Nanoparticulate Acetaminophen Formulations

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) to U.S. provisional application No. 60/687,114, filed on June 3, 2005, the entire contents of which are incorporated herein by reference.

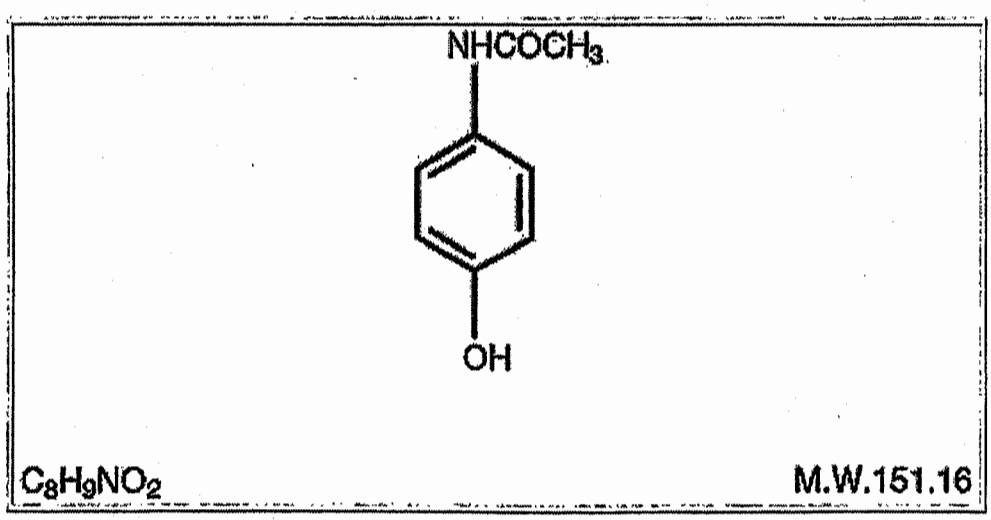
FIELD OF INVENTION

The present invention relates generally to compounds and compositions useful in the treatment of aches and pain, and reduction of fever and related conditions. More specifically, the invention relates to nanoparticulate acetaminophen compositions. The nanoparticulate acetaminophen compositions have an effective average particle size of less than about 2000 nm.

BACKGROUND OF INVENTION

A. Background Regarding Acetaminophen

Acetaminophen, chemically known as 4'-hydroxyacetanilide, has an empiric formula of $C_8H_9NO_2$ and a molecular weight of 151.16. Acetaminophen has the chemical structure shown below:



Acetaminophen, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It is commercially available from multiple sources, such as under the trade name TYLENOL® Tablet, from McNeil Consumer, and is available in

several strengths, such as 325 mg, 500 mg, and 650 mg. Representative inactive ingredients include cellulose, corn starch, magnesium stearate, sodium starch glycolate.

Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center. It is useful for temporarily relief of minor aches and pains due to headaches, muscular aches, backaches, arthritis, colds, toothaches, menstrual cramps and reduction of fever.

Acetaminophen compounds have been disclosed, for example, in United States Patent No. 4,439,453 to Vogel for "Directly Compressible Acetaminophen Granulation", United States Patent No. 4,661,521 to Salpekar et al. for "Direct Tableting Acetaminophen Compositions", United States Patent No. 4,771,077 to Reuter et al. for "Spray Dried Acetaminophen", United States Patent Nos. 4,820,522; 4,968,509; and 5,004,613 to Radebaugh et al. for "Oral Sustained Release Acetaminophen Formulation and Process", United States Patent No. 4,943,565 to Tencza et al. for "Analgesic Tablet or Aspirin and Caffeine Containing Low-Substituted Hydroxypropyl Cellulose", United States Patent No. 5,336,691 to Raffa et al. for "Composition Comprising a Tramadol Material and Acetaminophen and Its Use", United States Patent No. 5,972,916 to Armellino et al. for "Compositions Containing the Nonprescription Combination of Acetaminophen, Aspirin and Caffeine to Alleviate the Pain and Symptoms of Migraine", United States Patent No. 6,126,967 to Clemente et al. for "Extended Release Acetaminophen Particles", United States Patent No. 6,254,891 to Anaebonam et al. for "Extended Release Acetaminophen Particles", and United States Patent No. 6,391,337 to Hunter et al. for "Directly Compressible High Load Acetaminophen Formulations". All of these patents are incorporated herein by reference

Acetaminophen has high therapeutic value in the treatment of aches and pain, and reduction of fever and related conditions. However, because acetaminophen is practically insoluble in water, the dissolution of conventional acetaminophen tablets is reduced in the fasting state as compared to the fed state. The slow dissolution rate results in a slow absorption rate. Because of the slow absorption rate, maximum plasma concentrations of acetaminophen do not occur until approximately 0.4 to 1 hour after administration of a dose. The improvement in dissolution rate would enhance the rate of absorption of acetaminophen allowing the maximal plasma concentration to be achieved much more quickly and therefore therapeutic efficacy would begin much sooner. In addition, food delays the time to maximum serum concentration of acetaminophen. Thus, acetaminophen has limited bioavailability in the fasted state as compared to the fed state which limits the therapeutic outcome for all treatments requiring acetaminophen. There is a need in the art for acetaminophen formulations which overcome this

and other problems associated with the use of acetaminophen in the treatment of aches and pain, and the reduction of fever and related conditions. The present invention satisfies this need.

B. Background Regarding Nanoparticulate Active Agent Compositions

Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles comprising a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of acetaminophen.

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

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 Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-) Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;"

6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," 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;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" 6,969,529 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" and 6,976,647 for "System and Method for Milling Materials," all of which are specifically incorporated by reference. In addition, U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions;" U.S. Patent Publication No. 20050276974 for "Nanoparticulate Fibrate Formulations;" U.S. Patent Publication No. 20050238725 for "Nanoparticulate compositions having a peptide as a surface stabilizer;" U.S. Patent Publication No. 20050233001 for "Nanoparticulate megestrol formulations;" U.S. Patent Publication No. 20050147664 for "Compositions comprising antibodies and methods of using the same for targeting nanoparticulate active agent delivery;" U.S. Patent Publication No. 20050063913 for "Novel metaxalone compositions;" U.S. Patent Publication No. 20050042177 for "Novel compositions of sildenafil free base;" U.S. Patent Publication No. 20050031691 for "Gel stabilized nanoparticulate active agent compositions;" U.S. Patent Publication No. 20050019412 for " Novel glipizide compositions;" U.S. Patent Publication No. 20050004049 for "Novel griseofulvin compositions;" U.S. Patent Publication No. 20040258758 for "Nanoparticulate topiramate formulations;" U.S. Patent Publication No. 20040258757 for " Liquid dosage compositions of stable nanoparticulate active agents;" U.S. Patent Publication No.

20040229038 for "Nanoparticulate meloxicam formulations;" U.S. Patent Publication No. 20040208833 for "Novel fluticasone formulations;" U.S. Patent Publication No. 20040195413 for " Compositions and method for milling materials;" U.S. Patent Publication No. 20040156895 for "Solid dosage forms comprising pullulan;" U.S. Patent Publication No. U.S. Patent Publication No. U.S. Patent Publication No. 20040156872 for "Novel nimesulide compositions;" U.S. Patent Publication No. 20040141925 for "Novel triamcinolone compositions;" U.S. Patent Publication No. 20040115134 for "Novel nifedipine compositions;" U.S. Patent Publication No. 20040105889 for "Low viscosity liquid dosage forms;" U.S. Patent Publication No. 20040105778 for "Gamma irradiation of solid nanoparticulate active agents;" U.S. Patent Publication No. 20040101566 for "Novel benzoyl peroxide compositions;" U.S. Patent Publication No. 20040057905 for "Nanoparticulate beclomethasone dipropionate compositions;" U.S. Patent Publication No. 20040033267 for "Nanoparticulate compositions of angiogenesis inhibitors;" U.S. Patent Publication No. 20040033202 for "Nanoparticulate sterol formulations and novel sterol combinations;" U.S. Patent Publication No. 20040018242 for "Nanoparticulate nystatin formulations;" U.S. Patent Publication No. 20040015134 for "Drug delivery systems and methods;" U.S. Patent Publication No. 20030232796 for "Nanoparticulate polycosanol formulations & novel polycosanol combinations;" U.S. Patent Publication No. 20030215502 for "Fast dissolving dosage forms having reduced friability;" U.S. Patent Publication No. 20030185869 for "Nanoparticulate compositions having lysozyme as a surface stabilizer;" U.S. Patent Publication No. 20030181411 for "Nanoparticulate compositions of mitogen-activated protein (MAP) kinase inhibitors;" U.S. Patent Publication No. 20030137067 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Patent Publication No. 20030108616 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Patent Publication No. 20030095928 for "Nanoparticulate insulin;" U.S. Patent Publication No. 20030087308 for "Method for high through put screening using a small scale mill or microfluidics;" U.S. Patent Publication No. 20030023203 for "Drug delivery systems & methods;" U.S. Patent Publication No. 20020179758 for "System and method for milling materials; and U.S. Patent Publication No. 20010053664 for "Apparatus for sanitary wet milling," describe nanoparticulate active agent compositions and are specifically incorporated by reference.

In particular, U.S. Patent No. 5,518,738, for "Nanoparticulate NSAID Compositions,: and U.S. Patent No. 5,552,160 for "Surface Modified NSAID Nanoparticles," describe nanoparticulate NSAID compositions. The '738 patent describes compositions comprising a

crystalline NSAID in combination with polyvinylpyrrolidone, hygroscopic sugar and sodium lauryl sulfate. The '160 patent describes crystalline NSAIDs having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm. These patents do not specifically disclose nanoparticulate acetaminophen.

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

There is a need in the art for improved dosage forms of acetaminophen. The present invention satisfies this need.

SUMMARY OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising acetaminophen, or a salt or derivative thereof. The compositions comprise nanoparticulate acetaminophen particles and at least one surface stabilizer. The surface stabilizer can be adsorbed on or associated with the surface of the acetaminophen particles. The nanoparticulate acetaminophen particles have an effective average particle size of less than about 2,000 nm.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate acetaminophen, or a salt or derivative thereof, particle and at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

One embodiment of the invention encompasses a nanoparticulate acetaminophen composition, wherein the pharmacokinetic profile of the nanoparticulate acetaminophen is not significantly affected by the fed or fasted state of a subject ingesting the composition.

In yet another embodiment, the invention encompasses a nanoparticulate acetaminophen composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

Another embodiment of the invention is directed to nanoparticulate acetaminophen compositions comprising one or more additional compounds useful in the treatment of aches and pain, and/or reduction of fever and related conditions.

This invention further discloses a method of making the inventive nanoparticulate acetaminophen compositions. Such a method comprises contacting acetaminophen, or a salt or derivative thereof, with at least one surface stabilizer for a time and under conditions sufficient to provide a stabilized nanoparticulate acetaminophen composition having an effective average particle size of less than about 2000 nm.

The present invention is also directed to methods of treatment including but not limited to, the treatment of aches and pain, and/or reduction of fever and related conditions, using the novel nanoparticulate acetaminophen compositions disclosed herein. Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate acetaminophen, or a salt or derivative thereof, compositoin. Other methods of treatment using the nanoparticulate acetaminophen compositions of the invention are known to those of skill in the art.

Both the foregoing summary of the invention and the following brief description of the drawings and detailed description of the invention are exemplary and explanatory and are intended to provide further details 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 DRAWINGS

Figure 1: Shows a 100x phase objective using immersion oil of a nanoparticulate formulation of 10% (w/w) acetaminophen, 2.5% (w/w) hydroxypropyl cellulose SL (HPC-SL), and 0.1% (w/w) docusate sodium; and

Figure 2: Shows a 100x phase objective using immersion oil of a nanoparticulate formulation of 10% (w/w) acetaminophen, 2.5% (w/w) Plasdone K29/32, and 0.1% (w/w) sodium lauryl sulfate.

DETAILED DESCRIPTION OF THE INVENTION

I. Nanoparticulate Acetaminophen Compositions

The present invention is directed to nanoparticulate compositions comprising an acetaminophen, or a salt or derivative thereof. The compositions comprise acetaminophen, or a salt or derivative thereof, and preferably at least one surface stabilizer adsorbed on or associated

with the surface of the drug. The acetaminophen, or a salt or derivative thereof, particles have an effective average particle size of less than about 2000 nm.

As taught by the '684 patent, and as exemplified in the examples below, not every combination of surface stabilizer and active agent will results in a stable nanoparticulate composition. It was surprisingly discovered that stable, nanoparticulate acetaminophen, or a salt or derivative thereof, formulations can be made.

Advantages of the nanoparticulate acetaminophen formulations of the invention as compared to prior non-nanoparticulate or microcrystalline acetaminophen compositions include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the acetaminophen compositions when administered in the fed versus the fasted state; (5) bioequivalency of the acetaminophen compositions when administered in the fed versus the fasted state; (6) improved pK profiles; (7) an increased rate of dissolution; and (8) the acetaminophen compositions can be used in conjunction with other active agents useful in the treatment of aches and pain, and reduction of fever and related conditions.

The present invention also includes nanoparticulate acetaminophen, or a salt or derivative thereof, 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 parental injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments, or drops), buccal, intracisternal, intraperitoneal, or topical administrations, and the like.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

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

The term "effective average particle size," as used herein, means that at least about 50% of the nanoparticulate acetaminophen particles have a size of less than about 2000 nm, by

weight or by other suitable measurement technique (e.g., such as by volume, number, etc.), when measured by, for example, sedimentation flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

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

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

The term "conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

The phrase "poorly water soluble drugs" as used herein refers to drugs having a solubility in water 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.

As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

A. Preferred Characteristics of the Nanoparticulate Acetaminophen Compositions of the Invention

1. Increased Bioavailability

The nanoparticulate acetaminophen, or a salt or derivative thereof, formulations of the invention are proposed to exhibit increased bioavailability, and require smaller doses as compared to prior conventional acetaminophen formulations.

2. Improved Pharmacokinetic Profiles

The invention also provides nanoparticulate acetaminophen, or a salt or derivative thereof, compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the compositions comprising acetaminophen includes but is not limited to: (1) a C_{max} for a acetaminophen, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage; and/or (2) an AUC for acetaminophen, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage; and/or (3) a T_{max} for acetaminophen, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of acetaminophen or a salt or derivative thereof.

In one embodiment, a composition comprising a nanoparticulate acetaminophen exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate acetaminophen formulation.

In another embodiment, the composition comprising a nanoparticulate acetaminophen exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at

least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate acetaminophen formulation.

In yet another embodiment, the composition comprising a nanoparticulate acetaminophen exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate acetaminophen formulation.

In one embodiment of the invention, the T_{max} of acetaminophen, when assayed in the plasma of the mammalian subject, is less than about 6 to about 8 hours. In other embodiments of the invention, the T_{max} of acetaminophen is less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after administration.

[0001] The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of acetaminophen or a salt or derivative thereof. The compositions can be formulated in any way as described herein and as known to those of skill in the art.

3. The Pharmacokinetic Profiles of the Acetaminophen Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses acetaminophen composition wherein the pharmacokinetic profile of acetaminophen is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate acetaminophen compositions are administered in the fed versus the fasted state.

For conventional acetaminophen formulations, *i.e.*, TYLENOL®, the absorption of acetaminophen is increased when administered with food. This difference in absorption observed with conventional acetaminophen formulations is undesirable. The acetaminophen formulations of the invention overcome this problem, as the acetaminophen formulations reduce or preferably substantially eliminate significantly different absorption levels when administered under fed as compared to fasting conditions.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed, *i.e.*, increased pain or fever for poor subject compliance with acetaminophen.

4. Bioequivalency of Acetaminophen Compositions of the Invention When Administered in the Fed Versus the Fasted State

The invention also encompasses provides a nanoparticulate acetaminophen composition in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

The difference in absorption (AUC) or C_{max} of the nanoparticulate acetaminophen compositions of the invention, when administered in the fed versus the fasted state, preferably is less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

In one embodiment of the invention, the invention encompasses compositions comprising a nanoparticulate acetaminophen, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 0.80 to 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for C_{max} must between 0.70 to 1.43.

5. Dissolution Profiles of the Acetaminophen Compositions of the Invention

The nanoparticulate acetaminophen, or a salt or derivative thereof, compositions of the invention are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of the acetaminophen it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

The acetaminophen compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments of the invention, at least about 30% or about 40% of the acetaminophen composition is dissolved within about 5 minutes. In yet other embodiments of the invention, preferably at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the acetaminophen composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the acetaminophen composition is dissolved within 20 minutes.

Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; i.e., the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

6. Redispersability of the Acetaminophen Compositions of the Invention

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

This is because nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not disperse into the small particle sizes upon administration, them "clumps" or agglomerated active agent 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 formulation of such agglomerated particles, the bioavailability of the dosage form my fall well below that observed with the liquid dispersion form of the nanoparticulate active agent.

In other embodiments of the invention, the redispersed acetaminophen, or a salt or derivative thereof, particles of the invention have an effective average particle size of less than about 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.

Moreover, the nanoparticulate acetaminophen or a salt or derivative thereof compositions of the invention exhibit dramatic redispersion of the nanoparticulate acetaminophen particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed acetaminophen 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 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.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. See e.g., Lindahl et al.,

"Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," Pharm. Res., 14 (4): 497-502 (1997).

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.

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.

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

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

In other embodiments of the invention, the redispersed acetaminophen or a salt or derivative thereof particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 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 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350

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. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

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."

7. Acetaminophen Compositions Used in Conjunction with Other Active Agents

The acetaminophen, or a salt or derivative thereof, compositions of the invention can additionally comprise one or more compounds useful in the treatment of aches and pain, and reduction of fever and related conditions, or the acetaminophen compositions can be administered in conjunction with such a compound. Such compounds include, but are not limited to narcotic analgesics, such as, but not limited to, morphine, codeine, hydrocodone, and oxycodone.

B. Nanoparticulate Acetaminophen Compositions

The invention provides compositions comprising acetaminophen, or a salt or derivative thereof, particles and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the acetaminophen particles. Surface stabilizers especially useful herein preferably physically adhere on, or associate with, the surface of the nanoparticulate acetaminophen particles, but do not chemically react with the acetaminophen particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The present invention also includes acetaminophen, or a salt or derivative thereof, 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 administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

1. Acetaminophen Particles

The compositions of the invention comprise particles of acetaminophen or a salt or derivative thereof. The particles can be in a crystalline phase, semi-crystalline phase, amorphous phase, semi-amorphous phase, or a combination thereof.

2. Surface Stabilizers

Combinations of more than one surface stabilizers 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 excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Exemplary surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, 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 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose 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.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and

SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; 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.

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

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary 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, $C_{12\text{-}15}$dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride or bromide, N-alkyl ($C_{12\text{-}18}$)dimethylbenzyl ammonium chloride, N-alkyl ($C_{14\text{-}18}$)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and ($C_{12\text{-}14}$) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl($C_{12\text{-}14}$) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl

ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

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

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

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

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

3. Other Pharmaceutical Excipients

Pharmaceutical 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.

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® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

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

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

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 quarternary compounds such as benzalkonium chloride.

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® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

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

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids 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 sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Acetaminophen Particle Size

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

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the acetaminophen particles have a particle size of less than the effective average, by weight (or by other suitable measurement technique, such as by volume, number, etc.), *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. In other embodiments of the invention, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the acetaminophen particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc.*

In the present invention, the value for D50 of a nanoparticulate acetaminophen composition is the particle size below which 50% of the acetaminophen particles fall, by weight. Similarly, D90 is the particle size below which 90% of the acetaminophen particles fall, by weight.

5. Concentration of Acetaminophen and Surface Stabilizers

The relative amounts of acetaminophen, or a salt or derivative thereof, and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the particular acetaminophen and/or surface stabilizer selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the surface stabilizer, *etc.*

The concentration of the acetaminophen 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 weight of the acetaminophen and at least one surface stabilizer, not including other excipients.

The concentration of the 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 the acetaminophen and at least one surface stabilizer, not including other excipients.

6. Exemplary Nanoparticulate Acetaminophen Tablet Formulations

Several exemplary acetaminophen tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of acetaminophen which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Table 1: Exemplary Nanoparticulate Acetaminophen Tablet Formulation #1

Component	g/Kg
Acetaminophen	about 50 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrate, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

Table 2: Exemplary Nanoparticulate Acetaminophen Tablet Formulation #2

Component	g/Kg
Acetaminophen	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10
Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

Table 3: Exemplary Nanoparticulate Acetaminophen Tablet Formulation #3	
Component	**g/Kg**
Acetaminophen	about 200 to about 225
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 200 to about 225
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 200 to about 205
Silicified Microcrystalline Cellulose	about 130 to about 135
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

Table 4: Exemplary Nanoparticulate Acetaminophen Tablet Formulation #4	
Component	**g/Kg**
Acetaminophen	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224
Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

C. Methods of Making Nanoparticulate Acetaminophen Compositions

The nanoparticulate acetaminophen, or a salt or derivative thereof, compositions can be made using, for example, milling, homogenization, precipitation, freezing, or template emulsion techniques. Exemplary methods of making nanoparticulate active agent compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;"

U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

The resultant nanoparticulate acetaminophen compositions or dispersions can be utilized 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.

1. Milling to Obtain Nanoparticulate Acetaminophen Dispersions

Milling an acetaminophen, or a salt or derivative thereof, to obtain a nanoparticulate dispersion comprises dispersing the acetaminophen particles in a liquid dispersion medium in which the acetaminophen is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the acetaminophen to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion medium is water.

The acetaminophen particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, acetaminophen particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the acetaminophen/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Acetaminophen Compositions

Another method of forming the desired nanoparticulate acetaminophen, or a salt or derivative thereof, 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 the acetaminophen 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 be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain Nanoparticulate Acetaminophen Compositions

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles of an acetaminophen, or a salt or derivative thereof, in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of an acetaminophen to the desired effective average particle size. The acetaminophen particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the acetaminophen 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 acetaminophen/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

4. Cryogenic Methodologies to Obtain Nanoparticulate Acetaminophen Compositions

Another method of forming the desired nanoparticulate acetaminophen, or a salt or derivative thereof, composition is by spray freezing into liquid (SFL). This technology comprises an organic or organoaqueous solution of acetaminophen with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the acetaminophen solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nanostructured acetaminophen particles. Depending on the choice of solvent system and processing conditions, the nanoparticulate acetaminophen particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the acetaminophen particles.

As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to created equivalent nanostructured acetaminophen particles with greatly enhanced surface area. URF comprises an organic or organoaqueous solution of acetaminophen with stabilizers onto a cryogenic substrate.

5. Emulsion Methodologies to Obtain Nanoparticulate Acetaminophen Compositions

Another method of forming the desired nanoparticulate acetaminophen, or a salt or derivative thereof, composition is by template emulsion. Template emulsion creates nanostructured acetaminophen particles with controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the acetaminophen and stabilizers. The particle size distribution of the acetaminophen particles is a direct result of the size of the emulsion droplets prior to loading with the acetaminophen a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured acetaminophen particles are recovered. Various acetaminophen particles morphologies can be achieved by appropriate control of processing conditions.

D. Methods of Using the Nanoparticulate Acetaminophen Compositions of the Invention

The invention provides a method of increasing bioavailability of an acetaminophen, or a salt or derivative thereof, in a subject. Such a method comprises orally administering to a subject an effective amount of a composition comprising an acetaminophen. In one embodiment of the invention, the acetaminophen compositions, in accordance with standard pharmacokinetic practice, have a bioavailability that is about 50% greater than a conventional dosage form, about 40% greater, about 30% greater, about 20% or about 10% greater.

The compositions of the invention are useful in the treatment of aches and pain, and reduction of fever and related conditions.

The acetaminophen, or a salt or derivative thereof, compounds of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, otically, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or 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.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, 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.

The nanoparticulate acetaminophen, or a salt or derivative thereof, compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or 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, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to an acetaminophen, 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.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

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

One of ordinary skill will appreciate that effective amounts of an acetaminophen 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 an acetaminophen in the nanoparticulate compositions of the invention may be varied to obtain an amount of an acetaminophen 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 acetaminophen, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: 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, 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.

The following examples are given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in the examples but should only be limited by the scope of the

claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference.

Example 1

The purpose of this example was to prepare nanoparticulate acetaminophen compositions using various combinations of surface stabilizers.

An aqueous dispersion of acetaminophen combined with one or more surface stabilizers, at the concentrations shown in Table 5, below, was milled in a 10 mL or 50 mL chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see e.g., U.S. Patent No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical) (89% media load). The milling time and mill speed used for preparation of each formulation is also shown in Table 5.

Table 5: Acetaminophen Formulations

Sample	Acetaminophen Concentration	Surface Stabilizer(s)	Deionized Water (w/w)	Mill Volume (mL)	Milling Time (min.)	Mill Speed (rpm)
1	5% (w/w)	2.0% (w/w) Plasdone S-630	93%	10	60	2500
2	10% (w/w)	2.5% (w/w) HPC-SL (hydroxypropylcellulose) 0.1% (w/w) docusate sodium	87.4%	10	90	2500
3	10% (w/w)	2.5% (w/w) Pharmacoat 603 0.1% (w/w) docusate sodium	87.4%	50	90	1333
4	10% (w/w)	2.5% (w/w) Plasdone C-13 (Polyvinylpyrrolidone C-13) 0.1% (w/w) deoxycholic acid sodium salt	87.4%	10	90	2800
5	15% (w/w)	3.75% (w/w) Lutrol (Pluronic) F68 (Poloxamer 188) 0.15% (w/w) Docusate Sodium	81.1%	50	90	1333
6	10% (w/w)	2.5% (w/w) Lutrol F-108 (Poloxamer 338) 2.5% (w/w) Tween 80 (Polysorbate 80)	85%	50	90	1333
7	10% (w/w)	2.5% (w/w) Tween 80 (Polysorbate 80) 0.1% (w/w) lecithin	87.4%	10	90	2800
8	10% (w/w)	2.5% Tyloxapol	87.5%	50	90	1333
9	10% (w/w)	2.5% (w/w) Plasdone S-630 0.1% (w/w) sodium lauryl sulfate	87.4%	50	90	1333
10	10% (w/w)	2.5% (w/w) Plasdone K-17 0.1% (w/w) benzalkonium chloride	87.4%	10	90	2800
11	10% (w/w)	2.5% (w/w) Plasdone K29/32 0.1% (w/w) sodium lauryl sulfate	87.4%	50	90	1333

The milled compositions were harvested and analyzed via microscopy. Microscopy was done using a Lecia DM5000B and Lecia CTR 5000 light source (Laboratory Instruments and

Supplies Ltd., Ashbourne Co., Meath, Ireland). The microscopy observations for each formulation are shown below in Table 6.

Table 6

Formulation	Microscopy Observations
1	There were no signs of acetaminophen nanoparticles or Brownian motion in this sample.
2	This sample appeared very well dispersed with acetaminophen nanoparticles present. Brownian motion was also clearly evident. There were no signs of acetaminophen crystal growth or acetaminophen particle flocculation. Figure 1 shows a 100x phase objective using immersion oil of this nanoparticulate acetaminophen formulation (10% (w/w) acetaminophen, 2.5% (w/w) hydroxypropyl cellulose SL (HPC-SL), and 0.1% (w/w) docusate sodium).
3	Microscopy was performed the day following milling for this sample. The nanoparticulate acetaminophen dispersion appeared well dispersed throughout the slide, without signs of acetaminophen particle flocculation or acetaminophen crystal growth. Brownian motion was clearly evident.
4	This sample seemed to contain severely agglomerated acetaminophen nanoparticles. There was no sign of Brownian motion. There were also no signs of un-milled drug crystals or crystal growth.
5	There appeared to be a lot of crystal rod like material throughout the sample, which may be acetaminophen particle flocculation or acetaminophen crystal growth. There were some acetaminophen nanoparticles present. However, no Brownian motion was observed.
6	Some acetaminophen nanoparticles were present in the sample but very little evidence of Brownian motion was observed. There were a lot of rod-like crystals clumped together throughout the sample.
7	Some acetaminophen nanoparticles were present in the sample and Brownian motion was also observed. However, there were a lot of rod-like crystals evident and the sample appeared severely flocculated and agglomerated.
8	Some acetaminophen nanoparticles were visible which displayed Brownian motion. However, the majority of the slide displayed rod-like crystals which appeared to be severely agglomerated.
9	The sample appeared to be well dispersed with acetaminophen nanoparticulates clearly visible. Brownian motion was also seen. There was some evidence of partially milled acetaminophen particles throughout the sample but the majority of these were no bigger than 2000 nm. There was no sign of acetaminophen particle flocculation or acetaminophen crystal growth.
10	Microscopy showed acetaminophen nanoparticles throughout the sample to be severely agglomerated. There was no sign of Brownian motion.
11	This sample appeared well dispersed with acetaminophen nanoparticles visible. Brownian motion was also clearly evident. Some isolated acetaminophen particle flocculation was also observed. There were no signs of acetaminophen crystal growth or unmilled drug particles. Figure 2 shows a 100x phase objective using

Table 6	
Formulation	**Microscopy Observations**
	immersion oil of this nanoparticulate acetaminophen formulation (10% (w/w) acetaminophen, 2.5% (w/w) Plasdone K29/32, and 0.1% (w/w) sodium lauryl sulfate).

The particle size of the milled acetaminophen particles was measured, in Milli Q Water, using a Horiba LA-910 Particle Sizer (Particular Sciences, Hatton Derbyshire, England). Vitamin K2 particle size was measured initially and then again following 60 seconds sonication. The results are shown below in Table 10.

TABLE 10

Sample	Mean (nm)	D50 (nm)	D90 (nm)	D95 (nm)	Sonication ?	Comments
1	No results available: The nanoparticulate acetaminophen dispersion sample seemed to dissolve when added to the diluent in the Horiba reservoir. This was also supported by the observation that no light scattering signal was observed during sample addition. This seemed very unusual as the milled nanoparticulate acetaminophen dispersion sample was white in color, which indicates the presence of drug particles.				N Y	Particle size analysis and microscopy were performed on harvested material after the 60 min milling processing. Based on the microscopy results, this was **not** a successful formulation.
2	No results available: The nanoparticulate acetaminophen dispersion sample seemed to dissolve when added to the diluent in the Horiba reservoir. There was no light scattering signal observed during sample addition into the reservoir. As with Sample 1, the sample was white in color which normally indicates the presence of milled nanoparticulate drug.				N Y	The nanoparticulate vitamin K2 dispersion was yellow in color and appeared to have a low viscosity which harvested easily. Based on the microscopy results, this was a successful formulation, as nanoparticles of acetaminophen were observed.
3	494 1340	409 1429	818 2462	1091 2795	N Y	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. This formulation is acceptable as the microscopy analysis supports the particle size distribution results: when undisturbed (i.e. no sonication), no flocculation seems to occur, and the D50 <2000 nm criteria is met.
4	No results available: The nanoparticulate acetaminophen dispersion sample seemed to dissolve when added to the diluent in the Horiba reservoir. This was also supported by the observation that no light scattering signal was observed during sample addition. This seemed very unusual as the milled nanoparticulate acetaminophen dispersion sample was white in color, which indicates the presence of drug particles.				N Y	Particle size analysis and microscopy were performed on harvested material after the 60 min milling processing. Based on the microscopy results, this was **not** a successful formulation.
5	9637	5609	18006	23753	N	Particle size analysis and

TABLE 10

Sample	Mean (nm)	D50 (nm)	D90 (nm)	D95 (nm)	Sonication ?	Comments
	No post sonication results available as the lamp transmittance reached about 100%, causing a "baseline" error with the Horiba.				Y	microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy results and pre-sonication particle size data, this was <u>not</u> a successful formulation.
6	1105	607	2561	3621	N	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy and particle size distribution results, this was a successful formulation, as the D50 particle size was less than 2000 nm.
	1170	642	2677	3871	Y	
7	2767	2338	5152	6408	N	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy and particle size distribution results, this was <u>not</u> a successful formulation.
	2831	2777	5109	5842	Y	
8	333855	368745	660533	727928	N	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy and particle size distribution results, this was <u>not</u> a successful formulation.
	35565	37700	64407	71786	Y	
9	187	178	254	287	N	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy and particle size distribution results, this was a successful formulation, as the D50 particle size was less than 2000 nm.
	270	264	363	393	Y	
10	No results available: The nanoparticulate acetaminophen dispersion sample seemed to dissolve when added to the diluent in the Horiba reservoir. There was no light scattering signal observed during sample addition into the reservoir. Again the sample was white in color which normally indicates the presence of milled nanoparticulate acetaminophen particles.				N	Particle size analysis and microscopy were performed on harvested material after the 90 min milling processing. Based on the microscopy results, this was <u>not</u> a successful formulation.
					Y	
11	282	269	421	469	N	Particle size analysis and microscopy were performed on
	No post sonication results available as the				Y	

TABLE 10						
Sample	**Mean (nm)**	**D50 (nm)**	**D90 (nm)**	**D95 (nm)**	**Sonication ?**	**Comments**
	lamp transmittance reached about 100%, causing a "baseline" error with the Horiba.					harvested material after the 90 min milling processing. Based on the microscopy results and pre-sonication particle size data, this was a successful formulation, as the D50 particle size was less than 2000 nm.

Particle sizes that vary significantly following sonication are undesirable, as it is indicative of the presence of acetaminophen aggregates. Such aggregates result in compositions having highly variable particle sizes. Such highly variable particle sizes can result in variable absorption between dosages of a drug, and therefore are undesirable.

The data demonstrate the successful preparation of nanoparticulate acetaminophen formulations utilizing various surface stabilizers, including various combination of surface stabilizers.

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 inventions without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of the invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A stable nanoparticulate acetaminophen composition comprising:

(a) particles consisting of acetaminophen or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer adsorbed on the surface of the acetaminophen particles.

2. The composition of claim 1, wherein the particles of acetaminophen or a salt or derivative thereof are selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

3. The composition of claim 1 or claim 2, wherein the effective average particle size of the acetaminophen or a salt or derivative thereof 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.

4. The composition of any one of claims 1 to 3, wherein the composition is formulated:

(a) for administration selected from the group consisting of parental injection, oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, otically, ocular, local, buccal, intracisternal, intraperitoneal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, sachets, solutions, aerosols, ointments, tablets, capsules, creams, and mixtures thereof;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination thereof.

5. The composition of any one of claims 1 to 4, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition any one of claims 1 to 5, wherein:

(a) acetaminophen is present in an amount 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 weight of acetaminophen and at least one surface stabilizer, not including other excipients;

(b) at least one surface stabilizer is present in an amount of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of acetaminophen and at least one surface stabilizer, not including other excipients; or

(c) a combination thereof.

7. The composition of any one of claims 1 to 6, wherein the surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

8. The composition of any one of claims 1 to 7, wherein the surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives,

polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl

ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

9. The composition of any one of claims 1 to 8, wherein:

(a) upon administration to a mammal the particles of acetaminophen or a salt or derivative thereof redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700

nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm;

(b) the particles of acetaminophen or a salt or derivative thereof redisperse in a biorelevant media such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm; or

(c) a combination of (a) and (b).

10. The composition of claim 9, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

11. The composition of any one of claims 1 to 10, wherein:

(a) the T_{max} of acetaminophen or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a non-nanoparticulate composition of the same acetaminophen, administered at the same dosage;

(b) the C_{max} of acetaminophen or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is greater

than the C_{max} for a non-nanoparticulate composition of the same acetaminophen, administered at the same dosage;

(c) the AUC of acetaminophen or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same acetaminophen, administered at the same dosage; or

(d) any combination thereof.

12. The composition of claim 11, wherein:

(a) the T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the T_{max} exhibited by a non-nanoparticulate composition of the same acetaminophen, administered at the same dosage;

(b) the C_{max} is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by a non-nanoparticulate composition of the same acetaminophen, administered at the same dosage;

(c) the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the

AUC exhibited by the non-nanoparticulate formulation of the same acetaminophen, administered at the same dosage; or

(d) any combination thereof.

13. The composition of any one of claims 1 to 12, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

14. The composition of claim 13, wherein the difference in absorption of the acetaminophen, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

15. The composition of any one of claims 1 to 14, wherein the pharmacokinetic profile of the composition is not significantly affected by the fed or fasted state of a subject ingesting the composition.

16. The composition of any one of claims 1 to 15, wherein administration of the composition to a human in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

17. The composition of claim 16, wherein "bioequivalency" is established by:

(a) a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC; or

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

18. Use of a composition according to any one of claims 1 to 17 for the manufacture of a medicament.

19. The use of claim 18, wherein the medicament further comprises one or more active agents selected from the group consisting of an narcotic analgesic selected from the group consisting of morphine, codeine, hydrocodone, oxycodone, and combinations thereof.

20. A method of preparing a composition comprising nanoparticulate acetaminophen or a salt or derivative thereof, comprising contacting particles of acetaminophen or a salt or derivative thereof with at least one surface stabilizer for a time and under conditions sufficient to provide an acetaminophen composition having an effective average particle size of less than about 2000 nm and having the surface stabilizer adsorbed on the surface of the acetaminophen particles.

21. The method of claim 20, wherein the contacting comprises grinding, wet grinding, homogenization, template emulsion, precipitation, freezing, or a combination thereof.

22. The method of claim 20 or claim 21, wherein the effective average particle size of the acetaminophen particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 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.