

- (51) International Patent Classification:

A61K 47/14 (2017.01)

A61P 11/12 (2006.01)

A61K 47/24 (2006.01)

A61K 31/133 (2006.01)

A61K 9/08 (2006.01)

A61K 31/138 (2006.01)
- (21) International Application Number:

PCT/US2024/032391
- (22) International Filing Date:

04 June 2024 (04.06.2024)
- (25) Filing Language:

English
- (26) Publication Language:

English
- (30) Priority Data:

63/471,352

06 June 2023 (06.06.2023)

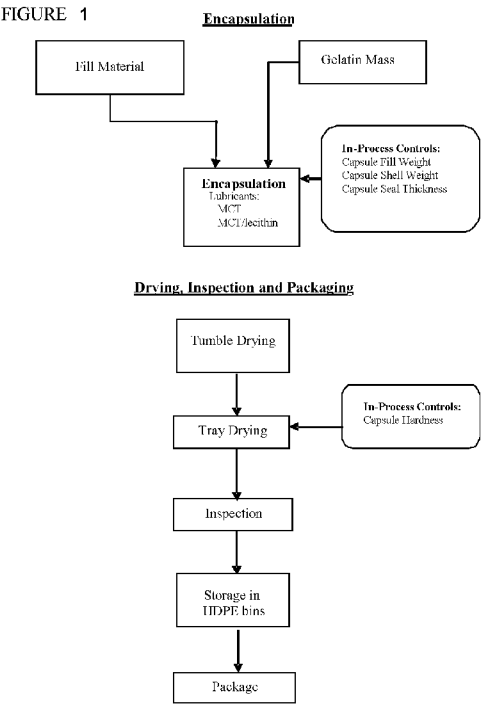
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available):

ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: AMBROXOL LIQUID FORMULATION



(57) Abstract: Disclosed in certain embodiments is a liquid formulation for oral administration comprising an amphiphilic material and ambroxol or a pharmaceutically acceptable salt thereof.

Published:

— *with international search report (Art. 21(3))*

AMBROXOL LIQUID FORMULATION

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] The present application claims priority to U.S. Provisional Patent Application No. 63/471,352, filed on June 8, 2023, the entire contents of which are incorporated in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to ambroxol liquid formulations, and in certain embodiments to a softgel capsule, wherein the softgel capsule includes a shell composition and a fill composition. Methods of preparation of such formulations and methods of use thereof are also disclosed.

BACKGROUND OF THE INVENTION

[0003] Ambroxol is commonly used as a phlegm loosening agent in the case of productive cough accompanying lung and bronchial illnesses. Commercially available pharmaceutical formulations containing ambroxol are oral solution, syrup, tablet and lozenges.

[0004] Liquid dosage forms are convenient formulations for the delivery of active agents. Liquids allows for precise measurement of personalized dosing. They also provide alternatives to patients that have difficulty in swallowing standard oral dosage forms such as tablets.

[0005] Capsule dosage forms are commonly used for oral administration of a variety of pharmaceuticals. The capsules can be, for example, soft gelatin shell or hard shell (animal or vegetable variety). Softgel capsules provide numerous advantages including fast dissolution, taste-masking, ease of swallowing, fewer excipients as compared to tablets, delivery of a liquid matrix that solubilizes and improves oral bioavailability of a marginally hydrophilic compound, delivery of low and ultra-low doses of a compound, delivery of low melting temperature compounds and minimization of dust generation during manufacturing and thus, improved safety for production personnel.

[0006] Soft capsules, such as soft gelatin or carrageenan capsules (or softgel capsules), provide a dosage form which is more readily accepted by patients, since the capsules are easy to swallow and need not be flavored in order to mask any

unpleasant taste of the active agent. Softgel encapsulation of drugs further provides the potential to improve the bioavailability of the pharmaceutical agents. For example, active ingredients may be rapidly released in liquid or solution form as soon as the gelatin shell ruptures.

[0007] There continues to exist a need in the art for new formulations of ambroxol that may result in one or more of improved compliance, therapeutic outcome, ease in swallowing, or maintenance of stability.

SUMMARY OF THE INVENTION

[0008] The present invention advances the state of the art by developing in certain embodiments, a liquid formulation of ambroxol.

[0009] In certain embodiment, the present invention is directed to a liquid formulation that contains ambroxol and one or more amphiphilic material, e.g., a lipid, a surfactant, an amphiphilic block polymer, or an amphiphilic protein or peptide or a combination thereof.

[0010] In alternative embodiments, the liquid formulation may be administered as a liquid or the liquid may be incorporated into an oral solid dosage form such as a softgel or hard capsule, or into primary packaging, e.g., a bottle or a syringe.

[0011] In certain embodiments, the invention is directed to softgel capsules, that include a fill material and a shell composition, wherein the fill material includes ambroxol.

[0012] In an embodiment of the present disclosure, an oral solid dosage form such as a softgel capsule is suitable to be swallowed intact for release in the gastro-intestinal system.

[0013] In other embodiments of the present disclosure, an oral solid dosage form such as a softgel capsule is suitable for chewing in the oral cavity.

[0014] In certain embodiments, the present invention is directed to a process for producing a pharmaceutical formulation as disclosed herein, e.g., a liquid or softgel. In certain embodiments, the process includes encapsulating the ambroxol liquid as disclosed herein in a shell composition to form the softgel capsule and drying the softgel capsule.

[0015] In certain embodiments, the present invention is directed to treating a pulmonary disease comprising administering a pharmaceutical formulation as

disclosed herein to a patient in need thereof. The treatment can include, e.g., loosening phlegm and treating cough.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The Figure shows the manufacturing process from encapsulation to bulk packaging of a softgel capsule.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention advances the state of the art by developing in certain embodiments a liquid formulation of ambroxol. In certain embodiments, the liquid ambroxol comprises an amphiphilic material, e.g., a lipid material. In other embodiments, the liquid ambroxol formulation may be incorporated into a softgel capsule. The softgel capsule may comprise (a) a fill material comprising a lipid material including a triglyceride, a hydrophobic surfactant, a hydrophilic surfactant, a hydrophilic solvent, or a combination thereof, and ambroxol or a pharmaceutically acceptable salt thereof and (b) a shell composition.

[0018] As used herein, “pharmaceutically active ingredient” refers to a drug or compound that may be used in the diagnosis, cure, mitigation, treatment, or prevention of a condition. The term “condition” or “conditions” refers to those medical conditions that can be treated or prevented by administration to a subject of an effective amount of an active agent.

[0019] As used herein, the term “active ingredient” 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 and crystalline forms thereof, where the salts, solvates and crystalline forms are pharmaceutically active.

[0020] As used herein, the terms “therapeutically effective” and an “effective amount” refer to the amount of active agent or the rate at which it is administered which is needed to produce a desired therapeutic result.

[0021] As used herein, “shell” or “shell composition” refers to the shell of a softgel capsule which encapsulates a fill material.

[0022] All references to wt% throughout the specifications and the claims refer to the weight of the component in reference to the weight of the entire composition and may also be designated as w/w.

[0023] As used herein, “fill material” or “fill” refers to the composition that is encapsulated by the capsule shell and contains at least one pharmaceutically active ingredient.

[0024] As used herein, “about” refers to any values that are within a variation of $\pm 10\%$, such that “about 10” would include from 9 to 11. As used herein, “a,” “an,” or “the” refers to one or more, unless otherwise specified. Thus, for example, reference to “an excipient” includes a single excipient as well as a mixture of two or more different excipients, and the like.

[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.

[0026] The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to illuminate certain materials and methods and does not pose a limitation on scope. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosed materials and methods.

[0027] In certain embodiments, an oral solid dosage form such as a softgel is suitable for swallowing whole and can be formulated, e.g., for gastric delivery, intestinal delivery or a combination thereof.

[0028] In certain embodiments, an oral solid dosage form such as a softgel is suitable for chewing and can be swallowed for gastrointestinal absorption, absorbed in the oral cavity, or a combination thereof. As used herein, “oral cavity” may refer to being absorbed in an area of the mouth.

[0029] In certain softgel embodiments, the shell composition comprises gelatin, carrageenan or as combination thereof.

[0030] In certain softgel embodiments, the shell composition comprises about 10 wt% to about 85 wt% gelatin, about 45 wt% to about 75 wt% gelatin or about 15 wt% to about 45 wt% gelatin.

[0031] In certain softgel embodiments, the gelatin is selected from the group consisting of Type A gelatin, Type B gelatin, and mixtures thereof.

[0032] In certain softgel embodiments, the gelatin is selected from the group consisting of fish gelatin, hide gelatin, bone gelatin, porcine gelatin, bovine gelatin, and mixtures thereof.

[0033] In certain softgel embodiments, the shell composition includes carrageenan and does not include an animal based component.

[0034] In certain softgel embodiments, the shell composition includes a plasticizer. The plasticizer can include about 10 wt% to about 75 wt% plasticizer, about 20 wt% to about 50 wt% plasticizer, or about 30 wt% to about 60 wt% plasticizer.

[0035] In certain softgel embodiments, the plasticizer is selected from the group consisting of glycerin, propylene glycol, aqueous sorbitol and sorbitan solution and combinations thereof.

[0036] In certain embodiments, the shell further includes a starch. In some embodiments, the starch may include potato starch, corn starch, or tapioca starch. In some embodiments, the shell composition may include starch in an amount of about 5 wt% to about 20 wt%, about 8 wt% to about 15 wt%, or about 6 wt% to about 10 wt% based on total weight of the shell composition.

[0037] The amphiphilic materials that can be utilized in the present invention include, e.g., a lipid, a surfactant, an amphiphilic block polymer, an amphiphilic protein or peptide, and combinations thereof.

[0038] A lipid may include, but is not limited to, saturated and unsaturated lipids; neutral, cationic, or anionic lipids; or natural or synthetic lipids. In other embodiments, lipids may be one or a mixture of two or more from any of the following classes including, but not limited to: phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphosphatidylinositol (PI), phosphatidylserine (PS), phosphatidic acid (PA) sphingomyelin (SM). In alternative embodiments, the lipid material may include triglycerides. The triglycerides may include, e.g., medium chain triglycerides, caprylic triglycerides, capric triglycerides, myristic triglycerides, stearic triglycerides, and combinations thereof. In further embodiments, the lipids may be, e.g., neutral lipids—dioleoyl phosphatidylcholine (DOPC), dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), egg phosphatidylcholine (egg PC), soy phosphatidylcholine (soy PC), partially or fully

hydrogenated phosphatidylcholines (PHSPC or HSPC), palmitoyl-oleoyl phosphatidylcholine (POPC), stearyl-oleoylphosphatidylcholine (SOPC); and anionic lipids—dioleoyl phosphatidylglycerol (DOPG), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylglycerol (DPPG), distearoylphosphatidylglycerol (DSPG). The lipid may also be a PEG (polyethylene glycol)-lipid such as mPEG-DPPE, mPEG-DMPE, mPEG-DSPE, -mPEG-ceramide-DSPE, or mPEG-DS. In alternative embodiments, anti-oxidant lipid agents can be utilized such as vitamin E, α -tocopherol, or ascorbic acid.

[0039] In certain embodiments, the liquid formulation further includes at least one surfactant in addition to or in place of the lipid. The surfactant may be, e.g., a non-ionic surfactant such as caprylocaproyl macrogol-8-glycerides, caprylic/capric triglyceride, polyoxyl hydrogenated castor oil, pegylated castor oil, or a combination thereof. In some embodiments, the surfactant may include a hydrophobic surfactant or hydrophilic surfactant.

[0040] In certain embodiments of the dosage forms of the present invention, the dosage form may also include a surfactant. Surfactants useful in accordance with the present invention, include for example, ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, including but not limited to castor oil derivatives, cholesterol, polyglycolized glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polysorbates, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene compounds, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glycerol esters, polyglycerol fatty acid esters, SPAN's (e.g., sorbitan esters), TWEEN's (i.e., sucrose esters), glucose (dextrose) esters, alkali metal sulfates, quaternary ammonium compounds, amidoamines, and aminimides, simethicone, lecithins, alcohols, phospholipids, and mixtures thereof.

[0041] Mixed surfactant/wetting agents useful in accordance with the present invention include, for example, sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid, etc.

[0042] Block copolymer surfactants (e.g., Pluronic® surfactants or Pluronic® surfactant F-127), or sorbitan esters structurants (e.g., Span® 80, Sigma Aldrich Chemical Co.) can also be utilized.

[0043] In certain embodiments, the liquid formulation further includes a viscosifier such as acacia, agar, alginic acid, aluminum monostearate, bentonite, purified bentonite, magma bentonite, carbomer, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carboxymethylcellulose sodium 12, carrageenan, microcrystalline and carboxymethylcellulose sodium cellulose, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminum silicate, methylcellulose, pectin, polyethylene oxide, polyvinyl alcohol, povidone, alginate, silicon dioxide, colloidal silicon dioxide, sodium alginate, tragacanth, xanthan gum).

[0044] In other embodiments, the liquid formulation may include a sweetening agents or flavoring agents such as aspartame, dextrates, dextrose, excipient dextrose, fructose, mannitol, saccharin, calcium saccharin, sodium saccharin, sorbitol, solution sorbitol, sucrose, compressible sugar, confectioner's sugar, syrup).

[0045] In certain embodiments, the liquid formulation further includes an emulsifier such as lecithin, monoglycerides, sucrose/fatty acid esters, polyglycerol/fatty acid esters, sorbitan/fatty acid esters, potassium and sodium salts of rosin acids and higher fatty acids, as well as sulfates and sulfonates of these acids, amine salts of hydroxylamines of long-chain fatty acid esters, quaternary ammonium salts such as stearyl-dimethylbenzylammonium chloride and tridecylbenzenehydroxyethylimidazole chloride, phosphoric esters of higher alcohols such as capryl and octyl alcohol, and monoesters of oleic acid and pentaerythritol such as sorbitan monooleates, and mixtures thereof.

[0046] In certain embodiments, the liquid formulation includes medium chain triglycerides, caprylic/capric/myristic/stearic triglycerides, caprylic/capric triglycerides and caprylocaproyl macrogol-8-glycerides.

[0047] In other embodiments, the liquid formulation includes medium chain triglycerides, PEG-40 castor oil, caprylic/capric/myristic/stearic triglycerides, soybean lecithin, flavors and sweeteners.

[0048] In certain embodiments, the liquid formulation includes about 5% to about 15% ambroxol hydrochloride, about 20% to about 50% medium chain triglycerides, about 15% to about 45% caprylic/capric/myristic/stearic triglycerides, about 5% to

about 25% caprylic/capric triglycerides and about 1% to about 10% caprylocaproyl macrogol-8-glycerides.

[0049] In certain embodiments, the liquid formulation includes about 5% to about 15% ambroxol hydrochloride, about 30% to about 60% medium chain triglycerides, about 0.5% to about 5% PEG-40 castor oil, about 10% to about 40% caprylic/capric/myristic/stearic triglycerides, about 0.5% to about 5% soybean lecithin, flavors and sweeteners.

[0050] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 10% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0051] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 60% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0052] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 80% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0053] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0054] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 15% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0055] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 65% at 10 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0056] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0057] In certain softgel embodiments, the invention provides an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0058] In certain softgel embodiments, about 92% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

[0059] In certain softgel embodiments, at least about 95% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

[0060] In certain softgel embodiments, at least about 97% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

[0061] In certain softgel embodiments, at least about 92% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

[0062] In certain softgel embodiments, at least about 95% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

[0063] In certain softgel embodiments, at least about 97% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

[0064] In certain softgel embodiments, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 5% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0065] In certain softgel embodiments, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 50% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0066] In certain softgel embodiments, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 75% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0067] In certain softgel embodiments, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

[0068] In certain softgel embodiments, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 50% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0069] In certain softgel embodiments, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 60% at 10

minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0070] In certain softgel embodiments, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0071] In certain softgel embodiments, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

[0072] In certain embodiments, the total ambroxol impurity does not exceed about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1% or about 0.01%, wherein the total impurity is measured by HPLC.

[0073] In certain embodiments, the invention is directed to a process for producing the softgel capsule comprising encapsulating the fill composition in the shell composition to form the softgel capsule and drying the softgel capsule.

[0074] In certain embodiments, a method is provided for producing a softgel capsule according to the present disclosure. As described herein, the fill of the softgel capsule may be prepared such that the capsule can be swallowed or can be chewed. The method includes preparing a gelatin mass using an automated process. The automated process may occur in a melting reactor. The melting reactor may be controlled by a programmable logic controller, using predetermined parameters. The parameters may include a predetermined temperature, mixing speed, vacuum and duration.

[0075] In some embodiments, the method may include adding a plasticizer and water to the melting reactor, which may be heated while mixing. The method may also include adding gelatin to the melting reactor, which may be mixed under heat and vacuum to melt, blend and de-aerate the molten gelatin.

[0076] In some embodiments, the melted mass may be discharged into a heated storage vessel. The temperature of the storage vessel may be between about 50°C to about 65°C.

[0077] In some embodiments, an opacifier may be added into the gelatin mass. The mixture is mixed until a homogeneous gelatin mass forms. The gelatin mass may be stored in the heated vessel until the end of the encapsulation step of production.

[0078] In some embodiments, the gelatin mass may be filtered before being used in an encapsulation machine.

[0079] In certain embodiments, an encapsulation machine is used to form the softgel capsule using the gel mass and fill of either preparation described above. In some embodiments, the encapsulation machine is a rotary die machine. After the capsules are discharged from the encapsulation machine, the capsules are then dried.

[0080] In certain embodiments, the invention is directed to a method of treating cough comprising administering a formulation, e.g., a softgel capsule as disclosed herein. The treatment may comprise, e.g., phlegm loosening. In other embodiments, the cough is accompanied by lung or bronchial illness.

[0081] Other embodiments are directed to a liquid pharmaceutical dosage form comprising an amphiphilic material and ambroxol or a pharmaceutically acceptable salt thereof. The liquid can be administered directly to the patient or incorporated into a dosage form such as a softgel, hard capsule, or lozenge.

[0082] In other embodiments, the liquid formulation may include additional fill components such as flavoring agents, sweetening agents, coloring agents and fillers, an antioxidant or other pharmaceutically acceptable excipients or additives such as synthetic dyes and mineral oxides.

[0083] In some embodiments, the antioxidant may be butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), alpha tocopherol, vitamin E TPGS, propyl gallate, cysteine, sodium metabisulfite, or a combination thereof.

[0084] In some embodiments, the liquid formulation may include the pharmaceutically active ingredient, i.e., ambroxol, in an amount of about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, or about 120 or any range of these values. In some embodiments, the liquid formulation may include the pharmaceutically active ingredient, ambroxol, in an amount from about 10 mg to about 40 mg, from about 30 mg to about 60 mg, or from about 40 mg to about 50 mg, or any sub ranges or values within.

[0085] In some embodiments, an antioxidant may be included in the liquid composition. The antioxidant may be included in an amount of about 0.001 parts by weight to about 2 parts by weight based on 100 parts by weight based on the fill composition.

[0086] In one embodiment, the shell composition includes dextrose. In an embodiment, the amount of dextrose in the shell composition is about 0.005 wt% to about 5 wt%, or about 0.01 wt% to about 4 wt%, or about 0.01 wt% to about 3 wt%, or about 0.01 wt% to about 2 wt%, or about 0.01 wt% to about 1 wt%, or from about 0.1 wt% to about 3 wt%, or from about 0.1 wt% to about 2 wt%, or from about 0.1 wt% to about 1 wt%, or from about 0.15 wt % to about 2 wt%, or from about 0.15 to about 1 wt%. The dextrose may be added to the capsule shell to mitigate potential reduction in gel strength. The concentration of dextrose in the shell composition may be in an effective amount to improve the enteric property but not so high that it would interfere with the rupture of the softgel capsule.

[0087] In an embodiment, the shell composition may also include a plasticizer. In some embodiments, the plasticizer in the shell composition may include glycerin, aqueous sorbitol and sorbitan solution and combinations thereof. Other suitable plasticizers may include, but not be limited to, sugar alcohol plasticizer such as isomalt, maltitol, xylitol, erythritol, adonitol, dulcitol, pentaerythritol, or mannitol; or polyol plasticizer such as diglycerin, dipropylene glycol, a polyethylene glycol up to 10,000 MW, neopentyl glycol, propylene glycol, 1,3-propanediol, 2-methyl-1,3-propanediol, trimethylolpropane, a polyether polyol, ethanol amines; and mixtures thereof. Other exemplary plasticizers may also include, without limitations, 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, citrate ester-type plasticizers, and triacetin. Such plasticizers may include 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, 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, glyceryl monostearate, polysorbate 80, acetyl triethyl citrate, tributyl citrate and allyl glycolate, and mixtures thereof.

[0088] In an embodiment, the amount of plasticizer in the shell composition is about 2 wt% to about 40 wt%, or from about 5 wt% to about 35 wt%, or from about 10 wt% to about 30 wt%, or from about 15 wt% to about 25 wt%.

[0089] In an embodiment, the shell composition may also include a gelling agent. In some embodiments, the gelling agent may be a gellan gum, agar, alginate, guar gum

or Locus bean gum. For example, the gellan gum may be a low acyl gellan gum, for example Kelcogel CG-LA.

[0090] The shell composition may also include water. In some embodiments, water may be included in the shell composition prior to processing the softgel in an amount of 5 wt% to about 35 wt%, or from about 10 wt% to about 25 wt%, or about 15 wt% to about 20 wt% based on the total shell composition.

[0091] In an embodiment, the shell composition may optionally comprise additional agents such as coloring agents, flavorings agents, sweetening agents, fillers, antioxidants, diluents, pH modifiers or other pharmaceutically acceptable excipients or additives such as synthetic dyes and mineral oxides.

[0092] Exemplary suitable coloring agents may include, but not be limited to, colors such as e.g., white, black, yellow, blue, green, pink, red, orange, violet, indigo, and brown. In specific embodiments, the color of the dosage form can indicate the contents (e.g., one or more active ingredients) contained therein.

[0093] Exemplary suitable flavoring agents may include, but not be limited to, “flavor extract” obtained by extracting a part of a raw material, e.g., animal or plant material, often by using a solvent such as ethanol or water; natural essences obtained by extracting essential oils from the blossoms, fruit, roots, etc., or from the whole plants.

[0094] Additional exemplary flavoring agents that may be in the dosage form may include, but not be limited to, breath freshening compounds like menthol, spearmint, and cinnamon, coffee beans, other flavors or fragrances such as fruit flavors (e.g., cherry, orange, grape, etc.), especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

[0095] Exemplary sweetening agents may include, but not be limited to, one or more artificial sweeteners, one or more natural sweeteners, or a combination thereof. Artificial sweeteners include, e.g., acesulfame and its various salts such as the potassium salt (available as Sunett®), alitame, aspartame (available as NutraSweet® and Equal®), salt of aspartame-acesulfame (available as Twinsweet®), neohesperidin dihydrochalcone, naringin dihydrochalcone, dihydrochalcone compounds, neotame, sodium cyclamate, saccharin and its various salts such as the sodium salt (available as Sweet'N Low®), stevia, chloro derivatives of sucrose such as sucralose (available as

Kaltame® and Splenda®), and mogrosides. Natural sweeteners include, e.g., glucose, dextrose, invert sugar, fructose, sucrose, glycyrrhizin; monoammonium glycyrrhizinate (sold under the trade name MagnaSweet®); Stevia rebaudiana (Stevioside), natural intensive sweeteners, such as Lo Han Kuo, polyols such as sorbitol, mannitol, xylitol, erythritol, and the like.

[0096] In some embodiments, a methacrylic copolymer may be included in the shell composition. In an embodiment, the shell composition may include a methacrylic copolymer in an amount of about 0.1 wt% to about 5 wt%, or from about 1 wt% to about 4 wt%, or from about 2 wt% to about 3 wt% based on the total weight of the shell composition. In some embodiments, the methacrylic copolymer may be Kollicoat MAE 100P. Without being limited to a theory, the inventors believe that the methacrylic copolymer enhances the enteric property of the shell composition.

[0097] In some embodiments, the softgel capsule may provide a delayed release or modified release of the active agent.

[0098] In some embodiments, the softgel capsule may have a stability of at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least 96%, at least 97%, at least about 98% or at least 99% when tested at 25 °C/60%RH at 1 month, 2 months, 3 months, 6 months, 12 months, or 24 months. In some embodiments, the softgel capsule may have a stability from about 90% to about 110%, from about 92% to about 108%, from about 94% to about 106%, from about 96% to about 104%, from about 98% to about 102% or from about 99% to about 101% when tested at 25 °C/60%RH at 1 month, 2 months, 3 months, 6 months, 12 months or 24 months.

[0099] In some embodiments, the softgel capsule may have a stability of at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least 96%, at least 97%, at least about 98% or at least 99% when tested at 30 °C /65%RH at 1 month, 2 months, 3 months, 6 months or 12 months.

[00100] In some embodiments, the softgel capsule may have a stability of at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least 96%, at least 97%, at least about 98% or at least 99% when tested at 40°C/75%RH at 1 month, 2 months, 3 months, 6 months, 12 months, or 24 months.

[00101] In certain embodiments, any of the compositions described herein may exhibit any of the above described chemical stability upon storage for an extended duration (e.g., one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fifteen months, eighteen months, twenty one months, or twenty four months, or any sub-range or single value therein) at a temperature ranging from about 5 °C to about 50 °C, from about 10 °C to about 40 °C, from about 20 °C to about 30 °C, or any sub-range or single value therein, at a relative humidity ranging from about 20% to about 75%.

[00102] In some embodiments, the capsules as described herein may be stored in a packaging. The packaging may include a plastic bottle, such as high density polyethylene (HDPE) bottles, or a blister pack.

[00103] In certain embodiments, any of the compositions described herein may exhibit physical stability upon storage for an extended duration (e.g., one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, fifteen months, eighteen months, twenty one months, or twenty four months, or any sub-range or single value therein) at a temperature ranging from about 5 °C to about 50 °C, from about 10 °C to about 40 °C, from about 20 °C to about 30 °C, or any sub-range or single value therein, at a relative humidity ranging from about 20% to about 75%.

[00104] Encapsulation of the fill material can be accomplished in any conventional manner. As an example, a rotary die encapsulation may be used. In some embodiments, gel conversion may be used to encapsulate the fill composition. In some embodiments, the gel conversion includes the shell composition, an opacifier and a colorant. The opacifier may be titanium dioxide. The colorant may include FD&C Yellow #6. The gel conversion may also include water. In some embodiments, the colorant may be included in an amount of about 0.5 g to about 2.5 g per kilogram of the shell composition. In some embodiments, the opacifier may be included in an amount of about 2 g to about 10 g per kilogram of the shell composition. In other embodiments, water may be included in an amount of about 40 grams to about 60 grams per kilogram of the shell composition.

[00105] According to an embodiment, the softgel capsule is prepared by (a) preparing the fill composition, the fill composition including a pharmaceutically

active ingredient; and (b) encapsulating the fill composition in a shell composition. The encapsulation process may also include a sub-step of preparing the shell composition by, for example, admixing a gelatin, dextrose, and optionally a plasticizer. The shell composition may further undergo a gel conversion before encapsulation by adding colorants and water.

[00106] The softgel capsule of the present disclosure may be packaged in a blister pack, bottle or a volume pack.

ITEMS

1. A liquid formulation comprising an amphiphilic material and ambroxol or a pharmaceutically acceptable salt thereof.
2. The liquid formulation of item 1, wherein the amphiphilic material comprises a lipid, a surfactant, an amphiphilic block polymer, or an amphiphilic protein or peptide or a combination thereof.
3. The liquid formulation of item 2, wherein the lipid comprises a saturated lipid, an unsaturated lipid, a neutral lipid, a cationic lipid, an anionic lipid, a natural lipid, a synthetic lipid, triglycerides, a PEG (polyethylene glycol)-lipid, or an anti-oxidant lipid agent.
4. The liquid formulation of item 2, wherein the surfactant comprises an ionic surfactant, nonionic surfactant or wetting agents.
5. The liquid formulation of item 1, wherein the amphiphilic material comprises medium chain triglycerides, caprylic/capric/myristic/stearic triglycerides, caprylic/capric triglycerides and caprylocaproyl macrogol-8-glycerides.
6. The liquid formulation of item 1, wherein the amphiphilic material comprises medium chain triglycerides, PEG-40 castor oil, caprylic/capric/myristic/stearic triglycerides, soybean lecithin, flavors and sweeteners.
7. The liquid formulation of any of items 1-6, wherein the liquid formulation comprises about 20% to about 50% medium chain triglycerides, about 15% to about

45% caprylic/capric/myristic/stearic triglycerides, about 5% to about 25% caprylic/capric triglycerides and about 1% to about 10% caprylocaproyl macrogol-8-glycerides.

8. The liquid formulation of any of items 1-6, wherein the liquid formulation comprises about 5% to about 15% ambroxol hydrochloride, about 30% to about 60% medium chain triglycerides, about 0.5% to about 5% PEG-40 castor oil, about 10% to about 40% caprylic/capric/myristic/stearic triglycerides, about 0.5% to about 5% soybean lecithin, flavors and sweeteners.

9. The liquid formulation of any preceding claim, wherein the ambroxol or pharmaceutically acceptable salt comprises ambroxol hydrochloride.

10. The liquid formulation of item 9, wherein the ambroxol hydrochloride is included in an amount of about 5% to about 15%, based on total weight of the liquid formulation.

11. A softgel capsule for oral administration comprising (a) a fill material comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof (b) a shell composition.

12. The softgel capsule of item 11, wherein the softgel is suitable for swallowing whole.

13. The softgel capsule of item 11 or 12, that is formulated for gastric delivery, intestinal delivery or a combination thereof.

14. The softgel of item 11 or 13, wherein the capsule is suitable for chewing.

15. The softgel of item 14, that is formulated for mouth delivery.

16. The softgel capsule of any of items 11-15, wherein the shell composition comprises gelatin, carrageenan or as combination thereof.

17. The softgel of item 16, wherein the shell composition comprises about 10 wt% to about 85 wt% gelatin
18. The softgel of item 16, wherein the shell composition comprises about 45 wt% to about 75 wt% gelatin.
19. The softgel of item 16, wherein the shell composition comprises about 15 wt% to about 45 wt% gelatin.
20. The softgel capsule of any of claims 16 to 19, wherein the gelatin is selected from the group consisting of Type A gelatin, Type B gelatin and mixtures thereof.
21. The softgel capsule of any of items 16-19, wherein the gelatin is selected from the group consisting of fish gelatin, hide gelatin, bone gelatin, porcine gelatin, bovine gelatin, and mixtures thereof.
22. The softgel capsule of any of items 11-16, wherein the shell composition comprises a plasticizer.
23. The softgel of item 22, wherein the shell composition comprises about 10 wt% to about 75 wt% plasticizer.
24. The softgel of item 22, wherein the shell composition comprises about 20 wt% to about 50 wt% plasticizer.
25. The softgel of item 22, wherein the shell composition comprises about 30 wt% to about 60 wt% plasticizer.
26. The softgel capsule of items 22-25, wherein the plasticizer comprises carrageenan and does not include an animal based component.
27. The softgel capsule of any of items 22-25, wherein the plasticizer is selected from the group consisting of glycerin, propylene glycol, aqueous sorbitol and sorbitan solution and combinations thereof.

28. The softgel capsule of any of items 11-27, wherein the shell composition comprises about 0.01 wt% to about 1.0 wt% of dextrose.
29. The softgel capsule of any of items 11-28, wherein the shell further comprises a starch.
30. The softgel capsule of any of items 11-29, wherein the lipid material comprises triglycerides.
31. The softgel capsule of item 30, wherein the triglycerides comprise medium chain triglycerides, caprylic triglycerides, capric triglycerides, myristic triglycerides, stearic triglycerides, and combinations thereof.
32. The softgel capsule of any of items 11-31, wherein the fill material further comprises at least one surfactant.
33. The softgel capsule of item 32, wherein the surfactant is a non-ionic surfactant.
34. The softgel capsule of item 33, wherein the non-ionic surfactant comprises caprylocaproyl macrogol-8-glycerides, caprylic/capric triglyceride, polyoxyl hydrogenated castor oil, pegylated castor oil, or a combination thereof.
35. The softgel of any of items 11-34, wherein the fill material further comprises an emulsifier.
36. The softgel capsule of item 35, wherein the emulsifier comprises lecithin.
37. The softgel capsule of any of items 11-37, wherein the fill material comprises medium chain triglycerides, caprylic/capric/myristic/stearic triglycerides, caprylic/capric triglycerides and caprylocaproyl macrogol-8-glycerides.

38. The softgel capsule of any of items 11-37, wherein the fill material comprises medium chain triglycerides, PEG-40 castor oil, caprylic/capric/myristic/stearic triglycerides, soybean lecithin, flavors and sweeteners.

39. The softgel capsule of any of items 11-37, wherein the fill material comprises about 5% to about 15% ambroxol hydrochloride, about 20% to about 50% medium chain triglycerides, about 15% to about 45% caprylic/capric/myristic/stearic triglycerides, about 5% to about 25% caprylic/capric triglycerides and about 1% to about 10% caprylocaproyl macrogol-8-glycerides.

40. The softgel capsule of any of items 11-37, wherein the fill material comprises about 5% to about 15% ambroxol hydrochloride, about 30% to about 60% medium chain triglycerides, about 0.5% to about 5% PEG-40 castor oil, about 10% to about 40% caprylic/capric/myristic/stearic triglycerides, about 0.5% to about 5% soybean lecithin, flavors and sweeteners.

41. The softgel capsule of any of items 11-40, providing an ambroxol dissolution of at least about 10% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

42. The softgel capsule of any of items 11-41, providing an ambroxol dissolution of at least about 60% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

43. The softgel capsule of any of items 11-42, providing an ambroxol dissolution of at least about 80% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

44. The softgel capsule of any of items 11-43, providing an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

45. The softgel capsule of any of items 11-40, providing an ambroxol dissolution of at least about 15% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
46. The softgel capsule of any of items 11-40 and 45, providing an ambroxol dissolution of at least about 65% at 10 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
47. The softgel capsule of any of items 11-40 and 45-46, providing an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
48. The softgel capsule of any of items 11-40 and 45-47, providing an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
49. The softgel capsule of any of items 11-48, wherein at least about 92% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.
50. The softgel capsule of any of items 11-48, wherein at least about 95% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.
51. The softgel capsule of any of items 11-48, wherein at least about 97% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.
52. The softgel capsule of any of items 11-48, wherein at least about 92% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

53. The softgel capsule of any of items 11-48, wherein at least about 95% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

54. The softgel capsule of any of items 11-48, wherein at least about 97% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

55. The softgel capsule of any of items 11-48, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 5% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

56. The softgel capsule of any of items 11-48, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 50% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

57. The softgel capsule of any of items 11-48, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 75% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

58. The softgel capsule of any of items 11-48, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

59. The softgel capsule of any of items 11-48, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 50% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

60. The softgel capsule of any of items 11-48, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 60% at 10 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

61. The softgel capsule of any of items 11-48, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
62. The softgel capsule of any of items 11-48, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.
63. The softgel capsule of any of items 11-62, wherein the total ambroxol impurity does not exceed about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1% or about 0.01%, wherein the total impurity is measured by HPLC.
64. A process for producing the softgel capsule of any preceding item, comprising encapsulating the fill composition in the shell composition to form the softgel capsule and drying the softgel capsule.
65. A method of treating cough comprising administering a liquid or softgel capsule of any of items 1-63.
66. The method of item 65, wherein the treatment comprises phlegm loosening.
67. The method of item 65 or 66, wherein the cough is accompanied by lung or bronchial illness.
68. The method of any of items 65-67, wherein the softgel is swallowed whole.
69. The method of any of item 65-67, wherein the softgel is chewed.
70. A liquid pharmaceutical dosage form comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof.

71. A lozenge pharmaceutical dosage form comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof.
72. A process for producing a swallowable softgel capsule, comprising preparing a gel mass for a shell composition and preparing a fill composition including ambroxol, and inserting the gel mass and the fill composition into an encapsulation machine.
73. The process of item 72, wherein the encapsulation machine is a rotary die machine.
74. The process of item 72 or 73, wherein preparing the gel mass includes mixing a plasticizer and water, and then adding gelatin while mixing to form gel mass.
75. The process of any of items 72-74, wherein the gel mass is stored in a storage vessel at a temperature of about 50°C to about 65°C.
76. The process of any one of items 72 to 75, wherein preparing the fill composition includes forming an active pharmaceutical premix including ambroxol and a second premix.
77. The process of item 76, wherein the active pharmaceutical premix includes a first portion of medium chain triglycerides and ambroxol or a pharmaceutically acceptable salt thereof.
78. The process of item 76 or 77, wherein the second premix includes mixing additional triglyceride, a surfactant, and an emollient in a homogeneity mixer.
79. The process of any one of items 76 to 78, wherein the active pharmaceutical premix and the second premix are mixed in the homogeneity mixer at a temperature of about 20°C to about 25°C for about 15 min.
80. The process of any one of items 72 to 79, wherein the encapsulation machines produces the softgel capsule.

81. The process of any one of items 72 to 80, further comprising drying the softgel capsules in a rotary dryer.

82. A process for producing a chewable softgel capsule, comprising preparing a gel mass for a shell composition and preparing a fill composition including ambroxol, and inserting the gel mass and the fill composition into an encapsulation machine.

83. The process of item 82, wherein the preparing a gel mass comprises forming a first premix including a starch, glycerol and water, and forming a second premix including a plasticizer and water.

84. The process of item 83, wherein the first premix and the second premix are added to an automated mixer to form the gel mass.

85. The process of any of items 82-84, wherein the gel mass is stored in a storage vessel at a temperature of about 50°C to about 65°C.

86. The process of any of items 82-85, wherein the preparing a fill composition comprises forming a first active pharmaceutical ingredient (API) premix comprising ambroxol and a first portion of medium chain triglycerides, a second premix comprising lecithin, citric acid, sugar and a second portion of medium chain triglycerides, and a third premix comprising a flavoring agent and a third portion of medium chain triglycerides.

87. The process of any of items 83-86, wherein the second premix is mixed in a homogeneity mixer at a temperature of about 40°C for about 5 minutes, and then cooling the homogeneity mixer to a temperature of about 20°C to about 25°C.

88. The process of item 87, wherein the first API premix is then added to the homogeneity mixer and mixed for about 5 minutes.

89. The process of item 87 or 88, wherein the third premix is added to the homogeneity mixer and mixed for about 5 minutes to form the fill composition.

90. The process of any one of items 82 to 89, wherein the encapsulation machine is a rotary die machine

91. The process of any one of items 82 to 90, wherein the encapsulation machine produces the softgel capsule.

92. The process of any of items 82-91, further comprising drying the softgel capsule in a rotary dryer.

EXAMPLES

[00107] The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction of the invention.

Example 1: Manufacturing process of a Liquid Formulation

A liquid formulation is prepared by mixing the components of Table 1 below:

Table 1

Component	Quantity	
	Mg/capsule	% w/w
Ambroxol HCl	30.0	10.0
Masester E8120	46.5	15.5
Labrasol ALF	18.0	6.0
Softisan 378	97.5	32.5
Medium Chain Triglycerides	108.0	36.0
Total fill weight	300	100

Example 1A

A liquid formulation is prepared by mixing the components of Table 1A below:

Table 1A

Component	Quantity	
	Mg/capsule	% w/w
Ambroxol HCl	30.0	10.0
Medium Chain Triglycerides	130.8	43.6
Kolliphor RH40	45.0	15.0
Softisan 378	84.0	28.0
Soybean Lecithin	6.0	2.0
Tetrarome orange flavor 501433	1.2	0.4
Citric acid anhydrous	1.5	0.5
Sucralose	1.5	0.5
Total fill weight	300	100

Example 2: Manufacturing process of a Swallowable Softgel Capsule

[00108] The manufacture of a swallowable softgel capsule including ambroxol was prepared. The softgel capsule was prepared by forming a gelatin mass for the shell composition and a fill material (the liquid formulation of Example 1) that was then used in an encapsulation machine to form the capsule. The manufacturing process will be described herein and is illustrated in the Figure.

Gelatin Mass Preparation

[00109] The gelatin mass preparation was prepared using an automated process using a melting reactor controlled by a programmable logic controller (PLC). The gelatin mass was prepared to form the shell composition as described in Table 2.

Table 2: Shell composition of swallowable softgel capsule

Component	Quantity	
	Mg/capsule	% w/w
Gelatin 195 Bloom	104.7	44.7
Glycerol	58.4	24.9
Purified Water	69.5	29.7
Red iron oxide 1/1 in glycerol	1.4	0.7
Approximate total wet shell weight	234	100

[00110] The gelatin mass preparation was prepared using an automated process using a melting reactor controlled by a programmable logic controller (PLC).

Encapsulation Method

[00111] After forming the gel mass and the liquid formulation, an encapsulation method was performed. The encapsulation machine was of the rotary die type and provided a continuous form, fill and seal operation.

[00112] The machine was fed by two (2) receivers. One receiver contained the melted gel mass used to form the shell as described above; the second receiver contained the fill solution as described above.

[00113] A first drying occurs immediately after encapsulation in a rotary dryer system physically connected to the encapsulation machine, where the soft gelatin capsules were tumbled for a pre-determined period of time.

Drying Step

[00114] After discharge from the rotary dryer, the capsules were spread on shallow drying trays. These trays were put in the drying tunnels and low humidity air were allowed to circulate over the capsules. The manufactured process as described herein is shown in the Figure.

Example 2: Manufacturing of a Chewable Softgel Capsule

[00115] The manufacture of a chewable softgel capsule including ambroxol was prepared. The softgel capsule was prepared by forming a gelatin mass for the shell composition and a fill material (the liquid formulation of Example 1A) that was then used in an encapsulation machine to form the capsule. The manufacturing process will be described herein.

Gelatin Mass Preparation

[00116] The gelatin mass preparation was prepared using an automated process using a melting reactor controlled by a programmable logic controller (PLC). The gelatin mass was prepared to form the shell composition as described in Table 3.

Table 3: Shell composition of chewable softgel capsule

Component	Quantity	
	Mg/capsule	% w/w
Gelatin 195 Bloom	60.8	26.0
Glycerol	84.2	36.0
Purified Water	51.5	22.0
Perfactamyl Gel MB	14.1	6.0
Perfactamyl Gel E1404	23.4	10.0
Approximate total wet shell weight	234	100

Encapsulation Step

[00117] The encapsulation machine was of the rotary die type and provided a continuous form, fill and seal operation.

[00118] The machine was fed by two (2) receivers. One contained the melted gel masses used to form the shell as described above; the second contained the fill solution described above.

[00119] A first drying occurs immediately after encapsulation in a rotary dryer system physically connected to the encapsulation machine, where the soft gelatin capsules are tumbled for a pre-determined period of time.

Drying Step

[00120] After discharge from the rotary dryer, the capsules were spread on shallow drying trays. These trays were put in the drying tunnels and low humidity air were allowed to circulate over the capsules. Each encapsulation line had its own drying tunnels. The manufacturing process described herein is illustrated in the Figure.

Dissolution Study

[00121] An in vitro dissolution study between an ambroxol tablet and softgel capsule as described above was conducted. The dissolution media composition for the swallowable capsule was HCl 0.1 N, while the dissolution media composition for the chewable capsule was phosphate buffer pH 6.8.

[00122] The dissolution conditions of the swallowable capsule were determined using a Type II propeller in 500 mL at a temperature of 37°C at a speed of 50 rpm.

One capsule was placed in each of the six dissolution vessels which contained the dissolution media. After each time point, 1.5 mL of a sample was collected and filtered through 0.45 µm nylon filter, diameter 25 mm.

[00123] The dissolution conditions of the chewable capsule were determined using a type III reciprocating cylinder in 900 mL at a temperature of 37°C at a speed of 30 deep per minute. One capsule was placed in each of the six dissolution vessels which contained the dissolution media. After each time point, 5.0 mL of sample was collected and filtered through 0.45 µm nylon filter, diameter 25 mm.

[00124] The results of the dissolution study is presented below in Tables 4 – 6.

Table 4 – Dissolution Result of Tablet

	% drug release in HCl 0.1 N/ 100 rpm Basket/ 500 mL						
	Tablet 30 mg						
Tablet No.	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	Infinity 60 mins
1	69	98	100	101	100	100	101
2	81	97	98	98	98	98	98
3	64	97	98	98	99	99	98
4	76	98	101	100	100	101	100
5	68	98	100	100	100	100	100
6	54	96	99	99	100	99	100
Mean	69	97	99	99	99	100	100
Min	54	96	98	98	98	98	98
Max	81	98	101	101	100	101	101
%RSD	13	1	1	1	1	1	1

Table 5 – Dissolution Result of Swallowable Capsule

	% drug release in HCl 0.1 M/ 50 rpm Paddles/ 500 mL						
	Ambroxol HCl 30 mg Soft Gelatin Capsules – Release testing						
Tablet No.	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	Infinity 60 mins
1	34	96	102	102	102	102	102

2	6	36	69	91	100	102	102
3	28	94	101	103	103	100	103
4	4	41	85	95	101	101	101
5	14	96	103	104	103	104	103
6	25	101	103	104	103	104	104
Mean	19	77	94	100	102	102	102
Min	4	36	69	91	100	100	101
Max	34	101	103	104	103	104	104
%RSD	65	39	15	5	2	2	1

Table 6 – Dissolution Result of Chewable Capsule

	% drug release in Phosphate Buffer pH 6.8/ 30 dpm Reciprocating cylinder / 500 mL Ambroxol 30 mg Chewable Soft Gelatin Capsules – Release testing						
Tablet No.	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	60 mins
1	37	89	89	93	91	94	78
2	31	82	90	91	89	91	88
3	31	84	90	91	45*	85	78
4	29	86	88	91	88	91	90
5	30	82	88	91	90	92	89
6	33	85	87	90	89	90	87
Mean	32	85	89	91	82	90	85
Min	30	82	87	90	45	85	78
Max	37	89	90	93	91	94	90
%RSD	10	3	1	1	22	3	1

[00125] The results reveal that 100% (w/w) of the ambroxol HCl dissolved was released after 15 minutes for the tablet and after 20 minutes for both the swallowable and chewable capsules.

Chemical and Physical Stability Study

[00126] A chemical and physical stability study was performed for swallowable and chewable softgel capsules in blister at 40°C/75%RH, 30°C/65%RH, and 25°C/60% RH storage conditions over three months. After 3 months, no impurities were detected and the percentage of ambroxol recovery (HPLC analysis) verse T0 was 98% for swallowable capsules at 40°C/75%RH and 98% for chewable capsules at 30°C/65%RH.

[00127] The dissolution results revealed that 100% (w/w) of the Ambroxol HCl dissolved was released after 20 min for the swallowable capsules after 3 months at 40°C/75%RH and after 20 min for the chewable capsules after 3 months at 30°C/65%RH. No delay of API release was observed, and no crosslinking phenomenon observed after 3months of storage.

[00128] The results of this study are shown in Tables 7 and 8.

Table 7 - % Drug Release of Swallowable Capsules

Tablet No.	% drug release in HCl 0.1 M/ 50 rpm Paddles/ 500 mL Ambroxol HCl 30 mg Soft Gelatin Capsules – T3M 40°C/75% RH Testing						
	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	Infinity 60 mins
1	13	81	98	100	101	101	101
2	8	63	93	102	103	103	103
3	9	72	95	101	102	103	102
4	15	91	81	91	98	102	102
5	3	75	98	103	103	104	104
6	8	56	82	91	99	103	103
Mean	9	68	91	98	101	103	102
Min	3	56	81	91	98	101	101
Max	15	81	98	103	103	104	104
%RSD	45	14	8	6	2	1	1

Table 8 - % Drug Release of Chewable Capsules

	% drug release in Phosphate Buffer pH 6.8/ 30 dpm Reciprocating cylinder / 900 mL Ambroxol 30 mg Chewable Soft Gelatin Capsules – T3M 40°C/75% RH Testing						
Tablet No.	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	Infinity 60 mins
1	81	89	90	90	92	92	93
2	75	82	88	90	92	93	94
3	66	79	87	90	91	92	93
4	80	87	89	90	90	91	92
5	73	87	89	91	91	91	91
6	77	89	90	91	91	92	92
Mean	75	86	89	90	91	92	93
Min	66	79	87	90	90	91	91
Max	81	89	90	91	92	93	94
%RSD	7	5	1	1	1	1	1

Stability Study

[00129] An additional stability study was performed for swallowable and chewable softgel capsules in blister packaging and HDPE bottles. The results of the 12 month stability study are presented in Tables 9-11.

Table 9: Swallowable softgel capsule of Ambroxol HCl 30 mg, 5 oval

Storage condition	Packaging	Time point	Assay	RS
25°C / 60%RH	HDPE Bottles	12 months	101.1%	ND
30°C / 65%RH	HDPE Bottles	6 months	102.8%	ND
40°C / 75%RH	HDPE Bottles	6 months	101.4%	ND

Table 10: Chewable softgel capsule of Ambroxol HCl 30 mg, 5 oval, 6CHEW, blister packaging

Storage condition	Packaging	Time point	Assay	RS
25°C / 60%RH	Blister	12 months	93.9%	0.13%
30°C / 65%RH	Blister	6 months	95.0%	0.13%
40°C / 75%RH	Blister	4 weeks	95.5%	ND

Table 11: Chewable softgel capsule of Ambroxol HCl 30 mg, 5 oval, 6CHEW, HDPE bottles packaging

Storage condition	Packaging	time point	Assay	RS
25°C / 60%RH	HDPE Bottles	12 Months	95.0%	ND
40°C / 75%RH	HDPE Bottles	6 months	92.5%	0.33%

WHAT IS CLAIMED IS:

1. A liquid formulation comprising an amphiphilic material and ambroxol or a pharmaceutically acceptable salt thereof.
2. The liquid formulation of claim 1, wherein the amphiphilic material comprises a lipid, a surfactant, an amphiphilic block polymer, or an amphiphilic protein or peptide or a combination thereof.
3. The liquid formulation of claim 2, wherein the lipid comprises a saturated lipid, an unsaturated lipid, a neutral lipid, a cationic lipid, an anionic lipid, a natural lipid, a synthetic lipid, triglycerides, a PEG (polyethylene glycol)-lipid, or an anti-oxidant lipid agent.
4. The liquid formulation of claim 2, wherein the surfactant comprises an ionic surfactant, nonionic surfactant or wetting agents.
5. The liquid formulation of claim 1, wherein the amphiphilic material comprises medium chain triglycerides, caprylic/capric/myristic/stearic triglycerides, caprylic/capric triglycerides and caprylocaproyl macrogol-8-glycerides.
6. The liquid formulation of claim 1, wherein the amphiphilic material comprises medium chain triglycerides, PEG-40 castor oil, caprylic/capric/myristic/stearic triglycerides, soybean lecithin, flavors and sweeteners.
7. The liquid formulation of claim 1, wherein the liquid formulation comprises about 20% to about 50% medium chain triglycerides, about 15% to about 45% caprylic/capric/myristic/stearic triglycerides, about 5% to about 25% caprylic/capric triglycerides and about 1% to about 10% caprylocaproyl macrogol-8-glycerides.
8. The liquid formulation of claim 1, wherein the liquid formulation comprises about 5% to about 15% ambroxol hydrochloride, about 30% to about 60% medium chain triglycerides, about 0.5% to about 5% PEG-40 castor oil, about 10% to about

40% caprylic/capric/myristic/stearic triglycerides, about 0.5% to about 5% soybean lecithin, flavors and sweeteners.

9. The liquid formulation of claim 1, wherein the ambroxol or pharmaceutically acceptable salt comprises ambroxol hydrochloride.

10. The liquid formulation of claim 9, wherein the ambroxol hydrochloride is included in an amount of about 5% to about 15%, based on total weight of the liquid formulation.

11. A softgel capsule for oral administration comprising (a) a fill material comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof (b) a shell composition.

12. The softgel capsule of claim 11, wherein the softgel is suitable for swallowing whole.

13. The softgel capsule of claim 12, that is formulated for gastric delivery, intestinal delivery or a combination thereof.

14. The softgel of claim 11, wherein the capsule is suitable for chewing.

15. The softgel of claim 14, that is formulated for mouth delivery.

16. The softgel capsule of claim 11, wherein the shell composition comprises gelatin, carrageenan or as combination thereof.

17. The softgel of claim 16, wherein the shell composition comprises about 10 wt% to about 85 wt% gelatin

18. The softgel of claim 12, wherein the shell composition comprises about 45 wt% to about 75 wt% gelatin.

19. The softgel of claim 14, wherein the shell composition comprises about 15 wt% to about 45 wt% gelatin.
20. The softgel capsule of claim 16, wherein the gelatin is selected from the group consisting of Type A gelatin, Type B gelatin and mixtures thereof.
21. The softgel capsule of claim 16, wherein the gelatin is selected from the group consisting of fish gelatin, hide gelatin, bone gelatin, porcine gelatin, bovine gelatin, and mixtures thereof.
22. The softgel capsule of claim 11, wherein the shell composition comprises a plasticizer.
23. The softgel capsule of claim 22, wherein the shell composition comprises about 10 wt% to about 75 wt% plasticizer.
24. The softgel capsule of claim 12, wherein the shell composition comprises about 20 wt% to about 50 wt% plasticizer.
25. The softgel capsule of claim 14, wherein the shell composition comprises about 30 wt% to about 60 wt% plasticizer.
26. The softgel capsule of claim 22, wherein the plasticizer comprises carrageenan and does not include an animal based component.
27. The softgel capsule of claim 22, wherein the plasticizer is selected from the group consisting of glycerin, propylene glycol, aqueous sorbitol and sorbitan solution and combinations thereof.
28. The softgel capsule of claim 11, wherein the shell composition comprises about 0.01 wt% to about 1.0 wt% of dextrose.
29. The softgel capsule of claim 14, wherein the shell further comprises a starch.

30. The softgel capsule of claim 11, wherein the lipid material comprises triglycerides.

31. The softgel capsule of claim 30, wherein the triglycerides comprise medium chain triglycerides, caprylic triglycerides, capric triglycerides, myristic triglycerides, stearic triglycerides, and combinations thereof.

32. The softgel capsule of claim 11, wherein the fill material further comprises at least one surfactant.

33. The softgel capsule of claim 32, wherein the surfactant is a non-ionic surfactant.

34. The softgel capsule of claim 33, wherein the non-ionic surfactant comprises caprylocaproyl macrogol-8-glycerides, caprylic/capric triglyceride, polyoxyl hydrogenated castor oil, pegylated castor oil, or a combination thereof.

35. The softgel capsule of claim 11, wherein the fill material further comprises an emulsifier.

36. The softgel capsule of claim 35, wherein the emulsifier comprises lecithin.

37. The softgel capsule of claim 12, wherein the fill material comprises medium chain triglycerides, caprylic/capric/myristic/stearic triglycerides, caprylic/capric triglycerides and caprylocaproyl macrogol-8-glycerides.

38. The softgel capsule of claim 14, wherein the fill material comprises medium chain triglycerides, PEG-40 castor oil, caprylic/capric/myristic/stearic triglycerides, soybean lecithin, flavors and sweeteners.

39. The softgel capsule of claim 12, wherein the fill material comprises about 5% to about 15% ambroxol hydrochloride, about 20% to about 50% medium chain triglycerides, about 15% to about 45% caprylic/capric/myristic/stearic triglycerides, about 5% to about 25% caprylic/capric triglycerides and about 1% to about 10% caprylocaproyl macrogol-8-glycerides.

40. The softgel capsule of claim 14, wherein the fill material comprises about 5% to about 15% ambroxol hydrochloride, about 30% to about 60% medium chain triglycerides, about 0.5% to about 5% PEG-40 castor oil, about 10% to about 40% caprylic/capric/myristic/stearic triglycerides, about 0.5% to about 5% soybean lecithin, flavors and sweeteners.

41. The softgel capsule of claim 12, providing an ambroxol dissolution of at least about 10% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

42. The softgel capsule of claim 12, providing an ambroxol dissolution of at least about 60% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

43. The softgel capsule of claim 12, providing an ambroxol dissolution of at least about 80% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

44. The softgel capsule of claim 12, providing an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

45. The softgel capsule of claim 14, providing an ambroxol dissolution of at least about 15% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

46. The softgel capsule of claim 14, providing an ambroxol dissolution of at least about 65% at 10 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

47. The softgel capsule of claim 14, providing an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

48. The softgel capsule of claim 14, providing an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

49. The softgel capsule of claim 12, wherein at least about 92% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

50. The softgel capsule of claim 12, wherein at least about 95% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

51. The softgel capsule of claim 12, wherein at least about 97% ambroxol is recovered after storage for 3 months at 40°C/75% relative humidity as compared to T0 using HPLC analysis.

52. The softgel capsule of claim 14, wherein at least about 92% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

53. The softgel capsule of claim 14, wherein at least about 95% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

54. The softgel capsule of claim 14, wherein at least about 97% ambroxol is recovered after storage for 3 months at 30°C/65% relative humidity as compared to T0 using HPLC analysis.

55. The softgel capsule of claim 12, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 5% at 5 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

56. The softgel capsule of claim 12, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 50% at 10 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

57. The softgel capsule of claim 12, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 75% at 15 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

58. The softgel capsule of claim 12, after storage for 3 months at 40°C/75% relative humidity providing an ambroxol dissolution of at least about 90% at 20 minutes using Apparatus type II (propeller) in 500 mL 0.1N HCl at 37° C at 50 rpm.

59. The softgel capsule of claim 14, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 50% at 5 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

60. The softgel capsule of claim 14, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 60% at 10 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

61. The softgel capsule of claim 14, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 70% at 15 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

62. The softgel capsule of claim 14, after storage for 3 months at 30°C/65% relative humidity providing an ambroxol dissolution of at least about 80% at 20 minutes using Apparatus type III (reciprocating cylinder) in 500 mL phosphate buffer pH 6.8 at 30 deep per minute.

63. The softgel capsule of claim 11, wherein the total ambroxol impurity does not exceed about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1% or about 0.01%, wherein the total impurity is measured by HPLC.

64. A process for producing the softgel capsule of claim 11, comprising encapsulating the fill composition in the shell composition to form the softgel capsule and drying the softgel capsule.

65. A method of treating cough comprising administering a softgel capsule of any of claim 11.

66. The method of claim 65, wherein the treatment comprises phlegm loosening.

67. The method of claim 65, wherein the cough is accompanied by lung or bronchial illness.

68. The method of claim 65, wherein the softgel is swallowed whole.

69. The method of claim 65, wherein the softgel is chewed.

70. A liquid pharmaceutical dosage form comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof.

71. A lozenge pharmaceutical dosage form comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof.

72. A process for producing a swallowable softgel capsule, comprising preparing a gel mass for a shell composition and preparing a fill composition including ambroxol, and inserting the gel mass and the fill composition into an encapsulation machine.

73. The process of claim 72, wherein the encapsulation machine is a rotary die machine.

74. The process of claim 72, wherein preparing the gel mass includes mixing a plasticizer and water, and then adding gelatin while mixing to form gel mass.

75. The process of claim 74, wherein the gel mass is stored in a storage vessel at a temperature of about 50°C to about 65°C.

76. The process of claim 72, wherein preparing the fill composition includes forming an active pharmaceutical premix including ambroxol and a second premix.

77. The process of claim 76, wherein the active pharmaceutical premix includes a first portion of medium chain triglycerides and ambroxol or a pharmaceutically acceptable salt thereof.

78. The process of claim 77, wherein the second premix includes mixing additional triglyceride, a surfactant, and an emollient in a homogeneity mixer.

79. The process of claim 76, wherein the active pharmaceutical premix and the second premix are mixed in the homogeneity mixer at a temperature of about 20°C to about 25°C for about 15 min.

80. The process of claim 72, wherein the encapsulation machines produces the softgel capsule.

81. The process of claim 72, further comprising drying the softgel capsules in a rotary dryer.

82. A process for producing a chewable softgel capsule, comprising preparing a gel mass for a shell composition and preparing a fill composition including ambroxol, and inserting the gel mass and the fill composition into an encapsulation machine.

83. The process of claim 82, wherein the preparing a gel mass comprises forming a first premix including a starch, glycerol and water, and forming a second premix including a plasticizer and water.

84. The process of claim 83, wherein the first premix and the second premix are added to an automated mixer to form the gel mass.

85. The process of claim 84, wherein the gel mass is stored in a storage vessel at a temperature of about 50°C to about 65°C.

86. The process of claim 82, wherein the preparing a fill composition comprises forming a first active pharmaceutical ingredient (API) premix comprising ambroxol and a first portion of medium chain triglycerides, a second premix comprising lecithin, citric acid, sugar and a second portion of medium chain triglycerides, and a third premix comprising a flavoring agent and a third portion of medium chain triglycerides.

87. The process of claim 86, wherein the second premix is mixed in a homogeneity mixer at a temperature of about 40°C for about 5 minutes, and then cooling the homogeneity mixer to a temperature of about 20°C to about 25°C.

88. The process of claim 87, wherein the first API premix is then added to the homogeneity mixer and mixed for about 5 minutes.

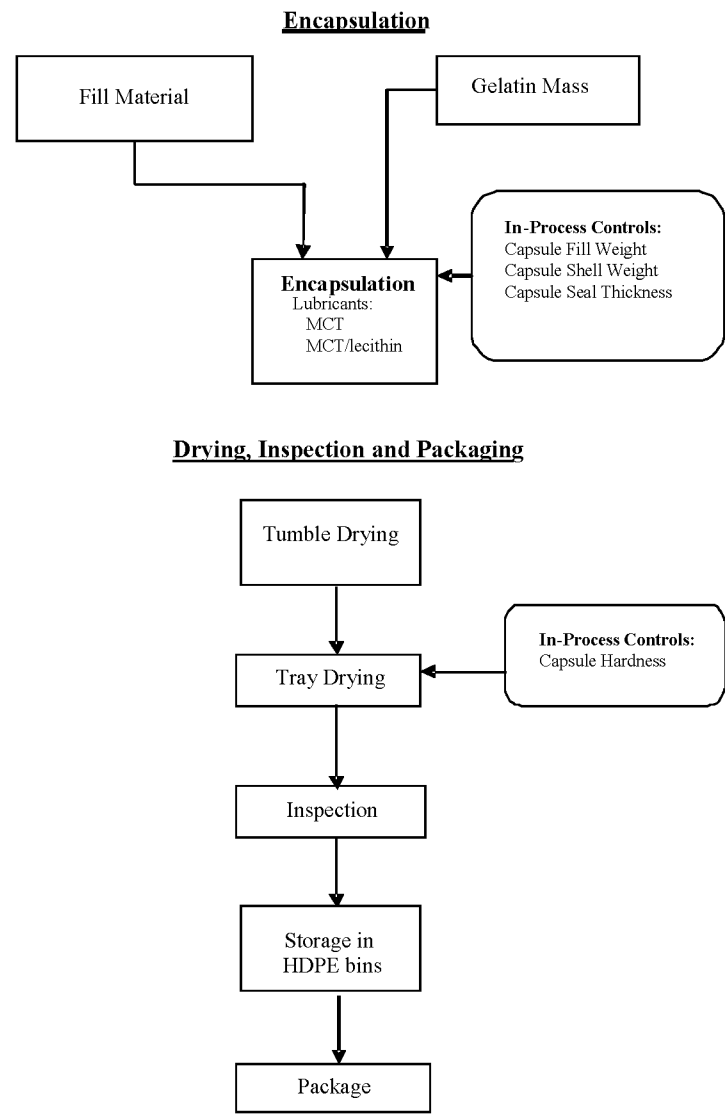
89. The process of claim 88, wherein the third premix is added to the homogeneity mixer and mixed for about 5 minutes to form the fill composition.

90. The process of claim 82, wherein the encapsulation machine is a rotary die machine

91. The process of claim 82, wherein the encapsulation machine produces the softgel capsule.

92. The process of claim 91, further comprising drying the softgel capsule in a rotary dryer.

FIGURE



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/032391

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 47/14** (2024.01); **A61K 47/24** (2024.01); **A61K 9/08** (2024.01); **A61P 11/12** (2024.01); **A61K 31/133** (2024.01); **A61K 31/138** (2024.01)CPC: **A61K 47/14; A61K 31/133; A61K 31/138; A61K 47/24; A61K 9/08; A61P 11/12**

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	CN 115707459 A (FUDAN UNIVERSITY) 21 February 2023 (21.02.2023) machine translation	1-3, 70
X	US 2014/0066518 A1 (SAUERLAND et al.) 06 March 2014 (06.03.2014) entire document	1, 2, 4, 9, 10
A	EP 1543826 A1 (ADVANCE HOLDINGS LIMITED) 22 June 2005 (22.06.2005) entire document	1-10, 70
A	US 2014/0348879 A1 (BANNER PHARMACAPS INC.) 27 November 2014 (27.11.2014) entire document	1-10, 70
A	CN 105496992 A (QINGDAO CHIA TAI HAIER PHARMACEUTICAL CO., LTD.) 20 April 2016 (20.04.2016) entire document	1-10, 70



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

29 July 2024 (29.07.2024)

Date of mailing of the international search report

19 September 2024 (19.09.2024)

Name and mailing address of the ISA/US

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Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-10 and 70 are drawn to liquid formulations and liquid pharmaceutical dosage forms.

Group II: claims 11-63 are drawn to softgel capsules for oral administration.

Group III: claims 64 and 72-92 are drawn to processes for producing a softgel capsule, process for producing a swallowable softgel capsule, and process for producing a chewable softgel capsule.

Group IV: claims 65-69 are drawn to methods of treating cough.

Group V: claim 71 is drawn to lozenge pharmaceutical dosage forms.

The inventions listed in Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, liquid formulations and liquid pharmaceutical dosage forms, are not present in Groups II-V; The special technical features of Group II, softgel capsules for oral administration, are not present in Groups I and III-V; The special technical features of Group III, processes for producing a softgel capsule, process for producing a swallowable softgel capsule, and process for producing a chewable softgel capsule, are not present in Groups I, II, IV and V; The special technical features of Group IV, methods of treating cough, are not present in Groups I-III and V; and the special technical features of Group V, lozenge pharmaceutical dosage forms, are not present in Groups I-IV.

Additionally, even if Groups I-V were considered to share the technical features of a liquid pharmaceutical dosage form comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof and a softgel capsule for oral administration comprising (a) a fill material comprising a lipid material and ambroxol or a pharmaceutically acceptable salt thereof (b) a shell composition, these shared technical features do not represent a contribution over the prior art as disclosed by CN 115707459 A to Fudan University (hereinafter, "Fudan") and US 2014/0348879 A1 to Banner Pharmacaps, Inc. (hereinafter, "Banner").

Fudan teaches a liquid pharmaceutical dosage form (para [0009] a synergistic composition of a drug for treating drug-resistant tumors; para [0010] The synergistic composition is further prepared into a solution) comprising a lipid material (para [0010] a phospholipid composition) and ambroxol or a pharmaceutically acceptable salt thereof (para [0010] containing ambroxol).

Banner teaches a softgel capsule for oral administration (para [0024] enteric oral solid dosage forms, namely tablets, and hard and soft capsules) comprising (a) a fill material (para [0009] a filled enteric soft capsule) (b) a shell composition (para [0009] a soft capsule enteric shell composition).

The inventions listed in Groups I-V therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/032391

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-10, 70**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.