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(54) **EPINEPHRINE FORMULATIONS**

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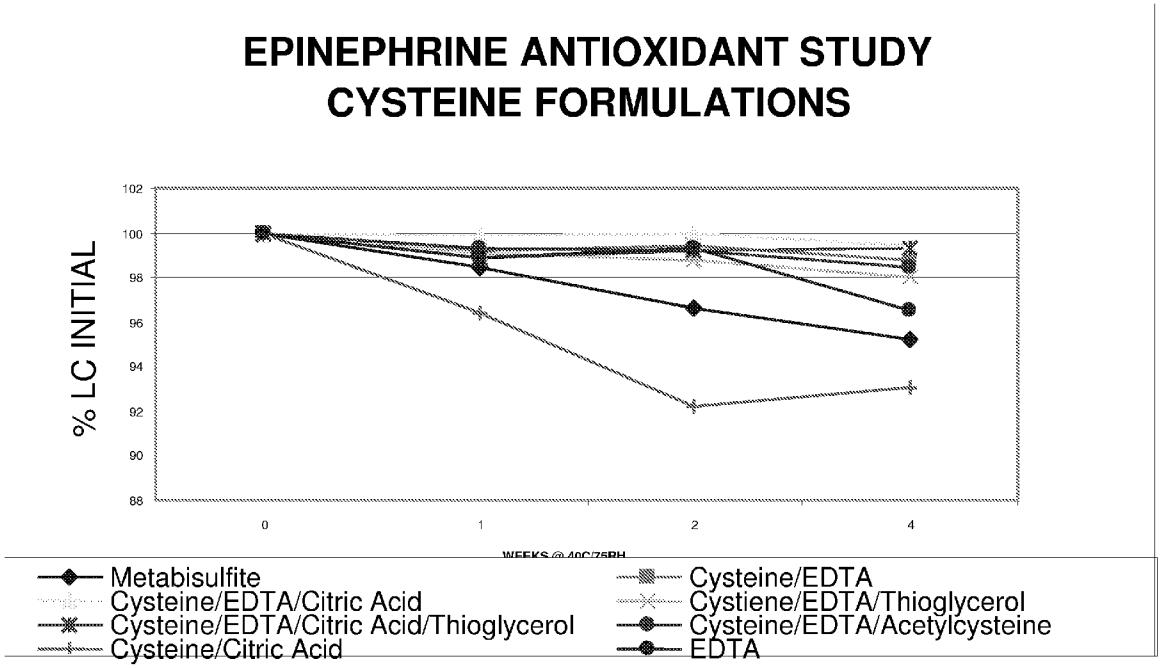
(57) **ABSTRACT**

The present invention generally concerns an epinephrine formulation that has enhanced stability. In particular embodiments, the formulation is an injectable formulation. In specific aspects, the formulation comprises epinephrine, EDTA, and one or more of an antioxidant such as cysteine, citric acid, acetylcysteine, or thioglycerol. The formulations are suitable for any medical condition that is in need of epinephrine, although in specific embodiments the medical condition is anaphylaxis, asthma, or cardiac arrest.



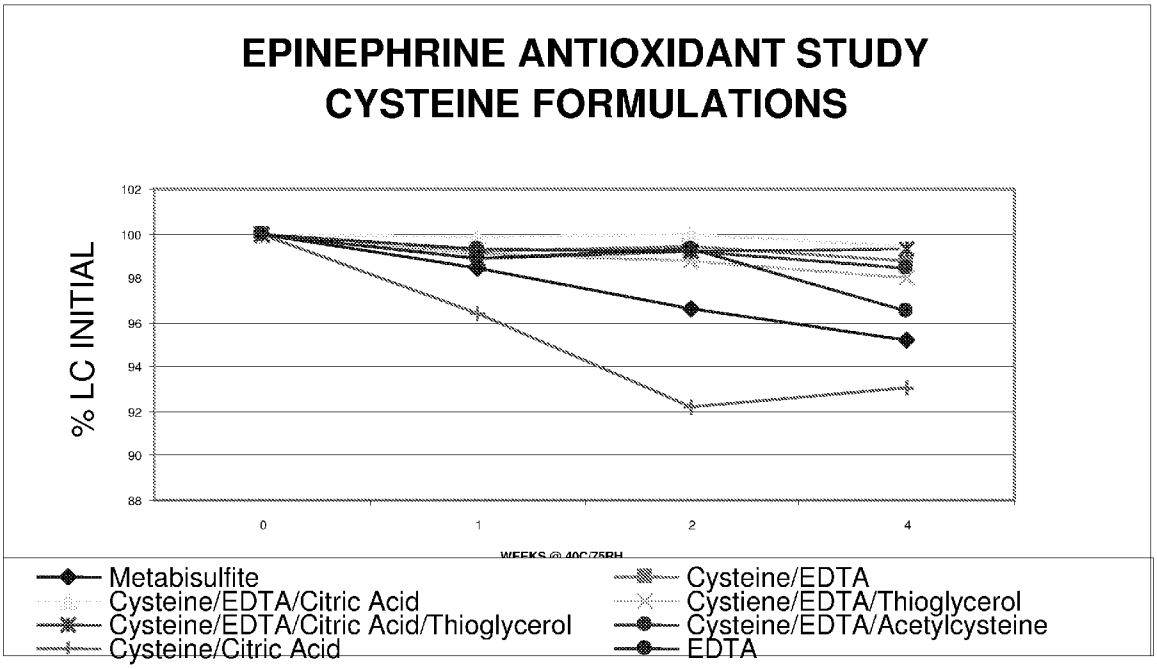


FIG. 1

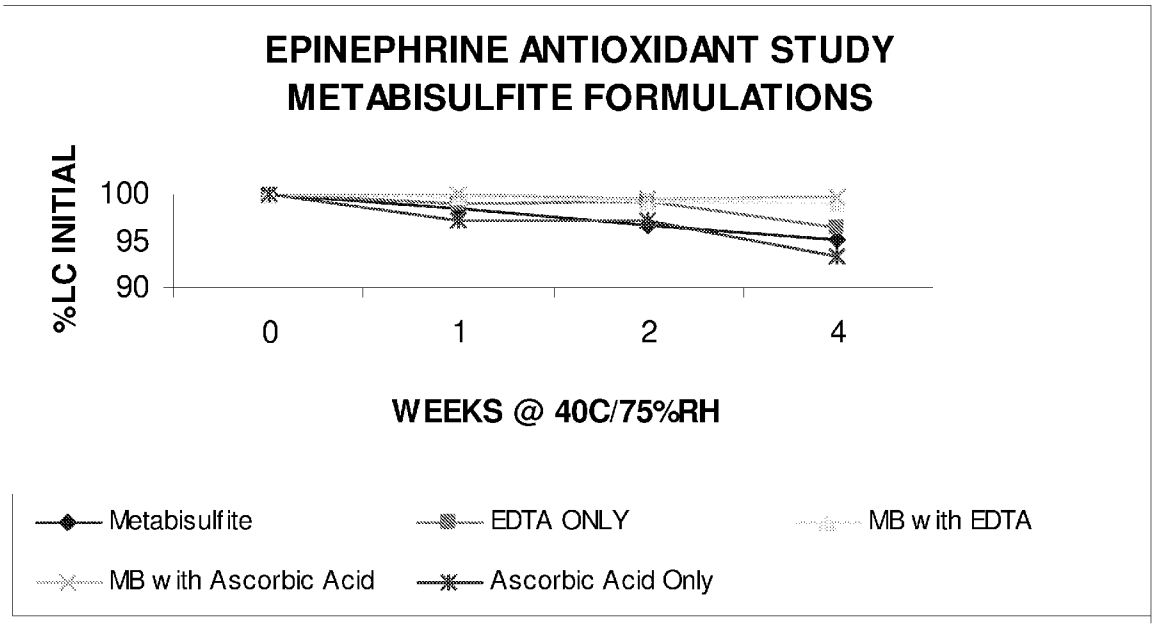


FIG. 2

EPINEPHRINE FORMULATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 60/847,823, filed Sep. 28, 2006, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The fields of the present invention include at least molecular biology, cell biology, and medicine. In certain fields of the invention, there are new compositions of epinephrine and devices and methods of using such epinephrine formulations.

BACKGROUND OF THE INVENTION

[0003] Epinephrine, or (−)-3,4-Dihydroxy-[(methylamino) methyl]benzyl alcohol, is an endogenous adrenergic neurotransmitter synthesized and stored in the adrenal medulla. It is a polar compound characterized structurally by a catechol (a dihydroxybenzene) and an amine, and it is commonly available in a salt form. Epinephrine is water soluble and interacts in a variety of ways, depending on the type of receptor areas of target cells.

[0004] Epinephrine is one of the neural hormones responsible for the regulation of the heart, blood pressure, airway resistance, and energy metabolism. It is classified as a sympathomimetic drug, acting on both alpha and beta receptors. Epinephrine generates an inotropic effect, wherein it increases the heart rate, the force of contraction of the heart, narrows the blood vessels thus increasing blood pressure, reduces airway resistance to make it easier to breath, and raises blood glucose and blood fatty acids to supply the body energy during stress. Epinephrine is available in a variety of formulations suited for different clinical indications and routes of administration, for example by injection, by inhalation, or topically. Its uses include at least the following: combating low blood pressure during hemorrhagic or allergic shock; opening the airways during asthmatic attack; restricting the distribution of locally administered drugs such as local anesthetics; reducing nasal congestion; and/or performance aid in emergency situations.

[0005] Epinephrine can be prepared synthetically by one of several processes readily available to one in the art. One such process starts with 1,2-dihydroxybenzene that is converted successively to (chloroacetyl)catechol with chloroacetyl chloride, then to (methyl-aminoacetyl)catechol with methylamine and to racemic epinephrine by hydrogenation. The racemic form is resolved with D-tartaric acid to provide a white to nearly-white powder that is sensitive to light, air, heat, or alkaline conditions. Salts with acids are readily formed and provide some stability. The hydrochloride, sulphate, and bitartrate salts are known in the art.

[0006] Allergic emergencies, such as anaphylaxis, are a growing concern, given the increasing awareness of members of the public of their frequency and potential severity. Anaphylaxis is a sudden, severe, systemic allergic reaction that can be fatal, in many cases, if left untreated. Anaphylaxis can involve various areas of the body, such as the skin, respiratory tract, gastrointestinal tract, and cardiovascular system. Acute symptoms occur from within minutes to two hours after contact with the allergy-causing substance, but in rare instances anaphylactic reaction, can be extremely unpredictable. Accordingly, allergists recommend that persons who have a personal or family history of anaphylaxis be prepared to self-administer emergency treatment at all times. Additionally, adults charged with caring for children who are at risk for anaphylaxis should also be prepared to administer anti-anaphylactic first aid.

[0007] The symptoms of anaphylaxis include one or more of the following, generally within 1 to about 15 minutes of exposure to the antigen: agitation, a feeling of uneasiness, flushing, palpitations, paresthesias, pruritus, throbbing in the ears, coughing, sneezing, urticaria, angioedema, difficulty breathing due to laryngeal edema or brochospasm, nausea, vomiting, abdominal pain, diarrhea, shock, convulsions, incontinence, unresponsiveness and death. An anaphylactic reaction may include cardiovascular collapse, even in the absence of respiratory symptoms.

[0008] According to the Merck Manual, immediate treatment with epinephrine is imperative for the successful treatment of anaphylaxis (Merck Manual, 17.sup.th Ed., 1053-1054 (1999)). The recommended dose is about 0.01 mL/Kg in adults: usually about 0.3 to 0.5 mL of a 1:1000 dilution of epinephrine in a suitable carrier. While the dose may be given manually, such as either subcutaneously or intramuscularly, for example, in recent years automatic injectors have become an accepted first aid means of delivering epinephrine. It is recommended that persons at risk of anaphylaxis, and persons responsible for children at risk for anaphylaxis, maintain one or more automatic epinephrine injectors in a convenient place at all times. It is further recommended that, if the symptoms of anaphylaxis persist after the first dose of epinephrine is injected, the patient should be treated with a second dose of epinephrine (about 0.3 mL of the 1:1000 dilution).

[0009] Certain formulations of epinephrine are known. Epinephrine Injection, USP is a sterile, non-pyrogenic solution administered parenterally by the intravenous or intracardiac (left ventricular chamber) routes, or via endotracheal tube into the bronchial tree. Each milliliter (mL) of the 1:10,000 solution contains epinephrine 0.1 mg; sodium chloride 8.16 mg; sodium metabisulfite added 0.46 mg; citric acid, anhydrous 2 mg and sodium citrate, dihydrate 0.6 mg added as buffers. Sodium metabisulfite is used with Epinephrine formulations as a preservative. Sodium metabisulfite has been associated with severe allergic reactions. The formulation may contain additional citric acid and/or sodium citrate for pH adjustment. pH 3.3 (2.2 to 5.0).

[0010] Epinephrine Injection, USP is administered by intravenous injection and/or in cardiac arrest, by intracardiac injection into the left ventricular chamber or via endotracheal tube directly into the bronchial tree. The adult intravenous dose for hypersensitivity reactions or to relieve bronchospasm usually ranges from 0.1 to 0.25 mg (1 to 2.5 mL of 1:10,000 solution), injected slowly. Neonates may be given a dose of 0.01 mg per kg of body weight; for the infant 0.05 mg is an adequate initial dose and this may be repeated at 20 to 30 minute intervals in the management of asthma attacks.

[0011] In cardiac arrest, 0.5 to 1.0 mg (5 to 10 mL of 1:10,000 solution) may be given. During a resuscitation effort, 0.5 mg (5 mL) should be administered intravenously every five minutes. Intracardiac injection may be administered, if there has not been sufficient time to establish an

plated is dose delivery from vials with formulation comprising concentrated epinephrine solution and/or storage at room temperature.

[0012] Because of its catechol nucleus, epinephrine oxidizes easily and darkens slowly on exposure to air. Dilute solutions are partially stabilized by the addition of chlorobutanol and by reducing agents, such as sodium bisulfate or ascorbic acid. As the free amine, it is available in an oil solution for inhalation. Like other amines it forms salts with acids including the hydrochloride, the borate, and the bitartrate. The bitartrate has the advantage of being less acidic and is used in the eye because its solutions have a pH close to that of lacrimal fluid. Epinephrine is destroyed readily in alkaline solutions by aldehydes, weak oxidizing agents and oxygen of the air.

[0013] Along with its advantages, Epinephrine has several disadvantages that include a short duration of action, decomposition of its salts in solution, vasoconstriction action frequently followed by vasodilation and inactivity on oral administration.

[0014] The primary determinant of catecholamine stability in intravenous admixtures is the pH of the solution. Epinephrine hydrochloride is unstable in dextrose (5% in water) at a pH above 5.5. The pH of optimum stability is from about 3 to about 4. In one study, the decomposition rate increased two-fold (from 5 to 10% in 200 days at 30° C.) when the pH was increased form 2.5 to 4.5. Epinephrine hydrochloride is rapidly destroyed by alkali or by oxidizing agents including halogens, permanganates, chromate, nitrates, nitrites and salts of easily reducible metals such as iron, copper, and zinc. In alkaline solution and when exposed to air or light, it turns pink from oxidation to adenochrome and then brown from the formation of polymers. Epinephrine should not be mixed with aminophlline-containing solutions because of the alkalinity of these solutions. In one evaluation with aminophylline stored at 25° C., a color change was noted after about 8 hours and only 40% of the initial drug was still present in the admixture at 24 hours.

[0015] Instability has also been observed when drugs are combined with epinephrine. For example, when lidocaine hydrochloride is mixed with epinephrine hydrochloride the buffering capacity of the lidocaine raises the pH of the intravenous admixtures above 5.5, the maximum necessary for stability of the epinephrine, to about 6. Under these conditions, the epinephrine hydrochloride will begin to deteriorate within several hours.

SUMMARY OF THE INVENTION

[0016] The present invention concerns particular formulations of epinephrine, which itself may also be referred to as epi, adrenaline, epinephrin, or adrenalin, for example, and it has a chemical formula of $C_9H_{13}NO_3$. The formulation is injectable, in particular embodiments. In certain aspects of the invention, the formulation has no sodium metabisulfite and has enhanced stability, such as being able to refrain from degradation before a certain period of time. In a particular embodiment, the formulation is enhanced to remain effective under any condition that would otherwise degrade the formulation, at least for an amount of time greater than that for an epinephrine formulation without a stability-enhancing agent, which in at least some cases may be an antioxidant. In specific cases, the formulation is enhanced to be stable in light, oxy-

enhanced to be stable for at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months, for example.

[0017] In particular aspects of the invention, the epinephrine formulation comprises ethylenediamine tetraacetic acid (also referred to as EDTA, H4EDTA, diaminoethanetetraacetic acid, edetic acid, edetate, edetate disodium, ethylenedinitrilotetraacetic acid, versene, or ethylene diamine tetracetic acid) and one or more antioxidants. Although any suitable antioxidant may be employed, in specific aspects the antioxidant is cysteine, citric acid, thioglycerol, ascorbic acid, acetylcysteine, or a combination thereof.

[0018] The formulations of the invention may be employed for any medical condition that epinephrine is useful. In particular embodiments, the epinephrine is utilized for anaphylaxis, cardiac arrest, or asthma, for example. Epinephrine is the preferred treatment for anaphylaxis even though the product contains sodium metabisulfite, which in other products may cause allergic-type reactions including anaphylactic symptoms or life-threatening asthma in certain susceptible persons.

[0019] The invention may be applied to any individual, but in specific embodiments the invention is useful for a mammal, including a human, dog, cat, horse, cow, goat, sheep, and so forth.

[0020] In a particular embodiment of the invention, there is an injectable pharmaceutical composition 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.

[0021] In another embodiment of the invention, there is an injectable pharmaceutical composition consisting essentially of epinephrine, EDTA, and at least one stability-enhancing agent, wherein the antioxidant is selected from the group consisting of cysteine, citric acid, thioglycerol, acetylcysteine, and a combination thereof.

[0022] In a further embodiment of the invention, there is a composition comprising a pharmaceutical composition 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; and an injection apparatus. The pharmaceutical composition may be housed in the injection apparatus or housed separately from the injection apparatus. The injection apparatus may be further defined as a syringe. The injection apparatus may be further defined as an autoinjector.

[0023] In an additional embodiment of the invention, there is a method of improving at least one symptom of an epinephrine-requiring medical condition in an individual in need thereof, comprising injecting into the individual a formulation comprising epinephrine; EDTA; a pharmaceutically acceptable carrier; and at least one antioxidant, wherein the antioxidant is selected from the group consisting of cysteine, citric acid, thioglycerol, acetylcysteine, and a combination thereof. In a specific embodiment of the invention, the medical condition is anaphylaxis, asthma or cardiac arrest. The formulation may be housed in an injection apparatus or housed separately from an injection apparatus. The injection may be by an autoinjector. The injection may be in the thigh of the individual, intracardially into the individual, or endotracheally into the individual, for example.

[0024] In another embodiment of the invention, there is a

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