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(54) **COMPOSITIONS CONTAINING THERAPEUTICALLY ACTIVE COMPONENTS HAVING ENHANCED SOLUBILITY**

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(58) **Field of Search** 514/772.4, 772.6; 424/400

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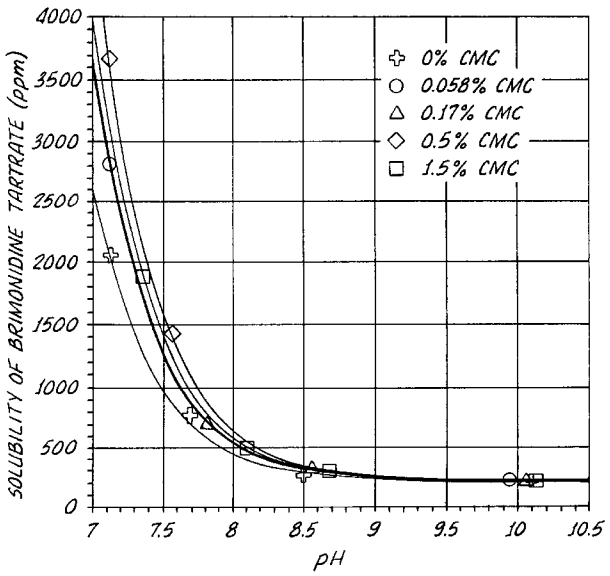
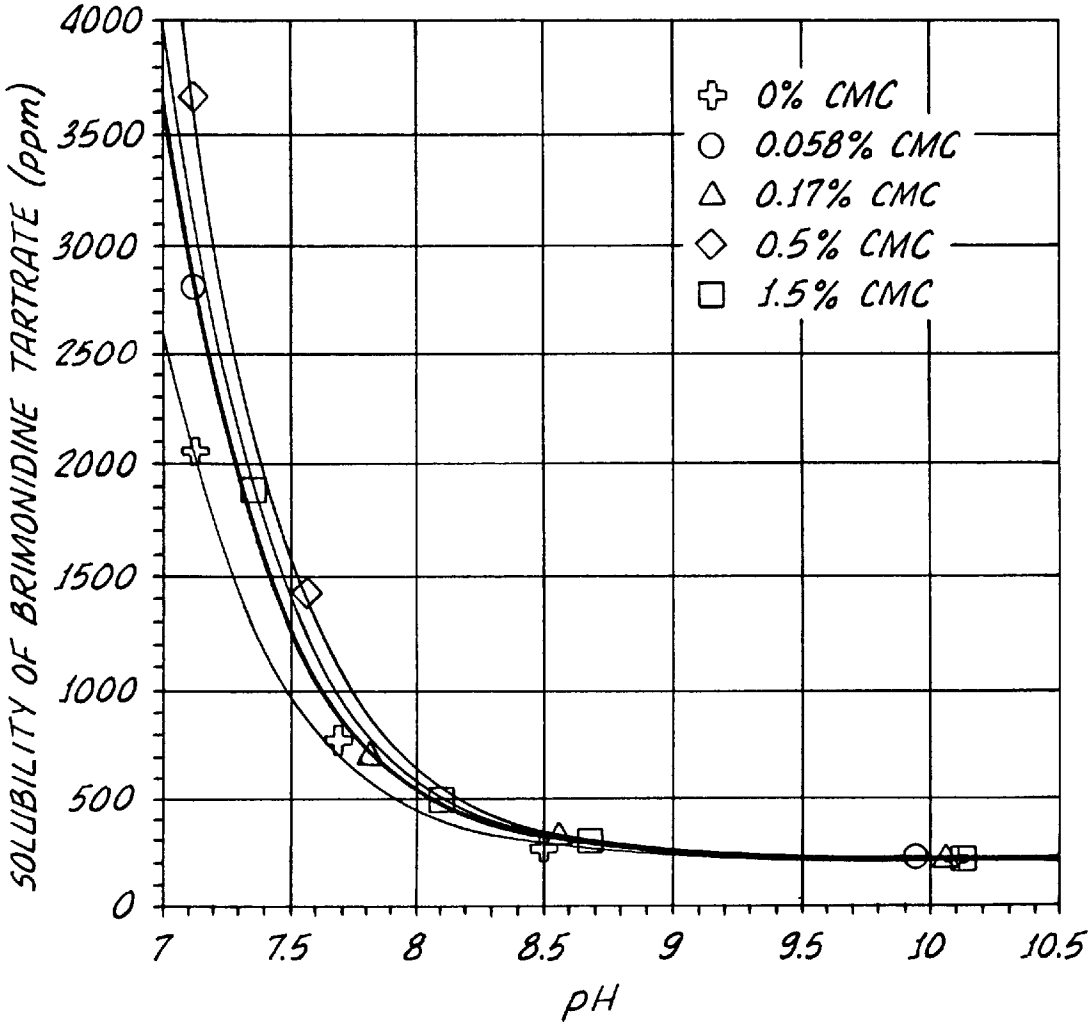
(57) **ABSTRACT**

Compositions which include therapeutically active components, solubility enhancing components other than cyclodextrins, and oxy-chloro components, wherein the oxy-chloro components are substantially effective as preservatives. In one embodiment, the oxy-chloro components are useful for preserving the therapeutically active components. In one embodiment, the oxy-chloro components include chlorite components. In a useful embodiment, the solubility enhancing components include carboxymethylcellulose.

49 Claims, 1 Drawing Sheet





COMPOSITIONS CONTAINING THERAPEUTICALLY ACTIVE COMPONENTS HAVING ENHANCED SOLUBILITY

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/218,206 filed Jul. 14, 2000.

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing therapeutically active components having enhanced solubility. More particularly, the invention relates to compositions which include therapeutically active components (TACs) and components effective to enhance the solubility of the TACs at therapeutically effective concentrations.

TACs in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration. Additionally, the dispensed or administered TACs should be soluble in the biological system or environment into which they are administered, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Furthermore, solubilized TACs provide other benefits, for example, reduced irritation to tissues that interact with TACs.

It is sometimes necessary to include solubilizing agents in the compositions to solubilize the TACs. However, the inclusion of solubilizing agents may reduce the effectiveness of the preservatives in the compositions.

For example, cyclodextrins are widely known in the literature to increase the solubility of poorly water soluble therapeutically active components. However, typical preservatives are rendered relatively ineffective by cyclodextrins at normal concentrations in these compositions.

There continues to be a need to provide new compositions containing TACs.

BRIEF SUMMARY OF THE INVENTION

New TAC-containing compositions have been discovered. The present compositions provide for enhanced TAC solubility substantially without detrimentally affecting the effectiveness of the preservative or preservatives being employed. Solubility enhancing components (SECs) have been found which very effectively increase the solubility of the TACs in the present compositions, and preferably in the biological systems or environments into which the components are introduced. Also, preferably, such solubilization allows the provision of more reliable and reproducible dosage forms of the drugs. This solubility enhancement in accordance with the present invention is achieved substantially without degrading preservative effectiveness. In addition, TAC-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the TACs and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

The present compositions include oxy-chloro components which are effective in at least assisting in preserving the compositions without detrimentally affecting the TACs and substantially without being detrimentally affected by the SECs. Moreover, the present oxy-chloro components provide preservative action with reduced or even substantially

no harm or irritation to the tissues to which the present compositions are administered.

The present SECs preferably are effective in solubilizing the TACs in the environment to which they are introduced, for example, a biological environment. Such solubilization preferably facilitates the advantageous transport of TACs across lipid membranes.

Soluble TACs for use in the present compositions include those components, e.g., compounds, mixtures of compounds, mixtures of other materials, useful to provide a therapeutic benefit or effect when administered to a patient, e.g. a human patient. The TACs useful in this invention include, without limitation, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics and the like and mixtures thereof. Specific examples of such TACs are conventional and well known in the art.

In one embodiment, the TACs include adrenergic agonists, precursors thereof, metabolites thereof and combinations thereof. Preferably, the TACs include alpha-2-adrenergic agonists, for example, imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. In one embodiment, the TACs include quinoxlaine components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Preferably, the quinoxaline components, including the quinoxaline derivatives, are alpha-2-adrenergic agonists. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a useful embodiment, the SEC is other than cyclodextrin and includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the TAC. This interaction preferably is sufficient to render the TAC substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The oxy-chloro components included in the present compositions are effective to at least assist in preserving the compositions. Any suitable oxy-chloro component effective to at least assist in preserving the compositions may be employed. Such oxy-chloro components include, without limitation, hypochlorite components, perchlorate components, chlorite components and the like and mixtures thereof.

In one useful embodiment, the oxy-chloro component includes a chlorite component. Preferably, the chlorite component includes stabilized chlorine dioxides, alkali metal chlorites and the like and mixtures thereof. Chlorite components are very effective in the present compositions and provide preservative effectiveness, often at a relatively reduced concentration, with little or no detrimental effect on the tissue to which the composition is administered. In addition, the oxy-chloro components, e.g., the chlorite components, substantially maintain preservative effectiveness in the presence of the SECs, for example, the polyanionic components. Without wishing to limit the invention to any particular theory or mechanism of operation, it is believed that such oxy-chloro components are substantially free in the presence of the SECs or do not substantially interact the SECs.

The oxy-chloro components may be effective in the compositions in the amount of less than about 1% (w/v) or about 0.8% (w/v). In a useful embodiment, the oxy-chloro components may be in the compositions in the range of about 500 ppm (w/v) or less, preferably about 10 ppm (w/v) to about 200 ppm (w/v).

In one embodiment, additional preservatives other than the oxy-chloro components are used in the compositions. Any suitable additional preservative component may be employed in accordance with the present invention, provided that it is compatible with the oxy-chloro component, the TAC and the SEC. Preservative components which are well known and/or conventionally used in the pharmaceutical field may be employed. Examples include, without limitation, sorbic acids, benzalkonium chlorides, chlorbutols and alkyl esters of p-hydroxybenzoic acids and the like and mixtures thereof. If additional preservative component is included, it preferably is present in an amount, together with the oxy-chloro component, to effectively preserve the composition.

The compositions include a liquid carrier component, for example, an aqueous liquid carrier component. Preferably, the compositions have pH's of about 7 or greater, more preferably about 7 to about 9.

In one broad aspect of the present invention, compositions are provided which comprise a TAC, a SEC, a chlorite component and an aqueous liquid carrier. Preferably the TAC is Brimonidine tartrate. The SEC is preferably an anionic cellulose derivative, more preferably a carboxymethylcellulose, for example, in an amount in the range of about 0.2% to about 0.6% (w/v).

In another broad aspect of the present invention, compositions are provided which comprise a Brimonidine tartrate, a SEC, a chlorite component and an aqueous liquid carrier component. The Brimonidine tartrate is present in an amount effective to provide a desired effect to a human or an animal after the composition is administered to the human or animal, and the SEC is preferably a carboxymethylcellulose.

In another broad aspect of the present invention, compositions are provided which comprise a TAC and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the TACs in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrin.

The present compositions preferably are ophthalmically acceptable, e.g. the compositions do not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising TACs, SECs and oxy-chloro components are provided. The TACs in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. Suitable SECs for solubilizing TACs may be used concurrently with oxy-chloro components in the present compositions to increase the solubility of the TACs substantially without detrimentally affecting the preservative effectiveness of the oxy-chloro components. In other words, SECs employed in the present compositions may effectively increase the solubility of TACs without substantially interfering with the functions of other components in the compositions. The SECs employed in the present compositions may be effective in the solubilization of ionized TACs, unionized TACs or both.

Oxy-chloro components are included in the present compositions to assist in preserving the compositions. Particularly, the oxy-chloro components are not substantially detrimentally affected by the SECs present in the compositions. Moreover, the oxy-chloro components in the compositions are effective substantially without causing undue harm or irritation to the tissue to which the present compositions are administered.

The present compositions may, and preferably do, include liquid carrier components. For example, the components often have the characteristics of a liquid, for example, a liquid solution.

The presently useful TACs preferably are chosen to benefit from the presence of the SECs and the oxy-chloro components. In general, the TACs are provided with

increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

Preferably, the TACs have increased solubility in the present compositions at pH's greater than 7, as compared to identical TACs, at comparable concentrations in similar compositions, without the SECs. More preferably, the TACs have increased solubility in the present compositions at pH's in the range of about 7 to about 10, as compared to TACs in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized TACs are better able to cross the lipid membranes relative to unsolubilized TACs. It is further believed that the solubilized TACs are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the TACs in the environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and a TAC may be administered to the cornea of a human eye, which has a pH of about 7, wherein the TAC is substantially solubilized at the administered area. Furthermore, in one embodiment, the TACs solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than TACs which are not solubilized by SECs. The solubilization of TACs preferably reduces irritation to sensitive tissues in contact or interacting with the TACs.

Examples of the therapeutically active components which may be included in the present compositions include, but are not limited to, antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoylthienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin and sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acid and its analogs such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogs thereof; antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogs thereof; mast-cell inhibitors of histamine release, such as cromolyn; anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indainethacin, sulindac, its salts and its corresponding sulfides, and analogs thereof; miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivaloylepinephrine, neostigmine echothiopate iodide, demecarim bromide, carbamoyl choline chloride, methacholine, bethanechol, and analogs thereof; mydriatics such as atrophine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine; and the like and mixtures thereof.

Other TACs are: antiglaucama drugs, for example, timalol, and especially its maleic salt and R-timolol and a combination of timolol or R-timolol with pilocarpine; other adrenergic agonists and/or antagonists such as epinephrine and an epinephrine complex, or prodrugs such as bitartrate, borate, hydrochloride and dipivefrine derivatives; carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)-thiothiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide, and 6-pivaloyloxy-2-benzothiazolesulfonamide; antiparasitic compounds and/or anti-protozoal compounds such as ivermectin, pyrimethamine, trisulfapidimidine, clindamycin and corticosteroid preparations; compounds having antiviral activity such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, interferon, and interferon-inducing agents such as poly I:C; antifungal agents such as amphotericin B, nystatin, flucytosine, natamycin and miconazole; anesthetic agents such as etidocaine cocaine, benoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine; ophthalmic diagnostic agents, such as: (a) those used to examine the retina such as sodium fluorescein, (b) those used to examine the conjunctiva, cornea and lacrimal apparatus, such as fluorescein and rose bengal and (c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine; ophthalmic agents used as adjuncts in surgery, such as alpha-chymotrypsin and hyaluronidase; chelating agents such as ethylenediaminetetraacetic acid (EDTA) and deferoxamine; immunosuppressants and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine and azathioprine and combinations of the compounds mentioned above, such as antibiotics/antiinflammatories combinations such as the combination of neomycin sulfate and dexamethasone sodium phosphate and combinations concomitantly used for treating glaucoma, for example, a combination of timolol maleate and aceclidine; and the like and mixtures thereof.

In a preferred embodiment, the useful TACs include adrenergic agonists. The adrenergic agonists preferably are molecules containing amines. Also, the adrenergic agonists preferably are amine-containing molecules with pKa's of greater than 7, preferably about 7 to about 9.

More preferably, the useful TACs include alpha-adrenergic agonists. Examples of alpha-adrengergic agonists include, but not limited to, adrafinil, adrenolone, amidephrine, apraclonidine, budralazine, clonidine, cyclopentamine, detomidine, dimetofrine, dipivefrin, ephedrine, epinephrine, fenoxazoline, guanabenz, guanfacine, hydroxyamphetamine, ibopamine, indanazoline, isometheptene, mephentermine, metaraminol, methoxamine, methylhexaneamine, metizolene, midodrine, naphazoline, norepinephrine, norfenefrine, octodrine, octopamine, oxymetazoline, phenylephrine, phenylpropanolamine, phenylpropylmethylamine, pholedrine, propylhexedrine, pseudoephedrine, rilmenidine, synephrine, tetrahydrozoline, tiamenidine, tramazoline, tuaminoheptane, tymazoline, tyramine, xylometazoline, and the like and mixtures thereof.

In a still more preferred embodiment, the useful TACs include alpha-2-adrenergic agonists. As used herein, the term "alpha-2 adrenergic agonist" includes chemical entities, such as compounds, ions, complexes and the like, that produces a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or, for example, to postsynaptic alpha-2

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