiment, the antioxidant is about 0.3 % w/w dL alpha-tocopherol.

[00051] In a most preferred embodiment, the antioxidant is about 0.02% w/w of sodium ascorbate.

[00052] In the present formulations, water is used as the solvent. Preferably, formulations of the present invention contain from about 10% to about 99% w/w water, more preferably, from about 10% to about 98% w/w water, more preferably from about 35% to about 85% w/w, more preferably from about 35% to about 84% w/w and more preferably about 29.8%, 33.2%, 31.32 %, 34.5%, or 35.5%,37.5%, 65.2%, 71.1%, 79.3%, 81.1%, or 83.9% w/w water. Hydro-alcohol formulations of the present invention preferably contain from about 40 % to about 90% w/w water, more preferably, from about 50 % to about 90 % w/w water. In preferred embodiments, hydro-alcoholic formulations contain about from about 30 % to about 80 % w/w water.

[00053] In a preferred embodiment, the formulations of the present invention have a pH of from about 2 to about 7. In a more preferred embodiment, the formulations of the present invention have a pH of from about 3 to about 6, even more preferably from about 3 to about 4.5.

[00054] In a most preferred embodiment, the formulations of the present invention have a pH of about 3.0 ± 0.2 or 3.5 ± 0.2 or 4.0 ± 0.2 or 4.5 ± 0.2.

[00055] In another preferred embodiment, the formulations contain ethanol as the co-solvent.

[00056] In yet another preferred embodiment, the formulations contain propylene glycol as the co-solvent.

[00057] In a more preferred embodiment, the formulations contain a mixture of ethanol and propylene glycol as the co-solvent.

[00058] In another embodiment, the formulations of the present invention contain a chelating agent. In a preferred embodiment, the chelating agent is edetate disodium dihydrate, (also known as edetate disodium or ethylenediaminetetraacetic acid disodium salt or EDTA)

preferably at a concentration from about 0.0001% to about 0.5% w/w and more preferably from about 0.001% to about 0.05% w/w and even more preferably from about 0.005% to about 0.05% w/w and even more preferably from about 0.001% to about 0.02% w/w.

[00059] In a preferred embodiment, the present invention is directed to liquid spray formulations comprising naloxone, a pharmaceutically acceptable salt or a derivative thereof, in an amount from about 1% to about 16 % w/w, water in an amount from about 10% to about 95% w/w, a co-solvent in an amount from about 2% to about 90% w/w, and a chelating agent in an amount from about 0.0001% to 0.05% w/w.

[00060] In a preferred embodiment, the present invention is directed to liquid spray formulations comprising naloxone, a pharmaceutically acceptable salt or a derivative thereof, in an amount from about 1% to about 20 % w/w, water in an amount from about 30 % to about 99% w/w, a co-solvent in an amount from about 2% to about 90% w/w, and a chelating agent in an amount from about 0.0005% to 0.05% w/w.

[00061] In a preferred embodiment, the liquid spray formulations of the present invention further comprise a permeation enhancer selected from the group consisting of menthol in an amount from about 0.001% to about 10.0% w/w, caprylic acid in an amount from about 0.1% to 10% w/w, benzalkonium chloride ("BKC") in an amount from about 0.001% to 10 % w/w and a combination thereof.

[00062] In another preferred embodiment, the formulation contains edetate disodium dihydrate as the chelating agent at 0.001 % w/w or 0.05 % w/w.

[00063] In yet another embodiment, the present invention is directed to naloxone, a pharmaceutically acceptable salt or a derivative thereof, in an amount from about 24% to about 16% w/w, water in an amount from about 20% to about 85% w/w, a co-solvent in an amount from about 5% to about 55% w/w, and a chelating agent in an amount from about 0.0001% to 0.05%. In a preferred embodiment of the formulation, naloxone is a salt. In yet another preferred embodiment, the formulation further comprises a permeation enhancer selected from menthol in an amount from about 0.01% to about 10 % w/w, caprylic acid in an amount from about 0.1% to 10% w/w, BKC in an amount from about 0.001% to 10 % w/w, and a combination thereof.

[00064] In another preferred embodiment, the chelating agent is edetate disodium dihydrate, preferably at a concentration from about 0.001% to about 0.5% w/w.

[00065] In yet another embodiment, the present invention is directed to naloxone, a pharmaceutically acceptable salt or a derivative thereof, in an amount from about 1% to about 10% w/w, water in an amount from about 30% to about 85% w/w, a co-solvent in an amount from about 7% to about 55% w/w, and a chelating agent in an amount from about 0.0001% to 0.05%, In a preferred embodiment of the formulation, naloxone is a salt. In another preferred embodiment, the formulation further comprises a preservative, preferably from about 0.01% to about 0.5% w/w. In a more preferred embodiment the chelating agent is edetate disodium dihydrate. In another preferred embodiment, the preservative is methyl paraben.

[00066] In another embodiment, formulations of the present invention do not contain a preservative.

[00067] In a further embodiment, the present invention is directed to naloxone, a pharmaceutically acceptable salt or a derivative thereof in an amount from about 1% to about 10% w/w, water in an amount from about 35% to about 85% w/w, a co-solvent in an amount from about 7% to about 55% w/w, and a chelating agent in an amount from about 0.001% to about 0.02% w/w. In a preferred embodiment of this formulation, naloxone is a salt. In another preferred embodiment, the formulation also contains a preservative in an amount from about 0.05% to about 0.2% w/w. In yet another preferred embodiment, the formulation contains edetate disodium dihydrate as the chelating agent.

[00068] In a further embodiment, the present invention is directed to liquid spray formulations comprising naloxone hydrochloride dihydrate from about 1% to about 10% w/w, water from about 35% to about 84% w/w, ethanol from about 2% to about 50% w/w, EDTA from about 0.001% to about 0.02% w/w and optionally propylene glycol from about 5% to about 10% w/w and optionally, methyl paraben at about 0.1% w/w.

[00069] In another embodiment, the liquid spray formulations of the present invention do not contain an isotonicity agent.

[00070] In another embodiment, the liquid spray formulations of the present invention do not contain sodium chloride.

[00071] In another embodiment, the liquid spray formulations of the present invention do not contain benzalkonium chloride.

[00072] In another embodiment, the liquid spray formulations of the present invention do not contain a buffer.

[00073] In another embodiment, the liquid spray formulations of the present invention do not contain citric acid.

[00074] In some embodiments, the formulations of the present invention contain citric acid or sodium hydroxide or hydrochloric acid solution as a pH adjustor.

[00075] Pharmaceutically acceptable salts that can be used in accordance with the current invention include but are not limited to hydrochloride, hydrochloride dihydrate, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

[00076] In preferred embodiments, the pharmaceutically acceptable salt is hydrochloride.

[00077] Derivatives of naloxone that can be used in accordance with the current invention include but are not limited to 3-O-acyl, phenylhydrazone, and methiodide derivatives.

[00078] The solvent used with the present invention is United States Pharmacopeia ("USP") purified water.

[00079] Co-solvents that can be used in accordance with the current invention are alcohols, and glycols or a mixture thereof.

[00080] Alcohols that can be used in accordance with the current invention include but are not limited to methanol, ethanol (also known as dehydrated alcohol), propyl alcohol, butyl alcohol and the like, but do not include benzyl alcohol.

[00081] In formulations of the current invention that do not contain an alcohol, the term "alcohol" includes all alcohols including benzyl alcohol.

[00082] Glycols that can be used in accordance with the current invention include but are not limited to propylene glycol, polypropylene glycol, and butylene glycol and polyethylene glycols such as PEG 200, PEG 300, PEG 400 and PEG 600 and the like.

[00083] In preferred embodiments, the co-solvent is ethanol or propylene glycol or a mixture thereof.

[00084] In another preferred embodiment, the amount of co-solvent included in the formulation is from about 2% to about 90% w/w. In other more preferred embodiments, the amount of co-solvent included in the formulation is about 5% or about 10% w/w propylene glycol.

In other more preferred embodiments, the amount of co-solvent included in the formulation is about 2%, about 10%, about 20% or about 50% w/w ethanol.

[00085] In other more preferred embodiments the co-solvent is a mixture of propylene glycol at about 5% w/w and ethanol at about 50% w/w, or a mixture of propylene glycol at about 5% w/w and ethanol at about 20% w/w, or a mixture of propylene glycol at about 10% w/w and ethanol at about 10% w/w, or propylene glycol at about 10% w/w and ethanol at about 2% w/w or 10% w/w ethanol.

[00086] Solubilizers that can be used in accordance with the current invention are hydroxypropyl beta-cyclodextrin ("HPβCD") and sulfobutylether cyclodextrin or a mixture thereof.

[00087] In preferred embodiments, the solubilizer is HPβCD.

[00088] In more preferred embodiments the amount of HPβCD is about 30% w/w.

[00089] Permeation enhancers that can be used in accordance with the current invention include but are not limited to menthol, limonene, carvone, methyl chitosan, polysorbates including Tween® 80 (polysorbate 80; Tween is a registered trademark of Uniqema Americas, LLC), sodium lauryl sulfate, glyceryl oleate, caprylic acid, pelargonic acid, capric acid, undecylenic acid, lauric acid, myristic acid, palmitic acid, oleic acid, stearic acid, linolenic acid, arachidonic acid, benzalkonium chloride (BKC), cetylpyridium chloride, edetate disodium dihydrate, sodium desoxycholate, sodium deoxyglycolate, sodium glycocholate, sodium caprate, sodium taurocholate, sodium hydroxybenzoyal amino caprylate, dodecyl dimethyl aminopropionate, L-lysine, glycerol oleate, glyceryl monostearate, citric acid, and peppermint oil. Preferably the permeation enhancer is selected from the group consisting of menthol, benzalkonium chloride, edetate disodium dihydrate, caprylic acid, and a combination thereof.

[00090] In preferred embodiments, the amount of permeation enhancer is from about 0.001% to about 10 % w/w. In a more preferred embodiment, the formulations contain from about 0.01% to about 5.0% w/w permeation enhancer. In a preferred embodiment, the formulations contain from about 0.02% to about 2.0 % w/w permeation enhancer. In a most preferred embodiment, the formulations contain 2.0 % w/w permeation enhancer.

[00091] In preferred embodiment, the permeation enhancer is L-menthol, caprylic acid, BKC, edetate disodium dihydrate (EDTA) or combination thereof, the preferred amount of L-menthol is from about 0.001% to about 10.0 % w/w, caprylic acid is from about 0.1% to about

10% w/w, BKC is from about 0.001 to about 10 % w/w, and EDTA is from about 0.0005% to 0.1% w/w. In a more preferred embodiment, the formulations contain from about 0.01% to about 0.5% w/w L-menthol, about 0.5% to about 5% w/w caprylic acid, about 0.005 to about 0.1% w/w BKC, about 0.005% to about 0.05% w/w EDTA, or a combination thereof. In an even more preferred embodiment, the formulations contain from about 0.02% to about 0.5% w/w L-menthol, about 1% to about 2% w/w caprylic acid, about 0.01 to about 0.1% w/w BKC, about 0.005 to about 0.05 % w/w EDTA or a combination thereof. In a most preferred embodiment, the formulations contain about 0.5 % w/w L-menthol, about 2% w/w caprylic acid, about 0.01 % w/w BKC, about 0.005 % edetate disodium dihydrate, or a combination thereof.

[00092] In yet another embodiment, the permeation enhancer is about 0.5% w/w of menthol.

[00093] In yet another preferred embodiment, the permeation enhancer is about 2.0 % w/w caprylic acid.

[00094] In a most preferred embodiment, the permeation enhancer is about 0.01% w/w of benzalkonium chloride (BKC).

[00095] In a most preferred embodiment, the permeation enhancer is about 0.005%, 0.01%, 0.015% or 0.02% w/w of edetate disodium dihydrate (EDTA).

[00096] In a further most preferred embodiment, the permeation enhancer is a combination of 2.0 % w/w caprylic acid and 0.01% w/w of benzalkonium chloride.

[00097] Formulations of the present invention may have a pH range from about 2.0 to about 7.0, preferably from about 3 to about 6 and more preferably from about 3 to about 4.5 pH, most preferably 3 or 4.5 ± 01, pH adjustors that can be used in accordance with the present invention include but are not limited to citric acid and sodium hydroxide. In preferred embodiments, the amount of sodium hydroxide or citric acid is from about 0.002% to about 0.03% w/w. In more preferred embodiments, the amount of sodium hydroxide is about 0.015% w/w. In other more preferred embodiments, the amount of sodium hydroxide is about 0.012% w/w.

[00098] In a further embodiment, the formulation contains a permeation enhancer, a sweetener, a sweetness enhancer, a pH modifier, a flavoring agent, a preservative, or a combination thereof.

[00099] In a preferred embodiment, the formulations contain a sweetener. In a more preferred embodiment, the sweetener is selected from the group consisting of sucralose, aspartame, saccharin, dextrose, mannitol, glycerin, and xylitol. In a preferred embodiment, the formulations

contain from about 0.001% w/w to about 2% w/w of sweetener. In a more preferred embodiment, the formulations contain from about 0.05% w/w to about 1% w/w of the sweetener. In a most preferred embodiment, the formulations contain sucralose as sweetener at about 0.8% w/w.

[000100] In another embodiment, the formulations contain a flavoring agent. In a preferred embodiment, the formulations contain a flavoring agent selected from the group consisting of peppermint oil, menthol, spearmint oil, citrus oil, cinnamon oil, strawberry flavor, cherry flavor, raspberry flavor, orange oil, and a combination thereof. Other appropriate flavoring agents known by those of skill in art could also be added to formulations of the present invention. In a preferred embodiment, the formulations contain from about 0.001% w/w to about 1% w/w of the flavoring agent. In a more preferred embodiment, the formulations contain from about 0.005% w/w to about 0.5% w/w of the flavoring agent. In a most preferred embodiment, the formulations contain strawberry as flavoring agent at about 0.08% w/w.

[000101] In yet another embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(10) is from about 11 to about 35 microns during administration.

[000102] In a further embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(50) is from about 25 to about 55 microns during administration.

[000103] In yet another embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(90) is from about 75 to about 600 microns during administration. Preferably, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(90) is from about 85 to about 500 microns during administration.

Formulations Without An Alcohol

[000104] In a further embodiment, the invention is directed to stable liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt or a derivative thereof, water, a chelating agent and optionally, a co-solvent and the formulations do not contain an alcohol.

[000105] In a further embodiment, the invention is directed to stable liquid spray formulations comprising an effective amount of naloxone, a pharmaceutically acceptable salt or a

derivative thereof, water, and a permeation enhancer or a chelating agent, and optionally, a co-solvent and the formulations do not contain an alcohol.

[000106] In another embodiment, the stable liquid spray formulations of the present invention contain a preservative, preferably from about 0.01% to about 0.5% w/w. In a more preferred embodiment, the preservative is methyl paraben.

[000107] In another embodiment, the stable liquid spray formulations of the present invention do not contain a preservative.

[000108] In another embodiment, the stable liquid spray formulations of the present invention are suitable for nasal administration.

[000109] In another embodiment, the liquid spray formulations of the present invention do not contain an isotonicity agent.

[000110] In another embodiment, the liquid spray formulations of the present invention do not contain sodium chloride.

[000111] In another embodiment, the liquid spray formulations of the present invention do not contain benzalkonium chloride.

[000112] In another embodiment, the liquid spray formulations of the present invention do not contain a buffer.

[000113] In another embodiment, the liquid spray formulations of the present invention do not contain citric acid.

[000114] In a preferred embodiment, the liquid spray formulation comprises from about 0.01% w/w to about 20 % w/w naloxone or a salt or derivative thereof. In a more preferred embodiment, the liquid spray formulation comprises from about 1% w/w to about 12% w/w naloxone or a salt or derivative thereof. In an even more preferred embodiment, the formulations contain from about 2% w/w to about 10% w/w naloxone or a salt or derivative thereof.

[000115] In another embodiment, the formulations contain from about 20% w/w to about 99% water. In a preferred embodiment, the formulations contain from about 30% w/w to about 98% w/w water. In a more preferred embodiment, the formulations contain from about 80% w/w to about 98% w/w water. In a most preferred embodiment, the formulations contain from about 81% w/w to about 98% w/w water. Aqueous formulations of the present invention preferably contain from about 70% to about 99% w/w water, more preferably, from about 80% to about 99%

w/w water. In most preferred embodiments, aqueous formulations contain about from about 84% to about 98% w/w water.

[000116] In an embodiment, the formulations contain from about 5% w/w to about 50% w/w glycerol. In a preferred embodiment, the formulations contain from about 10% w/w to about 40% w/w glycerol. In a more preferred embodiment, the formulations contain from about 15% w/w to about 35% w/w glycerol.

[000117] In another embodiment, the formulations may contain from about 0.1% w/w to about 50% w/w polyethylene glycol 400. In a more preferred embodiment, the formulations contain from about 10% w/w to about 40% w/w polyethylene glycol 400.

[000118] In another embodiment, the formulations contain from about 0.1% w/w to about 50% w/w propylene glycol. In a more preferred embodiment, the formulations contain from about 10% w/w to about 40% w/w propylene glycol. In an even more preferred embodiment, the present invention contains from about 5% to about 10% w/w propylene glycol.

[000119] In another embodiment, the formulation contains a pharmaceutically acceptable salt of naloxone. In a preferred embodiment, the formulation contains a salt selected from the group consisting of hydrochloride, citrate, halide, phosphate, sulfate, acetate, ascorbate, maleate, succinate, carbonate, mesylate and lactate. One of skill in the art could use other pharmaceutically acceptable naloxone salts in the formulations of the present invention.

[000120] In a preferred embodiment, the antioxidant is selected from the group consisting of ascorbic acid, cysteine HCl monohydrate, citric acid, ethylenediamine tetra acetic acid (EDTA), methionine, sodium citrate, sodium ascorbate, sodium thiosulfate, sodium metabisulfite, sodium bisulfite, glutathione and thioglycerol. Other appropriate antioxidants known by those of skill in the art could also be added to formulations of the present invention.

[000121] In a preferred embodiment, the formulations contain from about 0.0001% w/w to about 0.5% w/w of the antioxidant. In a more preferred embodiment, the formulations may contain from about 0.005% w/w to about 0.2% w/w of the antioxidant. In a most preferred embodiment, the formulations contain 0.05%w/w or 0.02% w/w of the antioxidant.

[000122] In another embodiment, the formulations of the present invention contain a chelating agent. In a preferred embodiment, the chelating agent is edetate disodium dihydrate

[000123] In an embodiment, the formulations contain from about 0.0001% to about 0.5% w/w of the chelating agent. In a preferred embodiment, the formulations contain from about

0.001% to about 0.50% w/w of the chelating agent. In a more preferred embodiment, the formulations contain from about 0.005% to about 0.05% w/w of the chelating agent.

[000124] In a further embodiment, the formulation contains a permeation enhancer, a sweetener, a sweetness enhancer, a pH modifier, a flavoring agent, a preservative, or a combination thereof.

[000125] In another embodiment, the formulation contains a permeation enhancer. In a preferred embodiment, the permeation enhancer is selected from the group consisting of menthol, limonene, carvone, methyl chitosan, caprylic acid pelargonic acid, capric acid, undecylenic acid, lauric acid, myristic acid, palmitic acid, oleic acid, stearic acid, linolenic acid, arachidonic acid, polysorbates including Tween® 80, sodium edetate, benzalkonium chloride (BKC), cetylpyridinium chloride, sodium lauryl sulfate, citric acid, sodium desoxycholate, sodium deoxyglycolate, glyceryl oleate, glyceryl monostearate, Sodium hydroxybenzoyal amino caprylate, sodium caprate, dodecyl dimethyl aminopropionate, L-lysine, sodium glycocholate, citric acid, peppermint oil and a combination thereof. In a more preferred embodiment, the permeation enhancer is selected from the group consisting of polysorbates including Tween® 80, sodium edetate, benzalkonium chloride (BKC), cetylpyridinium chloride, sodium lauryl sulfate, citric acid, sodium desoxycholate, sodium deoxyglycolate, glyceryl oleate, glyceryl monostearate, L-lysine, sodium glycocholate, sodium taurocholate, citric acid, and a combination thereof. In an even more preferred embodiment, the permeation enhancer is selected from the group consisting of menthol, caprylic acid and BKC.

[000126] In preferred embodiments, the amount of permeation enhancer is from about 0.001% to about 10 % w/w. In a more preferred embodiment, the formulations contain from about 0.001% to about 2.5% w/w permeation enhancer. In a most preferred embodiment, the formulations contain from about 0.02% to about 2.0 % w/w permeation enhancer.

[000127] In a preferred embodiment, the permeation enhancer is menthol, caprylic acid, BKC or a combination thereof, the preferred amount of L-menthol is from about 0.001% to about 10 % w/w, caprylic acid is from about 0.1% to 10% w/w, BKC is from about 0.001 to 10% w/w. In a more preferred embodiment, the formulations contain from about 0.01% to about 0.5% w/w L-menthol, about 0.5% to 5% w/w caprylic acid, about 0.005 to 0.1% w/w BKC. In an even more preferred embodiment, the formulations contain from about 0.02% to about 0.5% w/w L-menthol, about 1% to 2% w/w caprylic acid, about 0.01 to 0.1% w/w BKC. In a most preferred embodiment,

the formulations contain about 0.5 % w/w L-menthol, about 2% w/w caprylic acid and about 0.005 w/w BKC.

[000128] In yet another embodiment, the permeation enhancer is about 0.5% w/w of menthol.

[000129] In yet another preferred embodiment, the permeation enhancer is about 2.0 % w/w caprylic acid.

[000130] In a most preferred embodiment, the permeation enhancer is about 0.01% w/w of benzalkonium chloride (BKC).

[000131] In a preferred embodiment, the formulations contain a sweetener. In a more preferred embodiment, the sweetener is selected from the group consisting of sucralose, aspartame, saccharin, dextrose, mannitol, glycerin, and xylitol. In a preferred embodiment, the formulations contain from about 0.001% w/w to about 2% w/w of sweetener. In a more preferred embodiment, the formulations contain from about 0.05% w/w to about 1% w/w of the sweetener. In a most preferred embodiment, the formulations contain sucralose as a sweetener at about 0.8% w/w.

[000132] In a further embodiment, the formulation may contain a sweetness enhancer, an ammonium salt form of crude and refined Glycyrrhizic Acid, for example, Magnasweet® product (available from Mafco Worldwide Corporation, Magnasweet is a registered trademark of Mafco Worldwide Corporation). Magnasweet® products use the ammonium salt forms of crude and refined Glycyrrhizic Acid. Glycyrrhizic Acid is also available as a pure derivative in the sodium and potassium salt forms.

[000133] In another embodiment, the formulations contain a pH modifier. In a preferred embodiment, the pH modifier adjusts the pH of the formulation to from about 2 to about 7. In a more preferred embodiment, the pH modifier adjusts the pH of the formulation to from about 3 to about 6, from about 4 to about 5 or from about 2 to about 4. In most preferred embodiments, the pH modifier adjusts the pH of the formulations to about 2.5, or 3, or 4.5 ± 0.1.

[000134] In another embodiment, the formulations contain a flavoring agent. In a preferred embodiment, the formulations contain a flavoring agent selected from the group consisting of peppermint oil, menthol, spearmint oil, citrus oil, cinnamon oil, strawberry flavor, cherry flavor, raspberry flavor, orange oil, and a combination thereof. Other appropriate flavoring agents known by those of skill in the art could also be added to formulations of the present invention. In a preferred embodiment, the formulations contain from about 0.001% w/w to about 1% w/w of the flavoring agent. In a more preferred embodiment, the formulations contain from about 0.005%

w/w to about 0.5% w/w of the flavoring agent. In a most preferred embodiment, the formulations contain strawberry as the flavoring agent at about 0.08% w/w.

[000135] In yet another embodiment, the formulations may contain a preservative. In a preferred embodiment, the preservative is selected from the group consisting of butyl paraben, methyl paraben, ethyl paraben, propyl paraben, sodium benzoate, and benzoic acid. In a preferred embodiment, the formulations contain from about 0.001% w/w to about 1% w/w of the preservative. In a more preferred embodiment, the formulations contain from about 0.005% w/w to about 0.2% w/w of the preservative. In a most preferred embodiment, the formulations contain methyl paraben as a preservative at about 0.1% w/w.

[000136] In a further embodiment, the invention is directed to stable liquid spray formulations comprising from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, about 10% to about 98% w/w water, about 0.005% to about 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate and optionally, about 2% to about 90% w/w of a co-solvent, preferably propylene glycol and the formulations do not contain an alcohol.

[000137] In a further embodiment, the invention is directed to stable liquid spray formulations comprising from about 1% to about 16% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, about 30% to about 98% w/w water, about 0.005% to about 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate and optionally, about 5% to about 55% w/w of a co-solvent, preferably propylene glycol and the formulations do not contain an alcohol.

[000138] In a further embodiment, the invention is directed to stable liquid spray formulations comprising from about 1% to about 10% w/w naloxone, a pharmaceutically acceptable salt or a derivative thereof, about 80% to about 98% w/w water, about 0.005% to about 0.05% w/w of a chelating agent, preferably edetate disodium dihydrate and optionally, about 5% to about 10% w/w of a co-solvent, preferably propylene glycol, and optionally about 0.1% w/w of a preservative, preferably methyl paraben and the formulations do not contain an alcohol.

[000139] In yet another embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(10) is from about 12 to about 20 microns during administration.

[000140] In a further embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(50) is from about 25 to about 35 microns during administration.

[000141] In yet another embodiment, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(90) is from about 40 to about 150 microns during administration. Preferably, the formulations of the present invention are capable of producing a droplet size distribution wherein the mean Dv(90) is from about 60 to about 110 microns during administration.

[000142] All claims, aspects and embodiments of the invention, and specific examples thereof, are intended to encompass equivalents thereof.

[000143] In a further embodiment, the invention is directed to treating patients by administering the formulations (with or without an alcohol) of the present invention to the patient. In a preferred embodiment, the formulations are administered in order to treat opioid dependence, opioid overdose, and/or congenital insensitivity to pain with anhidrosis.

Definitions

[000144] As used herein, all numerical values relating to amounts, weights, and the like, that are defined as "about" each particular value is plus or minus 10%. For example, the phrase "about 10% w/w" is to be understood as "9% to 11% w/w." Therefore, amounts within 10% of the claimed value are encompassed by the scope of the claims.

[000145] As used herein "% w/w" refers to the percent weight of the total formulation.

[000146] As used herein the term "effective amount" refers to the amount necessary to treat a patient in need thereof.

[000147] As used herein the term "patient" refers but is not limited to a person that is being treated for opioid dependence, opioid overdose, insensitivity to pain with anhidrosis, or another affliction or disease that can be treated with naloxone.

[000148] As used herein the phrase "pharmaceutically acceptable" refers to ingredients that are not biologically or otherwise undesirable in a sublingual or intranasal dosage form.

[000149] As used herein, "stable" refers to formulations which maintain greater than 95% purity following at least four weeks at about 40°C.

[000150] Preferably, the (alcohol and alcohol-free) formulations of the present invention are propellant free. As used herein, "propellant free" refers to a formulation that is not administered using compressed gas.

[000151] As used herein, the term "isotonicity agent" refers to any compound used to alter or regulate the osmotic pressure of a formulation.

[000152] As used herein, the term "buffer" refers to any compound used to maintain the pH of a formulation.

[000153] The following examples are intended to illustrate the present invention and to teach one of ordinary skill in the art how to make and use the invention. They are not intended to be limiting in any way.

Examples

Example 1: Preparation of Naloxone Formulations Containing Ethanol

[000154] Liquid spray formulations were created by first degassing ethanol and USP purified water, separately. Next, the ethanol and purified water were each purged with nitrogen. Soluble excipients were then dissolved in either the ethanol or the purified water based on their solubility. Next, the solutions were combined. Naloxone was added to the final solution and mixed until dissolved.

[000155] Strawberry flavor was used as the source of the flavoring agent.

Table 1. Stable Liquid Naloxone Spray Formulations

Formulation	Control	#1A	#2A	#3A	#4A	#5A	#6A	#7A
Naloxone Hydrochloride Dihydrate	2.44	2.44	2.44	2.44	2.44	4.00	6.7	10.1
Water (USP)	37.56	37.55	37.55	37.54	37.54	34.45	33.23	29.83
Ethanol	55	55	55	55	55	55	55	55
Propylene Glycol	5	5	5	5	5	5	5	5
L-menthol						0.05		
Sodium Thiosulfate		0.01	0.01					
Citric Acid		0.0025						
Flavoring agent						0.08		
Edetate disodium dihydrate			0.005	0.005	0.005	0.005	0.005	0.005
BHA				0.01				
BHT				0.005				
Sodium Ascorbate					0.02	0.02	0.02	0.02

values = % w/w

Example 2: Stability Testing of Naloxone Formulations

[000156] The formulations listed in Table 1 were subjected to stability testing at 40°C and 55°C ± 2°C under 75% ± 5% relative humidity for eight weeks. The stability data was collected at zero, one, two, three, four, and eight weeks at 55°C and at zero, four, and eight weeks at 40°C. Assay and impurities were detected using high performance liquid chromatography with an ultraviolet detector. The assay was performed at 288 nm and indicated as a % of initial concentration. For all impurities, analysis was performed at 240 nm and expressed as a % area. Amounts of particular impurities are listed in Tables 2A to 2F and 3A to 3H as a percentage of the area of each formulation along with amount of total impurities. "BQL" refers to "Below Quantifiable Limit" and "ND" refers to "Not Detected."

Tables 2A to 2F. Stability Data for Liquid Naloxone Spray Formulations stored at 40°C ± 2°C under 75% ± 5% relative humidity

2A. Stability of Control Stored at 40°C

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Impurity C	0.66	ND	0.81%	0.92%
Impurity A	0.83	ND	0.37%	0.51%
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	5.59%	5.53%
Impurity B	3.21	ND	ND	ND
Unknown Impurities	0.30	ND	0.13%	0.18%
	0.50	ND	0.28%	0.46%
Total Impurities		0.00%	7.18%	7.60%

2B. Stability of Form. #1A (with Sod. Thiosulphate & Citric Acid) Stored at 40˚C

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Impurity C	0.66	ND	BQL	BQL
Impurity A	0.83	ND	BQL	BQL
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	ND	ND
Impurity B	3.21	ND	ND	ND
Total Impurities		0.00%	0.00%	0.00%

2C. Stability of Form. #2A (with Sod. Thiosulphate & Edetate Disodium Dihydrate) Stored at 40˚C

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Impurity C	0.66	ND	BQL	BQL
Impurity A	0.83	ND	BQL	BQL
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	ND	ND
Impurity B	3.21	ND	ND	ND
Total Impurities		0.00%	0.00%	0.00%

2D. Stability of Form. #3A (with BHA & BHT) Stored at 40˚C

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Impurity C	0.66	ND	BQL	BQL
Impurity A	0.83	ND	BQL	BQL
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	ND	ND
Impurity B	3.21	ND	ND	ND
Total Impurities		0.00%	0.00%	0.00%

2E. Stability of Form. #4A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 40˚C

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Impurity C	0.66	ND	BQL	BQL
Impurity A	0.83	ND	0.15%	0.19%
Impurity F	0.93	ND	ND	ND

Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	ND	ND
Impurity B	3.21	ND	ND	ND
Total Impurities		0.00%	0.15%	0.19%

2F. Stability of Form. #5A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 40°C

Naloxone	RRT	T=0	4 Weeks	3 Months
Assay (%)		100	97.77	97.6
Impurity C	0.66	ND	ND	0.03
Impurity A	0.83	0.11	0.12	0.15
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	2.85	ND	0.13	0.13
Impurity B	3.21	ND	ND	ND
Total Impurities		0.11 %	0.25 %	0.29 %

[000157] Liquid naloxone formulations of the present invention contained less than one percent total impurities after eight weeks at 40°C. This is a stark contrast to the control formulation which contained 7.6% impurities at the same time. Specifically, the formulations which contained sodium thiosulfate or BHA and BHT resulted in 0% detected impurities after eight weeks. Also, formulations which contain sodium ascorbate (0.02% wt/wt) and edetate disodium dihydrate (0.005% wt/wt) resulted in only 0.29% total impurities after 3 months.

Tables 3A to 3H. Stability Data for Liquid Naloxone Spray Formulations stored at 55°C ±2°C

3A. Stability of Control Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
Impurity C	0.66	ND	ND	ND	0.54%	0.33%	0.35%
Impurity A	0.83	ND	ND	ND	1.31%	1.39%	1.59%
Impurity F	0.93	ND	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND	ND
Impurity E	2.85	ND	ND	ND	ND	ND	ND
Impurity B	3.21	ND	ND	ND	ND	ND	ND
Unknown Impurities	0.30	-	-	-	-	0.1%	0.32%
	0.35	-	-	-	0.15%	0.16%	0.08%
	0.50	-	-	-	0.83%	0.81%	0.67%
	2.85	-	-	-	4%	7.50%	6.65%

Total Impurities	0.00%	0.00%	0.00%	6.83%	10.29%	9.66%

3B. Stability of Form. #1A (with Sod. Thiosulphate & Citric Acid) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
Impurity C	0.66	ND	ND	ND	0.12%	0.37%	0.29%
Impurity A	0.83	ND	ND	ND	0.14%	0.67%	1.01%
Impurity F	0.93	ND	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND	ND
Impurity E	2.85	ND	ND	ND	0.55%	1.88%	1.52%
Impurity B	3.21	ND	ND	ND	ND	ND	ND
Unknown Impurities	0.32	-	-	-	-	0.09%	0.25%
	0.52	-	-	-	0.06%	0.51%	0.59%
Total Impurities		0.00%	0.00%	0.00%	0.87%	3.52%	3.66%

3C. Stability of Form. #2A (with Sod. Thiosulphate & Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
Impurity C	0.66	ND	ND	ND	ND	BQL	BQL
Impurity A	0.83	ND	ND	ND	BQL	0.07%	0.11%
Impurity F	0.93	ND	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND	ND
Impurity E	2.85	ND	ND	ND	ND	ND	ND
Impurity B	3.21	ND	ND	ND	ND	ND	ND
Unknown Impurities	0.52	-	-	-	-	-	0.08%
Total Impurities		0.00%	0.00%	0.00%	0.00%	0.07%	0.19%

3D. Stability of Form. #3A (with BHA & BHT) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
Impurity C	0.66	ND	ND	ND	ND	ND	BQL
Impurity A	0.83	ND	ND	ND	BQL	0.07%	0.13%
Impurity F	0.93	ND	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND	ND
Impurity E	2.85	ND	ND	ND	ND	ND	ND
Impurity B	3.21	ND	ND	ND	ND	ND	ND

Unknown Impurities	0.50	-	-	-	-	-	0.08%
Total impurities		0.00%	0.00%	0.00%	0.00%	0.07%	0.21%

3E. Stability of Form. #4A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
Impurity C	0.66	ND	ND	ND	ND	ND	0.06%
Impurity A	0.83	ND	ND	ND	0.11%	0.19%	0.19%
Impurity F	0.93	ND	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND	ND
Impurity E	2.85	ND	ND	ND	ND	ND	ND
Impurity B	3.21	ND	ND	ND	ND	ND	ND
Total Impurities		0.00%	0.00%	0.00%	0.11%	0.19%	0.25%

3F. Stability of Form. # 5A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Assay (%)		100	102.37	98.75	98.51	100.76
Impurity C	0.66	ND	ND	ND	ND	0.05%
Impurity A	0.83	0.11	0.14	0.15	0.19	0.17%
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND
Impurity E	2.85	ND	0.13	0.11	0.12	0.12%
Impurity B	3.21	ND	ND	ND	ND	ND
Unknown Impurities	0.49	-	-	-	0.06%	0.05%
	0.79	-	-	-	0.03%	-
	3.90	-	-	0.05%	0.07%	0.05%
Total Impurities		0.11%	0.27 %	0.31%	0.47%	0.44%

3H. Stability of Form. #6A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	2 Weeks	4 Weeks	8 Weeks
Assay (%)		100.00	101.35	102.69	102.99
Impurity C	0.66	ND	BQL	BQL	0.08%
Impurity A	0.81	BQL	0.08%	0.19%	0.18%

Impurity F	0.93	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND
Impurity E	2.85	0.04%	0.07%	0.06%	0.10%
Impurity B	3.21	ND	ND	ND	0.12%
Unknown Impurities	0.50	-	-	-	0.06%
Total Impurities		0.04%	0.15%	0.25%	0.54%

3G. Stability of Form. #7A (with Sod. Ascorbate and Edetate Disodium Dihydrate) Stored at 55°C

	RRT	T=0	2 Weeks	4 Weeks	8 Weeks
Assay (%)		100.00	100.91	100.92	102.05
Impurity C	0.66	ND	0.06%	0.05%	0.11%
Impurity A	0.81	BQL	0.11%	0.22%	0.17%
Impurity F	0.93	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND
Impurity E	2.85	0.06%	0.07%	0.06%	0.11%
Impurity B	3.21	ND	ND	ND	0.13%
Unknown Impurities	0.50	-	-	-	0.05%
	2.41	-	-	-	0.05%
Total Impurities		0.06%	0.24%	0.33%	0.62%

[000158] Similar to the stability study at 40°C, all of the formulations of the present invention had significantly fewer impurities at eight weeks compared to the control. The superior stability characteristics of the formulations of the present invention will allow the formulations to be effective when used by patients.

Example 3: Droplet Testing

[000159] In order to determine the spray profile of Formulation #5A, it was subjected to standardized droplet testing. A challenge of creating a Naloxone sublingual and/or intranasal spray formulation is that it must be capable of producing spray droplets that are over 10 microns in diameter. Spray droplets 10 microns or smaller could be inhaled into the lungs. The optimal particle size for sublingual and intranasal spray droplets is from 20 to about 200 microns in diameter. It is desirable for the formulation to have droplet sizes near 20 because this increases the surface area and increased surface area exposure is one factor that contributes to a high

bioavailability. Sublingual and intranasal formulations should be able to maintain a consistent droplet size throughout its shelf life.

[000160] Droplet analysis was conducted using standard laser analysis procedures known by those of skill in the art. Droplet size distribution (Dv10, Dv50, Dv90, and Span were tested at two distances, 3 cm and 6 cm). Dv10 refers to droplet size for which 10% of the total volume is obtained; Dv50 refers to droplet size for which 50% of the total volume is obtained; Dv90 refers to droplet size for which 90% of the total volume is obtained; Span refers to distribution span (Dv90-Dv10)/Dv50; %RSD refers to the percent relative standard deviation. The results of these tests can be seen below in Tables 4 to 9. Applicant found during testing that formulations of the present invention yielded desirable droplet sizes for sublingual and intranasal administration. The testing also revealed that the formulation dose remains consistent when administered with a spray pump.

Table 4. Spray Profile of Naloxone Spray Formulation #5A, Particle Size at 3 cm

Formulation #5A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10µ	Span
3 cm	Actuation 1	14.79	28.92	389.9	1.225	12.97
	Actuation 2	17.98	32.05	455.6	0.001	13.65
	Actuation 3	13.46	36.92	584.8	4.747	15.48
	Average	15.41	32.63	476.8	1.991	14.03

Table 5. Spray Profile of Naloxone Spray Formulation #5A, Particle Size at 6 cm

Formulation #5A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10µ	Span
6 cm	Actuation 1	20.58	38.64	498.6	1.918	12.37
	Actuation 2	18.67	37.59	529.4	1.537	13.59
	Actuation 3	21.26	36.44	452.3	1.767	11.83
	Average	20.17	37.56	493.4	1.741	12.60

Table 6. Spray Profile of Naloxone Spray Formulation #5A, Spray Pattern at 3 cm

Formulation #5A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
3 cm	Actuation 1	21.2	33.4	1.577
	Actuation 2	23.5	31.5	1.342

	Actuation 3	17.6	30.9	1.755
	Average	20.8	31.9	1.558

Table 7. Spray Profile of Naloxone Spray Formulation #5A, Spray Pattern at 6 cm

Formulation #5A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
6 cm	Actuation 1	24.5	55.6	2.268
	Actuation 2	34.3	49.7	1.447
	Actuation 3	33.9	52	1.535
	Average	30.9	52.4	1.750

Table 8. Spray Profile of Naloxone Spray Formulation #5A, Plume geometry data at 3 cm

Formulation #5A		Plume Geometry	
		Width (mm)	Angle (°)
3 cm	Actuation 1	28.7	51.1
	Actuation 2	25.5	45.9
	Actuation 3	35.4	60.4
	Average	29.9	52.5

Table 9. Spray Profile of Naloxone Spray Formulation #5A, Plume geometry data at 6 cm

Formulation #5A		Plume Geometry	
		Width (mm)	Angle (°)
6 cm	Actuation 1	54.3	48.4
	Actuation 2	52.6	47.3
	Actuation 3	-	-
	Average	53.5	47.9

[000161] As can be seen in Tables 4 to 9, Formulation #5A of the present invention provided excellent plume geometry and spray patterns.

Example 4: Preparation of Naloxone Formulations that are Alcohol-Free

[000162] In order to prepare a naloxone liquid formulation, the components as indicated in "*Table 10. The Components of Formulation #1AF*" below were weighed. The components were mixed until a clear solution was formed.

[000163] Naloxone HCL dihydrate base U.S.P. was used as the source of naloxone in the formulations that follow. Methyl paraben, U.S.P., (available from Spectrum) was used as the preservative source. Strawberry flavor, Nat&Art 915.0543 U, (available from FONA) was used as the source of flavoring agent. Edetate Disodium Dihydrate, U.S.P., (available from Spectrum) was used as the source of chelating agent or as antioxidant. Water, U.S.P., purified, (available from RICCA) was used as the source of solvent.

Table 10. The Components of Formulation #1AF

Ingredients	**% w/w**
Naloxone HCl Dihydrate	4.82
Sucralose	0.80
Methyl Paraben	0.10
Flavoring agent	0.08
Edetate Disodium Dihydrate	0.05
Water USP	94.15
	100.0

Example 5. Preparation of Additional Naloxone Liquid Formulations

[000164] In order to prepare naloxone liquid formulations, the components as indicated in "*Table 11. The Components of Control and Formulations #1AF to #6AF*" below were weighed. The components were mixed until a clear solution was formed.

Strawberry flavoring was used as the source of flavoring agent.

Table 11. The Components of Control and Formulations #1AF to #6AF

Formulation	Control	#1AF	#2AF	#3AF	#4AF	#5AF	#6AF
Naloxone HCL Dihydrate	4.83	4.82	4.89	4.89	4.89	4.83	4.82
Water (USP)	94.19	94.15	95.01	94.08	93.98	94.16	94.15
Sucralose	0.8	0.8		0.8	0.8	0.8	0.8
Methyl Paraben	0.1	0.1		0.1	0.1	0.1	0.1
Flavoring	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Edetate Disodium Dihydrate		0.05	0.005	0.05	0.05	0.005	0.05
L-cysteine Hydrochloride Monohydrate					0.1		
Sodium Ascorbate			0.02			0.02	
pH	3.03	2.5	4.46	4.16	2.56	3.02	3

Example 6: Stability Testing of Naloxone Formulations

[000165] The formulations listed in Table 11 were subjected to stability testing at 40°C and 55°C ± 2°C under 75% ± 5% relative humidity for eight weeks. The stability data was collected at zero, one, two, three, four, at 55°C and at zero, four weeks at 40°C. Assay and impurities were detected using high performance liquid chromatography with an ultraviolet detector. The assay was performed at 288 nm and indicated as a % of initial concentration. For all impurities, analysis was performed at 240 nm and expressed as a % area. Amounts of particular impurities are listed in Tables 12Ato 12G and 13A to 13C as a percentage of the area of each formulation along with amount of total impurities. "BQL" refers to "Below Quantifiable Limit" and "ND" refers to "Not Detected." "Ppm" refers to parts per million.

Tables 12A to 12G. Stability Data for Liquid Naloxone Spray Formulations stored at 55°C

12A. Stability of Control Stored at 55°C

Naloxone	RRT	T=0	1 Week 55°C
Assay (%)		100	101.48
Impurity C	0.66	ND	ND
Impurity A	0.83	0.15	0.15
Impurity F	0.93	ND	ND
Impurity D	1.14	ND	ND
Impurity E	3.20	0.07	0.62
Impurity B	3.40	ND	ND
Unknown	0.49	-	0.07
Impurities	0.59	-	0.12
Total Impurities		0.22%	0.96%

12B. Stability of Form. #2AF (with Sod. ascorbate & Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks
pH		4.469	4.21	4.239	4.02	4.224
Assay (%)		100	99.6	101.48	98.07	98.00
Impurity C	0.66	ND	BQL	BQL	BQL	BQL
Impurity A	0.83	BQL	0.09	0.28	0.27	0.18%
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND

Impurity E	3.20	ND	ND	ND	ND	ND
Impurity B	3.40	ND	ND	ND	ND	ND
Unknown Impurities	0.33	-	-	0.07	0.1	0.13
	0.49	-	-	0.05	0.07	0.07%
	0.56	-	0.08	0.08	0.09	0.08
	0.59	-	0.07	0.12	0.14	0.14
	3.90	-	0.09	0.15	0.13	0.14
Total Impurities		0.00%	0.33%	0.82%	0.80%	0.74%

12C. Stability of Form. #3AF (Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Weeks	2 Weeks	3 Weeks	4 Weeks
pH		4.16	4.23	4.168	3.94	4.33
Assay (%)		100	100.5	100.7	98.03	98.63
Impurity C	0.66	ND	ND	ND	ND	ND
Impurity A	0.83	BQL	BQL	0.21	0.18	0.07
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND	ND
Impurity E	3.20	0.13	0.11	0.09	0.09	0.08
Impurity B	3.40	ND	ND	ND	ND	ND
Unknown Impurities	0.33	-	-	0.11	0.12	0.18
	0.49	-	-	0.09	0.1	0.11%
	0.59	ND	0.12	0.11	0.14	0.15
	3.67	-	-	-	-	0.07
	3.90	-	0.08	0.14	0.13	0.13
Total Impurities		0.13%	0.31%	0.72%	0.76%	0.79%

12D. Stability of Form. #4AF (Edetate Disodium Dihydrate and L-Cysteine hydrochloride) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks
pH		2.56	2.5	2.44	2.38	2.413
Assay (%)		100	98.5	100.03	97.87	98.59
Impurity C	0.66	ND	ND	0.13	0.11	0.09%
Impurity A	0.83	BQL	ND	0.22	0.29	0.17%
Impurity F	0.93	ND	ND	ND	ND	ND

Impurity D	1.14	ND	ND	ND	ND	ND
Impurity E	3.20	ND	ND	ND	ND	ND
Impurity B	3.40	ND	ND	ND	ND	ND
Unknown Impurities	0.56	ND	ND	0.05	0.07	0.06
Total Impurities		0.00%	0.00%	0.40%	0.47%	0.32%

12E. Stability of Form. #5AF (Edetate Disodium dihydrate and Sodium ascorbate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks
pH		NP	NP	3.185
Assay (%)		100	98.37	98.12
Impurity C	0.66	ND	BQL	BQL
Impurity A	0.83	0.15	0.18	0.11
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	3.20	0.07	0.16	0.12
Impurity B	3.40	ND	ND	ND
Total Impurities		0.22%	0.34%	0.23%

12F. Stability of Form. #6AF (Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks
pH		3.013	3.443	3.132	3.241	3.21
Assay (%)		100.00%	98.34%	98.36%	98.34%	100.07%
Impurity C	0.66	0.10%	0.10%	0.21%	0.13%	0.13%
Impurity A	0.83	BQL	BQL	BQL	BQL	BQL
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	0.83 ppm	1.79 ppm	1.74 ppm	ND
Impurity E	3.20	0.15%	0.15%	0.15%	0.17%	0.17%
Impurity B	3.40	ND	ND	ND	ND	ND
Unknown Impurities	0.49	-	-	0.06%	0.06%	0.12%
	0.77	-	-	BQL	BQL	0.05%
Total Impurities		0.25%	0.25%	0.42%	0.36%	0.47%

12G. Stability of Form. #1AF (Edetate Disodium Dihydrate) Stored at 55°C

Naloxone	RRT	T=0	1 Week	2 Weeks	3 Weeks	4 Weeks
pH		2.505	2.907	2.581	2.616	2.62
Assay (%)		100.00%	107.80%	100.51%	100.17%	102.39%
Impurity C	0.66	0.10%	0.10%	0.10%	0.10%	0.09%
Impurity A	0.83	BQL	BQL	BQL	BQL	BQL
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	NP	0.95 ppm	1.25 ppm	1.59 ppm	ND
Impurity E	3.20	0.15%	0.14%	0.15%	0.16%	0.18%
Impurity B	3.40	ND	ND	ND	ND	ND
Unknown Impurities	0.06	0.13%	0.13%	0.13%	0.13%	ND
	0.49	-	-	0.08%	0.06%	0.05%
	4.63	ND	ND	ND	BQL	ND
Total Impurities		0.38%	0.37%	0.46%	0.45%	0.32%

[000166] Liquid naloxone formulations of the present invention contained less than 0.8% of total impurities after four weeks at 55°C. This is a stark contrast to the control formulation which contained 0.96% impurities after 1 week at 55°C. Specifically, the formulations which contained sodium ascorbate or edetate disodium dihydrate exhibited lower impurities after four weeks. Additionally, the formulations which contained edetate disodium dihydrate were very stable.

Tables 13A to 13C. Stability Data for Liquid Naloxone Spray Formulations stored at 40°C under 75% Relative Humidity

13A. Stability of Form. #2AF (with Sod. ascorbate & Edetate Disodium Dihydrate) Stored at 40°C under 75% Relative Humidity

Naloxone	RRT	T=0	4 Weeks
pH		4.469	4.394
Assay (%)		100	98.12
Impurity C	0.66	ND	0.06
Impurity A	0.83	BQL	0.12
Impurity F	0.93	ND	ND
Impurity D	1.14	ND	ND
Impurity E	3.20	ND	ND

Impurity B	3.40	ND	ND
Unknown Impurities	0.49	ND	0.06
	0.59	ND	0.06
	3.90	ND	0.14
Total Impurities		0.00%	0.44%

13B. Stability of Form. #3AF (Edetate Disodium Dihydrate) Stored at 40°C under 75% Relative Humidity

Naloxone	RRT	T=0	4 Weeks
pH		4.16	4.596
Assay (%)		100	99.69
Impurity C	0.66	ND	ND
Impurity A	0.83	BQL	BQL
Impurity F	0.93	ND	ND
Impurity D	1.14	ND	ND
Impurity E	3.20	0.13	ND
Impurity B	3.40	ND	ND
Unknown Impurities	0.59	ND	0.11
	3.90	ND	0.11
Total Impurities		0.13%	0.22%

13C. Stability of Form. #4AF (Edetate Disodium Dihydrate and L-Cysteine hydrochloride) Stored at 40°C under 75% Relative Humidity

Naloxone	RRT	T=0	4 Weeks
pH		2.56	2.502
Assay (%)		100	97.08
Impurity C	0.66	ND	ND
Impurity A	0.83	BQL	BQL
Impurity F	0.93	ND	ND
Impurity D	1.14	ND	ND
Impurity E	3.20	ND	ND
Impurity B	3.40	ND	ND
Total Impurities		0.00%	0.00%

[000167] The naloxone formulations of the present invention contained less than 0.45% of total impurities after four weeks at 40°C.

Example 7: Freeze/Thaw Testing

[000168] In order to further determine the stability of Formulations #1AF and #6AF, the formulations were subjected to standard freeze/thaw stability testing. The results are below in "*Table 14. Stability of Formulations #1AF and #6AF to Freeze/Thaw Testing.*"

Table 14. Stability of Formulations #1AF and #6AF to Freeze/Thaw Testing

Formulation #1AF to #6AF	Drug Substance	t=0	Cycle 1, -20°C	Cycle 1, 25°C	Cycle 2, -20°C	Cycle 2, 25°C	Cycle 3, -20°C	Cycle 3, 25°C
Date Observed:		3/12/2015	3/16/2015	3/18/2015	3/20/2015	3/22/2015	3/24/2015	3/26/2015
Physical appearance	clear	clear	clear	clear	clear	Clear	clear	clear
Color	colorless	colorless	colorless	colorless	colorless	colorless	colorless	Colorless

[000169] The naloxone formulations #1AF to #6AF were clear and colorless after several cycles of freezing and thawing. This study further demonstrates the stability of the formulations.

Example 8: Droplet Testing

[000170] In order to determine the spray profile of Formulation #1AF, it was subjected to standardized droplet testing. As previously explained, the optimal particle size for sublingual and intranasal spray droplets is from 20 to about 200 microns in diameter. It is desirable for the formulation to have droplet sizes near 20 because this increases the surface area and increased surface area exposure is one factor that contributes to a high bioavailability. Sublingual and intranasal formulations should be able to maintain a consistent droplet size throughout its shelf life.

[000171] Droplet analysis was conducted using standard laser analysis procedures known by those of skill in the art. Droplet size distribution (Dv10, Dv50, Dv90, and Span were tested at two distances, 3 cm and 6 cm). Dv10 refers to droplet size for which 10% of the total volume is obtained; Dv50 refers to droplet size for which 50% of the total volume is obtained; Dv90 refers to droplet size for which 90% of the total volume is obtained; Span refers to distribution span (Dv90-Dv10)/Dv50; %RSD refers to the percent relative standard deviation. The results of these tests can be seen below in Tables 15 to 20. Applicant found during testing that formulations of the present invention yielded desirable droplet sizes for sublingual and intranasal administration.

The testing also revealed that the formulation dose remains consistent when administered with a spray pump.

Table 15. Spray Profile of Naloxone Spray Formulation #1AF, Particle Size at 3 cm

Formulation #1AF		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10µ	Span
3 cm	Actuation 1	13.16	26.23	63.21	2.792	1.908
	Actuation 2	11.52	27	90.85	6.547	2.939
	Actuation 3	12.95	28.39	144	3.505	4.615
	Average	12.54	27.21	99.4	4.281	3.15

Table 16. Spray Profile of Naloxone Spray Formulation #1AF, Particle Size at 6 cm

Formulation #1AF		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10µ	Span
6 cm	Actuation 1	20.18	32.51	53.9	1.198	1.037
	Actuation 2	18.02	31.45	58.48	0.024	1.286
	Actuation 3	16.81	33.44	77.92	1.799	1.828
	Average	18.34	32.47	63.4	1.007	1.38

Table 17. Spray Profile of Naloxone Spray Formulation #1AF, Spray Pattern at 3 cm

Formulation #1AF		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
3 cm	Actuation 1	26.5	41.3	1.557
	Actuation 2	24.8	43.5	1.751
	Actuation 3	29	40.6	1.402
	Average	26.8	41.8	1.570

Table 18. Spray Profile of Naloxone Spray Formulation #1AF, Spray Pattern at 6 cm

Formulation #1AF		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
6 cm	Actuation 1	52.6	68.6	1.304
	Actuation 2	40.3	61.4	1.524
	Actuation 3	47.5	59.7	1.256
	Average	46.8	63.2	1.361

Table 19. Spray Profile of Naloxone Spray Formulation #1AF, Plume geometry data at 3 cm

Formulation #1AF		Plume Geometry	
		Width (mm)	Angle (°)
3 cm	Actuation 1	39.7	66.7
	Actuation 2	37.7	64.3
	Actuation 3	33.5	58
	Average	37.0	63.0

Table 20. Spray Profile of Naloxone Spray Formulation #1AF, Plume geometry data at 6 cm

Formulation #1AF		Plume Geometry	
		Width (mm)	Angle (°)
6 cm	Actuation 1	63	54.9
	Actuation 2	67.1	58.3
	Actuation 3	68	59
	Average	66.0	57.4

[000172] As can be seen in Tables 15 to 20, Formulation #1AF of the present invention provided excellent plume geometry and spray patterns.

Example 9. Preparation of Additional Naloxone Liquid Formulations

[000173] In order to prepare naloxone liquid formulations, the components as indicated in "*Table 21. The Components of Formulations #8A, #9A, #7AF and #8AF*" below were weighed. The components were mixed until a clear solution was formed.

Strawberry flavoring was used as the source of flavoring agent.

Table 21. The Components of Formulations #8A, #9A, #7AF and #8AF

Formulation	Control	#8A	#9A	#7AF	#8AF
Naloxone	2.44	10.419	10.265	4.4196	4.4196
Water (USP)	37.56	29.506	31.324	94.769	94.779
Ethanol	55	55	50		
Propylene Glycol	5	5	5		
L-menthol		0.05	0.5		
BKC			0.01	0.01	
Sodium Chloride				0.8	0.8
Flavoring agent			0.08		
Edetate disodium dihydrate		0.005	0.001	0.001	0.001
Sucralose			0.8		
Caprylic Acid			2		

Sodium Ascorbate		0.02	0.02			

pH - 4.5±0.2

Example 10. Preparation of Additional Naloxone Nasal Spray Formulations

[000174] In order to prepare naloxone liquid formulations, the components as indicated in Tables 22, 23 and 24 below were weighed. The components were mixed until a clear solution was formed.

Table 22. Stable Naloxone Nasal Spray Formulations

	#10A	#11A	#12A	#13A	#14A	#15A	#16A
Naloxone	9.49	8.85	8.75	8.57	4.0	8.75	8.75
Water (USP)	35.505	66.14	71.135	79.31	83.88	81.135	81.135
Ethanol	50.0	20.0	10.0	2.0	2.0	10.0	10.0
Propylene Glycol	5.0	5.0	10.0	10.0	10.0	-	-
EDTA	0.005	0.01	0.015	0.02	0.02	0.015	0.015
Methyl Paraben	-	-	0.1	0.1	0.1	0.1	0.1
pH	4.5±0.1	4.5±0.1	4.5±0.1	4.5±0.1	4.5±0.1	4.5±0.1	3.0±0.1

Table 23. Stable Naloxone Nasal Spray Formulations

	#17A	#18A	#19A	#20A
Naloxone	2.405	2.52	4.788	4.477
Water (USP)	42.594	72.738	40.207	40.513
Ethanol	50.0	20.0	50.0	20.0
Propylene Glycol	5.0	5.0	5.0	5.0
EDTA	0.005	0.01	0.005	0.01
pH	4.5±0.1	4.5±0.1	4.5±0.1	4.5±0.1

values = % w/w

Table 24. Stable Non-Alcoholic Naloxone Nasal Spray Formulations

	#9AF	#10AF	#11AF	#12AF
Naloxone	4.83	4.4	8.55	4.0
Water (USP)	95.02	90.495	81.33	85.88
Propylene Glycol	-	5.0	10.0	10.0

EDTA	0.05	0.005	0.02	0.02
Methyl Paraben	0.1	0.1	0.1	0.1
pH	3.0±0.1	4.5±0.1	4.5±0.1	4.5±0.1

values = % w/w

[000175] All formulations of Tables 22, 23 and 24 were stable upon mixing. Formulations of Tables 22, 23 and 24 differ from prior art naloxone nasal spray formulations because the formulations of Tables 22, 23 and 24 do not contain an isotonicity agent, specifically sodium chloride, a buffer, specifically citric acid, an anti-microbial agent, specifically benzyl alcohol or benzalkonium chloride. Further, formulations of Tables 22, 23 and 24 contain EDTA at a concentration of no more than 0.05% w/w.

Table 25. Stability of Formulations # 9A and # 8A to Freeze/Thaw Testing

Formulation	**Drug Substance**	**t=0**	**Cycle 1, 20°C**	**Cycle 1, 40 °C**	**Cycle 2, 20°C**	**Cycle 2, 40 °C**	**Cycle 3, 20°C**	**Cycle 3, 40°C**
Date Observed:		1/12/2016	1/14/2016	1/16/2016	1/18/2016	1/20/2016	1/22/2016	3/ 24/2015
Physical appearance	clear	clear	clear	clear	clear	Clear	clear	clear
Color	colorless	colorless	colorless	colorless	colorless	colorless	colorless	Colorless

[000176] The naloxone formulations #8A and #9A were clear and colorless after several cycles of freezing and thawing. This study further demonstrates the stability of the formulations.

Example 11: Droplet Testing

[000177] In order to determine the spray profile of Formulation #9A, it was subjected to standardized droplet testing. As previously explained, the optimal particle size for sublingual and intranasal spray droplets is from 20 to about 200 microns in diameter. It is desirable for the formulation to have droplet sizes near 20 because this increases the surface area and increased surface area exposure is one factor that contributes to a high bioavailability. Sublingual and intranasal formulations should be able to maintain a consistent droplet size throughout its shelf life.

[000178] Droplet analysis was conducted using standard laser analysis procedures known by those of skill in the art. Droplet size distribution (Dv10, Dv50, Dv90, and Span were tested at

two distances, 3 cm and 6 cm). Dv10 refers to droplet size for which 10% of the total volume is obtained; Dv50 refers to droplet size for which 50% of the total volume is obtained; Dv90 refers to droplet size for which 90% of the total volume is obtained; Span refers to distribution span (Dv90-Dv10)/Dv50; %RSD refers to the percent relative standard deviation. The results of these tests can be seen below in Tables 26 to 41. Applicant found during testing that formulations of the present invention yielded desirable droplet sizes for sublingual and intranasal administration. The testing also revealed that the formulation dose remains consistent when administered with a spray pump.

Table 26. Spray Profile of naloxone Spray Formulation #9A, Particle Size at 3 cm

Formulation #9A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10μ	Span
3 cm	Actuation 1	23.06	44.28	99.7	0	1.731
	Actuation 2	22.08	44.34	104.4	0.661	1.856
	Actuation 3	22.27	55.05	107.5	1.012	2.82
	Average	22.47	47.89	103.9	0.558	2.14

Table 27. Spray Profile of Naloxone Spray Formulation #9A, Particle Size at 6 cm

Formulation #9A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10μ	Span
6 cm	Actuation 1	28.54	51.29	91.87	2.113	1.235
	Actuation 2	25.75	50.01	103.7	1.594	1.56
	Actuation 3	31.99	51.77	85	0	1.024
	Average	28.76	51.02	93.5	1.236	1.27

Table 28. Spray Profile of Naloxone Spray Formulation #9A, Spray Pattern at 3 cm

Formulation #9A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
3 cm	Actuation 1	14.7	22.7	1.544
	Actuation 2	14.4	21.8	1.517
	Actuation 3	15.2	20.9	1.372
	Average	14.8	21.8	1.478

Table 29. Spray Profile of Naloxone Spray Formulation #9A, Spray Pattern at 6 cm

Formulation #9A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
6 cm	Actuation 1	23.5	30.4	1.291
	Actuation 2	24.5	41.8	1.707
	Actuation 3	20.5	32.7	1.597
	Average	22.8	35.0	1.532

Table 30. Spray Profile of Naloxone Spray Formulation #9A, Plume geometry data at 3 cm

Formulation #9A		Plume Geometry	
		Width (mm)	Angle (°)
3 cm	Actuation 1	22.5	39.9
	Actuation 2	15.5	28.6
	Actuation 3	25.7	44.3
	Average	21.2	37.6

Table 31. Spray Profile of Naloxone Spray Formulation #9A, Plume geometry data at 6 cm

Formulation #9A		Plume Geometry	
		Width (mm)	Angle (°)
6 cm	Actuation 1	26.4	24.3
	Actuation 2	25	23.3
	Actuation 3	37.6	33.2
	Average	29.7	26.9

Table 32. Spray Profile of Naloxone Spray Formulation # 10A, Particle Size at 3 cm

Formulation # 10A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10μ	Span
3 cm	Actuation 1	19.84	46.86	112.10	3.744	2.011
	Actuation 2	21.21	48.69	110.70	2.503	1.837
	Average	20.53	47.77	111.40	1.924	3.124

Table 33. Spray Profile of Naloxone Spray Formulation # 10A, Spray Pattern at 3 cm

Formulation # 10A	Spray Pattern	

		Dmin (mm)		Dmax (mm)	Ovality Ratio
3 cm	14.6	18.4		14.6	1.261
	14.1	17.9		14.1	1.265
	15.1	17.9		15.1	1.182
	14.6	18.1		14.6	1.2

Table 34. Spray Profile of Naloxone Spray Formulation # 10A, Spray Pattern at 6 cm

Formulation # 10A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
6 cm	Actuation 1	23.7	29.8	1.259
	Actuation 2	20.2	31.6	1.566
	Actuation 3	22.0	32.0	1.453
	Average	22.0	31.20	1.40

Table 35. Spray Profile of Naloxone Spray Formulation #10A, Plume geometry data at 3 cm

Formulation # 10A		Plume Geometry	
		Width (mm)	Angle (°)
3 cm	Actuation 1	36.7	19.97
	Actuation 2	36.82	19.97
	Average	36.76	19.97

Table 36. Spray Profile of Naloxone Spray Formulation # 10A, Plume geometry data at 6 cm

Formulation #10A		Plume Geometry	
		Width (mm)	Angle (°)
6 cm	Actuation 1	27.23	29.29
	Actuation 2	21.96	23.3
	Average	24.60	26.30

Table 37. Spray Profile of Naloxone Spray Formulation # 11A, Particle Size at 3 cm

Formulation # 11A		Particle Size				
		DV(10)	DV(50)	DV(90)	%<10μ	Span
3 cm	Actuation 1	15.7	38.14	90.81	4.56	1.969
	Actuation 2	15.11	37.9	86.75	5.09	1.89
	Average	15.405	38.02	88.78	4.83	1.93

Table 38. Spray Profile of Naloxone Spray Formulation # 11A, Spray Pattern at 3 cm

Formulation # 11A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
3 cm	Actuation 1	15.9	22.4	1.410
	Actuation 2	18.8	20.4	1.086
	Actuation 3	16.2	22.5	1.392
	Average	16.9	21.8	1.30

Table 39. Spray Profile of Naloxone Spray Formulation # 11A, Spray Pattern at 6 cm

Formulation # 11A		Spray Pattern		
		Dmin (mm)	Dmax (mm)	Ovality Ratio
6 cm	Actuation 1	20.8	29.4	1.411
	Actuation 2	20.8	31.1	1.495
	Actuation 3	23.1	31.8	1.376
	Average	21.6	30.8	1.40

Table 40. Spray Profile of Naloxone Spray Formulation #11A, Plume geometry data at 3 cm

Formulation # 11A		Plume Geometry	
		Width (mm)	Angle (°)
3 cm	Actuation 1	31.30	19.98
	Actuation 2	36.63	19.97
	Average	33.97	19.98

Table 41. Spray Profile of Naloxone Spray Formulation # 11A, Plume geometry data at 6 cm

Formulation #11A		Plume Geometry	
		Width (mm)	Angle (°)
6 cm	Actuation 1	21.1	16.98
	Actuation 2	21.22	22.64
	Average	21.16	19.81

[000179] As can be seen in Tables 26 to 41, Formulation #9A, # 10A, and 11A of the present invention provided excellent plume geometry and spray patterns.

Example 12. Pharmacokinetic Analysis

[000180] The naloxone formulations described in Example 9, Table 21 of the instant specification were used. For formulations #7AF and #8AF a 4-mg dose was administered. For formulations #8A and #9A a 16-mg dose was administered.

Pharmacokinetic and Bioavailability Analysis

[000181] Protocol was a single dose crossover study. Five healthy male Yucatan minipigs weighing approximately forty kilograms each were sublingually administered the formulations of Table 21. The minipigs were fasted overnight and through four hours' post administration. Administration was followed by a one week washout period. Blood samples were taken prior to administration and 1, 3, 5, 7, 10, 15, 30 min, 1, 2, 4, 8 and 24 hours' post dose. Blood samples were measured for naloxone concentrations via liquid chromatography-tandem mass spectrometry.

[000182] The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}) and area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{0-t}).

Results and Conclusions

[000183] Results of the pharmacokinetic and statistical analysis for the naloxone formulations in Table 21 of the present invention are shown in Table 42.

Table 42. Summary of pharmacokinetic parameters for naloxone after sublingual administration of single doses of 4 mg and 16 mg of naloxone formulations to Yucatan minipigs under fasted conditions.

Parameter*	#7AF	#8AF	#8A	#9A	#9A (repeat)
C_{max} (ng/mL)	8.9 ± 2.2	6.8 ± 2.2	26.3 ± 1.8	86.4 ± 2.4	58.6 ± 2.8
Conc. @ 1 min (ng/mL)	NA	0.1	NA	24.2	NA
Conc. @ 3 min (ng/mL)	0.2	0.3	5	68.5	12.9
Conc. @ 5 min (ng/mL)	1.4	1.9	6.3	62.7	36.9
Conc. @ 7 min (ng/mL)	1.6	2.6	9.1	28.8	50.5
$AUC_{(0-t)}$ (ng*min/mL)	746.2 ± 2.2	432.3 ± 2.0	2382.5 ± 2.0	3108.5 ± 2.2	3564.8 ± 2.8
AUC @ 15 min (ng*min/mL)	41.6	38	188.2	615.8	515.6

AUC @ 30 min (ng*min/mL)	151.8	106.8	504.4	987.4	1063.3

*Geometric mean ± geometric standard deviation. Sample size is 5.

[000184] The peak mean naloxone concentration was significantly higher for formulation #9A and #8A over #8AF and #7AF. Additionally, the area under the concentration-time curve from time-zero to the time of the last quantifiable concentration was significantly higher for formulations #9A and #8A over #8AF and #7AF. To determine if this result was based on the four-fold increase in the dose of naloxone in formulation #9A and #8A over #8AF and #7AF the geometric mean was normalized to 4 mg dose. See Figure 1. A similar pattern remains even after normalization. Further, the peak mean naloxone concentration was significantly higher for formulation #9A, over #8A, which cannot be explained by the dosage as formulations #9A and #8A were each administered at 16 mg doses.

[000185] Additionally, formulation #9A reached about 80% of its peak mean naloxone concentration within 3 minutes of administration. In comparison, formulation #8A had reached only 35% of its peak mean naloxone concentration within 7 minutes, #8AF 38% in 7 minutes and #7AF 19% in 7 minutes. In a similar comparison formulation #9A reached 19% of its $AUC_{(0-t)}$ within 15 minutes of administration, #8A reached 7.9% in 15 minutes, #8AF reached 8.8% in 15 minutes and #7AF reached 5.6% in 15 minutes.

[000186] Administration of naloxone in formulations with co-solvents resulted in superior bioavailability. Compare formulation #9A and #8A to #8AF and #7AF. Further, the addition of permeation enhancers such as caprylic acid and BKC resulted in further increase in bioavailability. Compare formulations #9A to #8A and #7AF to #8AF.

Example 13. Stability testing of additional Naloxone Formulations

[000187] Formulation #9A, # 10A, and 11A from Table 21 above was subjected to stability testing at 25°C/60% RH ± 5%, 40°C/75% ± 5% relative humidity and 55°C ± 2°C. The stability data was collected at predetermined time points. Assay and impurities were detected using high performance liquid chromatography with an ultraviolet detector. The assay was performed at 288 nm and indicated as a % of initial concentration. For all impurities, analysis was performed at 240 nm and expressed as a % area. Amounts of particular impurities are listed in Tables 43 A to I as a percentage of the area of each formulation along with amount of total impurities.

Table 43A. Stability Data for the Formulation #9A Stored at 25°C ± 2°C / 60% ± 5% RH

Naloxone	RRT	T=0	4 Weeks	3 Months	6 months
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Colorless	Clear, Pale yellow
Assay (%)		100	98.7	99.01	98.89
Impurity C	0.53	ND	0.01	ND	ND
Impurity A	0.63	0.02	0.03	0.02	0.04
Impurity F	0.93	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND
Impurity E	1.42	0.05	0.02	0.02	0.03
Impurity B	1.87	ND	ND	ND	ND
Unknown Impurities	0.90	ND	ND	0.07	0.04
	1.48	ND	0.01	0.05	0.1
Total Impurities		0.07%	0.07%	0.16%	0.21%

ND = Not Detected
ppm = parts per million

Table 43B. Stability Data for the Formulation #9A Stored at 40 °C ± 2°C / 75 % ± 5% RH

Naloxone	RRT	T=0	4 Weeks	3 Months	6 months
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, light yellow	Clear, light brownish yellow	Clear, light brownish yellow
Assay (%)		100	99.09	98.63	98.08
Impurity C	0.53	ND	0.01	0.01	0.02
Impurity A	0.63	0.02	0.04	0.06	0.16
Impurity F	0.93	ND	ND	ND	ND
Impurity D	1.14	ND	ND	ND	ND
Impurity E	1.42	0.05	0.01	0.01	0.02
Impurity B	1.87	ND	ND	ND	ND
Unknown Impurities	0.56	ND	0.05	0.04	0.10
	0.71	ND	0.04	0.03	0.06
	0.79	ND	ND	0.01	0.05
	0.90	ND	ND	0.05	ND
	1.23	ND	ND	ND	0.05
	1.27	ND	ND	0.02	0.05
	1.48	ND	0.07	0.14	0.21
	1.56	ND	ND	ND	0.07
	1.84	ND	ND	0.05	0.02

Total Impurities		0.07%	0.22%	0.42%	0.81%

ND = Not Detected

ppm = parts per million

Table 43C. Stability Data for the Formulation # 9A Stored at 55 °C ± 2°C

Naloxone	RRT	T=0	4 Weeks	6 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, yellow	Clear, yellow	Clear, yellow
Assay (%)		100	97.28	97.28	94.28
Impurity C	0.53	ND	0.03	0.03	0.04
Impurity A	0.63	0.02	0.21	0.28	0.39
Impurity F	0.93	ND	ND	ND	ND
Impurity D	1.14	ND	9.36 ppm	ND	ND
Impurity E	1.42	0.05	0.05	0.05	0.05
Impurity B	1.87	ND	ND	ND	ND
Unknown Impurities	0.56	ND	0.13	0.14	0.19
	0.71	ND	0.06	0.07	0.06
	0.79	ND	0.08	0.11	0.19
	1.13	ND	0.01	0.05	0.05
	1.23	ND	0.04	0.06	0.08
	1.30	ND	ND	ND	0.06
	1.38	ND	0.02	0.06	0.12
	1.48	ND	0.11	0.12	0.13
	1.54	ND	0.06	0.07	0.15
	1.66	ND	0.03	0.05	ND
Total Impurities		0.07%	0.83%	1.09%	1.51%

Table 43D. Stability Data for the Formulation # 10A Stored at 25°C ± 2°C / 60% ± 5% RH

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Colorless
Assay (%)		100	98.9	101.55
Naloxone N-oxide		ND	ND	ND
Impurity C	0.53	ND	ND	ND
Impurity A	0.63	ND	ND	ND

Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	1.42	0.05	0.04	0.04
Impurity B	1.87	ND	ND	ND
	1.07	0.07	0.08	0.1
	1.50	ND	0.07	0.11
Total Impurities		0.12%	0.19%	0.25%

Table 43E. Stability Data for the Formulation # 10A Stored at 40 °C ± 2°C / 75 % ± 5% RH

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Colorless
Assay (%)		100	100.65	99.4
Naloxone n-oxide		ND	0.02	NP
Impurity C	0.53	ND	ND	ND
Impurity A	0.63	ND	0.01	ND
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	NP
Impurity E	1.42	0.05	0.04	0.14
Impurity B	1.87	ND	ND	ND
Unknown Impurities	0.71	0.01	0.05	0.03
	1.07	0.07	0.05	0.08
	1.50	ND	0.14	0.21
Total Impurities		0.13%	0.31%	0.46%

Table 43F. Stability Data for the Formulation # 10A Stored at 55 °C ± 2°C

Naloxone	RRT	T=0	1 Weeks	2 Weeks	4 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Light yellow	Clear, yellow	Clear, yellow
Assay (%)		100	98.11	98.89	99.96	100.34
Naloxone n-oxide		ND	ND	0.05	0.03	NP
Impurity C	0.53	ND	0.01	0.01	0.01	0.01

Impurity A	0.63	ND	0.02	0.02	0.03	0.03
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	2.31 ppm	NP	NP
Impurity E	1.42	0.05	0.04	0.02	0.01	0.02
Impurity B	1.87	ND	ND	ND	ND	ND
Unknown Impurities	0.56	ND	0.02	0.02	0.02	0.06
	0.71	0.01	0.05	0.03	0.02	0.03
	0.75	ND	ND	0.03	0.03	0.05
	1.07	0.07	0.07	0.07	0.07	0.07
	1.27	ND	ND	ND	0.04	0.08
	1.30	ND	ND	0.01	0.04	0.05
	1.39	ND	ND	0.02	0.03	0.05
	1.50	ND	0.1	0.14	0.17	0.18
Total Impurities		0.13%	0.31%	0.42%	0.50%	0.63%

Table 43G. Stability Data for the Formulation # 11A Stored at 25°C ± 2°C / 60% ± 5% RH

Naloxone	RRT	T=0	4 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Colorless
Assay (%)		100	101.44	104.95
Naloxone n-oxide		ND	ND	NP
Impurity C	0.53	ND	ND	ND
Impurity A	0.61	ND	ND	0.01
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	1.42	0.03	0.09	0.03
Impurity B	1.87	ND	ND	ND
Unknown Impurities	0.71	0.02	0.05	0.06
	1.07	0.07	0.1	0.1
	1.50	ND	0.02	0.04
Total Impurities		0.12%	0.17%	0.24%

Table 43H. Stability Data for the Formulation # 11A Stored at 40 °C ± 2°C / 75 % ± 5% RH

Naloxone	RRT	T=0	4 Weeks	8 Weeks

Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Colorless
Assay (%)		100	100.39	101.31
Naloxone n-oxide		ND	0.02	ND
Impurity C	0.53	ND	0.01	ND
Impurity A	0.61	ND	0.02	0.03
Impurity F	0.93	ND	ND	ND
Impurity D	1.14	ND	ND	ND
Impurity E	1.42	0.03	0.05	0.04
Impurity B	1.87	ND	ND	ND
Unknown Impurities	0.71	0.02	0.06	0.04
	1.07	0.07	0.05	0.06
	1.27	ND	ND	0.07
	1.50	ND	0.05	0.08
Total Impurities		0.12%	0.26%	0.32%

Table 43I. Stability Data for the Formulation # 11A Stored at 55 °C ± 2°C

Naloxone	RRT	T=0	1 Weeks	2 Weeks	4 Weeks	8 Weeks
Physical appearance (Clarity, Color)		Clear, Colorless	Clear, Colorless	Clear, Light yellow	Clear, Light yellow	Clear, yellow
Assay (%)		100	98.48	102.74	101.14	103.18
Naloxone n-oxide (%)		ND	ND	0.04	0.02	NP
Impurity C	0.53	ND	ND	0.01	0.02	0.01
Impurity A	0.61	ND	0.03	0.04	0.05	0.07
Impurity F	0.93	ND	ND	ND	ND	ND
Impurity D	1.14	ND	ND	3.18ppm		ND
Impurity E	1.42	0.03	0.04	0.02	0.02	0.04
Impurity B	1.87	ND	ND	ND	ND	ND
Unknown Impurities	0.71	0.02	0.07	0.04	0.02	0.02
	1.07	0.07	0.09	0.07	0.06	0.09
	1.16	ND	ND	0.01	0.02	0.05
	1.30	ND	ND	0.02	0.05	0.03
	1.32	ND	ND	ND	0.01	0.06
	1.50	ND	0.01	0.05	0.10	0.13
	1.59	ND	ND	ND	0.02	0.05

	1.62	ND	ND	ND	0.01	0.07
	1.63	ND	ND	ND	ND	0.07
	1.73	ND	ND	0.02	0.03	0.05
Total Impurities		0.12%	0.24%	0.32%	0.43%	0.74%

ND = Not Detected

ppm = parts per million

[000188] The data suggest that formulation #9A, #10A, and #11A demonstrates satisfactory stability with no significant increase in individual or total impurities. Based upon these results, the formulation containing 0.02 % w/w of sodium ascorbate as an antioxidant and 0.001 % edetate disodium dihydrate as a chelating agent is chemically stable. Additionally, formulations containing 0.01 % and 0.005% edetate disodium dihydrate as a chelating agent are chemically stable.

Example 14. Intranasal and Sublingual Administration of Naloxone Spray Formulations

Method

[000189] Protocol design was a Phase I, open-label, randomized, single-dose, five-way crossover study. The study assessed the bioavailability of a single 8 milligrams and 16 milligrams dose of naloxone in a formulation of the present invention either intranasally or sublingually to a single 0.4 milligram intramuscular dose of naloxone under fasted conditions. 145 subjects were randomly assigned to one of five groups including 8 milligrams sublingual dose, 16 milligrams sublingual dose, 8 milligrams intranasal dose, 16 milligrams intranasal dose and 0.4 milligram naloxone dose. Plasma concentrations were taken at pre-dose, 0.03, 0.07, 0.1, 0.13, 0.17, 0.25, 0.5, 1, 2 4, 8 and 12 hours' post-dose.

Results

[000190] As seen in Table 31 below each of intranasal administration and sublingual administration resulted in significantly greater plasma concentrations than intramuscular administration at all time points tested up to 1 hour after administration. Further intranasal administration of naloxone resulted in significantly greater plasma concentration than sublingual administration at all times points tested up to 1 hour after administration.

[000191] However, at 2 and 4 hours post-dose the mean plasma concentration of naloxone in subjects that were intranasally administered 16 milligrams of naloxone was significantly lower

than that for those subject that were sublingually administered 16 milligrams of naloxone. The same pattern was found with those subjects administered 8 milligram doses of naloxone.

[000192] Further, peak concentration in plasma (C_{max}) and area under the concentration-time curve from time-zero to 1 hour post dose (AUC) followed the exact same pattern as described above for mean plasma concentrations.

Table 44. Mean Plasma Concentration for 8 mg and 16 mg Intranasal and Sublingual Administration

Parameters*	8 mg SL	8 mg IN	16 mg SL	16 mg IN	0.4 mg IM
N	29	28	29	29	30
Conc. @ 0.03 h (ng/mL)	0.18 ± 0.29	6.19 ± 14.47	0.52 ± 0.8	9.29 ± 14.31	0.15 ± 0.29
Conc. @ 0.07 h (ng/mL)	0.62 ± 0.96	13.95 ± 19.06	1.69 ± 1.85	29.69 ± 28.01	0.36 ± 0.38
Conc. @ 0.1 h (ng/mL)	0.88 ± 0.94	18.75 ± 15.61	2.31 ± 2.08	46.34 ± 36.64	0.51 ± 0.41
Conc. @ 0.13 h (ng/mL)	1.17 ± 1.13	20.48 ± 13.11	3.16 ± 3.39	49.31 ± 33.98	0.58 ± 0.39
Conc. @ 0.17 h (ng/mL)	1.54 ± 1.1	19.96 ± 10.73	3.63 ± 3.83	45.77 ± 24.58	0.63 ± 0.36
Conc. @ 0.25 h (ng/mL)	1.98 ± 1.29	16.49 ± 6.71	4.39 ± 4.24	35.04 ± 13.23	0.69 ± 0.4
Conc. @ 0.5 h (ng/mL)	2.03 ± 1.28	9.88 ± 4.42	3.94 ± 2.96	22.35 ± 8.19	0.62 ± 0.22
Conc. @ 1 h (ng/mL)	1.61 ± 0.85	6.29 ± 2.7	2.96 ± 1.66	14.07 ± 5.61	0.51 ± 0.16
C_{max} (ng/mL)	2.03	20.48	4.39	49.31	0.69
AUC @ 1h (ng*h/mL)	1.68	11.18	3.42	24.91	0.57

*Mean ± Standard Deviation

SL denotes sublingual administration

IN denotes intranasal administration

IM denotes intramuscular administration

N denotes number of subjects tested

h denotes hours

Eon7The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

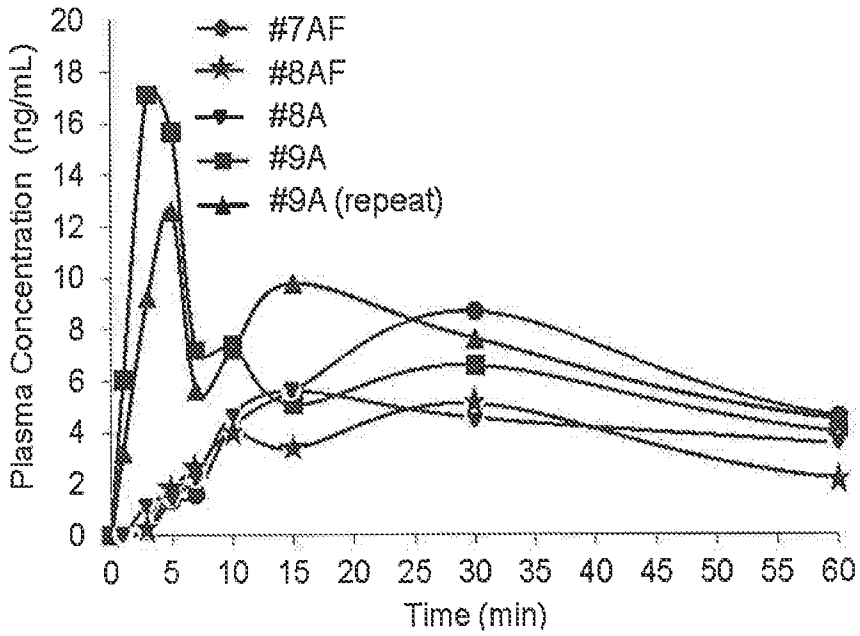
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A liquid spray intranasal formulation comprising an effective amount of naloxone, or a pharmaceutically acceptable salt thereof, from about 10 to about 20% w/w ethanol, water, and a chelating agent, wherein the intranasal formulation does not contain an isotonicity agent or a buffer, wherein w/w denotes weight by total weight of the intranasal formulation.
2. The liquid spray formulation of claim 1, wherein the formulation does not contain sodium chloride, citric acid, benzyl alcohol, or benzalkonium chloride.
3. The liquid spray formulation of claim 1, wherein:
   the formulation further comprises a glycol; and
   the chelating agent is edetate disodium dihydrate.
4. The liquid spray formulation of claim 3, wherein the glycol is propylene glycol.
5. The liquid spray formulation of claim 1, wherein the formulation has a pH from about 3.0 to about 6.0.
6. The liquid spray formulation of claim 1, wherein the formulation further comprises an antioxidant.
7. The liquid spray formulation of claim 7, wherein the antioxidant is sodium ascorbate.
8. A liquid spray intranasal formulation comprising:
   from about 1% to about 16% w/w naloxone, or a pharmaceutically acceptable salt, thereof;
   from about 10 to about 20% w/w ethanol;
   from about 35 to about 85% w/w water; and
   from about 0.0001% to 0.05% w/w of a chelating agent,
   wherein the intranasal formulation does not contain an isotonicity agent or a buffer, wherein w/w denotes weight by total weight of the intranasal formulation.
9. The liquid spray formulation of claim 8, wherein:
   naloxone, or a pharmaceutically acceptable salt thereof is at a concentration from about 2% to about 10% w/w.
10. The liquid spray formulation of claim 8, wherein the chelating agent is edetate disodium dihydrate and wherein the formulation further comprises propylene glycol.

11. The liquid spray formulation of claim 10, wherein the propylene glycol is at a concentration from about 5% to about 10% w/w.
12. The liquid spray formulation of claim 10, wherein the propylene glycol is at a concentration of about 5 % w/w.
13. The liquid spray formulation of claim 8, wherein the chelating agent is edetate disodium dihydrate.
14. The liquid spray formulation of claim 1, wherein the formulation is administered in a nasal spray device.
15. The liquid spray formulation of claim 14, wherein the nasal spray device has a single reservoir comprising about 125 µl to 127 µL of the formulation.
16. The liquid spray formulation of claim 14, wherein about 100 µL of the formulation is delivered by a single actuation.
17. A method of treating opioid dependence, opioid overdose, or congenital insensitivity to pain with anhidrosis in a subject in need thereof, said method including the step of administering a liquid spray formulation according to anyone of claims 1 to 16, wherein the formulation is administered intranasally to said subject.
18. Use of a liquid spray formulation according to anyone of claims 1 to 16 in the manufacture of a medicament for treating opioid dependence, opioid overdose, or congenital insensitivity to pain with anhidrosis in a subject in need thereof, wherein the medicament is administered intranasally to said subject.
19. A liquid spray formulation when used intranasally comprising an effective amount of naloxone, or a pharmaceutically acceptable salt thereof, from about 10 to about 20% w/w ethanol, water, and a chelating agent, wherein the formulation does not contain an isotonicity agent or a buffer, wherein w/w denotes weight by total weight of the formulation.

FIG. 1


Plasma Concentration (ng/mL)
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (min)
#7AF
#8AF
#8A
#9A
#9A (repeat)