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**WO 2005/013937 A2**

(54) Title: NOVEL COMPOSITIONS OF SILDENAFIL FREE BASE

(57) Abstract: The present invention is directed to nanoparticulate compositions comprising sildenafil free base. The sildenafil free base particles of the composition have an effective average particle size of less than about 2000 nm.

## NOVEL COMPOSITIONS OF SILDENAFIL FREE BASE

### RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Patent  
5 Application No. 60/489,101, filed on July 23, 2003.

### FIELD OF THE INVENTION

[0002] The present invention relates to compositions of sildenafil free base  
having an effective average particle size of less than about 2 microns.  
Preferably, the compositions also comprise at least one surface stabilizer  
10 associated with the surface of the sildenafil free base particles. The  
compositions of the invention surprisingly substantially eliminate fed/fasted  
variability of absorption of the drug.

### BACKGROUND OF THE INVENTION

#### A. Background Regarding Nanoparticulate Compositions

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[0003] Nanoparticulate 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 associated with the surface thereof a  
non-crosslinked surface stabilizer. The '684 patent does not describe  
20 nanoparticulate compositions of sildenafil, including sildenafil free base.

[0004] Methods of making nanoparticulate 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.  
25 Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions

Containing Nanoparticles.” These patents do not describe methods of making nanoparticulate sildenafil, including sildenafil free base.

[0005] Nanoparticulate 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 Non-Magnetic 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  
5 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  
10 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 Anhydrides 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  
15 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  
20 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  
25 "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  
30 "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  
5 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  
10 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  
15 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  
20 Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,582,285 for "Apparatus for sanitary wet milling;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;"  
25 6,742,734 for "System and Method for Milling Materials;" and 6,745,962 for "Small Scale Mill and Method Thereof;" all of which are specifically incorporated by reference. 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  
30 for Milling Materials," describe nanoparticulate active agent compositions, and

are specifically incorporated by reference. None of these references describe nanoparticulate compositions of sildenafil, including sildenafil free base.

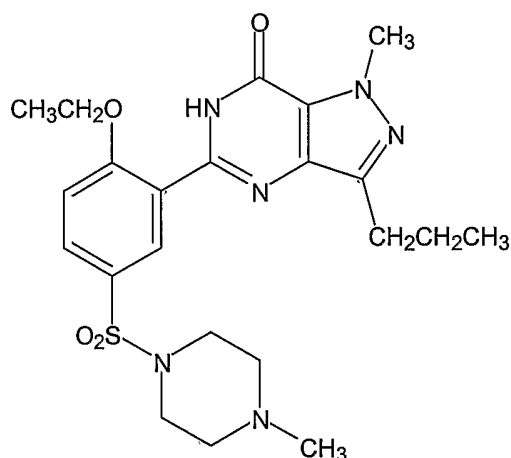
**[0006]** Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized  
5 Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method 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  
10 Porous Particles for Enhancing Ultrasound Back Scatter." These references do not describe nanoparticulate sildenafil free base.

**B. Background Regarding Sildenafil Free Base and Sildenafil Citrate**

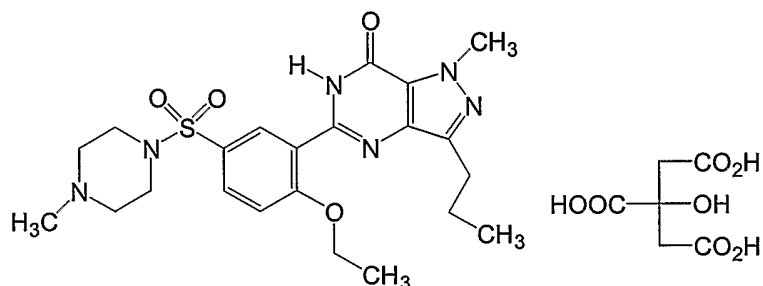
[0007] Sildenafil, including sildenafil free base and sildenafil citrate, is a phosphodiesterase 5 (PDE5) inhibitor. PDE5 is a cyclic guanosine-3',5'-  
5 monophosphate (cGMP)-specific phosphodiesterase belonging to a class of phosphodiesterases which regulate various cell functions by catalyzing the hydrolysis of the second messenger molecules (cGMP) and cyclic adenosine-3',5'-monophosphate (cAMP). Boolell et al., *Int'l J. Impot. Res.*, 8:47 (1996).

[0008] Sildenafil, also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-  
10 1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, as well as methods of preparing this compound and salts and derivatives thereof, and methods of use for treatment of erectile dysfunction (ED), are discussed in U.S. Patent Nos. 5,250,534 for "Pyrazolopyrimidinone Antianginal Agents" and 6,469,012 for  
15 "Pyrazolopyrimidinones for the Treatment of Impotence." See also EP 463,756.

[0009] Sildenafil free base has the following structure:



[0010] According to the *Physician's Desk Reference* (2003), sildenafil citrate  
20 has the following chemical structural formula:



**[0011]** Sildenafil, including sildenafil free base and sildenafil citrate, is a selective inhibitor of cGMP-specific PDE5. See *The Physicians' Desk Reference*, 55<sup>th</sup> Ed., pp. 2454 (2001). Sildenafil shows the following  
 5 selectivity with respect to PDE5: > 80-fold for PDE1, >1000-fold for PDE2 and PDE4, and >~4,000-fold for PDE3. Sildenafil is only approximately 10-fold as potent for PDE5 as compared to PDE6, however, and the inhibition of PDE6 has caused visual disturbances in some subjects.

**[0012]** Sildenafil citrate, which is marketed under the tradename VIAGRA®  
 10 (Pfizer, Inc., USA) in 25, 50, and 100 mg tablets, is also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4 methylpiperazine citrate.

**[0013]** Sildenafil citrate has a an empirical formula of  $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$  and a molecular weight of 666.71. See *The Physicians' Desk Reference*, 55<sup>th</sup>  
 15 Ed., pp. 2534 (2001); and *The Merck Index*, 13<sup>th</sup> Ed., pp. 1523 (Merck & Co. 2001). Sildenafil citrate has a solubility of 3.5 mg/mL in water. See *The Physicians' Desk Reference* at pp.2534.

**[0014]** The absolute bioavailability of sildenafil citrate is 40% and the pharmacokinetics are dose-proportional in the range of 25-100 mg. See *The  
 20 Physicians' Desk Reference*, 55<sup>th</sup> Ed., pp. 2535 (2001).

**[0015]** In healthy adult males, a 100 mg oral dose of sildenafil citrate results in a mean  $C_{max}$  of 440 ng/mL, a  $T_{max}$  of 60 minutes, and a  $t_{1/2}$  of about 4 hours. Absorption takes place mainly from the small intestine, thus gastric emptying is important in the onset of action. Administration of sildenafil citrate  
 25 with a high fat meal causes a mean delay in  $T_{max}$  of 60 minutes and a mean reduction in  $C_{max}$  of 29%. See *The Physicians' Desk Reference*, 55<sup>th</sup> Ed., pp. 2535 (2001).



[0016] Sildenafil citrate has been tested and approved by the FDA for relief treatment of ED in males only; however, it also may be useful in treating female sexual dysfunction and is currently being tested for this purpose.

[0017] The side effects associated with sildenafil citrate include headache, flushing, visual effects, and dyspepsia. Sildenafil citrate is contraindicated in subjects taking organic nitrates.

## 1. Sildenafil and Sexual Dysfunction

[0018] PDE5, which is specifically inhibited by sildenafil, is implicated in the mechanisms of both male and female sexual dysfunction. Research related to male sexual dysfunction focuses mainly on ED, which is defined as the persistent inability of a man to achieve and/or maintain an erection adequate for satisfactory sexual performance. *NIH Consensus Statement of Impotence, Int'l J. Impot. Res.*, 5:181 (1993). Sildenafil citrate (VIAGRA®; Pfizer, Inc., USA) is the first, and currently the only, PDE5 inhibitor approved by the FDA for the treatment of ED. Sildenafil citrate is not presently approved for use in treating female sexual dysfunction; however, this use of sildenafil citrate is currently being evaluated in clinical trials.

[0019] ED affects an estimated 152 million men worldwide. Aytac et al., *BJU Int'l*, 84:50 (1999). Between 2 and 7% of the human male population suffers from ED, with the prevalence increasing with age. Leu, *N. Engl. J. Med.*, 342:1802 (2000). In the United States alone, for example, it is estimated that there are up to 30 million males currently afflicted with ED, and 617,000 new cases of ED are expected annually in men between the ages of 40 and 69. *NIH Publication No. 95-3923* (1995). In addition to age, other factors that increase the likelihood of ED are heart disease, hypertension, diabetes, and medications associated with these conditions. Feldman et al., *J. Urol.*, 151:54 (1994).

[0020] Because up to 80% ED cases have a physiological etiology, it is desirable to effectively manage ED by targeting the physiological source of

the problem. *NIH Publication No. 95-3923* (1995). Sildenafil, which is a selective inhibitor of PDE5, is useful in treating ED. Boolell et al., *Br. J. Urol.*, 78:257-61 (1996).

**[0021]** In the healthy male, sexual stimulation triggers release of nitric oxide (NO) from the non-adrenergic, non-cholinergic neurons in the corpus cavernosum of the penis. NO activates guanylate cyclase, which catalyzes the conversion of 5-guanosine triphosphate (5-GTP) to 3', 5'-cGMP. cGMP mediates intracellular signal transduction via a protein activation cascade. This cell signaling cascade results in reduced intracellular  $Ca^{2+}$  concentrations causing relaxation of the smooth muscles in the penis, vasodilation in the corpus cavernosum, and ultimately erection. Moreland et al., *JPET*, 296:225 (2001).

**[0022]** Inhibition of PDE5 by sildenafil enhances the normal action of NO and cGMP. See Boolell et al., *Br. J. Urol.*, 78:257-61 (1996); and Boolell et al., *Int. J. Impot. Res.*, 8:47-52 (1996). PDE5 inhibition by sildenafil in the corpus cavernosum leads to an increase in the intracellular cGMP level, relaxing the smooth musculature of the corpus cavernosum and allowing the flow of blood into the corpus cavernosum resulting in an erection. As such, sildenafil does not cause an erection directly, but rather intensifies the action of the NO released during sexual stimulation. Andersson and Wagner, *Physiol Rev.*, 75:191-236 (1995).

**[0023]** Female sexual dysfunction has only recently been the focus of studies involving sildenafil, but it is now thought to have a physiological basis similar to ED. Female sexual dysfunction is defined as disturbances in sexual desire, arousal, or ability to achieve orgasm. Female sexual dysfunction also includes sexual pain disorders. It is estimated that about 40 million women in the United States experience some form of sexual disorder. In contrast to males, the incidence of female sexual dysfunction does not correlate with age. The incidence of female sexual dysfunction is evenly distributed among women 18 to 59 years of age.

[0024] Due to the similarities between the corpus cavernosum and the clitoris with respect to both structure and innervation, it is thought that the mechanism of female sexual dysfunction and, as a result, the treatment of female sexual dysfunction, mirrors that of ED in males.

5 [0025] A sildenafil composition useful in treating sexual dysfunction must have certain features. It must be easily absorbed from the gastrointestinal tract, rapidly reach the target tissue without affecting the vascular system, selectively inhibit PDE5, and have negligible deposition in other tissues. Sildenafil compositions lacking sufficient selectivity for PDE5 as compared to  
10 other PDE isoforms can cause unpleasant or potentially dangerous side effects due to inhibition of PDE isoforms responsible for modulating the signal for other cellular processes.

## 2. Sildenafil and Other Conditions

15

[0026] Although the focus of research of sildenafil has been sexual dysfunction, the ability of this compound to effect smooth muscle relaxation makes it useful in treating other conditions. For example, sildenafil can be particularly useful in treating diseases characterized by disorders of gut  
20 motility, e.g., irritable bowel syndrome.

## 3. Adverse Properties of Sildenafil Citrate

[0027] Despite the demonstrated safety of sildenafil citrate for the treatment  
25 of ED, the drug still causes side effects. Subjects report gastrointestinal distress, visual disturbances, flushing, head, back and muscle aches, and hypotension. These side effects are due, in part, to inhibition of PDE isoforms other than PDE5 as well as to the significantly different absorption levels observed between administration under fed and fasted conditions. For  
30 example, it is known that the visual disturbances experienced by sildenafil

citrate are caused by inhibition of PDE6, and that flushing is due to inhibition of PDE1.

**[0028]** Thus, it is desirable to obtain dosage forms of sildenafil having fewer side effects. In addition, it is desirable to administer the minimum amount of sildenafil required to provide a satisfactory therapeutic response.

**[0029]** Sildenafil is contraindicated for concomitant use of organic nitrates, such as nitroglycerine, because the drug potentiates nitrate-induced vasodilation. The amount of time required to clear sildenafil from a subject's system to allow for safe administration of nitrates is not currently known.

10 Because there is significant overlap between the population most likely to suffer from ED and those who have heart disease and may require use of nitrates, this is of particular concern. Minimizing the dosage of sildenafil will result in faster clearing of the compounds.

#### 4. Prior Descriptions Relating to Sildenafil

[0030] U.S. Patent No. 6,395,300 for "Porous Drug Matrices and Methods of Manufacture Thereof," describes dosage forms of poorly water soluble drugs, including sildenafil citrate. The dosage form consists of a porous drug matrix of drug microparticles. The drug matrices are made by: (i) dissolving a drug, such as sildenafil citrate, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound.

[0031] One disadvantage of this dosage form and method of preparation is that the method requires the use of volatile solvents. Solvent precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents cannot be completely removed by practical manufacturing techniques, and it can be very difficult and expensive, if not impossible, to adequately remove the residual solvents to pharmaceutically acceptable levels.

[0032] The amounts of residual solvents present in pharmaceutical products are strictly limited. For example, USP Method 467 specifies that the permissible levels of solvents in pharmaceuticals may not exceed 50 ppm for chloroform and 100 ppm for several other organic volatile impurities. See AN 228-255, "Headspace Analysis of Organic Volatile Impurities in Bulk Pharmaceutical Chemicals," 1-6, at 2 (Hewlett Packard 1995).

[0033] Even trace amounts of organic solvents are undesirable because, in addition to lacking any therapeutic benefit, such solvents can be highly toxic. See R. James' "The Toxic Effects of Organic Solvents," *Ind. Tox.*, P.L. Williams et al., Eds., 230-259 (Van Nostrand Reinhold Co., New York, NY 1985). Organic solvents can cause depression of the central nervous

systems (CNS) activity and irritation of membranes and tissues. *Id.* at 230-231. Because most organic solvents with few or no functional groups (which usually serve to increase water solubility) are highly lipophobic, they all possess varying degrees of CNS-depressant activity. *Id.* at 231. All organic solvents have some irritant properties. Because cell membranes within the body are largely a protein-lipid matrix, organic solvents are ideal for extracting the fat or lipid portion out of the membrane. This defatting of the skin causes irritation and cell damage, and may seriously injure the skin, lungs, and eyes. After systemic absorption, other acute toxicities are hepatotoxicity (liver toxicity), nephrotoxicity (kidney), and cardiac arrhythmias induced by a sensitization of the heart to catecholamines. *Id.* at 232.

**[0034]** U.S. Patent No. 6,395,300 teaches that nanoparticulate active agents are undesirable, as they “can be difficult to produce and maintain in a stable form due to the tendency of the nanoparticles to flocculate or agglomerate, particularly without the presence of surface modifying agents adsorbed or coated onto the particles.” The patent also teaches that milling or wet grinding of pharmaceutical active agents is undesirable “as it can take several days to process a single batch, scaling-up of the milling or grinding process can be difficult and/or costly, the process can be difficult to conduct aseptically, and it is difficult to eliminate shedding of milling media into the product.”

**[0035]** U.S. Patent Application Publication No. 20020142050, for “Porous Drug Matrices and Methods of Manufacture Thereof,” has the same disclosure as and claims priority of U.S. Patent No. 6,395,300.

**[0036]** U.S. Patent Nos. 6,395,736 and 6,391,869, both for “Compositions and Methods for the Treatment of Anorectal Disorders”, refer to compositions and methods for treating anorectal disorders. The compositions comprise a nitric oxide donor in combination with a second agent, which can be a PDE5 inhibitor such as sildenafil.

**[0037]** U.S. Patent No. 6,395,736 teaches that “to increase bioavailability of drugs, to extend therapeutic efficacy, and to improve patient compliance,

various dosage forms have been developed over the years. These include . . . liposomal and drug delivery via nanoparticles (emulsion, suspension, etc.), and ointment (See Edman, *Biopharmaceutics of Ocular Drug Delivery*, CRC Press, 1993).” This reference to “nanoparticles” does not teach the  
5 nanoparticulate compositions of the present invention; rather, it refers to lipid nanoparticles containing solubilized drug.

**[0038]** U.S. Patent Application Publication No. 20020003179, for “Media Milling,” describes a process for preparing a dispersion of solid particles of a milled substrate in a fluid carrier. An example of a compound to be milled is  
10 sildenafil. The method comprises utilizing two sizes of milling media: large and small (the use of multiple sizes of grinding media to mill active agents is also taught, for example, in U.S. Patent No. 6,431,478 for “Small Scale Mill.”). The reference does not teach milling of sildenafil free base, nor does it teach a sildenafil composition having a minimal difference in pharmacokinetic profiles  
15 when administered under fed as compared to fasted conditions.

**[0039]** There is a need in the art for sildenafil compositions which overcome these and other problems associated with prior sildenafil formulations. The present invention satisfies these needs.

### SUMMARY OF THE INVENTION

20 **[0040]** The present invention relates to compositions comprising sildenafil free base particles having an effective average particle size of less than about 2 microns. Preferably, the compositions comprise particles of sildenafil free base and at least one surface stabilizer associated with the surface of the sildenafil free base particles. The nanoparticulate sildenafil free base  
25 compositions substantially eliminate the effect of food on the pharmacokinetic profiles of the compositions.

**[0041]** The present invention also relates to compositions of nanoparticulate sildenafil free base in combination with one or more non-nanoparticulate (*i.e.*, solubilized or microparticulate) sildenafil or non-sildenafil compounds, or  
30 nanoparticulate non-sildenafil free base active agents. If such other non-

sildenafil free base active agents have a nanoparticulate particle size, then preferably such other non-sildenafil free base active agents have one or more surface stabilizers associated with the surface of the active agent.

**[0042]** Another aspect of the invention is directed to pharmaceutical compositions comprising a sildenafil free base composition of the invention. The pharmaceutical compositions preferably comprise particles of sildenafil free base having an effective average particle size of less than about 2 microns and a pharmaceutically acceptable carrier, as well as any desired excipients. Preferably, the compositions also comprise at least one surface stabilizer associated with the surface of the sildenafil free base particles. Such pharmaceutical compositions can additionally comprise one or more of the following: (1) non-nanoparticulate sildenafil (free base and citrate forms), (2) non-nanoparticulate non-sildenafil free base active agents, or (3) nanoparticulate non-sildenafil free base active agents.

**[0043]** This invention is also directed to a method of making a nanoparticulate sildenafil free base composition according to the invention. Such a method comprises contacting sildenafil free base and at least one surface stabilizer for a time and under conditions sufficient to provide a sildenafil free base composition having an effective average particle size of less than about 2 microns. The one or more surface stabilizers can be contacted with sildenafil free base either before, preferably during, or after particle size reduction. In addition, one or more non-sildenafil free base active agents can be reduced in size at the same time as sildenafil free base, to produce a nanoparticulate sildenafil free base composition and nanoparticulate non-sildenafil free base active agent composition. A non-sildenafil free base active agent, which is either non-nanoparticulate (solubilized or microparticulate) or nanoparticulate, can also be added to the nanoparticulate sildenafil free base composition after particle size reduction.

**[0044]** The present invention is directed to methods of using the nanoparticulate sildenafil free base compositions of the invention for conditions in which a PDE5 inhibitor is prescribed. Such conditions include,



but are not limited to, for example, male erectile dysfunction, impotence, female sexual dysfunction, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder, female sexual orgasmic dysfunction, and sexual dysfunction due to spinal  
5 cord injury.

**[0045]** Other conditions that may be treated using the nanoparticulate sildenafil free base compositions of the invention include, but are not limited to, premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal)  
10 angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, post-percutaneous transluminal coronary angioplasty, peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis,  
15 glaucoma, diseases characterized by disorders of gut motility, irritable bowel syndrome, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, hemorrhoids, and hypoxic  
20 vasoconstriction.

**[0046]** Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate sildenafil free base composition according to the invention. Alternatively, such methods comprise administering to a subject a therapeutically effective amount of a  
25 nanoparticulate sildenafil free base composition according to the invention in combination with one or more non-sildenafil free base agents. Such non-sildenafil free base active agents can be either non-nanoparticulate (solubilized or microparticulate) or nanoparticulate.

**[0047]** Both the foregoing general description and the following brief  
30 description of the drawings and 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

- 5 [0048] Figure 1: shows the mean sildenafil concentration (ng/mL) for Formulation #2 (nanoparticulate sildenafil free base), Formulation #4 (nanoparticulate sildenafil citrate), and Formulation #5 (microparticulate sildenafil citrate; Viagra®), given under fed and fasted conditions, over a 2 hour time
- 10 period; and
- [0049] Figure 2: shows the mean sildenafil concentration (ng/mL) for Formulation #2 (nanoparticulate sildenafil free base), Formulation #4 (nanoparticulate sildenafil citrate), and Formulation #5 (microparticulate sildenafil citrate; Viagra®),
- 15 given under fed and fasted conditions, over an 8 hour time period.

### DETAILED DESCRIPTION OF THE INVENTION

[0050] The present invention is directed to compositions comprising particles of sildenafil free base having an effective average particle size of

20 less than about 2 microns. Preferably, the sildenafil free base particles have one or more surface stabilizers associated with the surface of the sildenafil free base particles.

[0051] It was surprisingly discovered that the nanoparticulate sildenafil free base compositions of the invention demonstrate substantially similar

25 pharmacokinetic profiles when administered under fed and fasted conditions.

[0052] In another embodiment of the invention, preferably the compositions of the invention are bioequivalent when administered under fed and fasted conditions. Under U.S. Food and Drug Administration (USFDA) guidelines,

two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for  $C_{max}$  (peak concentration) and the AUC (area under the concentration/time curve) are between 0.80 to 1.25. For Europe, the test for bioequivalency is if two products or methods have a 90% CI for AUC of  
5 between 0.80 to 1.25 and a 90% CI for  $C_{max}$  of between 0.70 to 1.43. ( $T_{max}$  is not relevant to bioequivalency determinations under USFDA and European regulatory guidelines.)

**[0053]** This is significant, as it means that there is no substantial difference in the quantity of sildenafil free base absorbed, or the rate of sildenafil free  
10 base absorption, when the nanoparticulate sildenafil free base compositions are administered in the fed versus the fasted state. Therefore, the nanoparticulate sildenafil free base compositions of the invention can substantially eliminate the effect of food on the pharmacokinetics of the drug.

**[0054]** Prior to the present invention, it was known that non-nanoparticulate  
15 forms of sildenafil citrate (*i.e.*, Viagra®) exhibit a substantial difference in drug absorption when administered under fed as compared to fasted conditions. It was surprisingly discovered that this same fed/fasted variability is observed with nanoparticulate forms of sildenafil citrate; *only* nanoparticulate sildenafil free base dosage forms exhibited a substantially similar pharmacokinetic  
20 profile when administered under fed and fasted conditions.

**[0055]** As described in the examples below, Viagra® administered under fed and fasted conditions exhibited an  $AUC_{inf}$  of 2514 ng/mL·h and 1749.6 ng/mL·h, respectively – a difference of 764.4 ng/mL·h or ~ 30%. A nanoparticulate sildenafil citrate composition administered under fed and  
25 fasted conditions exhibited an  $AUC_{inf}$  of 1335.2 ng/mL·h and 897.8 ng/mL·h, respectively – a difference of 437.4 ng/mL·h or ~ 33%. In surprising contrast to these results, a nanoparticulate sildenafil free base composition, administered under fed and fasted conditions, exhibited an  $AUC_{inf}$  of 2127.8 ng/mL·h and 2105.3 ng/mL·h, respectively – a difference of 22.5 ng/mL·h or  
30 about 1%. A difference of 22.5 ng/mL·h is almost *40 times* less than the fed/fasted variability observed with Viagra®, and over *19 times* less than the

fed/fasted variability observed with a nanoparticulate sildenafil citrate composition.

**[0056]** Moreover, as further described in the examples below, the  $T_{max}$  and  $C_{max}$  profiles for the nanoparticulate sildenafil free base composition were  
5 substantially similar when administered under fed and fasted conditions: ~ 11% difference for  $C_{max}$  and a 4% difference for  $T_{max}$ . In contrast, both the Viagra® and nanoparticulate sildenafil citrate compositions showed dramatically different results for  $T_{max}$  and  $C_{max}$  when the formulations were administered under fed as compared to fasted conditions: for Viagra®, a  
10 ~23% difference in  $C_{max}$  and 60% difference in  $T_{max}$ , and for the nanoparticulate sildenafil citrate composition, a 49% difference in  $C_{max}$  and 52% difference in  $T_{max}$ .

**[0057]** Benefits of a dosage form which substantially eliminates the effect of food include a safer dosage form, as well as an increase in subject  
15 convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

**[0058]** Preferably, the difference in the AUC of the nanoparticulate sildenafil free base compositions of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about  
20 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, less than about 1%, or essentially no difference.

**[0059]** In addition, preferably the difference in the  $C_{max}$  of the nanoparticulate sildenafil free base compositions of the invention, when  
25 administered in the fed versus the fasted state, is 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.

**[0060]** Finally, preferably the difference in the  $T_{max}$  of the nanoparticulate  
30 sildenafil free base compositions of the invention, when administered in the fed versus the fasted state, is 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.

**[0061]** Other advantages of the sildenafil free base compositions of the invention as compared to non-nanoparticulate sildenafil compositions and/or nanoparticulate sildenafil citrate compositions may include, but are not limited to: (1) faster onset of action; (2) smaller tablet or other solid dosage form size, or smaller volume if in a liquid dosage form; (3) smaller doses of drug required to obtain the same pharmacological effect; (4) faster clearance from the bloodstream due to the smaller doses, thereby enabling safe administration of nitrates; (5) increased bioavailability; (6) improved pharmacokinetic profiles, such as improved  $C_{max}$ ,  $T_{max}$ , and/or AUC profiles; (7) an increased rate of dissolution; (8) bioadhesive sildenafil free base compositions; (9) the compositions do not require the use of potentially toxic solvents; and (10) the sildenafil free base compositions of the invention can be used in conjunction with other active agents.

**[0062]** In addition, the invention encompasses the sildenafil free base compositions of the invention formulated or coadministered with one or more non-sildenafil free base active agents, either non-nanoparticulate (solubilized or microparticulate) or nanoparticulate. Methods of using such combination compositions are also encompassed by the invention.

**[0063]** Nanoparticulate formulations of sildenafil free base can be administered with supplements known to be involved in the biosynthesis of cGMP. For example, L-arginine is involved in the biosynthesis of NO and thus administration of sildenafil free base in combination with L-arginine can enhance the overall efficacy of the composition.

**[0064]** Other exemplary types of active agents which can be used in combination with the nanoparticulate sildenafil free base compositions of the invention are described below. If the non-sildenafil free base active agent has a nanoparticulate particle size, then preferably such a non-sildenafil free base active agent has one or more surface stabilizers associated with the surface

of the active agent. The surface stabilizer(s) can be the same as or different from the surface stabilizer(s) associated with the surface of the nanoparticulate sildenafil free base.

5 [0065] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0066] "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  
10 particular term.

[0067] 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 sildenafil free base particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly  
15 increase in particle size over time; (2) that the physical structure of the sildenafil free base particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the sildenafil free base particles are chemically stable; and/or (4) where sildenafil free base has not been subject to a heating step at or above the melting point of sildenafil  
20 free base in the preparation of the nanoparticles of the invention.

[0068] "Non-nanoparticulate active agents" refers to compositions of solubilized active agents, or particulate active agents having 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  
25 about 2 microns.

#### **A. Additional Preferred Characteristics of the Sildenafil Free Base Compositions of the Invention**

##### **30 1. Fast Onset of Activity**

[0069] The use of conventional formulations of sildenafil for the treatment of male and female sexual dysfunction is not ideal due to delayed onset of

action. Conventional formulations of sildenafil have a  $T_{max}$  of approximately 60 minutes. Thus, conventional formulations of sildenafil require advance planning of sexual activity, precluding spontaneity. In addition, slow acting conventional formulations of sildenafil encourage unnecessary dosing, due to  
5 anticipation of sexual activity that may or may not transpire.

**[0070]** In contrast, the nanoparticulate sildenafil free base compositions of the invention, when formulated into a suitable dosage form enabling fast onset of activity, such as a nasal or pulmonary aerosol spray (either dry powder, non-aqueous, or aqueous), can provide faster therapeutic effects. Such  
10 dosage forms of the nanoparticulate sildenafil free base compositions of the invention are useful in treating sexual dysfunction where spontaneity is important and where the potential for pharmacological habituation exists.

## 2. Increased Bioavailability

[0071] The sildenafil free base compositions of the invention preferably exhibit increased bioavailability, at the same dose, and require smaller doses as compared to prior non-nanoparticulate sildenafil compositions as well as compared to nanoparticulate sildenafil citrate compositions.

[0072] Any drug, including sildenafil, can have adverse side effects. Thus, lower doses of sildenafil which can achieve the same or better therapeutic effects as those observed with larger doses of non-nanoparticulate sildenafil compositions and/or nanoparticulate sildenafil citrate compositions are desired. Such lower doses can be realized with the sildenafil free base compositions of the invention because the greater bioavailability observed with the nanoparticulate sildenafil free base compositions means that smaller doses of sildenafil free base are required to obtain the desired therapeutic effect.

## 3. Redispersibility Profiles of the Sildenafil Free Base Compositions of the Invention

[0073] An additional feature of the sildenafil free base compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed sildenafil free base particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate sildenafil free base compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating sildenafil free base into a nanoparticulate particle size.

[0074] Nanoparticulate sildenafil free base compositions benefit from the small particle size of sildenafil free base; if the nanoparticulate sildenafil free base particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated sildenafil free base particles are formed, owing to the extremely high surface free energy of the



nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate sildenafil free  
5 base composition.

**[0075]** Moreover, the nanoparticulate sildenafil free base compositions of the invention preferably exhibit dramatic redispersion of the nanoparticulate sildenafil free base particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a  
10 biorelevant aqueous media such that the effective average particle size of the redispersed sildenafil free base particles is less than about 2 microns. 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  
15 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.

**[0076]** Biorelevant pH is well known in the art. For example, in the human stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the human small intestine the pH can range from 4 to 6, and in the human 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).

**[0077]** 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.*

**[0078]** 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.

**[0079]** 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  
5 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.

**[0080]** Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to  
10 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.

**[0081]** In other embodiments of the invention, the redispersed sildenafil free  
15 base 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 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than  
5 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.

**[0082]** By “an effective average particle size of less than about 2000 nm” it is meant that at least 50% of the sildenafil free base particles have a particle  
10 size less than the effective average, by weight, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. Preferably, at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the sildenafil free base particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm,  
15 1700 nm, *etc.*

**[0083]** 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.”  
20

#### 4. Bioadhesive Sildenafil Free Base Compositions

**[0084]** Bioadhesive sildenafil free base compositions of the invention comprise at least one cationic surface stabilizer, which are described in more  
25 detail below. Bioadhesive formulations of sildenafil free base exhibit exceptional bioadhesion to biological surfaces, such as mucous.

**[0085]** The term bioadhesion refers to any attractive interaction between two biological surfaces or between a biological and a synthetic surface. In the case of bioadhesive nanoparticulate sildenafil free base compositions, the  
30 term bioadhesion is used to describe the adhesion between the nanoparticulate sildenafil free base composition 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," which is specifically incorporated by reference.

**[0086]** The bioadhesive sildenafil free base compositions of the invention  
5 are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive sildenafil free base compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

**[0087]** A bioadhesive sildenafil free base composition slows the transit of  
10 the composition, and some sildenafil free base particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to sildenafil free base, thereby increasing absorption and the bioavailability of the administered dosage.

## 5. Pharmacokinetic Profiles of the Sildenafil Free Base Compositions of the Invention

**[0088]** The present invention provides nanoparticulate sildenafil free base compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile can include one or more of the following characteristics: (1) the  $T_{max}$  of an administered dose of a nanoparticulate sildenafil free base composition can be less than that of a non-nanoparticulate sildenafil composition, or less than that of a nanoparticulate sildenafil citrate composition, administered at the same dosage; (2) the  $C_{max}$  of a nanoparticulate sildenafil free base composition can be greater than the  $C_{max}$  of a non-nanoparticulate sildenafil composition, or greater than the  $C_{max}$  of a nanoparticulate sildenafil citrate composition, administered at the same dosage; and/or (3) the AUC of a nanoparticulate sildenafil composition can be greater than the AUC of a non-nanoparticulate sildenafil composition, or greater than the AUC of a nanoparticulate sildenafil citrate composition, administered at the same dosage.

**[0089]** In healthy adult males, a 100 mg oral dose of sildenafil citrate results in a mean  $C_{max}$  of 440 ng/mL and a  $T_{max}$  of 60 minutes.

**[0090]** For nanoparticulate compositions of sildenafil free base according to the invention, a 100 mg oral dose in healthy adult males results in a mean  $C_{max}$  of greater than about 440 ng/mL, a  $T_{max}$  of less than about 60 minutes, or a combination thereof.

**[0091]** In comparative pharmacokinetic testing with a non-nanoparticulate sildenafil composition (e.g., Viagra®), or a nanoparticulate composition of sildenafil citrate, a nanoparticulate sildenafil free base composition, administered at the same dosage, preferably exhibits a  $T_{max}$  which is less than about 200%, less than about 175%, less than about 150%, less than about 125%, 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%, or less than about 10% of the  $T_{max}$  exhibited by the non-

nanoparticulate sildenafil composition or nanoparticulate sildenafil citrate composition.

**[0092]** The sildenafil free base compositions of the invention preferably have a  $T_{max}$  of less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 45 minutes, less than about 35 minutes less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, or less than about 10 minutes.

**[0093]** In comparative pharmacokinetic testing with a non-nanoparticulate sildenafil composition (*e.g.*, Viagra®) or a nanoparticulate sildenafil citrate composition, a nanoparticulate sildenafil free base composition, administered at the same dosage, preferably exhibits a  $C_{max}$  which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the  $C_{max}$  exhibited by the non-nanoparticulate sildenafil composition or nanoparticulate sildenafil citrate composition.

**[0094]** Following administration of a 100 mg oral dose of a nanoparticulate sildenafil free base composition of the invention, the resulting  $C_{max}$  is preferably greater than about 440 ng/mL, greater than about 450 ng/mL, greater than about 500 ng/mL, greater than about 550 ng/mL, greater than about 600 ng/mL, greater than about 650 ng/mL, greater than about 700 ng/mL, greater than about 750 ng/mL, greater than about 800 ng/mL, greater than about 850 ng/mL, greater than about 900 ng/mL, greater than about 950 ng/mL, greater than about 1000 ng/mL, greater than about 1050 ng/mL, greater than about 1100 ng/mL, greater than about 1150 ng/mL, greater than about 1200 ng/mL, greater than about 1250 ng/mL, greater than about 1300 ng/mL, about 1350 ng/mL, or greater than about 1400 ng/mL.

**[0095]** In comparative pharmacokinetic testing with a non-nanoparticulate sildenafil composition (e.g., Viagra®) or a nanoparticulate sildenafil citrate composition, a nanoparticulate sildenafil free base composition, administered at the same dosage, preferably exhibits an AUC which is greater than about  
5 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about  
10 140%, or greater than about 150% than the AUC exhibited by the non-nanoparticulate sildenafil composition or nanoparticulate sildenafil citrate composition.

**[0096]** The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after an initial dose of sildenafil free base.  
15 The compositions can be formulated in any way as described below.

**[0097]** Any sildenafil free base composition according to the invention, and providing a desired pharmacokinetic profile, is suitable for administration according to the methods of the invention.

## 6. Combination Pharmacokinetic Profile Compositions

[0098] In yet another embodiment of the invention, a first sildenafil free base composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other sildenafil  
5 composition that generates a desired different pharmacokinetic profile. More than two sildenafil compositions can be co-administered, sequentially administered, or combined. While at least one of the sildenafil compositions is a sildenafil free base composition having a nanoparticulate particle size, the additional one or more sildenafil compositions (sildenafil free base, sildenafil  
10 citrate, or other suitable sildenafil form) can be nanoparticulate, solubilized, or have a conventional microparticulate particle size.

[0099] For example, a first sildenafil free base composition can have a nanoparticulate particle size, conferring a short  $T_{max}$  and typically a higher  $C_{max}$ . This first sildenafil free base composition can be combined, co-  
15 administered, or sequentially administered with a second composition comprising: (1) sildenafil free base having a larger (but still nanoparticulate) particle size, and therefore exhibiting slower absorption, a longer  $T_{max}$ , and typically a lower  $C_{max}$ ; or (2) a microparticulate sildenafil composition exhibiting a longer  $T_{max}$ , and typically a lower  $C_{max}$ .

20 [0100] The second, third, fourth, *etc.*, sildenafil compositions can differ from the first, and from each other, for example, (1) in the effective average particle sizes of each sildenafil composition; (2) in the dosage of sildenafil; and/or (3) in the form of sildenafil utilized. Such a combination composition can reduce the dose frequency required.

25 [0101] 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.

### B. Compositions

30



**[0102]** The invention provides compositions comprising nanoparticulate sildenafil free base particles and, preferably, at least one surface stabilizer. Preferably, the one or more surface stabilizers are associated with the surface of the sildenafil free base particles. Surface stabilizers useful herein  
5 preferably do not chemically react with the sildenafil free base particles or itself, but are believed to be adsorbed or associated with the surface of the sildenafil free base particles. Moreover, preferably individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

**[0103]** The present invention includes nanoparticulate sildenafil free base  
10 compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral (in solid, liquid, or aerosol form), vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal,  
15 intracisternal, intraperitoneal, or topical administration, and the like.

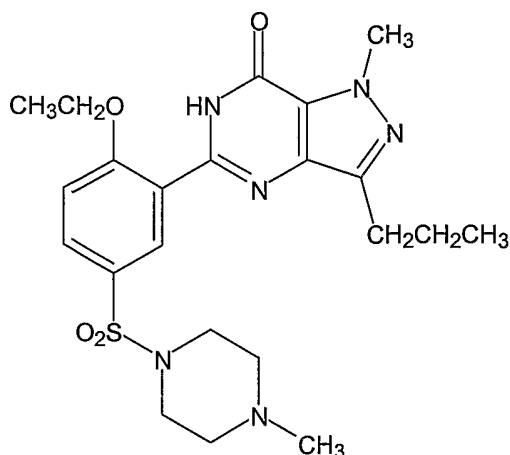
**[0104]** Nanoparticulate sildenafil free base compositions intended for fast onset of activity are preferably formulated into an aerosol or nasal spray.

## 1. Sildenafil Free Base Particles

20

**[0105]** "Sildenafil" as used herein encompasses sildenafil free base or a derivative thereof, which is a deprotonated form of a sildenafil salt, and which is a selective inhibitor of cGMP-specific PDE5.

**[0106]** Sildenafil free base has the following structure:



**[0107]** The sildenafil free base particles can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

**[0108]** Nanoparticulate sildenafil free base compositions are contemplated to be useful in treating a wide range of conditions and disorders for which a potent and selective PDE5 inhibitor is indicated, including but not limited to the prevention or treatment of mammalian sexual disorders and conditions characterized by decreased gut motility. In particular, such compositions have the potential for reduced side effects such as headache, back ache, muscle ache, painful or prolonged erection, priapism, hematuria, dizziness, rash, flushing, dyspepsia, nasal congestion, visual disturbances, and hypotension, when compared to compositions of conventional sildenafil.

Thus, nanoparticulate sildenafil free base compositions of the invention are particularly useful as an alternative to conventional sildenafil in subjects who are prone to experience significant side effects from traditional non-nanoparticulate sildenafil compositions.

**[0109]** Furthermore, nanoparticulate sildenafil free base compositions also have the potential for reduced adverse reactions with nitrates because nanoparticulate formulations enable administration of smaller doses of sildenafil free base, thus enabling faster clearance of sildenafil free base from the bloodstream.

## 2. Non-Sildenafil Active Agents

**[0110]** The nanoparticulate sildenafil free base compositions of the invention can additionally comprise another sildenafil form – such as sildenafil citrate – or one or more non-sildenafil active agents, in either a conventional or nanoparticulate particle size. The additional active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

**[0111]** If the additional active agent has a nanoparticulate particle size, then preferably it will have one or more surface stabilizers associated with the surface of the active agent. In addition, if the active agent has a nanoparticulate particle size, then it is preferably poorly soluble and 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.

**[0112]** Such active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including biologics such as amino acids, proteins, peptides, and nucleotides. The active agent can be selected from a variety of known classes of drugs, including, for example, non-sildenafil PDE5 inhibitors, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, 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, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough  
5 suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones (including steroids),  
10 anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

**[0113]** A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia*, 31<sup>st</sup> Edition (The Pharmaceutical Press, London, 1996),  
15 specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

**[0114]** Exemplary non-sildenafil PDE5 inhibitors include, but are not limited to, vardenafil, tadalafil, TA-1790, UK-114542, Compound 14, EMD221829, EMR 62 203, T-1032, M-54033, M-54018, or E-4010. The term "PDE5  
20 inhibitor" is used to mean any compound capable of inhibiting the enzyme phosphodiesterase type 5.

**[0115]** Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical  
25 Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements*, 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines*, 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known  
30 as phytochemicals or functional foods, 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,

5 glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (e.g., arginine, iso-leucine, leucine, lysine, methionine, phenylalanine, 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.

10 Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

**[0116]** Preferred combination therapies comprise a composition useful in methods of the invention with one or more active agents selected from alpha-  
15 adrenergic receptor blocking agents, such as yohimbine, delaquamine, phenotolamine and doxazosin, prostaglandins and prostoglandin analogs such as alprostadil and misoprostol, testosterone, anti-depressants such as trazodone, L-arginine, apomorphine, NO donors, and central nervous system stimulants.

20 **[0117]** Particularly preferred herbs and nutraceuticals of the invention are those known to be involved in biosynthesis/mediation of NO and cGMP, such as L-arginine and those known to be enhance sexual health and well-being, such as yohimbine, *Cornus officinalis*, *Cinnamomum aromaticum*, *Panax ginseng*, and *Pulsatilla pratensis*.

25 **[0118]** The compound to be administered in combination with a nanoparticulate sildenafil free base composition of the invention can be formulated separately from the sildenafil free base composition or co-  
30 formulated with the sildenafil free base composition. Where a sildenafil free base composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

### 3. Surface Stabilizers

[0119] The choice of one or more surface stabilizers for nanoparticulate  
5 sildenafil free base is non-trivial and required extensive experimentation to  
realize a desirable formulation.

[0120] Combinations of more than one surface stabilizer can be used in the  
invention. Useful surface stabilizers which can be employed in the invention  
include, but are not limited to, known organic and inorganic pharmaceutical  
10 excipients. Such excipients include various polymers, low molecular weight  
oligomers, natural products, and surfactants. Surface stabilizers include  
nonionic, cationic, ionic, and zwitterionic compounds.

[0121] Representative examples of surface stabilizers include, but are not  
limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose,  
15 polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, 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  
20 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty  
acid esters (e.g., the commercially available Tweens<sup>®</sup> such as e.g., Tween  
20<sup>®</sup> and Tween 80<sup>®</sup> (ICI Speciality Chemicals)); polyethylene glycols (e.g.,  
Carbowaxs 3550<sup>®</sup> and 934<sup>®</sup> (Union Carbide)), polyoxyethylene stearates,  
colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium,  
25 carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose,  
hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium  
aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-  
tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also  
known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronic F68<sup>®</sup>  
30 and F108<sup>®</sup>, which are block copolymers of ethylene oxide and propylene  
oxide); poloxamines (e.g., Tetronic 908<sup>®</sup>, also known as Poloxamine 908<sup>®</sup>,

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<sup>®</sup> (T-1508, a poloxamine) (BASF Wyandotte Corporation), Tritons X-200<sup>®</sup>, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110<sup>®</sup>, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-IOG<sup>®</sup> or Surfactant 10-G<sup>®</sup> (Olin Chemicals, Stamford, CT); Crodestas SL-40<sup>®</sup> (Croda, Inc.); and SA9OHCO, which is C<sub>18</sub>H<sub>37</sub>CH<sub>2</sub>C(O)N(CH<sub>3</sub>)-CH<sub>2</sub>(CHOH)<sub>4</sub>(CH<sub>2</sub>OH)<sub>2</sub> (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-nonyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

**[0122]** Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulose, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

**[0123]** 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, decyl

triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C<sub>12-15</sub>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)<sub>4</sub> ammonium chloride or bromide, N-alkyl (C<sub>12-18</sub>)dimethylbenzyl ammonium chloride, N-alkyl (C<sub>14-18</sub>)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C<sub>12-14</sub>) dimethyl 1-naphthylmethyl 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<sub>12-14</sub>) 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<sub>12</sub>, C<sub>15</sub>, C<sub>17</sub> 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 (ALQUAT 336™), POLYQUAT 10™ (polyquaternium 10; Buckman Laboratories, TN), tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearylalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ (quaternized ammonium salt polymers) and ALKAQUAT™ (benzalkonium chloride) (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  
5 quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

**[0124]** Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic*  
10 *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).

**[0125]** Nonpolymeric surface stabilizers are any nonpolymeric compound,  
15 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 ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary  
20 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  $CH_3$ ;
- 25 (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  $R_1$ -  
30  $R_4$  is an alkyl chain of nineteen carbon atoms or more;

- (vii) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub> and one of R<sub>1</sub>-R<sub>4</sub> is the group C<sub>6</sub>H<sub>5</sub>(CH<sub>2</sub>)<sub>n</sub>, where n>1;
- (viii) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub>, one of R<sub>1</sub>-R<sub>4</sub> is C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, and one of R<sub>1</sub>-R<sub>4</sub> comprises at least one heteroatom;
- 5 (ix) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub>, one of R<sub>1</sub>-R<sub>4</sub> is C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, and one of R<sub>1</sub>-R<sub>4</sub> comprises at least one halogen;
- (x) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub>, one of R<sub>1</sub>-R<sub>4</sub> is C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, and one of R<sub>1</sub>-R<sub>4</sub> comprises at least one cyclic fragment;
- (xi) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub> and one of R<sub>1</sub>-R<sub>4</sub> is a phenyl ring; or
- 10 (xii) two of R<sub>1</sub>-R<sub>4</sub> are CH<sub>3</sub> and two of R<sub>1</sub>-R<sub>4</sub> are purely aliphatic fragments.

**[0126]** Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, 15 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) oleyl 20 ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearakonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine 25 hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearakonium bentonite, stearakoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

30 **[0127]** The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Many 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, 2000), specifically incorporated by reference.

#### 4. Other Pharmaceutical Excipients

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[0128] Pharmaceutical sildenafil free base compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0129] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel<sup>®</sup> PH101 and Avicel<sup>®</sup> PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC<sup>™</sup>).

[0130] Suitable lubricants, including agents that act on the flowability of a powder to be compressed, are colloidal silicon dioxide, such as Aerosil<sup>®</sup> 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0131] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents are Magnasweet<sup>®</sup> (trademark of MAFCO), bubble gum flavor, mint flavor, and fruit flavors, and the like.

[0132] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride.

[0133] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel<sup>®</sup> PH101 and Avicel<sup>®</sup> PH102;

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lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose<sup>®</sup> DCL21; dibasic calcium phosphate such as Emcompress<sup>®</sup>; mannitol; starch; sorbitol; sucrose; and glucose.

[0134] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, 5 croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0135] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids 10 include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the 15 sodium bicarbonate component of the effervescent couple may be present.

## 5. Nanoparticulate Sildenafil Free Base and Non-Sildenafil Active Agent Particle Size

[0136] The compositions of the invention comprise sildenafil free base 20 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 sildenafil free base particles 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 25 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, 30 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.

**[0137]** If the composition additionally comprises one or more nanoparticulate non-sildenafil free base active agents, then such active agents may have an effective average particle size of less than about 2000 nm, 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.

**[0138]** By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the sildenafil free base or non-sildenafil free base active agent particles have a particle size, by weight, of less than the effective average particle size when measured by the above-noted techniques, *e.g.*, 50% of the particles have a size, by weight, of less than about 2 microns (or less than about 1900 nm, less than about 1800 nm, *etc.*). 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 sildenafil free base or non-sildenafil free base active agent particles have a particle size less than the effective average, *e.g.*, less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, *etc.*

**[0139]** If the nanoparticulate sildenafil free base is combined with a non-nanoparticulate active agent composition, then such a composition is either solubilized or has an effective average particle size of 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 active agent particles have a particle size of 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% of the active agent particles have a particle size greater than about 2 microns.

**[0140]** In the present invention, the value for D50 of a nanoparticulate sildenafil free base composition is the particle size below which 50% of the  
5 sildenafil free base particles fall, by weight. Similarly, D90 and D95 are the particle sizes below which 90% and 95%, respectively, of the sildenafil free base particles fall, by weight.

## 6. Concentration of Nanoparticulate Sildenafil Free Base and Surface Stabilizer

5 [0141] The relative amounts of nanoparticulate sildenafil free base and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the surface stabilizer, *etc.*

10 [0142] The concentration of sildenafil free base 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 sildenafil free base and at least one surface stabilizer, not including other excipients.

15 [0143] The concentration of at least one 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 sildenafil free base and at least one surface stabilizer, not including other excipients.

## 20 C. Methods of Making Nanoparticulate Sildenafil Free Base Compositions

[0144] The sildenafil free base compositions of the invention can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in 25 U.S. Patent No. 5,145,684.

[0145] 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 30 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," all of which are specifically incorporated by reference.

10 **[0146]** One or more non-sildenafil free base active agents can be reduced in size at the same time as sildenafil free base, to produce a nanoparticulate sildenafil free base and nanoparticulate non-sildenafil free base active agent composition. A non-sildenafil free base active agent, which is either non-nanoparticulate or nanoparticulate sized, can also be added to the  
15 nanoparticulate sildenafil free base composition after particle size reduction.

**[0147]** In yet another embodiment of the invention, nanoparticulate sildenafil free base compositions of the invention can be made in which the formulation comprises multiple nanoparticulate sildenafil free base compositions, each of which has a different effective average particle size. Such a composition can  
20 be made by preparing the individual nanoparticulate sildenafil free base compositions using, for example, milling, precipitation, or homogenization techniques, followed by combining the different compositions to prepare a single dosage form.

**[0148]** The nanoparticulate sildenafil free base compositions can be utilized  
25 in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.* Aerosols,  
30 including both nasal sprays and pulmonary aerosols, are expected to be



particularly useful for delivering nanoparticulate sildenafil free base compositions having a fast onset of activity.

### 1. Milling to Obtain Nanoparticulate Sildenafil Free Base Compositions

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**[0149]** Milling sildenafil free base to obtain a nanoparticulate composition comprises dispersing particles of sildenafil free base in a liquid dispersion media in which sildenafil free base is poorly soluble, followed by applying mechanical means in the presence of rigid grinding media to reduce the particle size of sildenafil free base 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.

**[0150]** The sildenafil free base particles are preferably reduced in size in the presence of at least one surface stabilizer. Alternatively, the sildenafil free base particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the sildenafil free base/surface stabilizer composition during the particle size reduction process. Dispersions can be manufactured continuously or in a batch mode.

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### 2. Precipitation to Obtain Nanoparticulate Sildenafil Free Base Compositions

**[0151]** Another method of forming the desired nanoparticulate sildenafil free base composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers 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 sildenafil free base in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can

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be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the resultant nanoparticulate sildenafil free base dispersion by conventional means.

### 3. Homogenization to Obtain Nanoparticulate Sildenafil Free Base Compositions

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[0152] Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing sildenafil free base particles in a liquid dispersion media, followed by subjecting the dispersion to homogenization to reduce the particle size of sildenafil free base to the desired effective average particle size. The sildenafil free base particles are preferably reduced in size in the presence of at least one surface stabilizer. Alternatively, the sildenafil free base particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the sildenafil free base/surface stabilizer composition either before, during, or after the particle size reduction process. Dispersions can be manufactured continuously or in a batch mode.

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#### D. Methods of Using the Sildenafil Free Base Compositions of the Invention

[0153] The present invention provides a method of rapidly increasing the plasma levels of sildenafil in a subject. Such a method comprises administering to a subject an effective amount of a nanoparticulate sildenafil free base composition of the invention.

[0154] The sildenafil free base compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or

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nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

**[0155]** Compositions suitable for parenteral injection may comprise  
5 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,  
10 ethanol, polyols (propyleneglycol, polyethylene-glycol, 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.

**[0156]** The nanoparticulate sildenafil free base compositions may also  
15 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  
20 of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

**[0157]** Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, sildenafil free base is admixed with at least one of the following: (a)  
25 one or more inert excipients (or carriers), 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, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as  
30 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.

**[0158]** Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to sildenafil free base, 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.

**[0159]** Besides such inert diluents, the sildenafil free base composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

**[0160]** One of ordinary skill will appreciate that effective amounts sildenafil free base can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of sildenafil free base in the nanoparticulate compositions of the invention may be varied to obtain an amount of sildenafil free base 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 sildenafil free base, the desired duration of treatment, and other factors.

**[0161]** Dosage unit compositions may contain such amounts of such sub-multiples 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: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, 5 body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

## 10           **1.       Use of Additional Active Agents**

**[0162]** The methods of the invention also encompass administering a nanoparticulate sildenafil free base composition of the invention in combination with one or more non-sildenafil active agents, in either a 15 conventional or nanoparticulate form. These additional active agents are discussed above.

## **2.       Treatment Applications**

20 **[0163]** The sildenafil free base compositions of the invention are useful in treating and/or preventing, among other conditions, mammalian sexual disorders. In particular, the compositions are of value in the treatment of mammalian sexual dysfunctions such as male erectile dysfunction, impotence, female sexual dysfunction, clitoral dysfunction, female hypoactive 25 sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic dysfunction, as well as sexual dysfunction due to spinal cord injury.

**[0164]** The sildenafil free base compositions of the invention are useful for treating other medical conditions for which a PDE5 inhibitor is indicated. Such 30 conditions include but are not limited to premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable,

unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility, e.g. irritable bowel syndrome and diabetic gastroparesis.

**[0165]** Further medical conditions for which a PDE5 inhibitor is indicated, and for which treatment with the sildenafil free base compositions of the present invention may be useful, include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, hemorrhoids and hypoxic vasoconstriction.

\* \* \* \* \*

**[0166]** The following examples 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. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

### **Example 1**

**[0167]** The purpose of this example was to prepare a composition of nanoparticulate sildenafil free base.

**[0168]** Sildenafil free base was prepared from sildenafil citrate as follows. 5 grams of sildenafil citrate (Cipla) was dissolved into approximately 1500 mL of DI water. The sildenafil citrate solution was mixed for a 6 to 12 hour time period. Once the drug was sufficiently dissolved, any remaining undissolved drug was filtered off using 1 micron glass fiber filter paper. The substrate was

collected into a large filtration flask and then transferred into a large beaker and placed on a magnetic stir plate. 1N NaOH was titrated in approximately 7 mL increments to the mixing solution until the sildenafil free base precipitate was formed and the solution was approximately pH 10. The sildenafil free base precipitate was then collected via filtration using 1 micron glass fiber filter paper. The beaker was rinsed with DI water to collect any residual precipitate and added to the filter paper. The filter paper and the filtration funnel were placed in an oven set at 40°C and dried overnight. Once dry the sildenafil free base was harvested from the filter paper into a tared vial.

10 **[0169]** 4.0 g of the sildenafil free base was added to a solution containing hydroxypropylmethylcellulose (HPMC, Hypromellose, USP, Pharmacoat® 603, substitution type 2910, 3 cp) (Shin Etsu Chemical Co., Ltd.) (0.8 g), docusate sodium (DOSS) (Cytotec Industries, Inc.) (0.04 g), and water (75.16 g). This mixture was then milled for 90 minutes in a DYNO-Mill KDL (Willy A. 15 Bachofen AG, Maschinenfabrik, Basel, Switzerland) at 4200 RPM with PM-500 polymeric media.

**[0170]** The final mean (weight average) particle size of the sildenafil particles was 281 nm, with a D50 of 274 nm, a D90 of 371 nm, and a D95 of 407 nm, as measured on a Horiba LA-910 particle size analyzer (Horiba 20 Instruments, Irvine, CA).

**[0171]** This example demonstrates the successful preparation of a dispersion of nanoparticulate sildenafil free base.

**Example 2**

[0172] The purpose of this example was to prepare a lyophilized wafer dosage form of the nanoparticulate sildenafil free base dispersion prepared in Example 1.

5 [0173] 30 grams of the nanoparticulate sildenafil free base dispersion from Example 1 was added to 3.0 grams mannitol USP/NF (Spectrum) and 1.5 grams pullulan (Hayashibara).

[0174] A wafer tray was then filled by adding 0.5 grams of the diluted sildenafil free base dispersion to each 0.5 cc well and the wafer tray was then  
10 placed in a lyophilizer for 48 hours to produce the final lyophilized wafer dosage form.

[0175] The sildenafil free base particle size in the lyophilized wafers appeared stable. After reconstitution in an aqueous media, the mean particle size (by weight) of sildenafil free base was 306 nm, with a D50 of 283 nm, a  
15 D90 of 443 nm, and a D95 of 522 nm.

[0176] A summary of the sildenafil free base particle size data from Examples 1 and 2 is shown in the following table.

<b>TABLE 1</b>				
<b>Composition</b>	<b>Mean Particle Size (nm)</b>	<b>D50 (nm)</b>	<b>D90 (nm)</b>	<b>D95 (nm)</b>
Sildenafil Free Base + HPMC + DOSS	281	274	371	407
Sildenafil Free Base + HPMC + Doss: Reconstituted in Water	306	283	443	522

[0177] This example demonstrates the successful preparation of a solid  
20 dosage form of a dispersion of nanoparticulate sildenafil free base. Moreover, this example demonstrates the successful preparation of a solid dosage form of a dispersion of nanoparticulate sildenafil free base in which the sildenafil free base particles redisperse upon reconstitution in an aqueous media such that the particle size of sildenafil is substantially equivalent to the particle size  
25 prior to incorporation into a solid dosage form.

**Example 3**



[0178] The purpose of this example was to prepare a composition of nanoparticulate sildenafil citrate.

[0179] To identify the best surface stabilizer for sildenafil citrate, the compound was screened in a NanoMill® (Elan Drug Delivery, Inc.) (see e.g.,  
5 WO 00/72973 for "Small-Scale Mill and Method Thereof") with the following surface stabilizers: hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC-SL), polyvinylpyrrolidone (PVP K29\32), and Plasdone® S630. The HPMC and HPC-SL formulations looked the best under a microscope, with the HPC-SL looking the better of the two. Thus,  
10 while HPMC was used in the nanoparticulate formulation of sildenafil free base, HPC-SL was chosen as the best surface stabilizer for a nanoparticulate formulation of sildenafil citrate.

[0180] Sildenafil citrate (Cipla) (4.0 g) was added to a solution containing hydroxypropylcellulose (HPC-SL) (Nisso) (0.8 g) and water (75.2 g). The  
15 mixture was then milled for 90 minutes in a DYNO-Mill KDL (Willy A. Bachofen AG, Maschinenfabrik, Basel, Switzerland) at 4200 RPM with PM-500 polymeric media.

[0181] Small (nanoparticulate), well dispersed sildenafil citrate particles were observed in the milled sildenafil dispersion on a Leica microscope.  
20 (Because sildenafil citrate is very soluble, and because only a small volume of nanoparticulate sildenafil citrate dispersion was available, it was not possible to specifically measure the sildenafil citrate particle size, at the dilute concentration of sildenafil citrate present in the nanoparticulate dispersion, using, e.g., Horiba LA-910 particle size analyzer. Particle size of  
25 nanoparticulate sildenafil citrate could potentially be measured using, e.g., a Horiba particle size analyzer, if a saturated dispersion of sildenafil citrate, or a larger volume of dispersion to be measured, was used.)

#### **Example 4**

[0182] The purpose of this example was to prepare a lyophilized wafer dosage form of the nanoparticulate sildenafil citrate composition prepared in Example 3.

5 [0183] 42 grams of the nanoparticulate sildenafil citrate dispersion of Example 3 were added to 4.2 grams mannitol USP/NF (Spectrum) and 2.2 grams pullulan (Hayashibara).

[0184] A wafer tray was filled by adding 0.5 grams of the diluted nanoparticulate sildenafil citrate dispersion to each 0.5 cc well. The wafer tray was then placed in a lyophilizer for 48 hours to produce the final lyophilized  
10 wafer dosage form.

[0185] The particle size of the reconstituted sildenafil citrate lyophilized dosage form was not measured, for the same reasons given above in Example 3. However, the presence of nanoparticles of sildenafil citrate, following reconstitution in an aqueous media, was optically confirmed via a  
15 Leica microscope.

#### **Example 5**

[0186] The purpose of this example was to evaluate the *in vivo* pharmacokinetics, under fed and fasted conditions, for the nanoparticulate  
20 sildenafil free base and nanoparticulate sildenafil citrate dosage forms of Examples 2 and 4, respectively, and Viagra®, which is a non-nanoparticulate sildenafil citrate dosage form.

**Dog Study Protocol**

[0187] Eight male and four female Beagle dogs were used in a study having five different phases. The three sildenafil formulations evaluated in the study are summarized in Table 2. Preparation of the samples is described above in

5 Examples 1-4.

<b>TABLE 2</b>			
<b>Summary of Sildenafil Formulations</b>			
<b>Sample</b>	<b>Components</b>	<b>Dosage Form</b>	<b>Particle Size of Sildenafil</b>
Formulation #1 (Example 1)	sildenafil free base, HPMC, DOSS,	dispersion	281 nm
Formulation #2 (Example 2)	sildenafil free base, HPMC, DOSS, mannitol, pullulan	wafer; 25 mg	306 nm (redispersed)
Formulation #3 (Example 3)	sildenafil citrate, HPC-SL	dispersion	Could not specifically measure particle size; Visually confirmed via microscope the presence of nanosized particles
Formulation #4 (Example 4)	sildenafil citrate, HPC-SL, mannitol, pullulan	wafer; 25 mg	Could not specifically measure particle size; Visually confirmed via microscope the presence of redispersed nanosized particles
Formulation #5	sildenafil citrate (Viagra® tablets; Pfizer Labs)	tablet; 25 mg	Microparticulate

[0188] In all phases of the study, two hours before dosing each dog received 22.5 mg of Zantac® (15 g/mL Zantac® syrup). Zantac® was administered to reduce the highly acidic conditions present in dog stomachs.

10 The reduced acidity correlates more accurately to human stomach conditions. In addition, sildenafil citrate and sildenafil free base solubilize in highly acidic conditions. If such solubilization occurred in the stomach, the drugs would

then likely precipitate into larger particles in the intestine, thus negating the benefits of formulating the drugs into a nanoparticulate dosage form.

**Phase 1 of the Study (Fed Conditions):**

5 [0189] In Phase 1, all dogs were fed. Six dogs (4 males and 2 females) received Formulation #2, a 25 mg lyophilized wafer of a dispersion of nanoparticulate sildenafil free base, and six dogs (4 males and 2 females) receive a 25 mg tablet of Viagra® (micronized sildenafil citrate).

**Phase 2 of the Study (Fed Conditions):**

10 [0190] After a four day washout period, Phase 2 was initiated in fed dogs. The six dogs which received Formulation #2 (25 mg lyophilized wafer of a dispersion of nanoparticulate sildenafil free base) in Phase 1 now received a 25 mg tablet of Viagra®, and the other 6 dogs received Formulation #4, a 25 mg lyophilized wafer of a dispersion of nanoparticulate sildenafil citrate.

**Phase 3 of the Study (Fasted Conditions):**

15 [0191] After another four-day washout period, the dosing regimen used in Phase 1 was used in Phase 3. Phase 3 dogs were fasted overnight and for four hours post dose.

**Phase 4 of the Study (Fasted Conditions):**

20 [0192] After another four days washout period, the dosing regimen used in Phase 2 was used in Phase 4. Phase 4 dogs were fasted overnight and for four hours post dose.

**Phase 5 of the Study (Fasted Conditions):**

25 [0193] Finally, after another four day washout period, the Phase 5 dogs were fasted overnight and for four hours postdose. The first six dogs received Formulation #4 (25 mg lyophilized wafer of a dispersion of nanoparticulate sildenafil citrate), while the second six dogs received Formulation #2 (25 mg lyophilized wafer of a dispersion of nanoparticulate sildenafil free base).

30 [0194] Blood samples (approximately 1.0 mL) were collected at specified time points (pre-dose, 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 4, 6, and 8 hours postdose) into tubes containing sodium heparin. The samples were

[0195] A summary of the five phase study is shown below in Table 3.

Phase	Compound	Fed/ Fasted	Number of Males/ Females	Dose Route	Dose Level (mg)	Matrix Collected
1	Nano Sildenafil Free Base (#2) /Viagra®	Fed	4/2;4/2	Wafer/ Tablet	25	Blood <sup>a</sup>
2	Viagra®/ Nano Sildenafil Citrate (#4)	Fed	4/2;4/2	Tablet/ Wafer	25	Blood <sup>a</sup>
3	Nano Sildenafil Free Base (#2) /Viagra®	Fasted	4/2;4/2	Wafer/ Tablet	25	Blood <sup>a</sup>
4	Viagra®/ Nano Sildenafil Citrate (#4)	Fasted	4/2;4/2	Tablet/ Wafer	25	Blood <sup>a</sup>
5	Nano Sildenafil Citrate (#4)/ Nano Sildenafil Free Base (#2)	Fasted	4/2;4/2	Wafer/ Wafer	25	Blood <sup>a</sup>

[0196] The blood samples were then evaluated to determine the  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  for Viagra® given under fed and fasted conditions, and for the nanoparticulate sildenafil free base (Formulation #2) and nanoparticulate sildenafil citrate (Formulation #4) compositions, given under fed and fasted conditions. The results are shown below in Table 4 and in Figures 1 and 2.

	$C_{max}$ (ng/mL)	$T_{max}$ (hours)	$AUC_{last}$ (ng/mL.h)	$AUC_{inf}$ (ng/mL.h)
Viagra® FASTED	234.6	1.85	1124.4	2514
Viagra®, FED	303.4	0.74	1166.25	1749.6
Formulation #2 (nanoparticulate sildenafil free base) FASTED	285.3	1.08	1332.1	2127.8
Formulation #2 (nanoparticulate sildenafil free base) FED	319.7	1.125	1329.3	2105.3
Formulation #4 (nanoparticulate sildenafil citrate)	319.7	0.6	1035.9	1335.3

<b>TABLE 4</b>				
<b>Pharmacokinetic Results of the Dog Study</b>				
	<b>C<sub>max</sub></b> <b>(ng/mL)</b>	<b>T<sub>max</sub></b> <b>(hours)</b>	<b>AUC<sub>last</sub></b> <b>(ng/mL·h)</b>	<b>AUC<sub>inf</sub></b> <b>(ng/mL·h)</b>
<b>FASTED</b>				
Formulation #4 (nanoparticulate sildenafil citrate) FED	162.9	1.25	647.6	897.8

[0197] Figure 1 shows the mean sildenafil concentration (ng/mL) for nanoparticulate sildenafil free base (Formulation #2), nanoparticulate sildenafil citrate (Formulation #4), and Viagra®, given under fed and fasted conditions, over a 2 hour time period. Figure 2 shows the mean sildenafil concentration (ng/mL) for Formulations 2, 4, and Viagra®, given under fed and fasted conditions, over an 8 hour time period.

[0198] The results show that the nanoparticulate sildenafil free base composition of the invention demonstrates substantially similar AUC profiles when administered under fed and fasted conditions.

[0199] This is significant, as it means that there is no substantial difference in the quantity of sildenafil free base absorbed or the rate of sildenafil free base absorption when the nanoparticulate sildenafil free base composition is administered in the fed versus the fasted state.

[0200] Viagra® administered under fed and fasted conditions exhibited an AUC<sub>inf</sub> of 2514 ng/mL·h and 1749.6 ng/mL·h, respectively – a difference of 764.4 ng/mL·h or ~ 30%. The nanoparticulate sildenafil citrate composition administered under fed and fasted conditions exhibited an AUC<sub>inf</sub> of 1335.2 ng/mL·h and 897.8 ng/mL·h, respectively – a difference of 437.4 ng/mL·h or ~ 33%. In surprising contrast to these results, the nanoparticulate sildenafil free base composition, administered under fed and fasted conditions, exhibited an AUC<sub>inf</sub> of 2127.8 ng/mL·h and 2105.3 ng/mL·h, respectively – a difference of 22.5 ng/mL·h or ~ 1%.

[0201] The AUC<sub>last</sub> difference of 22.5 ng/mL·h for administration under fed and fasted conditions for the nanoparticulate sildenafil free base composition

AUC<sub>inf</sub> of 2127.8 ng/mL·h and 2105.3 ng/mL·h, respectively – a difference of 22.5 ng/mL·h or ~ 1%.

5 [0201] The AUC<sub>last</sub> difference of 22.5 ng/mL·h for administration under fed and fasted conditions for the nanoparticulate sildenafil free base composition is almost *40 times* less than the fed/fasted variability observed with Viagra®, and over *19 times* less than the fed/fasted variability observed with the nanoparticulate sildenafil citrate composition.

10 [0202] Moreover, the T<sub>max</sub> and C<sub>max</sub> profiles for the nanoparticulate sildenafil free base composition were substantially similar when administered under fed and fasted conditions: ~ 11% difference for C<sub>max</sub> and a 4% difference for T<sub>max</sub>. In contrast, both the Viagra® and nanoparticulate sildenafil citrate compositions showed dramatically different results for T<sub>max</sub> and C<sub>max</sub> when the formulations were administered under fed as compared to fasted conditions: for Viagra®, a ~23% difference in C<sub>max</sub> and 60% difference in T<sub>max</sub>, and for the  
15 nanoparticulate sildenafil citrate composition, a 49% difference in C<sub>max</sub> and 52% difference in T<sub>max</sub>.

\* \* \* \*

20 [0203] 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 without departing from the spirit or scope of the 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.

25

**WHAT IS CLAIMED IS:**

1. A nanoparticulate sildenafil free base composition comprising:
  - (a) particles of sildenafil free base having an effective average  
5 particle size of less than about 2000 nm; and
  - (b) at least one surface stabilizer,wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.  
10
2. A composition of claim 1, wherein the difference in the AUC of the nanoparticulate sildenafil free base composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 35%, less than about 30%, less than about 25%,  
15 less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, and less than about 1%.
3. A composition of claim 1 or claim 2, wherein the  $T_{max}$  of the composition is not significantly different following administration under fed as  
20 compared to fasting conditions.
4. A composition of any one of claims 1 to 3, wherein the difference in the  $T_{max}$  for the nanoparticulate sildenafil free base composition of the invention, when administered in the fed versus the fasted state, is less  
25 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%, and less than about 3%.
5. A composition of of any one of claims 1 to 4, wherein the  $C_{max}$  of  
30 the composition is not significantly different following administration under fed as compared to fasting conditions.



6. A composition of any one of claims 1 to 5, wherein the difference in the  $C_{max}$  for the nanoparticulate sildenafil free base composition of the invention, when administered in the fed versus the fasted state, is 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%, and less than about 3%.

7. A composition of any one of claims 1 to 6, wherein sildenafil free base is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

8. A composition of any one of claims 1 to 7, wherein the effective average particle size of sildenafil free base 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 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 100 nm, less than about 75 nm, and less than about 50 nm.

9. A composition of any one of claims 1 to 8, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

30

10. A composition of any one of claims 1 to 9, wherein the composition is formulated into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

11. A composition of any one of claims 1 to 10, formulated into an aerosol or nasal spray and having a  $T_{max}$  which is less than that observed with a composition of non-nanoparticulate sildenafil.

12. A composition of any one of claims 1 to 11, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

13. A composition of any one of claims 1 to 12, wherein sildenafil free base 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 sildenafil free base and at least one surface stabilizer, not including other excipients.

14. A composition of any one of claims 1 to 13, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of 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 sildenafil free base and at least one surface stabilizer, not including other excipients.

30

15. A composition of any one of claims 1 to 14, comprising at least two surface stabilizers.

16. A composition of any one of claims 1 to 15, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, an ionic surface stabilizer, and a zwitterionic surface stabilizer.

17. A composition of any one of claims 1 to 16, wherein at least one 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, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose 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,  $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$ , p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl  $\beta$ -D-glucopyranoside; n-decyl  $\beta$ -D-maltopyranoside; n-dodecyl  $\beta$ -D-glucopyranoside; n-dodecyl  $\beta$ -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- $\beta$ -D-glucopyranoside; n-heptyl  $\beta$ -D-thioglucoside; n-hexyl  $\beta$ -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl  $\beta$ -D-glucopyranoside;

octanoyl-N-methylglucamide; n-octyl- $\beta$ -D-glucopyranoside; octyl  $\beta$ -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone; cationic lipids, polymethylmethacrylate  
5 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  
10 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<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride, C<sub>12-15</sub>dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl  
15 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)<sub>4</sub> ammonium chloride, lauryl dimethyl (ethenoxy)<sub>4</sub> ammonium bromide, N-alkyl (C<sub>12-18</sub>)dimethylbenzyl ammonium chloride, N-alkyl (C<sub>14-18</sub>)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl  
20 ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C<sub>12-14</sub>) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated  
25 alkylamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C<sub>12-14</sub>) dimethyl 1-naphthylmethyl ammonium chloride,  
30 dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C<sub>12</sub> trimethyl ammonium

bromides, C<sub>15</sub> trimethyl ammonium bromides, C<sub>17</sub> trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, 5 decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of 10 quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

15           18.    A composition of claim 17, wherein the composition is bioadhesive.

              19.    A composition of any one of claims 1 to 18, wherein the surface stabilizer is selected from the group consisting of 20 hydroxypropylmethylcellulose (HPMC), docusate sodium, and a combination thereof.

              20.    A composition of any one of claims 1 to 19, additionally comprising at least one nanoparticulate sildenafil free base composition 25 having an effective average particle size of less than about 2 microns, wherein said additional nanoparticulate sildenafil free base composition has an effective average particle size which is different than the particle size of the nanoparticulate sildenafil free base composition of claim 1.

30           21.    A composition of any one of claims 1 to 20, additionally comprising at least one non-sildenafil free base active agent.

22. A composition of claim 21, wherein the non-sildenafil free base active agent is selected from the group consisting of alpha adrenergic receptor blocking agents, delaquamine, phenotolamine, doxazosin, prostaglandins, prostoglandin analogs, alprostadil misoprostol, testosterone, antidepressants, trazodone, apomorphine, NO donors, central nervous system stimulants, PDE5 inhibitors, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous symptom stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, 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, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood 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, vasomodulator, xanthines, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

23. A composition of claim 22, wherein the nutraceutical is selected from the group consisting of yohimbine, *Cornus officinalis*, *Cinnamomum aromaticum*, *Panax ginseng* and *Pulsatilla pratensis*.

24. A composition of claim 23, wherein the amino acid is L-arginine.

25. A composition of claim 22, wherein the non-sildenafil free base  
5 PDE5 inhibitor is selected from the group consisting of vardenafil, tadalafil,  
TA-1790, UK-114542, Compound 14, EMD221829, EMR 62 203, T-1032, M-  
54033, M-54018, and E-4010.

26. A composition of any of claims 22 to 25, wherein at least one  
10 non-sildenafil free base active agent has an effective average particle size of  
less than about 2 microns or an effective average particle size of greater than  
about 2 microns.

27. A composition of any of claims 22 to 26, wherein upon  
15 administration the composition redisperses such that the sildenafil free base  
particles have a 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  
20 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.

25

28. A composition of any one of claims 1 to 27, wherein upon  
administration the  $T_{max}$  is less than that of a composition of non-  
nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate,  
administered at the same dosage.

30

29. A composition of any one of claims 1 to 28, wherein in comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits a  $T_{max}$  which is selected from the group consisting of less than about 200%, less than about 175%, less than about 150%, less than about 125%, 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%, and less than about 10% of the  $T_{max}$  exhibited by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

30. A composition of any one of claims 1 to 29, having a  $T_{max}$  following administration in a human selected from the group consisting of less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 45 minutes, less than about 35 minutes less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

31. A composition of any one of claims 1 to 30, wherein upon administration the  $C_{max}$  of the composition is greater than the  $C_{max}$  of a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

32. A composition of any one of claims 1 to 31, wherein in comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits a  $C_{max}$  which is selected from the group consisting of greater



than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than  
5 about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% of the  $C_{max}$  exhibited by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

10 33. A composition of any one of claims 1 to 32, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition, in a healthy adult male, results in a mean  $C_{max}$  of greater than about 440 ng/mL, a  $T_{max}$  of less than about 60 minutes, or a combination thereof.

15 34. A composition of any one of claims 1 to 33, wherein administration of a 100 mg oral dose of the nanoparticulate sildenafil free base composition produces a  $C_{max}$  which is selected from the group consisting of greater than about 440 ng/mL, greater than about 450 ng/mL, greater than  
20 about 500 ng/mL, greater than about 550 ng/mL, greater than about 600 ng/mL, greater than about 650 ng/mL, greater than about 700 ng/mL, greater than about 750 ng/mL, greater than about 800 ng/mL, greater than about 850 ng/mL, greater than about 900 ng/mL, greater than about 950 ng/mL, greater than about 1000 ng/mL, greater than about 1050 ng/mL, greater than about  
25 1100 ng/mL, greater than about 1150 ng/mL, greater than about 1200 ng/mL, greater than about 1250 ng/mL, greater than about 1300 ng/mL, about 1350 ng/mL, and greater than about 1400 ng/mL.

30 35. A composition of any one of claims 1 to 34, wherein upon administration the AUC of the composition is greater than the AUC of a

composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, administered at the same dosage.

36. A composition of any one of claims 1 to 35, wherein in  
5 comparative pharmacokinetic testing with a composition of non-nanoparticulate sildenafil or a composition of nanoparticulate sildenafil citrate, the nanoparticulate sildenafil free base composition, administered at the same dosage, exhibits an AUC which is selected from the group consisting of  
greater than about 5%, greater than about 10%, greater than about 15%,  
10 greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150% of the AUC exhibited  
15 by the composition of non-nanoparticulate sildenafil or the composition of nanoparticulate sildenafil citrate.

37. A pharmaceutical composition comprising a composition according to any one of claims 1 to 36 in combination with at least one  
20 pharmaceutically acceptable excipient.

38. Use of a pharmaceutical composition according to claim 37 for preparation of a medicament.

25 39. A use of claim 38, wherein the medicament is useful in treating a condition selected from the group consisting of a condition where a selective PDE5 inhibitor is indicated, male erectile dysfunction, impotence, female sexual dysfunction, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder, female  
30 sexual orgasmic dysfunction, sexual dysfunction due to spinal cord injury, premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet

obstruction, incontinence, stable angina, unstable angina, variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, post-percutaneous transluminal coronary angioplasty, peripheral vascular disease, stroke, nitrate induced  
5 tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, diabetic gastroparesis, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin  
10 necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, hemorrhoids, hypoxic vasoconstriction, diseases characterized by disorders of gut motility, and irritable bowel syndrome.

40. A method of making a nanoparticulate sildenafil free base  
15 composition comprising contacting particles of sildenafil free base with at least one surface stabilizer for a time and under conditions sufficient to provide a composition comprising sildenafil free base particles having an effective average particle size of less than about 2 microns,  
wherein the resultant nanoparticulate sildenafil free base composition  
20 does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

41. The method of claim 40, wherein said contacting comprises grinding.  
25

42. The method of claim 41, wherein said grinding comprises wet grinding.

43. The method of claim 40, wherein said contacting comprises  
30 homogenizing.

44. The method of claim 40, wherein said contacting comprises:
- (a) dissolving the sildenafil free base particles in a solvent;
  - (b) adding the resulting sildenafil free base solution to a solution comprising at least one surface stabilizer; and
  - (c) precipitating the solubilized sildenafil free base having at least one surface stabilizer associated with the surface thereof by the addition thereto of a non-solvent.

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