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(54) **Title:** INJECTION DEVICE OF FENTANYL

(57) **Abstract:** The present invention relates to an injection device having a reservoir (2) made up of plastic or polymeric material having a rubber stopper (1), filled with an aqueous solution (4) comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof as a sole active agent and ethylenediamine tetraacetic acid or its salt, the aqueous solution having a pH in the range of 4.0 to 5.0 and an impurity at relative retention time of 0.5 minutes is not more than 0.2 % by weight; wherein the aqueous solution is in contact with the rubber stopper (3); wherein the injection device is sterilized by autoclaving and the aqueous solution is stable upon storage at room temperature.

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INJECTION DEVICE OF FENTANYL

FIELD OF THE INVENTION

The present invention relates to an injection device having a reservoir made up of plastic or polymeric material having a rubber stopper, filled with an aqueous solution comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

Fentanyl (N-(1-phenethyl-4-piperidyl)propionanilide) is a potent opioid analgesic. The approved products of fentanyl include tablets, lozenges, transdermal patches and injectable solutions.

The injectable products of fentanyl or its salt are commercially available in the form of conventional vials or ampoules such as for example, Sublimaze™ solution marketed by Akorn Inc. or fentanyl citrate solution marketed by West-ward Pharmaceutical Corp. The solution by West-ward is available in vials having volumes of 2 mL, 5 mL, 20 mL, 50 mL and ampoules having volumes of 2 mL, 5 mL and 20 mL. Sublimaze™ solution is available in ampoules having volumes of 2 mL, 5 mL, 10 mL and 20 mL.

Fentanyl injection products like Sublimaze™ are indicated for analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance and in the immediate post-operative period (recovery room) as the need arises. It is also indicated for use as an opioid/narcotic analgesic supplement in general and regional anaesthesia. It is further indicated for administration with a neuroleptic as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia. It is also indicated for use as an anaesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopaedic procedures.

Fentanyl when formulated as an aqueous solution is prone to chemical degradation and adsorption on surface of containers leading to stability problems. There are no injection products of fentanyl available in the market which are autoclaved and contain aqueous solution of fentanyl in an injection device made up of plastic or polymeric material. While developing such an injectable product of fentanyl, the present inventors faced the problem of

loss of assay and chemical degradation of fentanyl when the aqueous solution of fentanyl having a pH of 4.0 to 5.0 is stored in a reservoir made up of plastic material stoppered with a rubber stopper. Unacceptably high levels of total impurities and other unknown impurity, along with reduction in assay of fentanyl is observed. It is further observed that when the dosage form is autoclaved, it results in further generation of higher levels of impurities.

The present inventors have unexpectedly discovered that use of ethylenediamine tetraacetic acid or its salt like disodium EDTA or disodium edetate prevented the chemical degradation and loss of assay of fentanyl. The present inventors has found that the aqueous solution of fentanyl and ethylenediamine tetraacetic acid or its salt at pH of 4.0 to 5.0 when stored in a plastic container of an injection device, provide stable dosage form. It is surprisingly found that ethylenediamine tetraacetic acid or its salt is able to control not only the drop in assay but also control level of one specific impurity at relative retention time of 0.5 minutes separated using High Performance Liquid Chromatographic technique. Further, inclusion of ethylenediamine tetraacetic acid allow the injection device to be terminally sterilized by autoclaving. This is particularly advantageous in that an injection device filled with solution of fentanyl that is stable to autoclaving is obtained while avoiding otherwise needed costly materials, for instance, lacquered or film coated stoppers, without compromising on the chemical stability of fentanyl.

SUMMARY OF THE INVENTION

The present invention provides an injection device having a reservoir made up of plastic or polymeric material having a rubber stopper, filled with an aqueous solution comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof as a sole active agent and ethylenediamine tetraacetic acid or its salt, the aqueous solution having a pH in the range of 4.0 to 5.0; the solution is in contact with the rubber stopper; wherein the injection device is sterilized by autoclaving.

The present invention preferably provides an injection device having a reservoir made up of plastic or polymeric material having a rubber stopper, filled with an aqueous solution comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof as a sole active agent and ethylenediamine tetraacetic acid or its salt, the aqueous solution having a pH in the range of 4.0 to 5.0 and an impurity at relative retention time of 0.5 minutes is not more than 0.2 % by weight; wherein the aqueous solution is in contact with

the rubber stopper; wherein the injection device is sterilized by autoclaving and the aqueous solution is stable upon storage at room temperature.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents a line diagram of pre-filled syringe according to one embodiment of the present invention, depicting (1) tip cap stopper, (2) reservoir/barrel, (3) plunger stopper having provision of getting attached to a plunger rod and (4) solution of fentanyl that remains in contact with the plunger/rubber stopper filled in the reservoir during shelf life.

DETAILED DESCRIPTION OF THE INVENTION

The term 'stable' as used herein means that the aqueous solution of fentanyl contained in the injection device according to the present invention remains physically and chemically stable upon storage at room temperature (25^0C/60% relative humidity) for a period of at least 12 months. The injection device of the present invention is said to be physically stable when the solution upon visual inspection remains clear and there occurs no precipitation or crystal formation upon storage at room temperature (25^0C/60% relative humidity) for at least 12 months. The injection device of the present invention is said to be chemically stable when the impurity at relative retention time of 0.5 is not more than 0.2 % by weight of fentanyl upon storage at room temperature (25^0C/60% relative humidity) for at least 12 months. As used herein, the percentage of impurities is expressed as percentage by weight of fentanyl. The content of highest unknown impurity is not more than 0.2 % by weight of fentanyl and the content of total impurities is not more than 2.0 % by weight of fentanyl, preferably 0.01 to 1.0 % by weight of fentanyl upon storage at room temperature (25^0C/60% relative humidity) for at least 12 months. Particularly, the injection device of the present invention is said to be chemically stable when the impurity at relative retention time of 0.5 minutes is not more than 0.2 % by weight of fentanyl upon storage at room temperature (25^0C/60% relative humidity) for at least 6 months, the impurity level being 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10 % (or less) by weight of fentanyl.

This impurity at relative retention time of 0.5 minutes is the one that is separated and quantified using the following High Performance Liquid Chromatographic method. The High Performance Liquid Chromatographic separation for the determination of % impurities is achieved on a Inertsil ODS 3V column (250 X 4.6mm, 5µ particle size) using a mobile phase consisting of mixture of buffer (Potassium dihydrogen orthophosphate buffer, pH 3.2 ± 0.1),

acetonitrile and methanol in the ratio of 67:11:22 %v/v respectively. The High Performance Liquid Chromatographic analysis is done at the flow rate of 1.0 ml/min with UV detection at 215 nm. The run time for the analysis is 90 minutes.

The High Performance Liquid Chromatographic analysis for the determination of % assay of fentanyl is achieved on a Inertsil ODS 3V column (250 X 4.6mm, 5µ particle size) using a mobile phase consisting of mixture of buffer (ammonium acetate buffer), methanol, acetonitrile and glacial acetic acid in the ratio of 400:400:200:0.6 by volume respectively adjusted to pH of 6.6 ± 0.1 with glacial acetic acid. The High Performance Liquid Chromatographic analysis is done at the flow rate of 2.0 ml/min with UV detection at 230 nm. The run time for the analysis is 15 minutes. The % assay of fentanyl in the aqueous solution contained in the injection device according to the present invention is in the range of 90-110 % of label claim of fentanyl, preferably in the range of 95 % -105 % of label claim.

Preferably, the aqueous solution of fentanyl according to the present invention remains stable for at least 24 months upon storage at room temperature (25^0C/60% relative humidity). The stability of the solution tested at accelerated storage condition of 40^0C/25% relative humidity for a period of three months and six months corresponds to room temperature stability for a period of 12 months and 24 months, respectively.

'Total impurities' comprise summation of all known and unknown impurities of fentanyl. The total impurities are expressed as % by weight of fentanyl i.e. % of the labelled fentanyl content that is present in the aqueous solution.

The term "consisting essentially of" as used herein denotes the nature of the solution used according to the present disclosure and is intended to mean a ready-to-administer solution of fentanyl or pharmaceutically acceptable salt thereof that does not include excipients employed to prepare nasal formulations like chitosan and pectin or other mucoadhesive polymers, organic solvents like ethanol and propylene glycol, surfactants such as tween 80, polysorbates, poloxamers, spans and the like; preservatives and antioxidants. The term "consisting essentially of" according to the present invention excludes nasal formulations of fentanyl.

According to one aspect of the present invention, the solution according to the present disclosure is suitable for direct parenteral administration, i.e., it is "ready-to-administer", which means that the solution is prepared and filled into the reservoir of the injection device

at the manufacturing site itself and at the time of parenteral administration there is no need of any reconstitution, dilution, mixing or manipulation and the solution can be directly administered parenterally from the injection device to the patient.

The aqueous solution according to the injection device of the present invention comprises fentanyl or pharmaceutically acceptable salt thereof as the sole active ingredient in therapeutically effective amounts. Examples of suitable pharmaceutically acceptable salts of fentanyl for use in accordance with the present disclosure include for example, but are not limited to, citrate, hydrochloride, chloride, sulphate, tartrate, or other similar salt forms. In certain embodiments, the fentanyl may be employed as the free base. In preferred embodiments, the pharmaceutically acceptable salt of fentanyl is fentanyl citrate.

Fentanyl or its pharmaceutically acceptable salt is present in the aqueous solution in an amount ranging from 0.001 mg/ml to 0.15 mg/ml, preferably from about 0.001 to 0.10 mg/ml such as about 0.002, 0.003, 0.004, 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035, 0.04, 0.045, 0.05, 0.055, 0.06, 0.065, 0.07, 0.075, 0.08, 0.085, 0.09 or 0.095 mg/ml, more preferably in an amount ranging from 0.005 mg/ml to 0.08 mg/ml or from about 0.005 to 0.05 mg/ml. Suitably, the amount of fentanyl or its salt used in the present disclosure is expressed as amounts equivalent to fentanyl base.

In one embodiment, fentanyl or its pharmaceutically acceptable salt is fentanyl citrate and it is present in the aqueous solution in an amount equivalent to 0.001 mg/ml to about 0.1 mg/ml of fentanyl base, preferably an amount equivalent to about 0.005 mg/ml to 0.075 mg/ml of fentanyl base, more preferably in an amount equivalent to about 0.005 mg/ml to about 0.05 mg/ml of fentanyl base, more preferably from 0.01 mg/ml to 0.05 mg/ml of fentanyl base. In one embodiment, the ready-to-administer aqueous solution contains fentanyl citrate in an amount equivalent to 0.001 mg/ml to 0.02 mg/ml of fentanyl base. In a separate embodiment, the ready-to-administer aqueous solution contains fentanyl citrate in an amount equivalent to 0.02 mg/ml to about 0.05 mg/ml of fentanyl base. In one specific embodiment, the aqueous solution comprises fentanyl citrate in an amount equivalent to 0.05 mg/ml of fentanyl base. In another specific embodiment, the aqueous solution comprises fentanyl citrate in an amount equivalent to 0.02 mg/ml of fentanyl base. In another embodiment, the aqueous solution comprises fentanyl citrate in an amount equivalent to 0.01 mg/ml of fentanyl base. In a separate embodiment, the aqueous solution comprises fentanyl citrate in an amount equivalent to 0.005 mg/ml of fentanyl base.

The aqueous solution of fentanyl or pharmaceutically acceptable salt thereof is formulated in pharmaceutically acceptable aqueous vehicle such as water for injection.

The aqueous solution of fentanyl according to the injection device of the present invention comprises ethylenediamine tetraacetic acid (EDTA) or its salts. Non limiting example of salts of ethylenediamine tetraacetic acid includes disodium EDTA, disodium edetate, dipotassium EDTA, dipotassium edetate, their hydrates and solvates such as for example disodium EDTA dihydrate, disodium edetate dihydrate, dipotassium EDTA dihydrate and the like. It is unexpectedly discovered by the present inventors that use of ethylenediamine tetraacetic acid or its salt like disodium EDTA prevents chemical degradation of fentanyl citrate in aqueous solution having a pH of 4.0 to 5.0 stored in a plastic or polymeric container of an injection device having a rubber stopper. It is further unexpectedly discovered that ethylenediamine tetraacetic acid or its salt like disodium EDTA allows the solution to be autoclaved without any chemical degradation and provides long term stability. Advantageously, use of costly materials for example lacquered or film coating on stoppers of the injection device may be avoided without compromising the solution stability.

In one embodiment, the ethylenediamine tetraacetic acid or its salt is present in the aqueous solution at a concentration ranging from about 0.3 mg/ml to 3.5 mg/ml, preferably from about 0.4 mg/ml to 3.0 mg/ml, more preferably from about 0.4 mg/ml to 2.5 mg/ml such as for example 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 1.60, 1.70, 1.80, 1.90, 2.0, 2.1, 2.2, 2.3, 2.4 or 2.5 mg/ml. In one embodiment, ethylenediamine tetraacetic acid or its salt is present in the aqueous solution at a concentration ranging from about 0.4 to 2.0 mg/ml. In some embodiments, ethylenediamine tetraacetic acid or its salt is present at a concentration ranging from about 1.0 mg/ml to 2.0 mg/ml. In one embodiment, ethylenediamine tetraacetic acid or its salt is disodium EDTA and it is present in the aqueous solution at a concentration ranging from about 0.3 mg/ml to 3.5 mg/ml, preferably from about 0.4 mg/ml to 3.0 mg/ml, more preferably from about 0.4 to 2.5 mg/ml. In preferred embodiment, disodium EDTA is present in the aqueous solution at a concentration ranging from 0.4 to 2.0 mg/ml. In some other embodiments, ethylenediamine tetraacetic acid or its salt is present at a concentration ranging from about 1.0 to 2.5 mg/ml, or 1.5 to 2.0 mg/ml.

In aqueous solutions having pH in the range of 4.0 to 5.0 adjusted using citric acid- sodium citrate buffer but having lower amount of disodium salt of ethylenediamine tetraacetic acid i.e. 0.1 mg/ml or 0.2 mg/ml, the level of impurity at RRT 0.5 minutes was found to increase

beyond the acceptable limit of 0.2 % by weight upon storage at 40^0C/25% relative humidity for 3 months and 6 months respectively (see Table 3- stability data of comparative examples 5 and 6 respectively). Therefore, the aqueous solution of fentanyl according to the present invention preferably comprises ethylenediamine tetraacetic acid or its salt in an amount of 0.4 mg/ml or more, preferably in the range of 0.4 mg/ml to 2.0 mg/ml, such as for example 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 1.60, 1.70, 1.80, 1.90 or 2.0 mg/ml. The stability study results lead to a novel finding that a specific amount of ethylenediamine tetraacetic acid or its salt is required to control the impurity at RRT 0.5 minutes, when storage at 40^0C/25% relative humidity.

The pH of the aqueous solution of fentanyl according to the injection device of the present invention is in the range of 4.0 to 5.0, preferably 4.0 to 4.8, such as for example 4.05, 4.10, 4.15, 4.20, 4.25, 4.30, 4.35, 4.40, 4.45, 4.50, 4.55, 4.6, 4.65, 4.70, 4.75 and 4.80 or intermediate ranges thereof. In one embodiment, the pH of the aqueous solution of fentanyl is in the range of about 4.1 to 4.7. In some embodiments, the pH of the aqueous solution of fentanyl is in the range of about 4.2 to 4.6 or 4.7. The term "about" as used herein refers to the pH of ± 0.1 of the stated pH value. The pH is adjusted in the given range by use of a pH adjusting agent. Examples of suitable pharmaceutically acceptable pH adjusting agents that may be used, include, but are not limited to, citric acid, acetic acid, lactic acid, tartaric acid, fumaric acid, malic acid, hydrochloric acid, sulphuric acid, methane sulphonic acid, potassium hydroxide, sodium hydroxide or combinations thereof. In one or more embodiments, the aqueous solution of fentanyl according to the injection device of the present invention may further comprise a buffer or buffering agent to maintain the pH of the solution in the range of 4.0 to 5.0. Example of suitable buffers or buffering agents that may be used to adjust and maintain the pH of the solution may be selected from buffers that provide a pH in the range of 4.0 to 5.0 such as for example but not limited to pharmaceutically acceptable buffer systems such as citrate buffer, tartrate buffer, acetate buffer, lactate buffer and the like or mixtures thereof. The aqueous solution of fentanyl according to preferred embodiments is free of buffers that provide pH above 5.0, 6.0, 7.0 or 8.0 such as for example but not limited to, phosphate buffers. In a preferred embodiment, the buffering agent is selected from citric acid, sodium citrate or combination thereof, i.e. citrate buffer. Citric acid may be present in an amount ranging from about 0.01 mg/ml to 1.0 mg/ml, preferably in an amount ranging from about 0.05 mg/ml to about 0.5 mg/ml, more preferably in an amount ranging from about 0.05 mg/ml to about 0.35 mg/ml. In one embodiment, citric

acid is present at a concentration of about 0.35 mg/ml. Sodium citrate is present in the aqueous solution in an amount ranging from about 0.01 mg/ml to 2.0 mg/ml, preferably in an amount ranging from about 0.1 mg/ml to about 1.0 mg/ml, more preferably in an amount ranging from about 0.2 mg/ml to about 0.8 mg/ml,. In one embodiment, sodium citrate is present at a concentration of about 0.5 mg/ml.

The presence of citric acid and/or sodium citrate has been found to impact the level of impurity at relative retention time of 0.5 minutes. When the pH of the solution is adjusted to pH range of 4 to 5 using other inorganic acids such as hydrochloric acid, but no citric acid and/or sodium citrate is added, the impurity at relative retention time of 0.5 minutes has been found to be little higher, for example, 0.126 % (see Table 3 -stability data of example 2- 6 month storage at 40^0C/25% relative humidity), compared to the aqueous solution that have citric acid or citrate buffer (for example, 0.023 %, see Table 3- stability data of example 1-6 month storage at 40^0C/25% relative humidity).

According to one embodiment, the sterile, aqueous solution of fentanyl is free of non-aqueous solvents or co-solvents such as alcohols or glycols. In one embodiment, the solution is free of ethanol and propylene glycol. Preferably, the sterile aqueous solution of fentanyl is free of sugar or sugar alcohols like dextrose, sorbitol, mannitol and the like.

In one embodiment, the sterile, aqueous solution of fentanyl is free of mucoadhesive polymers like pectin or chitosan and surfactants like tweens, spans, poloxamers, polysorbates and the like. These excipients are generally used to formulate nasal compositions and are not intended to be used in the injectable solution of the present invention. Nasal compositions besides having these added excipients generally have higher concentration of fentanyl such as for example 0.5 mg/ml to 20 mg/ml, which are not suitable for preparing ready-to-administer injectable formulations.

In one embodiment, the sterile, aqueous solution of fentanyl is free of preservatives such as for example benzalkonium chloride, phenol, benzyl alcohol, phenyl ethyl alcohol, propyl hydroxybenzoate, sorbic acid or its salts. In one embodiment, the sterile aqueous solution of fentanyl is free of antioxidants such as for example sodium metabisulphite, sodium sulphite and the like.

The sterile, injection device of the present invention is suitable for administering fentanyl by parenteral routes such as, but not limited to, intravenous (IV), intra-muscular (IM) or sub-

cutaneous (SC) routes. In some embodiments, the sterile, injection device of the present invention is in the form of a prefilled syringe or autoinjector device suitable for intra-muscular (IM) or sub-cutaneous (SC) administration of fentanyl. The sterile, injection device of the present invention is preferably adapted for one time or single administration and not for multiple administrations.

The present invention provides an injection device having a reservoir made up of plastic or polymeric material having a rubber stopper, the reservoir being filled with an aqueous solution comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof as a sole active agent and ethylenediamine tetraacetic acid or its salt, the aqueous solution having a pH in the range of 4.0 to 5.0; wherein the injection device is sterilized by autoclaving, wherein the solution remains in contact with the rubber stopper throughout the shelf life.

In one embodiment according to the present invention, the injection device of fentanyl comprises a reservoir made up of plastic or polymeric material having a rubber stopper filled with an aqueous solution, the solution comprising:

i) fentanyl citrate as a sole active ingredient in an amount equivalent to about 0.005 mg/ml to 0.1 mg/ml of fentanyl base,
ii) 0.4 to 3.0 mg/ml of disodium EDTA,
iii) a pH adjusting agent and/or buffering agent,
iv) pH in the range of 4.0 to 5.0,
v) water for injection, and
vi) an impurity at relative retention time of 0.5 minutes of not more than 0.2 % by weight of fentanyl;

wherein the aqueous solution is in contact with the rubber stopper,

wherein the injection device is sterilized by autoclaving,

wherein the aqueous solution is stable upon storage at room temperature for a period of at least 12 months.

In one embodiment according to the present invention, the injection device of fentanyl comprises a reservoir made up of plastic or polymeric material having a rubber stopper filled with an aqueous solution, the solution comprising:

i) fentanyl citrate as a sole active ingredient in an amount equivalent to 0.01 mg/ml to 0.05 mg/ml of fentanyl base,
ii) 0.4 mg/ml to 2.0 mg/ml of disodium EDTA,
iii) a pH adjusting agent and/or buffering agent,
iv) pH in the range of about 4.1 to 4.7 or 4.8,
v) water for injection, and
vi) an impurity at relative retention time of 0.5 minutes of not more than 0.2 % by weight of fentanyl,

wherein the plastic or polymeric material comprises a cyclo-olefin polymer,
wherein the aqueous solution is in contact with the rubber stopper,
wherein the injection device is sterilized by autoclaving at a temperature in the range of 110°C to 130°C for time period in the range of 5 to 60 minutes,
wherein the aqueous solution is stable upon storage at room temperature for a period of at least 12 months.

In one embodiment, the present invention provides an injection device of fentanyl comprising a reservoir made up of plastic or polymeric material having a rubber stopper filled with an aqueous solution, the solution comprising or consisting essentially of:

i) fentanyl citrate as a sole active ingredient in an amount equivalent to 0.01 mg/ml to 0.05 mg/ml of fentanyl base,
ii) disodium EDTA in amount ranging from about 0.4 mg/ml to 2.0 mg/ml,
iii) citric acid in amount ranging from about 0.05 mg/ml to about 0.35 mg/ml,
iv) optionally a pH adjusting agent,
v) pH in the range of about 4.2 to 4.7,
vi) water for injection, and
vii) an impurity at relative retention time of 0.5 minutes of not more than 0.2 % by weight of fentanyl;

wherein the aqueous solution is in contact with the rubber stopper,

wherein the injection device is sterilized by autoclaving,

wherein the aqueous solution is stable upon storage at room temperature for a period of at least 12 months.

In one specific embodiment, the present invention provides an injection device of fentanyl comprising a reservoir made up of plastic or polymeric material having a rubber stopper filled with an aqueous solution, the solution comprising or consisting essentially of:

i) fentanyl citrate as a sole active ingredient in an amount equivalent to 0.05 mg/ml of fentanyl base,
ii) disodium EDTA in amount ranging from about 0.4 to 2.0 mg/ml,
iii) citric acid in amount ranging from about 0.05 mg/ml to about 0.35 mg/ml,
iv) sodium citrate in an amount ranging from about 0.2 mg/ml to about 0.8 mg/ml,
v) optionally a pH adjusting agent,
vi) pH in the range of 4.2 to 4.7,
vii) water for injection, and
viii) an impurity at relative retention time of 0.5 minutes of not more than 0.2 % by weight of fentanyl;

wherein the aqueous solution is in contact with the rubber stopper,

wherein the injection device is sterilized by autoclaving,

wherein the aqueous solution is stable upon storage at room temperature for a period of at least 12 months.

In another aspect, the present invention provides a sterile, ready-to-administer aqueous solution of fentanyl suitable for parenteral administration comprising fentanyl citrate as the sole active ingredient, ethylenediamine tetra-acetic acid or its salt, water for injection, and an impurity at relative retention time of 0.5 minutes of not more than 0.2 % by weight of fentanyl; wherein the pH of the solution is in the range of 4.0 to 5.0, wherein the solution is contained in a reservoir of an injection device, said reservoir comprising a plastic or polymeric material and having a rubber stopper, wherein the solution is in contact with a rubber stopper, wherein the solution is sterilized by autoclaving, further wherein the solution is stable upon storage at room temperature for a period of at least 12 months.

The injection device of the present invention comprises a reservoir for holding the sterile, aqueous solution of fentanyl or pharmaceutically acceptable salt thereof. The reservoir of the injection device may be made up of a plastic or polymeric material. The plastic or polymeric material is selected from, but not limited to, cycloolefin polymer, cycloolefin copolymer,

polyolefins, styrene-polyolefin based polymers and block co-polymers, polycarbonates and the like.

According to the present invention, the injection device may be selected from, but not limited to, a prefilled syringe, a pen injector or an autoinjector device. In preferred embodiments, the injection device is a prefilled syringe.

In one embodiment, the prefilled syringe comprises following components: a reservoir such as for example a barrel or a cartridge which stores the aqueous solution; a stalked needle attached at one end of the reservoir; a needle shield or tip cap that covers the needle and seals the needle tip opening, optionally a rigid shield covering the needle shield or tip cap; a plunger stopper at other end of the reservoir that stoppers and seals the aqueous solution filled in the reservoir; a plunger rod that fits into the plunger stopper and is used to push the plunger stopper along with the solution towards the needle end while administering the drug. The stalked needle may be made up of stainless steel.

In one or more embodiments, the prefilled syringe comprises a reservoir such as for example a barrel or a cartridge which is needleless and has a luer tipped lock or tip cap stopper at one end with provision for attaching a needle before use. The reservoir containing the sterile aqueous solution of drug is further sealed with a stopper such as a plunger stopper at the other end. The plunger stopper has provision of getting attached to a plunger rod that fits into the plunger stopper and is used to push the plunger stopper along with the solution towards the needle end while administering the drug.

The stoppers such as plunger stopper or tip cap stopper or needle shields provides physical and sterility barrier against exterior environment. The plunger stopper, the tip cap stopper or needle shields of the injection device may be made up of a rubber or elastomeric material or other suitable material such as high density polyethylene or low density polyethylene. In preferred embodiment, the plunger stopper or tip cap stopper or needle shield is made up of rubber or elastomeric material selected from bromobutyl rubber, chlorobutyl rubber, styrene butadiene rubber and the like and may be referred to as rubber stoppers. Preferably, the tip cap stopper is made up of chlorobutyl rubber and the plunger stopper is made up of bromobutyl rubber.

The volume of the sterile aqueous solution of fentanyl contained in the reservoir of the injection device ranges from about 5 ml to 100 ml, preferably from about 10 ml to 60 ml,

more preferably from about 20 ml to 50 ml. According to one preferred embodiment, the volume of sterile aqueous solution of fentanyl filled in the reservoir is 20 ml. According to another preferred embodiment, the volume of sterile aqueous solution of fentanyl filled in the reservoir is 50 ml.

The container may optionally be packaged or enclosed in a secondary packaging. The secondary packaging may comprise a blister pack or an overwrap pouch and/or an opaque carton. A suitable oxygen scavenger may optionally be placed inside the secondary packaging. In one embodiment, the secondary packaging comprises an aluminium overwrap pouch and an oxygen scavenger. In a separate embodiment, the secondary packaging comprises an EVOH blister with AlOx lidding film and an oxygen scavenger.

The aqueous solution of fentanyl contained in the injection device according to the present invention is sterilized by autoclaving the aqueous solution filled in the injection device. The aqueous solution is terminally sterilized by moist heat sterilization in an autoclave. The autoclaving is preferably carried out at a temperature of 121° C. for 15 minutes. In one or more embodiments, the autoclaving may be carried out at temperatures varying from about 110° C to 130° C, at sterilization pressure in the range of about 2.0 to 4.0 bar G, for a period of time varying from about 5 minutes to 60 minutes. In one preferred embodiment, the ready-to-administer aqueous solution of the present disclosure is subjected to membrane filtration followed by filling the solution into the reservoir of an injection device and subjecting it to terminal sterilization by autoclaving at 121° C for 15 minutes.

The injection device of fentanyl according to the present invention is suitable for use as an analgesic of short duration during anaesthetic periods, premedication, induction and maintenance and in the immediate post-operative period (recovery room) as the need arises. It is also suitable for use as an opioid or narcotic analgesic supplement in general and regional anaesthesia. It can also be administered with a neuroleptic as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia. It is also suitable for use as an anaesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopaedic procedures.

The present disclosure, in one embodiment, provides a kit comprising plurality of injection devices having different volumes of solution of fentanyl, wherein the injection devices may have same or different concentration of fentanyl, such as for example, injection device having

volume in the range of 5 to 50 ml and concentration of fentanyl in the range of 5 to 50 mcg/ml. The kit comprising the injection devices are suitable for administering the desired dose of fentanyl for the particular indication, such as administering the low, moderate or high doses for the indication of adjunct to general anaesthesia. In one embodiment, the present disclosure provides a kit comprising plurality of injection devices having one set of large volume injection devices and further sets of small volume injection devices filled with solution of fentanyl or a salt thereof at same or different concentrations, such that one or more injection device (s) from the first set and/or one or more injection device(s) from the second or further third set, directly administers the desired dose of fentanyl calculated based on body weight and approved indication.

According to the present invention, the desired dosage of fentanyl can be administered by using one or more injection device/s of the present invention, for example, one or more injection device having varying volume and concentration of fentanyl. For example, to administer fentanyl citrate injection for adjunct to general anaesthesia for low, moderate and high doses, following injection device/s (pre-filled syringe/s) having varying strength and volume specified therein can be used to achieve the desired daily dose for a 100 kg person.

Dose Indication	Recommended Dose (mcg/kg)	Desired Dose for a 100 kg person (mcg)	Details of Injection Devices used for administering desired dose				
			Fentanyl Strength in solution (mcg/ml)	Fill Volume (mL)	Drug content per device mcg	No of device	Dose administered (mcg)
Low dose	2	200	5	20	100	2	200
Moderate dose (2 to 20mcg/kg)	2	200	10	20	200	1	200
	3	300	10	30	300	1	300
	5	500	10	50	500	1	500
	10	1000	20	50	1000	1	1
High dose (20 to 50 mcg/kg)	20	2000	50	20	1000	2	2000
	30	3000	50	30	1500	2	3000
	50	5000	50	50	2500	2	5000

The desired volume of the fentanyl solution from the injection device/s is suitably injected or infused to administer the desired dose.

Hereinafter, the invention will be more specifically described by way of examples. The examples are not intended to limit the scope of the invention and are merely used as illustrations.

EXAMPLES

Table 1: Examples 1 to 4

Composition	Working Examples according to the present invention (Amount in mg/ml)			
	1	2	3	4
Fentanyl citrate equivalent to fentanyl base	0.05	0.05	0.05	0.05
Disodium EDTA dihydrate	2.0	2.0	2.0	0.4
Citric acid	0.05	-	0.35	0.35
Sodium citrate	-	-	0.5	0.5
NaCl	9	9	-	-
HCl/NaOH	q.s. to adjust pH			
pH	4.2	4.2	4.63	4.65
Water for injection	q.s. to 1 ml			

Method of Preparation: Water for injection was taken in a container and was purged with Nitrogen to keep the dissolved oxygen content to less than 1 ppm. All the excipients were added and dissolved gradually in water for injection with stirring. To this, fentanyl citrate was added and dissolved gradually with stirring. The pH of the solution was checked, and was adjusted to the desired pH value using suitable volume of hydrochloric acid or sodium hydroxide solution. The volume was made up with water for injection. The solution was filtered aseptically using 0.2 µm membrane filter into a filling vessel. The solution (50ml) was aseptically filled in reservoir of prefilled syringe made up of polymeric material comprising cyclo-olefin polymer and stoppered by a plunger stopper made up of an elastomeric material comprising bromobutyl rubber. The solution comes in contact with the rubber stopper. After filling, the solution was autoclaved at 121°C for 15 minutes. After autoclaving, the pre-filled syringes were packaged in a blister packaging comprising an EVOH blister with AlOx lidding film and an oxygen scavenger. The manufacturing operations were carried out under sodium vapour lamp.

COMPARATIVE EXAMPLES

Table 2: Comparative Examples 1 to 6

Composition	Comparative Examples (Amount in mg/ml)					
	1	2	3	4	5	6
Fentanyl citrate equivalent to fentanyl base	0.05	0.05	0.05	0.01	0..05	0.05
Disodium EDTA dihydrate	-				0.1	0.2
Citric acid	0.05	-	-	-	0.35	0.35
Sodium citrate	-	-	-	-	0.5	0.5
NaCl	9	9	-	9	--	--
HCl/NaOH	q.s to adjust pH					
pH	4.2	4.2	4.2	4.2	4.72	4.64
Water for injection	q.s. to 1 ml					

Method of Preparation: Method similar to that followed for examples 1 to 4, described above was followed, except that the excipients varied as per composition given in Table 2. In comparative example 4, the plunger rubber stopper was coated with a fluoropolymer film made up of ethylene tetrafluoro ethylene. In comparative examples 1, 2, 3, 5 and 6, the plunger stopper were uncoated, similar to examples 1 to 4.

Stability Study: The sterile, aqueous solution of fentanyl citrate of examples 1 to 4 (of the present invention) and comparative examples 1 to 6 contained in the pre-filled syringe were stored at room temperature (25°C/60% relative humidity) and at accelerated testing condition of 40^0C/25% relative humidity and were evaluated for stability indicating parameters at various time points. The assay (%) of fentanyl and the content of impurities were analyzed by High Performance Liquid Chromatographic procedure as described above under the definition 'stable'. The observed values of stability indicating parameters, i.e. assay (%); content (%) of total impurities and content (%) of Impurity at relative retention time 0.5, for the comparative and working examples are given below in Table 3:

Table 3: Stability Indicating Parameters

	Parameters monitored to evaluate stability of the solution when stored in prefilled syringe and autoclaved									Observation regarding stability
	Assay (%)			Total Impurities (%)			Impurity at RRT 0.5 (%)			
Storage Condition	Before autoclaving	After autoclaving	Upon storage at 40^0C/ 25%RH	Before autoclaving	After autoclaving	Upon storage at 40^0C/ 25%RH	Before Autoclaving	After autoclaving	Upon storage at 40^0C/ 25%RH	
Time Point	Initial	Initial	(*month)	Initial	Initial	(*month)	Initial	Initial	(*month)	
COMPARATIVE EXAMPLES										
Comparative Example 1	99.1	98.12	94.0 (6*)	0.01	0.137	1.945 (6*) 1.9 (1*)	ND	ND	0.545 (6*) 0.535 (1*)	Impurity at RRT 0.5 increased to unacceptable levels.
Comparative Example 2	100.69	98.97	96.85 (6*)	0.163	0.33	1.659 (6*) 1.423 (1*)	0.046	0.08	0.421 (6*) 0.437 (1*)	Impurity at RRT 0.5 increased to unacceptable levels
Comparative Example 3	99.73	98.56	98.49 (6*)	0.153	0.354	1.522 (6*)	ND	0.078	0.453 (6*)	Impurity at RRT 0.5 increased to unacceptable levels
Comparative Example 4	NA	100.35	94.91 (1*)	NA	0.499	3.437 (1*)	NA	0.184	0.879 (1*)	Impurity at RRT 0.5 increased to unacceptable levels and undesirable drop in assay observed upon storage
Comparative Example 5	NA	100.86	94.0 (3*)	NA	0.193	1.208 (3*);	NA	ND	0.33 (3*);	Impurity at RRT 0.5 increased to unacceptable levels after 3 months.
Comparative Example 6	NA	98.26	94.08 (6*) 97.32 (3*);	NA	0.042	0.713 (6*); 0.465 (3*);	NA	ND	0.221 (6*); 0.12 (3*);	Impurity at RRT 0.5 increased to unacceptable levels after 6 month.
EXAMPLES OF THE INVENTION										No dramatic increase in the impurity at RRT 0.5 observed and % assay remains in limits upon autoclaving and upon storage
Example 1	100.31	99.02	97.55 (6*)	0.009	0.026	0.097 (6*); 0.075 (3*)	ND	ND	0.023 (6*); 0.032 (3*)	
Example 2	NA	99.42	97.93 (6*)	NA	0.046	0.511 (6*) 0.431 (3*);	NA	0.026	0.126 (6*); 0.114 (3*);	
Example 3	97.16	98.34	97.03 (6*)	NA	0.029	0.372 (6*); 0.20 (3*)	NA	0.009	0.086 (6*); 0.054 (3*)	
Example 4	NA	96.75	98.35 (6*)	NA	0.091	0.562 (6*); 0.269 (3*)	NA	ND	0.176 (6*); 0.062 (3*)	

ND-Not Detected; NA- Not Analyzed; RRT-relative retention time; (*) represents number of months

Conclusion: The solutions of comparative examples 1, 2, 3 and 4 that are devoid of ethylene diamine tetra acetic acid or its salt like disodium EDTA, are unstable upon storage such that the content of Impurity at relative retention time 0.5 increased to unacceptable levels (>0.2 %) upon storage at accelerated testing condition of 40^0C/25% relative humidity. It is

important to note that there was an undesirable drop in assay of fentanyl observed upon storage in case of comparative example 4 in which the rubber stopped was coated. This indicates that there are factors other than rubber stopper that also impact the stability of the fentanyl, when subjected to autoclaving. Further, a substantial rise in content of total impurities was observed upon storage.

In contrast, the solution of working examples 1 to 4 according to the present invention, were found to be stable upon autoclaving and upon storage, such that the content of Impurity at relative retention time of 0.5 minutes was not more than 0.2 % by weight upon storage at accelerated testing condition of 40^0C/25% relative humidity for six months. Also, there was no substantial drop in assay of fentanyl and no substantial increase in the content of total impurities observed upon storage. Further, the solution remains clear without any sign of precipitation or crystal formation upon storage at 40^0C/25% relative humidity for 6 months. The stability at accelerated testing condition of 40^0C/25% relative humidity for six months corresponded to room temperature stability for shelf life period of 24 months.

CLAIMS:

1. An injection device having a reservoir made up of plastic or polymeric material having a rubber stopper, filled with an aqueous solution comprising therapeutically effective amount of fentanyl or pharmaceutically acceptable salt thereof as a sole active agent and ethylenediamine tetraacetic acid or its salt, the aqueous solution having a pH in the range of 4.0 to 5.0 and an impurity at relative retention time of 0.5 minutes is not more than 0.2 % by weight; wherein the aqueous solution is in contact with the rubber stopper; wherein the injection device is sterilized by autoclaving and the aqueous solution is stable upon storage at room temperature.

2. The injection device as claimed in claim 1, wherein pharmaceutically acceptable salt of fentanyl is fentanyl citrate and it is present in an amount equivalent to about 0.001 mg/ml to 0.10 mg/ml of fentanyl base.

3. The injection device as claimed in claim 2, wherein fentanyl citrate is present in an amount equivalent to about 0.005 mg/ml to 0.05 mg/ml of fentanyl base.

4. The injection device as claimed in claim 1, wherein salt of ethylenediamine tetraacetic acid is a disodium salt.

5. The injection device as claimed in claim 4, wherein disodium salt of ethylenediamine tetraacetic acid is present in the aqueous solution in an amount ranging from about 0.4 mg/ml to about 2.0 mg/ml.

6. The injection device as claimed in claim 1, wherein the volume of solution contained in the reservoir of the injection device ranges from 10 ml to 100 ml.

7. The injection device as claimed in claim 1, wherein the aqueous solution further comprises a buffering agent selected from citric acid, sodium citrate or combination thereof.

8. The injection device as claimed in claim 7, wherein citric acid is present in an amount ranging from about 0.01 mg/ml to 1.0 mg/ml.

9. The injection device as claimed in claim 1, wherein the aqueous solution is free of a surfactant, non-aqueous alcoholic solvent, mucoadhesive agent, preservative and antioxidant.

10. The injection device as claimed in claim 1, wherein the injection device is a pre-filled syringe.

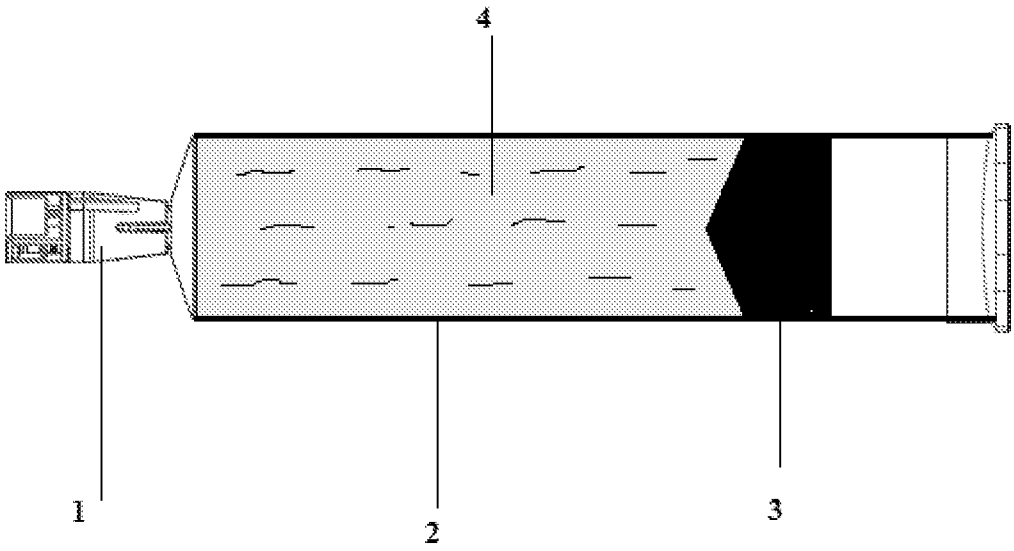

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2019/050537

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/4468*** (2006.01); ***A61M 5/28*** (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, A61M

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

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

EPODOC, TXTE, TXTG, medline, xpesp

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016203497 A1 (SUN PHARMACEUTICAL INDUSTRIES LTD) 22 December 2016 (22.12.2016) claims 1,4,5,8,9	1-8,10
A	Donnelly RF, "Stability of Fentanyl Citrate in Polyolefin Bags", Int. J. Pharm. Compd., 2016 Nov-Dec.; 20(6); pages 514-516 whole document	1-8,10
A	McCluskey S.V. et al.,"Stability of fentanyl 5 µg/ml diluted with 0.9% sodium chloride injection and stored in polypropylene syringe", American Journal of Health-System Pharmacy, Vol 66, Issue 9, 1 May 2009, pages 860-863 whole document	1-8,10
A	Roy S D. et al.,"Solubility Behaviour of Narcotic Analgesics in Aqueous Media: Solubility and Dissociation Constants of Morphine, Fentanyl, and Sufentanil", Pharmaceutical Research, Vol. 6, No. 2, 1989 whole document	1-8,10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2019 (22.10.2019)	04 November 2019 (04.11.2019)
Name and mailing address of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24-535	Authorized officer KRENN M. Telephone No. +43 / 1 / 534 24-435

INTERNATIONAL SEARCH REPORT

International application No.

PCT / IN 2019/050537

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

A negative characterization is only allowed in case of a delimitation of a subject matter from the state of the art. This is presently not the case.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT / IN 2019/050537

Patent document cited in search report			Patent family member(s)			Publication date
WO	A1	2016203497	WO	A1	2016203497	2016-12-22
			US	A1	2019117560	2019-04-25
			JP	A	2018517751	2018-07-05
			US	A1	2016367476	2016-12-22