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(54) **Title:** STABLE PHARMACEUTICAL FORMULATIONS AND METHODS OF USE THEREOF

(57) **Abstract:** The present invention provides pharmaceutical formulations characterized by improved stability of the pharmaceutically active compounds contained therein, methods for preparing the same, and methods of use thereof. The pharmaceutical compositions of the present invention comprise a stable water-insoluble complex of a pharmaceutically active compound and a carrier macromolecule. The advantages of the pharmaceutical compositions of the invention include, for example, the increased stability of a pharmaceutically active compound contained therein.

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STABLE PHARMACEUTICAL FORMULATIONS AND METHODS OF USE THEREOF

Related Applications

This application also claims priority to U.S. Provisional Application No.: 60/708536 entitled "Stable Pharmaceutical Formulations and Methods of Use Thereof", filed August 15, 2005, U.S. Provisional Application No.: 60/732545 entitled "Stable Pharmaceutical Formulations and Methods of Use Thereof", filed November 2, 2005 and U.S. Provisional Application No.: 60/798,555 entitled "Stable Pharmaceutical Formulations and Methods of Use Thereof", filed May 8, 2006. The entire contents of each of the foregoing applications are incorporated herein by reference.

Background of the Invention

Development of stable formulations of pharmaceutically active compounds requires an intimate knowledge of the active compound and its chemical and physical properties. In many instances, the therapeutic effectiveness of a pharmaceutically active compound depends upon its stability and continued therapeutic activity over prolonged time periods and under a variety of conditions. To achieve stability of a pharmaceutically active compound, various approaches have been used, including microencapsulation technologies, which permit continuous delivery over prolonged periods but do not provide long-term stability and/or therapeutic effectiveness of the pharmaceutically active compounds. Thus, additional formulations for maintaining stability and therapeutic effectiveness of pharmaceutically active compounds for prolonged time periods are needed.

Summary of the Invention

The present invention provides pharmaceutical compositions comprising a stable water-insoluble complex of a pharmaceutically active compound, *e.g.*, a peptidic compound and/or a non-peptidic compound, and a carrier macromolecule. The present invention also provides pharmaceutical compositions comprising a stable water-insoluble complex of a pharmaceutical compound and a carrier macromolecule, further comprising a biodegradable carrier matrix, *e.g.*, a microsphere, a microcapsule, a microparticle, and a liposome.

The formulations of the present invention not only increase the stability, *e.g.*, physical, chemical, and/or biological stability, *e.g.*, therapeutic effectiveness, of the pharmaceutically active compound over prolonged periods of time, (*e.g.*, both *in vivo* and *ex vivo*), but also increase the glass transition temperature of the water-insoluble

complex and decrease the rate of absorption of the pharmaceutically active compound from the gastrointestinal tract. Furthermore, the pharmaceutical formulations of the invention enable the maintenance of the blending uniformity of the pharmaceutically active compound within the formulation.

Accordingly, in one aspect, the present invention provides a method for increasing the stability (*e.g., in vivo* and/or *ex vivo* stability) of a pharmaceutically active compound. The method comprises providing a pharmaceutically active compound and a carrier macromolecule, combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the stability of the pharmaceutically active compound.

In another aspect, the invention provides a method for increasing the glass transition temperature (Tg) of the water-insoluble complex. The method includes selecting a pharmaceutically active compound whose water-insoluble complex would benefit from an increase in the glass transition temperature (Tg), combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the glass transition temperature (Tg) of the water-insoluble complex.

In another aspect, the invention provides a method for decreasing the rate of absorption of a pharmaceutically active compound from the gastrointestinal (GI) tract of a subject. The method includes selecting a pharmaceutically active compound for which a decrease in the rate of absorption from the GI tract would be beneficial, *e.g.,* Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, and Meperidine, combining the pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby decreasing the rate of absorption of the pharmaceutically active compound from the gastrointestinal (GI) tract of a subject.

In one aspect of the invention provides a method for preventing local irritation of the gastrointestinal (GI) tract of a subject. The method includes, selecting a pharmaceutically active compound that causes local irritation of the GI tract, *e.g.,* Rivastigmine, combining the pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby preventing local irritation of the GI tract of a subject.

In a further aspect, the invention provides a method for maintaining blending uniformity of a pharmaceutically active compound in a pharmaceutical composition by

selecting a pharmaceutically active compound that would benefit from an increased and/or maintained blending uniformity, *e.g.,* Flexeril, Exelon, and Adderall, combining the pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby maintaining blending uniformity of the pharmaceutically active compound in a pharmaceutical composition.

The pharmaceutically active compounds of the invention can be, for example, peptidic compounds. In one embodiment, the peptidic compounds are multivalent cationic or anionic. In another embodiment, the peptidic compounds have an isoelectric point of, for example, less than about 7.0, less than about 6.5, less than about 6.0, less than about 5.5, less than about 5.0, between about 4.5 and about 7.0, and between about 5.0 and about 6.5. In yet another embodiment, the peptidic compounds are, for example, 5 to 20 amino acids in length, 8 to 15 amino acids in length, and 8 to 12 amino acids in length.

In another embodiment of the invention the peptidic compound is selected from the group consisting of LHRH analogues, recombinant luteinizing hormone, *e.g.,* lutropin alpha, bradykinin analogues, parathyroid hormone, adenocorticotrophic hormone (ACTH), calcitonin, vasopressin analogues (*e.g.,* 1-deamino-8-D-arginine vasopressin (DDAVP)), and synthetic forms of vasopressin, *e.g.,* Desmopressin Acetate. Other non-limiting examples of pharmaceutically active peptides that can be used in the formulations and methods of the invention include octreotide, endorphin, liprecin, erythropoietin, protamine, platelet aggregation inhibitor (epoprostenol), platelet glycoprotein IIb/IIIa receptor, recombinant platelet glycoprotein IIb/IIIa receptor antibodies, *e.g.,* Abciximab and Eptifibatide, angiotensin II, antidiuretic hormone, neurotrophic factors, keratinocyte growth factor, leukemia inhibiting factor, monocyte chemoattractant protein-1, endothelial growth factors, thymosin alpha 1, thymosin alpha 1 IIb/IIa inhibitor, thymosin beta 10, thymosin beta 9, thymosin beta 4, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 (very late antigen-4), VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, *e.g.,* antibodies directed against the epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV), *e.g.,* PALIVIZUMAB, cystic fibrosis transmembrane regulator (CFTR) protein, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, oxytocin, growth hormones, *e.g.,* somatotropin, pituitary hormones, somatostatin, asparaginase, chorionic gonadotropin, growth hormone releasing hormone, growth hormone releasing peptide, interferons (*e.g.,* interferons α, β γ, interferon β-1a, interferon α-2a, interferon alfacon-1, interferon alpha-n3 (Human Leukocyte Derived), colony stimulating factor, bone morphogenic proteins (BMP) (*e.g.,* 1, 2, 3, 4, 5, 6, and 7), interleukins (*e.g.,* interleukin-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -13, -14, -15, -

16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28 , -29 and -30), *e.g.*, recombinant interleukin antibodies, *e.g.*, IL-2, *e.g.*, Aldesleukin, *e.g.*, recombinant interleukins, *e.g.*, IL-11, *e.g.*, oprelvekin, *e.g.*, interleukin receptor antagonists, *e.g.*, IL-1 receptor antagonist, *e.g.*, anakinra, glucocerebrosidase, *e.g.*, Imiglucerase, macrophage activating factor, macrophage peptide, B cell factor, T cell factor, protein A, suppressive factor of allergy, cell necrosis glycoprotein, immunotoxin, lymphotoxin, tumor necrosis factor, tumor inhibitory factor, transforming growth factor, HER2, *e.g.*, antibodies against HER2, *e.g.*, Trastuzumab, myelin, *e.g.*, synthetic forms or fragments thereof, *e.g.*, Glatiramer Acetate, alpha-1 antitrypsin, albumin, apolipoprotein-E, apolipoprotein A1, erythropoietin, hyper-glycosylated erythropoietin, factor VII, factor VIII, factor IX, plasminogen activator, urokinase, streptokinase, protein C, activated Protein C, *e.g.*, Drotrecogin alpha, protein S, C-reactive protein, renin inhibitor, collagenase inhibitor, superoxide dismutase, leptin, platelet derived growth factor, epidermal growth factor, epidermal growth factor receptor (EGFR), *e.g.*, recombinant EGFR antibodies, *e.g.*, Cetuximab, osteogenic growth factor, osteogenesis stimulating protein, calcitonin, insulin, insulin analogs, *e.g.*, Insulin Glulisine and Insulin Glargine, amylin, *e.g.*, synthetic analogues thereof, *e.g.*, Pramlintide, atriopeptin, cartilage inducing factor, connective tissue activator protein, follicle stimulating hormone, luteinizing hormone, FSH releasing hormone, nerve growth factor, parathyroid hormone, or a portion thereof, *e.g.*, Teriparatide, prostoglandin, relaxin, secretin, somatomedin, insulin-like growth factor, thrombolytics, pamiteplase, lanoteplase, and teneteplase; nerve growth factor (NGF), osteoprotegerin, Rhdnase, *e.g.*, dornase alpha and Tenecteplase, erythropoiesis stimulating protein (NESP), coagulation factors such as Factor V, Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor XII, Factor XIII, von Willebrand factor; ceredase, cerezyme, alpha-glucosidase, collagen, cyclosporin, alpha defensins, beta defensins, exedin-4, thrombopoietin (TPO), heparin, human serum albumin, low molecular weight heparin (LMWH), alpha-1 proteinase inhibitor, elcatonin, fibrinogen, filgrastim (granulocyte colony-stimulating factor, *e.g.*, Sargramostim), adrenocorticotrophic hormone, glucagon, glucagon-like peptide 1 (GLP-1) receptor or agonists thereof, *e.g.*, Exendin-4, glucagon-like peptide 1, or analogues thereof, *e.g.*, Exenatide, cholecystokinin, pancreatic polypeptide, gastrin releasing peptide, corticotropin releasing factor, or analogues thereof, *e.g.*, Corticorelin Ovine Triflutate, thyroid stimulating hormone, TNF receptor (*e.g.*, TNFR(P75) and TNFR(P55)), IL-1 receptor antagonist (*e.g.*, IL1-Ra), cell surface antigen (*e.g.*, CD2, 3, 4, 5, 7, 11a, 11b, 18, 19, 20, 23, 25, 33, 38, 40, 45 and 69), *e.g.*, recombinant CD20 antibodies, *e.g.*, Rituximab, TNF-α, *e.g.*, recombinant TNFα antibodies, *e.g.*, Infliximab, Etanercept, NF-κB, urate oxidase, *e.g.*, Rasburicase, cone snail peptide w-cenotoxin M-VII-A, *e.g.*, Ziconotide, antimicrobial antifungal and antibacterial analogues, non-limiting examples

of which include, Caspofungin acetate, ADENOREGULIN, Aureins, Gaegurins, Thanatin, Ranatuerin-2CB, Ranatuerin-2CA, Cecropin A, Cecropin B, Melittin B, Indolicidin, Tritrpticin, Androctonin, Tachystatin A, Dermaseptins, Gomesin, Hepcidin 20, Hepcidin 25, Peptide PGQ, Protegrins, RatNPs Seminalplasmin, Tracheal antimicrobial peptide, Dolabellanin B2, AFP1, AFP2, Dermaseptin BI, Buforin I, Buforin II, Histones, Opistoporins, Ponericins, Penaeidins, Spingerin, Skin peptide tyrosine-tyrosine, Lingual antimicrobial peptide, Tricholongin, Termicin, Holotricins, Penaeidins, Nk-Lysin, Magainin 2, Neutrophil defensins, Cyclic Defensin, Alpha-basrubrin, Melanotropin alpha (Alpha-MSH), Brevinin, Pseudins (1, 2, 3, 4), Anti-fungal protein 1(pafp-s), Misgurin, P-18, Pseudo-hevein (Minor hevein), MUC7 20-Mer, Histatins (3, 5, 8), Nigrocin, lactoferrin (Lf), Ranalexin, antiviral analogues, *e.g.,* Antiviral protein Y3, Alloferon 1, Lactoferricin B, hexapeptide, Tricyclic peptide RP, Indolicidin, GNCP-2, GNCP-1, HNP-1 Defensin, HNP-2 Defensin, Defensin, CORTICOSTATIN III (MCP-1) , CORTICOSTATIN IV (MCP-2), NP-3A defensin, Protegrin 2, Protegrin 3, Protegrin 3, Protegrin 4, Protegrin 5, RatNP-1, RatNP-2, RatNP-3, RatNP-4, Caerin 1.1, Circulin A (CIRA), Circulin B (CIRB), Cyclopsychotride A (CPT), Ginkbilobin, Alpha-basrubrin, Enfuvirtide, or other antiretroviral agents.

The pharmaceutically active compounds of the invention can also be, for example, non-peptidic compounds. In one embodiment, the non-peptidic compound is cationic, *e.g.,* has a charge of at least +1 and has a charge of at least +2. In another embodiment, the non-peptidic compound is anionic, *e.g.,* has a charge of at least -1 and has a charge of at least -2.

In one embodiment of the invention the non-peptidic compound has, for example, at least one functional group selected from the group consisting of primary amino groups, secondary amino groups, tertiary amino groups, imino groups, quaternary ammonium groups, amidino groups, guanidino groups, phosphonium groups and sulfonium groups, at least one functional group selected from the group consisting of carboxylate groups, sulfonate groups, phosphonate groups, sulfamate groups, sulfate ester groups, phosphate ester groups, sulfinate groups, phosphinate groups, carbonate groups, thiocarboxylate groups and carbamate groups, and has at least one functional group selected from the group consisting of carboxylate and sulfonate.

In yet another embodiment, the pharmaceutically active compound has, for example, a molecular weight of about 100-2200 amu. In one embodiment, the pharmaceutically active compound has a molecular weight of about 1000 amu or less. In another embodiment, the pharmaceutically active compound has a molecular weight of about 750 amu or less. In yet another embodiment, the pharmaceutically active compound has a molecular weight of about 500 amu or less.

The carrier macromolecule of the invention can be, for example, ionic, *e.g.,* may have at least one functional group selected from the group consisting of carboxylic acid, sulfonic acid, sulfamic acid, primary amine, secondary amine, tertiary amine, quaternary ammonium, guanidino and amidino. In other embodiments of the invention, the ionic carrier macromolecule is a polypeptide or a polysaccharide, an anionic polymer, an anionic polyalcohol derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof, an anionic polysaccharide derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof, carboxymethylcellulose, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of algin, alginate, anionic acetate polymers, anionic acrylic polymers, xantham gums, dextran sulfate, croscarmellose sodium, carbomers (poly(acrylic acid)), sodium hyaluronate, xanthan gum, and chitosan, and fragments, derivatives and pharmaceutically acceptable salts thereof, anionic carageenan derivatives, anionic polygalacturonic acid derivatives, sodium starch glycolate, and fragments, derivatives and pharmaceutically acceptable salts thereof, is anionic and selected from the group consisting of carboxymethylcellulose, poly(glutamic acid), poly(aspartic acid), poly(glutamic acid-co-glycine), poly(aspartic acid-co-glycine), poly(glutamic acid-co-alanine), poly(aspartic acid-co-alanine), starch glycolate, polygalacturonic acid, poly(acrylic acid), alginic acid, dextran sulfate, croscarmellose sodium, carbomers (poly(acrylic acid)), sodium hyaluronate, xanthan gum, and chitosan, is anionic and selected from the group consisting of poly(glutamic acid) and poly(aspartic acid), is anionic and is carboxymethylcellulose, and is cationic.

In one embodiment, the content of pharmaceutically active compound in the water-insoluble complex can be, for example, at least 50% by weight, at least 60% by weight, at least 70% by weight, 50% to 90% by weight, 60% to 90% by weight, or 65% to 0% by weight. In the embodiment in which the pharmaceutically active compound is a non-peptidic molecule, *e.g.,* a small molecule with a molecular weight of about 100-2200 amu, the content of pharmaceutically active compound in the water-insoluble complex can be, for example, at least 20% by weight, at least 25% by weight, at least 30% by weight, at least 35% by weight, at least 40% by weight, at least 45% by weight, 20% to 30% by weight, 30% to 45% by weight, or 20% to 45% by weight.

The weight ratio of carrier macromolecule:pharmaceutically active compound used to form the water-insoluble complex can be, for example, 0.5:1 to 0.1:1 and 1:1 to 0.1:1

In another aspect, the present invention provides a pharmaceutical composition comprising a water-insoluble complex of a pharmaceutically active compound and a carrier macromolecule, wherein the water-insoluble complex is further embedded in a biodegradable carrier matrix.

The pharmaceutical compositions of the invention comprising a water-insoluble complex and a biodegradable carrier matrix can interact, for example, physically and chemically. The biodegradable carrier matrix can be composed of, for example naturally derived polymer, *e.g.,* albumin, alginate, cellulose derivatives, collagen, fibrin, gelatin, and polysaccharides, or can be composed of synthetic polymers, *e.g.,* polyesters (PLA, PLGA), polyethylene glycol, poloxomers, polyanhydrides, pluronics, and polyethylene glycol (PEG).

Brief Description of the Drawings

Figures 1 and 2 are graphs showing that water-insoluble complexes of Naltrexone HCl and Dextromethorphan HBr, respectively, formulated as described herein, do not have increased dissolution rates in the presence of alcohol.

Detailed Description of the Invention

The present invention provides pharmaceutical formulations characterized by the improved stability of the pharmaceutically active compounds contained therein, methods for preparing the same, and methods of use thereof. The pharmaceutical compositions of the present invention comprise a stable water-insoluble complex of a pharmaceutically active compound and a carrier macromolecule. The advantages of the pharmaceutical compositions of the invention include, for example, an increased stability of the pharmaceutically active compound contained therein; a decrease in the rate of absorption of the pharmaceutically active compound from the gastrointestinal (GI) tract; a decrease in the local irritation of the GI tract; maintenance of blending uniformity of the pharmaceutically active compound; and an increase in the glass transition temperature (Tg) of the water-insoluble complex.

As used herein, the terms "stable" "stabilized" and "stability" are intended to include physical, chemical, and/or biological stability of a pharmaceutically active compound. Instability of a pharmaceutically active compound in a pharmaceutical formulation typically results in a decrease in, for example, the glass transition temperature of the water-insoluble complex and/or a decrease in the therapeutic efficacy of the pharmaceutically active compound. The increased stability of the pharmaceutically active compound in the formulations of the present invention allows for improved performance, safety, efficacy and/or patient compliance. For example, the pharmaceutical formulations of the invention are characterized by their sustained therapeutic effect; targeted gastrointestinal site delivery for local or systemic effects to the stomach, duodenum, ileum, jejunum, colon or rectum; reduced lingering side effects; increased bioavailability; improved solubility, membrane permeability, and/or *in vivo/ex vivo* stability of the pharmaceutically active compound; reduced variability in absorption

of the pharmaceutically active compound; reduced food effect; protection of the gastrointestinal tract; reduced irritating effect caused by the active ingredient; taste masking or odor masking; flavor augmentation; and improved physical and/or chemical stability of the pharmaceutically active compound and/or the dosage form during storage, and improved stability, both physical and chemical, of the pharmaceutically active compounds.

This improved stability of the pharmaceutically active compound is in comparison to currently available dosage forms, and the formulations of the invention provide about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100% improvement in the *in vivo* and *ex vivo* stability of the pharmaceutically active compound.

In one aspect of the invention, the pharmaceutical formulations of the present invention improve the stability of the pharmaceutically active compound. This improvement in stability encompasses both *in vivo* and/or *ex vivo* stability under, for example, adverse environmental conditions, such as acidic conditions of the gastrointestinal tract, as well as during storage when the formulation may be exposed to extremes in moisture, heat, cold, agitation, or during the sterilization processes, such as, for example, UV irradiation, gamma irradiation, and the like.

In another aspect of the invention, the improvement in stability of the pharmaceutically active compound in the pharmaceutical formulation described herein, involves a decrease in the rate of absorption of the pharmaceutically active compound from the gastrointestinal (GI) tract. Such formulations would be useful for, for example, with acid-labile drugs and in abuse prevention. It is common for persons wishing to abuse a pharmaceutically active compound, *e.g.,* Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, Naltrexone, Pseudoephedirine, Dextromethorphan, and Meperidine, to crush tablets containing these compounds. If the tablet coating is crushed, the immediate-release tablet is available for dissolution and injection or swallowing to achieve rapid high blood levels. Without wishing to be bound by theory, it is believed that the pharmaceutical formulations of the present invention will prevent the ready dissolution of the pharmaceutically active compound from the pharmaceutical formulation, thus, decreasing the rate of absorption of the pharmaceutically active compound from the GI tract, and also reducing the abuse potential of the pharmaceutically active compound.

In yet another aspect, the present invention provides methods for the prevention of accidental or intentional overdose caused by the consumption of alcohol simultaneously with drug intake. As demonstrated below, the pharmaceutical formulations of the invention are characterized by the fact that their dissolution profile does not change in the presence of alcohol (see Example 4). In other words, the rate of

release of the pharmaceutically active compound from the pharmaceutical formulations of the invention does not increase in the presence of alcohol. It is common for persons wishing to abuse a pharmaceutically active compound, *e.g.*, Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, Naltrexone, Pseudoephedirine, Dextromethorphan, and Meperidine, to consume the pharmaceutically active compound at the same time as consuming alcohol. Since the rate of release of the pharmaceutically active compound from the pharmaceutical formulations of the invention does not increase in the presence of alcohol, the formulations and methods of the invention may be used to reduce the potential for such intentional overdosing. Moreover, it is common for persons legitimately taking a pharmaceutically active compound, *e.g.*, for the treatment of pain, such as Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, Naltrexone, Pseudoephedirine, Dextromethorphan, and Meperidine, to accidentally consume alcohol leading to accidental overdosing. Since the rate of release of the pharmaceutically active compound from the pharmaceutical formulations of the invention does not increase in the presence of alcohol, the formulations and methods of the invention may be used to reduce the potential for such accidental overdosing.

The improvement in the *in vivo* and/or *ex vivo* stability of a pharmaceutically active compound provided by the formulations of the present invention is also beneficial for acid-labile drugs and/or drugs that cause local irritation of the gastrointestinal tract, such as for example, Rivastigmine and Tacrine, which cause GI stress when contacting the lining of the stomach and small intestines. The pharmaceutical formulations of the invention gradually release the pharmaceutically active compound at a dose that remains below the concentration of the pharmaceutically active compound that causes local irritation to the gastrointestinal tract while still maintaining its efficacy by, for example, binding to the drug and prohibiting its interactions with GI tract membranes.

Additional benefits of the pharmaceutical formulations of the present invention include the increased stability of the pharmaceutically active compound in the formulations of the invention. For example, the pharmaceutical formulations of the present invention can overcome physiological adversities such as short gastric residence time (GRT) and/or unpredictable gastric emptying time (GET). This effect can be achieved by, for example, further combining the water-insoluble complex of the invention with additional carriers, *e.g.*, a biodegradable carrier matrix. Pharmaceutically active compounds with poor or unfavorable pharmacodynamics (PD) and/or pharmacokinetics (PK), such as, for example, riboflavin, levodopa, beta-lactam, furosemide, misoprosotol, and 5-fluorouracil, have short GRT and/or unpredictable GET are suitable candidates for this embodiment of the invention. Accordingly, the formulations of the present invention can overcome poor colonic absorption of various

physiologically active compounds; enhance first-pass biotransformation by, for example, increasing the pre-systemic metabolism of drugs which maintain sustained therapeutic levels after exposure to metabolic enzymes, such as, for example, cytochrome P450; increase targeted delivery of pharmaceutically active compounds used for local therapy (by, for example, sustaining and prolonging targeted therapy for local ailments in the upper GI tract while minimizing systemic concentrations of the pharmaceutically active compound following drug adsorption and distribution); reduce the fluctuation in the concentrations of a pharmaceutically active compound and, thus, reduce potential adverse side-effects by, for example, producing blood concentrations of the pharmaceutically active compound in a narrower range, as compared to immediate release dosage forms; improve selectivity in receptor activation by minimizing the concentration of a pharmaceutically active compound that activates different types of receptors at different concentrations; enhance drug efficiency by reducing the counter-activity of the body that minimizes the drug activity (for example, the improved stabiltity of the water-insoluble complex leads to the slow release of the pharmaceutically active compound into the body, thus, enhancing drug efficiency by minimizing the impact of the body's pharmacological response, *e.g.,* adverse immune response). The formulations of the present invention can also extend the time over critical therapeutic concentration (CTC), for drugs which possess non-concentration dependent PD, *e.g.*, beta-lactam antibiotics, such that the pharmacological effect and clinical outcome is elicited; and minimize adverse activity at the colon, such as, for example, microorganism resistance in the case of beta-lactam antibiotics, by, for example, allowing the retention of the drug in the stomach or upper GI tract.

Moreover, the compositions described herein enable the improved absorption and/or bioavailability of a pharmaceutical active compound contained therein. More specifically, the oral bioavailability of pharmaceutical active compound is improved when the formulation is administered to mammals under a fed condition, *i.e.*, the state typically induced by the presence of food in the stomach. Once this fed mode has been induced, larger particles of food are retained in the stomach for a longer period of time than smaller particles. The compositions of the invention are less susceptible to food effects and, therefore, provide higher bioavailability resulting in superior performance. Without wishing to be bound by theory, it is believed that current formulations of proton pump inhibitors often experience a decrease in bioavailability of up to 50% when taken with food. This effect is likely due to the lowered duodenal pH upon gastric emptying and/or higher gastric retention that leads to drug instability. The compositions of the present invention will overcome these shortcomings of the prior art compositions.

In addition, the improvement in bioavailability of a pharmaceutically active compound with a short half-life provided by the formulations of the invention reduces

the frequency of dosing and improves patient compliance. The improvement in bioavailability of the pharmaceutical formulations of the present invention also improves the absorption of pharmaceutically active compounds which do not undergo oxidative metabolism due to reduced P-glycoprotein activity in the duodenum, such as, for example, digoxin.

Yet another benefit of the pharmaceutical formulations of the invention is the maintenance of the blending uniformity of the pharmaceutically active compound in the pharmaceutical formulation. For example, it is often necessary to deliver small oral doses of the pharmaceutically active compound very precisely in order to achieve efficacy without generating an unacceptable level of side-effects. For example, Flexeril, Exelon, and Adderall are pharmaceutical formulations that have a very small percentage of pharmaceutically active compound. In these instances, the pharmaceutically active compound is often many times diluted by blending with inactive ingredients leading to a non-uniform blending of the pharmaceutically active compound within the formulation. For example, the percentage of the total weight due to the pharmaceutically active compound is so small (typically < 1%) relative to the total weight of the tablet or capsule. The pharmaceutical formulations of the present invention allow for an increase in the weight contributed by the pharmaceutically active compound by substituting the carrier macromolecule instead of the pharmaceutically active compound alone. Due to the increased contribution of the pharmaceutically active compound to the total weight of the blend and because the carrier macromolecule is a better match in terms of particle size and morphology to the other excipients in the blend, the content uniformity is maintained.

In order that the invention may be more readily understood, certain terms are defined below.

As used herein, the term "pharmaceutically active compound" refers to a pharmaceutical compound suitable for inclusion in the water-insoluble complex of the invention, *e.g.*, a peptidic compound and/or a non-peptidic compound, that exhibits pharmacologic activity, either in its present form or upon processing *in vivo* (*i.e.*, pharmaceutically active peptidic compounds include peptidic compounds with constitutive pharmacologic activity and peptidic compounds in a "prodrug" form that have to be metabolized or processed in some way *in vivo* following administration in order to exhibit pharmacologic activity).

As used herein, "glass transition temperature" ("Tg") is the temperature below which molecules have very little mobility. For example, polymers are rigid and brittle below their glass transition temperature and can undergo plastic deformation above it.

Glass transition temperature is the temperature at which a material's characteristics change from that of a glass to that of rubber.

As used herein, the term "carrier macromolecule" refers to a macromolecule that can complex with a pharmaceutically active compound to form a water-insoluble complex. Prior to complexing with the pharmaceutically active compound, the carrier macromolecule typically is water-soluble. Preferably, the macromolecule has a molecular weight of at least 5 kDa, more preferably 10 kDa. The term "anionic carrier macromolecule" includes negatively charged high molecular weight molecules, such as anionic polymers. The term "cationic carrier macromolecule" includes positively charged high molecular weight molecules, such as cationic polymers.

As used herein, the term "water-insoluble complex" refers to a physically and chemically stable complex that forms upon appropriate combining of a pharmaceutically active compound and carrier macromolecule according to procedures described herein. This complex typically takes the form of a precipitate that is produced upon combining aqueous preparations of the pharmaceutically active compound and carrier macromolecule. Although not intending to be limited by mechanism, the formation of water-insoluble complexes of the invention is thought to involve (*e.g.*, be mediated at least in part by) ionic interactions in situations where the pharmaceutically active compound is cationic and the carrier molecule is anionic or *vice versa*. Additionally or alternatively, the formation of a water-insoluble complex of the invention may involve (*e.g.*, be mediated at least in part by) hydrophobic interactions. Still further, formation of a water-insoluble complex of the invention may involve (*e.g.*, be mediated at least in part by) covalent interactions. Description of the complex as being "water-insoluble" is intended to indicate that the complex does not substantially or readily dissolve in water, as indicated by its precipitation from aqueous solution. However, it should be understood that a "water-insoluble" complex of the invention may exhibit limited solubility (*i.e.*, partial solubility) in water either *in vitro* or in the aqueous physiological environment *in vivo*.

As used herein, the term "subject" is intended to include is intended to include warm-blooded animals, preferably mammals, more preferably primates and most preferably humans.

As used herein, the term "administering to a subject" is intended to refer to dispensing, delivering or applying a composition (*e.g.*, pharmaceutical formulation) to a subject by any suitable route for delivery of the composition to the desired location in the subject, including delivery by either the parenteral or oral route, intramuscular injection, subcutaneous/intradermal injection, intravenous injection, buccal administration, transdermal delivery, administration by the rectal, colonic, vaginal, intranasal, respiratory tract, intrathecal, or intracerebral route, administration to cells in

ex vivo treatment protocols, topical delivery, and delivery on a surface, *e.g.*, a biocompatible surface, for example on the surface of a surgically implanted device, *e.g.*, a stent, shunt, or catheter.

The pharmaceutically compounds suitable in the methods and formulations of the invention include any pharmaceutically active compounds as long as the compound has the ability to form a water-insoluble noncovalent complex with the carrier macromolecule upon combination of the compound and carrier macromolecule.

In one embodiment of the invention, the pharmaceutically active compound combined with the carrier macromolecule to form a water-insoluble complex is a peptidic compound. As used herein, the term "peptidic compound" refers to compounds composed, at least in part, of amino acid residues linked by amide bonds (*i.e.*, peptide bonds). The term "peptidic compound" is intended to encompass peptides, polypeptide and proteins. Any size peptidic compound may be suitable for use in the complex as long as the peptidic compound has the ability to form a water-insoluble noncovalent complex with the carrier macromolecule upon combination of the peptidic compound and carrier macromolecule. In one embodiment, the peptidic compound combined with the carrier macromolecule to form a water-insoluble complex is chemically modified. Suitable substances for chemical modification of peptidic compounds, include, for example, pegylating substances, *e.g.*, polyethylene glycol (PEG), glycosylating substance, *e.g.*, sugar and/or starch groups, and/or Poly-Lactic-Co-Glycolic Acid (PLGA).

A peptidic compound of the invention can be, for example, a monomeric or multimeric protein having a therapeutic activity. Preferred peptidic compounds can have a molecular weight of 100,000 daltons or less, 50,000 daltons or less, 40,000 daltons or less, 30,000 daltons or less, 20,000 daltons or less, 10,000 daltons or less, 5,000 daltons or less or 2,000 daltons or less. In one embodiment, the peptidic compound comprises a single peptide chain composed of 1000 or fewer amino acid residues. In another embodiment, the peptidic compound comprises a peptide chain composed of from about 5 to about 50 amino acid residues. The peptidic compound can also comprise two or more peptide chains which are joined together covalently, for example, by disulfide bridges. Each of these chains can be composed of from about 5 to about 1000 amino acid residues, from about 5 to about 500 residues, from about 5 to about 300 residues or from about 5 to about 100 residues. Typically, a peptidic compound will be composed of less than about 100 amino acids, more typically less than about 50 amino acid residues and even more typically, less than about 25 amino acid residues. However, in certain preferred embodiments, the peptidic compound is a peptide that is about 5 to about 20 amino acids in length, about 8 to about 15 amino acids in length or about 8 to about 12 amino acids in length.

The term "peptidic compound" is further intended to encompass peptide analogues, peptide derivatives and peptidomimetics that mimic the chemical structure of a peptide composed of naturally-occurring amino acids. Examples of peptide analogues include peptides comprising one or more non-natural amino acids. Examples of peptide derivatives include peptides in which an amino acid side chain, the peptide backbone, or the amino- or carboxy-terminus has been derivatized (*e.g.*, peptidic compounds with methylated amide linkages). Examples of peptidomimetics include peptidic compounds in which the peptide backbone is substituted with one or more benzodiazepine molecules (see *e.g.*, James, G.L. *et al.* (1993) *Science* 260:1937-1942), "inverso" peptides in which all L-amino acids are substituted with the corresponding D-amino acids, "retro-inverso" peptides (see U.S. Patent No. 4,522,752 by Sisto) in which the sequence of amino acids is reversed ("retro") and all L-amino acids are replaced with D-amino acids)"inverso") and other isosteres, such as peptide back-bone (*i.e.*, amide bond) mimetics, including modifications of the amide nitrogen, the α-carbon, amide carbonyl, complete replacement of the amide bond, extensions, deletions or backbone crosslinks. Several peptide backbone modifications are known, including $\psi[CH_2S]$, $\psi[CH_2NH]$, $\psi[CSNH_2]$, ψ[NHCO], $\psi[COCH_2]$, and ψ[(E) or (Z) CH=CH]. In the nomenclature used above, ψ indicates the absence of an amide bond. The structure that replaces the amide group is specified within the brackets. Other possible modifications include an N-alkyl (or aryl) substitution (ψ[CONR]), backbone crosslinking to construct lactams and other cyclic structures, and other derivatives including C-terminal hydroxymethyl derivatives, *O*-modified derivatives and N-terminally modified derivatives including substituted amides such as alkylamides and hydrazides.

Suitable peptidic compounds further include sequence variants and other analogues of the specific peptidic compound having desirable therapeutic activity. For example, variants having structural modifications which result in an improved property, such as increase stability, bioavailability or therapeutic activity, or decreased side effect profile, are included. Such variants include sequence variants, in which one or more amino acid residues of the parent polypeptide have been replaced with another amino acid residue, such as a conservative substitution or a non-natural amino acid residue. The variant can also be a fragment of the parent polypeptide, resulting, for example, from the removal of one or more amino acid residues at the N- and/or C-terminus of the parent polypeptide.

Further, the invention provides, in at least one embodiment, a pharmaceutical formulation comprising a water-insoluble complex of a peptidic compound having an isoelectric point higher than the physiological pH and in carrier macromolecule. Peptidic compounds contemplated by the present invention also include those which can be formulated according to the present invention and include peptidic compounds having

an isoelectric point which is below physiological pH. As used herein, the term "physiological pH' refers to a pH of 7.4. Preferably, the peptidic compound has an isoelectric point (pI) less than about 7.0, less than about 6.5 or less than about 6.0. In preferred embodiments, the polypeptide has an isoelectric point which is between about 4.0 and about 7.0, more preferably between about 4.5 and about 6.5, and most preferably between about 5.0 and about 6.5. For example, the peptidic compound can have a pI of about 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8 or 6.9.

The isoelectric point of a peptidic compound can be determined experimentally, for example, *via* isoelectric focusing, in which a polypeptide migrates in a pH gradient under the influence of an applied electric field. At its isoelectric pH ("isoelectric point" or "pI") the polypeptide has no net electric charge and stops moving. The isoelectric point of a peptidic compound can also be estimated theoretically based on the amino acid sequence of the polypeptide. Such calculated isoelectric points, however, fail to account for post-translational modifications, such as glycosylation, and the effects of the local environment on the pKa of amino acid side chains, which can significantly alter the acidity of a functional group.

Peptidic compound which are suitable for use in the present invention can be identified using methods known in the art.

A variety of pharmaceutically active peptides may be used in the formulations. Non-limiting examples of such peptides include peptides that contain one or more lysine and/or arginine residues and lysine-like and/or arginine-like amino acid residues, such as LHRH analogues, recombinant luteinizing hormone, *e.g.,* lutropin alpha, bradykinin analogues, parathyroid hormone, adenocorticotrophic hormone (ACTH), calcitonin, vasopressin analogues (*e.g.*, 1-deamino-8-D-arginine vasopressin (DDAVP)), and synthetic forms of vasopressin, *e.g.,* Desmopressin Acetate. Other non-limiting examples of pharmaceutically active peptides that can be used in the formulations and methods of the invention include octreotide, endorphin, liprecin, erythropoietin, protamine, platelet aggregation inhibitor (epoprostenol), platelet glycoprotein IIb/IIIa receptor, recombinant platelet glycoprotein IIb/IIIa receptor antibodies, *e.g.,* Abciximab and Eptifibatide, angiotensin II, antidiuretic hormone, neurotrophic factors, keratinocyte growth factor, leukemia inhibiting factor, monocyte chemoattractant protein-1, endothelial growth factors, thymosin alpha 1, thymosin alpha 1 IIb/IIa inhibitor, thymosin beta 10, thymosin beta 9, thymosin beta 4, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 (very late antigen-4), VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, *e.g.,* antibodies directed against the epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV), *e.g.,* PALIVIZUMAB, cystic fibrosis transmembrane regulator (CFTR) protein,

deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, oxytocin, growth hormones, *e.g.,* somatotropin, pituitary hormones, somatostatin, asparaginase, chorionic gonadotropin, growth hormone releasing hormone, growth hormone releasing peptide, interferons (*e.g.*, interferons α, β γ, interferon β-1a, interferon α-2a, interferon alfacon-1, interferon alpha-n3 (Human Leukocyte Derived), colony stimulating factor, bone morphogenic proteins (BMP) (*e.g.,* 1, 2, 3, 4, 5, 6, and 7), interleukins (*e.g.,* interleukin-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28 , -29 and -30), *e.g.,* recombinant interleukin antibodies, *e.g.,* IL-2, *e.g.,* Aldesleukin, *e.g.,* recombinant interleukins, *e.g.,* IL-11, *e.g.,* oprelvekin, *e.g.,* interleukin receptor antagonists, *e.g.,* IL-1 receptor antagonist, *e.g.,* anakinra, glucocerebrosidase, *e.g.,* Imiglucerase, macrophage activating factor, macrophage peptide, B cell factor, T cell factor, protein A, suppressive factor of allergy, cell necrosis glycoprotein, immunotoxin, lymphotoxin, tumor necrosis factor, tumor inhibitory factor, transforming growth factor, HER2, *e.g.,* antibodies against HER2, *e.g.,* Trastuzumab, myelin, *e.g.,* synthetic forms or fragments thereof, *e.g.,* Glatiramer Acetate, alpha-1 antitrypsin, albumin, apolipoprotein-E, apolipoprotein A1, erythropoietin, hyper-glycosylated erythropoietin, factor VII, factor VIII, factor IX, plasminogen activator, urokinase, streptokinase, protein C, activated Protein C, *e.g.,* Drotrecogin alpha, protein S, C-reactive protein, renin inhibitor, collagenase inhibitor, superoxide dismutase, leptin, platelet derived growth factor, epidermal growth factor, epidermal growth factor receptor (EGFR), *e.g.,* recombinant EGFR antibodies, *e.g.,* Cetuximab, osteogenic growth factor, osteogenesis stimulating protein, calcitonin, insulin, insulin analogs, *e.g.,* Insulin Glulisine and Insulin Glargine, amylin, *e.g.,* synthetic analogues thereof, *e.g.,* Pramlintide, atriopeptin, cartilage inducing factor, connective tissue activator protein, follicle stimulating hormone, luteinizing hormone, FSH releasing hormone, nerve growth factor, parathyroid hormone, or a portion thereof, *e.g.,* Teriparatide, prostoglandin, relaxin, secretin, somatomedin, insulin-like growth factor, thrombolytics, pamiteplase, lanoteplase, and teneteplase; nerve growth factor (NGF), osteoprotegerin, Rhdnase, *e.g.,* dornase alpha and Tenecteplase, erythropoiesis stimulating protein (NESP), coagulation factors such as Factor V, Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor XII, Factor XIII, von Willebrand factor; ceredase, cerezyme, alpha-glucosidase, collagen, cyclosporin, alpha defensins, beta defensins, exedin-4, thrombopoietin (TPO), heparin, human serum albumin, low molecular weight heparin (LMWH), alpha-1 proteinase inhibitor, elcatonin, fibrinogen, filgrastim (granulocyte colony-stimulating factor, *e.g.,* Sargramostim), adrenocorticotrophic hormone, glucagon, glucagon-like peptide 1 (GLP-1) receptor or agonists thereof, *e.g.,* Exendin-4, glucagon-like peptide 1, or analogues thereof, *e.g.,* Exenatide, cholecystokinin, pancreatic polypeptide, gastrin releasing peptide,

corticotropin releasing factor, or analogues thereof, *e.g.*, Corticorelin Ovine Triflutate, thyroid stimulating hormone, TNF receptor (*e.g.*, TNFR(P75) and TNFR(P55)), IL-1 receptor antagonist (*e.g.*, IL1-Ra), cell surface antigen (*e.g.*, CD2, 3, 4, 5, 7, 11a, 11b, 18, 19, 20, 23, 25, 33, 38, 40, 45 and 69), *e.g.*, recombinant CD20 antibodies, *e.g.*, Rituximab, TNF-α, *e.g.*, recombinant TNFα antibodies, *e.g.*, Infliximab, Etanercept, NF-κB, urate oxidase, *e.g.*, Rasburicase, cone snail peptide w-cenotoxin M-VII-A, *e.g.*, Ziconotide, antimicrobial antifungal and antibacterial analogues, non-limiting examples of which include, Caspofungin acetate, ADENOREGULIN, Aureins, Gaegurins, Thanatin, Ranatuerin-2CB, Ranatuerin-2CA, Cecropin A, Cecropin B, Melittin B, Indolicidin, Tritrpticin, Androctonin, Tachystatin A, Dermaseptins, Gomesin, Hepcidin 20, Hepcidin 25, Peptide PGQ, Protegrins, RatNPs Seminalplasmin, Tracheal antimicrobial peptide, Dolabellanin B2, AFP1, AFP2, Dermaseptin BI, Buforin I, Buforin II, Histones, Opistoporins, Ponericins, Penaeidins, Spingerin, Skin peptide tyrosine-tyrosine, Lingual antimicrobial peptide, Tricholongin, Termicin, Holotricins, Penaeidins, Nk-Lysin, Magainin 2, Neutrophil defensins, Cyclic Defensin, Alpha-basrubrin, Melanotropin alpha (Alpha-MSH), Brevinin, Pseudins (1, 2, 3, 4), Anti-fungal protein 1(pafp-s), Misgurin, P-18, Pseudo-hevein (Minor hevein), MUC7 20-Mer, Histatins (3, 5, 8), Nigrocin, lactoferrin (Lf), Ranalexin, antiviral analogues, *e.g.*, Antiviral protein Y3, Alloferon 1, Lactoferricin B, hexapeptide, Tricyclic peptide RP, Indolicidin, GNCP-2, GNCP-1, HNP-1 Defensin, HNP-2 Defensin, Defensin, CORTICOSTATIN III (MCP-1) , CORTICOSTATIN IV (MCP-2), NP-3A defensin, Protegrin 2, Protegrin 3, Protegrin 3, Protegrin 4, Protegrin 5, RatNP-1, RatNP-2, RatNP-3, RatNP-4, Caerin 1.1, Circulin A (CIRA), Circulin B (CIRB), Cyclopsychotride A (CPT), Ginkbilobin, Alpha-basrubrin, Enfuvirtide, or other antiretroviral agents. Fragments, analogues, derivatives, *e.g.*, peptidomimetics, of any of the foregoing peptidic compounds may be used in the pharmaceutical formulations of the present invention. Monoclonal antibodies, polyclonal antibodies, antibody fragments, and virus-derived vaccine antigens raised against any of the foregoing peptidic compounds are also contemplated for use in the pharmaceutical formulations of the present invention.

In another embodiment of the invention, the pharmaceutically active compound combined with the carrier macromolecule to form a water-insoluble complex is a non-peptidic compound. The pharmaceutically active compound of the invention can be any non-peptidic compound which forms a suitable solid ionic complex with a pharmaceutically acceptable carrier macromolecule. A "non-peptidic compound", as defined herein, is a compound which includes no more than one peptide bond. Preferred non-peptidic compounds have a molecular weight of 1000 daltons or less, more preferably 750 daltons or less, and most preferably 500 daltons or less. Preferably, the

pharmaceutically active non-peptidic compound is monomeric, *i.e.*, not polymeric or oligomeric. A "monomeric compound", as this term is used herein, does not comprise repeating structural units, for example, repeating backbone structural units. More preferably, the compound is a monomeric condensed compound. A "condensed compound", as this term is used herein, is a compound having a structure with ten or fewer contiguous linear (unbranched) chemical bonds, *i.e.*, a condensed compound has no more than ten contiguous linear bonds which do not define, or are not a part of, a cyclic structure. Preferably, a condensed molecule has nine, eight, seven, six, five or fewer contiguous linear chemical bonds. The cyclic structure is, preferably, a ten-membered monocyclic structure or smaller or a fused polycyclic structure. The cyclic structure can be aliphatic or aromatic, or, if polycyclic, a combination of aromatic and aliphatic.

In one embodiment, the non-peptidic pharmaceutically active compound has a net positive electronic charge of at least +1 or a net negative electronic charge of at least –1. As used herein, the term "electronic charge" refers to the greatest net electronic charge the molecule bears in the range of pH 5.0 to pH 9.0 (*e.g.*, pH 5.0, pH 6.0, pH 7.0, pH 8.0, or pH 9.0). Preferably, the compound has a net electronic charge at physiological pH (*e.g.*, pH 7.4). In a preferred embodiment, the pharmaceutically active compound has a net positive electronic charge of at least +2 or a net negative electronic charge of at least –2. Examples of suitable pharmaceutically active compounds include non-peptidic compounds having a molecular weight of about 1000 amu or less and a charge of at least +1 or –1. Preferred pharmaceutically active compounds have a molecular weight of 750 amu or less, 600 amu or less or 500 amu or less and have net electronic charge of +1, +2, +3 or +4 or greater, or -1, -2, -3 or -4 or greater.

Non-limiting examples of non-peptidic pharmaceutically active compounds that can be used in the pharmaceutical compositions and methods of the invention include antitumor antibiotics, such as bleomycin, dactinomycin, actinomycin D, mitomycin and plicamycin; analgesics and andronergics, such as codeine, chlorpheniramine, hydrocodone, phenylephrine, dihydrocodeine, phenylpropanolamine, pseudoephedrine, dichloralphenazone, isometheptene, oxycodone, pentazocine, phenyltoloxamine, propoxyphene, pseudoephedrine, alfentanil, aspirin, orphenadrine, propoxyphene, carisoprodol, meprobamate, methocarbamol, atropine, hyoscyamine; methenamine, buprenorphine, butorphanol, celecoxib, clonidine, diclofenac, misoprostol, diflunisal, etodolac, fenoprofen, fentanyl, flurbiprofen, ibuprofen, hydromorphone, indomethacin, ketoprofen, ketorolac, levomethadyl, levorphanol, salicylic acid, meclofenamate, mefenamic acid, meperidine, promethazine, methadone, morphine, nabumetone, nalbuphine, naloxone, naproxen, oxaprozin, oxycodone, oxymorphone,

phenazopyridine, sulfisoxazole, piroxicam, propoxyphene, salsalate, thiosalicylate, sufentanil, sulindac, tolmetin and tramadol.

Suitable pharmaceutically active non-peptidic compounds also include local anesthetics, such as antipyrine; benzocaine, butamben; tetracaine, bupivacaine, epinephrine, chloroprocaine, cocaine, dyclonine, etidocaine, proparacaine, lidocaine, prilocaine, mepivacaine, levonordefrin, procaine, proparacaine, ropivacaine and tetracaine.

Other suitable pharmaceutically active non-peptidic compounds include gastrointestinal agents, for example, difenoxin, hyoscyamine; phenobarbital, scopolamine, butabarbital, bethanechol, bisacodyl, chlordiazepoxide; clidinium, choline; dexpanthenol, cimetidine, cisapride, promethazine, dicyclomine, diltiazem, dimenhydrinate, diphenoxylate, docusate, dolasetron; dronabinol, droperidol, fentanyl, erythromycin, famotidine, glycopyrrolate, granisetron, pramoxine, lansoprazole, loperamide, mepenzolate, meperidine; mesalamine, 5-ASA, methscopolamine, metoclopramide, monoctanoin, nizatidine, olsalazine, omeprazole, ondansetron, orlistat, ochlorperazine, propantheline, ranitidine, sulfasalazine, thiethylperazine, trimethobenzamide, ursodeoxycholic acid, ursodiol; antipsychotic agents, such as amitriptyline; perphenazine, chlorpromazine, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, prochlorperazine, promazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, triflupromazine and zyprasidone; antimalarial agents, such as chloroquine, halofantrine, hydroxychloroquine, mefloquine, primaquine, pyrimethamine, pyrimethamine; sulfadoxine and quinine; antitussive agents, such as chlorpheniramine; dextromethorphan; guaifenesin; phenylpropanolamine, benzonatate, bromodiphenhydramine; brompheniramine; carbetapentane; carbinoxamine; and triprolidine; anticonvulsant agents, such as acetazolamide, carbamazepine, clonazepam, diazepam, ethosuximide, ethotoin, felbamate, fosphenytoin, gabapentin, lamotrigine, lorazepam, mephenytoin, mephobarbital, methsuximide, pentobarbital, phenobarbital, phenytoin, primidone, secobarbital, tiagabine, topiramate, valproic acid, divalproex; cholinesterase inhibitors, such as ambenonium, atropine; edrophonium, demecarium, donepezil, isoflurophate, neostigmine, physostigmine, pyridostigmine and tacrine; mydriatics, such as apraclonidine, atropine, cyclopentolate, homatropine, hydroxyamphetamine; tropicamide, scopolamine and sulfacetamide; sympathomimetics, such as acrivastine; albuterol, levalbuterol, amphetamine; dextroamphetamine, antazoline; naphazoline, antipyrine; apraclonidine, azatadine; benzphetamine, bitolterol, brompheniramine; bupivacaine; caramiphen; carbetapentane; carbidopa; levodopa, carbinoxamine; methscopolamine; phenindamine; phenyltoloxamine, iramine; pyrilamine, clemastine; triprolidine, dexbrompheniramine; dexchlorpheniramine;

diethylpropion, dipivefrin, dobutamine, dopamine, dyphylline; hydroxyzine; isoetharine, isoproterenol, loratadine; mazindol, mephentermine, levonordefrin, methoxamine, midodrine, naphazoline, phendimetrazine, phentermine, pirbuterol, ritodrine, salmeterol, terbutaline, formoterol and tetrahydrozoline; antihypertensive agents, such as acebutolol, amiloride, amlodipine, benazepril, atenolol, atenolol; chlorthalidone, bendroflumethiazide; betaxolol, bisoprolol, bumetanide, candesartan, captopril, carteolol, carvedilol, chlorothiazide, chlorthalidone, clonidine, methyclothiazide, diazoxide, diltiazem, enalapril, doxazosin, enalaprilat, felodipine, epoprostenol, esmolol, ethacrynic acid, felodipine, fosinopril, furosemide, guanabenz, guanadrel, guanethidine, guanfacine, hydralazine, reserpine, irbesartan, labetalol, lisinopril, losartan, metoprolol, moexipril, reserpine, spironolactone, timolol, triamterene, valsartan, hydroflumethiazide, indapamide, isradipine, mecamylamine, methyclothiazide, metolazone, minoxidil, nadolol, nicardipine, nifedipine, nisoldipine, penbutolol, phenoxybenzamine, phentolamine, pindolol, polythiazide, prazosin, quinapril, ramipril, sotalol, telmisartan, terazosin, timolol, tolazoline, torsemide, trandolapril, verapamil and triamterene; antiarrhythmia agents, such as acebutolol, amiodarone, atenolol, bretylium, disopyramide, encainide, esmolol, flecainide, ibutilide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, sotalol and tocainide; anti-obesity agents, such as sibutramine; anti-infective agents, such as Clindamycin, Gatifloxacin, Tigecycline, Levofloxacin, Moxifloxacin, Clarithromycin, Minocycline, Gemifloxacin, Ceftriaxone Sodium, Daptomycin, Quinupritin, Dalfopristin, Trimethoprim, Sulfamethoxazo, Streptomycin, Rifampicin, Esomerprazole, Enfuvirtide, Famiclovir, Sargarmostin, Topotecan, Gemifloxacin, Esomerprazole Magnesium, Gentamicin Sulfate, Voriconazole, abacavir, acyclovir, albendazole, amantadine, amikacin, aminosalicylic acid, amoxicillin, clavulanic acid, amphotericin B, ampicillin, sulbactam, atovaquone, azithromycin, aztreonam, bacampicillin, bacitracin, metronidazole, tetracycline, butenafine, butoconazole, capreomycin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cefdinir, cefepime, cefixime, cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, cefoxitin, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cephalexin, cephapirin, cephradine, chloramphenicol, chloroquine, chloroxine, ciclopirox, clioquinol, chlortetracycline, cidofovir, cinoxacin, ciprofloxacin, clarithromycin, clindamycin, clofazimine, clotrimazole, cloxacillin, colistimethate, colistin, crotamiton, cycloserine, dapsone, delavirdine, demeclocycline, dicloxacillin, didanosine, dirithromycin, doxycycline, econazole, efavirenz, enoxacin, erythromycin, sulfisoxazole, ethambutol, ethionamide, famciclovir, fluconazole, flucytosine, foscarnet, fosfomycin, furazolidone, ganciclovir, gentamicin, grepafloxacin, griseofulvin, halofantrine, hydroxychloroquine, imipenem; cilastatin, indinavir, ribavirin, iodoquinol, isoniazid, pyrazinamide, rifampin,

isoproterenol, itraconazole, ivermectin, kanamycin, ketoconazole, lamivudine, zidovudine, levofloxacin, lincomycin, lindane, lomefloxacin, loracarbef, mebendazole, mefloquine, meropenem, metaproterenol, mezlocillin, miconazole, minocycline, nafcillin, naftidine, nalidixic acid, natamycin, nelfinavir, neomycin, netilmicin, nevirapine, nitrofurantoin, norfloxacin, nystatin, triamcinolone, ofloxacin, oxacillin, oxytetracycline, oxiconazole, paromomycin, aminosidine, penicillin G, penicillin V, pentamidine, permethrin, phenazopyridine, sulfisoxazole, piperacillin; tazobactam, praziquantel, primaquine, prochlorperazine, pyrazinamide, pyrimethamine, sulfadoxine, quinine, rifampin, rifapentine, rimantadine, ritonavir, saquinavir, sparfloxacin, spectinomycin, stavudine, sulconazole, sulfabenzamide; sulfacetamide; sulfathiazole, sulfacetamide, sulfacytine, sulfadiazine, sulfamethoxazole, trimethoprim, sulfanilamide, sulfasalazine, sulfisoxazole, terbinafine, terconazole, thiabendazole, ticarcillin, tioconazole, tobramycin, triacetin, triamcinolone, trimethoprim, trimetrexate, troleandomycin, trovafloxacin, alatrofloxacin, valacyclovir, vancomycin, zalcitabine and zidovudine.

Additional non-peptidic pharmaceutically active compounds suitable for use in the present invention include Alprenolol Hydrochloride, Amifostine, Apomorphine Hydrochloride, Benztropine Mesylate, Bisoprolol Fumarate, Bupropion Hydrochloride, Buspirone hydrochloride, Cetirizine Hydrochloride, Cladribine, Clomipramine Hydrochloride, Colchicines, Cyclobenzaprine Hydrochloride, Cytarabine Hydrochloride, Dacarbazine, Diethylcarbamazine Citrate, Doxepin Hydrochloride, Duloxetine Hydrochloride, Epirubicin Hydrochloride, Ergometrine Maleate, Ertapenem, Escitalopram Oxalate, Fludarabine Phosphate, Fluoxetine Hydrochloride, Gemcitabine Hydrochloride, Idarubicin Hydrochloride, Levamisole Hydrochloride, Levetiracetam, Mafenide Acetate, Mechlorethamine Hydrochloride, Metaraminol Bitartrate, Metformin Hydrochloride, Mitoxantrone Hydrochloride, Naltrexone Hydrochloride, Nateglinide, Nefazodone Hydrochloride, Norepinephrine Bitartrate, Oxazepam, Oxprenolol Hydrochloride, Oxybutynin Chloride, Palonosetron Hydrochloride, Phenltoloxaime Citrate, Penicillamine, Pilocarpine Hydrochloride, Propranolol Hydrochloride, Pyridoxine Hydrochloride, Rosiglitazone Maleate, Salbutamol Sulfate, Sildenafil Citrate, Streptomycin Sulfate, Sumatriptan Succinate, Thiamine Hydrochloride, Tolterodine Tartrate, Trazodone Hydrochloride, Venlafaxine Hydrochloride, Vinorelbine Tartrate, Voriconazole, Zolmitriptan, and Zolpidem Tartrate.

The pharmaceutically active non-peptidic compounds of the invention can be in a free base or a salt form of inorganic or organic counter-part of the compound, including, but not limited to hydrochloride, hydrobromide, citrate, sulfate, besylate, mesylate, maleate, hyclate, oxalate, acetate, phosphate, tartrate, fumarate, or succinate, *etc.*

The compositions of the invention can additionally include combinations of two or more pharmaceutically active compounds, such as two or more of the compounds listed above.

In one embodiment, the non-peptidic pharmaceutically active compound includes one or more cationic or anionic functional groups. Suitable cationic groups include primary, secondary and tertiary amino groups, imino groups, quaternary ammonium groups, amidino groups, guanidino groups, phosphonium groups, and sulfonium groups. Suitable anionic groups include carboxylate, sulfonate, phosphonate, sulfamate, sulfate ester, phosphate ester, sulfinate, phosphinate, carbonate, thiocarboxylate and carbamate groups. Preferred cationic groups include primary, secondary and tertiary amino groups, imino groups and quaternary ammonium groups. Preferred anionic groups include carboxylate and sulfonate groups. Preferably, the pharmaceutically active non-peptidic compound comprises two or more anionic groups or two or more cationic groups. In one embodiment, the pharmaceutically active non-peptidic compound comprises three or more anionic groups or three or more cationic groups.

Certain non-peptidic pharmaceutically active compounds contain both acidic groups and cationic groups and exist as zwitterions at physiological pH. Such compounds can, optionally, be present in the compositions of the invention in a modified, or prodrug, form in which one or more acidic functional groups are esterified. Such esterification increases the net positive charge of the compound. Similarly, the pharmaceutically active non-peptidic compound can have amino groups which have been acylated or sulfonylated to form an amide or sulfonamide, respectfully. Such acylation results in an increase in the net negative charge of the pharmaceutically active compound.

A variety of carrier macromolecules are be suitable for formation of the water-insoluble complexes of the invention. In one embodiment, the macromolecules are polymers, *e.g.*, water-soluble polymers. In one embodiment, the carrier macromolecule is an anionic polymer, such as an anionic polyacohol derivative, or fragment thereof, and salts thereof (*e.g.*, sodium salts). Anionic moieties with which the polyalcohol can be derivatized include, for example, carboxylate, phosphate or sulfate groups. A particularly preferred anionic polymer is an anionic polysaccharide derivative, or fragment thereof, and salts thereof (*e.g.*, sodium salts). The carrier macromolecule may comprise a single molecular species (*e.g.*, a single type of polymer) or two or more different molecular species (*e.g.*, a mixture of two types of polymers). Examples of specific anionic polymers include carboxymethylcellulose, algin, alginate, anionic acetate polymers, anionic acrylic polymers, xantham gums, sodium starch glycolate, and fragments, derivatives and pharmaceutically acceptable salts thereof, as well as anionic carageenan derivatives, anionic polygalacturonic acid derivatives, and sulfated and

sulfonated polystyrene derivatives. A preferred anionic polymer is carboxymethylcellulose sodium salt. Examples of cationic polymers include poly-L-lysine and other polymers of basic amino acids.

In another embodiment of the invention, the carrier macromolecule is an ionic macromolecule, *e.g.*, anionic or cationic. The ionic macromolecule used in the formulations of the invention may be a linear or cross-linked polymer comprising monomers which bear a positive (*i.e.*, cationic polymer) or negative (*i.e.*, anioninc polymer) charge at a certain pH. In one embodiment, each of the monomeric units in the polymer comprises an acidic functional group or a basic functional group. In another embodiment, a fraction of the monomers within the polymer are functionalized with an acid functional group or a basic functional group. Preferably, the polymer comprises either anionic functional groups or cationic functional groups, although the polymer can comprise both cationic and anionic functional groups, so long as the proportion of these groups allows for the desired net ionic charge at the desired pH. Each of the cationic or anionic groups in the polymer can be the same or different, although in preferred embodiments they are the same.

In one embodiment, the polymer includes basic or cationic functional groups such as primary, secondary or tertiary amino groups, quaternary ammonium groups, guanidino groups, amidino groups, phosphonium groups or sulfonium groups. Preferably, the basic or cationic groups are primary, secondary or tertiary amino groups or quaternary ammonium groups.

In another embodiment, the polymer includes acidic or anionic functional groups, such as carboxylate, sulfonate, phosphonate, sulfate ester, phosphate ester, sulfamate or carbamate groups. Preferably the anionic groups are carboxyl groups. The ionic macromolecule is physiologically compatible and is, preferably, biodegradable or bioresorbable. Preferred ionic macromolecules are suitable for administration via intraperitoneal, intramuscular or intravenous injection or inhalation. Suitable ionic polymers include ionic polysaccharides; ionic polyesters; ionic polyamides, for example, ionic peptides; polyacrylates and polyamines.

Examples of suitable ionic polymers include, but are not limited to, carboxymethylcellulose, poly(arginine), poly(lysine), poly(glutamic acid), poly(aspartic acid), poly(arginine-co-glycine), poly(lysine-co-glycine), poly(glutamic acid-co-glycine), poly(aspartic acid-co-glycine), poly(arginine-co-alanine), poly(lysine-co-alanine), poly(glutamic acid-co-alanine), poly(aspartic acid-co-alanine), diethylaminoethyldextran, diethylaminoethylcellulose, starch glycolate, polygalacturonic acid, poly-d-glucosamine (chitosan), poly(acrylic acid), poly(ethyleneimine), poly(allylamine), polyvinylamine, carrageenan, and alginic acid. In another

embodiment, the carrier macromolecule may be dextran sulfate, croscarmellose sodium, carbomers (poly(acrylic acid)), sodium hyaluronate, xanthan gum, or chitosan.

Preferred ionic polymers include ionic polysaccharides and ionic polypeptides. The ionic polymer can be linear or cross-linked. For example, the ionic polymer can be cross-linked to varying extents, using ionic cross-linking or covalent cross-linking. In one embodiment, the ionic polymer bears a net ionic charge and is cross-linked by the addition of an amount of an oppositely charged cross-linking polymer. The relative amounts of the two polymers can be varied to provide different degrees of cross-linking, but should be such that the combination retains a net ionic charge sufficient to bind a desired amount of the pharmaceutically active compound. For example, an anionic polymer, such as carboxymethylcellulose, can be cross-linked with varying amounts of a cationic polymer, such as poly(lysine), while a cationic polymer, such as diethylaminoethylcellulose can be cross-linked with an anionic polymer, such as poly(glutamic acid).

In another embodiment, the ionic polymer is covalently cross-linked. In one example, ionic polymers comprising carboxylate groups are cross-linked as is known in the art by reacting a fraction of the carboxylate groups, or activated derivatives thereof, with a suitable cross-linking reagent such as a dialcohol, an aminoalcohol or a diamine, under conditions suitable for forming ester and/or amide linkages. In this case, the ionic polymer will comprise carboxylate groups and ester/amide groups, with the ester/amide groups on one polymer strand linked to ester/amide groups on another polymer strand by bridging groups derived from the dialcohol, amino alcohol or diamine used. Preferably, the dialcohol, amino alcohol or diamine is pharmaceutically acceptable.

In another example, a cationic polymer comprising primary, secondary or tertiary amino groups can be cross-linked by reacting a fraction of the amino groups with a cross-linking reagent comprising two or more functional groups capable of reacting with an amino group to form a carbon-nitrogen bond. For example, the cationic polymer can be reacted with a dicarboxylate, disulfonate or activated derivative thereof, or a compound comprising two or more alkylating functional groups, such as 1, 2-dihaloethane, epichlorohydrin and others known in the art. Such reactions result in a polymer in which a fraction of the amino nitrogen atoms in one polymer strand are connected to amino groups in other polymer strands via bridging groups derived from the cross-linking agent. When the nitrogen-carbon bond formed via cross-linking, such as an amide bond or a sulfonamide bond, is labile under physiological conditions, the cross-linking reagent is preferably physiologically acceptable.

The water-insoluble complex of the invention can have a range of compositions. For example, the complex can comprise from about 20% pharmaceutically active compound to about 95% pharmaceutically active compound. The complex can comprise

from about 80% carrier macromolecule to about 5% carrier macromolecule. Preferably, the water-insoluble complex comprises 20% or greater, 25% or greater, 30% or greater, 35% or greater, 40% or greater, 45% or greater, 50% or greater, 55% or greater, 60% or greater, 65% or greater, 70% or greater, 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater pharmaceutically active compound. Preferably, the water-insoluble complex comprises 80% or less; 75% or less; 70% or less; 65% or less; 60% or less; 55% or less; 50% or less; 45% or less; 40% or less; 35% or less; 30% or less; 25% or less; 20% or less; 15% or less; 10% or less; or 5% or less carrier macromolecule. All percentages disclosed herein are weight/weight unless otherwise indicated. Ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

The ratio (weight/weight) of the pharmaceutically active compound to the carrier macromolecule in the water-insoluble complex of the invention is, preferably, about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.75, 0.5, 0.25 or 0.1. Preferably the ratio of the pharmaceutically active compound to the carrier macromolecule is about 0.5, 0.75, 1 or greater.

In one embodiment, the water-insoluble complex consists essentially of the carrier macromolecule and the pharmaceutically active compound. Typically, such a water-insoluble complex will be hydrated and the mass of the complex will include some amount of water. The degree of hydration can be determined by subjecting the complex to dehydrating conditions, preferably conditions under which the pharmaceutically active compound and the carrier macromolecule are stable, and determining the resulting weight decrease.

The water-insoluble complex is, preferably, substantially insoluble in aqueous solvent at the desired pH, *e.g.*, physiological pH. The term "substantially insoluble" is used herein to refer to a material that has negligible solubility, *e.g.*, in water, under a given set of conditions. It is to be understood that a substantially insoluble material can have finite solubility, but generally is soluble to an extent providing a concentration of pharmaceutically active compound no greater than 10 mM, 1 mM, 100 μM, 10 μM or 1 μM. For a given pharmaceutically active compound, the carrier macromolecule and additional excipients, if any, can be selected to optimize the properties of the water-insoluble complex with respect to aqueous solubility and/or compound loading, among others. For example, the extent of cross-linking of the carrier macromolecule can be varied, with more extensive cross-linking expected to lead to less soluble complexes. Cross-linking can be accomplished using methods known in the art, such as covalent cross-linking or ionic cross-linking. Ionic cross-linking can be accomplished, for example, by including an amount of a polymer having at the desired pH a net ionic charge opposite in sign to that of the carrier macromolecule.

In addition to the water-insoluble complex, the pharmaceutical formulations of the invention can comprise additional pharmaceutically acceptable carriers and/or excipients. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for topical, oral, buccal, vaginal, rectal, pulmonary, nasal, transdermal, intravenous, intramuscular, subcutaneous, intrathecal, intracerebral, or parenteral administration (*e.g.*, by injection). Excipients include pharmaceutically acceptable stabilizers and disintegrants. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the peptidic compound, use thereof in the pharmaceutical formulations is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral, nasal, transdermal (topical), transmucosal, rectal, transvaginal, or buccal administration.

Pharmaceutical formulations suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the formulation must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the formulation. Solutions or suspensions for parenteral, intradermal, or subcutaneous administration may also include antioxidants such as ascorbic acid or sodium bisulfite, chelating agents such as ethylenediaminetetraacetic acid, buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as

sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral formulation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Sterile injectable solutions can be prepared by incorporating the water-insoluble complex in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by an appropriate sterilization method, such as, for example, filter sterilization, gamma-irradiation, and the like. In one embodiment, dispersions are prepared by incorporating the water-insoluble complex of the invention into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation may be vacuum drying and freeze-drying which yields a powder of the water-insoluble complex of the invention plus any additional desired ingredient from a previously sterile-filtered solution thereof. Other compositions useful for attaining systemic delivery of the water-insoluble complex of the invention include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The water-insoluble complex of the invention may also be combined with any other known depot preparation. In one embodiment, the water-insoluble complex of the invention is further combined with a biodegradable carrier matrix. In one embodiment, the water-insoluble complex of the invention is further combined with a compound to produce a controlled or sustained release gastroretentive dosage form (CR-GRDF) of formulation in the stomach or GI tract (see, for example, S.K.Jain, N.K.Jain, G.P.Agrawal. Drug Delivery Technology. "Gastroretentive Floating Drug Delivery: An Overview." July/August 2005. Vol. 5. No. 7. Pages 52-61, incorporated herein by reference), *e.g.*, a biodegradable carrier matrix. Suitable formulations include, for example, tablets, capsules, and the like. Other suitable formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the water-insoluble complex may be formulated with suitable polymeric, *e.g.*, naturally derived polymers, such as albumin, alginate, cellulose derivatives, collagen, fibrin, gelatin, and polysaccharides, synthetic polymers such as, polyesters (PLA, PLGA), polyethylene glycol, poloxomers, polyanhydrides, and pluronics, or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt. Accordingly, in one embodiment, the

biodegradable carrier matrix is a microsphere. In another embodiment, the biodegradable carrier matrix is a microcapsule. In yet another embodiment, the biodegradable carrier matrix is a microparticle. In one embodiment, the biodegradable carrier matrix is a liposome.

Peroral pharmaceutical formulations of the water-insoluble complex of the invention include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically acceptable carriers suitable for preparation of such formulations are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol. and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, tragacanth, and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid formulations may also contain one or more components such as sweeteners, flavoring agents and colorants.

Oral formulations generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral administration, the water-insoluble complex of the invention can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral formulations can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the formulation. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the water-insoluble complex is mixed with one or more pharmaceutically-acceptable carriers. In the case of capsules, tablets and pills, the pharmaceutical formulations may also comprise buffering agents. Solid formulations of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative,

disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the water-insoluble complex thereof moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Systemic administration of the water-insoluble complex of the invention can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal, *e.g.,* intranasal, administration can be accomplished through the use of, for example, nasal sprays, nasal drops, or powders.

Transmucosal formulations for rectal or vaginal administration may be presented as a suppository or retention enema, which may be prepared by mixing the water-insoluble complex of the invention with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate. Such excipients or carriers are generally solid at room temperature, but liquid at body temperature, and therefore, they will melt in the rectum or vaginal cavity and release water-insoluble complex.

The transdermal formulations of this invention can also be administered topically to a subject *via* percutaneous passage of the formulation into the systemic circulation of the subject., *e.g.*, by the direct laying on or spreading of the formulation on the epidermal or epithelial tissue of the subject. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions may comprise an effective amount, usually at least about 0.1%, or from about 1% to about 5%, of a water-insoluble complex of the invention. Suitable carriers for topical administration typically remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the water-insoluble complex. The carrier may include pharmaceutically acceptable emolients, emulsifiers, thickening agents, solvents and the like. Other components can be incorporated into the transdermal patches as well. For example, formulations and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl

hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like.

Dosage forms for topical administration of the water-insoluble complex can include creams, pastes, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, suppositories, and the like. In such dosage forms, the water-insoluble complex of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the formulations can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, *e.g.*, gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application.

Pharmaceutical formulations are also provided which are suitable for administration as an aerosol, by inhalation. For administration by inhalation, the water-insoluble complex may be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Dry Powder formulations for inhalation may be delivered using any suitable dry powder inhaler (DPI), *i.e.*, an inhaler device that utilizes a subject's inhaled breath as a vehicle to transport the dry powder pharmaceutical formulation to the lungs. Examples of such devices are Inhale Therapeutic Systems' dry powder inhalation devices as described in Patton, J.S., *et al.*, U.S. Patent No. 5,458,135, Oct. 17, 1995; Smith, A. E., *et al.*, U.S. Patent No. 5,740,794, Apr. 21, 1998; and in Smith, A. E., *et. al.*, U.S. Patent No. 5,785,049, July 28, 1998, herein incorporated by reference. When administered using a device of this type, the powdered formulation is contained in a receptacle having a puncturable lid or other access surface, preferably a blister package or cartridge, where the receptacle may contain a single dosage unit or multiple dosage units. Convenient methods for filling large numbers of cavities (*i.e.*, unit dose packages) with metered doses of dry powder formulation are described, *e.g.*, in Parks, D. J., *et al.*, International Patent Publication WO 97/41031, Nov. 6, 1997, incorporated herein by reference.

Other dry powder dispersion devices for pulmonary administration of dry powders include those described, for example, in Newell, R. E., *et al*, European Patent; No. EP 129985, Sept. 7, 1988); in Hodson, P. D., *et al.*, European Patent No. EP472598, July 3, 1996; in Cocozza, S., *et al.*, European Patent No. EP 467172, April 6, 1994, and in Lloyd, L.J. *et al.*, U.s. Patent No. 5,522,385, June 4, 1996, incorporated herein by reference. Also suitable for delivering the dry powders of the present invention are

inhalation devices such as the Astra-Draco "TURBUHALER". This type of device is described in detail in Virtanen, R., U.S. Patent No. 4,668,218, May 26, 1987; in Wetterlin, K., *et al.*, U.S. Patent No. 4, 667,668, May 26, 1987; and in Wetterlin, K., *et al.*, U.S. Patent No. 4, 805,811, Feb. 21, 1989, all of which are incorporated herein by reference. Other suitable devices include dry powder inhalers such as Rotahaler((Glaxo), DiscustD (Glaxo), Spiros_ inhaler (Dura Pharmaceuticals), and the Spinhaler (Fisons). Also suitable are devices which; employ the use of a piston to provide air for either entraining powdered formulation , lifting formulation from a carrier screen by passing air through the screen, or mixing air with powder formulation in a mixing chamber with subsequent introduction of the powder to the subject through the mouthpiece of the device, such as described in Mulhauser, P., *et al*, U.S. Patent No. 5,388,572, Sept. 30, 1997, incorporated herein by reference.

The water-insoluble complex of the present invention may also be delivered using a pressurized, metered dose inhaler (MDI), *e.g.*, the Ventolin metered dose inhaler, or a nebulizer, containing a solution or suspension of water-insoluble complex in a pharmaceutically inert liquid propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas., as described in Laube, *et al.*, U.S. Patent No. 5,32O,094, June 14, 1994, and in Rubsamen, R.M., *et al*, U.s. Patent No. 5,672,581 (1994), both incorporated herein by reference. Nebulizers for delivering an aerosolized solution include the AERx_ (Aradigm), the Ultravent (Mallinkrodt), the Pari LC Plus_ or the Pari LC Star_ (Part GmbH, Germany), the DeVilbiss Pulmo-Aide, and the Acorn II (Marquest Medical Products). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insulator may be formulated containing a powder mix of a water-insoluble complex of the invention and a suitable powder base such as lactose or starch.

According to yet another embodiment, the water-insoluble complex of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters (such as, balloon catheters and indwelling catheters), and/or shunts, including mechanical shunts. Suitable coatings and the general preparation of coated implantable devices are described in U.S. Patents 6, 099,562; 5,886,026; and 5,304,121, the disclosures of which are incorporated herein by reference. The coatings typically comprise biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The implantable medical devices useful in the methods of the present

invention can be metallic or plastic, and may comprise a biodegradable coating or porous non-biodegradable coating.

In one embodiment, the water-insoluble complex of the invention is coated on a medical device, *e.g.*, a stent, implanted into a subject during a medical procedure, such as, for example, angioplasty. In one embodiment, the pharmaceutically active compound incorporated into the water-soluble complex and coated on the medical device implanted into a subject prevents restenosis following the placement of the medical device in the subject. In one embodiment, restenosis is inhibited by inhibiting late-stage endothelialization

In another embodiment, the water-insoluble complex of the invention is irreversibly bonded to a medical device, *e.g.*, a stent, implanted into a subject during a medical procedure, such as, for example, angioplasty. Without wishing to be bound by theory, the irreversible bonding of the water-insoluble complex to the medical device may not only reduce restenosis, but may also encourage encapsulation of the carrier macromolecule and the stent into the vessel wall such that the carrier macromolecule is unavailable for release into the bloodstream and potentially form emboli or accumulate in the liver or spleen as circulating particulate matter. Accordingly, in one embodiment, restenosis is enhanced by promoting early stage re-endothelialization.

Non-limiting examples of pharmaceutically active peptidic compounds that are suitable for incorporation into a water-insoluble complex and coated or irreversibly bound on a medical device and implanted in a subject during a medical procedure, include angiogenesis inhibitors, such as Angiostatin, Aptamer antagonist of VEGF, Batimasta, Captopril, Cartilage Derived Inhibitor (CDI), Genistein, Endostatin, Interleukin 12, Lavendustin A, Medroxypregesterone Acetate, Recombinant human platelet factor 4(rPF4), Taxol, Tecogalan, Thalidomide, Thrombospondin, and TNP-470; vascular smooth muscle cell anti-proliferative agents, such as heparin/heparan sulfate, transforming growth factor beta, and nitric oxide; agents currently used to coat medical devices, such as stents, such as paclitaxel, rapamycin, or analogues of both; anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPACK (dextrophenylalanine proline arginine chloromethylketone); antioxidants such as probucol and retinoic acid; angiogenic and anti-angiogenic agents and factors; agents blocking smooth muscle cell proliferation such as rapamycin, angiopeptin, and monoclonal antibodies capable of blocking smooth muscle cell proliferation; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, acetyl salicylic acid, and mesalamine; calcium entry blockers such as verapamil, diltiazem and nifedipine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, cyclosporine, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and

thymidine kinase inhibitors; antimicrobials such as triclosan, cephalosporins, aminoglycosides, and nitorfurantoin; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; nitric oxide (NO) donors, such as lisidomine, molsidomine, L-arginine, NO-protein adducts, NO-carbohydrate adducts, polymeric or oligomeric NO adducts; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, thrombin inhibitors, *e.g.*, Bivalirudin, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, enoxaparin, hirudin, Warafin sodium, Dicumarol, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promotors such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promotors; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodialating-agents; agents which interfere with endogenous vascoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof.

The pharmaceutical formulation of the invention may also be administered intrathecally into the cerebrospinal fluid (CSF). The intrathecal administration of the water-insoluble complex of the present invention may comprise introducing the pharmaceutical formulation into a cerebral ventricle. Alternatively, the intrathecal administration may comprise introducing the pharmaceutical formulation into the lumbar area. In yet another alternative, the intrathecal administration comprises introducing the pharmaceutical composition into the cisterna magna. Any such administration is-preferably *via* a bolus injection. In other embodiments, the intrathecal administration is achieved by use of an infusion pump.

The administration of the pharmaceutical formulations of the invention may also be intracerebrally. Administration may be by, for example, direct intracerebral administration, or by, for example, stereotactic microinjection.

Intracerebral administration, may be provided by perfusion *via* a mechanized delivery system, such as an osmotic pump, or by implantation.

Preparation of the Pharmaceutical Compositions

The present invention also relates to a method of preparing a water-insoluble complex comprising a carrier macromolecule and a pharmaceutically active compound. The water-insoluble complex of the invention is prepared by combining the pharmaceutically active compound and the carrier macromolecule under conditions such

that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms. In one embodiment, the method includes providing a pharmaceutically active compound and an carrier macromolecule; and combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms. In another embodiment, the method comprises the steps of (1) providing a polypeptide having an isoelectric point below physiological pH and an anionic carrier macromolecule; and (2) combining the polypeptide and the anionic carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms.

The carrier macromolecule can be combined with the pharmaceutically active compound in a variety of ways. For example, a solution of the carrier macromolecule can be mixed with a solution of the pharmaceutically active compound under conditions suitable for precipitation of the water-insoluble complex. In certain embodiments, the solutions of the pharmaceutically active compound and the carrier macromolecule are aqueous solutions. In one embodiment, pharmaceutically active compound, *e.g.*, a pharmaceutically active peptidic compound, and the carrier macromolecule are combined in an aqueous solvent at a pH below the isoelectric point of the peptidic compound. For example, the peptidic compound and the anionic carrier macromolecule can be combined in solution in an aqueous buffer at a pH below the isoelectric point of the peptidic compound. In one embodiment, the pH is no more than 2 pH units below the isoelectric point of the peptidic compound; preferably the pH is no more than one pH unit below the isoelectric point of the peptidic compound. Alternatively, if the peptidic compound or the carrier molecule (or both) is not substantially water soluble prior to combination the two, then the peptidic compound and/or carrier macromolecule can be dissolved in a water-miscible solvent, such as an alcohol (*e.g.*, ethanol) prior to combining the two components of the complex. In another embodiment of the method of preparing the water-insoluble complex, the solution of the pharmaceutically active compound and the solution of the carrier macromolecule are combined and heated until a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule precipitates out of solution. Alternately, the carrier macromolecule can be added as a solid to a solution of the pharmaceutically active compound or the pharmaceutically active compound can be added to a solution of the carrier macromolecule.

The amounts of pharmaceutically active compound and carrier macromolecule necessary to achieve the water-insoluble complex may vary depending upon the particular pharmaceutically active compound and carrier macromolecule used, the particular solvent(s) used and/or the procedure used to achieve the complex. Typically,

however, the pharmaceutically active compound will be in excess relative to the carrier macromolecule on a molar basis. Often, the pharmaceutically active compound also will be in excess on a weight/weight basis. In certain embodiments, the carrier macromolecule, preferably carboxymethylcellulose sodium, and the pharmaceutically active compound are combined at a ratio of 0.2:1 (w/w) of carrier macromolecule: pharmaceutically active compound. In various other embodiments, the ratio of carrier macromolecule to pharmaceutically active compound (w/w) can be, for example, 0.5:1, 0.4:1, 0.3:1, 0.25:1, 0.15:1 or 0.1:1. The two solutions can include the same solvent or different solvents. Preferably, if the solvents are different, they are miscible. The carrier macromolecule can be added as a solid to a solution of the pharmaceutically active compound or the pharmaceutically active compound can be added to a solution of the carrier macromolecule.

In another embodiment, the carrier macromolecule, *e.g.,* an ionic carrier macromolecule, and the pharmaceutically active compound are added to a solvent in which neither is substantially soluble, but in which a by-product of the complexation, or ion-exchange process, is expected to be soluble. For example, a pharmaceutically active compound having a water-insoluble hydrochloride salt can be added to an aqueous suspension of the sodium salt of an ionic macromolecule. The resulting suspension can be agitated for a sufficient period of time for formation of the desired solid water-insoluble complex. In this case, the ion exchange process resulting in the desired water-insoluble complex is driven, at least in part, by the solubility of the sodium chloride product.

Once the water-insoluble complex precipitates, the precipitate can be removed from the solution by means known in the art, such as filtration (*e.g.*, through a 0.45 micron nylon membrane), centrifugation and the like. The recovered paste then can be dried (*e.g.*, *in vacuo* or in a 70° C oven) and the solid can be milled or pulverized to a powder by means known in the art (*e.g.*, hammer or gore milling, or grinding in mortar and pestle). Following milling or pulverizing, the powder can be sieved through a screen (preferably a 90 micron screen) to obtain a uniform distribution of particles. Moreover, the recovered paste can be frozen and lyophilized to dryness.

The powder form of the complex can be dispersed in a carrier solution to form a liquid suspension or semi-solid dispersion suitable for injection. Accordingly, in various embodiments, a pharmaceutical formulation of the invention is a dry solid, a liquid suspension or a semi-solid dispersion. Examples of liquid carriers suitable for use in liquid suspensions include saline solutions, glycerin solutions, lecithin solutions and oils suitable for injection.

In another embodiment, the pharmaceutical formulation of the invention is a sterile formulation. For example, following formation of the water-insoluble complex,

the complex can be sterilized, optimally by gamma irradiation or electron beam sterilization. Accordingly, the method of the invention for preparing a pharmaceutical formulation described above can further comprise sterilizing the water-insoluble complex by gamma irradiation or electron beam irradiation. Preferably, the formulation is sterilized by gamma irradiation using a gamma irradiation dose of at least 15 KGy. In other embodiments, the formulation is sterilized by gamma irradiation using a gamma irradiation dose of at least 19 KGy or at least 24 KGy. Alternatively, to prepare a sterile pharmaceutical formulation, the water-insoluble complex can be isolated using conventional sterile techniques (*e.g.*, using sterile starting materials and carrying out the production process aseptically). Accordingly, in another embodiment of the method for preparing a pharmaceutical formulation described above, the water-insoluble complex is formed using aseptic procedures.

Alternatively, to prepare a sterile pharmaceutical formulation, the water-insoluble complex can be isolated using conventional sterile techniques (*e.g.*, using sterile starting materials and carrying out the production process aseptically). Accordingly, in another embodiment of the method for preparing a pharmaceutical formulation described above, the water-insoluble complex is formed using aseptic procedures.

Pharmaceutical formulations, including powders, liquid suspensions, semi-solid dispersions, dry solids (*e.g.*, lyophilized solids), and sterilized forms thereof (*e.g.*, by gamma irradiation), prepared according to the methods of the invention, are also encompassed by the invention.

Use of the Pharmaceutical Compositions

In one embodiment, the present invention provides a method increasing the stability of a pharmaceutically active compound, *e.g., in vivo* and/or *ex vivo*, comprising providing a pharmaceutically active compound and a carrier macromolecule; combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the stability of the pharmaceutically active compound.

In another embodiment, the present invention provides a method for increasing the glass transition temperature (Tg) of a water-insoluble complex, comprising, selecting a pharmaceutically active compound whose water-insoluble complex would benefit from increasing the glass transition temperature (Tg), combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the glass transition temperature (Tg) of said water-insoluble complex.

Yet another embodiment of the invention provides a method for decreasing the rate of absorption of a pharmaceutically active compound from the gastrointestinal (GI) tract of a subject, comprising selecting a pharmaceutically active compound for which a decrease in the rate of absorption from the GI tract would be beneficial, *e.g.*, Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, and Meperidine, combining said pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby decreasing the rate of absorption of said pharmaceutically active compound from the gastrointestinal (GI) tract of a subject.

In one embodiment, the invention provides a method for preventing local irritation of the gastrointestinal (GI) tract of a subject, comprising selecting a pharmaceutically active compound that causes local irritation of the GI tract selecting a pharmaceutically active compound for which a decrease in the rate of absorption from the GI tract would be beneficial, *e.g.*, Rivastigmine, providing a pharmaceutically active compound and a carrier macromolecule, combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby preventing local irritation of the GI tract of a subject.

Yet another embodiment of the invention provides a method for maintaining blending uniformity of a pharmaceutically active compound in a pharmaceutical composition, comprising selecting a pharmaceutically active compound which needs to be blended uniformly, *e.g.*, Flexeril, Exelon, and Adderall, combining said pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby maintaining blending uniformity of said pharmaceutically active compound in a pharmaceutical composition.

In a further embodiment, the invention provides methods for preparing a formulation suitable for decreasing the potential of an accidental or intentional overdose, *e.g.*, accidental or intentional overdose caused by the consumption of alcohol simultaneously with drug intake. The methods include selecting a pharmaceutically active compound prone to being abused (intentionally or accidentally), *e.g.*, Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, Naltrexone, Pseudoephedirine, Dextromethorphan, and Meperidine, and combining the pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms (as described herein).

The subject can be any animal in need of treatment for which the pharmaceutically active compound is indicated, and is preferably a mammal, such as a canine, feline, bovine, equine, ovine or porcine animal or a primate, such as a monkey, an ape or a human. More preferably, the subject is a human. The subject can be an individual diagnosed with, or suspected of having, the medical condition, or an individual at risk of developing the medical condition.

In one embodiment, the subject is injected with the pharmaceutical composition using methods known in the art. The injection may be an intravenous, intramuscular, subcutaneous or intraparenteral injection. The subject's eye or eyes can also be contacted with the pharmaceutical composition.

In another embodiment, the subject is caused to inhale or swallow the composition using means which are known in the art, including the use of a dry powder inhaler, nebulizer or metered dose inhaler.

Devices which can be used to administer the pharmaceutical compositions of the invention are also contemplated. Examples include a syringe which houses a pharmaceutical composition comprising a solid ionic complex comprising the pharmaceutically active compound and an ionic bioerodable macromolecule, where the complex is suspended in a vehicle suitable for injection, and an inhalation device which houses a pharmaceutical composition comprising a solid ionic complex comprising the pharmaceutically active compound and an ionic bioerodable macromolecule and a carrier suitable for inhalation. The inhalation device can be, for example, a dry powder inhaler, a nebulizer or a metered dose inhaler.

The following examples, which further illustrate the invention, should not be construed as limiting. The contents of all references, pending patent applications and published patents, cited throughout this application, are hereby expressly incorporated by reference.

EXAMPLE 1: The methods of the invention increase the stability of Abarelix by increasing the glass transition temperature (Tg) relative to Abarelix acetate (API).

The methods of the present invention are amenable to many pharmaceutical peptides, proteins, and small molecules, potentially allowing for sustained-release injectable formulations of a wide variety of therapeutics.

An LHRH antagonist, Abarelix, was formulated using the methods of the invention as described herein and as described in PCT Publication No. WO 98/25642,

the contents of which are hereby incorporated by reference. The glass transition temperature of the complex was measured using Modulated Differential Scanning Calorimetry (TA Instruments, Model #2920) with the samples heated at an underlying rate of 1.25°C/minute with a modulation of 1.0°C/60sec and from ambient (25°C) up to a final temperature of 250°C. Stability was determined by HPLC (Agilent 1100 HPLC; Phenomenex Luna C18 column (150x4.6mm); 1.0mL/minute flow rate; NaC104 Buffer/ACN: 65/35, pH 2.7 mobile phase isocratic to 30 minutes/linear gradient to 50% ACN at 45 minute; 225nm UV detection).

The observed Tg of abarelix acetate and abarelix formulated using the methods of the invention were approximately 136°C and 168°C, respectively. Under high stress conditions (80°C/85%RH for 7 days), abarelix API degraded 82%, while abarelix formulated according to the present invention degraded 15%.

Abarelix formulated using the methods of the invention exhibited increased Tg and stability versus abarelix acetate. Specifically, at conditions which degraded the API, the methods of the invention stabilized the complexed compound five-fold.

EXAMPLE 2: The methods of the invention increase the stability of Abarelix under conditions of terminal sterilization by gamma irradiation.

Abarelix, a GnRH antagonist, was formulated as a one-month depot formulation using the methods of the invention described herein and as described in PCT Publication No. WO 98/25642, the contents of which are hereby incorporated by reference.

A solution of abarelix in water, abarelix-CMC suspension (Abarelix formulated using the methods of the invention) and abarelix-CMC powder were gamma-irradiated at a typical dose for terminal sterilization (*i.e.* 25kGy). Additionally, 3 batches of abarelix-CMC powder were irradiated at doses ranging from 0 to 45kGy in order to determine the relationship between radiation dose and degradation. HPLC-UV degradation profiles were compared (Agilent 1100 HPLC; Phenomenex Luna C18 column (150x4.6mm); 1.0mL/minute flow rate; NaClO4 Buffer/ACN: 65/35, pH 2.7 mobile phase isocratic to 30 minutes/linear gradient to 50% ACN at 45 minute; 225nm UV detection).

The abarelix in solution was 100% degraded upon exposure to gamma radiation at 25kGy; however, less than 2% degradation was seen in both the abarelix-CMC suspension and powder formulations at 25kGy. For abarelix-CMC powder, the % degradation was directly proportional (r^2=0.975) to the radiation dose, with greater degradation seen at increased radiation doses. Importantly, the degradation profiles were similar for each radiation dose, and the relative abundance of individual related substances remained unchanged.

EXAMPLE 3: Small Molecule CMC Complex Formation, Isolation, Milling and Analysis

A. FLUOXETINE CMC

Fluoxetine hydrochloride (1.0g, purchased from Spectrum, Lot TT0821) was dissolved in 60 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) by warming to 45° C to prepare a solution with a final concentration of 16.7 mg/mL. The solution was clear and the pH was 6.3. Under vigorous stirring, 100 mL of a 1% NaCMC solution (NaCMC, Hercules, Lot 71040 prepared in WFI) was added to the drug solution at ambient temperature. Immediately upon addition, the solution turned cloudy and contained white to off white precipitates. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30 minutes. During centrifugation, the rotor chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded.

The concentrated white solids in the centrifuge tubes (wet cake, approximately 9g) were dried in the vacuum for 24 hours. A 0.85 gram dry product was obtained (50% yield). The product appeared colorless.

The colorless product was transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, 0.70 g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%Fluoxetine Content by HPLC Analysis: 51.3% (97.2% of theoretical value)
Free Fluoxetine in WFI: 0.5 mg/mL
Free Fluoxetine in Saline: 3.9 mg/mL

B. BENZTROPINE CMC

Benztropine mesylate (2.0 g, purchased from Aldrich, Lot 13802TR) was dissolved in 10 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) to prepare a solution with a final concentration of 200 mg/mL. The solution was clear and the pH was 4.08. Under vigorously stirring, 88 mL of a 2% NaCMC

solution (NaCMC Hercules Lot 71040 prepared in WFI) was added to the drug solution at ambient temperature. Immediately upon addition, the solution mixture turned very cloudy. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30 minutes. During centrifugation, the rotor was chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded.

The concentrated white solids in the centrifuge tubes were dried in the vacuum for 24 hours. A 1.9 g dry product was obtained (65.5% yield). The product appeared colorless.

The product was then transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, 0.1.7g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%Benztropine Content by HPLC Analysis:
48.6% (92.6% of theoretical value)
Free Benztropine in WFI: 1.1 mg/mL
Free Benztropine in Saline: 2.4 mg/mL

C. STREPTOMYCIN CMC

Streptomycin sulfate (2.0 g, purchased from Fluka, Lot 424772/1) was dissolved in 25 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) to prepare a solution with a final concentration of 80 mg/mL. The solution was clear and the pH was approximately 5.8. Under vigorously stirring, 23 mL of a 2% NaCMC solution (NaCMC Hercules Lot 71040 prepared in WFI) was added to the drug solution at ambient temperature. Immediately upon addition, the solution mixture turned cloudy. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30min. During centrifugation, the rotor was chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded.

The concentrated white solids in the centrifuge tubes were dried in the vacuum for 24 hours. A 0.70 g dry product was obtained (32.1% yield). The product appeared colorless.

The product was then transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, 0.55 g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%Streptomycin Content by HPLC Analysis: 70.2% (85.1% of theoretical value)

Free Streptomycin in WFI: 4.2 mg/mL

Free Streptomycin in Saline: 10.3 mg/mL

D. DOXEPIN CMC

Doxepin hydrochloride (2.0 g, purchased from Spectrum, Lot OF0258) was dissolved in 40 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) to prepare a solution with a final concentration 50 mg/mL. The solution was clear and the pH was approximately 6.2. Under vigorously stirring, 64 mL of a 2% NaCMC solution (NaCMC Hercules Lot 71040 prepared in WFI) was added to the drug solution at ambient temperature. Immediately upon addition, the solution mixture turned cloudy. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30min. During centrifugation, the rotor was chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded. The concentrated white solids in the centrifuge tubes were dried in the vacuum for 24 hours. A 1.8 g dry product was obtained (51.4% yield). The product appeared colorless.

The colorless product was transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, 1.55 g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%Doxepin Content by HPLC Analysis: 46.1% (91.8% theoretical value)
Free Doxepin in WFI: 0.7 mg/mL
Free Doxepin in Saline: 1.6 mg/mL

E. DILTIAZEM CMC

Diltiazem hydrochloride (2.0 g, purchased from Spectrum, Lot SN0309) was dissolved in 20 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) to prepare a solution with a final concentration of 100 mg/mL. The solution was clear and the pH was approximately 4.3. Under vigorously stirring, 76 mL of a 2% NaCMC solution (NaCMC Hercules Lot 71040 prepared in WFI) was added to the drug solution at the ambient temperature. Immediately upon addition, the solution mixture turned cloudy with precipitates. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30min. During centrifugation, the rotor was chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded. The concentrated white solids in the centrifuge tubes were dried in the vacuum for 24 hours. A 1.2 g dry product was obtained (39.1% yield). The product appeared colorless.

The colorless product was transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, approximately 1 g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%Diltiazem Content by HPLC Analysis: 55.9% (93.3% of theoretical value)
Free Diltiazem in WFI: 1.8 mg/mL
Free Diltiazem in Saline: 3.8 mg/mL

F. TETRAHYDRO-9-AMINO-ACRIDINE CMC

Tetrahydro-9-amino-acridine (THA) hydrochloride hydrate (0.5 g, purchased from Aldrich, Lot 07220AV) was dissolved in 5 mL of Water for Irrigation, USP, (WFI, purchased from B. Braun, Lot J4L231) to prepare a solution with a final concentration of 100 mg/mL. The solution was clear and the pH was approximately 4.3. Under vigorously stirring, 36 mL of a 2% NaCMC solution (NaCMC Hercules

Lot 71040 prepared in WFI) was added to the drug solution at the ambient temperature. Immediately upon addition, the solution mixture turned cloudy with precipitates. The reaction mixture was stirred for an additional one hour at ambient temperature. It was then chilled in the refrigerator overnight.

The chilled mixture was transferred into several 50 mL centrifuge tubes and centrifuged using a Beckman Centrifuge at a speed of 13,000 rpm for 30min. During centrifugation, the rotor was chilled to 0° to 5° C. After centrifugation, white solids were concentrated at the bottoms of the centrifuge tubes. The top centrate fluid was discarded. The concentrated white solids in the centrifuge tubes were dried in the vacuum for 24 hours. A 0.49 g dry product was obtained (48.5% yield). The product appeared colorless.

The colorless product was transferred into a small milling jar. Milling was completed using the Retsch Centrifugal Ball Mill S-1000. The milled product was a white to off-white powder. After sieving through 150 μm sieve, approximately 0.4 g of milled product was obtained.

The product was analyzed by an isocratic HPLC method using a detection wavelength of 254 nm. The %Drug Content and free drug in WFI and Saline results were obtained and summarized below:

%THA Content by HPLC Analysis: 41.3% (98.9% of theoretical value)

Free THA in WFI: <0.01 mg/mL

Free THA in Saline: 0.0018 mg/mL

EXAMPLE 4: The compositions of the invention mitigate abuse and/or overdose

The methods of the present invention are amenable to many pharmaceutical peptides, proteins, and small molecules, potentially allowing for sustained-release formulations of a wide variety of therapeutics.

Naltrexone HCL and Dectromethorphan HBr were formulated using the methods of the invention as described herein and as described in PCT Publication No. WO 98/25642, the contents of which are hereby incorporated by reference. These formulations were analyzed *in vitro* under conditions simulating gastric fluid with and without alcohol. Similar to previous analyses with cola and orange juice, and as shown in Figures 1 and 2, the presence of alcohol does not increase the dissolution rate of these opioid pharmaceutically active compounds.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

We claim:

1. A method for increasing the stability of a pharmaceutically active compound, comprising:

selecting a pharmaceutically active compound in need of stabilization;

providing said pharmaceutically active compound and a carrier macromolecule;

combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the stability of the pharmaceutically active compound.

2. The method of claim 1, wherein the stability of the pharmaceutically active compound is maintained *in vivo*.

3. The method of claim 1, wherein the stability of the pharmaceutically active compound is maintained *ex vivo*.

4. A method for increasing the glass transition temperature (Tg) of a water-insoluble complex, comprising:

selecting a pharmaceutically active compound whose water-insoluble complex would benefit from an increase in the glass transition temperature (Tg);

combining the pharmaceutically active compound and the carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby increasing the glass transition temperature (Tg) of said water-insoluble complex.

5. A method for decreasing the rate of absorption of a pharmaceutically active compound from the gastrointestinal (GI) tract of a subject, comprising:

selecting a pharmaceutically active compound for which a decrease in the rate of absorption from the GI tract would be beneficial;

combining said pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby

decreasing the rate of absorption of said pharmaceutically active compound from the gastrointestinal (GI) tract of a subject.

6. The method of claim 5, wherein the pharmaceutically active compound for which a decrease in the rate of absorption from the GI tract would be beneficial is selected from the group consisting of Oxycodone, Amphetamine Sulphate, Morphine Sulfate, Methylphenidate, Hydromorphone, and Meperidine.

7. A method for preventing local irritation of the gastrointestinal (GI) tract of a subject, comprising:

selecting a pharmaceutically active compound that causes local irritation of the GI tract;

combining said pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby preventing local irritation of the GI tract of a subject.

8. The method of claim 7, wherein the pharmaceutically active compound that causes local irritation of the GI tract is Rivastigmine.

9. A method for maintaining blending uniformity of a pharmaceutically active compound in a pharmaceutical composition, comprising:

selecting a pharmaceutically active compound which needs to be blended uniformly;

combining said pharmaceutically active compound and a carrier macromolecule under conditions such that a water-insoluble complex of the pharmaceutically active compound and the carrier macromolecule forms, thereby maintaining blending uniformity of said pharmaceutically active compound in a pharmaceutical composition.

10. The method of claim 9, wherein the pharmaceutically active compound which needs to be blended uniformly is selected from the group consisting of Flexeril, Exelon, and Adderall.

11. The method of any one of claims 1, 4, 5, 7, or 9, wherein said pharmaceutically active compound is a peptidic compound.

12. The method of any one of claims 11, wherein said pharmaceutically active compound is a multivalent cationic or anionic peptide.

13. The method of claim 11, wherein the peptidic compound has an isoelectric point less than about 7.0.

14. The method of claim 11, wherein the peptidic compound has an isoelectric point less than about 6.5.

15. The method of claim 11, wherein the peptidic compound has an isoelectric point less than about 6.0

16. The method of claim 11, wherein the peptidic compound has an isoelectric point less than about 5.5.

17. The method of claim 11, wherein the peptidic compound has an isoelectric point less than about 5.0.

18. The method of claim 11, wherein the peptidic compound has an isoelectric point between about 4.5 and about 7.0.

19. The method of claim 11, wherein the peptidic compound has an isoelectric point between about 5.0 and about 6.5.

20. The method of claim 11, wherein the peptidic compound is 5 to 20 amino acids in length.

21. The method of claim 11, wherein the peptidic compound is 8 to 15 amino acids in length.

22. The method of claim 11, wherein the peptidic compound is 8 to 12 amino acids in length.

23. The method of claim 11, wherein said peptidic compound is selected from the group consisting of:

LHRH analogues, recombinant luteinizing hormone, *e.g.*, lutropin alpha, bradykinin analogues, parathyroid hormone, adenocorticotrophic hormone (ACTH), calcitonin, vasopressin analogues (*e.g.*, 1-deamino-8-D-arginine vasopressin (DDAVP)),

and synthetic forms of vasopressin, *e.g.,* Desmopressin Acetate. Other non-limiting examples of pharmaceutically active peptides that can be used in the formulations and methods of the invention include octreotide, endorphin, liprecin, erythropoietin, protamine, platelet aggregation inhibitor (epoprostenol), platelet glycoprotein IIb/IIIa receptor, recombinant platelet glycoprotein IIb/IIIa receptor antibodies, *e.g.,* Abciximab and Eptifibatide, angiotensin II, antidiuretic hormone, neurotrophic factors, keratinocyte growth factor, leukemia inhibiting factor, monocyte chemoattractant protein-1, endothelial growth factors, thymosin alpha 1, thymosin alpha 1 IIb/IIa inhibitor, thymosin beta 10, thymosin beta 9, thymosin beta 4, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 (very late antigen-4), VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, *e.g.,* antibodies directed against the epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV), *e.g.,* PALIVIZUMAB, cystic fibrosis transmembrane regulator (CFTR) protein, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, oxytocin, growth hormones, *e.g.,* somatotropin, pituitary hormones, somatostatin, asparaginase, chorionic gonadotropin, growth hormone releasing hormone, growth hormone releasing peptide, interferons (*e.g.,* interferons α, β γ, interferon β-1a, interferon α-2a, interferon alfacon-1, interferon alpha-n3 (Human Leukocyte Derived), colony stimulating factor, bone morphogenic proteins (BMP) (*e.g.,* 1, 2, 3, 4, 5, 6, and 7), interleukins (*e.g.,* interleukin-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28 , -29 and -30), *e.g.,* recombinant interleukin antibodies, *e.g.,* IL-2, *e.g.,* Aldesleukin, *e.g.,* recombinant interleukins, *e.g.,* IL-11, *e.g.,* oprelvekin, *e.g.,* interleukin receptor antagonists, *e.g.,* IL-1 receptor antagonist, *e.g.,* anakinra, glucocerebrosidase, *e.g.,* Imiglucerase, macrophage activating factor, macrophage peptide, B cell factor, T cell factor, protein A, suppressive factor of allergy, cell necrosis glycoprotein, immunotoxin, lymphotoxin, tumor necrosis factor, tumor inhibitory factor, transforming growth factor, HER2, *e.g.,* antibodies against HER2, *e.g.,* Trastuzumab, myelin, *e.g.,* synthetic forms or fragments thereof, *e.g.,* Glatiramer Acetate, alpha-1 antitrypsin, albumin, apolipoprotein-E, apolipoprotein A1, erythropoietin, hyper-glycosylated erythropoietin, factor VII, factor VIII, factor IX, plasminogen activator, urokinase, streptokinase, protein C, activated Protein C, *e.g.,* Drotrecogin alpha, protein S, C-reactive protein, renin inhibitor, collagenase inhibitor, superoxide dismutase, leptin, platelet derived growth factor, epidermal growth factor, epidermal growth factor receptor (EGFR), *e.g.,* recombinant EGFR antibodies, *e.g.,* Cetuximab, osteogenic growth factor, osteogenesis stimulating protein, calcitonin, insulin, insulin analogs, *e.g.,* Insulin Glulisine and Insulin Glargine, amylin, *e.g.,* synthetic analogues thereof, *e.g.,* Pramlintide, atriopeptin, cartilage inducing factor, connective tissue activator protein, follicle stimulating hormone, luteinizing hormone,

FSH releasing hormone, nerve growth factor, parathyroid hormone, or a portion thereof, *e.g.,* Teriparatide, prostoglandin, relaxin, secretin, somatomedin, insulin-like growth factor, thrombolytics, pamiteplase, lanoteplase, and teneteplase; nerve growth factor (NGF), osteoprotegerin, Rhdnase, *e.g.,* dornase alpha and Tenecteplase, erythropoiesis stimulating protein (NESP), coagulation factors such as Factor V, Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor XII, Factor XIII, von Willebrand factor; ceredase, cerezyme, alpha-glucosidase, collagen, cyclosporin, alpha defensins, beta defensins, exedin-4, thrombopoietin (TPO), heparin, human serum albumin, low molecular weight heparin (LMWH), alpha-1 proteinase inhibitor, elcatonin, fibrinogen, filgrastim (granulocyte colony-stimulating factor, *e.g.,* Sargramostim), adrenocorticotrophic hormone, glucagon, glucagon-like peptide 1 (GLP-1) receptor or agonists thereof, *e.g.,* Exendin-4, glucagon-like peptide 1, or analogues thereof, *e.g.,* Exenatide, cholecystokinin, pancreatic polypeptide, gastrin releasing peptide, corticotropin releasing factor, or analogues thereof, *e.g.,* Corticorelin Ovine Triflutate, thyroid stimulating hormone, TNF receptor (*e.g.*, TNFR(P75) and TNFR(P55)), IL-1 receptor antagonist (*e.g.*, IL1-Ra), cell surface antigen (*e.g.*, CD2, 3, 4, 5, 7, 11a, 11b, 18, 19, 20, 23, 25, 33, 38, 40, 45 and 69), *e.g.,* recombinant CD20 antibodies, *e.g.,* Rituximab, TNF-α, *e.g.,* recombinant TNFα antibodies, *e.g.,* Infliximab, Etanercept, NF-κB, urate oxidase, *e.g.,* Rasburicase, cone snail peptide w-cenotoxin M-VII-A, *e.g.,* Ziconotide, antimicrobial antifungal and antibacterial analogues, non-limiting examples of which include, Caspofungin acetate, ADENOREGULIN, Aureins, Gaegurins, Thanatin, Ranatuerin-2CB, Ranatuerin-2CA, Cecropin A, Cecropin B, Melittin B, Indolicidin, Tritrpticin, Androctonin, Tachystatin A, Dermaseptins, Gomesin, Hepcidin 20, Hepcidin 25, Peptide PGQ, Protegrins, RatNPs Seminalplasmin, Tracheal antimicrobial peptide, Dolabellanin B2, AFP1, AFP2, Dermaseptin BI, Buforin I, Buforin II, Histones, Opistoporins, Ponericins, Penaeidins, Spingerin, Skin peptide tyrosine-tyrosine, Lingual antimicrobial peptide, Tricholongin, Termicin, Holotricins, Penaeidins, Nk-Lysin, Magainin 2, Neutrophil defensins, Cyclic Defensin, Alpha-basrubrin, Melanotropin alpha (Alpha-MSH), Brevinin, Pseudins (1, 2, 3, 4), Anti-fungal protein 1(pafp-s), Misgurin, P-18, Pseudo-hevein (Minor hevein), MUC7 20-Mer, Histatins (3, 5, 8), Nigrocin, lactoferrin (Lf), Ranalexin, antiviral analogues, *e.g.,* Antiviral protein Y3, Alloferon 1, Lactoferricin B, hexapeptide, Tricyclic peptide RP, Indolicidin, GNCP-2, GNCP-1, HNP-1 Defensin, HNP-2 Defensin, Defensin, CORTICOSTATIN III (MCP-1) , CORTICOSTATIN IV (MCP-2), NP-3A defensin, Protegrin 2, Protegrin 3, Protegrin 3, Protegrin 4, Protegrin 5, RatNP-1, RatNP-2, RatNP-3, RatNP-4, Caerin 1.1, Circulin A (CIRA), Circulin B (CIRB), Cyclopsychotride A (CPT), Ginkbilobin, Alpha-basrubrin, Enfuvirtide, or other antiretroviral agents.

24. The method of any one of claims 1, 4, 5, 7, or 9, wherein said pharmaceutically active compound is a non-peptidic compound.

25. The method of claim 24, wherein said non-peptidic compound is cationic.

26. The method of claim 25, wherein the non-peptidic compound has a charge of at least +1.

27. The method of claim 25, wherein the non-peptidic compound has a charge of at least +2.

28. The method of claim 24, wherein said non-peptidic compound is anionic.

29. The method of claim 28, wherein the non-peptidic compound has a charge of at least -1.

30. The method of claim 28, wherein the non-peptidic compound has a charge of at least -2.

31. The method of claim 24, wherein the non-peptidic compound has at least one functional group selected from the group consisting of primary amino groups, secondary amino groups, tertiary amino groups, imino groups, quaternary ammonium groups, amidino groups, guanidino groups, phosphonium groups and sulfonium groups.

32. The method of claim 24, wherein the non-peptidic compound has at least one functional group selected from the group consisting of carboxylate groups, sulfonate groups, phosphonate groups, sulfamate groups, sulfate ester groups, phosphate ester groups, sulfinate groups, phosphinate groups, carbonate groups, thiocarboxylate groups and carbamate groups.

33. The method of claim 24, wherein the non-peptidic compound has at least one functional group selected from the group consisting of carboxylate and sulfonate.

34. The method of any one of claims 24, wherein said pharmaceutically active compound has a molecular weight of about 100-2200 amu.

35. The method of any one of claims 24, wherein said pharmaceutically active compound has a molecular weight of about 1000 amu or less.

36. The method of any one of claims 24, wherein said pharmaceutically active compound has a molecular weight of about 750 amu or less.

37. The method of any one of claims 24, wherein said pharmaceutically active compound has a molecular weight of about 500 amu or less.

38. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is ionic.

39. The method of claim 38, wherein the ionic carrier macromolecule comprises at least one functional group selected from the group consisting of carboxylic acid, sulfonic acid, sulfamic acid, primary amine, secondary amine, tertiary amine, quaternary ammonium, guanidino and amidino.

40. The method of claim 38, wherein the ionic carrier macromolecule is a polypeptide or a polysaccharide.

41. The method of any one of claims 1, 4, 5, 7, or 9, wherein said carrier macromolecule is an anionic polymer.

42. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is an anionic polyalcohol derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

43. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is an anionic polysaccharide derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

44. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is carboxymethylcellulose, or a pharmaceutically acceptable salt thereof.

45. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is selected from the group consisting of algin, alginate, anionic acetate polymers, anionic acrylic polymers, xantham gums, anionic carageenan derivatives, anionic polygalacturonic acid derivatives, sodium starch glycolate, dextran sulfate,

croscarmellose sodium, carbomers (poly(acrylic acid)), sodium hyaluronate, xanthan gum, chitosan, and fragments, derivatives and pharmaceutically acceptable salts thereof.

46. The method of any one of claims 1, 4, 5, 7, or 9, wherein carrier macromolecule is anionic and selected from the group consisting of carboxymethylcellulose, poly(glutamic acid), poly(aspartic acid), poly(glutamic acid-co-glycine), poly(aspartic acid-co-glycine), poly(glutamic acid-co-alanine), poly(aspartic acid-co-alanine), starch glycolate, polygalacturonic acid, poly(acrylic acid), and alginic acid.

47. The method of any one of claims 1, 4, 5, 7, or 9, wherein carrier macromolecule is anionic and selected from the group consisting of poly(glutamic acid) and poly(aspartic acid).

48. The method of any one of claims 1, 4, 5, 7, or 9, wherein said carrier macromolecule is anionic and is carboxymethylcellulose.

49. The method of any one of claims 1, 4, 5, 7, or 9, wherein the carrier macromolecule is cationic.

50. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound content of the solid ionic complex is at least 50% by weight.

51. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound content of the solid ionic complex is at least 60% by weight.

52. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound content of the solid ionic complex is at least 70% by weight.

53. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound content of the solid ionic complex is 50% to 90% by weight.

54. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound and the ionic macromolecule used to form the solid

ionic complex are combined at a weight ratio of ionic macromolecule:pharmaceutically active compound of 0.5:1 to 0.1:1

55. The method of any one of claims 1, 4, 5, 7, or 9, wherein the pharmaceutically active compound and the ionic macromolecule used to form the solid ionic complex are combined at a weight ratio of ionic macromolecule:pharmaceutically active compound of 1:1 to 0.1:1

56. A pharmaceutical composition comprising a water-insoluble complex of a pharmaceutically active compound and a carrier macromolecule, wherein said water-insoluble complex is further embedded in a biodegradable carrier matrix.

57. The pharmaceutical composition of claim 56, wherein there is a physical interaction between said water-insoluble complex and said biodegradable carrier matrix.

58. The pharmaceutical composition of claim 56, wherein there is a chemical interaction between said water-insoluble complex and said biodegradable carrier matrix.

59. The pharmaceutical composition of claim 56, wherein the stability of the pharmaceutically active compound is increased *in vivo*.

60. The pharmaceutical composition of claim 56, wherein the stability of the pharmaceutically active compound is increased *ex vivo*.

61. The pharmaceutical composition of claim 56, wherein said pharmaceutically active compound is a peptidic compound.

62. The pharmaceutical composition of claim 56, wherein said pharmaceutically active compound is a multivalent cationic or anionic peptide.

63. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point less than about 7.0.

64. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point less than about 6.5.

65. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point less than about 6.0

66. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point less than about 5.5.

67. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point less than about 5.0.

68. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point between about 4.5 and about 7.0.

69. The pharmaceutical composition of claim 61, wherein the peptidic compound has an isoelectric point between about 5.0 and about 6.5.

70. The pharmaceutical composition of claim 61, wherein the peptidic compound is 5 to 20 amino acids in length.

71. The pharmaceutical composition of claim 61, wherein the peptidic compound is 8 to 15 amino acids in length.

72. The pharmaceutical composition of claim 61, wherein the peptidic compound is 8 to 12 amino acids in length.

73. The pharmaceutical composition of claim 61, wherein said peptidic compound is selected from the group consisting of

LHRH analogues, recombinant luteinizing hormone, *e.g.*, lutropin alpha, bradykinin analogues, parathyroid hormone, adenocorticotrophic hormone (ACTH), calcitonin, vasopressin analogues (*e.g.*, 1-deamino-8-D-arginine vasopressin (DDAVP)), and synthetic forms of vasopressin, *e.g.*, Desmopressin Acetate. Other non-limiting examples of pharmaceutically active peptides that can be used in the formulations and methods of the invention include octreotide, endorphin, liprecin, erythropoietin, protamine, platelet aggregation inhibitor (epoprostenol), platelet glycoprotein IIb/IIIa receptor, recombinant platelet glycoprotein IIb/IIIa receptor antibodies, *e.g.*, Abciximab and Eptifibatide, angiotensin II, antidiuretic hormone, neurotrophic factors, keratinocyte growth factor, leukemia inhibiting factor, monocyte chemoattractant protein-1, endothelial growth factors, thymosin alpha 1, thymosin alpha 1 IIb/IIa inhibitor, thymosin beta 10, thymosin beta 9, thymosin beta 4, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 (very late antigen-4), VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, *e.g.*, antibodies directed against the

epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV), *e.g.*, PALIVIZUMAB, cystic fibrosis transmembrane regulator (CFTR) protein, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, oxytocin, growth hormones, *e.g.*, somatotropin, pituitary hormones, somatostatin, asparaginase, chorionic gonadotropin, growth hormone releasing hormone, growth hormone releasing peptide, interferons (*e.g.*, interferons α, β γ, interferon β-1a, interferon α-2a, interferon alfacon-1, interferon alpha-n3 (Human Leukocyte Derived), colony stimulating factor, bone morphogenic proteins (BMP) (*e.g.*, 1, 2, 3, 4, 5, 6, and 7), interleukins (*e.g.*, interleukin-1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28 , -29 and -30), *e.g.*, recombinant interleukin antibodies, *e.g.*, IL-2, *e.g.*, Aldesleukin, *e.g.*, recombinant interleukins, *e.g.*, IL-11, *e.g.*, oprelvekin, *e.g.*, interleukin receptor antagonists, *e.g.*, IL-1 receptor antagonist, *e.g.*, anakinra, glucocerebrosidase, *e.g.*, Imiglucerase, macrophage activating factor, macrophage peptide, B cell factor, T cell factor, protein A, suppressive factor of allergy, cell necrosis glycoprotein, immunotoxin, lymphotoxin, tumor necrosis factor, tumor inhibitory factor, transforming growth factor, HER2, *e.g.*, antibodies against HER2, *e.g.*, Trastuzumab, myelin, *e.g.*, synthetic forms or fragments thereof, *e.g.*, Glatiramer Acetate, alpha-1 antitrypsin, albumin, apolipoprotein-E, apolipoprotein A1, erythropoietin, hyper-glycosylated erythropoietin, factor VII, factor VIII, factor IX, plasminogen activator, urokinase, streptokinase, protein C, activated Protein C, *e.g.*, Drotrecogin alpha, protein S, C-reactive protein, renin inhibitor, collagenase inhibitor, superoxide dismutase, leptin, platelet derived growth factor, epidermal growth factor, epidermal growth factor receptor (EGFR), *e.g.*, recombinant EGFR antibodies, *e.g.*, Cetuximab, osteogenic growth factor, osteogenesis stimulating protein, calcitonin, insulin, insulin analogs, *e.g.*, Insulin Glulisine and Insulin Glargine, amylin, *e.g.*, synthetic analogues thereof, *e.g.*, Pramlintide, atriopeptin, cartilage inducing factor, connective tissue activator protein, follicle stimulating hormone, luteinizing hormone, FSH releasing hormone, nerve growth factor, parathyroid hormone, or a portion thereof, *e.g.*, Teriparatide, prostoglandin, relaxin, secretin, somatomedin, insulin-like growth factor, thrombolytics, pamiteplase, lanoteplase, and teneteplase; nerve growth factor (NGF), osteoprotegerin, Rhdnase, *e.g.*, dornase alpha and Tenecteplase, erythropoiesis stimulating protein (NESP), coagulation factors such as Factor V, Factor VII, Factor VIIa, Factor VIII, Factor IX, Factor X, Factor XII, Factor XIII, von Willebrand factor; ceredase, cerezyme, alpha-glucosidase, collagen, cyclosporin, alpha defensins, beta defensins, exedin-4, thrombopoietin (TPO), heparin, human serum albumin, low molecular weight heparin (LMWH), alpha-1 proteinase inhibitor, elcatonin, fibrinogen, filgrastim (granulocyte colony-stimulating factor, *e.g.*, Sargramostim), adrenocorticotrophic hormone, glucagon, glucagon-like peptide 1 (GLP-1) receptor or

agonists thereof, *e.g.*, Exendin-4, glucagon-like peptide 1, or analogues thereof, *e.g.*, Exenatide, cholecystokinin, pancreatic polypeptide, gastrin releasing peptide, corticotropin releasing factor, or analogues thereof, *e.g.*, Corticorelin Ovine Triflutate, thyroid stimulating hormone, TNF receptor (*e.g.*, TNFR(P75) and TNFR(P55)), IL-1 receptor antagonist (*e.g.*, IL1-Ra), cell surface antigen (*e.g.*, CD2, 3, 4, 5, 7, 11a, 11b, 18, 19, 20, 23, 25, 33, 38, 40, 45 and 69), *e.g.*, recombinant CD20 antibodies, *e.g.*, Rituximab, TNF-α, *e.g.*, recombinant TNFα antibodies, *e.g.*, Infliximab, Etanercept, NF-κB, urate oxidase, *e.g.*, Rasburicase, cone snail peptide w-cenotoxin M-VII-A, *e.g.*, Ziconotide, antimicrobial antifungal and antibacterial analogues, non-limiting examples of which include, Caspofungin acetate, ADENOREGULIN, Aureins, Gaegurins, Thanatin, Ranatuerin-2CB, Ranatuerin-2CA, Cecropin A, Cecropin B, Melittin B, Indolicidin, Tritrpticin, Androctonin, Tachystatin A, Dermaseptins, Gomesin, Hepcidin 20, Hepcidin 25, Peptide PGQ, Protegrins, RatNPs Seminalplasmin, Tracheal antimicrobial peptide, Dolabellanin B2, AFP1, AFP2, Dermaseptin BI, Buforin I, Buforin II, Histones, Opistoporins, Ponericins, Penaeidins, Spingerin, Skin peptide tyrosine-tyrosine, Lingual antimicrobial peptide, Tricholongin, Termicin, Holotricins, Penaeidins, Nk-Lysin, Magainin 2, Neutrophil defensins, Cyclic Defensin, Alpha-basrubrin, Melanotropin alpha (Alpha-MSH), Brevinin, Pseudins (1, 2, 3, 4), Anti-fungal protein 1(pafp-s), Misgurin, P-18, Pseudo-hevein (Minor hevein), MUC7 20-Mer, Histatins (3, 5, 8), Nigrocin, lactoferrin (Lf), Ranalexin, antiviral analogues, *e.g.*, Antiviral protein Y3, Alloferon 1, Lactoferricin B, hexapeptide, Tricyclic peptide RP, Indolicidin, GNCP-2, GNCP-1, HNP-1 Defensin, HNP-2 Defensin, Defensin, CORTICOSTATIN III (MCP-1) , CORTICOSTATIN IV (MCP-2), NP-3A defensin, Protegrin 2, Protegrin 3, Protegrin 3, Protegrin 4, Protegrin 5, RatNP-1, RatNP-2, RatNP-3, RatNP-4, Caerin 1.1, Circulin A (CIRA), Circulin B (CIRB), Cyclopsychotride A (CPT), Ginkbilobin, Alpha-basrubrin, Enfuvirtide, or other antiretroviral agents.

74. The pharmaceutical composition of claim 56, wherein said pharmaceutically active compound is a non-peptidic compound.

75. The pharmaceutical composition of claim 74, wherein said non-peptidic compound is cationic.

76. The pharmaceutical composition of claim 75, wherein said non-peptidic compound has a charge of at least +1.

77. The pharmaceutical composition of claim 76, wherein said non-peptidic compound has a charge of at least +2.

78. The pharmaceutical composition of claim 74, wherein said non-peptidic compound is anionic.

79. The pharmaceutical composition of claim 78, wherein said non-peptidic compound has a charge of at least -1.

80. The pharmaceutical composition of claim 78, wherein said non-peptidic compound has a charge of at least -2.

81. The pharmaceutical composition of claim 74, wherein said non-peptidic compound has at least one functional group selected from the group consisting of primary amino groups, secondary amino groups, tertiary amino groups, imino groups, quaternary ammonium groups, amidino groups, guanidino groups, phosphonium groups and sulfonium groups.

82. The pharmaceutical composition of claim 74, wherein said non-peptidic compound has at least one functional group selected from the group consisting of carboxylate groups, sulfonate groups, phosphonate groups, sulfamate groups, sulfate ester groups, phosphate ester groups, sulfinate groups, phosphinate groups, carbonate groups, thiocarboxylate groups and carbamate groups.

83. The pharmaceutical composition of claim 74, wherein said non-peptidic compound contains at least one functional group selected from the group consisting of primary amino groups, secondary amino groups, tertiary amino groups, imino groups and quaternary ammonium groups.

84. The pharmaceutical composition of claim 74, wherein said non-peptidic compound has at least one functional group selected from the group consisting of carboxylate and sulfonate.

85. The pharmaceutical composition of claim 74, wherein said pharmaceutically active compound has a molecular weight of about 100-2200 amu.

86. The pharmaceutical composition of claim 74, wherein said pharmaceutically active compound has a molecular weight of about 1000 amu or less.

87. The pharmaceutical composition of claim 74, wherein said pharmaceutically active compound has a molecular weight of about 750 amu or less.

88. The pharmaceutical composition of claim 74, wherein said pharmaceutically active compound has a molecular weight of about 500 amu or less.

89. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is ionic.

90. The pharmaceutical composition of claim 89, wherein the ionic carrier macromolecule comprises at least one functional group selected from the group consisting of carboxylic acid, sulfonic acid, sulfamic acid, primary amine, secondary amine, tertiary amine, quaternary ammonium, guanidino and amidino.

91. The pharmaceutical composition of claim 89, wherein the ionic carrier macromolecule is a polypeptide or a polysaccharide.

92. The pharmaceutical composition of claim 74, wherein said carrier macromolecule is an anionic polymer.

93. The pharmaceutical composition of claim 89, wherein the ionic carrier macromolecule is a polypeptide or a polysaccharide.

94. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is an anionic polyalcohol derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

95. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is an anionic polysaccharide derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

96. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is carboxymethylcellulose, or a pharmaceutically acceptable salt thereof.

97. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is selected from the group consisting of algin, alginate, anionic acetate polymers, anionic acrylic polymers, xantham gums, anionic carageenan derivatives,

anionic polygalacturonic acid derivatives, sodium starch glycolate, dextran sulfate, croscarmellose sodium, carbomers (poly(acrylic acid)), sodium hyaluronate, xanthan gum, and chitosan, and fragments, derivatives and pharmaceutically acceptable salts thereof.

98. The pharmaceutical composition of claim 74, wherein carrier macromolecule is anionic and selected from the group consisting of carboxymethylcellulose, poly(glutamic acid), poly(aspartic acid), poly(glutamic acid-co-glycine), poly(aspartic acid-co-glycine), poly(glutamic acid-co-alanine), poly(aspartic acid-co-alanine), starch glycolate, polygalacturonic acid, poly(acrylic acid), and alginic acid.

99. The pharmaceutical composition of claim 74, wherein carrier macromolecule is anionic and selected from the group consisting of poly(glutamic acid) and poly(aspartic acid).

100. The pharmaceutical composition of claim 74, wherein carrier macromolecule is anionic and is carboxymethylcellulose.

101. The pharmaceutical composition of claim 74, wherein the carrier macromolecule is cationic.

102. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound content of the water-insoluble complex is at least 50% by weight.

103. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound content of the water-insoluble complex is at least 60% by weight.

104. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound content of the water-insoluble complex is at least 70% by weight.

105. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound content of the water-insoluble complex is 50% to 90% by weight.

106. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound and the ionic macromolecule used to form the solid ionic complex are combined at a weight ratio of carrier macromolecule:pharmaceutically active compound of 0.5:1 to 0.1:1

107. The pharmaceutical composition of claim 74, wherein the pharmaceutically active compound and the ionic macromolecule used to form the solid ionic complex are combined at a weight ratio of carrier macromolecule:pharmaceutically active compound of 1:1 to 0.1:1

108. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is a microsphere.

109. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is a microcapsule.

110. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is a microparticle.

111. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is a liposome.

112. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is selected from the group consisting of naturally derived polymers, such as albumin, alginate, cellulose derivatives, collagen, fibrin, gelatin, and polysaccharides.

113. The pharmaceutical composition of claim 74, wherein said biodegradable carrier matrix is selected from the group consisting of synthetic polymers such as polyesters (PLA, PLGA), polyethylene glycol, poloxomers, polyanhydrides, and pluronics.

Figure 1

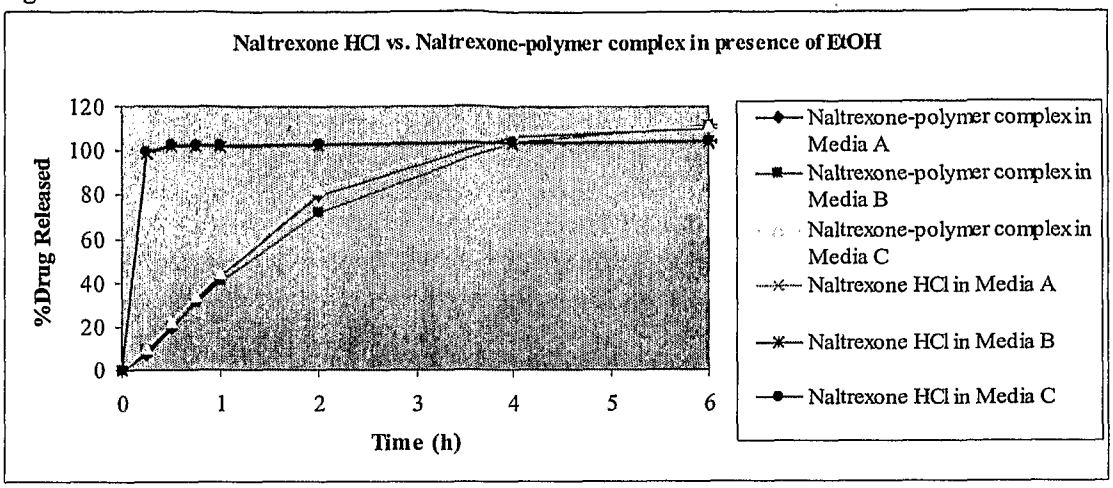
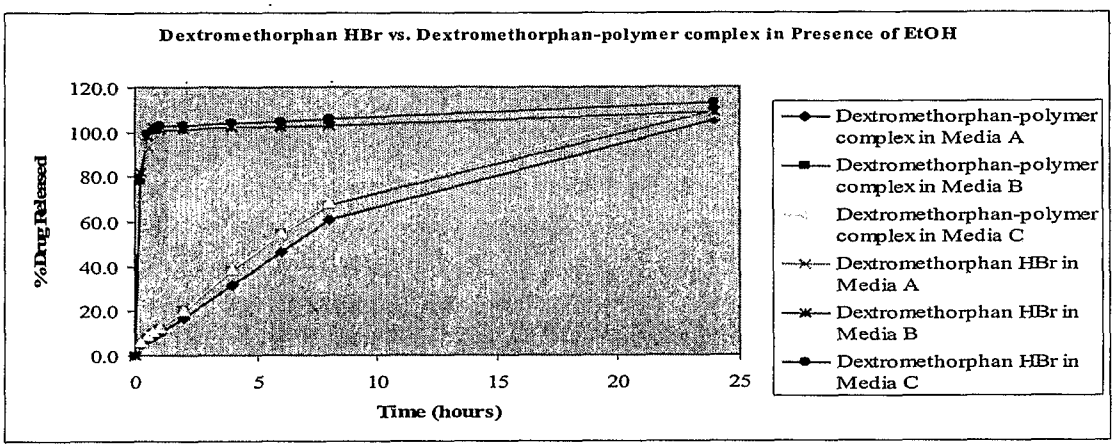


Figure 2



Media Legend

Media	Composition
A	900 mL Simulated Gastric Fluid
B	870 mL Simulated Gastric Fluid + 30 mL of Ethanol (Simulating 2 shots of 80 proof EtOH)
C	840 mL Simulated Gastric Fluid + 60 mL of Ethanol (Simulating 4 shots of 80 proof EtOH)