The invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere.
NEW METHODS FOR TASTE-MASKING

SPECIFICATION

BACKGROUND OF THE INVENTION

1. FIELD OF INVENTION

The present invention relates to a composition and method for the preparation of taste-masked active pharmaceutical ingredients (APIs) for oral delivery.

2. DESCRIPTION OF RELATED ART

The preparation of a palatable dosage form of an active pharmaceutical ingredient (API) has long been an approach for helping to ensure patient compliance with a prescribed oral drug treatment regimen. Taste masking of an API, particularly those APIs which have an extremely unpleasant taste, has generally been attempted by some combination of (i) coating the API with a film, or (ii) forming a complex of the API with an ion-exchange matrix material.

For example, U.S. 5,075,114 describes a fluidized bed method of coating a pharmaceutical agent for taste-masking purposes. The patent describes the coating as a blend of cellulosic materials, i.e., hydroxypropyl cellulose and either cellulose acetate, cellulose acetate butyrate, or both. A number of drugs are mentioned, including ibuprofen, loperamide, famotidine, cimetidine, and ranitidine.

U.S. 5,082,669 describes ethyl cellulose coatings for bitter-tasting drugs. A number of drugs are mentioned as possibilities (at column 3, lines 13-31). The coating is prepared using either a film-forming solution or dispersion, or a spraying technique (column 5, lines 36-50).

Based on its Abstract, it appears that JP 57058631 describes coating a granulated API using a combination of an insoluble polymer coating agent, such as ethyl cellulose, and several polymer coating agents of varying solubility characteristics as a way of masking a bitter taste of a drug.

U.S. 5,032,393 suggests that the bitter taste of ranitidine can be masked by absorbing ranitidine hydrochloride onto a sulfonated styrene resin crosslinked with divinylbenzene or a methacrylic acid-divinylbenzene resin.

U.S. 3,594,470 and the related publication, Borodkin and Sundberg, J. of Pharmaceutical Sciences, 60(10): 1523-1527 (1971), describe coating weak ion exchange resins previously complexed with basic-reacting APIs, such as dextromethorphan, with a mixture of ethylcellulose and hydroxypropylmethyl cellulose as a prelude to making chewable tablets.
Example XII of U.S. 4,851,226 describes a coating formulation for taste-masking loperamide, supplied as the HCl salt presumably in the form of granules having a particle size of 40-60 mesh, comprising a blend of cellulose acetate and polyvinylpyrrolidone.

In U.S. 5,075,114, loperamide, supplied as the HCl salt presumably in the form of granules having a particle size of 40-80 mesh, is taste-masked in Example X by a coating comprising a blend of cellulose acetate and hydroxypropyl cellulose.

U.S. 5,215,755 describes, in Example VIII, a coating formulation for taste-masking loperamide, supplied as the HCl salt presumably in the form of a powder having a particle size of 40-80 mesh, comprising a blend of hydroxyethyl cellulose and hydroxypropyl cellulose.

U.S. 5,489,436 describes a coating formulation for taste-masking loperamide in Example VI comprising a mixture of cellulose acetate, polyvinylpyrrolidone and a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic acid ester.

The art continues to explore new ways for taste masking APIs.

All references cited herein are incorporated herein by reference in their entireties.

**BRIEF SUMMARY OF THE INVENTION**

The invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere. The invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere.

The invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere, further wherein the porous microsphere component is selected from the group consisting of polyesters, polyamides, polyanhydrides, and polyacrylates, poly(lactic) acid, poly(glycolic) acid, copoly(lactic/glycolic) acid and poly[1,3-bis(-p-carboxyphenoxy)propane-co-sebacic acid], polyglycolic (PGA), polylactic (PLA) acids, copolymers of glycolide and L-lactide (PGL), gelatin, agar, starch, arabinogalactan, albumin, collagen, natural and synthetic materials or polymers, such as, poly(ε-caprolactone), poly(ε-caprolactone-CO-lactic acid), poly(ε-caprolactone-CO-glycolic acid), poly(β-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), (e.g., methyl, ethyl, butyl, etc.), hydrogels such as
poly(hydroxyethyl methacrylate), polyamides (e.g., polyacrylamide), poly(amino acids) (i.e., L-leucine, L-aspartic acid, beta.-methyl-L-aspartate, β-benzyl-L-aspartate, glutamic acid and the like), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane), poly(methyl methacrylate), Sephadex™, Separose™, and Superose™, Trisacryl™, Ultrogel™, ACA™ media, GF05™ and GF2000™, Sephacryl™ media, Superdex™ media, such as Superdex 75™ and Superdex 200™, variants thereof, and combinations thereof.

The invention provides a taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the API is incorporated into the pores of the porous microsphere, further wherein the API is selected from antibiotics, antiviral agents, analgesics, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, H2 antagonists, antitussives, cardiovascular drugs, antiarrhythmics, antihypertensives, ACE inhibitors, diuretics, vasodilators, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, psychostimulants, sedatives, antimigrane agents, antituberculosis agents, tranquilizers vitamins and mineral supplements.

The invention provides a pharmaceutical composition comprising an API-porous microsphere complex and a sweetener, wherein the sweetener is a member selected from the group consisting of aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose, sucrose, and acesulfame K. The invention provides a method of preparing the pharmaceutical composition of comprising combining an API-porous microsphere complex and a sweetener.

The invention provides a pharmaceutical unit dosage form comprising an API-porous microsphere complex, wherein the dosage form is coated with a pharmaceutically acceptable coating, wherein the pharmaceutically acceptable coating is a member selected from the group consisting of polyethylene glycols, waxes, cellulose derivatives, and polyacrylate derivatives.

The invention provides an oral pharmaceutical unit dosage form comprising an API-porous microsphere complex, wherein the oral dosage form is a member selected from the group consisting of a capsule, a tablet, a wafer, a chewable tablet, a buccal tablet, a sub lingual tablet, a quick-dissolve tablet, an effervescent tablet, a granule, a gum, a pellet, a bead, a pill, a sachet, a
sprinkle, a syrup, a dry syrup, a reconstitutable solid, a suspension, a lozenge, a troche, an oral suspension, a lozenge, an implant, a powder, a triturate, an enterics/controlled release coated tablet, a thin film, or a strip. The invention provides a method of preparing the oral dosage form, comprising combining an API and a porous microsphere into the oral dosage form.

The invention provides a method of making a taste-masked pharmaceutical composition comprising granulating a mixture of an active pharmaceutical ingredient and a porous microsphere component, wherein the porous microsphere component is selected from the group consisting of is selected from the group consisting of polyesters, polyamides, polyanhydrides, and polyacrylates, poly(lactic) acid, poly(glycolic) acid, copoly(lactic/glycolic) acid and poly[1,3-bis(-p-carboxyphenoxy)propane-co-sebacic acid], poly(glycolic) (PGA), poly(lactic) (PLA) acids, copolymers of glycolide and L(-lactide) (PGL), gelatin, agar, starch, arabinogalactan, albumin, collagen, natural and synthetic materials or polymers, such as, poly(ε-caprolactone), poly(ε-caprolactone-CO-lactic acid), poly(ε-caprolactone-CO-glycolic acid), poly(β-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), (e.g., methyl, ethyl, butyl, etc.), hydrogels such as poly(hydroxyethyl methacrylate), polyamides (e.g., polyacrylamide), poly(amino acids) (i.e., L-leucine, L-aspartic acid, β-methyl-L-aspartate, β-benzyl-L-aspartate, glutamic acid and the like), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane), poly(methyl methacrylate), Sephadex™, Separose™, and Superose™, Trisacryl™, Ultrogel™, ACA™ media, GF05™ and GF2000™, Sephacryl™ media, Superdex™ media, such as Superdex 75™ and Superdex 200™, variants thereof, and combinations thereof. The invention provides that the API is incorporated into the pores of the porous microsphere.

The invention provides a pharmaceutical composition comprising an API porous microsphere complex and at least one flavorant, wherein the flavorant is a member selected from the group consisting of cherry, strawberry, grape, cream, vanilla, chocolate, mocha, aniseed, eucalyptus, 1-menthol, carvone, anethole, essential oils such as peppermint or spearmint, cola, and combinations thereof. The invention provides a method of preparing the pharmaceutical composition comprising combining an API porous microsphere complex and at least one flavorant.

The invention provides a pharmaceutical composition comprising an API porous microsphere complex and further optionally comprising at least one flavorant, and/or at least one sweetener and/or at least one coating. The invention provides a method of preparing the
pharmaceutical composition, comprising combining an API-porous microsphere complex optionally with at least one flavorant, and/or at least one sweetener, and/or at least one coating.

The invention provides a method of administering a pharmaceutical composition comprising an API-porous microsphere complex to a patient in need thereof, the method comprising providing a unit dose comprising the pharmaceutical composition comprising an API-porous microsphere complex, administering to the patient the unit dosage form, wherein the patient is a mammal.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a composition and a related method for the preparation of taste-masked active pharmaceutical ingredients (APIs). Taste masking can be defined as the perceived reduction of an undesirable taste commonly associated with a particular API.

The present invention obtains the taste masking of an API by conventional granulating (e.g., rotogranulating) techniques. In accordance with the invention, the API is granulated with a porous microsphere component. The granulation of the API with the porous microspheres component loads the API into the pores of the microsphere. The taste of the API is masked by incorporation of the API into the pores of the microsphere. The advantages of this method are that there is no loss of active ingredient as a result of the process. Additionally, this process does not change the ionic form of the active ingredient.

The process does not impart taste in an aqueous formulation process, and the method can be adapted to yield product with extended release properties. Furthermore, it is an additional advantage that the taste-masking agent (i.e. the porous microsphere) is inert.

Porous spherical polymer matrices or microspheres having a diameter range between about 1 to about 1000 microns (μm) can be prepared. A more preferred range for the spherical polymer matrices of microspheres is between about 0.5 to 150 microns. The methods for preparing porous spherical matrices consistent with the present invention result in microspheres in which essentially all of the agent(s) incorporated within the pores of the drug delivery system is readily available for release.

As used in the specification and claims, the expression "pore incorporated API" is used to define the relative specific location of the agent confined essentially completely inside the pores of the porous microspheres of the invention. Similarly, the term "API" specifically encompasses any diagnostic or pharmacologically active material which would be generally classifiable as a drug suitable for introduction into a human or other animal
host, as well as other materials or compositions including, for instance, dyes, antigens, antibodies, enzymes, flavors, comestibles and the like and mixtures thereof.

In accordance with the present invention, a granular pharmaceutical preparation is produced by mixing an API in a granulating solvent with a porous microsphere component, and granulating the mixture. Exemplary granulation solvents include, but are not limited to, alcohols, acetone, ethylacetate and water. The various ingredients that are used are substantially pure and non-toxic. The granulated material so-produced then can be sized, and milled and made into tablets, capsules or a variety of other dosage forms as noted hereinafter.

One of the main advantages of the present invention is that by preparing the taste-masked API as a granular composition one is better able to obtain and/or control the particle size of the material destined for use in preparing the final dosage form. When using the prior art's approach of applying a taste-masking coating directly onto the API, it is very difficult to control particle size within specifically desired limits to the same degree. The prior art's alternative approach of forming a complex with an ion exchange agent is limited to APIs that have solubility and porous microsphere characteristics suitable for that approach. Thus, the present invention permits taste masking of APIs that could not be accommodated with that technology.

In accordance with the methods for making the porous microspheres of the invention, the desired polymer or copolymer and the API or other agent(s) are dissolved separately in a suitable solvent. The polymer and drug solutions are mixed together in the appropriate manner with a drug:polymer ratio ranging between about 0.05:1 to 3:1, with the preferred range about 0.8:1.

**Microspheres**

Suitable porous microsphere components microparticles are prepared from any suitable polymeric material, such as polyesters, polyamides, polyanhydrides, and polycrylates. Preferably, the polymer is one which will degrade over time in the body, such as poly(lactic) acid, poly(glycolic) acid, copoly(lactic/glycolic) acid and poly[1,3-bis(-p-carboxyphenoxy)propane-co-sebacic acid] and the like materials. Typically preferred of such polyesters are polyglycolic (PGA) and polylactic (PLA) acids, and copolymers of glycolide and L(-lactide) (PGL). The aforementioned polyesters are particularly suited for the methods and compositions of the present invention by reason of their characteristically low human toxicity and virtually complete biodegradability. It will be understood that the particular polyester or other polymer, oligomer, copolymer, etc., utilized as the microspheric
polymer matrix is not critical and a variety of polymers may be utilized as a consequence of the novel processing methods of the invention which yield the desired microspheres of the porosity, consistency, shape and size distribution essentially irrespective of the source of polymer utilized. Accordingly, other biodegradable or bioerodible polymers or copolymers evidencing the necessary low degree of toxicity suitable for use in the present invention include, for example, gelatin, agar, starch, arabinogalactan, albumin, collagen, natural and synthetic materials or polymers, such as, poly(ε-caprolactone), poly(ε-caprolactone-CO-lactic acid), poly(ε-caprolactone-CO-glycolic acid), poly(β-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), (e.g., methyl, ethyl, butyl, etc.), hydrogels such as poly(hydroxyethyl methacrylate), polyamides (e.g., polyacrylamide), poly(amino acids) (i.e., L-leucine, L-aspartic acid, β.-methyl-L-aspartate, glutamic acid and the like), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate), Microsponge by Cardinal Health, and the like materials.

The porous microspheres may also be prepared from size exclusion media. Examples of such size exclusion media include, but are not limited to, Sephadex™, Seprose™, and Superose™, by Amersham Biosciences, and Trisacryl™ and Ultrogel™ by Pall Corporation, ACA™ media, such as ACA 34™, ACA 44™, ACA 54™, and ACA 200™ (commercially available from BioSepra, Inc., Marlborough, Mass. USA), GF05™ and GF2000™ (commercially available from BioSepra, Inc., Marlborough, Mass. USA), Sephacryl™ media, such as S400™, S500™, and S-1000™ (commercially available from Pharmacia Biotech, Uppsala, Sweden), Superdex™ media, such as Superdex 75™ and Superdex 200™ (commercially available from Pharmacia Biotech, Uppsala, Sweden), and the like.

Processes for forming such particles will be apparent to the skilled artisan and include, but are not limited to, spray drying of the polymeric material to generate substantially spherical particles or freeze drying followed by ball milling to produce randomly shaped particles.

API

The kinds of APIs that may benefit from the present invention include, without being limiting, antibiotics, antiviral agents, analgesics, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, anti diarrheals, antihistamines, anti-inflammatory agents, antinauseants, antineoplastics, antiparkinsonism
drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, H2 antagonists, antitussives, cardiovascular drugs, antiarrythmics, antihypertensives, ACE inhibitors, diuretics, vasodilators, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, psychostimulants, sedatives, antimigrane agents antituberculosis agents, tranquilizers vitamins and mineral supplements.

Mention may be made in particular of antibiotics such as tetracycline, penicillin V, or neomycin; hypnotics such as the barbiturates, methaqualone or mecloqualone; oral antidiabetics such as sulfaamides or biguanides; antihistamines such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, phentoloxamine citrate, or promethazine; bronchodilators such as theophylline or hydroxyethyl theophylline; vasoconstrictors such as ephedrine or isoprenaline or naphazoline; and antitusssants such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlorphenidanol hydrochloride. As noted above, the following APIs, dextromethorphan, diphenhydramine, phenylephrine, loperamide, cetirizine, Zolpidem, chlorpheniramine, loratadine, and desloratadine, Chlorpropamide, Tromadol, Famotadine, Glipizide, Chlorpheniramine, Brompheniramine, Doxylamine, Fexofenadine, Lamotrigine, Resperdone, Meloxicam, Olanzapine, Toperimate, Paxil, Topamax are of special interest.

In the embodiments of the present invention which include active ingredients, the active ingredients suitable for use in the pharmaceutical compositions and methods of the present invention are not particularly limited, as the compositions are surprisingly capable of effectively delivering a wide variety of active ingredients. The active ingredient can be hydrophilic, lipophilic, amphiphilic or hydrophobic, and can be solubilized, dispersed, or partially solubilized and dispersed. Such active ingredients can be any compound or mixture of compounds having therapeutic or other value when administered to an animal, particularly to a mammal, such as drugs, nutrients, cosmeceuticals, diagnostic agents, nutriceuticals, nutritional agents, and the like.

Suitable APIs are not limited by therapeutic category, and can be, for example, analgesics, anti-inflammatory agents, antihelminthics, anti-arrhythmic agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarial, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents,
sedatives, hypnotics, neuroleptics, \(\beta\)-Blockers, cardiac inotropic agents, corticosteroids, diuretics, antiparkinsonian agents, gastro-intestinal agents, histamine receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, Cox-2 inhibitors, leukotriene inhibitors, macrolides, muscle relaxants, nutritional agents, opioid analgesics, protease inhibitors, sex hormones, stimulants, muscle relaxants, anti-osteoporosis agents, anti-obesity agents, cognition enhancers, anti-urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids, non-essential fatty acids, and mixtures thereof.

Specific, non-limiting examples of suitable APIs are: acetretin, albendazole, albuterol, aminoglutethimide, amiodarone, amlodipine, amphetamine, amphotericin B, atorvastatin, atovaquone, azithromycin, baclofen, beclomethasone, benezepril, benzonatate, betamethasone, bicalutamide, budesonide, bupropion, busulfan, butenafine, calcifediol, calcipotriene, calcitriol, camptothecin, candesartan, capsaicin, carbamezepine, carotenes, celecoxib, cerivastatin, cetirizine, chlorpheniramine, cholecalciferol, cilostazol, cimetidine, cinnarizine, ciprofloxacin, cisapride, clarithromycin, clemastine, clomiphene, clomipramine, clopidogrel, codeine, coenzyme Q10, cyclobenzaprine, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, dicoumarol, digoxin, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donepezil, efavirenz, eposartan, ergocalciferol, ergotamine, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, fluconazole, flurbiprofen, fluvidastatin, fosphenytoin, frovatriptan, furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glimepiride, griseofulvin, halofantrine, ibuprofen, irbesartan, irinotecan, isosorbide dinitrate, isoretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, lisinopril, loperamide, loratadine, lovastatin, L-thyroxine, lutein, lycopene, medroxyprogesterone, mifepristone, mefloquine, megestrol acetate, methadone, metohxsalen, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, nabumetone, nalbuphine, naratriptan, neflavinir, nifedipine, nilsolidipine, nilutanide, nitrofurantoin, nizatidine, omeprazole, opevelkin, oestradiol, oxaprozin, paclitaxel, paracalcitral, paroxetine, pentazocine, pioglitazone, pizofetin, pravastatin, prednisolone, probucol, progesterone, pseudoephedrine, pyridostigmine, rabeprazole, raloxifene, rofecoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosiglitazone, saquinavir, sertraline, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen,
tamsulosin, targretin, tazarotene, telmisartan, teniposide, terbinafine, terazosin, tetrahydrocannabinol, tiagabine, ticlopidine, tirofiban, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, valsartan, venlafaxine, verteporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, zolmitriptan, Zolpidem, and zopiclone. Of course, salts, isomers and derivatives of the above-listed hydrophobic active ingredients may also be used, as well as mixtures, and polymorphic forms.

Further suitable APIs are not limited by therapeutic category, and can be, for example, analgesics, anti-inflammatory agents, antihelminthics, anti-arrhythmic agents, antibacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, beta-Blockers, cardiac inotropic agents, corticosteroids, diuretics, antiparkinsonian agents, gastro-intestinal agents, histamine receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, cox-2 inhibitors, leukotriene inhibitors, macrolides, muscle relaxants, nutritional agents, opioid analgesics, protease inhibitors, sex hormones, stimulants, muscle relaxants, anti-osteoporosis agents, anti-obesity agents, cognition enhancers, anti-urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids, non-essential fatty acids, and mixtures thereof, and polymorphic forms.

Furthermore, the API can be a cytokine, a peptidomimetic, a peptide, a protein, a toxoid, a serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of genetic material, a nucleic acid, or a mixture thereof.

Specific, non-limiting examples of suitable APIs also include: acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; aglucerase; amantadine hydrochloride; ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human), antihemophilic factor (porcine); antihemophilic factor (recombinant), aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladona; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotaxime;
cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalexin; cephapirin sodium; cholera vaccine; chornorous microsphere gonadotropin; cidofovir; cisplatin; cladribine; clindamycin; clindamycin derivatives; ciprofloxacin; clodronate; colistimethate sodium; colistin sulfate; corticotropin; cosyntrropin; cromolyn sodium; cytarabine; dalteparin sodium; danaparoid; desferrioxamine; denileukin diflitox; desmopressin; diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine; dexamethasone; dexamethasone sodium phosphate; dexamethasone sodium succinate; dopamine; dopamine hydrochloride; doraase alpha; doxazosin; doxazosin mesylate; doxazosin metilsulfate; doxazosin mesylate; doxorubicin; etoposide; etoposide phosphate; etoposide succinate; etoposide sulfate; etoposide palmitate; etoposide vinolactate; ethyl-4-hydroxy-2-methyl-5-isoxazoleacetic acid (HDAC inhibitor); eptatuzumab; epoetin alpha; erythromycin; esmolol hydrochloride; factor IX; famciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones—recombinant human; growth hormone—bovine; glucagon; glycophosphate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; haemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human, insulin lispro; insulin proline; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; ifosfamide; Japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; is measles virus vaccine; meningococcal vaccine; menotropins; mepenzolate bormide; mesalamine; methenamine; methotrexate; methscopolamine; metformin hydrochloride; metoprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neurontin; norfloxacin; octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine; perflloxacin; pentamidine isethionate; pentostatin; pentoxifylline; periciclovir; pentagastrin; pentholamine mesylate; phenylalanine; physostigmine salicylate; plague vaccine; pipercillin sodium; platelet derived growth factor-human; pneumococcal vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymyxin B sulfate; pralidoxime chloride; pramlintide; pregabalin; propafenone; propenthaline bromide; pyridostigmine bromide; racabans; resivirionate; ribavirin; rimantadine hydrochloride; rotavirus vaccine; salmeterol xinafoate; simealide; small pox vaccine; solatol; somatostatin; sparflaxacin; spectinomycin; stavudine; streptokinase; streptozocin; succinamethionum chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta;
ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNF\textsubscript{r}Fc; TNK-tPA; trandolapril; trimetrexate gluconate; trospectinomyacin; trovafloxacin; tubocurarine chloride; tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valacyclovir; valsartan; varicella virus vaccine live; vasopressin and vasopressin derivatives; vecuronium bromide; vinblastine; vincristine; vinorelbine; vitamin B\textsubscript{12}; warfarin sodium; yellow fever vaccine; zalcitabine; zanamivir; zolendronate; zidovudine; pharmaceutically acceptable salts, isomers and derivatives thereof; and mixtures thereof, and polymorphic forms.

**Granulation Methods**

In most cases, standard granulating equipment and drying apparatus can be used to produce pharmaceutical compositions of the API - microsphere complex, or taste masked API - microsphere complexes of the present invention. Such equipment and apparatus are well known to those skilled in the art. For example, pan granulators and rotor granulators along with spray drying and drum drying procedures may be suitable. Preferred ways of performing the original salt/complex formation and subsequent granulation thereof may include use of paddle dryers or fluidized bed plow mixers. As one suitable piece of equipment one can use the Tilt-A-Mix mixer available from Processall, hie.

**Dosage Forms**

An advantage of the techniques used in practicing the present invention is that one can produce granules having a uniform distribution of the API - microsphere complex, or the taste masked API - microsphere complex. In this way, one can be confident that when these granules are used to prepare the ultimate oral dosage form, whether in the form of a film (such as a fast melt film), a tablet (including chewable tablets and fast dissolving tablets), a capsule, an oral suspension, a gum, a lozenge, or the like dosage forms, one is precisely providing the desired quantity of the API, and not an undesired lower or higher amount of the API. The invention provides an oral dosage form which may be a capsule, a tablet, a wafer, a chewable tablet, a buccal tablet, a sub-lingual tablet, a quick-dissolve tablet, an effervescent tablet, a granule, a gum, a pellet, a bead, a pill, a sachet, a sprinkle, a syrup, a dry syrup, a reconstitutable solid, a suspension, a lozenge, a troche, an oral suspension, a lozenge, an implant, a powder, a triturate, an enterics/controlled release coated tablet, a thin film, or a strip.

When making a final dosage form using the API - microsphere complex containing granules of the present invention any of the wide variety of excipients commonly used in making pharmaceutical preparations can be used. For example, disintegrants, coloring
agents, flavoring agents, lubricants, fillers and the like materials can be employed with the inventive granular composition of this invention. The present invention is not to be limited to any specific set of excipients. Suitable pharmaceutical excipients include but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, lactose, mannitol, sorbitol, tribasic calcium phosphate, dibasic calcium phosphate, compressible sugar, starch, calcium sulfate, dextro and microcrystalline cellulose, acacia, tragacanth, hydroxypropylcellulose, pregelatinized starch, gelatin, povidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sugar solutions, such as sucrose and sorbitol, and ethylcellulose, and the like.

The invention provides extended release formulations for the therapeutically active agent. For example, the pharmaceutical composition of the invention includes a controlled release, sustained release, or timed release dosage formulation for the therapeutically active agent. The extended release formulation as described herein can provide continuous and non-pulsating therapeutic levels of the therapeutically active agent to a mammal in need of such treatment over a period of time, such as a six-hour period or longer, e.g., a twelve-hour to twenty-four hour period. Such an extended release, controlled release, sustained release, or timed release dosage formulation employs a mixture of organic acid and water-soluble polymers, e.g., a high molecular weight hydroxypropyl methylcellulose and polyvinylpyrrolidone.

The invention provides pharmaceutical unit dosage forms, wherein the dosage form is coated with a pharmaceutically acceptable coating. The pharmaceutically acceptable coating material includes, but is not limited to, a rapid-disintegrating coating material, a colorant, an enteric polymer, a plasticizer, a water-soluble polymer, a water-insoluble polymer, a dye, a pigment, other disintegrants, combinations thereof, and polymorphic forms thereof, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose succinate, carboxymethylcellulose, cellulose acetophthalate. In addition, examples of plasticizers include polyethylene glycol (PEG), propylene glycol, and others, water-soluble polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene oxide, and others.
The invention provides pharmaceutically acceptable coating of bulk active material. The invention provides pharmaceutically acceptable coating of bulk material comprising microsphere complexes of APIs. The invention provides pharmaceutically acceptable coating of bulk active material, wherein the material is taste masked. The invention provides pharmaceutically acceptable coating of bulk material comprising microsphere complexes of APIs, wherein the material is taste masked. The pharmaceutically acceptable coating material includes, but is not limited to, a rapid-disintegrating coating material, a colorant, an enteric polymer, a plasticizer, a water-soluble polymer, a water-insoluble polymer, a dye, a pigment, other disintegrants, combinations thereof, and polymorphic forms thereof, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose succinate, carboxymethylcellulose, cellulose acetophthalate. In addition, examples of plasticizers include polyethylene glycol (PEG), propylene glycol, and others, water-soluble polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene oxide, and others.

The step of providing the pharmaceutically active agent with the coating includes a treatment for coating onto portions of the pharmaceutically active agent. The drying includes applying heat the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Useful methods for providing the pharmaceutically active agent with the coating include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating of the pharmaceutically active agent.

The pharmaceutically acceptable polymers of the instant invention include, but are not limited to, water-soluble hydrophilic polymers, maltodextrin, natural gums, arabic gum, guar gum, xanthan gum, tragacanth gum, agar, gellan gum, kaya gum, alginic acids, pectins, pre-gelatinized starch, dextrin, maltodextrin, and blends of these polymers, combinations thereof, and polymorphic forms thereof. Examples of water-soluble polymers include polyvinylpyrrolidone, hydroxypropyl cellulose (HPC; Klucel), hydroxypropyl methylcellulose (HPMC; Methocel), nitrocellulose, hydroxypropyl ethylcellulose, hydroxypropyl butylcellulose, hydroxypropyl pentyldextrin, methyl cellulose, ethylcellulose (Ethocel), hydroxyethyl cellulose, various alkyl celluloses and hydroxyalkyl celluloses, various cellulose ethers, cellulose acetate, carboxymethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, vinyl acetate/crotonic acid copolymers, poly-hydroxyalkyl methacrylate, hydroxymethyl methacrylate, methacrylic acid
copolymers, polymethacrylic acid, polymethylmethacrylate, maleic anhydride/methyl vinyl ether copolymers, poly vinyl alcohol, sodium and calcium polyacrylic acid, polyacrylic acid, acidic carboxy polymers, carboxypolymethylene, carboxyvinyl polymers, polyoxyethylene polyoxypropylene copolymer, polymethylvinylether co-maleic anhydride, carboxymethylamide, potassium methacrylate divinylbenzene co-polymer, polyoxyethyleneglycols, polyethylene oxide, and derivatives, salts, and mixtures thereof.

Suitable examples of pharmaceutically acceptable sweeteners for the oral formulations include, but are not limited to, aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose, sucrose, Acesulfame potassium, Alitame, Aspartame, and Aspartame-Acesulfame Salt, Cyclamate, Neohesperidine dihydrochalcone, Neotame, Saccharin, Sucralose, Stevia, Tagalose. Suitable sweeteners include both natural and artificial sweeteners. Non-limiting examples of suitable sweeteners include, e.g.: water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin; water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3, 4-dihydro-6-methyl-1, 2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3, 4-dihydro-6-methyl-1, 2,3-oxathiazine-4-one-2, 2-dioxide (acesulfame-K), the free acid form of saccharin and the like; dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame), L-alpha-aspartyl-N- (2, 2,4, 4- tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2, 5, dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L- (l-cyclohexyen)-alanine, and the like; d. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivatives of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and protein based sweeteners such as thaumatouccous danielli (Thaumatococcus danielli) and other natural sources.

Flavorants may also be used to improve the flavor of the composition and, as with the sweeteners, the pleasant flavor of the flavorant is not altered or reduced by the taste-masking component of the present invention. Flavorants may be used singly or in combination. Flavorants may be both natural and synthetic flavors. Examples of preferred flavorants include, but are not limited to, cherry, strawberry, grape, cream, vanilla, chocolate,
mocha, aniseed, eucalyptus, 1-menthol, carvone, anethole, citrus oils, essential oils such as peppermint, spearmint, or methyl salicylate (oil of wintergreen), cola, and the like.

The API - microsphere complex of the instant invention may optionally comprise a film-forming agent which can be selected from known pharmaceutical coating agents, many of which are polymeric materials and include cellulose-based coating agents; methacrylate-based coating agents, and polyvinyl acetate phthalate-based coating agents. Suitable cellulose-based coating agents include methyl, ethyl and propyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose, hydroxypropylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate, cellulose acetate butyrate, and nitrocellulose. Suitable methacrylate-based coating agents include aniporous microsphere polymers of methacrylic acid and methacrylates with a COOH group, catporous microsphere polymers with a dimethylaminoethyl ammonium group, copolymers of acrylate and methacrylates with quaternary ammonium groups, copolymers of acrylate and methacrylates with quaternary ammonium group in combination with sodium carboxymethylcellulose, waxes and the like materials.

In many instances it will be preferred to use a film-forming agent that is insoluble in water but soluble in an organic solvent. Such a film forming agent would embrace the alkyl derivatives of cellulose, preferably cellulose ethers such as methyl, ethyl and propyl cellulose, which are insoluble in water and soluble in organic solvents; cellulose esters such as cellulose acetate and cellulose acetate butyrate; nitrocellulose; poly(meth)acrylates, polyvinyl acetate, polyvinyl chloride, waxes and the like. One preferred film-forming agent (B) comprises ethyl cellulose.

The film-forming agent can be supplied to the granulating process dissolved in an organic solvent, such as ethanol, which then can provide at least a portion of the granulating liquid. Preferably, however, the film-forming agent is provided as a water-based dispersion and comprises an aqueous dispersion of ethyl cellulose. A suitable ethyl cellulose aqueous dispersion will normally have a concentration of water-insoluble ethyl cellulose of 3 to 40 wt. %, more usually 10 to 35 wt. %. The ethyl cellulose aqueous dispersion is preferably used in combination with at least one physiologically compatible lipophilic diester of (i) a C6-C40 and preferably a C10-C16 aliphatic or aromatic dicarboxylic acid and (ii) a C1-C8 and preferably a C2-C5 aliphatic alcohol, as a plasticizer. Suitable plasticizers include dibutyl phthalate, diethyl phthalate, dibutyl sebacate and diethyl sebacate. Usually, the quantity of plasticizer is from 5 to 50 wt. % and preferably 10 to 40 wt. %, relative to ethyl
cellulose.

The aqueous ethyl cellulose dispersion may be a commercial product such as, for example, sold under the names Aquacoat® or Surelease®. Such dispersions, such as for example Surelease®, may already contain the necessary plasticizer. Alternatively, it is possible to incorporate the plasticizers into the aqueous ethyl cellulose dispersion, possibly with the assistance of a surfactant or an emulsifier as needed.

The film-forming agent generally constitutes from 3 to 40 percent (%) by weight of the API-containing granule, preferably from 5 to 25 weight percent of the API-containing granule and more preferably from about 5 to 10 weight percent of the API-containing granule.

The API - microsphere complex of the instant invention may optionally comprise a water soluble binder. Suitable ingredients for use as the water soluble binder include organic polyols (typically non-toxic hydrocarbons having two or more hydroxyls) such as 1,3-dihydroxypropane, hexylene glycol, glycerine, sorbitol, inositol and carbohydrates such as glucose and sucrose; polyethylene glycol; hydroxypropyl cellulose; hydroxypropyl methylcellulose; hydroxyethyl cellulose; polyvinyl alcohol; polyvinylpyrrolidone; carboxymethylcellulose and the like materials. Thus, a suitable water soluble binder material may be a PEG having a molecular weight of 500 or more (preferably between 1000 and 6000) or a polyvinylpyrrolidone having a molecular weight of at least 10000 (preferably between 10000 and 360,000). The preferred binder material is polyethylene glycol (PEG), particularly PEGs having a number average molecular weight of 3000 to 4000.

As used in this specification and in the appended claims, the singular forms "a", "an" and "the" also are intended to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an API" includes reference to one or more APIs (drugs), and the like.

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLES

Example 1

Preparation of taste-masked Diphenhydramine HCl. An aqueous mixture is prepared from a diphenhydramine acid salt (the HCl salt), which is dissolved in water. Sephadex G-10 25 g is added to the solution, and the solution is stirred for 12 hours. The mixture is then concentrated to dryness under vacuum using external heat with a temperature of 60°C. The
dried product is milled and sieved to yield the taste-masked Diphenhydramine HCl - Sephadex complex.

**Example 2**

Sample Evaluation method. Routine organoleptic screening can be used to identify satisfactorily taste masked compositions from those that are not. In particular, a suitable screening test for evaluating the suitability of the methods of the present invention for taste masking a specific API involves preparing a solution or suspension of about 4 mmol of the taste masked API in 13 ml of water. The mixture is then agitated for about 1-2 hours and then an approximate 5µL sample of the mixture is tasted. The taste of an aqueous solution or suspension of the untreated API at the same concentration should be evaluated contemporaneously. The relative taste of the taste masked API can be rated on a scale of 1 to 4, where 4 signifies that the taste of the untreated API is the same as the taste masked sample and 1 signifies that the taste masked API has no significant taste. By having the taste masked APIs considered by a panel of tasters (preferably three or more), an average level of taste masking can be determined. While any rating below 4 indicates a level of taste masking, satisfactory taste masking is usually considered when an average of 2 or lower is attained, which is indicative of a significantly reduced negative taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.
WHAT IS CLAIMED IS:

1. A taste-masked pharmaceutical composition suitable for oral administration comprising a granulated mixture of an active pharmaceutical ingredient and a porous microsphere component.

2. A taste-masked pharmaceutical composition suitable for oral administration comprising a mixture of an active pharmaceutical ingredient and a porous microsphere component.

3. The taste-masked pharmaceutical composition of claim 1 or 2 wherein the API is incorporated into the pores of the porous microsphere.

4. The taste-masked pharmaceutical composition of claim 1 or 2 wherein the porous microsphere component is selected from the group consisting of polyesters, polyamides, polyanhydrides, and polycrylates, poly(lactic) acid, poly(glycolic) acid, copoly(lactic/glycolic) acid and poly[1,3-bis(-p-carboxyphenoxy)propane-co-sebac acid], polyglycolic (PGA), polylactic (PLA) acids, copolymers of glycolide and L(-lactide) (PGL), gelatin, agar, starch, arabinogalactan, albumin, collagen, natural and synthetic materials or polymers, such as, poly(ε-caprolactone), poly(ε-caprolactone-CO-lactic acid), poly(ε-caprolactone-CO-glycolic acid), poly(β-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), (e.g., methyl, ethyl, butyl, etc.), hydrogels such as poly(hydroxyethyl methacrylate), polyamides (e.g., polyacrylamide), poly(amino acids) (i.e., L-leucine, L-aspartic acid, β-methyl-L-aspartate, β-benzyl-L-aspartate, glutamic acid and the like), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-dioscyanatohexane), poly(methyl methacrylate), Sephadex™, Separose™, and Superose™, Trisacyr™, Ultrogel™, ACA™ media, GF05™ and GF2000™, Sephacyrl™ media, Superdex™ media, such as Superdex 75™ and Superdex 200™, variants thereof, and combinations thereof.

5. The taste-masked pharmaceutical composition of claim 1 or 2 wherein the API is selected from antibiotics, antiviral agents, analgesics, anesthetics, anorexics, antiarthritis, antiasthmatic agents, anticonvulsants, antidepressants, antidiabetic agents, antiarrheals, antihistamines, anti-inflammatory agents, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, H2 antagonists, antitussives, cardiovascular drugs, antiarrhythmics, antihypertensives, ACE inhibitors, diuretics, vasodilators, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympathomimetics,
parasympathomimetics, psychostimulants, sedatives, antimigrane agents, antituberculosis agents, tranquilizers vitamins and mineral supplements.

6. A pharmaceutical composition comprising an API-porous microsphere complex and at least one sweetener.

7. The pharmaceutical composition of claim 6, wherein the sweetener is a member selected from the group consisting of aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose, sucrose, acesulfame K, and combinations thereof.

8. A pharmaceutical composition comprising an API-porous microsphere complex and at least one flavorant.

9. The pharmaceutical composition of claim 8, wherein the flavorant is a member selected from the group consisting of cherry, strawberry, grape, cream, vanilla, chocolate, mocha, aniseed, eucalyptus, 1-menthol, carvone, anethole, essential oils such as peppermint or spearmint, cola, and combinations thereof.

10. A method of preparing the pharmaceutical composition of claim 6, comprising combining an API-porous microsphere complex and at least one sweetener.

11. A method of preparing the pharmaceutical composition of claim 8, comprising combining an API-porous microsphere complex and at least one flavorant.

12. A pharmaceutical unit dosage form comprising an API-porous microsphere complex, wherein the dosage form is coated with a pharmaceutically acceptable coating.

13. The pharmaceutical unit dosage form of claim 12, wherein the pharmaceutically acceptable coating is a member selected from the group consisting of polyethylene glycols, waxes, cellulose derivatives, polyacrylate derivatives, and combinations thereof.

14. An oral pharmaceutical unit dosage form comprising an API-porous microsphere complex, wherein the oral dosage form is a member selected from the group consisting of a capsule, a tablet, a wafer, a chewable tablet, a buccal tablet, a sublingual tablet, a quick-dissolve tablet, an effervescent tablet, a granule, a gum, a pellet, a bead, a pill, a sachet, a sprinkle, a syrup, a dry syrup, a reconstitutable solid, a suspension, a lozenge, a troche, an oral suspension, a lozenge, an implant, a powder, a triturate, an enterics/controlled release coated tablet, a thin film, or a strip.

15. A method of preparing the oral dosage form of claim 14, comprising combining an API and a porous microsphere into the oral dosage form.
16. A method of making a taste-masked pharmaceutical composition comprising granulating a mixture of an active pharmaceutical ingredient and a porous microsphere component.

17. The method of claim 16 wherein the porous microsphere component is selected from the group consisting of is selected from the group consisting of polyesters, polyamides, polyanhydrides, and polyacrylates, poly(lactic) acid, poly(glycolic) acid, copoly(lactic/glycolic) acid and poly[[1,3-bis(-p-carboxyphenoxy)propane-co-sebacic acid], polyglycolic (PGA), polylactic (PLA) acids, copolymers of glycolide and L(-lactide) (PGL), gelatin, agar, starch, arabinogalactan, albumin, collagen, and natural and synthetic materials or polymers, such as, poly(ε-caprolactone), poly(ε-caprolactone-CO-lactic acid), poly(ε-caprolactone-CO-glycolic acid), poly(β-hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), (e.g., methyl, ethyl, butyl, etc.), hydrogels such as poly(hydroxyethyl methacrylate), polyamides (e.g., polyacrylamide), poly(amino acids) (i.e., L-leucine, L-aspartic acid, β-methyl-L-aspartate, β-benzyl-L-aspartate, glutamic acid and the like), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane), poly(methyl methacrylate), Sephadex™, Separose™, and Superose™, Trisacryl™, Ultrogel™, ACA™ media, GF05™ and GF2000™, Sephacryl™ media, Superdex™ media, such as Superdex 75™ and Superdex 200™, variants thereof, and combinations thereof.

18. The method of claim 16 wherein the API is incorporated into the pores of the porous microsphere.

19. A method of administering a pharmaceutical composition comprising an API-porous microsphere complex to a patient in need thereof, the method comprising:

- providing a unit dose comprising the pharmaceutical composition comprising an API-porous microsphere complex;

- administering to the patient the unit dosage form.

20. The method of claim 19, wherein the patient is a mammal.

21. A pharmaceutical composition comprising an API-porous microsphere complex and further optionally comprising at least one flavorant, and/or at least one sweetener and/or at least one coating.

22. A method of preparing the pharmaceutical composition of claim 21, comprising combining an API-porous microsphere complex optionally with at least one flavorant, and/or at least one sweetener, and/or at least one coating.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/24 (2008.04)
USPC - 424/473
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
USPC - 424/473

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/486, 489, 430/101 (see search terms below)

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google
Search Terms Used
mannitol, taste masking microsphere, porous microsphere, medicine, polyester microsphere, granulation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tbody>
<tr>
<td>X</td>
<td>WO 2005/013944 A1 (DUMONT et al) 17 February 2005 (17 02 2005) pg 1, 2 and 6</td>
<td>1-3, 5-16 and 18-22</td>
</tr>
</tbody>
</table>

D. Further documents are listed in the continuation of Box C

"*" Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search
17 August 2008 (17 08 2008)

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Date of mailing of the international search report
20 AUG 2008

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PCT DSP 571-272-2774

Form PCT/ISA/2 10 (second sheet) (April 2007)