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(54) **COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF IONIZABLE HYDROPHOBIC THERAPEUTIC AGENTS**

(75) Inventors: **Feng-Jing Chen**; **Mahesh V. Patel**, both of Salt Lake City, UT (US)

(73) Assignee: **Lipocine, Inc.**, Salt Lake City, UT (US)

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Primary Examiner—Raj Bawa
(74) *Attorney, Agent, or Firm*—Dianne E. Reed; Reed & Associates

(57) **ABSTRACT**

The present invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of preparing such compositions by providing a composition of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compositions of the invention are particularly suitable for use in oral dosage forms.

COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF IONIZABLE HYDROPHOBIC THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to drug delivery systems, and in particular to pharmaceutical compositions for the improved delivery of ionizable hydrophobic compounds and methods therefor.

BACKGROUND

Hydrophobic therapeutic agents, i.e., therapeutic compounds having poor solubility in aqueous solution, present difficult problems in formulating such compounds for effective administration to patients. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment, while maintaining the hydrophobic compound in an absorbable form, and avoiding the use of physiologically harmful solvents or excipients.

A number of approaches to formulating hydrophobic therapeutic agents for oral or parenteral delivery are known. Such approaches include, for example, formulations in which the hydrophobic therapeutic agent is present in an oil-in-water emulsion, a microemulsion, or a solution of micelles, liposomes, or other multi-lamellar carrier particles. While such approaches may be appropriate for some ionizable as well as non-ionizable hydrophobic therapeutic agents, they fail to take advantage of the unique acid-base chemical properties, and associated solubility properties, of ionizable compounds.

In particular, unlike non-ionizable hydrophobic therapeutic agents, ionizable hydrophobic therapeutic agents can be rendered soluble in aqueous solution if the pH of the solution is adjusted to ionize the therapeutic agent. Such an approach is well known in the art. For example, U.S. Pat. No. 5,773,029 is directed to a pharmaceutical composition of an acidic drug, wherein the solubility of the acidic drug is enhanced by simultaneous salt formation with an organic or inorganic base and complexation with a cyclodextrin. The resultant drug/cyclodextrin/base complexes reportedly are readily soluble in water in high concentrations.

U.S. Pat. No. 5,360,615 discloses a pharmaceutical carrier system for an acidic, basic or amphoteric pharmaceutical agent in which the pharmaceutical agent is partially ionized by an acid or base in a polyethylene glycol-based solvent system. The pharmaceutical agent reportedly shows enhanced solubility in the partially ionized form. The reference also discloses that addition of glycerin, propylene glycol and/or polyvinylpyrrolidone further enhances the solubility of the pharmaceutical agent in the polyethylene glycol base. However, the invention is limited to polyethylene glycol-based solvent systems and a narrow range of ionizing agent concentration, and there is no disclosure of other solvent systems. Thus, its utility is severely limited.

Similarly, U.S. Pat. No. 5,376,688 discloses a pharmaceutical solution of an acidic, basic or amphoteric pharmaceutical agent. The solution includes a pharmaceutical agent, an ionizing species, and a solvent system. The solvent system can be diethylene glycol monoethyl ether, glycerol caprylate/caprate, polyglycerol oleate, alpha-hydro-w-hydroxypoly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) block copolymers, or mixtures of those components. The solvent system can also be a mixture of polyethylene glycol and a polyoxyethylene sorbitan ester. Optional components include water, glycerin, propylene glycol, and polyvinylpyrrolidone. However, the invention is limited to these particular compounds and a narrow range of ionizing agent concentration, rendering its utility severely limited. Moreover, some of the solvent system components show poor or questionable biocompatibility, and thus would be impractical for drug delivery to a patient.

A further problem with conventional approaches to solubilizing ionizable hydrophobic therapeutic agents is the difficulty in maintaining the solubilized therapeutic agent in solubilized form. Thus, for example, while ionizing an acidic therapeutic agent with a base may increase its solubility, the therapeutic agent is prone to precipitation in the gastrointestinal tract due to the acidic pH conditions encountered upon administration to a patient, and the approximately 10 to 100-fold dilution expected in gastrointestinal or intestinal fluids. This precipitation is particularly disadvantageous, since the precipitated therapeutic agent is essentially unavailable for absorption, leading to difficulties in controlling dosages, and a need to administer large doses of the therapeutic agent to ensure that a therapeutically effective amount reaches the absorption site in a bioavailable form. Such difficulties necessarily result in increased costs, and compromised patient safety and therapeutic effectiveness.

Thus, there is a need for versatile and effective pharmaceutical compositions that overcome these deficiencies in the prior art.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide pharmaceutical compositions capable of solubilizing therapeutically effective amounts of ionizable hydrophobic therapeutic agents.

It is another object of the invention to provide pharmaceutical compositions capable of maintaining a solubilized ionizable hydrophobic therapeutic agent in solubilized form upon administration to a patient.

It is another object of the invention to provide pharmaceutical compositions of ionizable hydrophobic therapeutic agents with improved delivery of the therapeutic agent to the absorption site.

It is a further object of the invention to provide improved methods of preparing pharmaceutical compositions of ionizable hydrophobic therapeutic agents.

It is still another object of the invention to provide methods of treating an animal with pharmaceutical compositions of ionizable hydrophobic therapeutic agents.

In accordance with these and other objects and features, the present invention provides pharmaceutical compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents.

In one embodiment, the invention is directed to a pharmaceutical composition including an ionizable hydrophobic therapeutic agent and a carrier. The carrier includes an ionizing agent to ionize the therapeutic agent, and a surfactant. Optionally, the carrier also includes solubilizers, triglycerides and neutralizing agents.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic thera-

peutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and a triglyceride.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group and present in a pre-reaction amount of greater than about 1.5 mole equivalents per mole of ionizable functional group, and a surfactant. In a further aspect of this embodiment, the composition further includes a neutralizing agent capable of neutralizing a portion of the ionizing agent.

In another embodiment, the invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group, a surfactant, and a solubilizer present in an amount of greater than about 10% by weight, based on the total weight of the composition. In this embodiment, the surfactant includes at least one compound from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

In another embodiment, the present invention is directed to a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group and a carrier, wherein the carrier includes an ionizing agent capable of ionizing the ionizable functional group, a surfactant, and a solubilizer. In this embodiment, the surfactant includes at least one compound selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; fatty acids; lower alcohol fatty acid esters; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polypropylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyglyceryl fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; fatty acid salts; bile salts; phospholipids; phosphoric acid esters; carboxylates; sulfates; and sulfonates.

The solubilizer in this embodiment includes at least one compound selected from the group consisting of alcohols, polyols, amides, esters, and propylene glycol ethers, the alcohol or polyol being selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, dimethyl isosorbide, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, maltodextrins, and cyclodextrins and cyclodextrin derivatives.

In another embodiment, the present invention provides a method of preparing a pharmaceutical composition of an ionizable hydrophobic therapeutic agent. In this embodiment, the method includes the steps of: providing a pharmaceutical composition having an ionizable hydrophobic therapeutic agent and a carrier which includes an ionizing agent and a surfactant; and providing a neutralizing agent to neutralize at least a portion of the ionizing agent.

In another embodiment, the present invention provides a method of treating an animal with an ionizable hydrophobic therapeutic agent. The method includes the steps of providing a pharmaceutical composition having an ionizable hydrophobic therapeutic agent and a carrier which includes an ionizing agent and a surfactant; and administering the pharmaceutical composition to an animal.

These and other objects and features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention overcomes the problems described above characteristic of conventional formulations, by providing pharmaceutical compositions including an ionizable hydrophobic therapeutic agent and a carrier. The carrier includes a surfactant, and an ionizing agent capable of ionizing the ionizable hydrophobic therapeutic agent. Optional components include one or more additional surfactants, solubilizers, triglycerides, neutralizing agents, and various additives. The carrier is able to solubilize the ionizable hydrophobic therapeutic agent and maintain the therapeutic agent in solubilized form for improved delivery to the absorption site The invention also encompasses various dosage forms of the pharmaceutical composition.

The present invention further provides a method of solubilizing ionizable hydrophobic therapeutic agents for improved performance in pharmaceutical compositions. The method includes the steps of providing a pharmaceutical composition as described above, and providing a neutralizing agent to neutralize a portion of the ionizing agent.

1. Ionizable Hydrophobic Therapeutic Agents

Ionizable hydrophobic therapeutic agents suitable for use in the pharmaceutical compositions of the present invention are not particularly limited, as the carrier is surprisingly capable of solubilizing and delivering a wide variety of ionizable hydrophobic therapeutic agents. Ionizable hydrophobic therapeutic agents are compounds with little or no water solubility at neutral pH. Intrinsic water solubilities (i.e., water solubility of the unionized form) for the ionizable hydrophobic therapeutic agents usable in the present invention are less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight. Such therapeutic agents can be any agents having therapeutic or other value when administered to an animal, particularly to a mammal, such as drugs, nutrients, and cosmetics (cosmeceuticals). It should be understood that while the invention is described with particular reference to its value in oral dosage form, the invention is not so limited. Thus, ionizable hydrophobic drugs, nutrients or cosmetics which derive their therapeutic or other value from, for example, topical or transdermal

administration, are still considered to be suitable for use in the present invention.

It is a particular feature of the present invention that a wide variety of therapeutic agents can be effectively incorporated in and delivered by the present pharmaceutical compositions. The essential feature of a suitable therapeutic agent is the presence of at least one ionizable functional group. Ionizable functional groups can be acidic groups, or basic groups, with "acidic" and "basic" referring to acidic or basic behavior in a Brønsted-Lowry or Lewis acid/base sense. Acidic functional groups are those groups that can be deprotonated by a suitable base to yield the corresponding anionic group (the conjugate base), or groups that can accept an electron pair. Basic functional groups are those groups that can be protonated by a suitable acid to yield the corresponding cationic group (the conjugate acid), or can donate an electron pair. It should be appreciated that the suitability of a therapeutic agent for use in the methods and compositions of the present invention is not determined by its therapeutic class, but is instead determined by the acid-base properties of its acidic or basic functional groups.

The terms "acid" and "base" as used herein refer to the ability of a functional group to act as a Brønsted-Lowry acid or Lewis acid, or as a Brønsted-Lowry base or Lewis base, in the presence of an appropriate ionizing agent. For simplicity, the acidic and basic properties of functional groups, ionizing agents, and neutralizing agents are described herein with particular reference to Brønsted-Lowry properties, but the corresponding Lewis acid/base properties are also included within the scope of these terms.

This usage should be contrasted with the terminology typically used in describing whether a compound is "acidic" or "basic" based on the pK_a of the compound in deionized water. For example, the equivalent pK_a of a functional group need not be less than 7 to be considered "acidic", since even functional groups with a large pK_a can be "acidic" if they can be deprotonated by a strong base. Similarly, a functional group with an equivalent pK_a of less than 7 may still be considered "basic" if it can be protonated by a stronger acid. Thus, it is the ability of a particular functional group to be ionized (protonated or deprotonated) by a suitable ionizing agent (acid or base) that determines whether a functional group is acidic or basic, rather than the particular pK_a associated with that group or with the compound as a whole.

As a specific example, itraconazole is a hydrophobic therapeutic agent having a pK_a of 3.7, and a pK_b of 10.3. Thus, itraconazole can be protonated by an acid having a pK_a less than 3.7, or deprotonated by a base having a pK_b less than 10.3.

Suitable therapeutic agents contain at least one ionizable functional group. Of course, many suitable therapeutic agents contain a plurality of such groups, and a single therapeutic agent may contain one or more acidic functional groups as well as one or more basic functional groups. Such therapeutic agents are also within tile scope of the present invention.

Acidic functional groups include, but are not limited to, carboxylic acids, imidazolidinediones, thiazolidinediones, pyrimidinetriones, hydroxyheteroaromatics, phenols, phosphoric acids, sulfuric acids, sulfonic acids, sulfonamides, aminosulfones, sulfonylureas, tetrazoles and thiols.

In order to avoid particularly cumbersome terminology, the functional groups, whether acidic or basic, are referred to by naming the corresponding free compound. For example, referring to a functional group, the term "aminosulfone" is used, rather than the more technically precise term "aminosulfonyl". This usage is common in the art, and is well understood by one skilled in the art.

Basic functional groups include, but are not limited to, aliphatic amines, aromatic amines, C-substituted aromatic amines, N-substituted aromatic amines, heterocyclic amines, C-substituted heterocyclic amines and N-substituted heterocyclic amines.

Examples of aromatic amines and substituted aromatic amines include, but are not limited to, aniline, N-methylaniline and p-toluidine.

Examples of heterocyclic and substituted heterocyclic amines include, but are not limited to, pyrrole, pyrazole, imidazole, indole, pyridine, pyridazine, pyrimidine, quinoline, piperidine, pyrrolidine, morpholine, thiazole, purine and triazole.

Specific examples of suitable therapeutic agents having at least one ionizable acidic functional group include, but are not limited to: acetazolamide, acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, aloxiprin, alprostadil, amodiaquine, amphotericin, amylobarbital, aspirin, atorvastatin, atovaquone, baclofen, barbital, benazepril, bezafibrate, bromfenac, bumetanide, butobarbital, candesartan, capsaicin, captopril, cefazolin, celecoxib, cephadrine, cephalexin, cerivastatin, cetrizine, chlorambucil, chlorothiazide, chlorpropamide, chlorthalidone, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, dichlorophen, diclofenac, dicloxacillin, dicumarol, diflunisal, dimenhydrinate, divalproex, docusate, dronabinol, enoximone, enalapril, enoxacin, enrofloxacin, epalrestat, eposartan, essential fatty acids, estramustine, ethacrynic acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, gliclazide, glipizide, glybenclamide, glyburide, glimepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, mesalamine, methotrexate, metolazone, montelukast, nalidixic acid, naproxen, natamycin, nimesulide, nitrofurantoin, non-essential fatty acids, norfloxacin, nystatin, ofloxacin, oxacillin, oxaprozin, oxyphenbutazone, penicillins, pentobarbital, perfloxacin, phenobarbital, phenytoin, pioglitazone, piroxicam, pramipexol, pranlukast, pravastatin, probenecid, probucol, propofol, propylthiouracil, quinapril, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfabenzamide, sulfacetamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethoxazole, sulfafurazole, sulfapyridine, sulfasalazine, sulindac, sulphasalazine, sulthiame, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, ursodeoxycholic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II) and zafirlukast.

Among the above-listed hydrophobic therapeutic agents having at least one acidic functional group, preferred hydrophobic therapeutic agents are: acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, amodiaquine, amphotericin, aspirin, atorvastatin, atovaquone, baclofen, benazepril, bezafibrate, bromfenac, butobarbital, candesartan, capsaicin, captopril, celecoxib, cerivastatin, cetrizine, chlorambucil, chlorpropamide, chlorthalidone, clinofibrate, cinoxacin, ciprofloxacin, clinofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproex, docusate, dronabinol, enalapril, enoxacin, eposartan, etodolac, etoposide, fenbufen

fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, fumagillin, gabapentin, gemfibrozil, gliclazide, glipizide, glyburide, glimepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, mesalamine, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pramipexol, pravastatin, probucol, propofol, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfadiazine, sulfamethoxazole, sulfasalazine, sulindac, sulphasalazine, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II) and zafirlukast.

Among the preferred hydrophobic therapeutic agents having at least one ionizable acidic functional group, the more preferred hydrophobic therapeutic agents are: acrivastine, alatrofloxacin, albuterol, aldlofenac, aspirin, atorvastatin, atovaquone, baclofen, benazepril, bezafibrate, bromfenac, butobarbital, celecoxib, cerivastatin, cetrizine, chlorpropamide, ciprofloxacin, cromoglicate, cromolyn, dantrolene, diclofenac, dicumarol, divalproex, dronabinol, enoxacin, etodolac, etoposide, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, gemfibrozil, glipizide, glyburide, glimepiride, grepafloxacin, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lomefloxacin, lovastatin, methotrexate, montelukast, naproxen, nimesulide, non-essential fatty acids, norfloxacin, ofloxacin, oxaprozin, phenytoin, pioglitazone, piroxicam, pravastatin, probucol, rabeprazole, repaglinide, rifampin, rifapentine, sulfamethoxazole, sulfasalazine, teniposide, tetrahydrocannabinol, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, valproic acid, vancomycin, vitamin K-S (II) and zafirlukast.

The most preferred hydrophobic therapeutic agents having at least one ionizable acidic functional group are: alclofenac, aspirin, atorvastatin, atovaquone, benazepril, bromfenac, celecoxib, cromoglicate, cromolyn, diclofenac, dronabinol, etodolac, fexofenadine, flurbiprofen, glimepiride, ibufenac, ibuprofen, isotretinoin, ketoprofen, ketorolac, levothyroxine, naproxen, non-essential fatty acids, oxaprozin, phenytoin, pioglitazone, rabeprazole, repaglinide, teniposide, tetrahydrocannabinol, tolmetin, tretinoin, troglitazone, trovafloxacin and vitamin K-S (II).

Specific examples of suitable hydrophobic therapeutic agents having at least one ionizable basic functional group include, but are not limited to: abacavir, acebutolol, acrivastine, alatrofloxacin, albuterol, albendazole, alprazolam, alprenolol, amantadine, amiloride, aminoglutethimide, amiodarone, amitriptyline, amlodipine, amodiaquine, amoxapine, amphetamine, amphotericin, amprenavir, amrinone, amsacrine, astemizole, atenolol, atropine, azathioprine, azelastine, azithromycin, baclofen, benethamine, benidipine, benzhexol, benznidazole, benztropine, biperiden, bisacodyl, bisanthrene, bromazepam, bromocriptine, bromperidol, brompheniramine, brotizolam, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cephadrine, cephalexin, cetrizine, cinnarizine, chlorambucil, chlorpheniramine, chlorproguanil, chlordiazepoxide, chlorpromazine, chlorprothixene, chloroquine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clenbuterol, clofazimine, clomiphene, clonazepam, clopidogrel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, cyproheptadine, dacarbazine, darodipine, decoquinate, delavirdine, demeclo-cycline, dexamphetamine, dexchlorpheniramine, dexfenfluramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, diltiazem, dimenhydrinate, diphenhydramine, diphenoxylate, diphenyl-imidazole, diphenylpyraline, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, doxycycline, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin, enrofloxacin, eperisone, ephedrine, ergotamine, erythromycin, ethambutol, ethionamide, ethopropazine, etoperidone, famotidine, felodipine, fenbendazole, fenfluramine, fenoldopam, fentanyl, fexofenadine, flecainide, flucytosine, flunarizine, flunitrazepam, fluopromazine, fluoxetine, fluphenthixol, fluphenthixol decanoate, fluphenazine, fluphenazine decanoate, flurazepam, flurithromycin, frovatriptan, gabapentin, granisetron, grepafloxacin, guanabenz, halofantrine, haloperidol, hyoscyamine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lanosprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclizine, medazepam, mefloquine, melonicam, meptazinol, mercaptopurine, mesalamine, mesoridazine, metformin, methadone, methaqualone, methylphenidate, methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone, molindone, montelukast, morphine, moxifloxacin, nadolol, nalbuphine, naratriptan, natamycin, nefazodone, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nitrazepam, nitrofurazone, nizatidine, norfloxacin, nortriptyline, nystatin, ofloxacin, olanzapine, omeprazole, ondansetron, omidazole, oxamniquine, oxantel, oxatomide, oxazepam, oxfendazole, oxiconazole, oxprenolol, oxybutynin, oxyphencyclimine, paroxetine, pentazocine, pentoxifylline, perchlorperazine, perfloxacin, perphenazine, phenbenzamine, pheniramine, phenoxybenzamine, phentermine, physostigmine, pimozide, pindolol, pizotifen, pramipexol, pranlukast, praziquantel, prazosin, procarbazine, prochlorperazine, proguanil, propranolol, pseudoephedrine, pyrantel, pyrimethamine, quetiapine, quinidine, quinine, raloxifene, ranitidine, remifentanil, repaglinide, reserpine, ricobendazole, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, ropinirole, rosiglitazone, roxatidine, roxithromycin, salbutamol, saquinavir, selegiline, sertraline, sibutramine, sildenafil, sparfloxacin, spiramycins, stavudine, sulconazole, sulphasalazine, sulpiride, sumatriptan, tacrine, tamoxifen, tamsulosin, temazepam, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tetramisole, thiabendazole, thioguanine, thioridazine, tiagabine, ticlopidine, timolol, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, triamterene, triazolam, trifluoperazine, trimethoprim, trimipramine, tromethamine, tropicamide, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K_5, vitamin K_6, vitamin K_7, zafirlukast, zolmitriptan, zolpidem and zopiclone.

Among the above-listed hydrophobic therapeutic agents having at least one ionizable basic functional group, pre-

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