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(54) **STABILIZATION OF QUINOL COMPOSITION SUCH AS CATECHOLAMINE DRUGS**

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(57) **ABSTRACT**

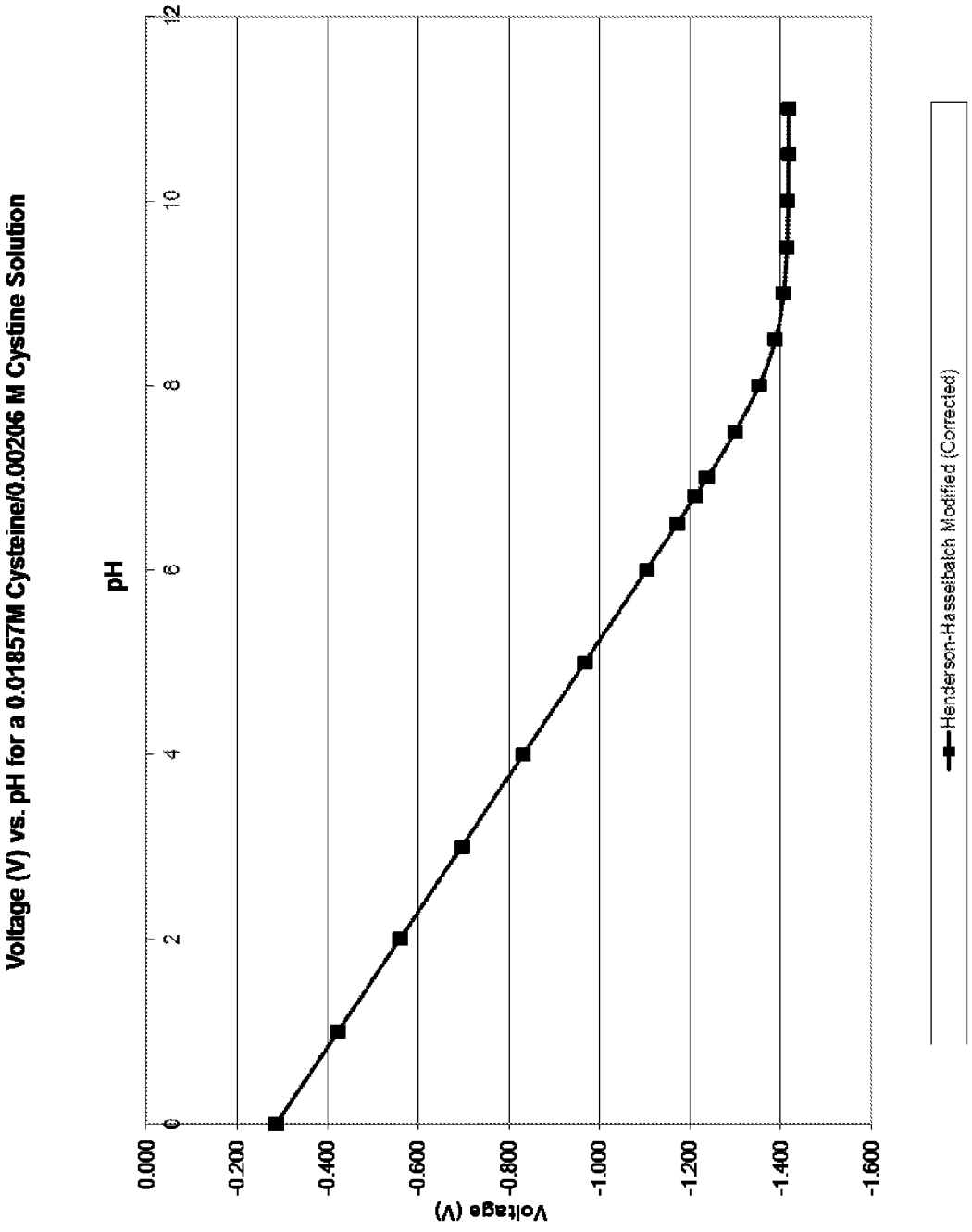
Compositions and methods are provided for obtaining stabilized quinol compositions, such as catecholamine drugs (e.g., epinephrine solutions), and also for obtaining stable pharmaceutical formulations that comprise a stabilized quinol composition and a second pharmacologically active component such as a local anesthetic or other active drug ingredient having a reversibly protonated amine group. Stability is achieved through the inclusion of an appropriately selected pH buffer and a thiol agent, based on redox and pH buffering principles including pKa of the buffer and of the reversibly protonated amine group.

FIGURE 1

Time (Days)	Solution A appearance containing 2.5 mg/mL cysteine	Solution B appearance without 2.5 mg/mL cysteine
0	Clear, colorless solution. No change in appearance. No precipitate present.	Solution initially clear with rapid discoloration. Solution light pink in color. No precipitate present.
1	Clear, colorless solution. No change in appearance. No precipitate present.	Solution dark pink in color. No precipitate present.
3	Clear, colorless solution. No change in appearance. No precipitate present.	Solution dark pink to red in color. No precipitate present.
7	Clear, colorless solution. No change in appearance. No precipitate present.	Solution red to brown in color with dark brown to black precipitate present.
14	Clear, colorless solution. No change in appearance. No precipitate present.	Solution red to brown in color with dark brown to black precipitate present.
28	Clear, colorless solution. No change in appearance. No precipitate present.	Solution red to brown in color with dark brown to black precipitate present.

Solution A contains 1.0 mg/ml epinephrine, 15 mM sodium phosphate adjusted to pH 6.8, and 2.5 mg/ml cysteine. Solution B contains 1.0 mg/ml epinephrine and 15 mM sodium phosphate adjusted to pH 6.8.

FIGURE 2



STABILIZATION OF QUINOL COMPOSITION SUCH AS CATECHOLAMINE DRUGS

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention relates to compositions and methods for preserving and maintaining the structural integrity, chemical stability and biological activity of quinol-containing compositions. More specifically, the invention relates to improved stability of quinol-containing compositions such as epinephrine and other catecholamine drugs, and of pharmaceutical formulations that include quinol compositions and other active drugs such as drugs having amine groups that can be reversibly protonated.

[0003] 2. Description of the Related Art

[0004] A number of chemical compounds having uses in the drug and food industries for a variety of purposes exhibit instabilities leading to oxidative degradation, which compromises their effectiveness and engenders undesirable costs associated with obtaining fresh reagents, discarding degraded reagents, and monitoring inventories of reagents that have only limited shelf-life. Among such chemical compounds are those that contain a quinol (dihydroxybenzene) moiety which can detrimentally undergo oxidative degradation to a corresponding quinone structure, which in turn may be compromised by further chemical degradation.

[0005] Exemplary compounds include members of the catecholamines (e.g., epinephrine, norepinephrine, levonordefrin; see, e.g., U.S. Pat. No. 5,002,973.), a family of compounds which includes naturally occurring neurotransmitters and also includes a number of synthetic products having applications as drugs in a wide variety of indications.

[0006] Catecholamines and other quinol compounds are susceptible to oxidation in solution (e.g., aqueous solution) that may be accompanied by a loss of pharmacological activity, and under current storage practices such oxidized compounds can be further converted to degradation products having potentially harmful properties. For instance, the catecholamine epinephrine is rapidly oxidized in aqueous solution, degrading to adrenochrome and adrenalone. (e.g., Kalyanaraman et al., 1984 *J. Biol. Chem.* 259:354; Kirchhoefer et al., 1986 *Am J. Hosp. Pharm.* 43:1741; Stepensky et al., 2004 *J. Pharm Sci.* 93:969; Newton et al., 1981 *Am. J. Hosp. Pharm.* 38:1314) At acidic pH values, degradation of epinephrine has also been reported to result from conversion of the biologically active L-enantiomer to the inactive D-enantiomer, yielding a racemic mixture of undesirably reduced potency (Stepensky et al., 2004 *J. Pharm Sci.* 93:969).

[0007] Presently available pharmaceutical formulations of catecholamine drug products and their structurally related analogues are typically plagued by efforts to stabilize the catecholamines, which efforts often result in disadvantageous and unwanted properties of the product. Many current epinephrine formulations, for example, contain bisulfite and/or metabisulfite additives that are included as mild reducing agents, and which are believed to inhibit oxidative degradation of the catecholamine. (e.g., Dalton-Bunnow, 1985 *Am. J. Hosp. Pharm.* 42:2220; Grubstein et al., 1992 *Drug Dev. Ind. Pharm.* 18:1549) These reducing agents, however, readily react with epinephrine to generate sulfonated derivatives that lack epinephrine biological activity. (e.g., Schroeter et al. 1958 *J. Am. Pharmaceut. Assoc.* 47:723; Hajratwala, 1975 *J.*

mulations containing bisulfites will be contraindicated in individuals having such allergies. (e.g., Campbell et al., 2001 *Anesth. Prog.* 48:21; Smolinske, 1992 *Clin. Toxicol.* 30:597) Moreover, epinephrine is unstable in solution for even brief time periods and must be kept at an acidic pH in order to avoid extremely rapid degradation that is associated with attempts to prepare epinephrine solutions having neutral pH values. (Robinson et al., 2000 *Anesthesia* 55:853; Newton et al., 1981 *Am. J. Hosp. Pharm.* 38:1314)

[0008] Another problem associated with efforts to provide storage conditions for quinol compounds relates to pharmaceutical formulations that contain a quinol compound along with a second pharmaceutical agent. For example, the quinol compound epinephrine is often included for its desirable pharmacological activity as a vasoconstrictor in formulations of local anesthetics, including amino ester local anesthetics (e.g., procaine) and amino amide local anesthetics (e.g., lidocaine). Many of these local anesthetics comprise an amine-containing compound having at least one amine group that is capable of being reversibly protonated. Such pharmaceutical formulations are typically provided in relatively acidic condition (e.g., pH<4) in an effort to preserve the quinol compound, which as described above, tends to degrade rapidly at pH values closer to neutrality.

[0009] Acidic formulations of such local anesthetics, however, suffer from other drawbacks, in particular, the problem that the low pH favors the presence of the protonated form of the reversibly protonated amine group. This problem manifests itself in an undesirably delayed onset of the desired pharmacological activity—anesthetic effect—insofar as the charge of the protonated amine group hinders the ability of the local anesthetic to traverse cellular membranes for purposes of exerting its pharmacological activity intracellularly. Hence, the anesthetic effect is delayed, and the efficiency of drug utilization at the desired local site is decreased by circulatory system clearance from the region of protonated drug molecules that have not yet equilibrated with the deprotonated form in the extracellular environment as a prelude to plasma membrane transit. Moreover, the acidic pH of such formulations typically results in pain experienced by the recipient at the site of injection, a seemingly inevitable consequence of the low pH used to protect the quinol compound.

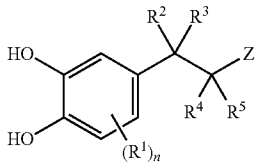
[0010] Clearly there remains a need for improved formulations of active drug compounds such as quinol compounds, and for improved pharmaceutical formulations containing both quinol compounds and active drug compounds having amine groups that can be reversibly protonated. The present invention provides improved compositions and methods that address these needs, and offers other related advantages.

BRIEF SUMMARY OF THE INVENTION

[0011] In certain embodiments, the present invention provides a stable pharmaceutical formulation, comprising (a) a first composition that comprises at least one quinol compound having a first desired pharmacological activity; (b) a second composition that comprises at least one local anesthetic compound, said local anesthetic compound comprising at least one amine group that is capable of being reversibly protonated, and being capable of reversibly binding to a voltage-gated Na^+ channel in a cell membrane to thereby alter Na^+ movement through the voltage-gated Na^+ channel; (c) at least one thiol agent; and (d) at least one pH buffer that

certain embodiments the quinol compound is present in a reduced form. In certain embodiments the quinol compound comprises an ortho-quinol moiety or a para-quinol moiety. In certain embodiments at least one quinol compound comprises a catecholamine.

[0012] In certain embodiments at least one quinol compound comprises a compound of Formula (I):



wherein:

[0013] n is 0, 1, 2 or 3

[0014] each R^1 is the same or different and independently hydrogen, alkyl, hydroxyl, alkoxide, —OC(O)alkyl, —OC(O)aralkyl, aralkyl, amino or halo;

[0015] R^2 and R^3 are the same or different and independently hydrogen, hydroxyl, alkoxide, alkyl, oxo, —OC(O)alkyl, —OC(O)aralkyl, amino, monoalkylamino, dialkylamino or halo;

[0016] R^4 and R^5 are the same or different and independently hydrogen, hydroxyl, alkoxide, —NR^6_2, —$NHNH_2$ or lower alkyl,

[0017] Z is —NR^6_2, —COOH or —CR^7_3;

[0018] each R^6 is the same or different and independently hydrogen, alkyl, aralkyl; or

[0019] R^5 and R^6 together with the atoms to which they are attached form a heterocycle; and

[0020] each R^7 is the same or different and independently hydrogen, alkyl, aralkyl, —COOH, amino, —C(O)Oalkyl, —C(O)Oaryl, —C(O)Oaralkyl, —$NHNH_2$, monoalkylamino, dialkylamino,

[0021] as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers; or as a pharmaceutically acceptable salt thereof.

[0022] In certain embodiments the quinol compound comprises a compound selected from 1,2-dihydroxybenzene (catechol, pyrocatechol), 1,4-dihydroxybenzene, epinephrine, norepinephrine, dopamine, dobutamine, isoproterenol, racepinephrine, arbutamine, carbidopa, deoxyepinephrine, dioxethedrine, 3-(3,4-dihydroxyphenyl)-alanine (L-, D- or DL-DOPA), dopexamine, droxidopa, ethylnorepinephrine, hexoprenaline, isoetharine, methyldopa, N-methylepinephrine, nordefrin, rimiterol, epinephrine bitartrate, L-epinephrine-D-hydrogentartate, adrenalone (CAS 99-45-6), arbutamine (CAS 128470-16-6), benserazide (CAS 322-35-0), carbidopa (CAS 28860-95-9), deoxyepinephrine (CAS 501-15-5), dioxethdrine (CAS 497-75-6), dobutamine (CAS 34368-04-02), dopa (CAS 63-84-3), dopamine (CAS 51-61-6), dopexamine (CAS 86197-47-9), droxidopa (CAS 23651-95-8), epinephrine (CAS 51-43-4), ethylnorepinephrine (CAS 536-24-3), fluorodopa (CAS 92812-82-3), hexoprenaline (CAS 3215-70-1), isoetharine (CAS 530-08-5), isoproterenol (CAS 7683-59-2), levodopa (CAS 59-92-7), methyldopa (CAS 555-30-6), N-methylepinephrine (CAS 554-99-

nordihydroguaiaretic acid and tetrahydropapaveroline (CAS 4747-99-3). In certain embodiments the quinol compound comprises epinephrine.

[0023] In certain embodiments the thiol agent is selected from cysteine, N-acetylcysteine, glutathione, monothioglycerol, cysteine ethyl ester, homocysteine, Coenzyme A, dithiothreitol, 2-mercaptoethanol, 2,3-dimercapto-1-propanol, 2,3-butanedithiol, 2-mercaptoethylamine, ethanedithiol, propanedithiol, 3-mercapto-2-butanol, dimercapto-propane-1-sulfonic acid, dimercaptosuccinic acid, trithiocyanuric acid, 2,5-dimercapto-1,3,4-thiadiazole, 3,4-dimercaptotoluene, 1,4-dimercapto-2,3-butanediol, 1,3-propanedithiol, 1,4-butanedithiol, N-Acetylpenicillamine, ACV, N-amyl mercaptan, bucillamine, N-butyl mercaptan, sec-butyl bercaptan, tert-butyl mercaptan, captopril, cysteamine, DBHBT, 2,3-dimercapto-1-propanesulfonic acid, dimercaprol, dithiosalicylic acid, 1,2-ethanedithiol, ethanethiol, isobutyl mercaptan, mecysteine, 2-mercaptoethanol, MESNA, methanethiol, pantetheine, penicillamine, 1,3-propanedithiol, succimer, thioacetic acid, thiobenzyl alcohol, thiocyanic acid, thioglycerol, thioglycolic acid, thiolactic acid, thiomalic acid, thionalide, 1-thiosorbitol, tiopronin, tixocortol and trithiocarbonic acid. In certain embodiments the thiol agent is N-acetylcysteine.

[0024] In certain embodiments the pH buffer is present under conditions and in sufficient quantity to maintain a pH that is from about pH 5.5 to about pH 9.0, or from about pH 5.5 to about pH 8.5, or from about pH 5.5 to about pH 8.25, or from about pH 5.75 to about pH 7.75, or from about pH 6.0 to about pH 7.5, or from about pH 6.6 to about pH 7.3, or from about pH 6.5 to about pH 7.1, or from about pH 6.3 to about pH 6.9. In certain embodiments the pH buffer comprises a compound that is selected from Tris (8.3), Tricine (8.15), citrate (pKa_3=5.4), acetate (4.75), phosphate (7.2), borate (9.24), HEPES (7.55), HEPPS (8), MES (6.15), ACES (6.9), imidazole (7), diethylmalonic acid (7.2), MOPS (7.2), PIPES (6.8), TES (7.5), carbonate, bicarbonate, malate, pyridine, piperazine, succinate, histidine, maleate, Bis-Tris, pyrophosphate, histidine, MOPSO, BES, DIPSO, MOBS, TAPSO, triethanolamine, POPSO, cacodylic acid, ADA, Bis-Tris propane and HEPPSO. In certain embodiments the pH buffer comprises sodium phosphate. In certain embodiments the quinol compound comprises epinephrine, the thiol agent is N-acetylcysteine and the pH buffer comprises sodium phosphate.

[0025] In certain embodiments the amine group that is capable of being reversibly protonated has a pKa of from about pH 7.5 to about pH 9.3, or a pKa of from about pH 7.6 to about pH 9.2, or a pKa of from about pH 7.7 to about pH 9.1, or a pKa of from about pH 7.8 to about pH 9.0, or a pKa of from about pH 7.9 to about pH 8.9, or a pKa of from about pH 8.0 to about pH 8.8, or a pKa of from about pH 8.1 to about pH 8.7, or a pKa of from about pH 8.2 to about pH 8.6, or a pKa of from about pH 8.3 to about pH 8.5.

[0026] In certain embodiments the local anesthetic compound is selected from the group consisting of an amino ester anesthetic and an amino amide anesthetic. In certain embodiments the cell membrane is a plasma membrane. In certain embodiments the cell membrane is present in a neuron. In certain embodiments the cell membrane is selected from a plasma membrane, a mitochondrial membrane, an endoplasmic reticulum membrane, a lysozomal membrane, an exo-

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