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# (54) NANOPARTICULATE COMPOSITIONS HAVING A PEPTIDE AS A SURFACE STABILIZER

NANOTEILCHENFÖRMIGE ZUSAMMENSETZUNGEN MIT EINEM PEPTID ALS OBERFLÄCHENSTABILISATOR

COMPOSITIONS NANOPARTICULAIRES COMPRENANT UN PEPTIDE COMME STABILISANT DE SURFACE

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(73) Proprietor: **Elan Pharma International Limited**
**County Westmeath (IE)**

(72) Inventors:
- **CUNNINGHAM, James**
  **Paoli, Pennsylvania 19301 (US)**
- **LIVERSIDGE, Elaine, Merisko**
  **West Chester, PA 19380 (US)**

(74) Representative: **Ryan, Anne Mary et al**
**Anne Ryan & Co.**
**60 Northumberland Road**
**Ballsbridge**
**Dublin 4 (IE)**

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## Description

### FIELD OF THE INVENTION

**[0001]** The present invention is directed to nanoparticulate active agent compositions having a peptide adsorbed onto or associated with the surface of the active agent as a surface stabilizer, and methods of making and using such compositions.

### BACKGROUND OF THE INVENTION

**[0002]** Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto, or associated with, the surface thereof a non-crosslinked surface stabilizer. The '684 patent describes the use of a variety of surface stabilizers for nanoparticulate compositions. The use of a peptide as a surface stabilizer for nanoparticulate active agent compositions is not described by the '684 patent.

**[0003]** The '684 patent describes a method of screening active agents to identify useful surface stabilizers that enable the production of a nanoparticulate composition. Not all surface stabilizers will function to produce a stable, non-agglomerated nanoparticulate composition for all active agents. Moreover, known surface stabilizers may be unable to produce a stable, non-agglomerated nanoparticulate composition for certain active agents. Thus, there is a need in the art to identify new surface stabilizers useful in making nanoparticulate active agent compositions. Additionally, such new surface stabilizers may have superior properties over prior known surface stabilizers.

**[0004]** Methods of making nanoparticulate active agent compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

**[0005]** Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble NonMagnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant

for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," Patent No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,742,734 for "System and Method for Milling Materials," and 6,745,962 for "Small Scale Mill and Method Thereof." In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate active agent compositions. None of these references describe nanoparticulate active agent compositions comprising a peptide surface stabilizer.

**[0006]** Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds; " 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

**[0007]** There is a need in the art for new surface stabilizers useful in preparing nanoparticulate active agent compositions. The present invention satisfies this need.

## SUMMARY OF THE INVENTION

**[0008]** The present invention is directed to nanoparticulate compositions comprising at least one active agent and poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer adsorbed on to, or associated with, the surface of the active agent, wherein the composition does not comprise nystatin or a salt thereof.

**[0009]** Another aspect of the invention is directed to compositions comprising a nanoparticulate active agent composition of the invention. The pharmaceutical compositions preferably comprise at least one active agent poly(Lysine, Tryptophan) 4:1 hydrobromide and a pharmaceutically acceptable carrier, as well as any desired excipients.

**[0010]** In yet another embodiment, the invention is directed to bioadhesive nanoparticulate active agent compositions comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer. Such compositions can coat the gut, or the desired site of application, and be retained for a period of time, thereby increasing the efficacy of the active agent as well as eliminating or decreasing the frequency of dosing.

**[0011]** This invention further discloses a method of making a nanoparticulate active agent composition having a peptide surface stabilizer adsorbed on or associated with the surface of the active agent. Such a method comprises contacting an active agent with poly(Lysine, Tryptophan) 4:1 hydrobromide for a time and under conditions sufficient to provide a Nanoparticle active agent/lpeptide composition. The peptide surface stabilizer can be contacted with the active agent either before, preferably during, or after size reduction of the active agent.

**[0012]** The present invention can be used in a method of treatment comprising administering to a mammal a therapeutically effective amount of a nanoparticulate active agent poly(Lysine, Tryptophan) 4:1 hydrobromide composition according to the invention.

**[0013]** Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

## BRIEF DESCRIPTION OF THE FIGURES

**[0014]**

FIGURE 1: Shows representative photomicrographs of nystatin crystals before (Fig. 1A) and after (Fig. 1B) milling;

FIGURE 2: Shows the results of monitoring the particle size stability over time at 5°C (solid line), 25°C (dashed line), and 40°C (dotted line) for a nanoparticulate nystatin composition comprising the peptide poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, and

FIGURE 3: Shows representative micrographs of cells with anionic particles (Fig.3A) and cationic particles (Fig.3B).

**[0015]** Figures 1 to 3 are retained for reasons of clarity, although the compound nystatin does not fall within the scope of the claims.

## DETAILED DESCRIPTION OF THE INVENTION

**[0016]** The present invention is directed to compositions comprising nanoparticulate active agents having at least poly (Lysine, Tryptophan) 4:1 hydrobromide adsorbed on or associated with the surface thereof, and methods of making and using such nanoparticulate compositions, wherein the composition does not comprise nystatin or a salt thereof.

**[0017]** As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. The discovery of the present invention is surprising in that peptides are biological compounds having secondary and tertiary structures which are critical to the activity of the peptide. It was surprising that poly(Lysine, Tryptophan) 4:1 hydrobromide could be successfully used to stabilize a nanoparticulate active agent. Moreover, it was even more surprising that milling of a peptide surface stabilizer did not change the activity or function of the peptide.

**[0018]** A "peptide" is defined as any compound consisting of two or more amino acids where the alpha carboxyl group of one is bound to the alpha amino group of another. A polypeptide is a long peptide chain. A protein is a large macromolecule composed of one or more polypeptide chains. In the context of the present invention, "peptide" refers to a peptide or a polypeptide, but not a protein.

**[0019]** A striking characteristic of peptides is that they have well-defined three dimensional structures. Peptides fold into compact structures with nominal bond lengths. The strong tendency of hydrophobic amino acid residues to flee from water drives the folding of soluble peptides.

**[0020]** A stretched-out or randomly arranged polypeptide chain is devoid of biological activity. This is because the function of a peptide arises from conformation, which is the three dimensional arrangement of atoms in a structure. *See e.g.,* L. Stryer, Biochemistry, 3rd Edition, p. 1-41 (W.H. Freeman & Co., NY, 1988). Amino acid sequences are important because they specify the conformation of peptides. *Id.*

**[0021]** Peptides have several different defined structures, including a primary, secondary, and tertiary structure. The primary structure of a peptide is generally the amino acid sequence of the peptide and the location of disulfides. *See e.g.,* L. Stryer, Biochemistry, 3rd Edition, p. 31 (W.H. Freeman & Co., NY, 1988). Secondary structure refers to the spatial arrangement of amino acid residues that are near one another in the linear sequence. Examples of these steric relationships are structures known as an alpha helix, a beta pleated sheet, and a collagen helix. *Id.* Tertiary structure refers to the spatial arrangement of amino acid residues in a peptide or polypeptide that are far apart in the linear sequence.

**[0022]** Proteins, comprising multiple polypeptide chains, also have a quaternary structure, which refers to the spatial arrangement of the polypeptide subunits and the nature of their contacts. *Id.*

**[0023]** In addition to enabling the use of poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stablizer for nanoparticulate active agents, this discovery is significant as the peptide surface stabilizer in the compositions of the invention may also have therapeutic or diagnostic properties. This is in contrast to prior art nanoparticulate active agent compositions, in which the surface stabilizer is generally a surfactant, which lacks such therapeutic or diagnostic properties.

**[0024]** The nanoparticulate active agent compositions of the invention may also offer the following advantages as compared to prior conventional or non-nanoparticulate active agent compositions: (1) faster onset of action; (2) a potential decrease in the frequency of dosing; (3) smaller doses of active agent required to obtain the same pharmacological effect; (4) increased bioavailability (5) an increased rate of dissolution; (6) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher active agent dose loading and smaller tablet or liquid dose volumes; (7) improved pharmacokinetic profiles, such as improved $T_{max}$, $C_{max}$ and AUC profiles; (8) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate active agent compositions when administered in the fed versus the fasted state; (9) bioadhesive active agent compositions, which can coat the gut or the desired site of application and be retained for a period of time, thereby increasing the efficacy of the active agent as well as eliminating or decreasing the frequency of dosing; (10) high redispersibility of the nanoparticulate active agent particles present in the compositions of the invention following administration; (11) the nanoparticulate active agent compositions can be formulated in a dried form which readily redisperses; (12) low viscosity liquid nanoparticulate active agent dosage forms can be made; (13) for liquid nanoparticulate active agent compositions having a low viscosity - better subject

compliance due to the perception of a lighter formulation which is easier to consume and digest; (14) for liquid Nanoparticulate active agent compositions having a low viscosity - ease of dispensing because one can use a cup or a syringe; (15) the nanoparticulate active agent compositions can be used in conjunction with other active agents; (16) the nanoparticulate active agent compositions can be sterile filtered; (17) the nanoparticulate active agent compositions are suitable for parenteral administration; and (18) the nanoparticulate active agent compositions do not require organic solvents or pH extremes.

**[0025]** A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, granules, liquid dispersions, oral suspensions, gels, aerosols (including nasal and pulmonary), ointments, and creams.

**[0026]** The dosage form of the invention can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

**[0027]** In addition, the compositions of the invention can be formulated for any suitable administration route, such as oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracistemal, intravaginal, intraperitoneal, local, buccal, nasal, or topical administration.

**[0028]** The present invention is described herein using several definitions, as set forth below and throughout the application.

**[0029]** As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

**[0030]** "Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2 microns. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2 microns.

**[0031]** "Pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

**[0032]** "Pharmaceutically acceptable salts" as used herein refers to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

**[0033]** "Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml. Such drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation.

**[0034]** As used herein with reference to stable drug particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the active agent particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the active agent particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the active agent particles are chemically stable; and/or (4) where the active agent has not been subject to a heating step at or above the melting point of the active agent in the preparation of the nanoparticles of the invention.

**[0035]** "Therapeutically effective amount" as used herein with respect to an active agent dosage, shall mean that dosage that provides the specific pharmacological response for which the active agent is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount' by those skilled in the art. It is to be further understood that active agent dosages are, in particular instances, measured as oral dosages, or with reference to active agent levels as measured in blood.

## I. Preferred Characteristics of the Nanoparticulate Active Agent Compositions of the Invention

### A. Increased Bioavailability, Frequency of Dosing, and Dosage Quantity

**[0036]** The nanoparticulate active agent compositions of the invention, having poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, may preferably exhibit increased bioavailability and require smaller doses as compared to prior non-nanoparticulate compositions of the same active agent administered at the same dose.

**[0037]** Any active agent can have adverse side effects. Thus, lower doses of an active agent that can achieve the same or better therapeutic effects as those observed with larger doses of a non-nanoparticulate composition of the same active agent are desired. Such lower doses may be realized with the nanoparticulate active agent compositions of the invention because the nanoparticulate active agent compositions may exhibit greater bioavailability as compared to non-nanoparticulate compositions of the same active agent, which means that smaller doses of the active agent are likely required to obtain the desired therapeutic effect.

**[0038]** The nanoparticulate active agent compositions of the invention may be administered less frequently and at lower doses, as compared to conventional non-nanoparticulate compositions of the same active agent, in dosage forms such as liquid dispersions, powders, sprays, aerosols (pulmonary and nasal), solid re-dispersable dosage forms, gels, ointments, creams, *etc.* of the nanoparticulate active agent. Lower dosages can be used because the small particle size of the active agent particles ensure greater absorption, and in the case of bioadhesive nanoparticulate active agent compositions, the active agent is retained at the desired site of application for a longer period of time as compared to conventional, non-nanoparticulate active agent dosage forms.

**[0039]** In one embodiment of the invention, the therapeutically effective amount of the nanoparticulate active agent compositions is 1/6,1/5, ¼, 1/3$^{rd}$, or ½ of the therapeutically effective amount of a non-nanoparticulate composition of the same active agent.

**[0040]** Such lower doses are preferred as they may decrease or eliminate adverse effects of the active agent. In addition, such lower doses decrease the cost of the dosage form and may increase patient compliance.

### B. Pharmacokinetic Profiles of the Nanoparticulate Active Agent Compositions of the Invention

**[0041]** The invention also preferably provides nanoparticulate active agent compositions, having at least one peptide as a surface stabilizer, and having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the active agent compositions preferably includes, but is not limited to: (1) a $T_{max}$ for an active agent, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the $T_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; (2) a $C_{max}$ for an active agent, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the $C_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; and/or (3) an AUC for an active agent, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate composition of the same active agent, administered at the same dosage.

**[0042]** The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of the active agent. The compositions can be formulated in any way as described herein and as known to those of skill in the art.

**[0043]** A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same dosage, a $T_{max}$ not greater than about 100%, not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 40%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the $T_{max}$ exhibited by the non-nanoparticulate active agent composition. This shorter $T_{max}$ translates into a faster onset of therapeutic activity.

**[0044]** A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same dosage, a $C_{max}$ which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 110%, at least about 120%, at least about 130%, at least about 140%, at least about 150%, at least about 160%, at least about 170%, at least about 180%, at least about 190%, or at least about 200% greater than the $C_{max}$ exhibited by the non-nanoparticulate active agent composition.

**[0045]** A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same dosage, an AUC which is at least about 10%, at least about 20%, at least about 30%, at least

about 40%, at least about 50%, at least about 60% at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 110%, at least about 120%, at least about 130%, at least about 140%, at least about 150%, at least about 160%, at least about 170%, at least about 180%, at least about 190%, or at least about 200% greater than the AUC exhibited by the non-nanoparticulate active agent formulation

**[0046]** Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods.

### C. The Pharmacokinetic Profiles of the Nanoparticulate Active Agent Compositions of the Invention are Preferably not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

**[0047]** The invention encompasses nanoparticulate active agent compositions, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, wherein preferably the pharmacokinetic profile of the active agent is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of active agent absorbed or the rate of active agent absorption when the nanoparticulate active agent compositions are administered in the fed versus the fasted state. Thus, the nanoparticulate active agent compositions of the invention can preferably substantially eliminate the effects of food on the pharmacokinetics of the active agent.

**[0048]** In another embodiment of the invention, the pharmacokinetic profile of the active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, when administered to a mammal in a fasted state, is bioequivalent to the pharmacokinetic profile of the same nanoparticulate active agent composition administered at the same dosage, when administered to a mammal in a fed state.

**[0049]** "Bioequivalency" is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both $C_{max}$ and AUC under U.S. Food and Drug Administration (USFDA) regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for $C_{max}$ of between 0.70 to 1.43 under the European Medicines Evaluation Agency (EMEA) regulatory guidelines ($T_{max}$ is not relevant for bioequivalency determinations under USFDA and EEBA regulators guidelines).

**[0050]** Preferably the difference in AUC (*e.g.*, absorption) of the nanoparticulate active agent composition of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

**[0051]** In addition, preferably the difference in $C_{max}$ of the nanoparticulate active agent composition of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

**[0052]** Finally, preferably the difference in the $T_{max}$ of the nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

**[0053]** Benefits of a dosage form that substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

### D. Redispersibility Profiles of the Nanoparticulate Active Agent Compositions of the Invention

**[0054]** An additional feature of the nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, is that the compositions redisperse such that the effective average particle size of the redispersed active agent particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate active agent particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating the active agent into a nanoparticulate particle size.

**[0055]** This is because the nanoparticulate active agent compositions of the invention benefit from the small particle size of the active agent; if the nanoparticulate active agent particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

**[0056]** Moreover, the nanoparticulate active agent compositions of the invention exhibit dramatic redispersion of the

active agent particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof which exhibit the desired pH and ionic strength.

**[0057]** Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.,* Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," Pharm. Res., 14 (4): 497-502 (1997).

**[0058]** It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

**[0059]** Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

**[0060]** Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

**[0061]** Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

**[0062]** In other embodiments of the invention, the redispersed active agent particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media), have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 mn, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

**[0063]** Redispersibility can be tested using any suitable means known in the art. *See e.g.*, the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate. "

### E. Bioadhesive Nanoparticulate Active Agent Compositions

**[0064]** Bioadhesive nanoparticulate active agent compositions of the invention comprise cationic peptide surface stabilizer poly(Lysine, Tryptophan) 4:1 hydrobromide. Bioadhesive formulations of active agents exhibit exceptional bioadhesion to biological surfaces, such as mucous and skin.

**[0065]** Cationic surface stabilizers generally confer relatively large, positive zeta potentials to particles on which they adsorb or associate. To increase the bioadhesive properties of a nanoparticulate composition, two or more cationic surface stabilizers can be utilized.

**[0066]** In the case of bioadhesive nanoparticulate active agent compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate active agent compositions and a biological substrate (*i.e.*, gastrointestinal mucin, lung tissue, nasal mucosa, *etc.*). *See e.g.,* U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers".

**[0067]** There are basically two mechanisms which may be responsible for this bioadhesion phenomena: mechanical or physical interactions and chemical interactions. The first of these, mechanical or physical mechanisms, involves the physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue, resulting from a good wetting of the bioadhesive surface, swelling of the bioadhesive polymer, penetration of the bioadhesive entity into a

crevice of the tissue surface, or interpenetration of bioadhesive composition chains with those of the mucous or other such related tissues. The second possible mechanism of bioadhesion incorporates forces such as ionic attraction, dipolar forces, van der Waals interactions, and hydrogen bonds. It is this form of bioadhesion which is primarily responsible for the bioadhesive properties of the nanoparticulate active agent compositions of the invention However, physical and mechanical interactions may also play a secondary role in the bioadhesion of such nanoparticulate active agent compositions.

**[0068]** The bioadhesive active agent compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive active agent compositions preferably coat the targeted surface in a continuous and uniform film that is invisible to the naked human eye.

**[0069]** A bioadhesive nanoparticulate active agent composition slows the transit of the composition, and some active agent particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to the active agent, thereby increasing absorption and the bioavailability of the administered dosage.

**[0070]** The adhesion exhibited by the inventive compositions means that nanoparticulate active agent particles are not easily washed off, rubbed off, or otherwise removed from the biological surface for an extended period of time. The period of time in which a biological cell surface is replaced is the factor that limits retention of the bioadhesive nanoparticulate active agent particles to that biological surface.

### F. Low Viscosity Active Agent Dosage Forms

**[0071]** A liquid dosage form of a conventional microcrystalline or non-nanoparticulate active agent composition would be expected to be a relatively large volume, highly viscous substance which would not be well accepted by patient populations. Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

**[0072]** Liquid dosage forms of the nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide provide significant advantages over a liquid dosage form of a conventional microcrystalline or solubilized active agent composition. The low viscosity and silky texture of liquid dosage forms of the nanoparticulate active agent compositions of the invention result in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of active agent resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

**[0073]** Liquid active agent dosage forms that are easier to consume are especially important when considering juvenile patients, terminally ill patients, and elderly patients. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by these patient populations. Liquid oral dosage forms can be particularly preferably for patient populations who have difficulty consuming tablets, such as infants and the elderly.

**[0074]** The viscosities of liquid dosage forms of a nanoparticulate active agent according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of a liquid oral dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent.

**[0075]** Typically liquid nanoparticulate active agent dosage forms of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, have a viscosity at a shear rate of 0.1 (1/s) measured at 20°C, is from about 2000 mPa s to about 1 mPa s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, or from about 5 mPa·s to about 1 mPa·s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

**[0076]** Viscosity is concentration and temperature dependent Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20°C. (The viscosity of water at 20°C is 1 mPa s.) The invention encompasses equivalent viscosities

measured at different temperatures.

**[0077]** Another important aspect of the invention is that the nanoparticulate active agent compositions of the invention, formulated into a liquid dosage form, are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate active agent compositions of the invention, formulated into a liquid dosage form, can be poured out of or extracted from a container as easily as water, whereas a liquid dosage form of a non-nanoparticulate or solubilized composition of the same active agent is expected to exhibit notably more "sluggish" characteristics.

**[0078]** The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than a liquid dosage form of a non-nanoparticulate composition of the same active agent.

### G. Sterile Filtered Nanoparticulate Active Agent Compositions

**[0079]** The nanoparticulate active agent compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade an active agent, as well as result in crystal growth and particle aggregation of the active agent.

**[0080]** Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize suspensions of micron-sized active agents because the active agent particles are too large to pass through the membrane pores.

**[0081]** A sterile nanoparticulate active agent dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

**[0082]** Because the nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer and formulated into a liquid dosage form, can be sterile filtered, and because the compositions can have a very small active agent effective average particle size, the compositions are suitable for parenteral administration.

### H. Combination Pharmacokinetic Profile Compositions

**[0083]** In yet another embodiment of the invention, a first nanoparticulate active agent composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other active agent composition that generates a desired different pharmacokinetic profile. More than two active agent compositions can be co-administered, sequentially administered, or combined. While the first active agent composition has a nanoparticulate particle size, the additional one or more active agent compositions can be nanoparticulate, solubilized, or have a microparticulate particle size.

**[0084]** The second, third, fourth, *etc.*, active agent compositions can differ from the first, and from each other, for example: (1) in the identity of the active agent; (2) in the effective average particle sizes of the active agent; or (3) in the dosage of the active agent. Such a combination composition can reduce the dose frequency required.

**[0085]** For example, a first active agent composition can have a nanoparticulate particle size, conferring a short $T_{max}$ and typically a higher $C_{max}$. This first active agent composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) the same active agent having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer $T_{max}$, and typically a lower $C_{max}$; or (2) a microparticulate or solubilized composition of the same active agent, exhibiting a longer $T_{max}$, and typically a lower $C_{max}$.

**[0086]** If the second active agent composition has a nanoparticulate particle size, then preferably the active agent particles of the second composition have at least one surface stabilizer associated with the surface of the active agent particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first active agent composition.

**[0087]** Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

### I. Miscellaneous Benefits of the Nanoparticulate Active Agent Compositions of the Invention

**[0088]** The nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide preferably exhibit an increased rate of dissolution as compared to microcrystalline or non-nanoparticulate forms of the same active agent. In addition, the nanoparticulate active agent compositions preferably exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading

and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate active agent compositions of the invention do not require organic solvents or pH extremes.

## II. Compositions

**[0089]** The compositions of the invention comprise a nanoparticulate active agent and poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer adsorbed to or associated with the surface of the active agent. In addition, the compositions can comprise one or more secondary surface stabilizers. Surface stabilizers useful herein physically adhere to or associate with the surface of the nanoparticulate active agent but do not chemically react with the active agent or itself. Individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

**[0090]** The present invention also includes nanoparticulate active agent compositions, having poly(Lysine, Tryptophan) 4:1 hydrobromide as at least one surface stabilizer, formulated into compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers.

### A. Peptide Surface Stabilizer

**[0091]** The choice of a surface stabilizer is non-trivial and usually requires extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that poly(Lysine, Tryptophan) 4:1 hydrobromide used as a nanoparticulate surface stabilizer, yields stable nanoparticulate active agent compositions that exhibit low degrees of aggregation.

**[0092]** The compositions of the invention may comprise further peptides in addition to poly (Lysine, Tryptophan) 4:1 hydrobromide, as surface stabilizers

**[0093]** A "peptide" is defined as any compound consisting of two or more amino acids, which are the basic structural units or "building blocks" of peptides. All peptides in all species, from bacteria to humans, are constructed from the same set of twenty commonly occurring, genetically encoded amino acids, as shown in the table below.

**[0094]** Each amino acid contains an "amine" group ($NH_3$), a "carboxy" group (COOH), a hydrogen atom, and a distinctive R group, or sidechain, bonded to a carbon atom. The amino acids vary in their sidechains, with variations in size, shape, charge, hydrogen-bonding capacity, and chemical reactivity. *See e.g.,* L. Stryer, Biochemistry, 3rd Edition, 1-40 (W.H. Freeman & Co., NY, 1988).

| Amino Acid | 3 Letter Abbreviation | 1 Letter Abbreviation |
|---|---|---|
| alanine | ALA | A |
| asparagine | ASN | N |
| aspartic acid | ASP | D |
| arginine | ARG | R |
| cysteine | CYS | C |
| glutamic acid | GLU | E |
| glutamine | GLN | Q |
| glycine | GLY | G |
| histidine | HIS | H |
| isoleucine | ILE | I |
| leucine | LEU | L |
| lysine | LYS | K |
| methionine | MET | M |
| phenylalanine | PHE | F |
| proline | PRO | P |
| serine | SER | S |
| threonine | THR | T |
| tryptophan | TRP | W |

(continued)

| Amino Acid | 3 Letter Abbreviation | 1 Letter Abbreviation |
|---|---|---|
| tyrosine | TYR | Y |
| valine | VAL | V |
| aspartic acid or asparagines | ASX | |
| glutamic acid or glutamine | GLX | |
| Unknown or other | Xaa | X |

**[0095]** Peptides useful in the present invention can also comprise substituents other than amino acids. There are also naturally occurring chemical modifications of these twenty genetically encoded amino acids, such as hydroxylation of proline, addition of carbohydrates and lipids, and phosphorylation of serine and tyrosine. In addition, D-isomers of the amino acids, as opposed to the L-isomers found in naturally-occuring peptides and proteins, have been synthesized.

**[0096]** The amino acids of a peptide are connected by a amide, covalent linkage between the alpha carboxyl group of one amino acid and the alpha amino group of another amino acid. Many amino acids are joined by peptide bonds to form a polypeptide chain, which is unbranched. A polypeptide chain is a long peptide chain, consisting of a regularly repeating part, called the main chain, and a variable part, comprising the distinctive sidechains. Disulfide cross-links can be formed by cysteine residues in polypeptides. Most natural polypeptide chains contain between 50 and 2000 amino acids residues. The mean molecular weight of an amino acid residue is about 110 daltons, and so the molecular weights of most polypeptide chains are between 5500 and 220,000. *See e.g.,* L. Stryer, Biochemistry, 3rd Edition, p. 22 (W.H. Freeman & Co., NY, 1988).

**[0097]** A protein is a large macromolecule composed of one or more polypeptide chains. In, the context of the present invention, a "peptide" refers to a peptide or a polypeptide, but not a protein.

**[0098]** Preferably, the peptide surface stabilizers of the invention are water soluble. By "water soluble," it is meant that the peptide has a water solubility of greater than about 1 mg/mL, greater than about 10 mg/mL, greater than about 20 mg/mL, or greater than about 30 mg/mL. This is in contrast to prior art compositions teaching the use of a peptide as an active agent in a nanoparticulate active agent composition. *See e.g.,* U.S. Patent Nos. 6,270,806; 6,592,903; 6,428,814; and 6,375,986. In such prior art references, when a peptide is utilized as an active agent in a nanoparticulate composition, the peptide is *poorly water soluble.*

**[0099]** There is an extensive catalog of commercially available peptides that can be used in the compositions of the invention. For example, the on-line peptide catalog http://www.peptide-catalog.com/PC/Peptides provides a list of hundreds of commercially available peptides, along with their structure and molecular weight. In addition, to the many commercially available peptides, custom peptides can be made and utilized in the compositions of the invention.

**B. Secondary or Auxiliary Surface Stabilizers**

**[0100]** The compositions of the invention can also include one or more auxiliary non-peptide surface stabilizers in addition to poly(Lysine, Tryptophan) 4:1 hydrobromide as at least one peptide surface stabilizer.

**[0101]** The auxiliary surface stabilizers of the invention are preferably adsorbed on, or associated with, the surface of the active agent particles. The auxiliary surface stabilizers especially useful herein preferably do not chemically react with the active agent particles or itself. Preferably, individual molecules of the auxiliary surface stabilizer are essentially free of intermolecular cross-linkages.

**[0102]** Two or more auxiliary surface stabilizers can be employed in the compositions and methods of the invention.

**[0103]** Suitable surface stabilizers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred auxiliary surface stabilizers include nonionic, anionic, cationic, zwitterionic, and ionic surfactants.

**[0104]** Representative examples of secondary surface stabilizers include gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, poly-

vinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®; also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (*e.g.*, Aerosol OT®, which is a dioctyl ester of sodium sulfosuccinic acid (DOSS) (American Cyanamid)); Duponol P®, which is a sodium lauryl sulfate (DuPont); Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHO which is $C_{18}H_{37}CH_2C(O)N(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-derivatized phospholipid, PEG-derivatized cholesterol, PEG- derivatized cholesterol derivative, PEG-derivatized vitamin A, PEG-derivatized vitamin E, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

**[0105]** Examples of useful cationic surface stabilizers include but are not limited to polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, a charged phospholipid such as dimyristoyl phophatidyl glycerol, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammonium-bromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

**[0106]** Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quaternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, dodecyl trimethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, $C_{12\text{-}15}$dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl ($C_{12\text{-}18}$)dimethylbenzyl ammonium chloride, N-alkyl ($C_{14\text{-}18}$)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and ($C_{12\text{-}14}$) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl($C_{12\text{-}14}$) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, $C_{12}$, $C_{15}$, $C_{17}$ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quatemized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUA™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

**[0107]** Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, Cationic Surfactants: Analytical and Biological Evaluation (Marcel Dekker, 1994); P. and D. Rubingh (Editor), Cationic Surfactants: Physical Chemistry (Marcel Dekker, 1991); and J. Richmond, Cationic Surfactants: Organic Chemistry, (Marcel Dekker, 1990).

**[0108]** Particularly preferred nonpolymeric primary stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an immonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quaternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of $R_1$-$R_4$ are $CH_3$;
(ii) one of $R_1$-$R_4$ is $CH_3$;
(iii) three of $R_1$-$R_4$ are $CH_3$;
(iv) all of $R_1$-$R_4$ are $CH_3$;
(v) two of $R_1$-$R_4$ are $CH_3$, one of $R_1$-$R_4$ is $C_6H_5CH_2$, and one of $R_1$-$R_4$ is an alkyl chain of seven carbon atoms or less;
(vi) two of $R_1$-$R_4$ are $CH_3$, one of $R_1$-$R_4$ is $C_6H_5CH_2$, and one of $R_1$-$R_4$ is an alkyl chain of nineteen carbon atoms or more;
(vii) two of $R_1$-$R_4$ are $CH_3$ and one of $R_1$-$R_4$ is the group $C_6H_5(CH_2)_n$, where n>1;
(viii) two of $R_1$-$R_4$ are $CH_3$, one of $R_1$-$R_4$ is $C_6H_5CH_2$, and one of $R_1$-$R_4$ comprises at least one heteroatom;
(ix) two of $R_1$-$R_4$ are $CH_3$, one of $R_1$-$R_4$ is $C_6H_5CH_2$, and one of $R_1$-$R_4$ comprises at least one halogen;
(x) two of $R_1$-$R_4$ are $CH_3$, one of $R_1$-$R_4$ is $C_6H_5CH_2$, and one of $R_1$-$R_4$ comprises at least one cyclic fragment;
(xi) two of $R_1$-$R_4$) are $CH_3$ and one of $R_1$-$R_4$ is a phenyl ring; or
(xii) two of $R_1$-$R_4$ are $CH_3$ and two of $R_1$-$R_4$ are purely aliphatic fragments.

**[0109]** Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonum chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

**[0110]** Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 1986). The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

### C. Active Agents

**[0111]** The nanoparticles of the invention comprise at least one active, therapeutic, or diagnostic agent, collectively referred to as a "drug." A therapeutic agent can be a pharmaceutical agent, including biologics such as proteins, peptides, and nucleotides, or a diagnostic agent, such as a contrast agent, including x-ray contrast agents.

**[0112]** The active agent exists as a crystalline phase, an amorphous phase, a semi-amorphous phase, a semi-crystalline phase, or mixtures thereof. The crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as those described in EP Patent No. 275,796.

**[0113]** The invention can be practiced with a wide variety of active agents. The active agent is preferably present in an essentially pure form, is poorly soluble, and is dispersible in at least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol. A preferred liquid dispersion media is water.

**[0114]** Two or more active agents can be used in combination.

#### 1. Active Agents Generally

**[0115]** The active agent can be selected from a variety of known classes of drugs, including, for example, nutraceuticals, COX-2 inhibitors, retinoids, anticancer agents, NSAIDS, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antipakinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, par-

athyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

**[0116]** Examples of representative active agents useful in this invention include, but are not limited to, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, setraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

**[0117]** Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Robert et al., Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods (American Nutraceutical Association, 2001). A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body. Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, iso-leucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

**[0118]** Active agents to be administered in an aerosol formulation are preferably selected from the group consisting of proteins, peptide, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

**2. Anticancer Active Agents**

**[0119]** Useful anticancer agents are preferably selected from alkylating agents, antimetabolites, natural products, hormones and antagonists, and miscellaneous agents, such as radiosensitizers.

**[0120]** Examples of alkylating agents include: (1) alkylating agents having the bis-(2-chloroethyl)-amine group such as, for example, chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlorethaminoxide, cyclophosphamide, ifosfamide, and trifosfamide; (2) alkylating agents having a substituted aziridine group such as, for example, tretamine, thiotepa, triaziquone, and mitomycine; (3) alkylating agents of the alkyl sulfonate type, such as, for example, busulfan, piposulfan, and piposulfam; (4) alkylating N-alkyl-N-nitrosourea derivatives, such as, for example, carmustine, lomustine, semustine, or streptozotocine; and (5) alkylating agents of the mitobronitole, dacarbazine and procarbazine type.

**[0121]** Examples of antimetabolites include: (1) folic acid analogs, such as, for example, methotrexate; (2) pyrimidine analogs such as, for example, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, and flucytosine; and (3) purine derivatives such as, for example, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine.

**[0122]** Examples of natural products include: (1) vinca alkaloids, such as, for example, vinblastine and vincristine; (2) epipodophylotoxins, such as, for example, etoposide and teniposide; (3) antibiotics, such as, for example, adriamycine, daunomycine, doctinomycin, daunorubicin, doxorubicin, mithramycin, bleomycin, and mitomycin; (4) enzymes, such as, for example, L-asparaginase; (5) biological response modifiers, such as, for example, alpha-interferon; (6) camptothecin; (7) taxol; and (8) retinoids, such as retinoic acid.

**[0123]** Examples of hormones and antagonists include: (1) adrenocorticosteroids, such as, for example, prednisone; (2) progestins, such as, for example, hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate; (3) estrogens, such as, for example, diethylstilbestrol and ethinyl estradiol; (4) antiestrogens, such as, for example, tamoxifen; (5) androgens, such as, for example, testosterone propionate and fluoxymesterone; (6) antiandrogens, such as, for example, flutamide; and (7) gonadotropin-releasing hormone analogs, such as, for example, leuprolide.

**[0124]** Examples of miscellaneous agents include: (1) radiosensitizers, such as, for example, 1,2,4-benzotriazin-3-amine 1,4-dioxide (SR 4889) and 1,2,4-benzotriazine-7-amine 1,4-dioxide (WIN 59075); (2) platinum coordination complexes such as cisplatin and carboplatin; (3) anthracenediones, such as, for example, mitoxantrone; (4) substituted

ureas, such as, for example, hydroxyurea; and (5) adrenocortical suppressants, such as, for example, mitotane and aminoglutethimide.

**[0125]** In addition, the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide.

**[0126]** The anticancer agent can also be a COX-2 inhibitor.

### 3. Analgesic Active Agents

**[0127]** An analgesic can be, for example, an NSAID or a COX-2 inhibitor.

**[0128]** Exemplary NSAIDS that can be formulated in compositions of the invention include, but are not limited to, suitable nonacidic and acidic compounds: Suitable nonacidic compounds include, for example, nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, and dapsone. Suitable acidic compounds include, for example, carboxylic acids and enolic acids. Suitable carboxylic acid NSAID include, for example: (1) salicylic acids and esters thereof, such as aspirin, diflunisal, benorylate, and fosfosal; (2) acetic acids, such as phenylacetic acids, including diclofenac, alclofenac, and fenclofenac; (3) carbo- and heterocyclic acetic acids such as etodolac, indomethacin, sulindac, tolmetin, fentiazac, and tilomisole; (4) propionic acids, such as carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, and pirprofen; and (5) fenamic acids, such as flufenamic, mefenanic, meclofenamic, and niflumic. Suitable enolic acid NSAIDs include, for example: (1) pyrazolones such as oxyphenbutazone, phenylbutazone, apazone, and feprazone; and (2) oxicams such as piroxicam, sudoxicam, isoxicam, and tenoxicam.

**[0129]** Exemplary COX-2 inhibitors that can be formulated in combination with the nanoparticulate nimesulide composition of the invention include, but are not limited to, celecoxib (SC-58635, CELEBREX®, Pharmacia/Searle & Co.), rofecoxib (MK-966, L-748731, VIOXX®, Merck & Co.), meloxicam (MOBIC®, co-marketed by Abbott Laboratories, Chicago, IL, and Boehringer Ingelheim Pharmaceuticals), valdecoxib (BEXTRA®, G.D. Searle & Co.), parecoxib (G.D. Searle & Co.), etoricoxib (MK-663; Merck), SC-236 (chemical name of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)] benzenesulfonamide; G.D. Searle & Co., Skokie, IL); NS-398 (N-(2-cyclohexyloxy-4-nitrophenyl)methane sulfonamide; Taisho Pharmaceutical Co., Ltd., Japan); SC-58125 (methyl sulfone spiro(2.4)hept-5-ene I; Pharmacia/Searle & Co.); SC-57666 (Pharmacia/Searle & Co.); SC-558 (Pharmacia/Searle & Co.); SC-560 (Pharmacia/Searle & Co.); etodolac (Lodine®, Wyeth-Ayerst Laboratories, Inc.); DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl) phenyl 2(5H)-furanone); monteleukast (MK-476), L-745337 ((5-methanesulphonamide-6-(2,4-difluorothio-phenyl)-1-indanone), L-761066, L-761000, L-748780 (all Merck & Co.); DUP-697 (5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl) phenyl; DuPont Merck Pharmaceutical Co.); PGV 20229 (1-(7-tert.-butyl-2,3-dihydro-3,3-dimethylbenzo(b)furan-5-yl)-4-cyclopropylbutan-1-one; Procter & Gamble Pharmaceuticals); iguratimod (T-614; 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1- benzopyran-4-one; Toyama Corp., Japan); BF 389 (Biofor, USA); CL 1004 (PD 136095), PD 136005, PD 142893, PD 138387, and PD 145065 (all Parke-Davis/Warner-Lambert Co.); flurbiprofen (ANSAID®; Pharmacia & Upjohn); nabumetone (FELAFEN®; SmithKline Beecham, plc); flosulide (CGP 28238; Novartis/Ciba Geigy); piroxicam (FELDANE®; Pfizer); diclofenac (VOLTAREN® and CATAFLAM®, Novartis); lumiracoxib (COX-189; Novartis); D 1367 (Celltech Chiroscience, plc); R 807 (3 benzoyldifluoromethane sulfonanilide, diflumidone); JTE-522 (Japan Tobacco, Japan); FK-3311 (4'-Acetyl-2'-(2,4-difluorophenoxy)methanesulfonanilide), FK 867, FR 140423, and FR 115068 (all Fujisawa, Japan); GR 253035 (Glaxo Wellcome); RWJ 63556 (Johnson & Johnson); RWJ 20485 (Johnson & Johnson); ZK 38997 (Schering); S 2474 ((E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide indomethacin; Shionogi & Co., Ltd., Japan); zomepirac analogs, such as RS 57067 and RS 104897 (Hoffmann La Roche); RS 104894 (Hoffmann La Roche); SC 41930 (Monsanto); pranlukast (SB 205312, Ono-1078, ONON®, ULTAIR®; SmithKline Beecham); SB 209670 (SmithKline Beecham); and APHS (heptinylsulfide).

### D. Nanoparticulate Active Agent Particle Size

**[0130]** The compositions of the invention contain nanoparticulate active agent particles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments of the invention, the active agent particles have a size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

**[0131]** By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% by weight of the active agent particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. In other embodiments of the invention, at least about

70%, at least about 90%, at least about 95%, or at least about 99% of the active agent particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*

**[0132]** If the nanoparticulate active agent composition is combined with a conventional active agent composition, then such a composition is either solubilized or has an effective average particle size greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the microparticulate active agent particles have a particle size greater than about 2 microns, by weight, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 90%, at least about 95%, or at least about 99%, by weight, of the microparticulate active agent particles have a particle size greater than about 2 microns.

**[0133]** In the present invention, the value for D50 of a nanoparticulate active agent composition is the particle size below which 50% of the active agent particles fall, by weight. Similarly, D90 and D99 are the particle sizes below which 90% and 99%, respectively, of the active agent particles fall, by weight.

**5. Concentration of Nanoparticulate Active Agent and poly(Lysine, Tryptophan) 4:1 hydrobromide**

**[0134]** The relative amounts of active agent and poly(Lysine, Tryptophan) 4:1 hydrobromide and optionally one or more secondary surface stabilizers, can vary widely. The optimal amount of the individual components can depend, for example, upon the particular active agent selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc*.

**[0135]** The concentration of the peptide surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the at least one active agent and poly(Lysine, Tryptophan) 4:1 hydrobromide not including other excipients.

**[0136]** The concentration of the at least one active agent can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the active agent and poly(Lysine, Tryptophan) 4:1 hydrobromide not including other excipients.

**B. Methods of Making Nanoparticulate Active Agent Formulations**

**[0137]** The nanoparticulate active agent compositions of the invention, comprising poly(Lysine, Tryptophan) 4:1 hydrobromide can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the 684 patent. Methods of making nanoparticulate active agent compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation".

**[0138]** The resultant nanoparticulate active agent compositions can be utilized in any desired dosage form.

**1. Milling to obtain Nanoparticulate Active Agent Dispersions**

**[0139]** Milling the active agent to obtain a nanoparticulate dispersion comprises dispersing active agent particles in a liquid dispersion media in which the active agent is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the active agent to the desired effective average particle size. The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. Water is a preferred dispersion media.

**[0140]** The active agent particles are preferably reduced in size in the presence of the poly(Lysine, Tryptophan) 4:1 hydrobromide. Alternatively, the active agent particles can be contacted with poly(Lysine, Tryptophan) 4:1 hydrobromide either during or after attrition. One or more secondary surface stabilizers may also be added before, during, or after attrition, Other compounds, such as a diluent, can be added to the active agent/peptide surface stabilizer composition before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

**2. Precipitation to Obtain Nanoparticulate** Active Agent Compositions

**[0141]** Another method of forming the desired nanoparticulate active agent composition is by microprecipitation. This

is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more peptide surface stabilizers including poly(Lysine, Tryptophan) 4:1 hydrobromide and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the poorly soluble active agent in a suitable solvent; (2) adding the formulations from step (1) to a solution comprising at least poly(Lysine, Tryptophan) 4:1 hydrobromide as peptide surface stabilizer and optionally one or more secondary surface stabilizers, to form a clear solution; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

**3. Homogenization to Obtain Nanoparticulate Active Agent Compositions**

**[0142]** Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

**[0143]** Such a method comprises dispersing active agent particles in a liquid dispersion media in which the active agent is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the active agent to the desired effective average, particle size. The active agent particles can be reduced in size in the presence of poly(Lysine, Tryptophan) 4:1 hydrobromide as at least one peptide surface stabilizer and, if desired, one or more additional surface stabilizers. Alternatively, the active agent particles can be contacted with poly(Lysine, Tryptophan) 4:1 hydrobromide and, if desired, one or more additional surface stabilizers, either during or after attrition. Other compounds, such as a diluent, can be added to the active agent/peptide surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

**C. Methods of Using Nanoparticulate Active Agent Formulations**

**[0144]** The nanoparticulate active agent compositions of the present invention can be administered to humans and animals via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (powders, ointments or drops), or as a buccal or nasal spray.

**[0145]** Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. 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 dispersions, and by the use of surfactants.

**[0146]** The nanoparticulate active agent compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

**[0147]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carrier), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

**[0148]** Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agent, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

**[0149]** Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying

and suspending agents, sweetening, flavoring, and perfuming agents.

**[0150]** Actual dosage levels of active agent in the nanoparticulate compositions of the invention may be varied to obtain an amount of active agent that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered active agent, the desired duration of treatment, and other factors.

**[0151]** Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body weight, general health, sex, diet, time and route of administration, potency of the administered active agent, rates of absorption and excretion, combination with other active agents, and the severity of the particular disease being treated.

**[0152]** The following examples, with the exception of Example 1 to 3, are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples.

**[0153]** Examples 1 to 3 are retained for reasons of clarity and for a fuller understanding of the invention.

**[0154]** The formulations in the examples that follow were also investigated using a light microscope. Here, "stable" nanoparticulate dispersions (uniform Brownian motion) were readily distinguishable from "aggregated" dispersions (relatively large, nonuniform particles without motion).

## Example 1

**[0155]** The purpose of this example was to prepare a nanoparticulate nystatin composition having poly(Lysine, Tryptophan) 4:1 hydrobromide as a peptide surface stabilizer.

**[0156]** Nystatin is a poorly water-soluble antimycotic polyene antibiotic obtained from *Streptomyces noursei.* It is an antifungal agent indicated for oral, gastrointestinal, and vaginal candidiasis. Oral candidiasis, in particular, is a common affliction of immunocompromised patients. Nystatin is indicated in the therapy of all infections caused by susceptible microorganisms in those patients in whom candidal (monilial) infections are most likely to complicate therapy.

**[0157]** A slurry of 2% (w/w) nystatin (Sigma-Aldrich Co.) and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide ("Poly(Lys,Trp)") (Sigma; St Louris, MO), which is a cationic random co-polyamino acid having a molecular weight of 38,000, in water was milled for 1 day using low energy (ball milling) techniques in the presence of ceramic YTZ grinding media.

**[0158]** The mean size of the nystatin particles following milling was 149 nm, with a D90 of 270 nm, as determined by static light scattering using a Horiba LA-910 light-scattering particle size analyzer (Horiba Instruments, Irvine, CA). The composition had a zeta potential of 47.7 mV, as measured by electrophoresis in $5\times10^{-4}$ M NaCl (Malvern ZetaSizer). Dispersibility was verified by phase contrast microscopy.

**[0159]** Figure 1 shows representative photomicrographs of the nystatin crystals before (Fig. 1A) and after (Fig. 1B) milling.

**[0160]** Particle size stability under controlled conditions was monitored over time. Figure 2 shows the results of monitoring the nystatin particle size stability over time at 5°C (solid line), 25°C (dashed line), and 40°C (dotted line) for the nanoparticulate nystatin/peptide composition.

**[0161]** These results demonstrate that a peptide surface stabilizer can be successfully used to stabilize an active agent at a nanoparticulate particle size. Moreover, such a peptide surface stabilizer may confer additional therapeutic advantages to the final formulation. For example, the peptide surface stabilizer Poly(Lys,Trp) is cationic and, therefore, nanoparticulate active agent compositions utilizing this surface stabilizer will be bioadhesive.

**[0162]** The resultant composition exhibited a mean particle sizes of 149 nm and were free of agglomeration. Moreover, the nanoparticulate nystatin/peptide composition exhibited virtually no particle size growth at all three temperatures tested.

## Example 2

**[0163]** The purpose of this example was to determine whether a cationic surface charge, such as that obtained with the use of a cationic peptide surface stabilizer, enhances the adhesion of small particles to cells.

**[0164]** Cell-binding experiments were performed with polystyrene latex microspheres as a model. A positive surface charge would be expected to enhance the interaction of particles with cell-surface macromolecules, which have a net negative charge.

**[0165]** Cationic microspheres with a mean zeta-potential (51.5 mV) comparable to the nanoparticulate nystatin/peptide composition of Example 1 were tested against anionic microspheres (mean zeta-potential = -50.9 mV). The microspheres were incubated with NIH/3T3 fibroblasts, washed thoroughly, fixed, and subjected to SEM analysis.

**[0166]** Figure 3 shows representative micrographs of cells with anionic particles (Fig. 3A) and cationic particles (Fig. 3B).

**[0167]** The results indicate that positively-charged particles interact more strongly with the cell surface than negatively-

charged particles, and it is believed that nanoparticulate active agent compositions having a cationic peptide as a surface stabilizer with comparable zeta potentials will follow the same trend.

**Example 3**

**[0168]** The purpose of this example was to determine if milling of an active agent, such as nystatin, having a peptide surface stabilizer affects the active agent's activity.

**[0169]** The minimum inhibitory concentration (MIC) of a milled nystatin composition having as a peptide surface stabilizer Poly(Lys, Trp) was compared to the MIC of two unmilled nystatin compositions. Nystatin for the milled nanoparticulate composition was obtained from Sigma-Aldrich Co. and the two unmilled nystatin compositions were obtained from Sigma-Aldrich Co. and Paddock Laboratories, Inc. Details regarding the milled and unmilled nystatin compositions are given in Table 1 below, including particle size of the milled nanoparticulate nystatin/Poly(Lys, Trp) composition and the potency (USP U/ml) and MIC for each nystatin composition.

**TABLE 1**

| Nystatin Concentration | Surface Stabilizer and Concentration | Mean Particle Size (nm) | Potency (USP U/ml) | MIC |
|---|---|---|---|---|
| 2% (Sigma) | 1% Poly(Lys, Trp) [1] | 129 | 101,200 | 1:10,000 |
| | | | | |
| 5% (Sigma) | N/A-unmilled | N/A | 253,000 | 1:10,000 |
| 4% (Paddock) | N/A - unmilled | N/A | 253,000 | 1:100,000 |
| [1]Poly(Lysine, Tryptophan) is a cationic random co-polyamino acid. | | | | |

The nanoparticulate sample was ball milled for 26 hours with ceramic YTZ milling media.

**[0170]** The minimum inhibitory concentration (MIC) of the milled nystatin/peptide composition and the two unmilled samples were determined in cultures of C. *albicans.* MIC as reported here is the maximum dilution of formulation in culture broth which inhibits growth of C *albicans.* As shown in Table 1, above, the milled nystatin/peptide composition did not exhibit any significant differences in MIC, and surprisingly, was more active than at least one of the unmilled nystatin samples. These data confirm that the milling process does not decrease the activity of nystatin.

**Example 4**

**[0171]** The purpose of this example was to prepare a nanoparticulate composition of a diuretic, Compound A, utilizing a peptide surface stabilizer. Diuretics can be used to reduce the swelling and fluid retention caused by various medical problems, including heart or liver disease. They are also is used to treat high blood pressure.

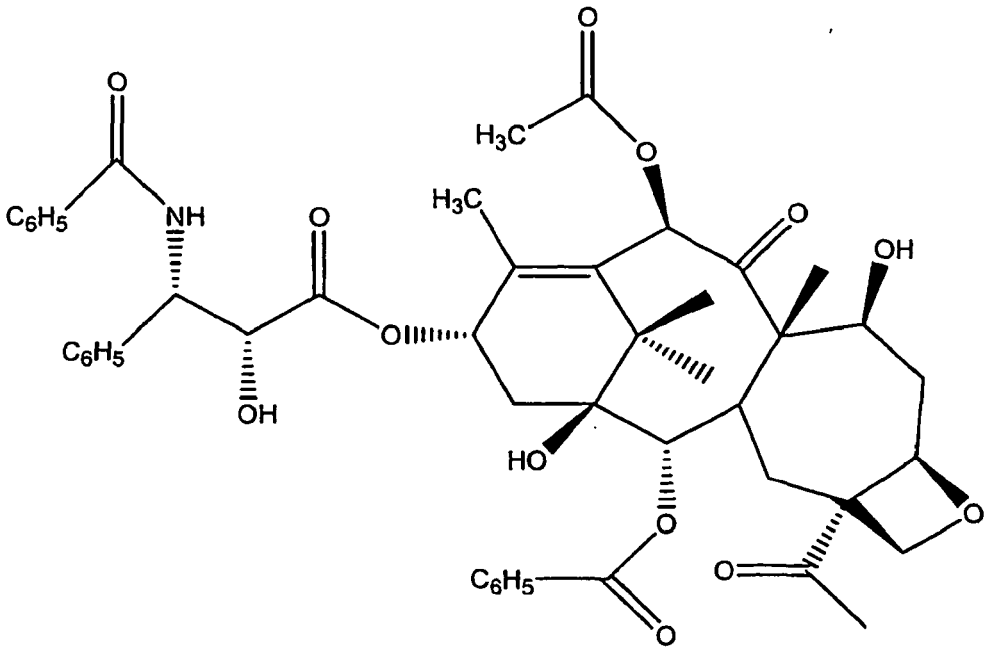
**[0172]** A slurry of 2% (w/w) Compound A and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide as a peptide surface stabilizer in water was milled for 3 days in an aqueous environment in a low energy mill, in the presence of 0.8 mm yttrium-stabilized ceramic media.

**[0173]** Particle size analysis of the resulting Compound A dispersion was conducted via laser light diffraction using the Horiba LA 910 particle size analyzer (Horiba Instruments, Irvine, CA) and water as a diluent. The mean particle size of the milled Compound A dispersion was 99 nm, with a D90 of 138 nm. The composition was stable.

**Example 5**

**[0174]** The purpose of this example was to prepare a nanoparticulate composition of paclitaxel utilizing a peptide surface stabilizer. Paclitaxel belongs to the group of medicines called antineoplastics. It is used to treat cancer of the ovaries, breast, certain types of lung cancer, and a cancer of the skin and mucous membranes more commonly found in patients with acquired immunodeficiency syndrome (AIDS). It may also be used to treat other kinds of cancer.

**[0175]** Paclitaxel has the following chemical structure:



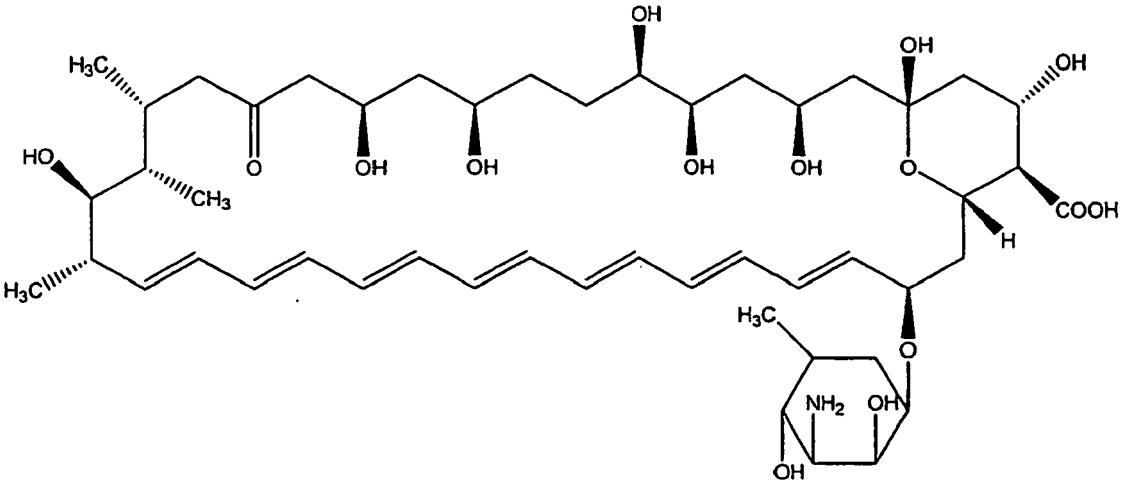
**[0176]** A slurry of 2% (w/w) paclitaxel and 1% (w/w) poly(Lysine, Tryptophan) 4:1 hydrobromide as a peptide surface stabilizer in water was milled for 3 days in an aqueous environment in a low energy mill, in the presence of 0.8 mm yttrium-stabilized ceramic media.

**[0177]** Particle size analysis of the resulting paclitaxel dispersion was conducted via laser light diffraction using the Horiba LA 910 particle size analyzer (Horiba Instruments, Irvine, CA) and water as a diluent. The mean particle size of the milled paclitaxel dispersion was 139 nm, with a D90 of 185 nm. The composition was stable.

**Example 6**

**[0178]** The purpose of this example was to prepare a nanoparticulate composition of amphotericin B utilizing a peptide surface stabilizer. Amphotericin B is a poorly water soluble antifungal agent. Topically, it is used to treat skin yeast infections; intravenously, it is used to treat a variety of life-threatening fungal infections.

**[0179]** Amphotericin B has the following chemical structure:



**[0180]** In this experiment, amphotericin B was milled with Poly (Lys, Trp) 4:1 Hydrobromide as a peptide surface stabilizer. A 2% (w/w) slurry of amphotericin B (Sigma) in water was prepared with 1% (w/w) poly (Lys, Trp) (Sigma). The composition was ball-milled for 24 hours with 0.8 mm ceramic YTZ milling media. The particle size of the resulting

amphotericin B dispersion was characterized by static laser light scattering on a Horiba LA-910 particle size distribution analyzer. The results are shown in Table 2, below.

**TABLE 2**

| Drug and Concentration | Surface Stabilizer and Concentration | Mean Particle Size (nm) | D50 (nm) | D90 (nm) |
|---|---|---|---|---|
| 2% Amphotericin B | 1% Poly(Lys, Trp) | 121 | 96 | 230 |

**[0181]** These results demonstrate that amphotericin B dispersions can be successfully stabilized by a peptide surface stabilizer, such as the random copolypeptide poly (Lys, Trp) 4:1 Hydrobromide.

**[0182]** It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

## Claims

**1.** A composition comprising:

(a) particles of at least one active agent having an effective average particles size of less than about 2000nm; and
(b) poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer, wherein the composition does not comprise nystatin or a salt thereof.

**2.** The composition of claim 1 further comprising at least one secondary surface stabilizer.

**3.** The composition of claim 2 wherein the secondary surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

**4.** The composition of claim 2 or claim 3, wherein the secondary surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid,dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamid, n-decyl-β-D-glucopyranoside; n-decyl-β-D-maltopyranoside, n-dodecyl-β-D-glucopyranoside, n-dodecyl-β-D-maltoside; Heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, $C_{12-15}$dimethyl hydroxyethyl ammonium chloride, $C_{12-15}$dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl ($C_{12-18}$)dimethylbenzyl ammonium chloride, N-alkyl ($C_{14-18}$)dimethyl-benzyl ammonium

chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and ($C_{12-14}$) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkydialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl($C_{12-14}$) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, $C_{12}$ trimethyl ammonium bromides, $C_{15}$ trimethyl ammonium bromides, $C_{17}$ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAG), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium, bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxythylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

**5.** The composition of any one of claims 1 to 4, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

**6.** The composition of any one of claims 1 to 5 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, tablets, capsules, sachets, lozenges, powders, pills, granules, controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulation, and mixed immediate release and controlled release formulations.

**7.** The composition of any one of claim 1 to 6, wherein:

(a) the active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the active agent and the poly(Lysine, Tryptophan) 4:1 hydrobromide not including other excipients; or
(b) the poly(Lysine, Tryptophan) 4:1 hydrobromide is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99-5% by weight, based on the total combined dry weight of the active agent and the poly(Lysine, Tryptophan) 4:1 hydrobromide not including other excipients.

**8.** The composition of any one of claims 1 to 7, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

**9.** The composition of any one of claims 1 to 8, wherein the effective average particle size of the active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 mn, less than about 1400 mn, less than about 1300 mn, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less man about 500 nm, less than about 400 nm, less than about 300 mn, less than about 250 mn, less than about 200 mn, less than about 100 nm, less than about 75 mn, and less than about 50 mn.

**10.** The composition of any one of claims 1 to 9, wherein at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the active agent particles have a particle size less than the effective average particle size.

**11.** The composition of any one of claims 1 to 10, further comprising at least one additional active agent composition having an effective average particle size which is different that the effective average particle size of the active agent composition of claim 1.

**12.** The composition of any one of claims 1 to 11, wherein the active agent is selected from the group consisting of paclitaxel amphotericin B, a diuretic, a dermal agent, nutraceuticals, COX-2 inhibitors, retinoids, anticancer agents,

NSAIDS, proteins, peptides, nucleotides, anti-obesity drugs, dietary supplements, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazern, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenalate, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

**13.** The composition of claim 12, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

**14.** The composition of claim 12, wherein the anticancer agent is selected from the group consisting of alkylating agents, antimetabolites, anthracenediones, natural products, hormones, antagonists, radiosensitizers, platinum coordination complexes, adrenocortical suppressants, immunosuppressive agent, substituted ureas, and COX-2 inhibitors.

**15.** The composition of claim 14, wherein:

(a) the alkylating agent is selected from the group consisting of chlormethine, chlorambucile, melphalan, uramustine, mannomustine, extramustinephoshate, mechlore-thaminoxide, cyclophosphamide, ifosfamide, trifosfamide, tretamine, thiotepa, triaziquone, mitomycine, busulfan, piposulfan, piposulfam, carmustine, lomustine, semustine, streptozotocine, mitobronitole, dacarbazine and procarbazine; or
(b) the antimetabolite is selected from the group consisting of methotrexate, fluorouracil, floxuridine, tegafur, cytarabine, idoxuridine, flucytosine, mercaptopurine, thioguanine, azathioprine, tiamiprine, vidarabine, pentostatin, and puromycine; or
(c) the natural product is selected from the group consisting of vinblastine, vincristine, etoposide, teniposide, adriamycine, daunomycine, doctinomycin, daunorubicin, doxarubicin, mithramycin, bleomycin, mitomycin, L-asparaginase, alpha-interferon, camptothecin, taxol, and retinoic acid; or
(d) the hormone or antagonist is selected from the group consisting of prednisone, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, ethinyl estradiol, tamoxifen, testosterone propionate, fluoxymesterone, flutamide, leuprolide; or
(e) the anticancer agent is selected from the group consisting of cisplatin, carboplatin, mitoxantrone,hydroxyurea, mitotane, aminoglutethimide, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide.

**16.** The composition of claim 12, wherein the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

**17.** The composition of claim 12, wherein the COX-2 inhibitor is selected from the group consisting of nimesulide, celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, flurbiprofen, nabumetone, etodolac, iguratimod, flosulide, piroxicam, diclofenac, humiracoxib, monteleukast, pranlukast, heptinylsulfide, SC-236, SC-58125, SC-

57666, SC-558, SC-560, SC 41930, NS-398, DFU, L-745337, L-761066, L-761000, L-748780, DUP-697, PGV 20229, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, RS 57067, RS 104897, RS 104894, and SB 209670.

**18.** The composition of any one of claims 1 to 17 wherein upon administration in a mammal the active agent particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

**19.** The composition of any one of claims 1 to 18, wherein the composition redisperses in a biorelevant media such that the active agent particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

**20.** The composition of claim 19,wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

**21.** The composition of any one of claims 1 to 20, wherein:

(a) the $T_{max}$ of the active agent, when assayed in the plasma of a mammalian subject following administration, is less than the $T_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; or
(b) the $C_{max}$ of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the $C_{max}$ for a non-nanoparticulate composition of the same active agent, administered at the same dosage; or
(c) the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same active agent, administered at the same dosage.

**22.** The composition of claim 21, wherein the $T_{max}$ is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the $T_{max}$ exhibited by a non-nanoparticulate composition of the same active agent, administered at the same dosage.

**23.** The composition of claim 21, wherein the $C_{max}$ is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the $C_{max}$ exhibited by a non-nanoparticulate composition of the same active agent, administered at the same dosage.

**24.** The composition of claim 21, wherein the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%,at least about 225%, at least about 250%, at least about 275%,at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 650%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at

least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate composition of the same active agent, administered at the same dosage.

**25.** The composition of any one of claims 1 to 24 which does not produce signficantly different absorption levels when administered under fed as compared to fasting conditions.

**26.** The composition of claim 25, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

**27.** The Composition of any one of claims 1 to 26, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

**28.** The composition of claim 27, wherein "bioequivalency" is established by:

(a) a 90% Confidence Interval of between 0.80 and 1.26 for both $C_{max}$ and AUC; or
(b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for $C_{max}$.

**29.** The composition of any one of claims 1 to 28, formulated into a liquid dosage form and having a viscosity at a shear rate of 0.1 (1/s), measured at 20°C, selected from the group consisting of less than about 2000 mPa·s, from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about I mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mpa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

**30.** The composition of claim 29, wherein the viscosity of the dosage from is:

(a) selected from the goup consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent; or
(b) selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a liquid dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent

**31.** The composition of any one of claims 1 to 30, further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

**32.** A composition according to any one of claims 1 to 31 for use in therapy.

**33.** A method of making a composition according to any one of claims 1 to 32, comprising contacting particles of at least one active agent with poly(Lysine, Tryptophan) 4:1 hydrobromide for a time and under conditions sufficient to provide an active agent composition having an effective average particle size of less than about 2000 nm.

## Patentansprüche

1. Zusammensetzung, umfassend:

   (a) Partikel mindestens eines Wirkstoffs mit einer effektiven durchschnittlichen Partikelgröße von weniger als etwa 2000 nm; und
   (b) Poly(Lysin, Tryptophan-) 4:1 Hydrobromid als Oberflächenstabilisator, wobei die Zusammensetzung kein Nystatin oder ein Salz davon umfasst.

2. Zusammensetzung nach Anspruch 1, ferner umfassend mindestens einen sekundären Oberflächenstabilisator.

3. Zusammensetzung nach Anspruch 2, wobei der sekundäre Oberflächenstabilisator ausgewählt ist aus der Gruppe bestehend aus einem anionischen Oberflächenstabilisator, einem kationischen Oberflächenstabilisator, einem zwitterionischen Oberflächenstabilisator und einem ionischen Oberflächenstabilisator.

4. Zusammensetzung nach Anspruch 2 oder Anspruch 3, wobei der sekundäre Oberflächenstabilisator ausgewählt ist aus der Gruppe bestehend aus Cetylpyridiniumchlorid, Gelatine, Casein, Phosphatiden, Dextran, Glycerin, Akaziengummi, Cholesterin, Tragant, Stearinsäure, Benzalkoniumchlorid, Calciumstearat, Glycerinmonostearat, Cetostearylalkohol, Cetomacrogol-Emulgierwachs, Sorbitanestern, Polyoxyethylenalkylethern, Polyoxyethylenrizinusölderivaten, Polyoxyethylensorbitanfettsäureestern, Polyethylenglycolen, Dodecyltrimethylammoniumbromid, Polyoxyethylenstearaten, kolloidalem Siliziumdioxid, Phosphaten, Natriumdodecylsulfat, Carboxymethylcellulose-Calcium, Hydroxypropylcellulosen, Hypromellose, Carboxymethylcellulose-Natrium, Methylcellulose, Hydroxyethylcellulose, Hypromellosephthalat, nichtkristalliner Cellulose, Magnesium-Aluminium-Silikat, Triethanolamin, Polyvinylalkohol, Polyvinylpyrrolidon, 4-(1,1,3,3-Tetramethylbutyl)-Phenolpolymer mit Ethylenoxid und Formaldehyd, Poloxameren, Poloxaminen, einem geladenen Phospholipid, Dioctylsulfosuccinat, Dialkylestern der Natriumsulfobernsteinsäure, Natriumlaurylsulfat, Alkylarylpolyethersulfonaten, Gemischen von Sucrosestearat und Sucrosedistearat, p-Isononylphenoxypoly-(glycidol), Decanoyl-N-methylglucamid, n-Decyl-β-D-glucopyranosid, n-Decyl-β-D-maltopyranosid, n-Dodecyl-β-D-glucopyranosid, n-Dodecyl-β-D-maltosid, Heptanoyl-N-methylglucamid, n-Heptyl-β-D-glucopyranosid, n-Heptyl-β-D-thioglucosid, n-Hexyl-β-D-glucopyranosid, Nonanoyl-N-methylglucamid, n-Noyl-β-D-glucopyranosid, Octanoyl-N-methylglucamid, n-Octyl-β-D-glucopyranosid, Octyl-β-D-thioglucopyranosid, Lysozym, PEG-Phospholipid, PEG-Cholesterin, PEG-Cholesterinderivat, PEG-Vitamin A, statistischen Copolymeren aus Vinylacetat und Vinylpyrrolidon, einem kationischen Polymer, einem kationischen Biopolymer, einem kationischen Polysaccharid, einer kationischen Cellulose, einem kationischen Alginat, einer kationischen nichtpolymeren Verbindung, kationischen Phospholipiden, kationischen Lipiden, Polymethylmethacrylattrimethylammoniumbromid, Sulfoniumverbindungen, Polyvinylpyrrolidon-2-dimethylaminoethylmethacrylatdimethylsulfat, Hexadecyltrimethylammoniumbromid, Phosphoniumverbindungen, quartären Ammoniumverbindungen, Benzyl-di(2-chloroethyl)ethylammoniumbromid, Kokostrimethylammoniumchlorid, Kokostrimethylammoniumbromid, Kokosmethyldihydroxyethylammoniumchlorid, Kokosmethyldihydroxyethylammoniumbromid, Decyltriethylammoniumchlorid, Decyldimethylhydroxyethylammoniumchlorid, Decyldimethylhydroxyethylammoniumchloridbromid, $C_{12-15}$-Dimethylhydroxyethylammoniumchlorid, $C_{12-15}$-Dimethylhydroxyethylammoniumchloridbromid, Kokosdimethylhydroxyethylammoniumchlorid, Kokosdimethylhydroxyethylammoniumbromid, Myristyltrimethylammoniummethylsulfat, Lauryldimethylbenzylammoniumchlorid, Lauryldimethylbenzylammoniumbromid, Lauryldimethyl(ethenoxy)$_4$-ammoniumchlorid, Lauryldimethyl(ethenoxy)$_4$-ammoniumbromid, N-Alkyl($C_{12-18}$)dimethylbenzylammoniumchlorid, N-Alkyl($C_{14-18}$)dimethylbenzylammoniumchlorid, N-Tetradecyldimethylbenzylammoniumchlorid Monohydrat, Dimethyldidecylammoniumchlorid, N-Alkyl und ($C_{12-14}$)Dimethyl-1-Napthylmethylammoniumchlorid, Trimethylammoniumhalogenid, Alkyltrimethylammoniumsalzen, Dialkyldimethylammoniumsalzen, Lauryltrimethylammoniumchlorid, ethoxyliertem Alkylamidoalkyldialkylammoniumsalz, einem ethoxylierten Trialkylammoniumsalz, Dialkylbenzoldialkylammoniumchlorid, N-Didecyldimethylammoniumchlorid, N-Tetradecyldimethylbenzylammoniumchlorid-Monohydrat, N-Alkyl ($C_{12-14}$)dimethyl 1-naphthylmethylammoniumchlorid, Dodecyldimethylbenzylammoniumchlorid, Dialkylbenzolalkylammoniumchlorid, Lauryltrimethylammoniumchlorid, Alkylbenzylmethylammoniumchlorid, Alkylbenzyldimethylammoniumbromid, $C_{12}$-Trimethylammoniumbromiden, $C_{15}$-Trimethylammoniumbromiden, $C_{17}$-Trimethylammoniumbromiden, Dodecylbenzyltriethylammoniumchlorid, Polydiallyldimethylammoniumchlorid (DADMAC), Dimethylammoniumchloriden, Alkyldimethylammoniumhalogeniden, Tricetylmethylammoniumchlorid, Decyltrimethylammoniumbromid, Dodecyltriethylammoniumbromid, Tetradecyltrimethylammoniumbromid, Methyltrioctylammoniumchlorid, POLYQUAT 10™, Tetrabutylammoniumbromid, Benzyltrimethylammoniumbromid, Cholinestern, Benzalkoniumchlorid, Stearalkoniumchlorid-Verbindungen, Cetylpyridiniumbromid, Cetylpyridiniumchlorid, Halogensalzen quartärer Polyoxyethylalkylamine, MIRAPOL™, ALKAQUAT™, Alkylpyridiniumsalzen, Aminen, Aminsalzen, Aminoxiden, Imidazoliniumsalzen, protonierten quartären Acrylamiden, methylierten quartären Polymeren und kationi-

schem Guar.

5. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei die Zusammensetzung formuliert ist zur Verabreichung, ausgewählt aus der Gruppe bestehend aus oraler, pulmonaler, rektaler und ophthalmologischer Verabreichung, Verabreichung über den Kolon, parenteraler, intrazisternaler, intravaginaler, intraperitonealer, lokaler, buccaler, nasaler und topischer Verabreichung.

6. Zusammensetzung nach einem derAnsprüche 1 bis 5, formuliert in eine Darreichungsform, ausgewählt aus der Gruppe bestehend aus flüssigen Dispersionen, oralen Suspensionen, Gelen, Aerosolen, Salben, Cremes, Tabletten, Kapseln, Tütchen, Pastillen, Pudern, Pillen, Granulaten, Formulierungen mit kontrollierter Freisetzung, schnell schmelzenden Formulierungen, lyophilisierten Formulierungen, Formulierungen mit verzögerter Freisetzung, Formulierungen mit verlängerter Freisetzung, Formulierungen mit pulsatiler Freisetzung und Formulierungen mit einer Mischung aus sofortiger und kontrollierter Freisetzung.

7. Zusammensetzung nach einem derAnsprüche 1 bis 6, wobei:

(a) der Wirkstoff in einer Menge enthalten ist, ausgewählt aus der Gruppe bestehend aus von etwa 99,5 Gew.-% bis etwa 0,001 Gew.-%, von etwa 95 Gew.-% bis etwa 0,1 Gew.-% und von etwa 90 Gew.-% bis etwa 0,5 Gew.-%, ausgehend vom gesamten kombinierten Trockengewicht des Wirkstoffs und des Poly(Lysin, Tryptophan)- 4:1 Hydrobromids, andere Hilfsstoffe nicht eingeschlossen, oder
(b) das Poly(Lysin, Tryptophan)- 4:1 Hydrobomid in einer Menge enthalten ist, ausgewählt aus der Gruppe bestehend aus von etwa 0,5 Gew.-% bis etwa 99,999 Gew.-%, von etwa 5,0 Gew.-% bis etwa 99,9 Gew.-% und von etwa 10 Gew.-% bis etwa 99,5 Gew.-%, ausgehend vom gesamten kombinierten Trockengewicht des Wirkstoffs und des Poly(Lysin, Tryptophan)- 4:1 Hydrobromids, andere Hilfsstoffe nicht eingeschlossen.

8. Zusammensetzung nach einem der Ansprüche 1 bis 7, wobei der Wirkstoff ausgewählt ist aus der Gruppe bestehend aus einer kristallinen Phase, einer amorphen Phase, einer semi-kristallinen Phase, einer semi-amorphen Phase und Mischungen davon.

9. Zusammensetzung nach einem der Ansprüche 1 bis 8, wobei die effektive durchschnittliche Partikelgröße der Wirkstoffpartikel ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 1900 nm, weniger als etwa 1800 nm, weniger als etwa 1700 nm, weniger als etwa 1600 nm, weniger als etwa 1500 nm, weniger als etwa 1400 nm, weniger als etwa 1300 nm, weniger als etwa 1200 nm, weniger als etwa 1100 nm, weniger als etwa 1000 nm, weniger als etwa 900 nm, weniger als etwa 800 nm, weniger als etwa 700 nm, weniger als etwa 600 nm, weniger als etwa 500 nm, weniger als etwa 400 nm, weniger als etwa 300 nm, weniger als etwa 250 nm, weniger als etwa 200 nm, weniger als etwa 100 nm, weniger als etwa 75 nm und weniger als etwa 50 nm.

10. Zusammensetzung nach einem der Ansprüche 1 bis 9, wobei mindestens etwa 70%, mindestens etwa 90%, mindestens etwa 95% oder mindestens etwa 99% der Wirkstoffpartikel eine Partikelgröße aufweisen, die geringer ist als die effektive durchschnittliche Partikelgröße.

11. Zusammensetzung nach einem der Ansprüche 1 bis 10, ferner umfassend mindestens eine zusätzliche Wirkstoffzusammensetzung mit einer effektiven durchschnittlichen Partikelgröße, die sich von der effektiven durchschnittlichen Partikelgröße der Wirkstoffzusammensetzung nach Anspruch 1 unterscheidet.

12. Zusammensetzung nach einem der Ansprüche 1 bis 11, wobei der Wirkstoff ausgewählt ist aus der Gruppe bestehend aus Paclitaxel, Amphotericin B, einem Diuretikum, einem dermalen Mittel, Nutrazeutika, COX-2-Hemmern, Retinoiden, Antikrebsmitteln, NSAIDS, Proteinen, Peptiden, Nukleotiden, Antiadiposita, Nahrungsergänzungsmitteln, Carotinoiden, Corticosteroiden, Elastasehemmern, Antimykotika, Krebstherapeutika, Antiemetika, Analgetika, kardiovaskulären Mitteln, Antiphlogistika, Anthelmintika, Antiarrhythmika, Antibiotika, Antikoagulantien, Antidepressiva, Antidiabetika, Antiepileptika, Antihistaminika, Antihypertensiva, Antimuskarinika, antimycobakteriellen Mitteln, antineoplastischen Mitteln, Immunsuppressiva, Thyreostatika, Virustatika, Anxiolytika, Sedativa, adstringierenden Mitteln, Beta-Adrenozeptor-Antagonisten, Blutprodukten und Blutersatzmitteln, Inotropika, Kontrastmitteln, Corticosteroiden, Hustenblockern, diagnostischen Mitteln, Mitteln zur bildgebenden Diagnostik, Diuretika, Dopaminergika, Hämostatika, immunologischen Mitteln, lipidregulierenden Mitteln, Muskelrelaxantien, Parasympathomimetika, parathyreoidalem Calcitonin und Biphosphonaten, Prostaglandinen, Radiopharmazeutika, Geschlechtshormonen, Antiallergika, Stimulantien, Anorektika, Sympathomimetika, Schilddrüsenmitteln, Vasodilatatoren, Xanthinen, Aciclovir, Alprazolam, Altretamin, Amilorid, Amiodaron, Benztropin-Mesylat, Bupropion, Cabergolin, Candesartan, Cerivasta-

tin, Chlorpromazin, Ciprofloxacin, Cisaprid, Clarithromycin, Clonidin, Clopidogrel, Cyclobenzaprin, Cyproheptadin, Delavirdin, Desmopressin, Diltiazem, Dipyridamol, Dolasetron, Enalaprilmaleat, Enalaprilat, Famotidin, Felodipin, Furazolidon, Glipizid, Irbesartan, Ketoconazol, Lansoprazol, Loratadin, Loxapin, Mebendazol, Mercaptopurin, Milrinon-Laktat, Minocyclin, Mitoxantron, Nelfinavir-Mesylat, Nimodipin, Norfloxacin, Olanzapin, Omeprazol, Penciclovir, Pimozid, Tacrolimus, Quazepam, Raloxifen, Rifabutin, Rifampin, Risperidon, Rizatriptan, Saquinavir, Sertralin, Sildenafil, Acetyl-Sulfisoxazol, Temazepan, Thiabendazol, Thioguanin, Trandolapril, Triamteren, Trimetrexat, Troglitazon, Trovafloxacin, Verapamil, Vinblastinsulfat, Mycophenolat, Atovaquon, Proguanil, Ceftazidim, Cefuroxim, Etoposid, Terbinafin, Thalidomid, Fluconazol, Amsacrin, Dacarbazin, Teniposid und Acetylsalicylat.

**13.** Zusammensetzung nach Anspruch 12, wobei das Nutrazeutikum ausgewählt ist aus der Gruppe bestehend aus Nahrungsergänzungsmitteln, Vitaminen, Mineralstoffen, Kräutern, Lutein, Folsäure, Fettsäuren, Fruchtextrakten, Gemüseextrakten, Phosphatidylserin, Liponsäure, Melatonin, Glucosamin/Chondroitin, Aloe Vera, Guggul, Glutamin, Aminosäuren, grünem Tee, Lycopen, Vollwertkost, Lebensmittelzusatzstoffen, Kräutern, sekundären Pflanzenstoffen, Antioxidantien, Flavonoidbestandteilen von Früchten, Nachtkerzenöl, Leinsamen, Fischölen, Ölen von Meerestieren und Probiotika.

**14.** Zusammensetzung nach Anspruch 12, wobei das Antikrebsmittel ausgewählt ist aus der Gruppe bestehend aus alkylierenden Mitteln, Antimetaboliten, Anthracendionen, Naturstoffen, Hormonen, Antagonisten, Radiosensibilisatoren, Platin-Koordinationskomplexen, adrenocorticalen Suppressiva, Immunsuppressiva, substituierten Harnstoffen und COX-2-Hemmern.

**15.** Zusammensetzung nach Anspruch 14, wobei:

(a) das alkylierende Mittel ausgewählt ist aus der Gruppe bestehend aus Chlormethin, Chlorambucil, Melphalan, Uramustin, Mannomustin, Estramustinphosphat, Mechlorethaminoxid, Cyclophosphamid, Ifosfamid, Trifosfamid, Tretamin, Thiotepa, Triaziquon, Mitomycin, Busulfan, Piposulfan, Piposulfam, Carmustin, Lomustin, Semustin, Streptozotocin, Mitobronitol, Dacarbazin und Procarbazin, oder
(b) derAntimetabolit ausgewählt ist aus der Gruppe bestehend aus Methotrexat, Fluorouracil, Floxuridin, Tegafur, Cytarabin, Idoxuridin, Flucytosin, Mercaptopurin, Thioguanin, Azathioprin, Tiamiprin, Vidarabin, Pentostatin und Puromycin, oder
(c) der Naturstoff ausgewählt ist aus der Gruppe bestehend aus Vinblastin, Vincristin, Etoposid, Teniposid, Adriamycin, Daunomycin, Doctinomycin, Daunorubicin, Doxorubicin, Mithramycin, Bleomycin, Mitomycin, L-Asparaginase, Alpha-Interferon, Camptothecin, Taxol und Retinsäure, oder
(d) das Hormon oder derAntagonist ausgewählt ist aus der Gruppe bestehend aus Prednison, Hydroxyprogesteroncaproat, Medroxyprogesteronacetat, Megestrolacetat, Diethylstilbestrol, Ethinylestradiol, Tamoxifen, Testosteronpropionat, Fluoxymesteron, Flutamid, Leuprolid, oder
(e) das Antikrebsmittel ausgewählt ist aus der Gruppe bestehend aus Cisplatin, Carboplatin, Mitoxantron, Hydroxyharnstoff, Mitotan, Aminoglutethimid, Cyclosporin, Azathioprin, Sulfasalazin, Methoxsalen und Thalidomid.

**16.** Zusammensetzung nach Anspruch 12, wobei das NSAID ausgewählt ist aus der Gruppe bestehend aus Nabumeton, Tiaramid, Proquazon, Bufexamac, Flumizol, Epirazol, Tinoridin, Timegadin, Dapson, Aspirin, Diflunisal, Benorylat, Fosfosal, Diclofenac, Alclofenac, Fenclofenac, Etodolac, Indomethacin, Sulindac, Tolmetin, Fentiazac, Tilomisol, Carprofen, Fenbufen, Flurbiprofen, Ketoprofen, Oxaprozin, Suprofen, Tiaprofensäure, Ibuprofen, Naproxen, Fenoprofen, Indoprofen, Pirprofen, Flufenamic, Mefenamic, Meclofenamic, Niflumic, Oxyphenbutazon, Phenylbutazon, Apazon, Feprazon, Piroxicam, Sudoxicam, Isoxicam und Tenoxicam.

**17.** Zusammensetzung nach Anspruch 12, wobei der COX-2-Hemmer ausgewählt ist aus der Gruppe bestehend aus Nimesulid, Celecoxib, Rofecoxib, Meloxicam, Valdecoxib, Parecoxib, Etoricoxib, Flurbiprofen, Nabumeton, Etodolac, Iguratimod, Flosulid, Piroxicam, Diclofenac, Lumiracoxib, Monteleukast, Pranlukast, Heptinylsulfid, SC-236, SC-58125, SC-57666, SC-558, SC-560, SC 41930, NS-398, DFU, L-745337, L-761066, L-761000, L-748780, DUP-697, PGV 20229, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, RS 57067, RS 104897, RS 104894 und SB 209670.

**18.** Zusammensetzung nach einem der Ansprüche 1 bis 17, wobei die Wirkstoffpartikel bei Verabreichung an ein Säugetier so redispergieren, dass die Partikel eine effektive durchschnittliche Partikelgröße aufweisen, die ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 2 Mikrometer, weniger als etwa 1900 nm, weniger als etwa 1800 nm, weniger als etwa 1700 nm, weniger als etwa 1600 nm, weniger als etwa 1500 nm, weniger als etwa 1400

nm, weniger als etwa 1300 nm, weniger als etwa 1200 nm, weniger als etwa 1100 nm, weniger als etwa 1000 nm, weniger als etwa 900 nm, weniger als etwa 800 nm, weniger als etwa 700 nm, weniger als etwa 600 nm, weniger als etwa 500 nm, weniger als etwa 400 nm, weniger als etwa 300 nm, weniger als etwa 250 nm, weniger als etwa 200 nm, weniger als etwa 150 nm, weniger als etwa 100 nm, weniger als etwa 75 nm und weniger als etwa 50 nm.

**19.** Zusammensetzung nach einem der Ansprüche 1 bis 18, wobei die Zusammensetzung in einem biorelevanten Medium so redispergiert, dass die Wirkstoffpartikel eine effektive durchschnittliche Partikelgröße aufweisen, die ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 2 Mikrometer, weniger als etwa 1900 nm, weniger als etwa 1800 nm, weniger als etwa 1700 nm, weniger als etwa 1600 nm, weniger als etwa 1500 nm, weniger als etwa 1400 nm, weniger als etwa 1300 nm, weniger als etwa 1200 nm, weniger als etwa 1100 nm, weniger als etwa 1000 nm, weniger als etwa 900 nm, weniger als etwa 800 nm, weniger als etwa 700 nm, weniger als etwa 600 nm, weniger als etwa 500 nm, weniger als etwa 400 nm, weniger als etwa 300 nm, weniger als etwa 250 nm weniger als etwa 200 nm weniger als etwa 150 nm, weniger als etwa 100 nm, weniger als etwa 75 nm und weniger als etwa 50 nm.

**20.** Zusammensetzung nach Anspruch 19, wobei das biorelevante Medium ausgewählt ist aus der Gruppe bestehend aus Wasser, wässrigen Elektrolytlösungen, wässrigen Lösungen eines Salzes, wässrigen Lösungen einer Säure, wässrigen Lösung einer Base und Kombinationen davon.

**21.** Zusammensetzung nach einem der Ansprüche 1 bis 20, wobei:

(a) der $T_{maX}$ Wert des Wirkstoffs bei Untersuchung im Plasma eines Säugetiersubjekts nach Verabreichung kleiner ist als der $T_{maX}$ Wert für eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs, der in derselben Dosierung verabreicht wird, oder
(b) der $C_{max}$-Wert des Wirkstoffs bei Untersuchung im Plasma eines Säugetiersubjekts nach Verabreichung größer als der $C_{max}$-Wert für eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs ist, der in derselben Dosierung verabreicht wird, oder
(c) die AUC des Wirkstoffs bei Untersuchung im Plasma eines Säugetiersubjekts nach Verabreichung größer als die AUC für eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs ist, der in derselben Dosierung verabreicht wird.

**22.** Zusammensetzung nach Anspruch 21, wobei der $T_{max}$-Wert ausgewählt ist aus der Gruppe bestehend aus einem $T_{max}$-Wert, der nicht größer als etwa 90%, nicht größer als etwa 80%, nicht größer als etwa 70%, nicht größer als etwa 60%, nicht größer als etwa 50%, nicht größer als etwa 30%, nicht größer als etwa 25%, nicht größer als etwa 20%, nicht größer als etwa 15%, nicht größer als etwa 10% und nicht größer als etwa 5% des $T_{max}$-Werts ist, den eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs aufweist, der in derselben Dosierung verabreicht wird.

**23.** Zusammensetzung nach Anspruch 21, wobei der $C_{maX}$ Wert ausgewählt ist aus der Gruppe bestehend aus einem $C_{max}$-Wert, der mindestens etwa 50%, mindestens etwa 100%, mindestens etwa 200%, mindestens etwa 300%, mindestens etwa 400%, mindestens etwa 500%, mindestens etwa 600%, mindestens etwa 700%, mindestens etwa 800%, mindestens etwa 900%, mindestens etwa 1000%, mindestens etwa 1100%, mindestens etwa 1200%, mindestens etwa 1300%, mindestens etwa 1400%, mindestens etwa 1500%, mindestens etwa 1600%, mindestens etwa 1700%, mindestens etwa 1800% oder mindestens etwa 1900% höher ist als der $C_{max}$-Wert, den eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs aufweist, der in derselben Dosierung verabreicht wird.

**24.** Zusammensetzung nach Anspruch 21, wobei die AUC ausgewählt ist aus der Gruppe bestehend aus einerAUC, die mindestens etwa 25%, mindestens etwa 50%, mindestens etwa 75%, mindestens etwa 100%, mindestens etwa 125%, mindestens etwa 150%, mindestens etwa 175%, mindestens etwa 200%, mindestens etwa 225%, mindestens etwa 250%, mindestens etwa 275%, mindestens etwa 300%, mindestens etwa 350%, mindestens etwa 400%, mindestens etwa 450%, mindestens etwa 500%, mindestens etwa 550%, mindestens etwa 600%, mindestens etwa 650%, mindestens etwa 700%, mindestens etwa 750%, mindestens etwa 800%, mindestens etwa 850%, mindestens etwa 900%, mindestens etwa 950%, mindestens etwa 1000%, mindestens etwa 1050%, mindestens etwa 1100%, mindestens etwa 1150% oder mindestens etwa 1200% größer ist als die AUC, die eine nicht-nanopartikuläre Zusammensetzung desselben Wirkstoffs aufweist, der in derselben Dosierung verabreicht wird.

**25.** Zusammensetzung nach einem der Ansprüche 1 bis 24, welche bei Verabreichung nach Nahrungsaufnahme im Vergleich zur Verabreichung im nüchternen Zustand keine signifikant unterschiedlichen Absorptionswerte hervorruft.

**26.** Zusammensetzung nach Anspruch 25, wobei der Unterschied in der Absorption der Wirkstoffzusammensetzung der Erfindung bei Verabreichung im Zustand nach Nahrungsaufnahme im Gegensatz zum nüchternen Zustand ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 100%, weniger als etwa 90%, weniger als etwa 80%, weniger als etwa 70%, weniger als etwa 60%, weniger als etwa 50%, weniger etwa 40%, weniger als etwa 30%, weniger als etwa 25%, weniger als etwa 20%, weniger als etwa 15%, weniger als etwa 10%, weniger als etwa 5% und weniger als etwa 3%.

**27.** Zusammensetzung nach einem der Ansprüche 1 bis 26, wobei die Verabreichung der Zusammensetzung an einen Menschen in nüchternem Zustand bioäquivalent zur Verabreichung der Zusammensetzung an ein Subjekt im Zustand nach Nahrungsaufnahme ist.

**28.** Zusammensetzung nach Anspruch 27, wobei "Bioäquivalenz" definiert ist durch:

(a) Ein 90%-Konfidenzintervall von zwischen 0,80 und 1,25 sowohl für den $C_{max}$-Wert als auch für die AUC oder
(b) Ein 90%-Konfidenzintervall von zwischen 0,80 und 1,25 für die AUC und ein 90%-Konfidenzintervall von zwischen 0,70 und 1,43 für den $C_{max}$-Wert.

**29.** Zusammensetzung nach einem der Ansprüche 1 bis 28, formuliert in eine flüssige Darreichungsform und mit einer Viskosität mit einer Schergeschwindigkeit von 0,1 (1/s), gemessen bei 20 °C, ausgewählt aus der Gruppe bestehend aus weniger als etwa 2000 mPa·s, von etwa 2000 mPa·s bis etwa 1 mPa·s, von etwa 1900 mPa·s bis etwa 1 mPa·s, von etwa 1800 mPa·s bis etwa 1 mPa·s, von etwa 1700 mPa·s bis etwa 1 mPa·s, von etwa 1600 mPa·s bis etwa 1 mPa·s, von etwa 1500 mPa·s bis etwa 1 mPa·s, von etwa 1400 mPa·s bis etwa 1 mPa·s, von etwa 1300 mPa·s bis etwa 1 mPa·s, von etwa 1200 mPa·s bis etwa 1 mPa·s, von etwa 1100 mPa·s bis etwa 1 mPa·s, von etwa 1000 mPa·s bis etwa 1 mPa·s, von etwa 900 mPa·s bis etwa 1 mPa·s, von etwa 800 mPa·s bis etwa 1 mPa·s, von etwa 700 mPa·s bis etwa 1 mPa·s, von etwa 600 mPa·s bis etwa 1 mPa·s, von etwa 500 mPa·s bis etwa 1 mPa·s, von etwa 400 mPa·s bis etwa 1 mPa·s, von etwa 300 mPa·s bis etwa 1 mPa·s, von etwa 200 mPa·s bis etwa 1 mPa·s, von etwa 175 mPa·s bis etwa 1 mPa·s, von etwa 150 mPa·s bis etwa 1 mPa·s, von etwa 125 mPa·s bis etwa 1 mPa·s, von etwa 100 mPa·s bis etwa 1 mPa·s, von etwa 75 mPa·s bis etwa 1 mPa·s, von etwa 50 mPa·s bis etwa 1 mPa·s, von etwa 25 mPa·s bis etwa 1 mPa·s, von etwa 15 mPa·s bis etwa 1 mPa·s, von etwa 10 mPa·s bis etwa 1 mPa·s und von etwa 5 mPa·s bis etwa 1 mPa·s.

**30.** Zusammensetzung nach Anspruch 29, wobei die Viskosität der Darreichungsform:

(a) ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 1/200, weniger als etwa 1/100, weniger als etwa 1/50, weniger als etwa 1/25 und weniger als etwa 1/10 der Viskosität einer flüssigen Darreichungsform einer nicht-nanopartikulären Zusammensetzung desselben Wirkstoffs, bei etwa derselben Konzentration des Wirkstoffs pro ml, oder
(b) ausgewählt ist aus der Gruppe bestehend aus weniger als etwa 5%, weniger als etwa 10%, weniger als etwa 15%, weniger als etwa 20%, weniger als etwa 25%, weniger als etwa 30%, weniger als etwa 35%, weniger als etwa 40%, weniger als etwa 45%, weniger als etwa 50%, weniger als etwa 55%, weniger als etwa 60%, weniger als etwa 65%, weniger als etwa 70%, weniger als etwa 75%, weniger als etwa 80%, weniger als etwa 85% und weniger als etwa 90% der Viskosität einer flüssigen Darreichungsform einer nicht-nanopartikulären Zusammensetzung desselben Wirkstoffs bei etwa derselben Konzentration des Wirkstoffs pro ml.

**31.** Zusammensetzung nach einem der Ansprüche 1 bis 30, ferner umfassend einen oder mehrere pharmazeutisch zulässige Hilfsstoffe, Trägerstoffe oder eine Kombination davon.

**32.** Zusammensetzung nach einem der Ansprüche 1 bis 31 für die Verwendung in der Therapie.

**33.** Verfahren zur Herstellung einer Zusammensetzung nach einem der Ansprüche 1 bis 32, umfassend Inkontaktbringen von Partikeln mindestens eines Wirkstoffs mit Poly(Lysin, Tryptophan) 4:1 Hydrobromid über einen ausreichend langen Zeitraum und unter Bedingungen, die ausreichend sind, eine Wirkstoffzusammensetzung mit einer effektiven durchschnittlichen Partikelgröße von weniger als 2000 nm bereitzustellen.

**Revendications**

**1.** Composition comprenant .

(a) des particules d'au moins un principe actif ayant une taille moyenne de particules effective inférieure à environ 2 000 nm ; et
(b) du bromhydrate de poly(lysine, tryptophane) 4:1 en tant que stabilisant de surface,

dans laquelle la composition ne comprend pas de nystatine ni un de sel de celle-ci.

**2.** Composition selon la revendication 1, comprenant en outre au moins un stabilisant de surface secondaire.

**3.** Composition selon la revendication 2, dans laquelle le stabilisant de surface secondaire est choisi dans le groupe formé par un stabilisant de surface anionique, un stabilisant de surface cationique, un stabilisant de surface zwitterionique et un stabilisant de surface ionique.

**4.** Composition selon la revendication 2 ou 3, dans laquelle le stabilisant de surface secondaire est choisi dans le groupe formé par le chlorure de cétylpyridinium, la gélatine, la caséine, les phosphatides, le dextrane, le glycérol, la gomme arabique, le cholestérol, la gomme adragante, l'acide stéarique, le chlorure de benzalkonium, le stéarate de calcium, le monostéarate de glycérol, l'alcool cétostéarylique, la cire émulsifiante au Cétomacrogol, les esters de sorbitan, les éthers de polyoxyéthylène alkyle, les dérivés d'huile de ricin polyéthoxylée, les esters d'acides gras et de sorbitan polyéthoxylé, les polyéthylèneglycols, le bromure de dodécyltriméthylammonium, les stéarates de polyoxyéthylène, le dioxyde de silicium colloïdal, les phosphates, le dodécylsulfate de sodium, la carboxyméthylcellulose calcique les hydroxypropylcelluloses, l'hypromellose, la carboxyméthylcellulose sodique, la méthylcellulose, l'hydroxyéthylcellulose, le phtalate d'hypromellose, la cellulose non cristalline, le silicate de magnésium et d'aluminium, la triéthanolamine, l'alcool de polyvinyle, la polyvinylpyrrolidone, le polymère de 4-(1,1,3,3-tétraméthylbutyl)phénol avec de l'oxyde d'éthylène et du formaldéhyde, les Poloxamers, les poloxamines, un phospholipide chargé, le dioctylsulfosuccinate, les esters dialkyliques d'acide sulfosuccinique de sodium, le laurylsulfate de sodium, les polyéthersulfonates d'alkylaryle, les mélanges de stéarate de saccharose et de distéarate de saccharose, le p-isononylphénoxypoly(glycidol), le décanoyl-N-méthylglucamide, le n-décyl-β-D-glucopyranoside, le n-décyl-β-D-maltopyranoside, le n-dodécyl-β-D-glucopyranoside, le n-dodécyl-β-D-maltoside, l'heptanoyl-N-méthylglucamide, le n-heptyl-β-D-glucopyranoside, le n-heptyl-β-D-thioglucoside, le n-hexyl-β-D-glucopyranoside, le nonanoyl-N-méthylglucamide, le n-noyl-β-D-glucopyranoside, l'octanoyl-N-méthylglucamide, le n-octyl-β-D-glucopyranoside, l'octyl-β-D-thioglucopyranoside, le lysozyme, le PEG-phospholipide, le PEG-cholestérol, les dérivés de PEG-cholestérol, le PEG-vitamine A et les copolymères statistiques d'acétate de vinyle et de vinylpyrrolidone, un polymère cationique, un biopolymère cationique, un polysaccharide cationique, une cellulose cationique, un alginate cationique, un composé non polymère cationique, les phospholipides cationiques, les lipides cationiques, le bromure de poly(méthacrylate de méthyle)-triméthylammonium, les composés sulfonium, le polyvinylpyrrolidone-2-diméthylaminoéthylméthacrylate-diméthylsulfate, le bromure d'hexadécyltriméthylammonium, les composés phosphonium, les composés d'ammonium quaternaire, le bromure de benzyl-di(2-chloroéthyl)éthylammonium, le chlorure de coprah-triméthylammonium, le bromure de coprah-triméthylammonium, le chlorure de coprahméthyldihydroxyéthylammonium, le bromure de coprahméthyldihydroxyéthylammonium, le chlorure de décyltriéthylammonium, le chlorure de décyldiméthylhydroxyéthylammonium, le chlorure-bromure de décyldiméthylhydroxyéthylammonium, le chlorure de $C_{12-15}$diméthylhydroxyéthylammonium, le chlorure-bromure de $C_{12-15}$ diméthylhydroxyéthylammonium, le chlorure de coprah-diméthylhydroxyéthylammonium, le bromure de coprah-diméthylhydroxyéthylammonium, le méthylsulfate de myristyltriméthylammonium, le chlorure de lauryldiméthylbenzylammonium, le bromure de lauryldiméthylbenzylammonium, le chlorure de lauryldiméthyl(éthénoxy)$_4$-ammonium, le bromure de lauryldiméthyl(éthénoxy)4-$_a$mmonium, le chlorure de N-alkyl(en $C_{12}$ à $C_{18}$)diméthylbenzylammonium, le chlorure de N-alkyl(en $C_{14}$ à $C_{18}$)diméthylbenzylammonium, le chlorure de N-tétradécyldiméthylbenzylammonium monohydraté, le chlorure de diméthyldidécylammonium, le chlorure de N-alkyl(en $C_{12}$ à $C_{14}$)- et diméthyl-1-naphtylméthylammonium, l'halogénure de triméthylammonium, les sels d'alkyltriméthylammonium, les sels de dialkyldiméthylammonium, le chlorure de lauryltriméthylammonium, un sel d'alkyamidoalkyldialkylammonium éthoxylé, un sel de trialkylammonium éthoxylé, le chlorure de dialkylbenzènedialkylammonium, le chlorure de N-didécyldiméthylammonium, le chlorure de N-tétradécyldiméthylbenzylammonium monohydraté, le chlorure de N-alkyl(en $C_{12}$ à $C_{14}$)diméthyl-1-naphtylméthylammonium, le chlorure de dodécyldiméthylbenzylammonium, le chlorure de dialkylbenzènealkylammonium, le chlorure de lauryltriméthylammonium, le chlorure d'alkylbenzylméthylammonium, le bromure d'alkylbenzyldiméthylammonium, les bromures de $C_{12}$triméthylammonium, les bromures de $C_{15}$triméthylammonium, les bromures des $C_{17}$triméthylammonium, le chlorure de dodécylbenzyltriéthylammonium, le poly(chlorure de diallyldiméthylammonium) (DADMAC), le chlorure de diméthylammonium, les halogénures d'alkyldiméthylammonium, le chlorure de tricétylméthylammonium, le bromure de décyltriméthylammonium, le bromure de dodécyltriéthylammonium, le bromure de tétradécyltriméthylammonium, le chlorure de méthyltrioctylammonium, le POLYQUAT 10™, le bromure de tétrabutylammonium, le bromure de benzyltriméthylammonium, les esters de choline, le chlorure de benzalkonium,

les composés de chlorure de stéaralkonium, le bromure de cétylpyridinium, le chlorure de cétylpyridinium, les halogénures de polyoxyéthylalkylamines quaternisées, le MIRAPOL™, l'ALKAQUAT™, les sels d'alkylpyridinium, les amines, les sels d'amine, les oxydes d'amine, les sels d'imide-azolinium, les acrylamides quaternaires protonés, les polymères quaternaires méthylés et la gomme de guar cationique.

**5.** Composition selon l'une quelconque des revendications 1 à 4, dans laquelle la composition est formulée pour une administration choisie dans le groupe formé par les administrations orale, pulmonaire, rectale, ophtalmique, colique, parentérale, sous-occipitale, intravaginale, intrapéritonéale, locale, buccale, nasale et topique.

**6.** Composition selon l'une quelconque des revendications 1 à 5, formulée en une forme galénique choisie dans le groupe formé par les dispersions liquides, les suspensions orales, les gels, les aérosols, les pommades, les crèmes, les comprimés, les gélules, les sachets, les trochisques, les poudres, les pilules, les granulés, les formulations à libération programmée, les formulations à fusion rapide, les formulations lyophilisées, les formulations à libération retardée, les formulations à libération prolongée, les formulations à libération pulsatile et les formulations à libération immédiate et à libération programmée mélangées.

**7.** Composition selon l'une quelconque des revendications 1 à 6, dans laquelle :

(a) le principe actif est présent dans une quantité choisie dans le groupe formé par environ 99,5% à environ 0,001%, environ 95% à environ 0,1% et environ 90% à environ 0,5%, en poids, par rapport au poids sec combiné total du principe actif et du bromhydrate de poly(lysine, tryptophane) 4:1 sans inclure les autres excipients ; ou
(b) le bromhydrate de poly(lysine, tryptophane) 4:1 est présent dans une quantité choisie dans le groupe formé par environ 0,5% à environ 99,999% en poids, environ 5,0% à environ 99,9% en poids et environ 10% à environ 99,5% en poids, par rapport au poids sec combiné total du principe actif et du bromhydrate de poly(lysine, tryptophane) 4:1 sans inclure les autres excipients.

**8.** Composition selon l'une quelconque des revendications 1 à 7, dans laquelle le principe actif est choisi dans le groupe formé par une phase cristalline, une phase amorphe, une phase semi-cristalline, une phase semi-amorphe et les mélanges de celles-ci.

**9.** Composition selon l'une quelconque des revendications 1 à 8, dans laquelle la taille moyenne de particules effective des particules de principe actif est choisie dans le groupe formé par moins d'environ 1 900 nm, moins d'environ 1 800 nm, moins d'environ 1 700 nm, moins d'environ 1 600 nm, moins d'environ 1 500 nm, moins d'environ 1 400 nm, moins d'environ 1 300 nm, moins d'environ 1 200 nm, moins d'environ 1 100 nm, moins d'environ 1 000 nm, moins d'environ 900 nm, moins d'environ 800 nm, moins d'environ 700 nm, moins d'environ 600 nm, moins d'environ 500 nm, moins d'environ 400 nm, moins d'environ 300 nm, moins d'environ 250 nm, moins d'environ 200 nm, moins d'environ 100 nm, moins d'environ 75 nm et moins d'environ 50 nm.

**10.** Composition selon l'une quelconque des revendications 1 à 9, dans laquelle au moins environ 70%, au moins environ 90%, au moins environ 95% ou au moins environ 99% des particules de principe actif ont une taille de particules inférieure à la taille moyenne de particules effective.

**11.** Composition selon l'une quelconque des revendications 1 à 10, comprenant en outre au moins un principe actif supplémentaire ayant une taille moyenne de particules effective qui est différente de la taille moyenne de particules effective de la composition de principe actif selon la revendication 1.

**12.** Composition selon l'une quelconque des revendications 1 à 11, dans laquelle le principe actif est choisi dans le groupe formé par le paclitaxel, l'amphotéricine B, un diurétique, un agent dermique, les nutraceutiques, les inhibiteurs de COX-2, les rétinoïdes, les agents anticancéreux, les AINS, les protéines, les peptides, les nucléotides, les médicaments anti-obésité, les compléments alimentaires, les caroténoïdes, les corticostéroïdes, les inhibiteurs de l'élastase, les antifongiques, les traitements d'oncologie, les antiémétiques, les analgésiques, les agents cardiovasculaires, les anti-inflammatoires, les anthelminthiques, les agents anti-arythmiques, les antibiotiques, les anticoagulants, les antidépresseurs, les agents antidiabétiques, les agents anti-épileptiques, les antihistaminiques, les antihypertenseurs, les agents antimuscariniques, les agents antimycobactériens, les agents antinéoplasiques, les immunosuppresseurs, les agents antithyroïdiens, les agents antiviraux, les anxiolytiques, les sédatifs, les astringents, les agents de blocage du β-adrénocepteur, les produits et substituts sanguins, les agents inotropes cardiaques, les milieux de contraste, les corticostéroïdes, les antitussifs, les agents diagnostiques, les agents d'imagerie diagnostique, les diurétiques, les agents dopaminergiques, les agents hémostatiques, les agents immunologiques,

les agents liporégulateurs, les myorelaxants, les agents parasympathomimétiques, la calcitonine parathyroïde et les biphosphonates parathyroïdes, les prostaglandines, les produits radiopharmaceutiques, les hormones sexuelles, les agents anti-allergiques, les stimulants, les agents anorexigènes, les agents sympathomimétiques, les agents thyroïdiens, les vasodilatateurs, les xanthines, l'acyclovir, l'alprazolam, l'altrétamine, l'amiloride, l'amiodarone, le mésylate de benztropine, le bupropion, la cabergoline, le candésartan, la cérivastatine, la chlorpromazine, la ciprofloxacine, le cisapride, la clarithromycine, la clonidine, le clopidogrel, la cyclobenzaprine, la cyproheptadine, la délavirdine, la desmopressine, le diltiazem, la dipyridamole, le dolasétron, le maléate d'énalapril, l'énalaprilat, la famotidine, la félodipine, la furazolidone, le glipizide, l'irbésartan, le kétoconazole, le lansoprazole, la loratadine, la loxapine, le mébendazole, la mercaptopurine, le lactate de milrinone, la minocycline, la mitoxantrone, le mésylate de nelfinavir, la nimodipine, la norfloxacine, l'olanzapine, l'oméprazole, le penciclovir, le pimozide, le tacolimus, le quazépam, le raloxifène, la rifabutine, la rifampine, la rispéridone, le rizatriptan, le saquinavir, la sertraline, le sildénafil, l'acétyl-sulfisoxazole, le témazépam, le thiabendazole, la thioguanine, le trandolapril, le triamtérène, le trimétrexate, la troglitazone, la trovafloxacine, le vérapamil, le sulfate de vinblastine, le mycophénolate, l'atovaquone, le proguanil, le ceftazidime, le céfuroxime, l'étoposide, la terbinafine, le thalidomide, le fluconazole, l'amsacrine, la dacarbazine, le téniposide et l'acétylsalicylate.

**13.** Composition selon la revendication 12, dans laquelle le nutraceutique est choisi dans le groupe formé par les compléments alimentaires, les vitamines, les minéraux, les herbes, la lutéine, l'acide folique, les acides gras, les extraits de fruits, les extraits de légumes, la phosphatidylsérine, l'acide lipoïque, la mélatonine, la glucosamine/chondroïtine, l'*Aloe vera,* le *Guggul,* la glutamine, les acides aminés, le thé vert, le lycopène, les aliments complets, les additifs alimentaires, les herbes, les phytonutriments, les antioxydants, les constituants flavonoïdes des fruits, l'huile d'onagre, les graines de lin, les huiles de poisson, les huiles d'animaux marins et les probiotiques.

**14.** Composition selon la revendication 12, dans laquelle l'agent anticancéreux est choisi dans le groupe formé par les agents alkylants, les antimétabolites, les anthracènediones, les produits naturels, les hormones, les antagonistes, les radiosensibilisateurs, les complexes de coordination du platine, les suppresseurs corticosurrénaux, les agents immunosuppresseurs, les urées substituées et les inhibiteurs de COX-2.

**15.** Composition selon la revendication 14, dans laquelle :

(a) l'agent alkylant est choisi dans le groupe formé par la chlorméthine, le chlorambucile, le melphalan, l'uramustine, la mannomustine, l'extramustinephosphate, le méchlore-thaminoxide, le cyclophosphamide, l'ifosfamide, le trifosfamide, la trétamine, le thiotépa, la triaziquone, la mitomycine, le busulfan, le piposulfan, le piposulfam, la carmustine, la lomustine, la sémustine, la streptozotocine, le mitobronitole, la dacarbazine et la procarbazine ; ou

(b) l'antimétabolite est choisi dans le groupe formé par le méthotrexate, le fluoro-uracile, la floxuridine, le tégafur, la cytarabine, l'idoxuridine, la flucytosine, la mercaptopurine, la thioguanine, l'azathioprine, la tiamipirine, la vidarabine, la pentostatine et la puromycine ; ou

(c) le produit naturel est choisi dans le groupe formé par la vinblastine, la vincristine, l'étoposide, le téniposide, l'adriamycine, la datinomycine, la doctinomycine, la daunorubicine, la doxorubicine, la mithramycine, la bleumycine, la mitomycine, la L-asparaginase, l'interféron alpha, la camptothécine, le taxol et l'acide rétinoïque ; ou

(d) l'hormone ou l'antagoniste est choisi dans le groupe formé par la prednisone, le caproate d'hydroxyprogestérone, l'acétate de médroxyprogestérone, l'acétate de mégestrol, le diéthylstilbestrol, l'éthinyl-oestradiol, le tamoxifène, le propionate de testostérone, la fluoxymestérone, le flutamide, le leuprolide ; ou

(e) l'agent anticancéreux est choisi dans le groupe formé par le cisplatine, le carboplatine, la mitoxantrone, l'hydroxyurée, le mitotane, l'aminoglutéthimide, la cyclosporine, l'azathioprine, la sulfasalazine, le méthoxsalen et le thalidomide.

**16.** Composition selon la revendication 12, dans laquelle l'AINS est choisi dans le groupe formé par la nabumétone, le tiaramide, la proquazone, le buféxamac, le flumizole, l'épirazole, la tinoridine, la timégadine, la dapsone, l'aspirine, le diflunisal, le bénorylate, le fosfosal, le diclofénac, l'alclofénac, le fenclofénac, l'étodolac, l'indométhacine, le sulindac, la tolmétine, le fentiazac, le tilomisole, le carprofène, le fenbufène, le flurbiprofène, le kétoprofène, l'oxaprozine, le suprofène, l'acide tiaprofénique, l'ibuprofène, le naproxène, le fénoprofène, l'indoprofène, le pirprofène, le flufénamique, le méfénamique, le méclofénamique, le niflumique, l'oxyphenbutazone, la phénylbutazone, l'apazone, la féprazone, le piroxicam, le sudoxicam, l'isoxicam et le ténoxicam.

**17.** Composition selon la revendication 12, dans laquelle l'inhibiteur de COX-2 est choisi dans le groupe formé par le nimésulide, le célécoxib, le rofécoxib, le méloxicam, le valdécoxib, le parécoxib, l'étoricoxib, le flurbiprofène, la

nabumétone, l'étodolac, l'iguratimod, le flosulide, le piroxicam, le diclofénac, le lumiracoxib, le montélukast, le pranlukast, l'heptinylsulfide, le SC-236, le SC-58125, le SC-57666, le SC-558, le SC-560, le SC 41930, le NS-398, le DFU, le L-745337, le L-761066, le L-761000, le L-748780, le DUP-697, le PGV 20229, le BF 389, le CL 1004, le PD 136005, le PD 142893, le PD 138387, le PD 145065, le D 1367, le R 807, le JTE-522, le FK-3311, le FK 867, le FR 140423, le FR 115068, le GR 253035, le RWJ 63556, le RWJ 20485, le ZK 38997, le S 2474, le RS 57067, le RS 104897, le RS 104894 et le SB 209670.

**18.** Composition selon l'une quelconque des revendications 1 à 17, dans laquelle, lorsqu'elles sont administrées à un mammifère, les particules de principe actif se redispersent de telle sorte que les particules ont une taille moyenne de particules effective choisie dans le groupe formé par moins d'environ 2 micromètres, moins d'environ 1 900 nm, moins d'environ 1 800 nm, moins d'environ 1 700 nm, moins d'environ 1 600 nm, moins d'environ 1 500 nm, moins d'environ 1 400 nm, moins d'environ 1 300 nm, moins d'environ 1 200 nm, moins d'environ 1 100 nm, moins d'environ 1 000 nm, moins d'environ 900 nm, moins d'environ 800 nm, moins d'environ 700 nm, moins d'environ 600 nm, moins d'environ 500 nm, moins d'environ 400 nm, moins d'environ 300 nm, moins d'environ 250 nm, moins d'environ 200 nm, moins d'environ 150 nm, moins d'environ 100 nm, moins d'environ 75 nm et moins d'environ 50 nm.

**19.** Composition selon l'une quelconque des revendications 1 à 18, dans laquelle la composition se redisperse dans une milieu biologiquement pertinent de telle sorte que les particules de principe actif ont une taille moyenne de particules effective choisie dans le groupe formé par moins d'environ 2 micromètres, moins d'environ 1 900 nm, moins d'environ 1 800 nm, moins d'environ 1 700 nm, moins d'environ 1 600 nm, moins d'environ 1 500 nm, moins d'environ 1 400 nm, moins d'environ 1 300 nm, moins d'environ 1 200 nm, moins d'environ 1 100 nm, moins d'environ 1 000 nm, moins d'environ 900 nm, moins d'environ 800 nm, moins d'environ 700 nm, moins d'environ 600 nm, moins d'environ 500 nm, moins d'environ 400 nm, moins d'environ 300 nm, moins d'environ 250 nm, moins d'environ 200 nm, moins d'environ 150 nm, moins d'environ 100 nm, moins d'environ 75 nm et moins d'environ 50 nm.

**20.** Composition selon la revendication 19, dans laquelle le milieu biologiquement pertinent est choisi dans le groupe formé par l'eau, les solutions électrolytiques aqueuses, les solutions aqueuses d'un sel, les solutions aqueuses d'un acide, les solutions aqueuses d'une base et les combinaisons de celles-ci.

**21.** Composition selon l'une quelconque des revendications 1 à 20, dans laquelle :

(a) la $T_{max}$ du principe actif, lorsque celui-ci est dosée dans le plasma d'un sujet mammifère à la suite d'une administration, est inférieure à la $T_{max}$ d'une composition non nanoparticulaire du même principe actif, administrée au même dosage ; ou
(b) la $C_{max}$ du principe actif, lorsque celui-ci est dosée dans le plasma d'un sujet mammifère à la suite d'une administration, est supérieure à la $C_{max}$ d'une composition non nanoparticulaire du même principe actif, administrée au même dosage ; ou
(c) l'AUC du principe actif, lorsque celui-ci est dosée dans le plasma d'un sujet mammifère à la suite d'une administration, est supérieure à l'AUC d'une composition non nanoparticulaire du même principe actif, administrée au même dosage.

**22.** Composition selon la revendication 21, dans laquelle la $T_{max}$ est choisie dans le groupe formé par pas plus d'environ 90%, pas plus d'environ 80%, pas plus d'environ 70%, pas plus d'environ 60%, pas plus d'environ 50%, pas plus d'environ 30%, pas plus d'environ 25%, pas plus d'environ 20%, pas plus d'environ 15%, pas plus d'environ 10% et pas plus d'environ 5% de la $T_{max}$ présentée par une composition non nanoparticulaire du même principe actif, administrée au même dosage.

**23.** Composition selon la revendication 21, dans laquelle la $C_{max}$ est choisie dans le groupe formé par au moins environ 50%, au moins environ 100%, au moins environ 200%, au moins environ 300%, au moins environ 400%, au moins environ 500%, au moins environ 600%, au moins environ 700%, au moins environ 800%, au moins environ 900%, au moins environ 1 000%, au moins environ 1 100%, au moins environ 1 200%, au moins environ 1 300%, au moins environ 1 400%, au moins environ 1 500%, au moins environ 1 600%, au moins environ 1 700%, au moins environ 1 800% ou au moins environ 1 900% supérieure à la $C_{max}$ présentée par une composition non nanoparticulaire du même principe actif, administrée au même dosage.

**24.** Composition selon la revendication 21, dans laquelle l'AUC est choisie dans le groupe formé par au moins environ 25%, au moins environ 50%, au moins environ 75%, au moins environ 100%, au moins environ 125%, au moins environ 150%, au moins environ 175%, au moins environ 200%, au moins environ 225%, au moins environ 250%,

au moins environ 275%, au moins environ 300%, au moins environ 350%, au moins environ 400%, au moins environ 450%, au moins environ 500%, au moins environ 550%, au moins environ 600%, au moins environ 650%, au moins environ 700%, au moins environ 750%, au moins environ 800%, au moins environ 850%, au moins environ 900%, au moins environ 950%, au moins environ 1 000%, au moins environ 1 050%, au moins environ 1 100%, au moins environ 1 150% ou au moins environ 1 200% supérieure à l'AUC présentée par une composition non nanoparticulaire du même principe actif, administrée au même dosage.

**25.** Composition selon l'une quelconque des revendications 1 à 24, qui ne produit pas de niveaux d'absorption significativement différents lorsqu'elle est administrée en conditions post-prandiales par rapport à des conditions à jeun.

**26.** Composition selon la revendication 25, dans laquelle la différence d'absorption de la composition de principe actif selon l'invention, lorsque celle-ci est administrée à l'état post-prandial par rapport à l'état à jeun, est choisie dans le groupe formé par moins d'environ 100%, moins d'environ 90%, moins d'environ 80%, moins d'environ 70%, moins d'environ 60%, moins d'environ 50%, moins d'environ 40%, moins d'environ 30%, moins d'environ 25%, moins d'environ 20%, moins d'environ 15%, moins d'environ 10%, moins d'environ 5% et moins d'environ 3%.

**27.** Composition selon l'une quelconque des revendications 1 à 26, dans laquelle l'administration de la composition à un être humain à jeun est biologiquement équivalente à une administration de la composition à un sujet en phase post-prandiale.

**28.** Composition selon la revendication 27, dans laquelle la « bioéquivalence » est déterminée par:

(a) un intervalle de confiance à 90% compris entre 0,80 et 1,25 à la fois pour la $C_{max}$ et pour l'AUC ; ou
(b) un intervalle de confiance à 90% compris entre 0,80 et 1,25 pour l'AUC et un intervalle de confiance à 90% compris entre 0,70 et 1,43 pour la $C_{max}$.

**29.** Composition selon l'une quelconque des revendications 1 à 28, formulée en une forme galénique liquide et ayant une viscosité, à une vitesse de cisaillement de 0,1 (1/s), mesurée à 20°C, choisie dans le groupe formé par moins d'environ 2 000 mPa·s, d'environ 2 000 mPa·s à environ 1 mPa·s, d'environ 1 900 mPa·s à environ 1 mpa·s, d'environ 1 800 mPa·s à environ 1 mPa·s, d'environ 1 700 mPa·s à environ 1 mPa·s, d'environ 1 600 mPa·s à environ 1 mPa·s, d'environ 1 500 mPa·s à environ 1 mPa·s, d'environ 1 400 mPa·s à environ 1 mPa·s, d'environ 1 300 mPa·s à environ 1 mPa·s, d'environ 1 200 mPa·s à environ 1 mPa·s, d'environ 1 100 mPa·s à environ 1 mPa·s, d'environ 1 000 mPa·s à environ 1 mPa·s, d'environ 900 mPa·s à environ 1 mPa·s, d'environ 800 mPa·s à environ 1 mPa·s, d'environ 700 mPa·s à environ 1 mPa·s, d'environ 600 mPa·s à environ 1 mPa·s, d'environ 500 mPa·s à environ 1 mPa·s, d'environ 400 mPa·s à environ 1 mPa·s, d'environ 300 mPa·s à environ 1 mPa·s, d'environ 200 mPa·s à environ 1 mPa·s, d'environ 175 mPa·s à environ 1 mPa·s, d'environ 150 mPa·s à environ 1 mPa·s, d'environ 125 mPa·s à environ 1 mPa·s, d'environ 100 mPa·s à environ 1 mPa·s, d'environ 75 mPa·s à environ 1 mPa·s, d'environ 50 mPa·s, à environ 1 mPa·s, d'environ 25 mPa·s à environ 1 mPa·s, d'environ 15 mPa·s à environ 1 mPa·s d'environ 10 mPa·s à environ 1 mPa·s et d'environ 5 mPa·s à environ 1 mPa·s.

**30.** Composition selon la revendication 29, dans laquelle la viscosité de la forme galénique est :

(a) choisie dans le groupe formé par moins d'environ 1/200, moins d'environ 1/100, moins d'environ 1/50, moins d'environ 1/25 et moins d'environ 1/10 de la viscosité d'une forme galénique liquide d'une composition non nanoparticulaire du même principe actif, à approximativement la même concentration par mL de principe actif ; ou
(b) choisie dans le groupe formé par moins d'environ 5%, moins d'environ 10%, moins d'environ 15%, moins d'environ 20%, moins d'environ 25%, moins d'environ 30%, moins d'environ 35%, moins d'environ 40%, moins d'environ 45%, moins d'environ 50%, moins d'environ 55%, moins d'environ 60%, moins d'environ 65%, moins d'environ 70%, moins d'environ 75%, moins d'environ 80%, moins d'environ 85% et moins d'environ 90% de la viscosité d'une forme galénique liquide d'une composition non nanoparticulaire du même principe actif, à approximativement la même concentration par mL de principe actif.

**31.** Composition selon l'une quelconque des revendications 1 à 30, comprenant en outre un ou plusieurs excipients ou véhicules acceptables sur le plan pharmaceutique ou une combinaison de ceux-ci.

**32.** Composition selon l'une quelconque des revendications 1 à 31, pour une utilisation thérapeutique.

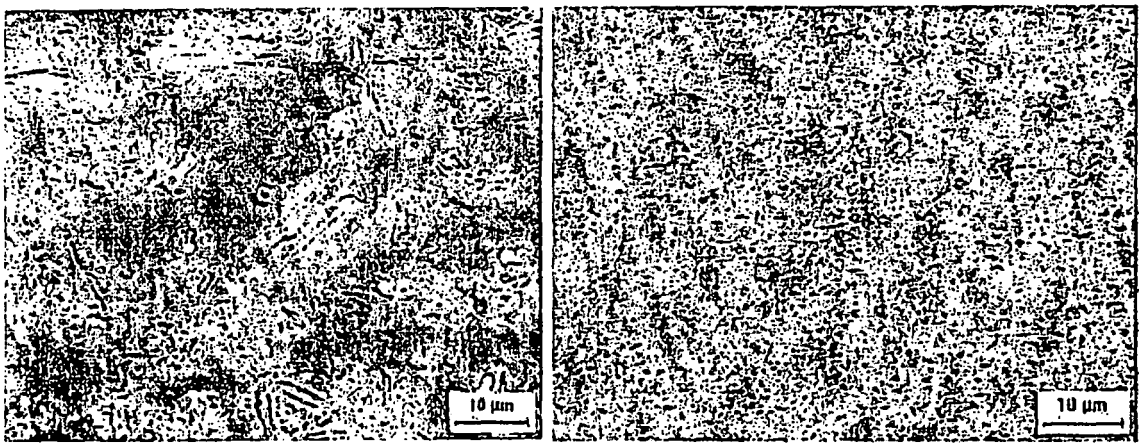
**33.** Procédé de fabrication d'une composition selon l'une quelconque des revendications 1 à 32, comprenant les étapes

consistant à mettre des particules d'au moins un principe actif en contact avec du bromhydrate de poly(lysine, tryptophane) 4:1 pendant une certaine durée et dans des conditions suffisantes pour fournir une composition de principe actif ayant une taille moyenne de particules effective inférieure à environ 2 000 nm.

# FIGURE 1

A

B



# FIGURE 2

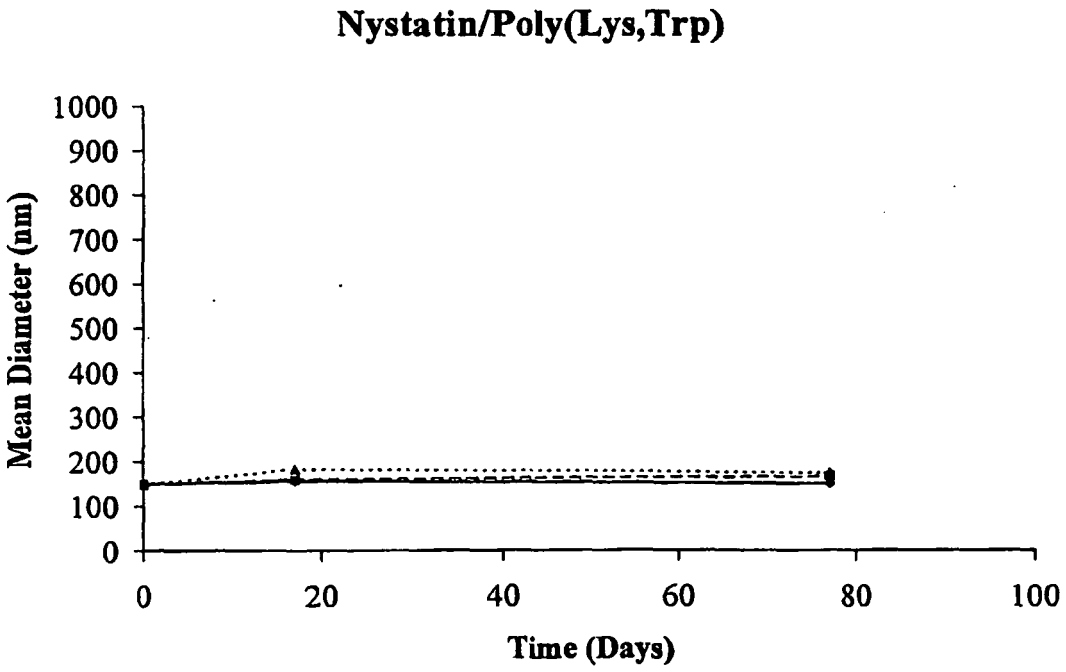
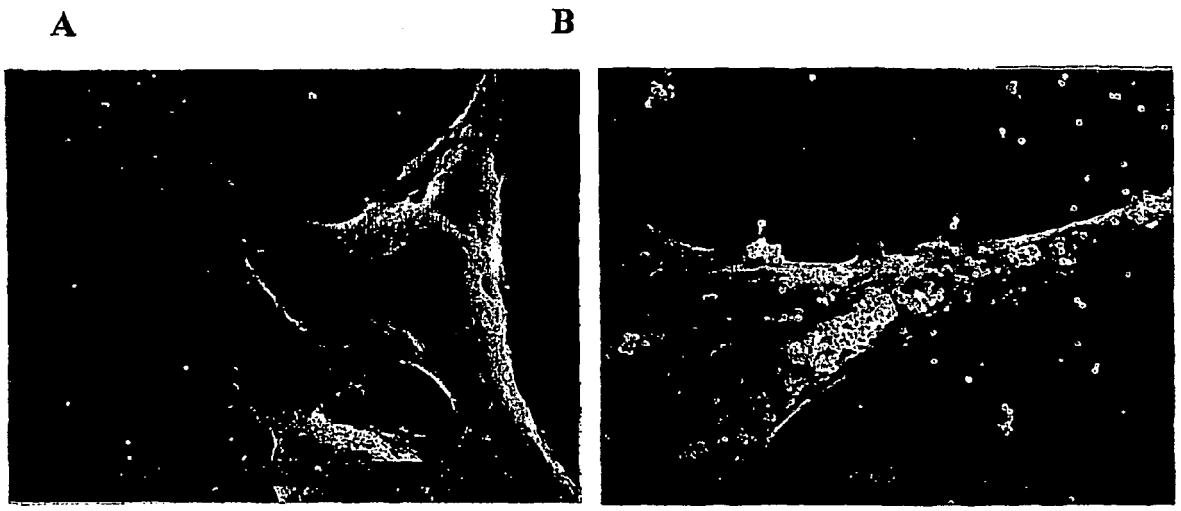

Nystatin/Poly(Lys,Trp)
Mean Diameter (nm)
1000
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
Time (Days)

FIGURE 3



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