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(54) **Title:** MODIFIED RELEASE FILL COMPOSITIONS FOR DOSAGE FORMS AND METHODS OF PREPARATION AND USE THEREOF

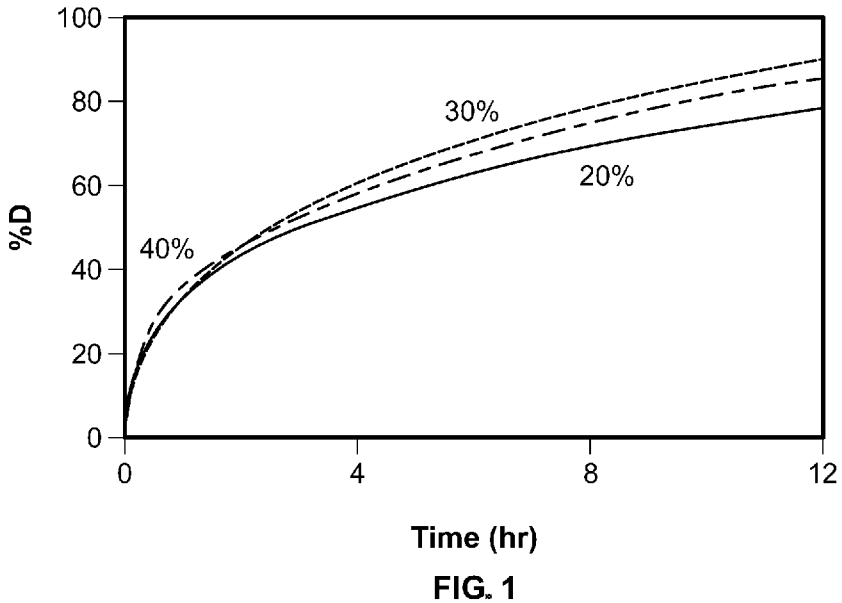

FIG. 1

(57) **Abstract:** Disclosed herein are embodiments of a softgel dosage form that includes a softgel capsule and a fdl composition within the softgel capsule. The fdl composition can include a matrix material, and a solvent. The fdl composition is flowable at a temperature of at least about 40 °C and solid or semi-solid at ambient conditions. Also disclosed are methods of preparation and use thereof and fdl compositions for use in such softgel dosage forms and methods.

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MODIFIED RELEASE FILL COMPOSITIONS FOR DOSAGE FORMS AND METHODS OF PREPARATION AND USE THEREOF

FIELD

[0001] Disclosed herein are modified release fill compositions for capsule dosage forms and capsule dosage forms containing such fill compositions. Also disclosed are methods of preparation and use thereof.

BACKGROUND

[0002] There are many benefits associated with formulating dosage forms to provide a modified release of an active agent contained therein. For example, some modified release dosage forms have improved efficacy (e.g., due to reduced fluctuations in drug plasma concentrations), reduced adverse events (e.g., reduced concentration-related side-effects), increased convenience and patient compliance (e.g., reduced dosing frequency), and optimized performance (e.g., controlling the site of drug delivery in the gastrointestinal tract).

[0003] To achieve a modified release profile, formulators often employ solid or semi-solid matrices wherein active agents are distributed and/or embedded within the matrices. In such formulations, drug release typically occurs via three main mechanisms: (1) matrices erode over time and drug releases from the surface (e.g., erosion); (2) matrices swell and generate a pathway for drugs to diffuse (e.g., diffusion, osmotic dosage forms); or (3) a combination of (1) and (2). While such modified release dosage forms are readily available in tablet form, encapsulating a modified release fill composition in capsules (e.g., softgels capsules) has presented challenges.

[0004] There is a need for improved modified release fill compositions for encapsulation within capsule dosage forms that are flowable and suitable for use within a capsule encapsulation process.

BRIEF SUMMARY

[0005] A capsule (e.g., softgel, hard shell) dosage form, comprising: a capsule; and a fill composition within the capsule, the fill composition comprising: a matrix material; and a solvent, wherein the fill composition is flowable at a temperature of at least about 40 °C and solid or semi-solid at ambient conditions.

[0006] A method of encapsulating a modified release fill composition in a capsule to form a dosage form according to embodiments herein, the method comprising: heating the modified release fill composition to a temperature of at least about 40 °C, at least about 45 °C, at least about 50 °C, at least about 55 °C, or at least about 60 °C to provide a flowable liquid; and

encapsulating the flowable liquid in the capsule.

[0007] A method of treating pain, comprising administering to a subject in need thereof, a dosage form according to embodiments herein, wherein the dosage form comprises a pharmaceutically active agent suitable for treating pain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 shows representative release profiles of diphenhydramine from various hydrophilic fill compositions having different concentrations of polyethylene oxide.

[0009] FIG. 2A shows representative diphenhydramine release profiles when incorporated in low viscosity hydroxypropyl methylcellulose matrices at different concentration loadings.

[0010] FIG. 2B shows representative diphenhydramine release profiles when incorporated in medium (moderate) viscosity hydroxypropyl methylcellulose matrices at different concentration loadings.

[0011] FIG. 2C shows representative diphenhydramine release profiles when incorporated in high viscosity hydroxypropyl methylcellulose matrices at different concentration loadings.

[0012] FIG. 3 shows representative release profiles of diphenhydramine from ethyl cellulose matrices.

[0013] FIG. 4 shows representative diphenhydramine release profiles in combined hydroxypropyl methylcellulose and ethyl cellulose matrices at different concentration ratios.

[0014] FIG. 5A shows representative diphenhydramine release profiles in mixed hydroxypropyl methylcellulose and ethyl cellulose matrices combined with sorbitan oleate.

[0015] FIG. 5B shows representative diphenhydramine release profiles in mixed hydroxypropyl methylcellulose and ethyl cellulose matrices combined with triethyl citrate.

[0016] FIG. 6 shows representative diphenhydramine release profiles in mixed hydroxypropyl methylcellulose and ethyl cellulose matrices combined with varying amounts of ethanol.

[0017] FIG. 7A shows representative diphenhydramine release profiles at different drug loadings for mixed hydroxypropyl methylcellulose and ethyl cellulose fill compositions containing a surfactant and ethanol.

[0018] FIG. 7B shows representative ibuprofen release profiles at different drug loadings for mixed hydroxypropyl methylcellulose and ethyl cellulose fill compositions containing a surfactant and ethanol.

[0019] FIG. 8 shows representative ibuprofen release profiles of ibuprofen MC/EC fills in four biorelevant media: Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated

Intestinal Fluid (FaSSIF), Fed State Simulated Intestinal Fluid (FeSSIF) and an aqueous solution adjusted to pH 4.5.

[0020] FIG. 9 shows representative diphenhydramine release profiles in hydrophobic matrices containing hydrophobic waxes.

[0021] FIG.10 shows the representative drug release profiles under 30 °C/65% relative humidity and 40 °C/75% relative humidity stability conditions for T0, T1M, T3M and T6M time points.

DEFINITIONS

[0022] As used herein, the singular forms "a," "an," and "the" include plural references unless the context clearly indicates otherwise. Thus, for example, reference to "an active agent" includes a single active agent as well as a mixture of two or more different active agents or a pharmaceutically acceptable salt, solvate, crystalline form, derivative, prodrug or analogue thereof; and reference to an "excipient" includes a single excipient as well as a mixture of two or more different excipients, and the like.

[0023] As used herein, the term "about" in connection with a measured quantity or time, refers to the normal variations in that measured quantity or time, as expected by one of ordinary skill in the art in making the measurement and exercising a level of care commensurate with the objective of measurement. In certain embodiments, the term "about" includes the recited number ±10%, such that "about 10" would include from 9 to 11, or "about 1 hour" would include from 54 minutes to 66 minutes.

[0024] The term "at least about" in connection with a measured quantity refers to the normal variations in the measured quantity, as expected by one of ordinary skill in the art in making the measurement and exercising a level of care commensurate with the objective of measurement and

precisions of the measuring equipment and any quantities higher than that. In certain embodiments, the term "at least about" includes the recited number minus 10% and any quantity that is higher such that "at least about 10" would include 9 and anything greater than 9. This term can also be expressed as "about 10 or more." Similarly, the term "less than about" typically includes the recited number plus 10% and any quantity that is lower such that "less than about 10" would include 11 and anything less than 11. This term can also be expressed as "about 10 or less."

[0025] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to illustrate certain materials and methods and does not pose a limitation on scope.

[0026] As used herein, the term "active agent" refers to any material that is intended to produce a therapeutic, prophylactic, or other intended effect, whether or not approved by a government agency for that purpose. This term with respect to a specific agent includes the pharmaceutically active agent, and all pharmaceutically acceptable salts, solvates, crystalline forms, derivatives, prodrugs or analogues thereof, where the salts, solvates, crystalline forms, derivatives, prodrugs or analogues are pharmaceutically active.

[0027] The term "pharmaceutically acceptable salt" as used herein refers to one or more salts of an active pharmaceutical ingredient (API). For example, pharmaceutically acceptable salts of basic APIs include hydrochloride, mesylate, hydrobromide, acetate and/or fumarate. Pharmaceutically acceptable salts for acidic APIs include sodium, calcium and/or potassium. A

pharmaceutically acceptable salt may be chosen for a particular modified release fill formulation based on its aqueous solubility, stability, toxicity, absorption, manufacturability and/or other physicochemical and/or biological considerations.

[0028] The term "polymorphism" refers to the ability of an active ingredient (AI) to exist in more than one crystalline form and the term "polymorph" refers to at least one of the crystalline forms of an AI.

[0029] As used herein, the terms "therapeutically effective" and an "effective amount" refer to that amount of an active agent, or the rate at which it is administered, needed to produce a desired therapeutic result.

[0030] The term "subject" refers to a human or animal, that has demonstrated a clinical manifestation of a condition. The term "subject" may include a person or animal (e.g., a canine) that is a patient being appropriately treated by a medical caregiver for a condition.

[0031] The terms "treatment of" and "treating" include the administration of an active agent(s) with the intent to lessen the severity of a condition and/or a symptom.

[0032] The terms "prevention of" and "preventing" include the avoidance of the onset of a condition by a prophylactic administration of the active agent.

[0033] The term "condition" or "conditions" as used herein includes, but is not limited to, a disease, a disorder, cardiovascular disease, chronic pain, inflammation, headache, arthritis, diabetes, fibromyalgia, irritable bowel syndrome, back pain, muscle aches and pains, fever, menstrual cramps, earaches, toothaches, surgical pain, cold, flu, sinusitis, sore throat, allergies, rhinitis, conjunctivitis, diarrhea, mononucleosis, stomach ache, nausea, vomiting, intestinal gas, and/or combinations thereof.

[0034] The term "concurrently" as used herein means that a dose of one agent (e.g., an anti-inflammatory) is administered prior to the end of the dosing interval of another agent (e.g., a decongestant). For example, a dose of a cannabinoid with a particular dosing interval would be concurrently administered with a modulator dose when administered within the dosing interval of the cannabinoid.

[0035] The term "simultaneously" as used herein means that a dose of one agent is administered approximately at the same time as another agent, regardless of whether the agents are administered separately via the same or different routes of administration or in a single pharmaceutical composition or dosage form. For example, a dose of an anti-inflammatory may be administered separately from, but at the same time as, a dose of a decongestant.

[0036] The term "sequentially" as used herein means that a dose of one agent is administered first and thereafter a dose of another agent is administered second. For example, a dose of an anti-inflammatory may be administered first, and thereafter a dose of a decongestant may be administered second. The subsequent administration of the second agent may be inside or outside the dosing interval of the first agent.

[0037] A "hydrophilic" or "water soluble" active agent as used herein is an agent having a water solubility of greater than or equal to 1 mg/ml at room temperature (20-25 °C.). The water solubility refers to the drug in any form including its free base, free acid or salt form.

[0038] A "hydrophobic" or "water insoluble" active agent as used herein is an agent having a water solubility of less than 1 mg/ml at room temperature (20-25 °C.). The water solubility refers to the drug in any form including its free base, free acid or salt form.

[0039] The terms "ambient" or "ambient conditions" as used herein refer to temperatures of about 15 °C to less than 37 °C at one (1) atmosphere of pressure.

[0040] The term "elevated temperature" as used herein refers to temperatures of 37 °C and above at one (1) atmosphere of pressure.

[0041] The terms "flow," "flowable," "flowable fluid," or "flowable liquid" as used herein refer to a fluid (e.g., a liquid) that has a viscosity of 100,000 cP or less at a temperature of 40 °C or 60 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 40 °C or 60 °C.

[0042] The term "semi-solid" as used herein refers to a fluid (e.g., a liquid containing solid components) that has a viscosity of about 50,000 cP to 1,000,000 cP at a temperature of 20 °C or 25 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C or 25 °C.

[0043] The term "solid" as used herein refers to a composition (e.g., a plug of fill composition) that has a viscosity of greater than 1,000,000 cP at a temperature of 20 °C or 25 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C or 25 °C.

[0044] The term "sub-units" as used herein refers to particles, granules, extrudates, powders, pellets, multi-particulates (e.g., coated sub-units, bi-layer sub-units, multi-layer sub-units), microspheres, minitablets, microcapsules and/or combinations thereof.

DETAILED DESCRIPTION

[0045] Described herein according to various embodiments are modified release fill compositions. In one or more embodiments, the fill compositions comprise a matrix material and a solvent. The fill compositions are flowable at a temperature of at least about 40 °C and solid or semi-solid at

ambient conditions. Further described are capsule dosage forms containing the modified release fill compositions. The capsules can be in any suitable form including softgel, hard shell, or a combination thereof. In one or more embodiments, the modified release fill composition is encapsulated in a capsule. Also described are methods of encapsulating the disclosed modified release fill compositions and methods of using such compositions and dosage forms containing such compositions.

[0046] Modified release compositions are useful for active agents that have efficacy when administered with release kinetics other than conventional immediate release kinetics. Modified release capsules are conventionally provided with an enteric coating on the exterior surface of the capsule in order to provide a delayed (or burst) release of the drug contained therein. Moreover, encapsulating modified release compositions is a challenge using standard encapsulation apparatus and processes mainly due to their viscosity and lack of flowability. The fill material needs to flow freely under gravity for processing in conventional encapsulation equipment, and it is very difficult to encapsulate solid or semi-solid materials into capsules. There is a need for modified release fill compositions that provide constant drug release over an extended prior of time and that are flowable and suitable for encapsulation using conventional equipment.

[0047] Modified release fill compositions as described herein can provide, over a prolonged period of time (e.g., at least about 8 hours), a linear or substantially linear release rate of drug contain therein without the need for an enteric coating on the capsule shell. This reduces processing time by eliminating the coating step. Such fill compositions can, for example, contain varying amounts of ingredients to ensure optimal release kinetics for each unique active. Capsules (e.g., softgel capsules) as described herein for encapsulating the modified release fill compositions can be

manufactured using renewable and biodegradable materials, significantly benefitting the environment.

[0048] According to one or more embodiments, modified release fill compositions as described herein are thermosensitive. Such fill compositions can flow at elevated temperature and remain solid or semi-solid at ambient conditions. During encapsulation, fill compositions according to various embodiments can be heated to reduce viscosity and enable flowability. However, developing formulations that are suitably flowable when heated, solid or semi-solid at ambient conditions and also provide optimal release kinetics for various drugs was complicated.

[0049] In at least one embodiment, the modified release fill composition releases an active agent over a period of at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, or at least about 24 hours, or any individual value or sub-range within these ranges, as measured by *in-vitro* dissolution in a USP Dissolution Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C. In one or more embodiments, the fill composition releases about 40% or less, 30% or less, 20% or less, or 10% or less, or any individual value or sub-range within these ranges, of an active agent within about 1 hour as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C. The fill composition releases, for example, about 80% or more, 85% or more, 95% or more, or 100% or more, or any individual value or sub-range within these ranges, of an active agent within about 12 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C. In at least one embodiment, the fill composition releases about 80% or more, 85% or more, 95% or more, or 100% or more, or any individual value or sub-range within these ranges, of an active agent within about 24 hours as

measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C.

[0050] According to one or more embodiments, the modified release fill compositions are flowable at an elevated temperature (e.g., a temperature above ambient conditions). In embodiments, the modified release fill compositions may be flowable at an elevated temperature of at least 37 °C, at least about 40 °C, at least about 45 °C, at least about 50 °C, at least about 55 °C, at least about 60 °C, at least about 70 °C, about 37 °C to about 70 °C or any individual value or sub-range within these ranges. According to one or more embodiments, the fill composition is solid or semi-solid at a temperature of about 15 °C to about 35 °C, about 18 °C to about 30 °C, about 20 °C to about 25 °C, or any individual value or sub-range within these ranges.

[0051] The viscosity of the fill composition may be at a suitable level to provide flowability of the modified release fill composition at elevated temperature. According to one or more embodiments, the modified release fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, less than about 10,000 cp, or any individual value or sub-range within these ranges, at a temperature of 40 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 40°C. In at least one embodiment, the modified release fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, or less than about 10,000 cp, or any individual value or sub-range within these ranges, at a temperature of 60 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 60°C.

[0052] The modified release fill compositions may be contained within a capsule shell of a dosage form (e.g., a softgel dosage form or a hard shell dosage form). Capsule dosage forms containing the modified release fill compositions provide a modified release of an active agent contained therein. In one or more embodiments, the capsule dosage form releases an active agent for a period of at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, or at least about 24 hours, or any individual value or sub-range within these ranges, as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water at about 37°C. Capsule dosage forms according to embodiments herein release about 40% or less, 30% or less, 20% or less, or 10% or less, or any individual value or sub-range within these ranges, of an active agent within about 1 hour as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water at about 37°C. Capsule dosage forms according to embodiments release about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 12 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water at about 37°C. In at least one embodiment, capsule dosage forms as described herein release about 80% or more, 85% or more, 95% or more, or 100% or more, or any individual value or sub-range within these ranges, of an active agent within about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water at about 37°C.

Matrix Materials

[0053] Modified release fill compositions according to various embodiments, include at least one matrix material. Matrix materials are polymer networks suitable for controlling release of a drug. A drug or API may be dispersed, for example, molecularly and/or as solid drug particles, within the polymer network. The polymer comprised in the matrix material can be swellable (e.g., hydrophilic) or non-swellable (e.g., hydrophobic). The matrix material properties affect the rate of drug release through factors including diffusion, permeation, and dissolution.

[0054] Modified release fill compositions according to various embodiments herein, can include a matrix material containing one or more polymer. The matrix material is configured to provide a target and/or steady state release of a drug from the modified release fill composition alone or when encapsulated in a capsule. Suitable polymers for use as matrix materials according to embodiments herein include, but are not limited to, a polyethylene oxide, a cellulose, a cellulose derivative, a natural gum, a synthetic gum, and/or combinations thereof. Cellulose and its derivatives can modify the release kinetics of certain APIs. Hydrophilicity of the cellulose can be altered by etherification in which the hydroxyl groups are converted into ethers. Hydroxypropyl methylcellulose and ethyl cellulose are prime examples of hydrophilic and hydrophobic cellulose derivatives, respectively.

[0055] Additionally or alternatively, the matrix material, according to one or more embodiments, contains a wax. Suitable waxes include, but are not limited to, natural or synthetic waxes, paraffin wax, stearoyl polyoxyl-32 glycerides, carnauba wax, beeswax, glycowax, castor wax, stearic acid, cetyl alcohol, cetostearyl alcohol, glyceryl monostearate, other wax-like substances and/or combinations thereof. A "wax-like" substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30° C to about 100° C.

[0056] According to one or more embodiments, the matrix materials contain one or more hydrophilic polymers (i.e., a hydrophilic matrix), one or more mixed hydrophilic-hydrophobic polymers (i.e., a mixed hydrophilic-hydrophobic matrix) or hydrophobic polymers (i.e., a hydrophobic matrix). A hydrophilic matrix is suitable for use with hydrophilic active agents as described herein. In at least one embodiment, a hydrophilic matrix includes a polyethylene oxide polymer. Suitable polyethylene oxides include, but are not limited to, those having a molecular weight of about 90,000 Da to about 7,000,000 Da, about 100,000 Da to about 5,000,000 Da, about 200,000 Da to about 2,000,000 Da, about 500,000 Da to about 1,000,000 Da, or any individual value or sub-range within these ranges. In one or more embodiments, the matrix material includes more than one polyethylene oxide, each polyethylene oxide having different molecular weight in the about 90,000 Da to about 7,000,000 Da, about 100,000 Da to about 5,000,000 Da, about 200,000 Da to about 2,000,000 Da, about 500,000 Da to about 1,000,000 Da, or any individual value or sub-range within these ranges. According to at least one embodiment, the matrix material comprises a polyethylene oxide or a plurality of polyethylene oxides in an amount of about 5 wt% to about 50 wt%, about 10 wt% to about 50 wt%, or any individual value or sub-range within these ranges, based on the total weight of the matrix material or the fill composition.

[0057] In at least one embodiment, a hydrophilic matrix comprises a cellulose or cellulose derivative. A suitable cellulose or cellulose derivative includes, but is not limited to, at least one methylcellulose, at least one hydroxypropylcellulose, at least one hydroxypropyl methylcellulose, derivatives thereof, and/or combinations thereof. According to one or more embodiments, the hydrophilic matrix includes a hydroxypropyl methylcellulose having a molecular weight of about 10,000 Da to about 1,500,000 Da, about 20,000 Da to about 1,000,000 Da, about 20,000 Da to about 500,000 Da, about 50,000 Da to about 200,000 Da, or any individual value or sub-range

within these ranges. In at least one embodiment, the matrix material comprises a plurality of hydroxypropyl methylcelluloses, each having a different molecular weight in the range of about 10,000 Da to about 1,500,000 Da, about 20,000 Da to about 1,000,000 Da, about 20,000 Da to about 500,000 Da, about 50,000 Da to about 200,000 Da, or any individual value or sub-range within these ranges.

[0058] According to one or more embodiments, the hydrophilic matrix can include at least one hydroxypropyl methylcellulose selected from (a) a hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, (b) a hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, (c) a hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, or combinations thereof. When (a) and (b) are present, the weight ratio of (a):(b) may be about 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1. When (a) and (c) are present the weight ratio of (a):(c) may be about1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1. In one or more embodiments, when (a), (b) and (c) are all present the weight ratio of (a):(b):(c) may

be about 1:1:1, about 1:1:100 to about 100:1:1, or about 1:100:1 to about 100:1:1, or any individual ratio combination or sub-range within these ranges.

[0059] In one or more embodiments, the hydrophilic matrix can include about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp, about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp, and/or about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp.

[0060] In one or more embodiments, matrix material is a mixed hydrophilic-hydrophobic matrix suitable for use with hydrophilic and/or hydrophobic active agents as described herein. The mixed hydrophilic-hydrophobic matrix can include a hydrophilic matrix material as described above in combination with a hydrophobic matrix material. Suitable hydrophobic matrix materials include, but are not limited to, an ethyl cellulose, a hydroxyethylcellulose, a sodium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose or a combination of any two or more thereof. The mixed hydrophilic-hydrophobic matrix can be modified to suitably achieve a target release rate for a particular active agent or a plurality of active agents.

[0061] In at least one embodiment, the mixed hydrophilic-hydrophobic matrix comprises an ethyl cellulose having a molecular weight of about 10,000 Da to about 200,000 Da, or a plurality of ethyl celluloses, each having a different molecular weight in the range of about 400 Da to about 2,000,000 Da. In some embodiments, the matrix material comprises an ethyl cellulose that

provides a viscosity of about 9 cp to about 11 cp when measured using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C.

[0062] According to various embodiments, the matrix material comprises at least one hydroxypropyl methylcellulose and at least one ethyl cellulose. In one or more embodiments, the weight ratio of the at least one hydroxypropyl methylcellulose to the at least one ethyl cellulose is about 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1.

[0063] In some embodiments, a hydrophobic matrix comprises one or more wax as described herein. Suitable waxes include, but are not limited to, paraffin wax, beeswax, jojoba, lanolin, spermaceti, or combinations of any two or more thereof. Hydrophobic matrices are suitable for hydrophobic active agents as described herein.

[0064] In some embodiments, in addition to the wax, the hydrophobic matrix includes, but is not limited to, one or more fatty acids, fatty acid esters, esters of fatty acids and glycerol, one or more triglyceride, one or more long chain fatty acid, fatty alcohols (e.g., lauryl, myristyl, stearyl, cetyl or cetostearyl alcohol), fatty acid glycerides (e.g., mono-, di-, and tri-glycerides), or combinations thereof. In some embodiments, the one or more esters of fatty acids and glycerol comprise esters of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid, lauric acid, caproic acid, caprylic acid, capric acid, or combinations two or more thereof, a monoglyceride, a diglyceride, a monoacylglycerol, a diacylglycerol, stearoyl polyoxylglyceride, lauroyl polyoxylglyceride, stearoyl polyoxyl-32 glycerides, lauroyl polyoxyl-32 glycerides, glycerol monostearate, glycerol monocaprylocaprate, glycerol dicaprylate, glycerol monooleate, or combinations of two or more thereof. The one or more triglycerides can include a medium chain triglyceride, a caprylic

triglyceride, a capric acid triglyceride, triglycerol esters of one or more of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid, caproic acid, caprylic acid, capric acid or lauric acid and one or more medium chain fatty acid having about 6 to about 12 carbon atoms, glyceryl tricaprylate/caprate, glycerol caprylate caprate, caprylic/capric triglyceride, or combinations of any two or more thereof. The one or more esters of fatty acids and glycerol can include stearoyl polyoxyl-32 glycerides, the surfactant comprises glyceryl dibehenate, and the plasticizer comprises stearic acid.

[0065] In some embodiments, dosage forms or fill compositions comprising the hydrophobic matrix comprise about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1 wt% to about 5 wt% of one or more esters of fatty acids and glycerol; about 0.1 wt% to about 50 wt%, or about 1 wt% to about 30 wt% of a surfactant; about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; and/or about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer based on the total weight of the dosage form or fill composition.

[0066] In some embodiments, dosage forms or fill compositions comprising the hydrophobic matrix comprise about 1 wt% to about 50 wt%, about 5 wt% to about 40 wt%, or about 10 wt% to about 30 wt% of the wax; about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of a hydroxypropyl methylcellulose; about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of one or more esters of fatty acids and glycerol; about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; or about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer based on the total weight of the dosage form or fill composition.

[0067] In some embodiments of the capsule dosage forms as described herein, the dosage forms include a hydrophobic matrix the wax comprises paraffin wax, the hydroxypropyl methylcellulose provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, the one or more esters of fatty acids and glycerol comprises lauroyl polyoxylglycerides, and the plasticizer comprises stearic acid.

Solvents

[0068] Modified release fill compositions according to various embodiments, include at least one solvent. Suitable solvents are capable of dissolving and/or dispersing the matrix material and/or active agent. In some embodiments, the at least one solvent in combination with the matrix material provides a suitable viscosity at elevated temperature to allow flowability of the composition.

[0069] Suitable solvents include, but are not limited to, water, soybean oil, ethanol, a low molecular weight polyethylene glycol, triethyl citrate, or a combination of any two or more thereof. The dosage forms or fill compositions can contain the solvent in an amount of about 1 wt% to about 70 wt%, about 2 wt% to about 60 wt%, about 5 wt% to about 50 wt%, about 10 wt% to about 20 wt%, or any individual value or sub-range within these ranges, based on the total weight of the dosage form or fill composition.

[0070] In some embodiments, the modified release fill compositions can contain a plurality of solvents (e.g., 2, 3, 4 and so on), for example, ethanol and soybean oil. In some embodiments, two solvents may be present at a weight ratio of about 1:100 to about 100:1, 1:50 to about 50:1, about

1:25 to about 25:1, about 5:1 to about 5:1, or any individual value or sub-range within these ranges. In some embodiments, the dosage form and/or fill composition contains soybean oil in an amount of about 0 wt% to about 75 wt%, ethanol in an amount of about 0 wt% to about 50 wt%, and water in an amount of about 1 wt% to about 75 wt%, or any individual value or sub-range within these ranges, based on the total weight of the dosage for and/or fill composition.

[0071] According to one or more embodiments, the dosage form and/or fill composition contains soybean oil in an amount of about 20 wt% to about 90 wt%, about 30 wt% to about 80 wt%, about 40 wt % to about 70 wt%, or about 50 wt% to about 65 wt%, based on the total weight of the fill composition; water in an amount of about 0.1 wt% to about 30 wt%, about 0.5 wt% to about 20 wt%, or about 1 wt% to about 10 wt%, based on the total weight of the dosage form and/or fill composition; and ethanol in an amount of about 0 wt% to about 40 wt%, about 1 wt% to about 30 wt%, about 5 wt% to about 20 wt%, based on the total weight of the dosage form and/or fill composition.

Active Agents

[0072] One or more embodiments of modified release fill compositions and capsule dosage forms (e.g., softgel capsules) containing such fill compositions are suitable for combination with one or more active agents. Suitable active agents include, but are not limited to, APIs, nutraceutical agents, hydrophilic active agents, hydrophilic nutraceutical agents, hydrophobic active agents, hydrophobic nutraceutical agents, and/or combinations thereof. Examples of suitable APIs include, but are not limited to, substances that produce a desired health effect in a subject that are known to those of ordinary skill in the art, such as pain management, diabetic treatment, anti-cancer and/or hormonal replacement.

[0073] The modified release fill compositions and/or capsule dosage forms containing such fill compositions according to various embodiments herein can contain one or more active agent within the fill composition, within the capsule shell composition, within a film on the surface of the capsule shell, within sub-units dispersed in the fill composition, within a film on sub-units within either the fill composition, the capsule composition or a film on the capsule shell, and/or combinations thereof. The fill compositions and/or capsule dosage forms can contain multiple groups of sub-units and/or films in any combination, at least one group containing a first active agent and at least one group containing a second active agent and so on. In one or more embodiments, the fill compositions and/or capsule dosage forms contain a first group of sub-units and/or film containing an active agent in a first amount and a second group of sub-units and/or film containing the active agent in a second amount.

[0074] Suitable hydrophilic active agents for inclusion in modified release fill compositions and/or capsule dosage forms according to embodiments herein include, but are not limited to, diphenhydramine, ibuprofen, acetaminophen, an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, caffeine, amphetamine, methamphetamine, lisdexamfetamine dimesylate, armodafinil, atomoxetine, methylphenidate, modafinil, oxybate, pitolisant, verapamil, cefdinir, propaphenone, hydroxyurea, hydrocodone, delavirdine, nelfinavir, sodium pentosan polysulfate, tocainide, quetiapine fumarate, fexofenadine, carafate, rifampin, moxifloxacin, praziquantel, ciprofloxacin, sodium phosphate/potassium, methenamine mandelate, sotalol, cefprozil, cefadroxyl, metformin, irbesartan, nefazodone, gatifloxacin, didanosine, modafinil, efavirenz, methataxalone, amantadine, morphine, mefenamic acid, dithiazem, sevelamer, albendazole, amoxicillin, potassium clavulanate, lithium carbonate, lamivudine, sumatriptan, nabumetone, zidovudine, cimetidine, chlorpromazine, valaciclovir,

bupropion, ranitidine, abacavir, acyclovir, potassium aminobenzoate, pyridostigmine bromide, isosorbide mononitrate, nisin, demeclocycline hydrochloride, cefixime, sodium naproxen, naproxen, tetracycline hydrochloride, cefuroxime axetyl, propoxyphene napsylate, pyrazinamide, acetic acid flecainide, simethicone, mebendazole, methdopa, chlorathiazide, indinavir, penicilla, metyrosine, losartan, thiabendazole, norfloxacin, hydroxyurea, procainamide, entacapone, valsartan, terbinafine, metoprolol, ofloxacin, levofloxacin, chlorzoxazone, tolmetine, tramadol, bepridil, phenytoin, atorvastatin, celecoxib, fluconazole, doxepin, trovafloxacin mesylate, azithromycin, sertraline, rifabutine, cefpodoxime proxetil, mesalamine, disodium etidronate, nitrofurantoin, choline magnesium trisalicylate, theophylline, nizatidine, creatine, quinidine, metcarbamol mycophenolate mofetil, ganciclovir, saquinavir mesylate, tolcapone, ticlopidine, valganciclovir, capecitabine, orlistat, colesevelam, irbesartan, succimer, meperidine, hydroxychloroquine, guaifenesin, eprosartan, amiodarone, felbamate, pseudoephedrine sulfate, carisoprodol, venlafaxine, propanolol hydrochloride, etodolac, acebutolol, chondroitin, pyruvate, an opioid analgesic, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, naltrexone, naloxone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan,

phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts, complexes (e.g., with a cyclodextrin), stereoisomers, ethers, esters, hydrates, solvates, and mixtures thereof, an opioid antagonist, dextrorphan, dextromethorphan, 3-(1-naphthalennyl)-5-(phosphonomethyl)-L-phenylalanine, 3-(1-naphthalenyl)-5-(phosphonomethyl)-DL-phenylalanine, 1-(3,5-dimethylphenyl)naphthalene, 2-(3,5-dimethylphenyl) naphthalene, 2SR,4RS-4-(((1H-Tetrazol-5-yl)methyl)oxy)piperidine-2-carboxylic acid, 2SR,4RS-4-((((1H-Tetrazol-5-yl)methyl)oxy)methyl)piperidine-2-carboxylic acid, E and Z 2SR-4-(O-(1H-Tetrazol-5-yl)methyl)ketoximino)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(((1H-Tetrazol-5-yl)thio)methyl)piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-1H-Tetrazol-1-yl)methyl) piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-2H-Tetrazol-2-yl)methyl)piperidine-2-carboxylic acid, any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, and/or combinations of any two or more of the foregoing.

[0075] Suitable hydrophilic nutraceutical agents include, but are not limited to, water-soluble vitamins, vitamin C (ascorbic acid), vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin B9 (folate – folic acid), vitamin B12 (cobalamin), creatine, isoflavone, betaine, psyllium, pantothenic acid, zinc chloride, zinc gluconate, zinc sulfate, phytoestrogens, pycnogenol,

proanthocyanidins, santheanine, methylsulfonyl-meta, L- glutamine, Korosutorumu, biotin, an amino acid, serine, threonine, asparagine, L-carnitine, acetyl-L-carnitine, inositol, L-tyrosine, s-adenosylmethionine, bromelain, 2-dimethylaminoethanol, chromium picolinate, medicinal herbs, ginseng, guarana, taurine, protein hydrolysates, medicinal herbs, prebiotics, dietary fibers, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, and combinations of any two or more of the foregoing.

[0076] Suitable hydrophobic active agents include, but are not limited to, an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, loratadine, antiproliferatives, paclitaxel, sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, pimecrolimus, analgesics and anti-inflammatory agents, aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, anti-arrhythmic agents, amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate, anti-bacterial agents, benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, anti-coagulants, dicoumarol, dipyridamole, nicoumalone, phenindione, anti-hypertensive agents, amlodipine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCl, reserpine, terazosin HCl, anti-muscarinic agents, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscy amine, mepenzolate bromide, oxyphencylcimine HCl, tropicamide;

anti-neoplastic agents and immunosuppressants such as aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone, beta-blockers, acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, cardiac inotropic agents, amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin, corticosteroids, beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, lipid regulating agents, bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol, anti-anginal agents, amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate, agents for treatment of hypertension, guanethidine. In a particular embodiment, the hydrophobic active agent includes chemotherapeutics, fluorouracils, carmustine, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

[0077] Suitable hydrophobic nutraceutical agents include, but are not limited to, a fat soluble vitamin, vitamin A (retinol, retinyl esters), vitamin D (calciferol), vitamin E (α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol), vitamin K1 (phytonadione), vitamin K2 (menaquinone), omega-3 eicosapentaenoic acid, omega-3 docosahexaenoic acid, coenzyme Q10, lutein, zeaxanthin, an amino acid, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

[0078] In one or more embodiments, modified release fill compositions and/or softgel dosage forms containing such fill compositions contain diphenhydramine, ibuprofen, acetaminophen or

any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

[0079] Active agents as described herein may be included in the modified release fill compositions and/or capsule dosage forms according to one or more embodiments in a therapeutically effective amount and/or in a recommended daily amount to provide a desired health effect to a subject. Active agents may be present in the modified release fill compositions and/or capsule dosage forms in an amount of about 0.001 mcg to about 2,000 mg, about 0.01 mcg to about 1,000 mg, about 0.1 mcg to about 500 mg, about 1 mcg to about 100 mg, about 1 mg to about 50 mg, or any individual value or sub-range within these ranges.

Pharmaceutically Acceptable Excipients

[0080] Compositions and/or dosage forms according to one or more embodiments herein can include at least one excipient, for example, a pharmaceutically acceptable excipient. Examples of possible excipients are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (2012), which is incorporated by reference herein, as well as other applicable excipients. Suitable excipients include, but are not limited to, plasticizers, colorants, lubricants, thermal lubricants, antioxidants, buffering agents, disintegrants or granulating agents, binding agents, diluents, glidants, anti-adherents, sweeteners, chelating agents, granulating agents, bulking agents, flavorants, surfactants, solubilizers, stabilizers, absorption enhancers, preservative, absorbent, cross-linking agents, bioadhesive polymers, pore formers, osmotic agents, polycarboxylic acids, and combinations of any two or more of the foregoing.

[0081] Examples of suitable binding agents include, but are not limited to, polyethylene glycol, an acrylic polymer, an acrylic copolymer, a graft copolymer of polyvinyl alcohol and polyethylene

glycol, a polyvinyl alcohol, alginic acid, sodium alginate, starch, pregelatinized starch, sucrose, guar gum, salts thereof, derivatives thereof and combinations thereof. Additional binders include, but are not limited to, hydrogenated fats, hydrocarbons, stearic acid, hydrophobic and hydrophilic materials having hydrocarbon backbones, acacia, tragacanth, sucrose, glucose, magnesium aluminum silicate, polysaccharides, polysaccharide acids, bentonites, polyvinylpyrrolidone (povidone), polymethacrylates, and pregelatinized starch (such as National™ 1511 and Starch 1500).

[0082] Additional examples of binders which may be used include, but are not limited to, digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. In certain embodiments, hydrocarbons having a melting point of between 25° C and 90° C may be included. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols can be incorporated into the mixture according to certain embodiments.

[0083] Examples of suitable disintegrants include, but are not limited to, sodium starch glycolate, clays (such as Veegum™ HV), starch, cross-linked polyvinylpyrrolidone (e.g., crospovidone), alginates, corn starches and pre-gelatinized corn starches (such as National™ 1551 and National™ 1550), gums (such as agar, guar, locust bean, pectin, and tragacanth) and mixtures thereof. Disintegrants can be added at any suitable step during the preparation of the compositions, such as prior to granulation or during a melting or lubrication step and/or prior to compression or encapsulation.

[0084] Suitable bulking agents include, but are not limited to, starches (e.g., corn starch), microcrystalline cellulose, lactose (e.g., lactose monohydrate), sucrose, dextrose, mannitol, calcium phosphate and dicalcium phosphate.

[0085] According to certain embodiments, the compositions may include a plasticizer. Plasticizers can interact with hydrophobic materials resulting in a lower viscosity of the mixture as compared to the mixture without the plasticizer when measured under the same conditions. Certain plasticizers may lower the glass transition temperature (Tg) of hydrophobic materials. Suitable plasticizers include, but are not limited to, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin. Plasticizers can include ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutyl sebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate.

[0086] In at least one embodiment, the composition includes a thermal stabilizer. A thermal stabilizer is an excipient that prevent degradation and/or aggregation of the composition. Suitable thermal stabilizers include, but are not limited to, silicon dioxide, colloidal silicon dioxide, cyclodextrin, microcrystalline cellulose, sodium carboxymethylcellulose, alginates, pectins, or combinations thereof. Silicon dioxide and colloidal silicon dioxide can be used as excipients for numerous purposes. In addition to being a suitable thermal stabilizer, silicon dioxide and colloidal

silicon dioxide can be used as an anticaking agent, emulsion stabilizer, suspending agent, viscosity-increasing agent, desiccant and/or solubility-enhancer.

[0087] Suitable diluents useful in compositions as described herein include, but are not limited to, lactose (e.g., lactose (anhydrous), lactose (spray dried), lactose monohydrate), starch (e.g., directly compressible starch), mannitol, sorbitol, dextrose monohydrate, microcrystalline cellulose, dibasic calcium phosphate dihydrate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate granular, dextrates (e.g., Emdex™), dextrose (e.g., Cerelose™), inositol, hydrolyzed cereal solids such as the Maltrons™ and Mor-Rex™, amylose, calcium carbonate, glycine, bentonite, polyvinylpyrrolidone, and the like.

[0088] Suitable lubricants include, but are not limited to, glyceryl behenate (Compritol™ 888), metallic stearates (e.g., magnesium, calcium and sodium stearates), stearic acid, hydrogenated vegetable oils (e.g., Sterotex™), talc, silica, fumed silica, colloidal silica, calcium stearate, long chain fatty alcohols, boric acid, sodium benzoate and sodium acetate, sodium chloride, DL-Leucine, polyethylene glycols (e.g., Carbowax™ 4000 and Carbowax™ 6000), sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, sodium stearyl fumarate (Pruv™), magnesium lauryl sulfate, stearic acid, stearyl alcohol, mineral oil, paraffin, micro crystalline cellulose, glycerin, propylene glycol and combinations thereof.

[0089] Suitable surfactants include, but are not limited to, non-ionic surfactants, cetyl alcohol, stearyl alcohol, cetyl stearyl alcohol, cholesterol, one or more sorbitan fatty acid esters such as sorbitan monooleate (e.g., SPAN 80), one or more polyoxyethylene sorbitan fatty acid esters such as polysorbate 20 and polysorbate 80 (e.g., TWEEN 80), one or more polyoxyethylene fatty acid glycerides such as macrogol 1000 glycerol monostearate, one or more polyoxyethylene fatty acid

esters such as polyoxyl 40 stearate, one or more polyoxyethylene fatty alcohol ethers such as polyoxyl oleyl ether, one or more glycerol fatty acid esters such as glycerol monostearate, or combinations of two or more of the foregoing. Nonionic surfactants are not ionized into any ions in an aqueous medium, and a high quantity of oxygen-containing groups form hydrophilic interactions, accomplishing suspension through hydrogen bonding with water.

[0090] Suitable anti-adherents include, but are not limited to, talc, cornstarch, colloidal silicone dioxide (Cab-O-Sil™), DL-Leucine, sodium lauryl sulfate, and metallic stearates.

[0091] Other excipients (such as colorants, flavorants and sweeteners) can be utilized in embodiments of the compositions where they impart little to no deleterious effect on the stability of the pharmaceutical composition.

[0092] In certain embodiments, the composition may include a film coat. The film coat may include, but is not limited to, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol or a mixture of any two or more thereof.

Dosage Forms

[0093] Dosage forms according to one or more embodiments herein contain a modified release fill composition as described herein. In one or more embodiments, the dosage form is a capsule dosage form containing a capsule shell containing the modified release fill composition. The capsule shell can be a soft shell capsule, a softgel capsule, a hard shell capsule, and/or combinations thereof. For example, a mixed capsule shell may contain a first capsule shell part of one material (e.g., soft, softgel and/or hard) and a second capsule shell part attached, connected and/or sealed to the first capsule shell part, wherein the second capsule shell part is a different material from the first capsule shell part. In one or more embodiments, the capsule dosage form contains multiple compartments.

A first compartment containing a first fill composition and a second compartment containing a second fill composition.

[0094] Capsule shells may be formed from any suitable material known to those of ordinary skill in the art. Suitable capsule shell materials include, but are not limited to, a gelatin, a carrageenan, a starch, a maltodextrin, and/or combinations thereof. In one or more embodiments, the capsule shell is gelatin-free. In one or more embodiments, the capsule shell is vegetarian. In one or more embodiments, the capsule shell is free of an enteric coating on a surface thereof. In particularly preferred embodiments, the capsule shell is a softgel capsule shell. In some embodiments, the capsule shell is a softgel capsule comprising gelatin, and the fill composition is flowable at a temperature of about 35 °C to about 45 °C, about 38 °C to about 42 °C, about 40 °C, about 50 °C, about 60 °C, about 35 °C to about 60 °C, or any individual value or sub-range within these ranges.

[0095] According to one or more embodiments, finished dosage forms (e.g., softgels dosage forms) can include the fill composition as a solid, a semi-solid, a liquid, or a combination thereof. In some embodiments, the solid comprises one or more of particles, granules, a powder, beads, microspheres, extrudates, multi-particulates, mini-tablets, or combinations thereof.

[0096] The semi-solid can be a gel, an aqueous gel, an organic solvent-based gel, particles, granules, a powder, beads, microspheres, extrudates and/or multi-particulates dispersed in a semi-solid medium, or combinations thereof. In some embodiments, the liquid comprises a slurry, a viscous liquid, or combinations thereof.

[0097] According to various embodiments, the capsule dosage form can include a first capsule shell part and a second capsule shell part. The first and second capsule shell parts may be configured to mechanically slide together. In some embodiments, the capsule contains a seal

attaching the first capsule shell part to the second capsule shell part. In some embodiments, the capsule dosage form (e.g., a softgels dosage form) is seamless.

[0098] According to various embodiments, the dosage form does not provide an immediate release of an active agent. In embodiments, the dosage form provides a modified or extended release of an active agent contained therein.

[0099] In some embodiments, the capsule dosage form is a softgel dosage form. The softgel dosage form may be cured at about 40 °C to about 75 °C, or about 50 °C to about 65 °C for about 15 minutes to about four days, or about 1 hour to about 24 hours.

Methods of Preparation

[0100] Further described herein are methods of encapsulating a modified release fill composition in a capsule to form a capsule dosage form. In one or more embodiments, the methods include heating the modified release fill composition to a temperature of at least about 40 °C, at least about 45 °C, at least about 50 °C, at least about 55 °C, or at least about 60 °C to provide a flowable liquid. Heating can be accomplished by any suitable apparatus known to those of ordinary skill in the art. Suitable heating apparatus includes, but is not limited to, water bath, heating element, tubular heating elements, heat exchanger or combination thereof.

[0101] The softgel capsules are manufactured using a rotary die encapsulation machine. Ribbons are formed to cover the surfaces of the rotary dies. The heated fill material is pumped into each of the die cavities and sealed to form a softgel capsule. The formed wet softgel capsules are then dried, inspected, washed and packaged into bulk cartons.

[0102] For hard shell capsules, once heated to an elevated temperature, the fill composition flows into a first capsule shell part. A second capsule shell part is then fitted and/or sealed to the first capsule shell part to encapsulate the flowable liquid in the capsule.

[0103] In embodiments, the methods further include cooling the capsule dosage form to ambient temperature. In some embodiments, when the flowable liquid cools it becomes solid or semi-solid at ambient temperature although in other embodiments, it may remain a liquid.

[0104] Fill compositions according to embodiments herein can be prepared using a variety of pharmaceutical techniques known to those of ordinary skill in the art. Such methods include, but are not limited to wet granulation, dry granulation, compression, extrusion, encapsulation, and any other suitable methods to prepare compositions and dosage forms as described herein. According to embodiments, one or more components of the compositions or dosage forms can be prepared in a matrix in the form of particles, a powder, granules, beads, microspheres and combinations thereof. For example, in one embodiment, granules can be formed from one or more active agent and/or excipient. The granules of each component can be combined into a matrix (e.g., to form a matrix material). Additional components can be added to the matrix as desired. In embodiments, the matrix can be compressed and shaped to form a micro-tablet for dispersion in a flowable fluid at elevated temperature. In further embodiments, the matrix can be converted into an extrudable form and then extruded to form extrudates for dispersion in a flowable fluid.

[0105] The granules can be formed by any procedure known to those of ordinary skill in the art. For example, the granules may be formed by wet granulation with water or by dry granulation. The components can be mixed using a planetary bowl mixer, ribbon/trough mixer, rotating drum mixer or high-speed mixer until a uniform powder mix (i.e., a matrix) is achieved. The mixing

efficiency can be enhanced by the use of powders that have similar average particle size, although this is often not the case in many mixing operations.

Methods of Use

[0106] Further described herein are methods of using modified release fill compositions and/or dosage forms. In some embodiments, disclosed are methods of treating pain, comprising administering to a subject in need thereof, a dosage form according to embodiments herein. The dosage form can contain a pharmaceutically active agent suitable for treating pain. For example, the active agent can include, but is not limited to, ibuprofen, acetaminophen, acetylsalicylic acid, naproxen, naproxen sodium, an opioid, an opioid agonist, oxycodone, hydrocodone, oxymorphone, hydromorphone, tapentadol, morphine, codeine, methadone, a cannabinoid, or combinations thereof.

[0107] Methods of use can further including administering dosage forms according to embodiments herein containing one or more active agents for treating signs and symptoms associated with Abdominal aortic aneurysm, Acne, Acute cholecystitis, Acute lymphoblastic leukemia, Acute myeloid leukemia, Acute pancreatitis, Addison's disease, Alcohol-related liver disease, Allergic rhinitis, Allergies, Alzheimer's disease, Cancer, Anaphylaxis, Angioedema, Ankylosing spondylitis, Anorexia nervosa, Anxiety, Appendicitis, Arthritis, Asbestosis, Asthma, Atopic eczema, Attention deficit hyperactivity disorder (ADHD), Autistic spectrum disorder (ASD), Bacterial vaginosis, Benign prostate enlargement, Bile duct cancer (cholangiocarcinoma), Binge eating, Bipolar disorder, Bladder cancer, Blood poisoning (sepsis), Bone cancer, Bowel cancer, Bowel incontinence, Bowel polyps, Brain tumors, Breast cancer, Bronchiectasis, Bronchitis, Bulimia, Carcinoid syndrome and carcinoid tumors, Catarrh, Cellulitis, Cerebral palsy,

Cervical cancer, Chest infection, Chest pain, Chickenpox, Chilblains, Chlamydia, Chronic fatigue syndrome, Chronic kidney disease, Chronic lymphocytic leukemia, Chronic myeloid leukaemia, Chronic obstructive pulmonary disease, Chronic pain, Chronic pancreatitis, Cirrhosis, Clostridium difficile, Coeliac disease, Cold sore, Coma, Common cold, Common heart conditions, Congenital heart disease, Conjunctivitis, Constipation, Coronavirus (COVID-19), Cough, Crohn's disease, Croup, Cystic fibrosis, Cystitis, Deaf blindness, Deep vein thrombosis, Dehydration, Dementia, Dementia with Lewy bodies, Dental abscess, Depression, Dermatitis herpetiformis, Diabetes, Diarrhea, Discoid eczema, Diverticular disease and diverticulitis, Dizziness (Lightheadedness), Down's syndrome, Dry mouth, Dysphagia (swallowing problems), Dystonia, Earache, Earwax build-up, Ebola virus disease, Ectopic pregnancy, Edwards' syndrome, Endometriosis, Epilepsy, Erectile dysfunction (impotence), Escherichia coli (E. coli) O157, Ewing sarcoma, Eye cancer, Febrile seizures, Feeling of something in your throat (Globus), Fever, Fibroids, Fibromyalgia, Flatulence, Flu, Fetal alcohol syndrome, Food poisoning, Functional neurological disorder (FND), Fungal nail infection, Gallbladder cancer, Gallstones, Ganglion cyst, Gastroenteritis, Gastro-esophageal reflux disease (GORD), Genital herpes, Genital symptoms, Genital warts, Germ cell tumors, Glandular fever, Gonorrhea, Gout, Gum disease, Hemorrhoids (piles), Hand, foot and mouth disease, Hay fever, Head and neck cancer, Head lice and nits, Headaches, Hearing loss, Heart failure, Hepatitis A, Hepatitis B, Hepatitis C, Hiatus hernia, High cholesterol, HIV, Hodgkin lymphoma, Huntington's disease, Hyperglycemia (high blood sugar), Hyperhidrosis, Hypoglycemia (low blood sugar), Idiopathic pulmonary fibrosis, Impetigo, Indigestion, Ingrown toenail, Inherited heart conditions, Insomnia, Iron deficiency anemia, Irritable bowel syndrome (IBS), Irritable hip, Itching, Itchy bottom, Kaposi's sarcoma, Kidney cancer, Kidney infection, Kidney stones, Labyrinthitis, Lactose intolerance, Laryngeal (larynx) cancer, Laryngitis, Leg

cramps, Lichen planus, Liver cancer, Liver disease, Liver tumors, Loss of libido, Lung cancer, Lupus, Lyme disease, Lymphoedema, Lymphogranuloma venereum (LGV), Malaria, Malignant brain tumor (cancerous), Malnutrition, Measles, Meningitis, Menopause, Mesothelioma, Middle ear infection (otitis media), Migraine, Miscarriage, Motor neuron disease (MND), Mouth cancer, Mouth ulcer, Multiple myeloma, Multiple sclerosis (MS), Mumps, Meniere's disease, Myasthenia gravis, Nasal and sinus cancer, Nasopharyngeal cancer, Neuroblastoma: Children, Neuroendocrine tumors, Non-alcoholic fatty liver disease (NAFLD), Non-Hodgkin lymphoma, Norovirus, Nosebleed, Obesity, Obsessive compulsive disorder (OCD), Obstructive sleep apnea, Esophageal cancer, Oral thrush in adults, Osteoporosis, Osteosarcoma, Otitis externa, Ovarian cancer, Ovarian cyst, Overactive thyroid, Paget's disease of the nipple, Pancreatic cancer, Panic disorder, Parkinson's disease, Patau's syndrome, Pelvic inflammatory disease, Pelvic organ prolapse, Penile cancer, Peripheral neuropathy, Personality disorder, Pleurisy, Pneumonia, Polymyalgia rheumatica, Post-polio syndrome, Post-traumatic stress disorder (PTSD), Postnatal depression, Pregnancy and baby, Pressure ulcers, Prostate cancer, Psoriasis, Psoriatic arthritis, Psychosis, Pubic lice, Rare tumors, Raynaud's phenomenon, Reactive arthritis, Restless legs syndrome, Retinoblastoma: Children, Rhabdomyosarcoma, Rheumatoid arthritis, Ringworm and other fungal infections, Rosacea, Scabies, Scarlet fever, Schizophrenia, Scoliosis, Septic shock, Shingles, Shortness of breath, Sickle cell disease, Sinusitis, Sjogren's syndrome, Skin cancer (melanoma), Skin cancer (non-melanoma), Slapped cheek syndrome, Soft tissue sarcomas, Soft tissue sarcomas: Teenagers and young adults, Sore throat, Spleen problems and spleen removal, Stillbirth, Stomach ache and abdominal pain, Stomach cancer, Stomach ulcer, Streptococcus A (strep A), Stress, anxiety and low mood, Stroke, Sudden infant death syndrome (SIDS), Suicide, Sunburn, Swollen glands, Syphilis, Testicular cancer, Testicular lumps and swellings, Thirst,

Threadworms, Thrush, Thyroid cancer, Tinnitus, Tonsillitis, Tooth decay, Toothache, Transient ischemic attack (TIA), Trigeminal neuralgia, Tuberculosis (TB), Type 1 diabetes, Type 2 diabetes, Trichomonas infection, Transverse myelitis, Ulcerative colitis, Underactive thyroid, Urinary incontinence, Urinary tract infection (UTI), Urticaria (hives), Vaginal cancer, Vaginal discharge, Varicose eczema, Venous leg ulcer, Vertigo, Vitamin B12 or folate deficiency anemia, Vomiting in adults, Vulval cancer, Warts and verrucas, Whooping cough, Wilms' tumor and/or Womb (uterus) cancer.

ILLUSTRATIVE EXAMPLES

[0108] The following examples illustrate various aspects of the present disclosure. They are exemplary of various embodiments described herein, but are not intended to be construed as limiting the scope claims.

[0109] In the following examples, fill compositions were prepared in laboratory scale experiments. The fill compositions were encapsulated in VEGICAPS® hardshell capsules, which are representative for proof of concept. The fill compositions were prepared at a lab scale (about 20 g – about 100 g) and about 500 mg of fill composition was introduced into the hardshell capsule. Diphenhydramine (DPH) was used as a model drug in the following examples unless otherwise indicated.

Example 1 – Preparation of a Hydrophilic Fill Compositions

[0110] Hydrophilic fill compositions were prepared by combining the components in Table 1. Hydrophilic matrices were prepared with different concentrations of polyethylene oxide at room temperature to evaluate the effect of polyethylene oxide on the release rate of the active pharmaceutical ingredient. The amounts of soybean oil, colloidal silicon dioxide, active agent

(i.e., model drug diphenhydramine) and water were varied to ensure flowability of the hydrophilic fill compositions at elevated temperature, ensure effective dissolution of the dry components, and evaluate a range of drug concentrations for each hydrophilic fill composition having a different concentration of polyethylene oxide.

Table 1 – Hydrophilic Fill Compositions

Component	% by Weight
Hydrophilic Matrix	
Polyethylene oxide (POLYOX® WSR 303)	10 – 40
Colloidal Silicon Dioxide	0 – 2
Active Pharmaceutical Ingredient (API)	
Diphenhydramine	5 – 10
Solvent	
Water	0 – 10
Soybean oil	44 – 74

[0111] Each of the components of the hydrophilic matrix and API was in dry powder form. The components were introduced into a blender in which they were combined. For the hydrophilic matrix, the components were mixed together at room/ambient temperature to form a granular mixture. The granular mixture was combined with the solvent. Each hydrophilic fill composition was filled into VEGICAPS® hardshell capsules (i.e., 25 mg drug per capsule) and cured in an oven at 65 °C for an hour prior to dissolution testing.

[0112] All hydrophilic fill compositions were liquid at elevated temperature (i.e., $T \geq 40$ °C) and solid or semi-solid at ambient temperature (i.e., T about 25 °C) inside the hardshell. Drug release profiles were evaluated using a fiberoptics probe over 12 hours. Water (500 - 900 mL) at 37.0 ± 0.5 °C was used as the dissolution medium and was agitated using a paddle apparatus (APP II) at 75 RPM.

[0113] FIG. 1 shows the representative release profiles of diphenhydramine contained within the hydrophilic pharmaceutical fill compositions having different concentrations of polyethylene oxide. As shown in **FIG. 1**, concentration of polyethylene oxide had a negligible impact on diphenhydramine release rates. For all cases, a steep slope was observed at the initial stage, indicating 30% drug release within an hour. Release then slowed and each fill composition began releasing the API at a steady rate until 80% of the diphenhydramine was released after 12 hours. As the majority of the API was released into the medium within the first few hours, it was contemplated to modify the fill compositions to include a hydrophobic component forming a hydrophilic-hydrophobic fill composition.

Example 2 – Preparation of Mixed Hydrophilic-Hydrophobic Fill Compositions

[0114] Mixed hydrophilic-hydrophobic fill compositions were prepared. Cellulose and its derivatives are useful to modify the release kinetics of certain APIs. Hydrophilicity of the cellulose can be altered by etherification in which the hydroxyl groups are converted into ethers. HPMC and EC are examples of hydrophilic and hydrophobic cellulose derivatives, respectively. Hydroxypropyl methylcellulose (HPMC)-based fill matrices, ethyl cellulose (EC)-based fill matrices and combined HPMC and EC fill matrices were prepared using diphenhydramine as the active agent including variations of other ingredients as set forth in Table 2, Table 3 and Table 4, respectively. A mixed hydrophilic-hydrophobic fill composition containing ibuprofen also was prepared having the formulation shown in Table. 5.

Table 2 – HPMC-Based Hydrophilic Fill Compositions

Component	% by Weight
HPMC Matrices	
Hydroxypropyl methylcellulose provides a viscosity of 4-6 cP in 2	20 – 30

Component	% by Weight
wt% water at 20 °C (Methocel® E5 LV)	
Hydroxypropyl methylcellulose provides a viscosity of 12-18 cP in 2 wt% water at 20 °C (Methocel® E15 LV)	20 – 30
Hydroxypropyl methylcellulose provides a viscosity of 80-120 cP in 2 wt% water at 20 °C (Methocel® K100 M)	20 – 30
Colloidal silicon dioxide	0 – 2
Active Pharmaceutical Ingredient (API)	
Diphenhydramine	5 – 10
Solvent	
Water	1 – 10
Soybean oil	54 – 65

Table 3 – EC-Based Mixed Hydrophilic-Hydrophobic Fill Compositions

Component	% by Weight
Mixed Hydrophilic-Hydrophobic Matrices	
Ethyl Cellulose provides a viscosity of 9-11 cP in 5 wt% solvent (i.e., toluene 80 wt% and ethanol 20 wt%) at 25 °C (Ethocel® 10P)	20 – 30
Colloidal silicon dioxide	0 – 2
Active Pharmaceutical Ingredient (API)	
Diphenhydramine	5 – 10
Solvent	
Water	1 – 10
Soybean oil	55 – 65

Table 4 – HPMC/EC-Based Mixed Hydrophilic-Hydrophobic Fill Compositions

Component	% by Weight
Mixed Hydrophilic-Hydrophobic Matrices	
Hydroxypropyl methylcellulose provides a viscosity of 4-6 cP in 2 wt% water at 20 °C (Methocel® E5 LV)	1 – 30

Component	% by Weight
Ethyl Cellulose provides a viscosity of 9-11 cP in 5 wt% solvent (i.e., toluene 80 wt% and ethanol 20 wt%) at 25 °C (Ethocel® 10P)	1 – 30
Triethyl citrate	0 – 20
Colloidal silicon dioxide	0 – 2
Sorbitan oleate (SPAN™ 80)	0 – 10
Active Pharmaceutical Ingredient (API)	
Diphenhydramine	5 – 10
Solvent	
Water	1 – 10
Ethanol	0 – 20
Soybean oil	30 – 65

Table 5 – HPMC/EC-Based Mixed Hydrophilic-Hydrophobic Fill Compositions

Component	% by Weight
Mixed Hydrophilic-Hydrophobic Matrices	
Hydroxypropyl methylcellulose provides a viscosity of 4-6 cP in 2 wt% water at 20 °C (Methocel® E5 LV)	1 – 30
Ethyl Cellulose provides a viscosity of 9-11 cP in 5 wt% solvent (i.e., toluene 80 wt% and ethanol 20 wt%) at 25 °C (Ethocel® 10P)	1 – 30
Triethyl citrate	5 – 20
Colloidal silicon dioxide	0 – 2
Sorbitan oleate (SPAN™ 80)	0 – 10
Active Pharmaceutical Ingredient (API)	
Ibuprofen	5 – 10
Solvent	
Water	1 – 10
Ethanol	0 – 20
Soybean oil	30 – 65
Excipient	
Potassium hydroxide	1 – 5

[0115] Each of the components of the mixed hydrophilic-hydrophobic matrices and API was in dry powder form. The components were introduced into a blender in which they were combined with one or more solvent at 40 °C or higher to form each mixed hydrophilic-hydrophobic fill composition. HPMC and EC were mixed in a solvent (ethanol and soybean oil) and plasticizer (TEC) until they were fully dispersed. Matrices containing the HPMC, EC and HPMC/EC blends were initially dispersed at a temperature of 95 °C for 3 hours. API, water and KOH was added to the dispersion at the very last step. Each mixed hydrophilic-hydrophobic fill composition was filled into VEGICAPS® hardshell capsules (i.e., 25 – 50 mg diphenhydramine or 200 – 400 mg ibuprofen) and cured in an oven at 65 °C for an hour prior to dissolution testing. The drug release profiles of the mixed hydrophilic-hydrophobic fill compositions with varying HPMC and EC concentrations as well as varying HPMC:EC weight ratios with diphenhydramine or ibuprofen incorporated therein were evaluated.

[0116] All mixed hydrophilic-hydrophobic fill compositions containing ibuprofen were liquid at elevated temperature (i.e., $T \geq 60$ °C) and solid or semi-solid at ambient temperature (i.e., T about 25 °C). Drug release profiles were evaluated using a fiberoptics probe over 12 hours. A 50 mM phosphate buffer at pH 7.2 (500 – 900 mL) at 37.0 ± 0.5 °C was used as the dissolution medium under agitation. Ibuprofen-filled capsules were subjected to four different biorelevant media, that is, Fasted State Simulated Gastric Fluid (FaSSGF), Fasted State Simulated Intestinal Fluid (FaSSIF), Fed State Simulated Intestinal Fluid (FeSSIF) or phosphate buffer at pH of 4.5, and their release profiles were obtained. For all fiberoptics measurement, a paddle apparatus (APP II) was used to agitate the medium at 75 RPM.

[0117] HPMC-based fill compositions were prepared using three different grades of HPMC as shown in Table 2. The impact of HPMC viscosity on drug release rates for each encapsulated

HPMC-based fill composition is shown in **FIGs. 2A-2C**. A dependence of drug release rate on HPMC viscosity was observed. The diphenhydramine was completely released within 2 hours, 4 hours and 10 hours for low (**FIG. 2A**), moderate (**FIG. 2B**) and high (**FIG. 2C**) HPMC viscosities, respectively. Drug release rates remained insensitive to polymer concentration for HPMC with moderate and high viscosities whereas the drug embedded in the low viscosity HPMC showed modest concentration dependence. This result is attributed to the presence or lack of polymer entanglement in the matrix. Viscosity is correlated with polymer entanglement and the extent of entanglement is influenced by the polymer chain length (molecular weight) and concentration. A highly entangled matrix generates tortuous pathways that hinder drug diffusion and, thus, the release rate. In the case of the low viscosity HPMC grade, it required a higher polymer concentration to achieve a more entangled network due to the shorter polymer chains. The degree of entanglement is dependent on polymer concentration; and therefore, it is logical to observe concentration sensitive drug release profiles. For the HPMC with moderate and high viscosities, the longer polymer chains were more susceptible to entanglement and, thus, exhibited lower concentration dependence.

[0118] The effect of EC concentration on diphenhydramine release kinetics and the resulting release profiles are shown in **FIG. 3**. The diphenhydramine embedded in various EC matrices showed concentration independent release profiles. Unlike HPMC-based matrices discussed above, only 20% of the diphenhydramine was released into the dissolution medium after 12 hours of exposure. This was due to the hydrophobic nature of the EC, which limits the polymer swelling and generates a pathway for drug diffusion. As a result, polymer concentration was not determinative of the overall drug release kinetics.

[0119] As set forth above, low viscosity grade hydrophilic HPMC fill compositions rapidly released the diphenhydramine whereas the hydrophobic EC fill compositions delayed the drug release. To achieve drug release kinetics between these two extremes, a mixed HPMC and EC fill composition was prepared at varying ratios. The lowest viscosity grade HPMC was combined with the EC to form HPMC/EC mixed fill compositions at the following weight ratios of HPMC to EC: 29:1, 1:2, 2:1 and 1:1. **FIG. 4** shows the representative release profiles of the four HPMC/EC mixed fill compositions.

[0120] Surprisingly, adding only 1 wt% of the hydrophobic EC into the HPMC dominant matrix slowed down the drug release to a significant extent with less than 20 wt% of the diphenhydramine released in 12 hours. Furthermore, the release rates of the 1:2 and 2:1 HPMC:EC matrices overlapped with each other and released about 20 wt% of diphenhydramine in 12 hours. This indicated that the drug release rate was not dictated by the hydrophilicity of the matrices and there was an additional factor that determined the overall release rates. HPMC and EC at an equimass ratio interestingly showed steady diphenhydramine release over time, achieving almost 60% of diphenhydramine released. Without being bound by any particular theory, there is believed to be a synergistic interplay between HPMC and EC at a 1:1 ratio such that the zeroth order release profile was achieved.

[0121] To obtain steady drug release and further expedite the rate to achieve 80% drug release in 12 hours, different surfactants have been incorporated into the formulations. The surfactants included sorbitan oleate (e.g., SPAN™ 80) and triethyl citrate (TEC), which provided promising release profiles, as shown in **FIGs. 5A and 5B**, respectively. Incorporating 5% sorbitan oleate slowed down release modestly; however, adding 10% sorbitan oleate increased the release rate, releasing 70% of DPH in 12 hours. Further increase in sorbitan oleate to 15% slowed the release

down. It was determined that about 10% sorbitan oleate provided an optimum surfactant amount to expedite drug release although the amount to obtain a steady release rate (zeroth-order release kinetics) remains under investigation.

[0122] To further achieve steady DPH release in the interim, TEC was incorporated at different loading levels. Adding TEC helped lower the release rate in between and 20% TEC addition yielded release profile close to the that of zeroth order release. Hence, we concluded that 10% SPAN80 and 20% TEC addition is necessary to generate zeroth order release profiles with steady drug release over time.

[0123] The viscosity of the mixed hydrophilic-hydrophobic (HPMC/EC) matrices were further evaluated at elevated temperature. For modified release fill compositions according to the present disclosure, viscosity plays a role in enabling encapsulation of such fill compositions. The viscosity of fill compositions including the 1:1 MC:EC matrix and surfactant was higher than desired. Additional formulations were prepared by replacing at least a portion of the solvent (i.e., soybean oil) with alcohol (i.e., ethanol) thereby increasing solubility of the MC and EC in the fill composition. The corresponding release profiles are shown in **FIG. 6**. Replacing a portion of soybean oil with 10% and 15% ethanol affected the release rate, reducing the total release percentage by 30% and 10%, respectively. Despite the decrease in release rate, the viscosities of the fill compositions were significantly reduced with the ethanol substitution. Adding 10% and 15% ethanol reduced the viscosity from 30,000 cP to 12,000 cP and 5,400 cP, respectively, at 70 °C. The viscosity of the resulting modified release fill compositions enabled encapsulation of the compositions.

[0124] Modified release fill compositions containing the MC:EC matrix together with one or more surfactant and one or more solvent provided a modified release rate with suitable viscosity at

elevated temperature for encapsulation of the fill compositions. These fill compositions were further evaluated with the use of a drug other than diphenhydramine, namely ibuprofen. About 40 wt% ibuprofen was incorporated in the modified release fill compositions. A drug loading study for both diphenhydramine and ibuprofen in the modified release fill compositions were conducted in parallel and their corresponding release profiles are shown in **FIGs. 7A and 7B**, respectively.

[0125] As shown in **FIG. 7A**, increasing the loading level of diphenhydramine from 25 mg to 50 mg per capsule increased the overall release rate and achieved 90% release in about 9 hours. In a similar manner, as shown in **FIG. 7B**, doubling the ibuprofen concentration from 200 mg to 400 mg per capsule increased the release rate to achieve 90% release in about 9 hours. The fill composition containing about 400 mg of ibuprofen was completely released at 12 hours. Regardless of having 40% more solid incorporated, the ibuprofen-based MC/EC fill composition had a lower viscosity as compared to the diphenhydramine-based MC/EC fill composition. Table 9 summarizes the viscosity values of MC/EC fill compositions.

Table 6 – Viscosities of MC/EC Fill Compositions with Diphenhydramine, Ibuprofen and Ethanol at Different Loading Levels When Measured at 70 °C

Drug Type	Ethanol Concentration (wt%)	Viscosity (cP)
Diphenhydramine	0	30,010
	10	11,960
	15	5,380
Ibuprofen	10	3,830

[0126] Mixed MC/EC fill compositions having ingredients as set forth in Table 5 were evaluated in biorelevant media. The release kinetics of the ibuprofen MC/EC fill compositions were observed and the results are shown in **FIG. 8**. The ibuprofen release rate was steady and completely released in the FaSSIF and FeSSIF media. There was no distinctive behavior difference under these two

conditions. However, different release profiles were observed in FaSSGF and in an aqueous solution adjusted to pH 4.5 as ibuprofen was barely and moderately released in both. This was due to the fact that ibuprofen was instable in the acidic environment and, thus, crystallized with extended exposure. Therefore, the low ibuprofen release in FaSSGF and the pH 4.5 media was not due to the fill, but due to the properties of ibuprofen.

Example 3 – Preparation of a Hydrophobic Fill Compositions Containing a Hydrophobic Wax

[0127] Modified release hydrophobic fill compositions containing a hydrophobic wax were prepared. The modified release hydrophobic wax fill compositions had similar flow properties as polyethylene oxide-based fill compositions. Formulations using different waxy ingredients were developed and their respective ingredients are shown in Table 7 and Table 8.

Table 7 – Hydrophobic Matrix Components

Component	Concentration (wt%)
Matrices	
Stearoyl polyoxyl-32 glycerides (Gattefossé Gelucire® 50/13)	1 – 5
Glyceryl dibehenate (Compritol® 888 ATO)	10 – 60
Stearic Acid	0 – 10
API	
Diphenhydramine	5 – 10
Water	1 – 10

Table 8 – Hydrophobic Matrix Fill Compositions

Component	Concentration (wt%)
Matrices	
Paraffin Wax	1 – 5
Methocel™ K100 M	10 – 60
Lauroyl polyoxylglyceride (Gelucire® 44-14)	0 – 10

Component	Concentration (wt%)
Medium chain triglyceride (fractionated coconut oil)	10 – 60
Stearic acid	0 – 10
API	
Diphenhydramine	5 – 10
Water	1 – 10

[0128] Modified release fill compositions having different hydrophobic waxy materials were prepared to evaluate their effect on diphenhydramine (as the model drug) release rate. All mixtures were liquid at elevated temperature (T > 60°C) and solid at ambient temperature. The fill compositions at elevated temperature in liquid form were filled into Vegicaps® hardshell capsules (25 mg diphenhydramine per capsule) and the resulting filled capsules were cured in an oven at 65 °C for an hour prior to testing. The drug release profiles were evaluated using a fiberoptics probe over 12 hours. Water (500 – 900 mL) at 37.0 ± 0.5 °C was used as the dissolution medium and was agitated using a paddle apparatus (APP II) at75 RPM.

[0129] As shown in **FIG. 9**, the incorporation of waxy ingredients provided a sustained release of the diphenhydramine. The release profiles differed depending on the nature of the wax. Modified release fill compositions containing the ingredients as set forth in Table 7 provided rapid drug release with 70% release of diphenhydramine within 4 hours of exposure. The modified release fill compositions containing paraffin wax as set forth in Table 8, on the other hand, exhibited the opposite behavior as only 20% of diphenhydramine was released within 4 hours. In addition, the paraffin wax matrix showed surprisingly steady diphenhydramine release as a function of time.

[0130] The modified release capsules placed under various stability conditions were tested for drug release profiles using dissolution tests. The dissolution test conditions were as follows:

USP APP II, Paddle speed: 75 RPM

Medium: 900 mL Phosphate buffer, 50 mM, pH 7.2

[0131] FIG.10 shows the representative drug release profiles under 30 °C/65% relative humidity and 40 °C/75% relative humidity for T0, T1M, T3M and T6M time points. The modified release capsules containing 200mg Ibuprofen demonstrated stable drug release profiles over time.

IN THE CLAIMS

I/We claim:

1. A softgel dosage form, comprising:

a softgel capsule; and

a fill composition within the softgel capsule, the fill composition comprising:

a matrix material; and

a solvent,

wherein the fill composition is flowable at a temperature of at least about 40 °C and solid or semi-solid at ambient conditions.

2. The softgel dosage form of claim 1, wherein the softgel dosage form further comprises at least one active agent.

3. The softgel dosage form of claim 2, wherein the at least one active agent is comprised in: a) the softgel capsule, b) the fill composition, c) a film on a surface of the softgel capsule, d) a film on a surface of one or more sub-units in softgel capsule or the film composition, or e) combinations of a) to d).

4. The softgel dosage form of any preceding claim, further comprising diphenhydramine, ibuprofen or acetaminophen.

5. The softgel dosage form of any of claims 2 to 4, wherein the at least one active agent comprises at least one pharmaceutically active agent, at least one nutraceutical agent, or combinations thereof.

6. The softgel dosage form of any of claims 2 to 5, wherein the at least one active agent is hydrophilic or hydrophobic.

7. The softgel dosage form of any preceding claim, further comprising a hydrophilic active agent comprising diphenhydramine, ibuprofen, acetaminophen, an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, caffeine, amphetamine, methamphetamine, lisdexamfetamine dimesylate, armodafinil, atomoxetine, methylphenidate, modafinil, oxybate, pitolisant, verapamil, cefdinir, propaphenone, hydroxyurea, hydrocodone, delavirdine, nelfinavir, sodium pentosan polysulfate, tocainide, quetiapine fumarate, fexofenadine, carafate, rifampin, moxifloxacin, praziquantel, ciprofloxacin, sodium phosphate/potassium, methenamine mandelate, sotalol, cefprozil, cefadroxyl, metformin, irbesartan, nefazodone, gatifloxacin, didanosine, modafinil, efavirenz, methataxalone, amantadine, morphine, mefenamic acid, dithiazem, sevelamer, albendazole, amoxicillin, potassium clavulanate, lithium carbonate, lamivudine, sumatriptan, nabumetone, zidovudine, cimetidine, chlorpromazine, valaciclovir, bupropion, ranitidine, abacavir, acyclovir, potassium aminobenzoate, pyridostigmine bromide, isosorbide mononitrate, nisin, demeclocycline hydrochloride, cefixime, sodium naproxen, naproxen, tetracycline hydrochloride, cefuroxime axetyl, propoxyphene napsylate, pyrazinamide, acetic acid flecainide, simethicone, mebendazole, methdopa, chlorathiazide, indinavir, penicilla, metyrosine, losartan, thiabendazole, norfloxacin,

hydroxyurea, procainamide, entacapone, valsartan, terbinafine, metoprolol, ofloxacin, levofloxacin, chlorzoxazone, tolmetine, tramadol, bepridil, phenytoin, atorvastatin, celecoxib, fluconazole, doxepin, trovafloxacin mesylate, azithromycin, sertraline, rifabutine, cefpodoxime proxetil, mesalamine, disodium etidronate, nitrofurantoin, choline magnesium trisalicylate, theophylline, nizatidine, creatine, quinidine, metcarbamol mycophenolate mofetil, ganciclovir, saquinavir mesylate, tolcapone, ticlopidine, valganciclovir, capecitabine, orlistat, colesevelam, irbesartan, succimer, meperidine, hydroxychloroquine, guaifenesin, eprosartan, amiodarone, felbamate, pseudoephedrine sulfate, carisoprodol, venlafaxine, propanolol hydrochloride, etodolac, acebutolol, chondroitin, pyruvate, an opioid analgesic, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, naltrexone, naloxone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts, complexes (e.g., with a cyclodextrin), stereoisomers, ethers, esters, hydrates, solvates, and mixtures thereof, an opioid antagonist, dextrorphan, dextromethorphan, 3-(1-naphthalennyl)-5-(phosphonomethyl)-L-phenylalanine, 3-

(1-naphthalenyl)-5-(phosphonomethyl)-DL-phenylalanine, 1-(3,5-dimethylphenyl)naphthalene, 2-(3,5-dimethylphenyl) naphthalene, 2SR,4RS-4-(((1H-Tetrazol-5-yl)methyl)oxy)piperidine-2-carboxylic acid, 2SR,4RS-4-((((1H-Tetrazol-5-yl)methyl)oxy)methyl)piperidine-2-carboxylic acid, E and Z 2SR-4-(O-(1H-Tetrazol-5-yl)methyl)ketoximino)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(((1H-Tetrazol-5-yl)thio)methyl)piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-1H-Tetrazol-1-yl)methyl) piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-2H-Tetrazol-2-yl)methyl)piperidine-2-carboxylic acid, any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

8. The softgel dosage form of any preceding claim, further comprising a hydrophilic nutraceutical agent comprising water-soluble vitamins, vitamin C (ascorbic acid), vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin B9 (folate – folic acid), vitamin B12 (cobalamin), creatine, isoflavone, betaine, psyllium, pantothenic acid, zinc chloride, zinc gluconate, zinc sulfate, phytoestrogens, pycnogenol, proanthocyanidins, santheanine, methylsulfonyl-meta, L-glutamine, Korosutorumu, biotin, an amino acid, serine, threonine, asparagine, L-carnitine, acetyl-L-carnitine, inositol, L-tyrosine, s-adenosylmethionine, bromelain, 2-dimethylaminoethanol, chromium picolinate, medicinal herbs, ginseng, guarana, taurine, protein

hydrolysates, medicinal herbs, prebiotics, dietary fibers, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, and combinations of any two or more of the foregoing.

9. The softgel dosage form of any preceding claim, further comprising a hydrophobic active agent comprising an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, loratadine, antiproliferatives, paclitaxel, sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, pimecrolimus, analgesics and anti-inflammatory agents, aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, anti-arrhythmic agents, amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate, anti-bacterial agents, benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, anti-coagulants, dicoumarol, dipyridamole, nicoumalone, phenindione, anti-hypertensive agents, amlodipine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCl, reserpine, terazosin HCl, anti-muscarinic agents, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscy amine, mepenzolate bromide, oxyphencylcimine HCl, tropicamide; anti-neoplastic agents and immunosuppressants such as aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine,

estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone, beta-blockers, acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, cardiac inotropic agents, amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin, corticosteroids, beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, lipid regulating agents, bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol, anti-anginal agents, amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate, agents for treatment of hypertension, guanethidine. In a particular embodiment, the hydrophobic active agent includes chemotherapeutics, fluorouracils, carmustine, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

10. The softgel dosage form of any preceding claim, further comprising a hydrophobic nutraceutical agent comprising a fat soluble vitamin, vitamin A (retinol, retinyl esters), vitamin D (calciferol), vitamin E (α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol), vitamin K1 (phytonadione), vitamin K2 (menaquinone), omega-3 eicosapentaenoic acid, omega-3 docosahexaenoic acid, coenzyme Q10, lutein, zeaxanthin, an amino acid, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

11. The softgel dosage form of any preceding claim, wherein the fill composition is flowable at a temperature of at least about 37 °C, at least about 45 °C, at least about 50 °C, at least about 55 °C, at least about 60 °C, or at least about 70 °C.

12. The softgel dosage form of any preceding claim, wherein the fill composition is solid or semi-solid at a temperature of about 15 °C to about 35 °C, about 18 °C to about 30 °C, or about 20 °C to about 25 °C.

13. The softgel dosage form of any preceding claim, wherein the fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, or less than about 10,000 cp at a temperature of 40 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 40°C.

14. The softgel dosage form of any preceding claim, wherein the fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, or less than about 10,000 cp at a temperature of 60 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 60°C.

15. The softgel dosage form of any preceding claim, wherein the softgel dosage form provides a modified release of an active agent.

16. The softgel dosage form of any preceding claim, wherein the softgel dosage form releases an active agent for a period of at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, or at least about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

17. The softgel dosage form of any preceding claim, wherein the softgel dosage form releases about 40% or less, 30% or less, 20% or less, or 10% or less of an active agent within about 1 hour as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

18. The softgel dosage form of any preceding claim, wherein the softgel dosage form releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 12 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

19. The softgel dosage form of any preceding claim, wherein the softgel dosage form releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

20. The softgel dosage form of any preceding claim, wherein the fill composition provides a modified release of an active agent.

21. The softgel dosage form of any preceding claim, wherein the fill composition releases an active agent over a period of at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, or at least about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

22. The softgel dosage form of any preceding claim, wherein the fill composition releases about 40% or less, 30% or less, 20% or less, or 10% or less of an active agent within about 1 hour as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

23. The softgel dosage form of any preceding claim, wherein the fill composition releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 12 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

24. The softgel dosage form of any preceding claim, wherein the fill composition releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within

about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 75 RPM in about 500 ml to about 900 ml water or buffer at about 37°C.

25. The softgel dosage form of any preceding claim, wherein the softgel capsule comprises a gelatin, a carrageenan, a starch, a maltodextrin, or combinations thereof, or

wherein the softgel capsule is gelatin-free.

26. The softgel dosage form of any preceding claim, wherein the matrix material comprises a polymer comprising a polyethylene oxide, a cellulose derivative, a natural gum, a synthetic gum, or combinations thereof, and/or

wherein the matrix material comprises a wax comprising paraffin wax, stearoyl polyoxyl-32 glycerides, carnauba wax, beeswax, stearic acid, cetyl alcohol, cetostearyl alcohol, glyceryl monostearate, or combinations thereof.

27. The softgel dosage form of any preceding claim, wherein the matrix material comprises:

a polyethylene oxide having a molecular weight of about 90,000 Da to about 7,000,000 Da, or

a plurality of polyethylene oxides, each having a different molecular weight in the range of about 90,000 Da to about 7,000,000 Da.

28. The softgel dosage form of claim 27, comprising the polyethylene oxide or plurality of polyethylene oxides in an amount of about 5 wt% to about 50 wt%, or about 10 wt% to about 50 wt% based on the total weight of the fill composition.

29. The softgel dosage form of any preceding claim, wherein the softgel capsule comprises gelatin, and wherein the fill composition is flowable at a temperature of about 35 °C to about 45 °C, about 38 °C to about 42 °C, or about 40 °C.

30. The softgel dosage form of claim 27 to 29, wherein the fill composition is hydrophilic.

31. The softgel dosage form of any preceding claim, wherein the cellulose derivative comprises a hydroxypropyl methylcellulose, an ethyl cellulose, a hydroxypropylcellulose, a hydroxyethylcellulose, a methylcellulose, a sodium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose or a combination of any two or more thereof.

32. The softgel dosage form of any preceding claim, wherein the matrix material comprises:

a hydroxypropyl methylcellulose having a molecular weight of about 10,000 Da to about 1,500,000 Da, or

a plurality of hydroxypropyl methylcelluloses, each having a different molecular weight in the range of about 10,000 Da to about 1,500,000 Da.

33. The softgel dosage form of any preceding claim, wherein the matrix material comprises:

an ethyl cellulose having a molecular weight of about 10,000 Da to about 200,000 Da, or

a plurality of ethyl celluloses, each having a different molecular weight in the range of about 400 Da to about 2,000,000 Da.

34. The softgel dosage form of any preceding claim, wherein the matrix material comprises at least one hydroxypropyl methylcellulose and at least one ethyl cellulose, optionally wherein a weight ratio of the at least one hydroxypropyl methylcellulose to the at least one ethyl cellulose is about 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1.

35. The softgel dosage form of claim 34, comprising one or more of:

(a) a hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C,

(b) a hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, or

(c) a hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C,

optionally wherein a weight ratio of (a):(b) is 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1, and a weight ratio of (a):(c) 1:100 to about

100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1.

36. The softgel dosage form of claim 34, comprising at least one of:

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp,

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp, or

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp.

37. The softgel dosage form of any one of claims 34 to 36, comprising an ethyl cellulose that provides a viscosity of about 9 cp to about 11 cp when measured using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C.

38. The softgel dosage form of any preceding claim, wherein the solvent comprises an aqueous component, an oil, an alcohol, a low molecular weight polymer, an emulsifier, a surface active agent, or combinations thereof.

39. The softgel dosage form of claim 38, wherein the oil comprises soybean oil, mineral oil, olive oil, a vegetable oil, sesame oil, sunflower oil, rapeseed oil, corn oil, oleic oil, coconut oil, almond oil, avocado oil, grape seed oil, or palm oil, or a combination of any two or more of the foregoing.

40. The softgel dosage form of any preceding claim, wherein the solvent comprises water, soybean oil, ethanol, a low molecular weight polyethylene glycol, triethyl citrate, or a combination of any two or more thereof.

41. The softgel dosage form of any preceding claim, wherein the solvent comprises at least one of:

soybean oil in an amount of about 20 wt% to about 90 wt%, about 30 wt% to about 80 wt%, about 40 wt % to about 70 wt%, or about 50 wt% to about 65 wt%, based on the total weight of the fill composition;

water in an amount of about 0.1 wt% to about 30 wt%, about 0.5 wt% to about 20 wt%, or about 1 wt% to about 10 wt%, based on the total weight of the fill composition, or

ethanol in an amount of about 0 wt% to about 40 wt%, about 1 wt% to about 30 wt%, about 5 wt% to about 20 wt%, based on the total weight of the fill composition.

42. The softgel dosage form of any preceding claim, wherein the fill composition further comprises at least one pharmaceutically acceptable excipient.

43. The softgel dosage form of claim 42, wherein the at least one pharmaceutically acceptable excipient comprises a plasticizer, colorant, lubricant, thermal lubricant, antioxidant, buffering agent, disintegrant, granulating agent, binding agent, diluent, anti-adherent, sweetener, chelating agent, granulating agent, bulking agent, suspending agent, flavorant, surfactant, solubilizer, stabilizer, absorption enhancer, preservative, absorbent, cross-linking agent, pore former, osmotic agent, polycarboxylic acid, emulsion stabilizer, suspending agent, thermal stabilizer, viscosity-increasing agent, desiccant, solubility-enhancer and combinations of any two or more of the foregoing.

44. The softgel dosage form of any preceding claim, further comprising a thermal stabilizer comprising silicon dioxide, colloidal silicon dioxide, a wax, cyclodextrin, microcrystalline cellulose, sodium carboxymethylcellulose, alginates, pectins, or combinations of any two or more thereof.

45. The softgel dosage form of any preceding claim, further comprising a surfactant comprising cetyl alcohol, stearyl alcohol, cetyl stearyl alcohol, cholesterol, sorbitan fatty acid esters, sorbitan monooleate, polyoxyethylene sorbitan fatty acid ester, polysorbate 20, polysorbate 80, polyoxyethylene fatty acid glyceride, polyethylene glycol hexadecyl ether, polyethylene glycol hexadecyl ether phosphate, glycerol monostearate, polyoxyethylene fatty acid ester, polyoxyl 40 stearate, polyoxyethylene fatty alcohol ether, polyoxyl oleyl ether, glycerol fatty acid ester, glycerol monostearate, glyceryl dibehenate, or combinations of two or more thereof.

46. The softgel dosage form of any preceding claim, further comprising a plasticizer comprising triethyl citrate, acetyltriethyl citrate, tributyl citrate, acetyltributyl citrate, stearic acid, one or more low molecular weight polymers, a low molecular weight oligomer, a low molecular weight copolymer, an oil, small organic molecule, low molecular weight polyol having one or more aliphatic hydroxyls, ester-type plasticizer, glycol ether, poly(propylene glycol), low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol, glycerin, ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, a poly(ethylene glycol) compound, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutyl sebacate, acetyltributylcitrate, allyl glycolate, or combinations of any two or more thereof.

47. The softgel dosage form of any preceding claim, further comprising a suspending agent comprising silicon dioxide, colloidal silicon dioxide, a wax, acacia, agar, alginic acid, aluminum monostearate, bentonite, camphor, a carbomer, a carrageenan, a starch, corn starch, a gelatin, guar gum, a hydroxyethyl cellulose, a hydroxypropyl cellulose, a hypromellose, a magnesium aluminum silicate, a methylcellulose, a pectin, polyvinyl alcohol, a povidone, sodium alginate, sodium hyaluronate, tragacanth, xanthan gum, or combinations of any two or more thereof.

48. The softgel dosage form of any preceding claim, wherein the matrix material comprises one or more esters of fatty acids and glycerol, one or more triglyceride, a long chain fatty acid or combinations thereof.

49. The softgel dosage form of claim 47 or 48, wherein the one or more esters of fatty acids and glycerol comprise esters of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid, lauric acid, caproic acid, caprylic acid, capric acid, or combinations two or more thereof, a monoglyceride, a diglyceride, a monoacylglycerol, a diacylglycerol, stearoyl polyoxylglyceride, lauroyl polyoxylglyceride, stearoyl polyoxyl-32 glycerides, lauroyl polyoxyl-32 glycerides, glycerol monostearate, glycerol monocaprylocaprate, glycerol dicaprylate, glycerol monooleate, or combinations of two or more thereof.

50. The softgel dosage form of any one of claims 47 to 49, wherein the one or more triglycerides comprises a medium chain triglyceride, a caprylic triglyceride, a capric acid triglyceride, triglycerol esters of one or more of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid, caproic acid, caprylic acid, capric acid or lauric acid and one or more medium chain fatty acid having about 6 to about 12 carbon atoms, glyceryl tricaprylate/caprate, glycerol caprylate caprate, caprylic/capric triglyceride, or combinations of any two or more thereof.

51. The softgel dosage form of any one of claims 47 to 50, wherein the wax comprises paraffin wax, beeswax, jojoba, lanolin, spermaceti, or combinations of any two or more thereof.

52. The softgel dosage form of any preceding claim, comprising at least one of:

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1 wt% to about 5 wt% of one or more esters of fatty acids and glycerol;

about 0.1 wt% to about 50 wt%, or about 1 wt% to about 30 wt% of a surfactant;

about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; or

about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer.

53. The softgel dosage form of claim 52, wherein the one or more esters of fatty acids and glycerol comprises stearoyl polyoxyl-32 glycerides, the surfactant comprises glyceryl dibehenate, and the plasticizer comprises stearic acid.

54. The softgel dosage form of any preceding claim, comprising at least one of:

about 1 wt% to about 50 wt%, about 5 wt% to about 40 wt%, or about 10 wt% to about 30 wt% of the wax;

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of a hydroxypropyl methylcellulose;

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of one or more esters of fatty acids and glycerol;

about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; or

about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer.

55. The softgel dosage form of claim 54, wherein the wax comprises paraffin wax, the hydroxypropyl methylcellulose provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation

frequency of 1 Hz, at 20 °C, the one or more esters of fatty acids and glycerol comprises lauroyl polyoxylglycerides, and the plasticizer comprises stearic acid.

56. The softgel dosage form according to any preceding claim, wherein the fill composition comprises a solid, a semi-solid, a liquid, or a combination thereof.

57. The softgel dosage form of claim 56, wherein the solid comprises one or more of particles, granules, a powder, beads, microspheres, extrudates, multi-particulates, mini-tablets, or combinations thereof.

58. The softgel dosage form of claim 55 or 56, wherein the semi-solid comprises a gel, an aqueous gel, an organic solvent-based gel, particles, granules, a powder, beads, microspheres, extrudates and/or multi-particulates dispersed in a semi-solid medium, or combinations thereof.

59. The softgel dosage form of any one of claims 55 to 58, wherein the liquid comprises a slurry, a viscous liquid, or combinations thereof.

60. The softgel dosage form of any preceding claim, wherein the softgel capsule comprises a first capsule shell part, a second capsule shell part and a seal attaching the first capsule shell part to the second capsule shell part, or

wherein the softgel capsule is seamless.

61. The softgel dosage form of any preceding claim, wherein the softgel dosage form does not provide an immediate release of an active agent.

62. The softgel dosage form of any preceding claim, wherein the softgel dosage form is cured at about 40 °C to about 75 °C, or about 50 °C to about 65 °C for about 15 minutes to about four days, or about 1 hour to about 24 hours.

63. A method of encapsulating a modified release fill composition in a softgel capsule to form a softgel dosage form according to any preceding claim, the method comprising:

heating the modified release fill composition to a temperature of at least about 40 °C, at least about 45 °C, at least about 50 °C, at least about 55 °C, or at least about 60 °C to provide a flowable liquid; and

encapsulating the flowable liquid in the softgel capsule.

64. The method of claim 63, further comprising cooling the softgel dosage form to ambient temperature.

65. The method of claim 63 or 64, wherein the flowable liquid forms a solid or a semi-solid at ambient temperature.

66. The method of claim 63, wherein encapsulating the flowable liquid comprises filling a first capsule shell part of the softgel capsule with the flowable liquid; and sealing a second capsule shell part to the first capsule shell part to form a seal.

67. A method of treating pain, comprising:

administering to a subject in need thereof, a softgel dosage form according to any preceding claim, wherein the softgel dosage form comprises a pharmaceutically active agent suitable for treating pain.

68. A fill composition for encapsulation within a softgel capsule, the fill composition comprising:

a matrix material; and

a solvent,

wherein the fill composition is flowable at a temperature of at least about 40 °C and solid or semi-solid at ambient conditions.

69. The fill composition of claim 68, further comprising at least one active agent.

70. The fill composition of claim 69, wherein the at least one active agent is comprised in: a) sub-units dispersed within the fill composition, b) a film on a surface of one or more sub-units in the fill composition, c) a bulk medium of the fill composition, or d) combinations of a) to c).

71. The fill composition of claim 68 or 69, further comprising diphenhydramine, ibuprofen or acetaminophen.

72. The fill composition of any of claims 69 to 71, wherein the at least one active agent comprises at least one pharmaceutically active agent, at least one nutraceutical agent, or combinations thereof.

73. The fill composition of any of claims 69 to 72, wherein the at least one active agent is hydrophilic or hydrophobic.

74. The fill composition of any one of claims 68 to 73, further comprising a hydrophilic active agent comprising diphenhydramine, ibuprofen, acetaminophen, an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, caffeine, amphetamine, methamphetamine, lisdexamfetamine dimesylate, armodafinil, atomoxetine, methylphenidate, modafinil, oxybate, pitolisant, verapamil, cefdinir, propaphenone, hydroxyurea, hydrocodone, delavirdine, nelfinavir, sodium pentosan polysulfate, tocainide, quetiapine fumarate, fexofenadine, carafate, rifampin, moxifloxacin, praziquantel, ciprofloxacin, sodium phosphate/potassium, methenamine mandelate, sotalol, cefprozil, cefadroxyl, metformin, irbesartan, nefazodone, gatifloxacin, didanosine, modafinil, efavirenz, methataxalone, amantadine, morphine, mefenamic acid, dithiazem, sevelamer, albendazole, amoxicillin, potassium clavulanate, lithium carbonate, lamivudine, sumatriptan, nabumetone, zidovudine, cimetidine, chlorpromazine, valaciclovir, bupropion, ranitidine, abacavir, acyclovir, potassium aminobenzoate, pyridostigmine bromide, isosorbide mononitrate, nisin, demeclocycline hydrochloride, cefixime, sodium naproxen, naproxen, tetracycline hydrochloride, cefuroxime axetyl, propoxyphene napsylate, pyrazinamide, acetic acid flecainide, simethicone, mebendazole, methdopa, chlorathiazide, indinavir, penicilla, metyrosine, losartan, thiabendazole, norfloxacin,

hydroxyurea, procainamide, entacapone, valsartan, terbinafine, metoprolol, ofloxacin, levofloxacin, chlorzoxazone, tolmetine, tramadol, bepridil, phenytoin, atorvastatin, celecoxib, fluconazole, doxepin, trovafloxacin mesylate, azithromycin, sertraline, rifabutine, cefpodoxime proxetil, mesalamine, disodium etidronate, nitrofurantoin, choline magnesium trisalicylate, theophylline, nizatidine, creatine, quinidine, metcarbamol mycophenolate mofetil, ganciclovir, saquinavir mesylate, tolcapone, ticlopidine, valganciclovir, capecitabine, orlistat, colesevelam, irbesartan, succimer, meperidine, hydroxychloroquine, guaifenesin, eprosartan, amiodarone, felbamate, pseudoephedrine sulfate, carisoprodol, venlafaxine, propanolol hydrochloride, etodolac, acebutolol, chondroitin, pyruvate, an opioid analgesic, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, naltrexone, naloxone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts, complexes (e.g., with a cyclodextrin), stereoisomers, ethers, esters, hydrates, solvates, and mixtures thereof, an opioid antagonist, dextrorphan, dextromethorphan, 3-(1-naphthalennyl)-5-(phosphonomethyl)-L-phenylalanine, 3-

(1-naphthalenyl)-5-(phosphonomethyl)-DL-phenylalanine, 1-(3,5-dimethylphenyl)naphthalene, 2-(3,5-dimethylphenyl) naphthalene, 2SR,4RS-4-(((1H-Tetrazol-5-yl)methyl)oxy)piperidine-2-carboxylic acid, 2SR,4RS-4-((((1H-Tetrazol-5-yl)methyl)oxy)methyl)piperidine-2-carboxylic acid, E and Z 2SR-4-(O-(1H-Tetrazol-5-yl)methyl)ketoximino)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl)piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl) piperidine-2-carboxylic acid, 2SR,4RS-4-(((1H-Tetrazol-5-yl)thio)methyl)piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-1H-Tetrazol-1-yl)methyl) piperidine-2-carboxylic acid, 2SR,4RS-4-((5-mercapto-2H-Tetrazol-2-yl)methyl)piperidine-2-carboxylic acid, any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

75. The fill composition of any one of claims 68 to 74, further comprising a hydrophilic nutraceutical agent comprising water-soluble vitamins, vitamin C (ascorbic acid), vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin B9 (folate – folic acid), vitamin B12 (cobalamin), creatine, isoflavone, betaine, psyllium, pantothenic acid, zinc chloride, zinc gluconate, zinc sulfate, phytoestrogens, pycnogenol, proanthocyanidins, santheanine, methylsulfonyl-meta, L-glutamine, Korosutorumu, biotin, an amino acid, serine, threonine, asparagine, L-carnitine, acetyl-L-carnitine, inositol, L-tyrosine, s-adenosylmethionine, bromelain, 2-dimethylaminoethanol, chromium picolinate, medicinal herbs, ginseng, guarana, taurine, protein

hydrolysates, medicinal herbs, prebiotics, dietary fibers, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, and combinations of any two or more of the foregoing.

76. The fill composition of any one of claims 68 to 75, further comprising a hydrophobic active agent comprising an antihistamine, a decongestant, an anti-inflammatory, a stimulant, a central nervous system stimulant, loratadine, antiproliferatives, paclitaxel, sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, pimecrolimus, analgesics and anti-inflammatory agents, aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcim, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, anti-arrhythmic agents, amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate, anti-bacterial agents, benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, anti-coagulants, dicoumarol, dipyridamole, nicoumalone, phenindione, anti-hypertensive agents, amlodipine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCl, reserpine, terazosin HCl, anti-muscarinic agents, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscy amine, mepenzolate bromide, oxyphencylcimine HCl, tropicamide; anti-neoplastic agents and immunosuppressants such as aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine,

estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone, beta-blockers, acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, cardiac inotropic agents, amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin, corticosteroids, beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, lipid regulating agents, bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol, anti-anginal agents, amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate, agents for treatment of hypertension, guanethidine. In a particular embodiment, the hydrophobic active agent includes chemotherapeutics, fluorouracils, carmustine, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

77. The fill composition of any one of claims 68 to 76, further comprising a hydrophobic nutraceutical agent comprising a fat soluble vitamin, vitamin A (retinol, retinyl esters), vitamin D (calciferol), vitamin E (α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol), vitamin K1 (phytonadione), vitamin K2 (menaquinone), omega-3 eicosapentaenoic acid, omega-3 docosahexaenoic acid, coenzyme Q10, lutein, zeaxanthin, an amino acid, or any pharmaceutically acceptable salt, isomer, enantiomer, ester, prodrug, and/or derivative thereof, or combinations of any two or more of the foregoing.

78. The fill composition of any one of claims 68 to 77, wherein the fill composition is flowable at a temperature of at least about 45 °C, at least about 50 °C, at least about 55 °C, at least about 60 °C, or at least about 70 °C.

79. The fill composition of any one of claims 68 to 78, wherein the fill composition is solid or semi-solid at a temperature of about 15 °C to about 35 °C, about 18 °C to about 30 °C, or about 20 °C to about 25 °C.

80. The fill composition of any one of claims 68 to 79, wherein the fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, or less than about 10,000 cp at a temperature of 40 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 40°C.

81. The fill composition of any one of claims 68 to 80, wherein the fill composition has a viscosity of less than about 100,000 cp, less than about 80,000 cp, less than about 50,000 cp, less than about 25,000 cp, less than about 15,000 cp, less than about 12,000 cp, or less than about 10,000 cp at a temperature of 60 °C when the viscosity is determined using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 60°C.

82. The fill composition of any one of claims 68 to 81, wherein the fill composition provides a modified release of an active agent.

83. The fill composition of any one of claims 68 to 82, wherein the fill composition releases an active agent over a period of at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, or at least about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C.

84. The fill composition of any one of claims 68 to 83, wherein the fill composition releases about 40% or less, 30% or less, 20% or less, or 10% or less of an active agent within about 1 hour as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C.

85. The fill composition of any one of claims 68 to 84, wherein the fill composition releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 12 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C.

86. The fill composition of any one of claims 68 to 85, wherein the fill composition releases about 80% or more, 85% or more, 95% or more, or 100% or more of an active agent within about 24 hours as measured by *in-vitro* dissolution in a USP Apparatus II (paddle) at about 50 RPM in about 900 ml 0.1N HCl at about 37°C.

87. The fill composition of any one of claims 68 to 86, wherein the matrix material comprises a polymer comprising a polyethylene oxide, a cellulose derivative, a natural gum, a synthetic gum, or combinations thereof, and/or

wherein the matrix material comprises a wax comprising paraffin wax, stearoyl polyoxyl-32 glycerides, carnauba wax, beeswax, stearic acid, cetyl alcohol, cetostearyl alcohol, glyceryl monostearate, or combinations thereof.

88. The fill composition of any one of claims 68 to 87, wherein the matrix material comprises:

a polyethylene oxide having a molecular weight of about 90,000 Da to about 7,000,000 Da, or

a plurality of polyethylene oxides, each having a different molecular weight in the range of about 90,000 Da to about 7,000,000 Da.

89. The fill composition of claim 88, comprising the polyethylene oxide or plurality of polyethylene oxides in an amount of about 5 wt% to about 50 wt%, or about 10 wt% to about 50 wt% based on the total weight of the fill composition.

90. The fill composition of any one of claims 68 to 89, wherein the fill composition is flowable at a temperature of about 35 °C to about 45 °C, about 38 °C to about 42 °C, or about 40 °C.

91. The fill composition of any one of claims 68 to 90, wherein the fill composition is hydrophilic.

92. The fill composition of any one of claims 68 to 91, wherein the cellulose derivative comprises a hydroxypropyl methylcellulose, an ethyl cellulose, a hydroxypropylcellulose, a hydroxyethylcellulose, a methylcellulose, a sodium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose or a combination of any two or more thereof.

93. The fill composition of any one of claims 68 to 92, wherein the matrix material comprises:

a hydroxypropyl methylcellulose having a molecular weight of about 10,000 Da to about 1,500,000 Da, or

a plurality of hydroxypropyl methylcelluloses, each having a different molecular weight in the range of about 10,000 Da to about 1,500,000 Da.

94. The fill composition of any one of claims 68 to 93, wherein the matrix material comprises:

an ethyl cellulose having a molecular weight of about 10,000 Da to about 200,000 Da, or

a plurality of ethyl celluloses, each having a different molecular weight in the range of about 400 Da to about 2,000,000 Da.

95. The fill composition of any one of claims 68 to 94, wherein the matrix material comprises at least one hydroxypropyl methylcellulose and at least one ethyl cellulose, optionally wherein a

weight ratio of the at least one hydroxypropyl methylcellulose to the at least one ethyl cellulose is about 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1.

96. The fill composition of claim 95, comprising one or more of:

(a) a hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C,

(b) a hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, or

(c) a hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C,

optionally wherein a weight ratio of (a):(b) is 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1, and a weight ratio of (a):(c) 1:100 to about 100:1, about 1:50 to about 50:1, about 1:25 to about 25:1, about 1:20 to about 20:1, about 1:15 to about 15:1, about 1:10 to about 10:1, about 1:5 to about 5:1, or about 1:1.

97. The fill composition of claim 95, comprising at least one of:

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 4 cp to about 6 cp,

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 12 cp to about 18 cp, or

about 5 wt% to about 50 wt%, about 10 wt% to about 40 wt%, or about 20 wt% to about 30 wt%, based on the total weight of the fill composition, of the hydroxypropyl methylcellulose that provides a viscosity of about 80 cp to about 120 cp.

98. The fill composition of any one of claims 95 to 97, comprising an ethyl cellulose that provides a viscosity of about 9 cp to about 11 cp when measured using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C.

99. The fill composition of any one of claims 68 to 98, wherein the solvent comprises an aqueous component, an oil, an alcohol, a low molecular weight polymer, an emulsifier, a surface active agent, or combinations thereof.

100. The fill composition of claim 99, wherein the oil comprises soybean oil, mineral oil, olive oil, a vegetable oil, sesame oil, sunflower oil, rapeseed oil, corn oil, oleic oil, coconut oil, almond

oil, avocado oil, grape seed oil, or palm oil, or a combination of any two or more of the foregoing.

101. The fill composition of any one of claims 68 to 100, wherein the solvent comprises water, soybean oil, ethanol, a low molecular weight polyethylene glycol, triethyl citrate, or a combination of any two or more thereof.

102. The fill composition of any one of claims 68 to 101, wherein the solvent comprises at least one of:

soybean oil in an amount of about 20 wt% to about 90 wt%, about 30 wt% to about 80 wt%, about 40 wt % to about 70 wt%, or about 50 wt% to about 65 wt%, based on the total weight of the fill composition;

water in an amount of about 0.1 wt% to about 30 wt%, about 0.5 wt% to about 20 wt%, or about 1 wt% to about 10 wt%, based on the total weight of the fill composition, or

ethanol in an amount of about 0 wt% to about 40 wt%, about 1 wt% to about 30 wt%, about 5 wt% to about 20 wt%, based on the total weight of the fill composition.

103. The fill composition of any one of claims 68 to 102, wherein the fill composition further comprises at least one pharmaceutically acceptable excipient.

104. The fill composition of claim 103, wherein the at least one pharmaceutically acceptable excipient comprises a plasticizer, colorant, lubricant, thermal lubricant, antioxidant, buffering agent, disintegrant, granulating agent, binding agent, diluent, anti-adherent, sweetener, chelating

agent, granulating agent, bulking agent, suspending agent, flavorant, surfactant, solubilizer, stabilizer, absorption enhancer, preservative, absorbent, cross-linking agent, pore former, osmotic agent, polycarboxylic acid, emulsion stabilizer, suspending agent, thermal stabilizer, viscosity-increasing agent, desiccant, solubility-enhancer and combinations of any two or more of the foregoing.

105. The fill composition of any one of claims 68 to 104, further comprising a thermal stabilizer comprising silicon dioxide, colloidal silicon dioxide, cyclodextrin, microcrystalline cellulose, sodium carboxymethylcellulose, alginates, pectins, or combinations of any two or more thereof.

106. The fill composition of any one of claims 68 to 105, further comprising a surfactant comprising cetyl alcohol, stearyl alcohol, cetyl stearyl alcohol, cholesterol, sorbitan fatty acid esters, sorbitan monooleate, polyoxyethylene sorbitan fatty acid ester, polysorbate 20, polysorbate 80, polyoxyethylene fatty acid glyceride, polyethylene glycol hexadecyl ether, polyethylene glycol hexadecyl ether phosphate, glycerol monostearate, polyoxyethylene fatty acid ester, polyoxyl 40 stearate, polyoxyethylene fatty alcohol ether, polyoxyl oleyl ether, glycerol fatty acid ester, glycerol monostearate, glyceryl dibehenate, or combinations of two or more thereof.

107. The fill composition of any one of claims 68 to 106, further comprising a plasticizer comprising triethyl citrate, acetyltriethyl citrate, tributyl citrate, acetyltributyl citrate, stearic acid, one or more low molecular weight polymers, a low molecular weight oligomer, a low molecular

weight copolymer, an oil, small organic molecule, low molecular weight polyol having one or more aliphatic hydroxyls, ester-type plasticizer, glycol ether, poly(propylene glycol), low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol, glycerin, ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, a poly(ethylene glycol) compound, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutyl sebacate, acetyltributylcitrate, allyl glycolate, or combinations of any two or more thereof.

108. The fill composition of any one of claims 68 to 107, further comprising a suspending agent comprising silicon dioxide, colloidal silicon dioxide, acacia, agar, alginic acid, aluminum monostearate, bentonite, camphor, a carbomer, a carrageenan, a starch, corn starch, a gelatin, guar gum, a hydroxyethyl cellulose, a hydroxypropyl cellulose, a hypromellose, a magnesium aluminum silicate, a methylcellulose, a pectin, polyvinyl alcohol, a povidone, sodium alginate, sodium hyaluronate, tragacanth, xanthan gum, or combinations of any two or more thereof.

109. The fill composition of any one of claims 68 to 108, wherein the matrix material comprises one or more esters of fatty acids and glycerol, one or more triglyceride, a long chain fatty acid or combinations thereof.

110. The fill composition of claim 113 or 109, wherein the one or more esters of fatty acids and glycerol comprise esters of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid,

lauric acid, caproic acid, caprylic acid, capric acid, or combinations two or more thereof, a monoglyceride, a diglyceride, a monoacylglycerol, a diacylglycerol, stearoyl polyoxylglyceride, lauroyl polyoxylglyceride, stearoyl polyoxyl-32 glycerides, lauroyl polyoxyl-32 glycerides, glycerol monostearate, glyceryl monocaprylocaprate, glycerol dicaprylate, glycerol monooleate, or combinations of two or more thereof.

111. The fill composition of any one of claims 113 to 110, wherein the one or more triglycerides comprises a medium chain triglyceride, a caprylic triglyceride, a capric acid triglyceride, triglycerol esters of one or more of linolenic acid, oleic acid, palmitic acid, linoleic acid, stearic acid, caproic acid, caprylic acid, capric acid or lauric acid and one or more medium chain fatty acid having about 6 to about 12 carbon atoms, glyceryl tricaprylate/caprate, glycerol caprylate caprate, caprylic/capric triglyceride, or combinations of any two or more thereof.

112. The fill composition of any one of claims 68 to 111, wherein the wax comprises paraffin wax, beeswax, jojoba, lanolin, spermaceti, or combinations of any two or more thereof.

113. The fill composition of any one of claims 68 to 112, comprising at least one of:

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1 wt% to about 5 wt% of one or more esters of fatty acids and glycerol;

about 0.1 wt% to about 50 wt%, or about 1 wt% to about 30 wt% of a surfactant;

about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; or

about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer.

114. The fill composition of claim 113, wherein the one or more esters of fatty acids and glycerol comprises stearoyl polyoxyl-32 glycerides, the surfactant comprises glyceryl dibehenate, and the plasticizer comprises stearic acid.

115. The fill composition of any one of claims 68 to 114, comprising at least one of:

about 1 wt% to about 50 wt%, about 5 wt% to about 40 wt%, or about 10 wt% to about 30 wt% of the wax;

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of a hydroxypropyl methylcellulose;

about 0.1 wt% to about 20 wt%, about 0.5 wt% to about 10 wt%, or about 1.0 wt% to about 5 wt% of one or more esters of fatty acids and glycerol;

about 1 w% to about 80 wt%, about 5 wt% to about 70 wt%, or about 10 wt% to about 60 wt% of a medium chain triglyceride; or

about 0 wt% to about 20 wt%, or about 0 wt% to about 10 wt% of a plasticizer.

116. The fill composition of claim 115, wherein the wax comprises paraffin wax, the hydroxypropyl methylcellulose provides a viscosity of about 80 cp to about 120 cp when a 2 % (by weight) aqueous solution of the hydroxypropyl methylcellulose using a Thermo Fischer Scientific HAAKE RheoStress 6000 parallel plate with shear stress at 10 Pa and an oscillation frequency of 1 Hz, at 20 °C, the one or more esters of fatty acids and glycerol comprises lauroyl polyoxylglycerides, and the plasticizer comprises stearic acid.

117. The fill composition according to any one of claims 68 to 116, wherein the fill composition comprises a solid, a semi-solid, a liquid, or a combination thereof.

118. The fill composition of claim 117, wherein the solid comprises one or more of particles, granules, a powder, beads, microspheres, extrudates, multi-particulates, mini-tablets, or combinations thereof.

119. The fill composition of claim 117 or 118, wherein the semi-solid comprises a gel, an aqueous gel, an organic solvent-based gel, particles, granules, a powder, beads, microspheres, extrudates and/or multi-particulates dispersed in a semi-solid medium, or combinations thereof.

120. The fill composition of any one of claims 117 to 119, wherein the liquid comprises a slurry, a viscous liquid, or combinations thereof.

121. The fill composition of any one of claims 68 to 120, wherein the fill composition does not provide an immediate release of an active agent.

122. A capsule dosage form, comprising:

a capsule shell; and

a fill composition within the softgel capsule, the fill composition comprising:

a matrix material; and

a solvent,

wherein the fill composition is flowable at a temperature of at least about 40 °C and solid or semi-solid at ambient conditions.

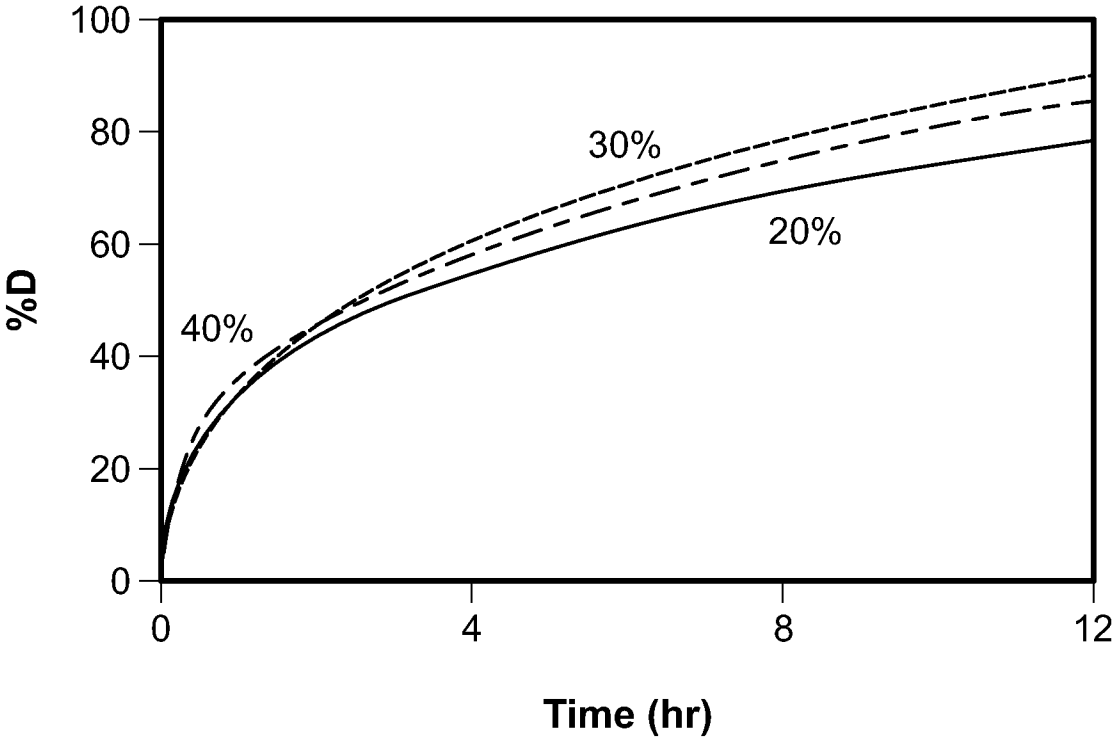
100
80
60
40
20
0
%D
30%
20%
40%
0
4
8
12
Time (hr)

FIG. 1

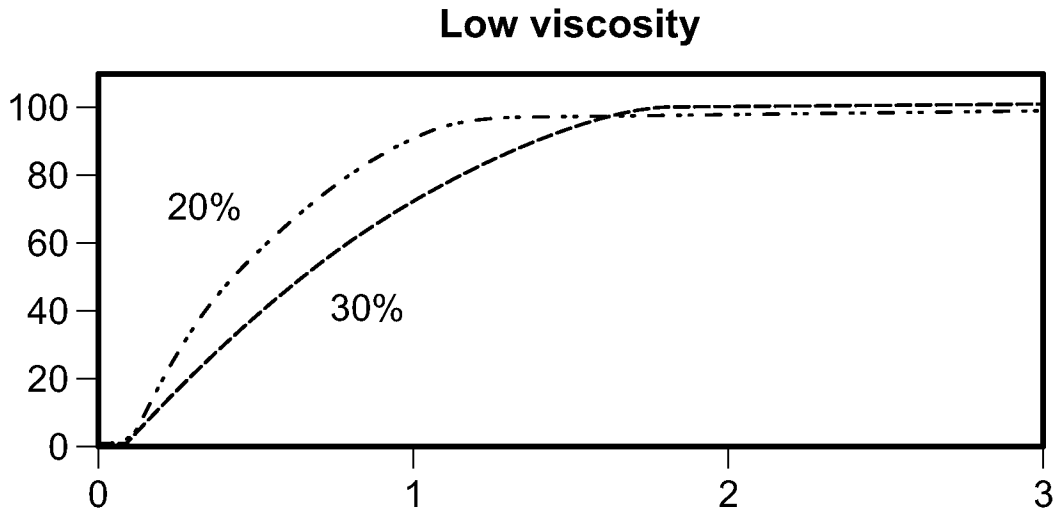
Low viscosity
100
80
60
40
20
0
20%
30%
0
1
2
3

FIG. 2A

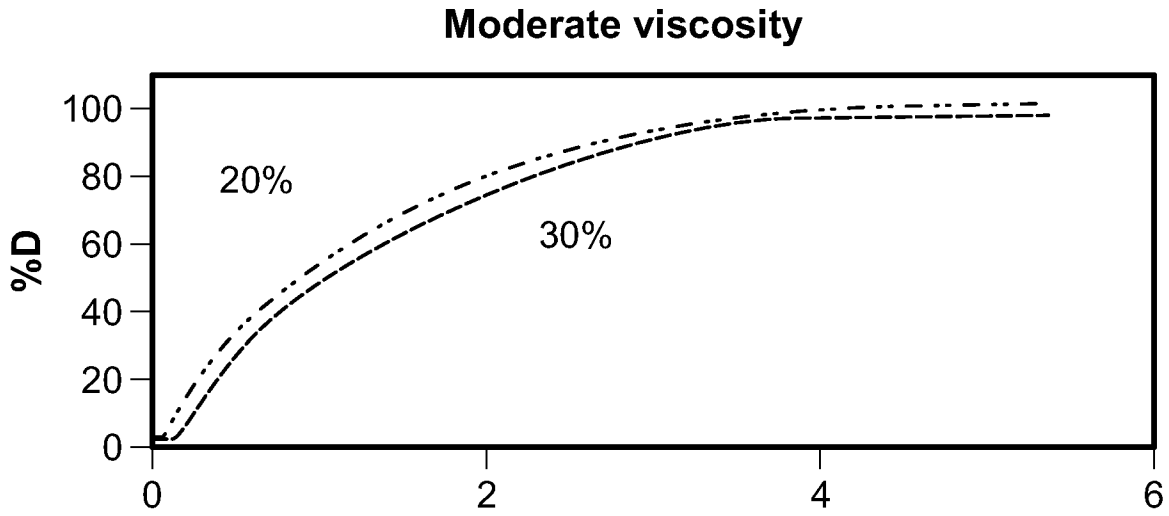
Moderate viscosity
100
80
60
40
20
0
%D
20%
30%
0
2
4
6

FIG. 2B

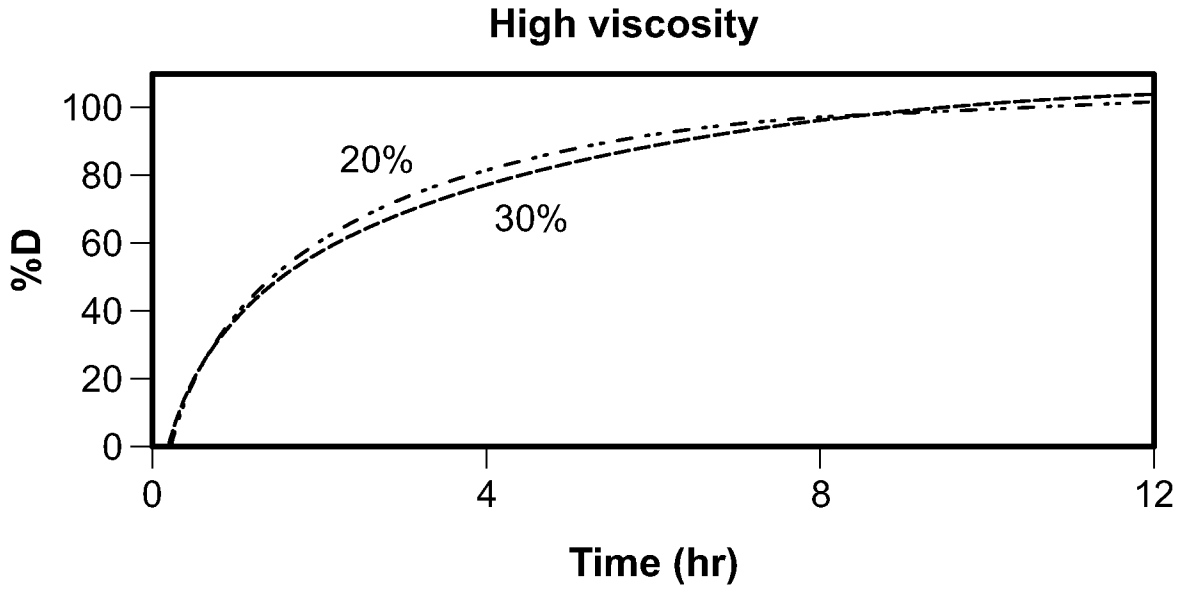
High viscosity
100
80
60
40
20
0
%D
20%
30%
0
4
8
12
Time (hr)

FIG. 2C

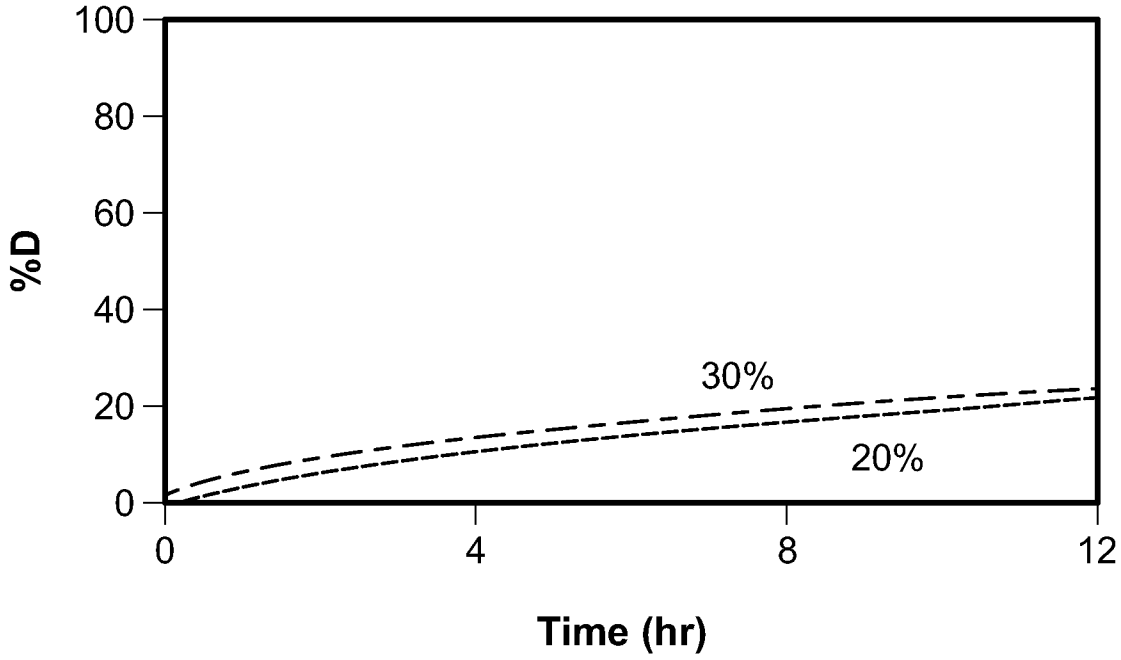
100
80
60
40
20
0
%D
30%
20%
0
4
8
12
Time (hr)

FIG. 3

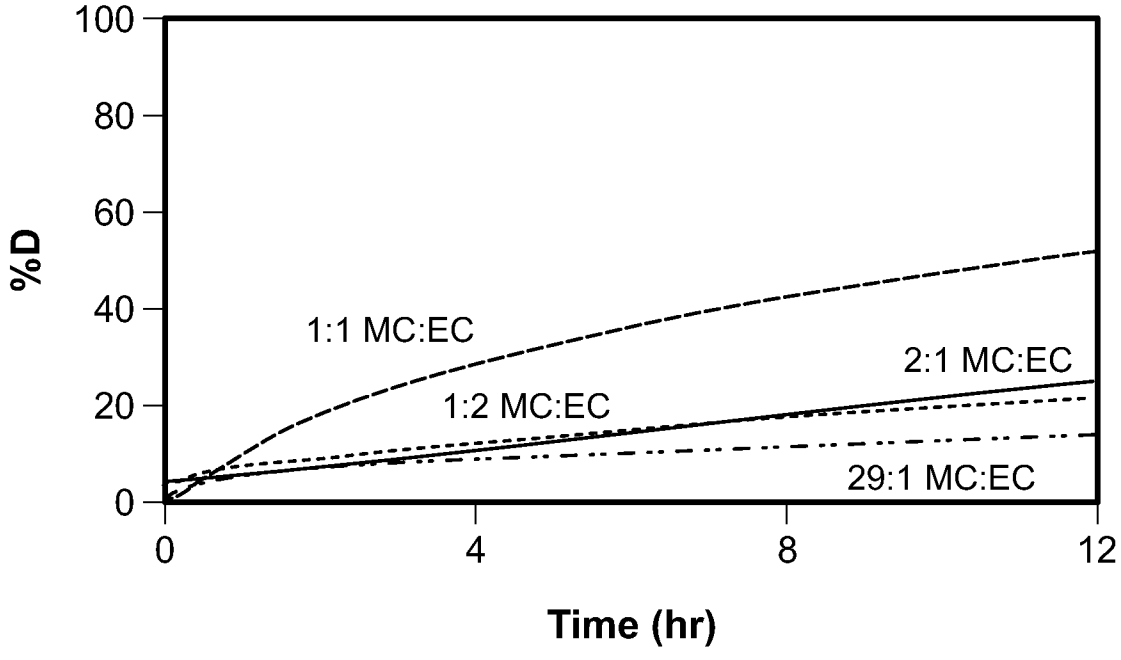
100
80
60
40
20
0
%D
1:1 MC:EC
2:1 MC:EC
1:2 MC:EC
29:1 MC:EC
0
4
8
12
Time (hr)

FIG. 4

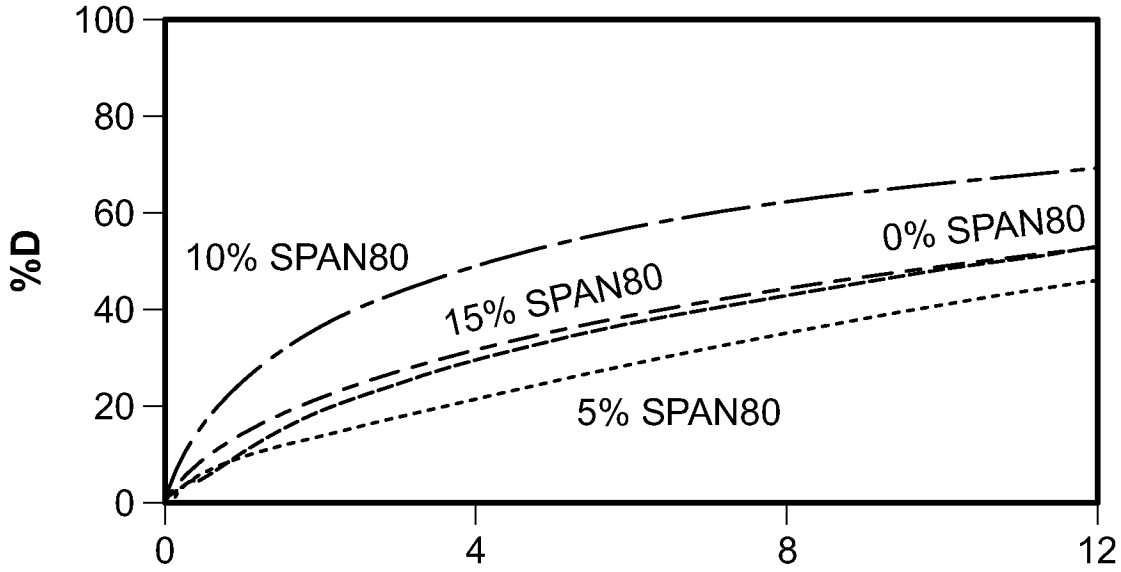
100
80
60
40
20
0
%D
10% SPAN80
15% SPAN80
0% SPAN80
5% SPAN80
0
4
8
12

FIG. 5A

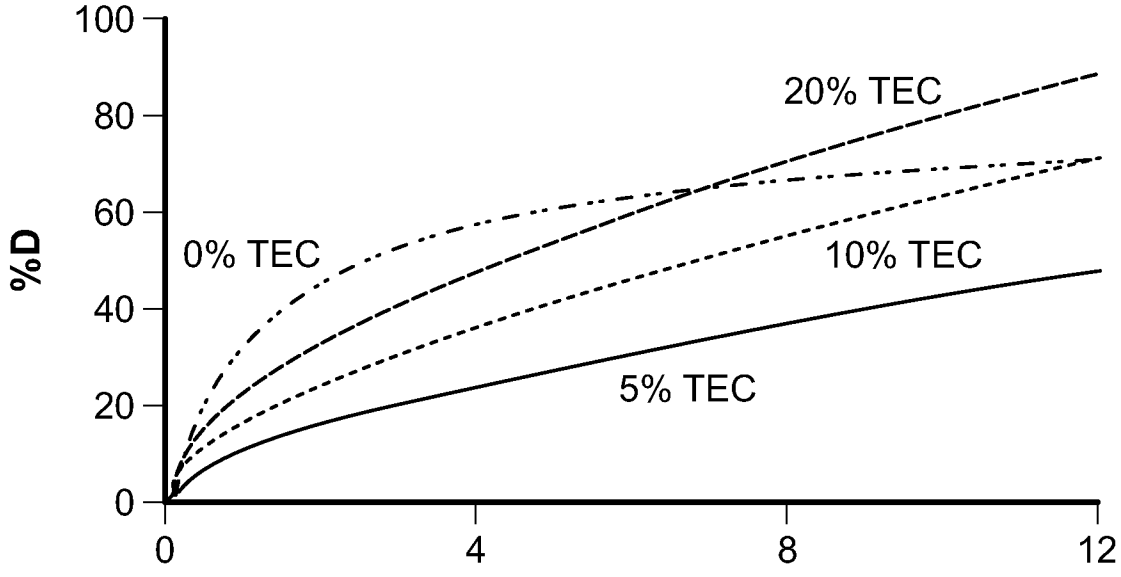
100
80
60
40
20
0
%D
0% TEC
20% TEC
10% TEC
5% TEC
0
4
8
12
Time (hr)

FIG. 5B

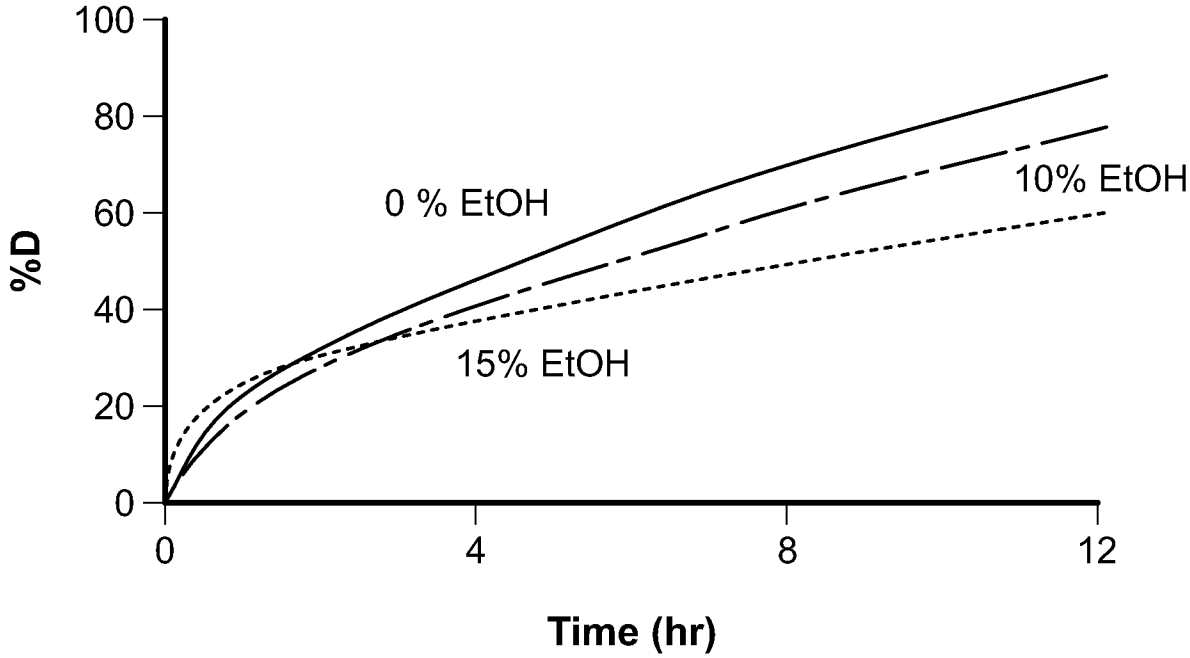
100
80
60
40
20
0
%D
0 % EtOH
10% EtOH
15% EtOH
0
4
8
12
Time (hr)

FIG. 6

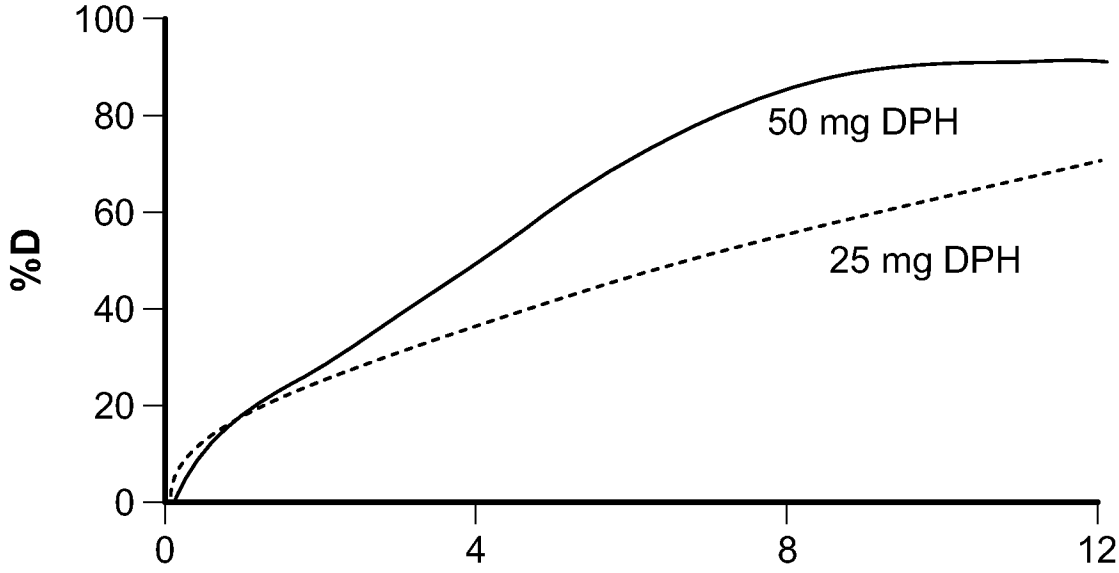
100
80
60
40
20
0
%D
50 mg DPH
25 mg DPH
0
4
8
12

FIG. 7A

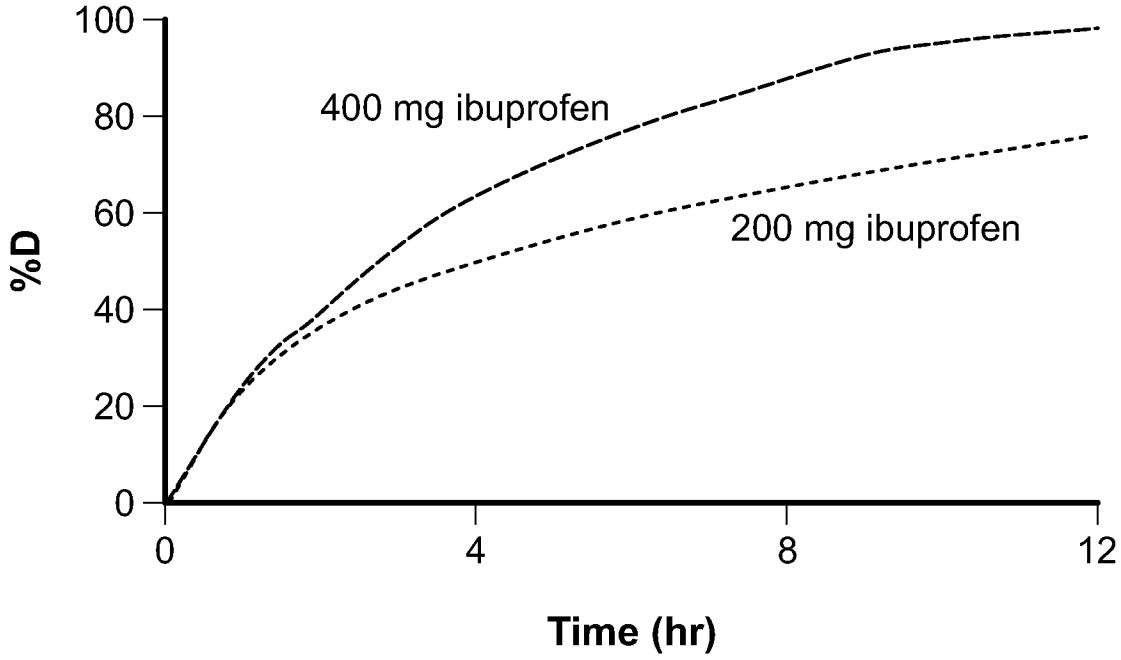
100
80
60
40
20
0
%D
400 mg ibuprofen
200 mg ibuprofen
0
4
8
12
Time (hr)

FIG. 7B

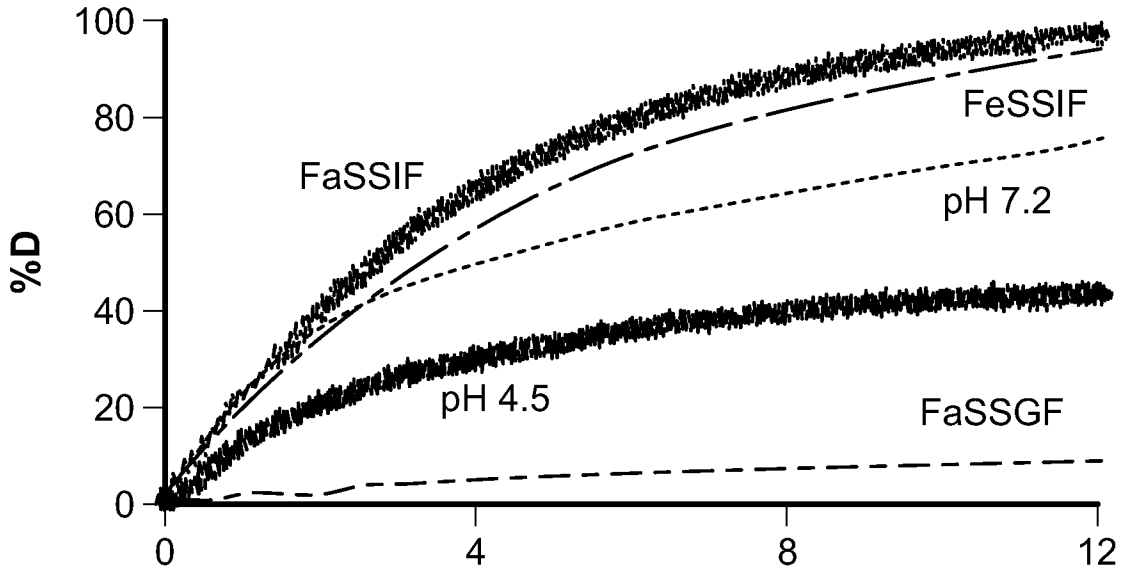
100
80
60
40
20
0
%D
FaSSIF
FeSSIF
pH 7.2
pH 4.5
FaSSGF
0
4
8
12
Time (hr)

FIG. 8

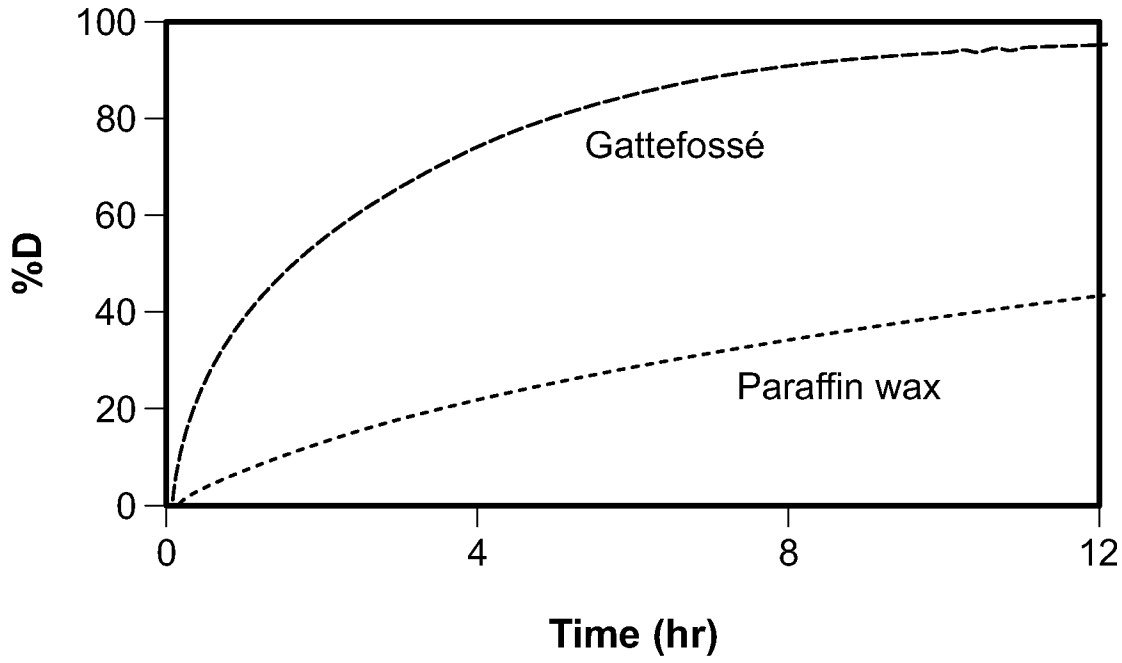

FIG. 9

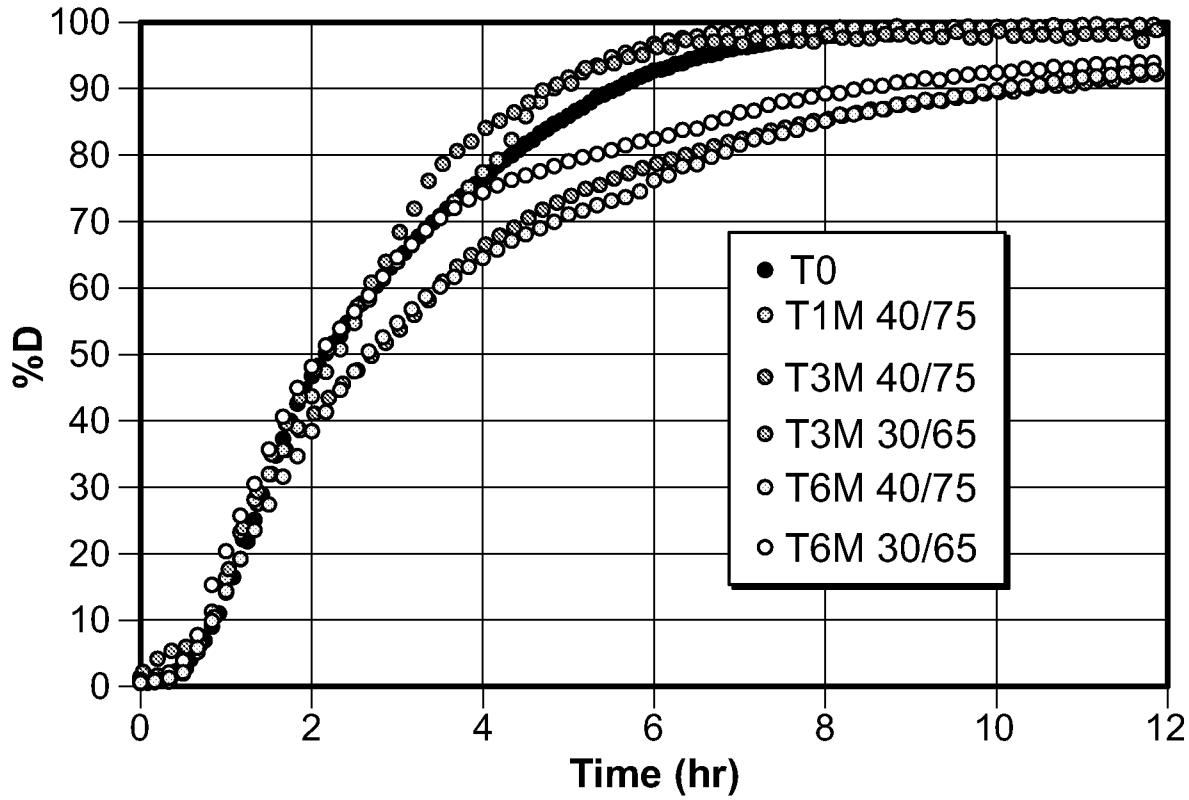
100
90
80
70
60
50
40
30
20
10
0
%D
0
2
4
6
8
10
12
Time (hr)
T0
T1M 40/75
T3M 40/75
T3M 30/65
T6M 40/75
T6M 30/65

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032389

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 9/48*** (2024.01); ***A61K 31/138*** (2024.01); ***A61K 31/167*** (2024.01); ***A61K 31/192*** (2024.01)

CPC: ***A61K 9/4808; A61K 31/138; A61K 31/167; A61K 31/192; A61K 9/4841; A61K 9/4825; A61K 9/4891***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,919,481 A (CODY et al.) 06 July 1999 (06.07.1999) entire document	1-5, 68-72, 122
A	US 2019/0091159 A1 (CAPTEK SOFTGEL INTERNATIONAL) 28 March 2019 (28.03.2019) entire document	1-5, 68-72, 122
A	US 4,002,718 A (GARDELLA et al.) 11 January 1977 (11.01.1977) entire document	1-5, 68-72, 122
A	US 2022/0362160 A1 (R.P. SCHERER TECHNOLOGIES LLC) 17 November 2022 (17.11.2022) entire document	1-5, 68-72, 122

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2024 (25.07.2024)	**02 August 2024 (02.08.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/032389

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **6-67, 73-121**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).