**FORM 2**

**THE PATENTS ACT 1970**
**(SECTION 39 OF 1970)**
**&**
**THE PATENTS RULES, 2003**

**COMPLETE SPECIFICATION**
**(See section 10; rule 13)**

# "STABLE INJECTABLE COMPOSITIONS OF EPINEPHRINE"

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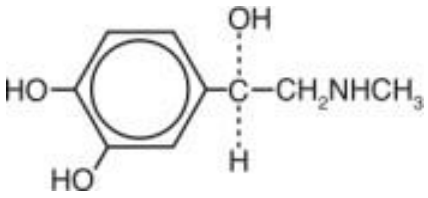
The following specification describes the invention and manner in which it is to be performed.

## FIELD OF THE INVENTION

The present subject matter relates to stable injectable compositions comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent and optionally other pharmaceutically acceptable excipients. Further, the subject matter provides a process of preparing such composition and use thereof.

## BACKGROUND OF THE INVENTION

Epinephrine, also known as adrenaline, is a sympathomimetic catecholamine. Chemically, epinephrine is (-)-3,4- Dihydroxy-α-[(methylamino)methyl]benzyl alcohol with the following structure:




Epinephrine is available in a variety of formulations suited for different clinical indications and routes of administration, for example by injection, by infusion, by inhalation, or by topical administration. Its uses include at treatment of allergic reactions (Type 1), including anaphylaxis, hypotension with septic shock or cardiogenic, hemorrhagic, and traumatic shock, bronchospasm or asthmatic attack, sensitivity reactions, cardiac arrhythmias, GI and renal hemorrhage, superficial bleeding, premature labor, hypoglycemia, and. restricting the distribution of locally administered drugs such as local anesthetics, reducing nasal congestion and/or as performance aid in emergency situations.

US 2008/0269347 discloses epinephrine formulations comprising epinephrine, EDTA, and at least one antioxidant, wherein the antioxidant is selected from the group consisting of cysteine, citric acid, thioglycerol, acetylcysteine, and a combination thereof.

US2016/113891 discloses stable epinephrine formulations with citric acid as antioxidant but with only very low epinephrine concentrations.

US9119876B1 discloses epinephrine formulations comprising a buffer system, an antioxidant, a transition metal complexing agent, a pH lowering agent, a tonicity regulating agent, optionally a preservative, and optionally a solvent; wherein the formulations comprise high buffer concentrations i.e., in the range of about 10mM to about 70mM.

US FDA approved and commercially available epinephrine compositions include Adrenalin® in the form of single and multi-dose vials, and other epinephrine injections including single dose ampoules, multi-dose vials, pre-filled syringes, and auto-injectors (ex: Epipen®, Adrenaclick® and Auvi-Q®) for treatment of allergic reactions and septic shock.

Adrenalin® formulation contains 1.0 mg/mL epinephrine, 7.3 mg/mL sodium chloride, 0.457 mg/mL sodium metabisulfite, 1mg/ml NaOH, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, 5.32 mg of 4% hydrochloric acid to adjust pH, and water for injection.

The Epipen® formulation contains 1.0 mg/mL epinephrine (Epipen® Jr formulation 0.5 mg/mL epinephrine), 6.0 mg/mL sodium chloride, 1.67 mg/mL sodium metabisulfite ($Na_2S_2O_5$), hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.2–5.0. The Epipen® has shelf-life of 20 months.

Adrenaclick® has a similar composition to Epipen®, but includes sodium bisulfite instead of sodium metabisulfite, chlorobutanol as preservative, hydrochloric acid and sodium hydroxide to adjust pH. Auvi-Q® has a similar composition to Adrenaclick® but does not contain chlorobutanol.

Epinephrine single-dose ampoule by Belcher contains 1 mg epinephrine, sodium chloride 8.6 mg, hydrochloric acid 6.00 mg as a dissolution agent and pH adjustment, water for injection and is free of preservatives and antioxidants.

Epinephrine pre-filled syringe by Belcher contains 1 mg epinephrine, 8.6 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid for pH adjustment and water for injection.

Epinephrine is destroyed readily in alkaline solutions by aldehydes, weak oxidizing agents, oxygen of the air and by auto-oxidation involving the formation of adrenaline-o-quinone, which in turn converts to adrenochrome. In alkaline solution and when exposed to air, light or elevated temperature epinephrine turns pink from oxidation to adrenochrome which is further degraded to

adrenolutin and melanin. Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.

In addition, antioxidants such as sulfite antioxidants can directly react with epinephrine to form a biologically inactive sulfonic acid derivative, epinephrine sulfonic acid (ESA). The safety and/or toxicity of ESA in commercial epinephrine products for anaphylactic treatment are still not well understood. In addition, the potency of epinephrine formulations also can be substantially degraded due to such reaction over product shelf-life.

pH plays vital role in stability of epinephrine. Using buffers, the pH of the product can be sustained throughout the shelf life which ultimately provide stable formulation with improved shelf life.

It is recommended that persons at risk of anaphylaxis, and persons responsible for children at risk for anaphylaxis, always maintain one or more automatic epinephrine injectors. Commercially available epinephrine auto injectors have a shelf –life of about 20 months. Thus an objective of the present subject matter was to develop stable epinephrine injection with improved degradation profile and therefore longer shelf-life.

The inventors of present subject matter, surprisingly found that the stable injectable pharmaceutical compositions of epinephrine can be obtained by using low concentrations of buffering agent with or without sulfite antioxidants and such composition is characterized by significantly low level of impurities and longer shelf-life.

**SUMMARY OF THE INVENTION:**

The present subject matter relates to a stable injectable pharmaceutical composition comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent and optionally other pharmaceutically acceptable excipients. Further, the subject matter provides a process of preparing such composition and use thereof.

In an embodiment, the stable injectable pharmaceutical composition comprises epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, water for injection, and optionally other pharmaceutically acceptable excipients.

In an embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, and optionally other pharmaceutically acceptable excipients.

In an embodiment, the present subject matter relates to a stable injectable aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof wherein said composition comprises low concentrations of buffering agent to sufficiently maintain the required pH and provide improved physiochemical stability.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof; wherein the composition comprises a buffering agent in an amount of about 0.1 mM to less than 10 mM, preferably in an amount of about 1 mM to 6 mM and more preferably in an amount of about 2 mM to 5 mM.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof; wherein the composition comprises a buffering agent in an amount of about 0.01 mg/ml to less than 2 mg/ml, preferably in an amount of about 0.2 mg/ml to 1.2 mg/ml and more preferably in an amount of about 0.3 mg/ml to 1 mg/ml.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof; wherein the composition comprises a buffering agent in an amount of about 0.1 to less than 2 mg/ml, preferably in an amount of about 0.1 to 1 mg/ml, and more preferably in an amount of about 0.5 to 1 mg/ml.

In an embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, and optionally other pharmaceutically acceptable excipients, wherein said buffering agent is present in an amount of about 0.1 mM to less than 10 mM.

In an embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, and optionally other pharmaceutically acceptable excipients, wherein said buffering agent is present in an amount of about 0.1 to less than 2 mg/ml, preferably in an amount of about 0.1 to about 1.5 mg/ml, and more preferably in an amount of about 0.5 to about 1.5 mg/ml.

In an aspect said buffering agent comprises acids or salt forms of one or more acids such as citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine or their salts and/or a combination thereof, as well as lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide, cesium hydroxide, calcium hydroxide, strontium hydroxide, and barium hydroxide. In another aspect the buffering agent is citric acid, or its salts or combinations thereof. In another aspect, the buffering agent is tartaric acid or sodium tartrate or combination thereof.

In an embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, citric acid, sodium metabisulfite, disodium edetate dihydrate, sodium chloride and hydrochloric acid to adjust the pH.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, sodium tartrate, sodium metabisulfite, disodium edetate dihydrate, sodium chloride and hydrochloric acid to adjust the pH.

In an embodiment, the stable aqueous injectable pharmaceutical composition comprising epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml, and a buffering agent in an amount of about 0.01 mg/ml to less than 2 mg/ml, wherein the buffering agent comprises one or more acids selected from citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine; salts of these acids and combinations thereof.

In an embodiment, the stable injectable pharmaceutical composition of epinephrine of the present subject matter has a pH in the range of about 2.2 to about 5.0.

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which may retain at least about 90 % potency, for example, at least about 95 % potency or at least about 99 % potency of the drug when stored at 25°C/60 % RH for more than 1 month, for example, for 3 months, for 6 months, for 12 months, for 18 months, for 24 months or for 36 months.

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which does not contain more than 3 % total impurities, for example, the composition does not contain more than 2 %, does not contain more than 1 % or does not contain more than 0.5 % of the total impurities when stored at 25°C/60 % RH for more than 1 month, for example, for 3 months, for 6 months, for 12 months, for 18 months, for 24 months or for 36 months, as determined by high performance liquid chromatography (HPLC).

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which remains stable for commercially relevant time period after manufacturing, such as for about 1, 3, 6, 12, 18, 24 or 36 months, when it is kept in its original packaging under the specified storage conditions.

In another aspect, the present subject matter provides a process for preparation of stable injectable pharmaceutical composition comprising epinephrine or salt thereof, which process comprises mixing epinephrine or salt thereof, citric acid, sodium chloride, sodium metabisulfite, EDTA disodium, water for injection, hydrochloric acid to adjust the pH and optionally one or more other pharmaceutically acceptable excipients.

In another aspect the compositions described herein are administered by using any suitable method and/or device. The composition provided herein is loaded into an administrative device that delivers an effective amount of medication. The administrative device is, by way of non-limiting example, a vial, an ampoule, a pre-filled syringe or a cartridge suitable for delivering injectable medications manually and/or through an auto injector.

In another aspect, the present subject matter provides use of stable injectable pharmaceutical composition of epinephrine for the preparation of medicaments useful for treating allergic reactions (Type 1), including anaphylaxis, hypotension with septic shock or cardiogenic, hemorrhagic, and traumatic shock, bronchospasm or asthmatic attack, sensitivity reactions, cardiac arrhythmias, GI and renal hemorrhage, superficial bleeding, premature labor, hypoglycemia, and. , restricting the

distribution of locally administered drugs such as local anesthetics, reducing nasal congestion and/or as performance aid in emergency situations

**DETAILED DESCRIPTION OF THE SUBJECT MATTER**:

The present subject matter relates to stable injectable pharmaceutical compositions comprising epinephrine, tonicity agent, buffering agent at low concentrations, one or more antioxidants and pH adjusting agent. Further, the subject matter provides a process of preparing such composition and use thereof.

The term "epinephrine", as used herein includes epinephrine and a pharmaceutically acceptable salt thereof such as epinephrine bitartrate or epinephrine hydrochloride.

The term "antioxidant" refers to a component in a composition that may prevent and/or inhibit the formation of unacceptable amounts of oxidative degradants in the composition after a certain period of shelf life. In some embodiments, the antioxidant may react with oxygen that might otherwise compromise the composition by producing impurities in the composition. In an aspect, the antioxidant is selected from sodium bisulfite, sodium metabisulfite, disodium edetate dihydrate, EDTA, or a combination thereof.

The term "buffering agent or buffer" refers to a component present in a composition or solution which may provide a resistance to significant change in pH caused by a strong acid or base. A buffering agent may comprise a single agent or more than one agent, such as a weak acid and its conjugate base. A buffering agent may provide a resistance to a significant pH change by interacting with a strong acid or strong base in a composition or solution, thereby at least partially preventing the pH of the composition or solution from changing significantly. Preferably, a buffering agent comprises acids or salt forms such as citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine or salts and/or a combination thereof, as well as lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide, cesium hydroxide, calcium hydroxide, strontium hydroxide, and barium hydroxide.

The term "low concentration" as used herein refers to an amount of a buffering agent of about 0.1 mM to less than 10 mM, or about 1 mM to 6 mM, or about 2 mM to 5 mM. For example, said amount may be about 0.1 mM, about 1.0 mM, about 1.5 mM, about 2 mM, about 2.6 mM or about

3.0 mM.

The term “low concentration” as used herein refers to an amount of a buffering agent of about 0.01 mg/ml to less than 2 mg/ml, or about 0.2 mg/ml to 1.2 mg/ml, or about 0.3 mg/ml to 1 mg/ml, or about 0.1 mg/ml to less than 2 mg/ml. For example, said amount may be about 0.1 mg/ml, about 0.3 mg/ml, about 0.5 mg/ml, about 1 mg/ml, about 1.5 mg/ml or about 2.0mg/ml.

The term “pH adjusting agent” refers to a component of a composition selected to adjust the composition's pH. The pH adjusting agents include, but not limited to, acetic acid, adipic acid, ascorbic acid, hydrochloric acid, lactic acid, malic acid, monopotassium phosphate, monosodium phosphate, phosphoric acid, pyrophosphoric acid, succinic acid, sulfuric acid, tartaric acid or a combination thereof. Preferably, the pH lowering agent is hydrochloric acid.

The term “tonicity” refers to the effective osmotic pressure gradient of a solution or composition. The tonicity agent may be present in the composition to maintain the tonicity of the composition in a physiological acceptable range. The tonicity agents include, but not limited to, sodium chloride, glucose, glycerin, hydroxypropyl methyl cellulose, mannitol, polysorbate, propylene glycol, sodium bromide, sodium chloride, sodium iodide, sorbitol, urea, xylitol, and/or combinations thereof. Preferably, the tonicity agent is sodium chloride.

The term “chelating agent” refers to a substance capable of chelation, i.e., the formation or presence of two or more separate coordinate bonds between a polydentate ligand and a single central atom. Preferably, transition metal complexing agents is selected from the group consisting of TPA (Tris[(2-pyridyl)methyl]amine), phanquinone (4,7-phenanthroline-5,6-dione), clioquinol (PN Gerolymatos SA), chloroquinol, penicillamine, trientine, N,N′-diethyldithiocarbamate (DDC), 2,3,2′-tetraamine (2,3,2′-tet), neocuproine, N,N,N′,N′-tetrakis(2-pyridylmethyl) ethylenediamine (TPEN), 1,10-phenanthroline (PHE), tetraethylenepentamine (TEPA), triethylene tetraamine and tris(2-carboxyethyl)phosphine (TCEP), bathophenanthroline disulfonic acid (BPADA), Disodium Edetate Dihydrate (EDTA), ethylene glycol (bis) aminoethyl ether tetra acetic acid (EGTA), nitrilotriacetic acid, TIRON™, N,N-bis(2-hydroxyethyl)glycine (bicine), O,O′-bis(2-aminophenyl ethylene glycol) ethylenediamine-N,N,N′,N′-tetraacetic acid (BAPTA), trans-1,2-diamino cyclohexane-ethylenediamine-N,N,N′,N′-tetraacetic acid (CyDTA), 1,3-diamino-2-hydroxy-propane-ethylenediamine-N,N,N′, N′-tetraacetic acid (DPTA-OH), ethylene-diamine-N,N′-dipropionic acid dihydrochloride (EDDP), ethylenediamine-N,N′-bis(methylenephosphonic acid)

hemihydrate (EDDPO), ethylenediamine-N,N,N′,N′-tetrakis(methylenephosphonic acid) (EDTPO), N,N′-bis(2-hydroxybenzyl)ethylene diamine-N,N′-diacetic acid (HBED), 1,6-hexamethylenediamine-N,N,N′,N′-tetraacetic acid (HDTA, or HEDTA), N-(2-hydroxyethyl)iminodiacetic acid (HIDA), iminodiacetic acid (IDA), 1,2-diaminopropane-N,N,N′,N′-tetraacetic acid (methyl-EDTA), nitriltriacetic acid (NTA), nitrilotripropionic acid (NTP), nitrilotris (methylenephosphonic acid) trisodium salt (NTPO), triethylenetetramine-N,N,N′,N″,N″-hexaacetic acid (TTHA), bathocuproine, bathophenanthroline, TETA, citric acid, salicylic acid, and/or malic acid, including analogues, derivatives, and pharmaceutically acceptable salts thereof. Preferably, the chelating agent comprises EDTA.

The term “stable” refers to any preparation of epinephrine or pharmaceutically acceptable salts thereof having sufficient physical and chemical stability to allow storage at a convenient temperature, such as between about 15°C to about 30° C, for a commercially reasonable period of time. The term “physical stability” refers to maintenance of color, pH range of 2.2 -5.0 and absence of particulate matter and the term “chemical stability” relates to no or acceptable level of drug-related impurities in terms of total impurity, maximum individual unknown impurity and single maximum individual impurity. Further, a pharmaceutical composition of the invention is “stable” or “stabilized” if one or more of the active agents therein exhibit good stability as determined by a standard potency test. More specifically, such compositions exhibit a potency loss of less than about 10%, preferably less than about 8%, more preferably less than about 5% as determined by the test. Potency can be evaluated by one or a combination of strategies known in the field.

Epinephrine is destroyed readily in alkaline solutions by aldehydes, weak oxidizing agents, oxygen of the air and by auto-oxidation involving the formation of adrenaline-o-quinone, which in turn converts to adrenochrome. In alkaline solution and when exposed to air, light or elevated temperature epinephrine turns pink from oxidation to adrenochrome which is further degraded to adrenolutin and melanin or oxidation leads to the formation of polymers both with brown color.

In another embodiment, compositions provided herein reduce a patient's risk of exposure to unwanted degradation products (e.g., high ESA levels and unnecessary asthma and/or allergy reactions associated therewith), a patient's risk of exposure to drastic dosage overages and/or underages depending on the manufacture date of the product, a patient's exposure to unnecessary additives and agents, etc.

In an embodiment provided herein are pharmaceutically acceptable compositions comprising epinephrine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In another embodiment, compositions provided herein comprise epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, or any combination therefor, and optionally other pharmaceutically acceptable excipients.

In another embodiment, provided herein are compositions comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent and optionally other pharmaceutically acceptable excipients.

In an embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent, and optionally other pharmaceutically acceptable excipients.

In an embodiment, compositions provided herein are formulated with any suitable epinephrine, such as the free base, conjugate acid, or a pharmaceutically acceptable salt thereof. In another embodiment, the epinephrine utilized to formulate a composition provided herein is selected from epinephrine (free base), epinephrine bitartrate, and epinephrine hydrochloride and/or a combination thereof. Generally, compositions described herein as comprising epinephrine refer to a dissolved epinephrine, whether dissolved free base, conjugate acid, or a salt thereof. Compositions provided herein optionally comprise epinephrine in the free base form and/or in a protonated cation (conjugate acid) or salt form. In an embodiment, the epinephrine is provided in a composition herein and/or formulated into a composition herein in a free base equivalent amount of about 0.01 wt. % to about 2 wt. %. In some instances, concentrations vary with varying subject age, therapeutic treatments and/or administration routes. In another embodiment, compositions provided herein comprise about 0.03 wt. % to about 1 wt. % epinephrine, more specifically about 0.05 wt. %.

In an embodiment, the present subject matter relates to a stable injectable aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof that, wherein said composition comprises low concentrations of buffering agent to sufficiently maintain the required pH and

provide improved physiochemical stability.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof; wherein the composition comprises a buffering agent in an amount of about 0.1 mM to less than 10 mM, preferably in an amount of about 1 mM to 6 mM, more preferably in an amount of about 2 mM to 5 mM.

In another embodiment, the stable injectable pharmaceutical composition comprises an aqueous solution comprising epinephrine or a pharmaceutically acceptable salt thereof; wherein the composition comprises a buffering agent in an amount of about 0.1 to less than 2 mg/ml, preferably in an amount of about 0.1 to 1.5 mg/ml, more preferably in an amount of about 0.5 to 1.5 mg/ml.
In an embodiment, buffering agent is present in an amount of about 0.1 to less than 10 mM, preferably in an amount of about 1 and 6 mM, more preferably in an amount of about 2 to 5 mM.

In an embodiment, buffering agent is provided in the composition in an amount of about 0.05 mg/mL to less than 4 mg/mL, about 0.05 mg/mL to about 3 mg/mL, about 0.05 to about 2 mg/mL, about 0.05 mg/mL to about 1 mg/mL, or, about 0.5 to about 1.5 mg/mL.

In an embodiment, citric acid as buffering agent is present in an amount of about 0.1 to less than 10 mM, preferably in an amount of about 1 and 5 mM, more preferably in an amount of about 2 to about 3 mM.

In some embodiments, the citric acid as buffering agent is present in an amount of about 0.1 to about 2 mg/mL, preferably in an amount of about 0.1 to about 1.5 mg/mL, more preferably in an amount of about 0.1 to about 1 mg/mL, and most preferably about 0.5 mg/mL.

In another embodiment, sodium tartrate as buffering agent is present in an amount of about 0.1 to less than 10 mM, preferably in an amount of about 1 to about 5 mM, more preferably in an amount of about 2 to about 3 mM.

In another embodiments, the sodium tartrate as buffering agent is present at a concentration in an amount of about 0.1 to about 2 mg/mL, preferably in an amount of about 0.1 to about 1.5 mg/mL, more preferably in an amount of about 1 mg/mL to about 1.5 mg/mL, most preferably about 1.33 mg/mL.

In an embodiment, the composition provided herein comprises suitable a tonicity agent. Tonicity agent is utilized to adjust the solution osmolality within body physiological range of about 200-400 mOsm/kg. Suitable tonicity agent which may be used in the present invention include, but not limited to sodium chloride, dextrose or a combination thereof, preferably sodium chloride.

In an embodiment, the composition provided herein comprises suitable pH adjusting agents suitable pH adjusting agents which may be used in the present invention include, but not limited to sodium hydroxide, hydrochloric acid, acetic acid, fumaric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, or combinations thereof, preferably hydrochloric acid to about pH 2.2 to about pH 5.0.

In one embodiment, the present subject matter provides a stable injectable dosage form comprising an aqueous solution comprising

a) epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
b) a buffering agent in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
c) a tonicity agent in an amount ranging from about 1 mg/ml to about 9 mg/ml,
d) a pH adjusting agent to adjust the pH of solution in a range of 2.2 to 5.0, and
e) an antioxidant in an amount of about 0.1 mg/ml to about 3 mg/ml; and
f) optionally other pharmaceutically acceptable excipients such as a chelating agent, a preservative, or a combination thereof

In one embodiment, the present invention provides a stable injectable dosage form comprising an aqueous solution comprising

a) epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
b) citric acid in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
c) sodium chloride in an amount ranging from about 1 mg/ml to about 9 mg/ml,
d) hydrochloric acid to adjust the pH of solution in a range of 2.2 to 5.0, and
e) one or more antioxidants in an amount ranging from about 0.1 mg/ml to about 3 mg/ml, wherein the antioxidant is selected from sodium bisulfite, sodium metabisulfite, EDTA or combination thereof,
f) disodium edetate dehydrate in an amount ranging from about 0.01 mg/ml to about 1 mg/ml, and
g) optionally other pharmaceutically acceptable excipients.

In one embodiment, the present invention provides, a stable aqueous injectable pharmaceutical composition comprising:

a. epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
b. a buffering agent in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
c. an antioxidant in an amount of about 0.1 mg/ml to about 3 mg/ml, and
d. optionally other pharmaceutically acceptable excipients such as a tonicity agent, a chelating agent, a preservative, a pH adjusting agent, or a combination thereof;

wherein the pH of the composition is 2.2 to 5.0

In one embodiment, the buffering agent is present in an amount of about 0.3 mg/ml to 1 mg/ml, and wherein the buffering agent is comprises one or more acids selected from one or more acids, such as citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine; salts of these acids and combination thereof.

In one embodiment, there is provided a stable injectable dosage form comprising an aqueous solution comprising

a) epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
b) sodium tartrate in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
c) sodium chloride in an amount ranging from about 1 mg/ml to about 9 mg/ml,
d) hydrochloric acid to adjust the pH of solution in a range of 2.2 to 5.0.
e) one or more antioxidants in an amount ranging from about 0.1 mg/ml to about 3 mg/ml; wherein the antioxidant is selected from sodium bisulfite, sodium metabisulfite, EDTA or combination thereof, and
f) optionally other pharmaceutically acceptable excipients

The present subject matter provides for a composition that may have a low level of impurities. The term "impurity" refers to an undesired substance in a composition. In an embodiment, an amount of impurities may be present in an initial composition and/or may be formed after a certain period of shelf life of a composition. In another embodiment, impurities may be formed via degradation of one or more components of the composition. Sources of degradation include, but are not limited to, oxidation, racemization, visible light, ultraviolet light, moisture, heat, changes in pH, and composition component interactions. Unless indicated otherwise, the percentages of impurities expressed herein are expressed as % w/w of the active agent.

Various methods of analyzing (characterization and quantification) the impurities are well established in the art. Various spectroscopic techniques, such as NMR, MS, IR etc. and chromatographic techniques, such as HPLC, HPLC-TLC, HPLC-CE and hyphenated methods, such as LC-MS-MS, HPLC-DAD-MS, HPLC-NMR, GC-MS & LCMS can be used for analyzing impurities.

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which may retain at least about 90 % potency, for example, at least about 95 % potency or at least about 99 % potency of the drug when stored at 25°C/60 % RH, for more than 1 month, for example, for 3 months, for 6 months, for 12 months, for 18 months, for 24 months or for 36 months.

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which does not contain more than 3 %, for example, does not contain more than 2 %, does not contain more than 1 % or does not contain more than 0 .5 % of the total impurities when stored at 25°C/60 % RH, for more than 1 month, for example, for 3 months, for 6 months, for 12 months, for 18 months, for 24 months or for 36 months as determined by high performance liquid chromatography.

In another aspect, there is provided a stable injectable pharmaceutical composition of epinephrine, which remains stable for commercially relevant time period after manufacturing, such as for about 1, 3, 6, 12, 18, 24 or 36 months, when it is kept in its original packaging under the specified storage conditions.

Further there is provided a stable injectable pharmaceutical composition of epinephrine, which remains stable and compliant as per ICH guideline for impurities for respective product, for more than 2 months, for example, for 3 months, for 6 months, for 12 months, for 24 months or for 36 months, when stored at 15° to 30°C temperature.

The present subject matter also provides a process of manufacturing stable injectable pharmaceutical composition of epinephrine. The process involves adding citric acid/sodium tartrate, EDTA disodium, sodium metabisulfite and sodium chloride to water for injection (WFI) under continuous nitrogen purging. Epinephrine was sequentially added to the solution under stirring to get clear solution.1N HCI solution was added to adjust the pH to 2.2 to 5.0. Final volume of the solution was made with water for injection. pH of the final solution can be adjusted using HCI

solution if required. The solution was then subjected to filtration through 0.22µm membrane filter and loaded into cartridge or pre-filled syringes.

In another embodiment, the present epinephrine compositions is used in a conjunction with an administrative device for administration into body. Any suitable device is utilized. In another embodiment, the device is, by way of non-limiting example, a vial, an ampoule, a pre-filled syringe or cartridge suitable for delivering injectable medications manually and/or through an auto injector. In some instances, such devices are calibrated and/or configured to precisely and accurately deliver effective amount of epinephrine medication.

In another embodiment, the epinephrine compositions can be used for treating anaphylactic shock by administrating epinephrine formulation to patients via intramuscular injection or subcutaneous injection or intravenous injection.

**Examples:**

The present subject matter is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present subject matter.

**Example 1: Composition of Epinephrine injection 0.15 mg/ml, 0.3 mg/mL & 1 mg/mL.**

| **Epinephrine Formulations** | **Example 1** | |
|---|---|---|
| | **Epinephrine Injection, USP 0.15 mg/ 0.3mL** | **Epinephrine Injection, USP 0.3 mg/ 0.3mL** |
| **Ingredients** | **Quantity (mg/mL)** | |
| Epinephrine | 0.55 mg | 1.10 mg* |
| Sodium chloride | 6.0 mg | 6.0 mg |
| Citric acid anhydrous | 0.5 mg | 0.5 mg |
| EDTA | 0.5 mg | 0.5 mg |
| Sodium tartrate | -- | -- |
| Sodium metabisulfite | 1.33 mg | 1.33 mg |

| | | |
|---|---|---|
| Hydrochloric acid | q.s to pH 2.2-5.0 | q.s to pH 2.2-5.0 |
| Water for Injection | q.s to 1.0 mL | q.s to 1.0 mL |
| Nitrogen # | q.s | q.s |

# nitrogen is used as processing aid. *Even though composition comprises Epinephrine as 1mg/ml, the1.10 mg corresponds to its overages.

**Manufacturing Process:** Sodium metabisulfite, EDTA, citric acid/sodium tartrate, sodium chloride, were dissolved in water for injection (WFI) under continuous nitrogen purging to maintain dissolved oxygen content less than 1%. Epinephrine was sequentially added to the solution under stirring to get clear solution.1N HCI solution was added to adjust the pH to 2.2 to 5.0. Final volume of the solution was made with water for injection. The solution was then subjected to filtration through 0.22µm membrane filter. The above manufacturing process was performed under the light intensity of not more than 400 lux. The solution was then filled in a sterile cartridge or prefilled syringes.

**Example 2 & 3:**

| **Epinephrine Formulations** | **Example 2** | **Example 3** |
|---|---|---|
| | **Epinephrine Injection, USP 1 mg/mL (PFS)** | |
| **Ingredients** | **Quantity (mg/mL)** | |
| Epinephrine | 1.10 mg# | 1.10 mg* |
| Sodium chloride | 8.6 mg | 8.6 mg |
| Citric acid anhydrous | 0.5 mg | -- |
| EDTA | 0.5 mg | -- |
| Sodium tartrate | -- | 1.33 mg |
| Sodium metabisulfite | 0.5 mg | 0.5 mg |
| Hydrochloric acid | q.s to pH 2.2-5.0 | q.s to pH 2.2-5.0 |
| Water for Injection | q.s to 1.0 mL | q.s to 1.0 mL |
| Nitrogen # | q.s | q.s |

#nitrogen is used as processing aid. * Even though composition comprises Epinephrine as 1mg/ml, the1.10 mg corresponds to its overages.

**Manufacturing Process:** The above compositions are prepared in similar manner as provided in examples 1.

**Example 4 - Stability Data of Example 1 - 0.15mg/0.3mL.**

| S. No | Test | Initial | 25°C/60%RH | | |
|---|---|---|---|---|---|
| | | | 1M | 3M | 6M |
| 1 | Description | Complies | Complies | Complies | Complies |
| 2 | Assay of Epinephrine (%) | 110.0 | 107.8 | 106.4 | 105.9 |
| 3 | pH | 3.42 | 3.77 | 3.99 | 4.04 |
| 4 | S-Epinephrine (%) | 0.2 | 0.2 | 0.3 | 0.3 |
| 5 | Limit of Degradation products (%) | | | | |
| | Epinephrine Sulfonic acid Impurity | ND | 0.75 | 1.20 | 2.15 |
| | Adrenalone,IMP C | 0.01 | ND | ND | 0.03 |
| | Total degradation products | 0.15 | 1.13 | 1.74 | 2.89 |
| 6 | Osmolality (mOsmol/Kg) | 225 | 230 | 224 | 231 |

ND: Not detected

**Example 5 - Stability Data of Example 1 - 0.3mg/0.3mL.**

| S. no | Test | Initial | 25°C/60%RH | | |
|---|---|---|---|---|---|
| | | | 1M | 3M | 6M |
| 1 | Description | Complies | Complies | Complies | Complies |
| 2 | Assay of Epinephrine (%) | 108.8 | 106.9 | 105.2 | 105.6 |
| 3 | pH | 3.44 | 3.76 | 3.96 | 4.11 |
| 4 | S-Epinephrine (%) | 0.3 | 0.3 | 0.3 | 0.2 |
| 5 | Limit of Degradation products (%) | | | | |
| | ESA (IMP F) | 0.05 | 0.48 | 1.22 | 2.12 |
| | Adrenalone | ND | 0.01 | 0.02 | 0.01 |
| | Total Degradation products | 0.16 | 0.64 | 1.64 | 2.24 |

**Example 6**: **Stability Data of Example 2:**

| S. No | Test | Initial | 25°C/60%RH | |
|---|---|---|---|---|
| | | | 1M | 3M |
| 1 | Description | Complies | Complies | Complies |

| | | | | |
|---|---|---|---|---|
| 2 | pH | 3.13 | 3.21 | 3.24 |
| 3 | Assay of Epinephrine (%) | 100.7 | 98.7 | 97.9 |
| 4 | S- Epinephrine (%) | 0.5 | 0.6 | 0.4 |
| 5 | Related substances (%) | | | |
| | Imp-F (ESA) | ND | 0.41 | 0.46 |
| | Adrenalone | 0.010 | 0.001 | 0.015 |
| | Total impurities | 0.091 | 0.706 | 0.742 |
| 6 | Osmolality (mOsmol/Kg) | 297 | 297 | 299 |

**Example 7: Stability Data of Example 3:**

| S. No | Test | Initial | 25°C/60%RH | |
|---|---|---|---|---|
| | | | 1M | 3M |
| 1 | Description | Complies | Complies | Complies |
| 2 | pH | 3.08 | 3.07 | 3.05 |
| 3 | Assay of Epinephrine (%) | 100.8 | 97.7 | 96.7 |
| 4 | S- Epinephrine (%) | 0.5 | 0.6 | 0.6 |
| 5 | Related substances (%) | | | |
| | Imp-F (ESA) | ND | 0.43 | 0.47 |
| | Adrenalone | 0.007 | 0.015 | 0.014 |
| | Total impurities | 0.144 | 0.755 | 1.897 |
| 6 | Osmolality (mOsmol/Kg) | 315 | 312 | 317 |

## CLAIMS

We claim:

1. A stable aqueous injectable pharmaceutical composition comprising epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml and a buffering agent in an amount of about 0.01 mg/ml to less than 2 mg/ml, wherein the buffering agent comprises one or more acids selected from citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine; salts of these acids and combinations thereof.

2. The composition as claimed in claim 1, wherein the buffering agent is selected from citric acid or its salts, tartaric acid or sodium tartrate and combination thereof.

3. The composition as claimed in claim 1, wherein the buffering agent is present in an amount of about 0.3 mg/ml to about 1 mg/ml.

4. The composition as claimed in claim 1, wherein said composition further comprises one or more pharmaceutically acceptable excipients such as a tonicity agent, a chelating agent, a preservative, an antioxidant, a pH adjusting agent or combinations thereof.

5. A stable aqueous injectable pharmaceutical composition comprising:
    e. epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
    f. a buffering agent in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
    g. an antioxidant in an amount of about 0.1 mg/ml to about 3 mg/ml, and
    h. optionally other pharmaceutically acceptable excipients such as a tonicity agent, a chelating agent, a preservative, a pH adjusting agent, or a combination thereof;

   wherein the pH of the composition is 2.2 to 5.0

6. The composition as claimed in claim 5, wherein the buffering agent is present in an amount of about 0.3 mg/ml to about 1 mg/ml, and wherein the buffering agent is comprises one or more acids selected from one or more acids, such as citric acid, glutamic acid, malic acid, maleic acid, gluconic acid, benzoic acid, succinic acid, acetic acid, tartaric acid, lactic acid, glutamate, aspartic acid, glycine; salts of these acids and combinations thereof.

7. The composition as claimed in claim 5, wherein the antioxidant is present in an amount of about 1 mg/ml to about 2 mg/ml, and wherein the antioxidant is selected from sodium bisulfite, sodium metabisulfite, disodium edetate dihydrate, EDTA and combinations thereof.

8. The composition as claimed in claim 5, wherein the tonicity agent is selected from sodium chloride, glucose, glycerin, hydroxypropyl methyl cellulose, mannitol, polysorbate, propylene glycol, sodium bromide, sodium chloride, sodium iodide, sorbitol, urea, xylitol and combinations thereof.

9. A stable aqueous injectable pharmaceutical composition comprising:
    a. epinephrine in an amount ranging from about 0.05 mg/ml to about 1.0 mg/ml,
    b. citric acid in an amount ranging from about 0.1 mg/ml to about 2 mg/ml,
    c. sodium chloride in an amount ranging from about 1 mg/ml to about 9 mg/ml,
    d. hydrochloric acid to adjust the pH,
    e. one or more antioxidants in an amount ranging from about 0.1 mg/ml to about 3 mg/ml, wherein the antioxidant is selected from sodium bisulfite, sodium metabisulfite and combinations thereof; and
    f. disodium edetate dehydrate an amount ranging from about 0.01 mg/ml to about 1 mg/ml, and optionally other pharmaceutically acceptable excipients;

wherein the pH of the composition is 2.2 to 5.0

10. The composition as claimed in claim 9, wherein said composition has total impurities in the aqueous solution of not more than 3.0% by weight after storage at 25°C/60% RH for at least 6 months.

Dated 11th day of September 2024

(Saritha Bommakanti)
For Alembic Pharmaceuticals Limited

**ABSTRACT:**

**Stable injectable compositions of epinephrine**

The present subject matter relates to stable injectable compositions comprising epinephrine or a pharmaceutically acceptable salt thereof, a tonicity agent, an antioxidant, a buffering agent, a pH adjusting agent and optionally other pharmaceutically acceptable excipients. Further, the subject matter provides a process of preparing such composition and use thereof.

Dated 11th day of September 2024

(Saritha Bommakanti)
For Alembic Pharmaceuticals Limited