(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 February 2016 (04.02.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/019066 A1

(51) International Patent Classification:
A61K 31/575 (2006.01) *A61K 9/10* (2006.01)
A61P 1/16 (2006.01)

(21) International Application Number:
PCT/US2015/042746

(22) International Filing Date:
29 July 2015 (29.07.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/030,397 29 July 2014 (29.07.2014) US

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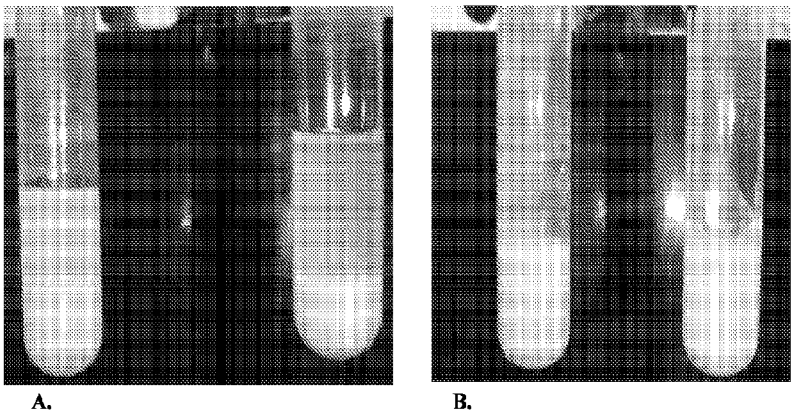
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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).

Published:

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

(54) **Title**: COMPOSITION AND METHOD FOR TREATING LIVER DISEASE



A. B.

Figure 1.

(57) **Abstract**: The presently disclosed subject matter relates to a composition and method of using the composition for treating liver disease. More specifically, the presently disclosed subject matter relates to a pharmaceutical composition comprising Ursodiol, a method of preparing the pharmaceutical composition, and a method of administering this pharmaceutical composition to treat liver disease.

WO 2016/019066 A1

COMPOSITION AND METHOD FOR TREATING LIVER DISEASE

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Attorney Docket Number: 18107N/14128W

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Patent Application 62/030,397, filed on July 29, 2014, the entirety of which is hereby incorporated by reference herein.

TECHNICAL FIELD

[0002] The presently disclosed subject matter relates to a composition and method of using the composition for treating liver disease. More specifically, the presently disclosed subject matter relates to a pharmaceutical composition comprising Ursodiol, a method of preparing the pharmaceutical composition, and a method of administering this pharmaceutical composition to treat liver disease.

INTRODUCTION

[0003] Infants born prematurely have a higher incidence of illness and comorbidity directly related to developmental complications caused by early birth. This situation led the Institute of Medicine, in 2006, to convene a committee to address the growing and significant problem of preterm birth. This committee deemed the improvement in the quality of care for infants born preterm as a priority area of research (Committee of Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Unfortunately, seven years later, this situation has not improved significantly and treatment strategies, commonly used in the neonatal intensive care unit, rely heavily on the use of extemporaneous preparations made *in situ* from available drugs that were formulated for adults. Insufficient stability information and improper manufacturing standardization are common practice for these pediatric preparations. Additionally, certain types of adult patients also rely on extemporaneous preparations of existing drug

formulations. Therefore, it is desirable to develop drug products prescribed for pediatric patients and other patients but not currently available in the market as a suitable dosage form.

SUMMARY OF THE INVENTION

[0004] This summary describes several embodiments of the presently-disclosed subject matter, and, in many cases, lists variations and permutations of these embodiments. This Summary is merely exemplary of the numerous and varied embodiments. Mention of one or more representative features of a given embodiment is likewise exemplary. Such an embodiment can typically exist with or without the feature(s) mentioned; likewise, those features can be applied to other embodiments of the presently-disclosed subject matter, whether listed in this Summary or not. To avoid excessive repetition, this Summary does not list or suggest all possible combinations of such features.

[0005] In some embodiments, the presently disclosed subject matter provides a composition that includes a liquid vehicle having an intermediate hydrophilic-lipophilic balance (HLB) as defined hereinbelow and an effective amount of Ursodiol. In some embodiments, the composition further includes a hydrophilic solvent such as water. In some embodiments, the composition further includes one or more of a surfactant, preservatives, a sweetener and an alkalinizing agent.

[0006] In some embodiments, the hydrophilic solvent is included in the composition at a concentration from about 65% to about 85% by weight. In specific embodiments, the hydrophilic solvent comprises about 65%, 70%, 75%, 80% or 85% by weight. Water is the preferred hydrophilic solvent.

[0007] In some embodiments, the hydrophilic-lipophilic balance (HLB) of the liquid vehicle of the composition ranges from about 11.0 to about 16.5. For purposes of the present invention, this range shall be understood to comprise the range for the "intermediate" HLB value. In other embodiments, the HLB ranges from about 12.5 to about 16.5. In some embodiments, the hydrophilic-lipophilic balance of the liquid vehicle ranges from about 11.0 to about 15.0. Some specific embodiments include HLB values for the vehicle of about 11.0, 11.5, 12.0, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, or 16.5.

[0008] In some embodiments, the amount of the liquid vehicle having the intermediate HLB in the composition is from about 1.0% to about 10.0% by weight. In other embodiments, it is from about 2.0% to 10.0 % by weight. In some embodiments, the liquid vehicle having the intermediate HLB is included in the composition at concentration of about 1.0% to about 6.0% by weight of the composition. In some embodiment, the concentration of the liquid vehicle is from about 1.0% to about 3.0% by weight of the composition. Some specific aspects of the invention include compositions in which the amount of the liquid vehicle is about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, or 10.0% by weight.

[0009] The surfactant included in the composition has an HLB range from about 14.0 to about 17.0. In some specific embodiments, the HLB of the surfactant is about 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, or 17.0. In some embodiments, the amount of surfactant included in the composition ranges from about 2.0% to about 9.0% by weight. In some embodiments, the concentration of the surfactant is from about 6.0% to about 9.0% by weight in the composition. In some specific embodiments, the amount of surfactant in the composition is about 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, or 9.0% by weight.

[00010] In some embodiments, the concentration of the Ursodiol in the composition is from about 40.0 to about 60.0 mg/ml. In specific embodiments, the Ursodiol concentration is about 40.0, 41.0, 42.0, 43.0, 44.0, 45.0, 46.0, 47.0, 48.0, 49.0, 50.0, 51.0, 52.0, 53.0, 54.0, 55.0, 56.0, 57.0, 58.0, 59.0, or 60.0 mg/ml. In some embodiments, the amount of Ursodiol in the composition is from about 3.5% to about 5.5% by weight. In specific embodiments, the amount of Ursodiol is about 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, or 5.5% by weight. Such amounts will be understood to be "effective" for purposes of the present invention and allow for one or more doses to be administered with therapeutic effect to a subject.

[00011] The amount of preservative included in the composition can range from about 0.15% to about 0.30% by weight while in some specific embodiments, the amount of preservative is about 0.15%, 0.20%, 0.25%, or 0.30% by weight.

[00012] The amount of sweetener included in the composition can range from about 0.25% to about 0.50% by weight with amounts of about 0.25%, 0.30%, 0.35%, 0.40%, 0.45%, or 0.50% by weight being used in some other embodiments.

[00013] The pH of the composition can range from about 7.7 to about 8.6 with values of about 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, or 8.6 being present for specific embodiments.

[00014] Further provided in the present invention are methods of treating liver disease in a subject in need thereof. The method includes administering to the subject an effective amount of a composition of described herein.

[00015] Still further embodiments of the present invention include methods of making aqueous pharmaceutical compositions containing Ursodiol. The method includes the steps of preparing a liquid solution at a temperature ranging from about 35°C to about 55°C, wherein the liquid solution includes: a hydrophilic solvent at an initial concentration from about 65% to about 85% by weight, from about 4.0 to about 7.0 % by weight of a liquid vehicle with an intermediate HLB from about 12.5 to about 16.5 such as propylene glycol , and from about 2.5 to about 5.5 % by weight of a surfactant having an HLB ranging from about 14.0 to about 17.0. The method further includes adding and dissolving into the liquid solution the Ursodiol at a concentration from about 40mg/ml to about 60mg/ml and about 3.5% to about 5.5% by weight, a preservative at a concentration from about 0.15 to about 0.30 % by weight, a sweetener in a concentration from about 0.25 to about 0.50 % by weight, and an alkalinizing agent in an amount sufficient to adjust the final pH of the composition to between about 7.7 and about 8.6. All amounts above refer to the final composition. Additionally, the method includes adding a further amount of the hydrophilic solvent, i.e. water, to make up the remaining final volume. In some embodiments, the aqueous pharmaceutical composition may be a clear solution while in others the aqueous pharmaceutical composition may be a slightly yellow solution or a clear, slightly yellow solution.

[00016] In a further aspect of the invention there are provided alcohol-free liquid Ursodiol compositions for oral delivery. The compositions include:

DESCRIPTION	range (mg/ml)	weight range (%)
Ursodiol	40.0 – 60.0	3.5 – 5.5
Liquid Vehicle, e.g. Propylene glycol	20.0 - 100.0	2.0 – 9.0
Surfactant, e.g. Tween 80	20.0 – 120.0	2.0 – 10.0
Alkalinizing agent, e.g. Sodium bicarbonate	15.0 – 30.0	1.5 – 3.0
Preservative(s), e.g. Methyl paraben, propyl paraben	1.5 – 3.3	0.15 – 0.33
Sweetener, e.g. Sucralose	2.5 – 5.0	0.25 – 0.50
Purified water	670.0 - 920.0	70.0 – 90.5

[00017] Advantages of the presently-disclosed subject matter will become evident to those of ordinary skill in the art after a study of the description, Figures, and non-limiting Examples disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[00018] **Figures 1A and 1B** are photographs showing the physical appearance of refrigerated Ursodiol suspension (20 mg/ml) (extemporaneous preparation 1). Figure 1A shows a still sample as retrieved from the refrigerator. Figure 1B shows a sample after one minute of vortex.

[00019] **Figures 2A and 2B** are photographs showing the physical appearance of refrigerated Ursodiol suspension (50 mg/ml) (extemporaneous preparation 2). Figure 2A shows a still sample as retrieved from the refrigerator. Figure 2B shows a sample after one minute of vortex.

[00020] **Figures 3A and 3B** are photographs showing the physical appearance of refrigerated Ursodiol solution (50 mg/ml) inventive formula 1. Figure 3A shows a still sample as retrieved from the refrigerator. Figure 3B shows a sample after one minute of vortex.

[00021] **Figures 4A and 4B** are photographs showing the physical appearance of refrigerated Ursodiol solution (50 mg/ml) inventive formula 2. Figure 4A shows a still sample as retrieved from the refrigerator. Figure 4B shows a sample after one minute of vortex.

[00022] **Figures 5A and 5B** are photographs showing the physical appearance of comparative Ursodiol extemporaneous preparations (1 and 2) poured from HDPE containers stored in an environmental chamber at 40°C. Figure 5A shows an Ursodiol suspension (20 mg/ml) prepared with Ora-plus: Ora Sweet (1:1) (v/v). Figure 5B shows an Ursodiol suspension (50 mg/ml) prepared from Sugar syrup NF.

[00023] **Figures 6A and 6B** are photographs showing the physical appearance of inventive Ursodiol solutions (50 mg/ml) (formulas 1 and 2) after pouring from HDPE bottles retrieved from an environmental chamber at 40°C. Figure 6A shows propylene glycol based Ursodiol solution (50mg/ml) (formula 1). Figure 6B shows ethanol based Ursodiol solution (50 mg/ml) (formula 2).

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[00024] The details of one or more embodiments of the presently-disclosed subject matter are set forth in this disclosure. Modifications to embodiments described in this disclosure, and other embodiments, will be evident to those of ordinary skill in the art after a study of the information provided in this disclosure. The information provided in this disclosure, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding

and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this disclosure, including definitions, will control.

[00025] While the terms used herein are believed to be well-understood by one of ordinary skill in the art, definitions are set forth to facilitate explanation of the presently-disclosed subject matter.

[00026] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the presently-disclosed subject matter belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently-disclosed subject matter, representative methods, devices, and materials are now described.

[00027] Following long-standing patent law convention, the terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a subject" includes a plurality of such subjects, and so forth.

[00028] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

[00029] As used herein, the term "about," when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments ±20%, in some embodiments ±10%, in some embodiments ±5%, in some embodiments ±1%, in some embodiments ±0.5%, and in some embodiments ±0.1% from the specified amount, as such variations are appropriate to achieve the intended result.

[00030] The presently disclosed subject matter relates to a composition, methods of making and methods of using the composition for treating liver disease. More specifically, the presently disclosed subject matter relates to pharmaceutical compositions comprising one or more doses of Ursodiol or

ursodeoxycholic acid, methods of preparing the compositions, and methods of administering the pharmaceutical compositions in order to treat liver disease.

[00031] As used herein, the term "Ursodiol" refers to ursodeoxycholic acid. Ursodiol is the predominant bile acid in bears, thus the name of "Urso". Ursodiol was identified in a recent survey conducted in 21 children's hospitals (50 beds or more) as one of the top 10 most commonly prescribed liquid formulations prepared extemporaneously (Lugo et al., 2009). It is FDA-approved for the dissolution of cholesterol-rich gallstones in patients with functioning gallbladders and in the treatment of primary biliary cirrhosis and has been extensively used off-label in children for treatment of some chronic cholestatic liver diseases (Black, 2010). Ursodiol is not water-soluble; the use of a traditional single solvent system is limited because of its potential long term accumulated toxicity in pediatric patients following chronic treatment (Khan, 2012).

[00032] The preference for a liquid dosage form for the selected compound is underscored by the extreme difficulty in young children when swallowing solids because of complex interactions between the developing nervous and physiological systems with the environment that evolves during growth (Bowles *et al.*, 2010). A number of anatomical differences, with respect to the general population, contribute to the difficulty by young children to swallow solids, the development of feeding and swallowing is the result of complex interactions between the different developing systems as well as the environment. In some embodiments, a liquid dosage form is provided in the present disclosure that makes the composition easier to swallow and also leads to a higher flexibility in dosage increments.

[00033] There is no appropriate dosage form of Ursodiol to be used in pediatric patients. The current standard of treatment is based on the compounding of the so-called extemporaneous preparations from either of two Reference Listed Drugs (RLD's) (Urso250® or Ursoforte® tablets) (US FDA Orange Book) or their generics. The package insert for each of which is incorporated herein by reference. There are, at least, three of these extemporaneous preparations (20 to 60 mg/ml) (Nahata and Pai, 2011). The preparation of a liquid formulation at 50 mg/ml will also represent a benefit for geriatric patients with swallowing problems (Zajicek, 2013).

[00034] In some embodiments, liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional techniques with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. Preparations for oral administration can be suitably formulated to give controlled release of the active compound.

[00035] In some embodiments, the present disclosure provides a method of preparing a pharmaceutical composition with a continuous phase which allows reproducibility during dosage administration. In some embodiments, a dosage form whose concentration is equivalent to the preparations used as the current standard of treatment is provided. In further embodiments, a dosage form physically stable when stored under refrigeration for extended periods of time before and after opening is provided. In another embodiment, a dosage form physically stable when stored at temperatures up to 40°C for no less than three months before opening is provided. Further still, in some embodiments, a dosage form with excipient levels adequate for use in pediatric patients for chronic liver disease treatment is provided.

[00036] The "liquid vehicle" as used herein (also referred to herein sometimes as a "vehicle", "solvent" or "co-solvent") refers to a liquid compound having an intermediate hydrophilic-lipophilic balance (HLB) as defined in the next paragraph. Non-limiting examples of the liquid vehicle or co-solvent useful for inclusion in the compositions of the present invention include propylene glycol (preferred in many embodiments), ethanol, and benzyl alcohol.

[00037] As used herein, the term "intermediate hydrophilic-lipophilic balance (HLB)" of the liquid vehicle refers to a HLB value situated between a relatively lipophilic value (11) and highly hydrophilic value (20). In some embodiments, the HLB value of the liquid vehicle ranges from about

11.0 to about 16.5. In some embodiments, the HLB value of the liquid vehicle ranges from about 12.5 to about 16.5 with the liquid vehicle being present from about 2.0 to about 10.0 % by weight of the composition. In some embodiments, the HLB of the liquid vehicle ranges from about 11.0 to about 15.0 and the amount of the liquid vehicle in the composition ranging from about 1.0% to about 6.0 % by weight. In some embodiments, the Ursodiol or ursodeoxycholic acid is at a concentration between about 40.0 and about 60.0 mg/ml of the composition or about 3.5% to about 5.5% by weight. In some embodiments, the concentration of the Ursodiol is about 50.0 mg/ml. In some embodiments, the composition further includes a hydrophilic solvent in amounts of from about 65% to about 85% by weight. A non-limiting example of a suitable hydrophilic solvent is water, including all pharmaceutically acceptable forms thereof suitable for inclusion in oral liquid dosage forms. The composition may further include a surfactant which, in some embodiments, has an HLB value of about 14.0 to about 17.0. The amount of surfactant in the compositions can be from about 2.0% to about 9.0% or from about 6.0% to about 9.0% by weight. Non-limiting examples of the surfactant include Tween 20 and Tween 80. Other suitable surfactants will be well known to those of ordinary skill.

[00038] Further provided, in some embodiments, the composition includes a preservative which is preferably is effective in alkaline pH (about 8.0) in amounts of from about 0.15% to about 0.30% by weight. A non-limiting example is a combination of methyl paraben used in a ratio to propyl paraben between 8 to 1 and 10 to 1. Other suitable preservatives will be well known to those of ordinary skill.

[00039] In some embodiments, the composition further includes a suitable amount of a sweetener. Amounts of from about 0.25 to about 0.50% by weight can be suitable with other amounts being determined by routine skill. Non-limiting examples of sweeteners include sugar, sodium aspartame, acesulfame potassium (Sucralose), saccharin or any of the sweeteners generally recognized as being safe for human consumption. In some embodiments, amount of sweetener in the composition, is an amount that provides a sufficient sweetening effect, e.g. equivalent to that obtained with Sucralose.

[00040] In some embodiments, the composition further includes an alkalinizing agent such as, without limitation, sodium bicarbonate, sodium carbonate, sodium hydroxide or potassium hydroxide. In some embodiments, the final pH of the composition is from about 7.7 to about 8.6.

[00041] In one specific embodiment, the composition includes: propylene glycol at about 2.0% to about 9.0% by weight, a surfactant having a HLB of about 14.0 to about 17.0 at about 2.0% to about 10.0% by weight, Ursodiol at about 3.5% to about 5.5% by weight, a preservative at about 0.15% to about 0.33% by weight, a sweetener at about 0.25% to about 0.50% by weight, water at about 70% to about 90.5% by weight, and an alkalinizing agent in an amount sufficient to adjust the final pH to a range from about 7.7 to about 8.6.

[00042] Further provided in some embodiments of the presently disclosed subject matter is a method of treating liver disease in a subject in need thereof. The method includes administering to the subject an effective amount of the pharmaceutical composition disclosed above. In some embodiments, the liver disease is chronic. In some embodiments, the liver disease is chronic pediatric liver disease. In some embodiments, the pharmaceutical composition is administered by oral administration. In some embodiments, the subject is a human.

[00043] The terms "treatment" or "treating" refer to the medical management of a subject with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease,

pathological condition, or disorder. In some embodiments, the associated disease is chronic pediatric liver disease.

[00044] The term "administering" refers to any method of providing a compound and/or pharmaceutical composition thereof to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition (e.g. liver disease). In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition. In some embodiments, the composition is used to treat liver diseases. In some embodiments, the liver disease is chronic. In some embodiments, the composition is used to treat chronic pediatric liver disease. Non-limiting liver diseases include Chronic Inflammation of the Liver, Hardening of Liver and Blockage of Bile Ducts, Gallstones, Inflammation with Fibrous Tissue Formation of Bile Ducts, Blockage of Normal Bile Flow, Closure of Some or All of the Major Bile Ducts, Rare Progressive Liver Disease - Primary Biliary Cirrhosis, Complications of Liver & Bile Ducts due to Cystic Fibrosis, Blockage of Normal Bile Flow From Total Parental Nutrition (TPN), and Hardening of the Liver caused by Alcohol.

[00045] In some embodiments, a subject will be administered an effective amount of the pharmaceutical composition. In this respect, the term "effective amount" refers to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will

depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the above mentioned package insert for the currently FDA approved Ursodiol products. For purposes of illustration, suitable amounts for most indications will range from about 1 to about 40 mg/kg/day in single or divided doses. Alternatively, doses in the range of from about 5 to about 30 mg/kg/day are suitable. Those of ordinary skill will determine suitable dosages based upon clinical experience and without undue experimentation.

[00046] In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[00047] Additionally, the terms "subject" or "subject in need thereof" refer to a target of administration, which optionally displays symptoms related to a particular disease, pathological condition, disorder, or the like. The subject of the herein disclosed methods can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human (preferred), non-human primate, dog, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. A patient refers to a subject afflicted with a disease or disorder. The term "subject" includes human and veterinary subjects.

[00048] Still further embodiments provide methods of producing an aqueous pharmaceutical composition containing Ursodiol or ursodeoxycholic acid. The methods include (1) preparing a liquid solution heated to a temperature from about 35 to about 55 °C that includes: a hydrophilic solvent at an initial concentration designed to achieve between about 65 and about 85 % by weight in the final composition, a vehicle with an intermediate HLB of about 12.5 to about 16.5 and an amount of from about 4.0 to about 7.0 % by weight, and a surfactant with an HLB of between about 14.0 and about 17.0 in amounts of from about 2.5 to about 5.5 % by weight; (2) adding and dissolving into the solution solids, which for the purposes of the present invention include Ursodiol at a concentration between about 40.0 and about 60.0 mg/ml, a preservative in an amount of between about 0.15 and about 0.30 %, by weight, a sweetener agent in an amount of between about 0.25 and about 0.50 % by weight, and an amount of an alkalinizing agent sufficient to adjust the final pH to between about 7.7 and about 8.6; and (3) adding a further amount of the hydrophilic solvent to reach the remaining final volume. The specified concentrations all refer to the final composition. In some embodiments, the final dosage form of the aqueous pharmaceutical composition is a clear and/or slightly yellow solution.

[00049] An alternative method of producing the aqueous Ursodiol compositions includes the steps of: (1) preparing a liquid solution heated to a temperature between about 35°C and about 55°C, comprising a hydrophilic solvent at initial concentration designed to achieve between about 65 and about 85 % by weight of the final composition, a liquid vehicle with an intermediate HLB between about 11.0 and about 15.0 in an amount of from between about 1.0 and about 3.0 % by weight, and a surfactant with an HLB between about 14.0 and about 17.0 in an amount of between about 6.0 and about 9.0 % by weight; (2) adding and dissolving into the liquid solution the solids, as described above, including the Ursodiol at a concentration between about 40.0 and about 60.0 mg/ml; a preservative in an amount of between about 0.15 and about 0.30 % by weight; a sweetener in an amount of between about 0.25 and about 0.50 % by weight, and an alkalinizing agent in an amount sufficient to adjust the final pH to a value between about 7.7 and about 8.6; and (3) making up the final volume by adding a further amount of the hydrophilic solvent after mixture and dissolution of all the other components. The

specified concentrations all refer to the final composition. In some embodiments, the final dosage form of the aqueous pharmaceutical composition is a clear and/or slightly yellow solution.

[00050] In some embodiments, the methods of preparing the liquid Ursodiol composition include: (1) preparing a clear liquid mixture solution, heated to a temperature of about 35°C to about 55 °C, including: (i) a hydrophilic solvent, preferably water, at initial concentration designed to achieve between about 60 and 90 % by weight of the final composition; (ii) a liquid vehicle with an intermediate HLB, e.g., between about 12.5 and about 16.5, such as but not limited to, propylene glycol or ethanol, in an amount of between about 2.0 and about 10.0 %, by weight of the final composition; and (iii) a surfactant with an HLB between 14.0 and 17.0, such as but not limited to, Tween 20 or Tween 80, in an amount of between about 2.0 and about 9.0 %, by weight of the final composition; and (2) adding and dissolving the solids including: (i) the Ursodiol, at a concentration of between about 40.0 and about 60.0 mg/ml; (ii) a preservative intended to be effective in alkaline pH (around 8.0) such as a combination of methyl paraben used in a ratio to propyl paraben between 8 to 1 and 10 to 1, in an amount of between about 0.15 and about 0.30%, by weight of the final composition; (iii) a sweetener, such as but not limited to, sugar, sodium aspartame, saccharin, etc. in a concentration between about 0.25 and about 0.50 %, by weight of the final composition; (iv) an alkalinizing agent such as but not limited to, sodium bicarbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide, sufficient to adjust the final pH to a value between about 7.7 and about 8.6; and (v) the remaining volume to be made up with the hydrophilic solvent. The specified concentrations all refer to the final composition. In some embodiments, the final dosage form is a clear and/or slightly yellow solution.

[00051] In another embodiment, the methods of preparing the Ursodiol compositions include: (1) preparing a clear liquid mixture or solution, heated to a temperature between about 35 °C and about 55 °C, that includes: (i) a hydrophilic solvent, preferably water, at an initial concentration between about 60 and about 90 %, by weight, of the final composition; (ii) a liquid vehicle with an intermediate HLB, between about 11.0 and about 15.0, such as but not limited to, propylene glycol, ethanol or benzyl alcohol, in an amount of between about 2.0 and about 6.0 %, by weight of the final composition; (iii) a

surfactant with an HLB of about 14.0 to about 17.0, such as but not limited to, Tween 20 or Tween 80 in an amount of between about 2.0 and about 9.0 % by weight of the final composition; (2) adding and dissolving into the clear mixture or solution solids including: (i) Ursodiol at a concentration between about 40.0 about 60.0 mg/ml of the final composition; (ii) a preservative as discussed above intended to be effective in alkaline pH (around 8.0) in an amount of between about 0.15 and about 0.30 %, by weight of the final composition; (iii) a sweetener agent as discussed above, in an amount of between about 0.25 and about 0.50 %, by weight of the final composition; (iv) an alkalinizing agent as described above to adjust the final pH to a value between about 7.7 and about 8.6, and (v) the remaining volume to be made up with the hydrophilic solvent. In some embodiments, the final dosage form is a clear and/or pale yellow solution.

[00052] In some embodiments, the composition is stable for up to about 6 months when stored at about 4 °C. The physical appearance of the composition is still as a clear and/or pale yellow solution after the storage period. In some embodiments, the clear and/or pale yellow physical appearance of the solution is retained after storage for up to about 3 months at a temperature of about 40 °C and at no more than 20% relative humidity.

[00053] The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples.

[00054] EXAMPLE 1

[00055] **Materials and methods**:

[00056] **i. <u>Product development:</u>** the current standard of treatment in pediatrics is based on the preparation *in situ* of extemporaneous formulations. Three of them are currently listed ranging in concentration from 20 mg/ml to 60 mg/ml. (Nahata et al., 2011.) Two of these comparative preparations (a. and b.) along with the present inventive solutions (c. and d, also referred to as formulas 1 and 2.) are described below.

[00057] **a. Ursodiol suspension (20 mg/ml)**: prepared from grinding the contents of Ursodiol capsules 300 mg and mixing with equal parts of Ora-plus® and Ora-Sweet® to form a suspension. The

powder is initially wetted and then diluted gradually with incremental volumes of the Ora-plus® and Ora-Sweet® mixture until final concentration is achieved. The suspension is vortexed under moderate speed for not less than a minute to obtain a homogeneous dispersion before distributing in specific containers according to the different environment conditions: as a non-limited example: semipermeable sealed plastic containers for storage at 40 ºC and semipermeable sealed plastic containers and/ or glass parafilm-sealed containers for storage under refrigeration.

[00058] **b. Ursodiol suspension (50 mg/ml)**: prepared from grinding the contents of Ursodiol capsules 300 mg, an initial volume of Glycerin USP (equivalent to 2.5 % of final volume) is added for wetting. Then Sugar syrup NF is added to form a homogeneous paste that becomes a dispersion with incremental volumes of the Glycerin USP. This dispersion becomes a suspension after vortexing at moderate speed for not less than a minute that can be distributed as described above.

[00059] **c. Ursodiol solution (50 mg/ml) formula 1:** in a typical example, but not limited, the active was prepared by direct dissolution at 40 °C with the following excipients (amounts expressed in mg per ml of the final drug product): propylene glycol (72.00); Tween® 80 (51.40); sodium bicarbonate (30.90); methyl paraben (2.50); propyl paraben (0.25); Sucralose (3.85); the final volume adjusted with USP purified water for a final pH of 8.0 (± 0.3). After cooling at room temperature the product was distributed as described above.

[00060] **d. Ursodiol solution (50 mg/ml) formula 2:** as per the previous formulation, the supplied drug powder was placed in a solution as described below by gently heating up to 40 °C with the following excipients (amounts expressed in mg per ml of the final drug product): ethanol (22.60); Tween® 80 (100.80); sodium bicarbonate (30.90); methyl paraben (2.50 mg); propyl paraben (0.25); Sucralose (3.85); the final volume adjusted with USP purified water for a final pH of 8.0 (± 0.3). Final distribution and storage is as described above.

[00061] ii. **Analytical method development:** the method is modified from one used to determine Ursodiol and metabolites in fecal material. (Cai et al., 2012) This method allows the measurement of the compound of interest in different matrices (formulations and biological fluids).

[00062] **a. Equipment configuration:** a Shimadzu Prominence UFLC system equipped with LC-20AD pumps, CTO-20AC column oven, a SIL-30AC autosampler, a DGU-$20A_{5R}$ degasser, a CBM-20A communication bus module, and a LCMS-2020 single quadrupole mass spectrometer controlled by LabSolutions software (Tokyo, Japan).

[00063] **b. Chromatographic procedure:** the chromatographic separation was run through a Luna® C_{18} column (300 x 3.9 mm, 5 µm) (Phenomenex (Torrance, CA)). The mobile phases were: (A) 10 mM ammonium acetate (pH 7.8, adjusted with ammonium hydroxide) and (B) 10 mM ammonium acetate in 3:1 acetonitrile/methanol (v/v) flow rate of 0.5 mL/min. The retention time for Ursodiol at these conditions was 11.4 min (± 0.2 min).

[00064] **c. Sample preparation:** the samples were diluted from specified amounts with mobile phase B and then filtered through a 0.45 µm syringe before preparing the vial for the autosampler.

[00065] **iii. Storage conditions:** the different conditions were:

[00066] **a. Refrigeration:** samples were filled into glass test tubes, closed with double parafilm layer. Tubes were placed in refrigeration (4 °C) for about 6 months and checked periodically visually to evaluate continuous phase (solutions) or dispersion characteristics (suspension).

[00067] **b. Accelerated conditions:** the product filled into semipermeable plastic containers for up to about 3 months: **high density polyethylene** (HDPE) and **polyethylene terephtalate** (PET). The cap liner was heat sealed before placing into an environmental chamber at 40 °C and no more than 20 % relative humidity (specified conditions for this dosage form and container). (International Committee of Harmonization, 2003).

[00068] **Results:**

[00069] The physical appearance for the extemporaneous preparation of Ursodiol suspension (20 mg/ml), prepared with Ora-plus: Ora Sweet (1:1) (v/v), retrieved from the refrigerator is shown in **Figure 1. Figure 1 (A)** illustrates still samples just retrieved from the refrigerator, and **(B)** after vortexing for a minute.

[00070] The physical appearance for the extemporaneous preparation of Ursodiol (50 mg/ml) prepared from Sugar syrup NF, retrieved from the refrigerator is shown in **Figure 2**. **Figure 2(A)** shows still samples just retrieved from the refrigerator; and **Figure 2(B)** shows samples after vortexing for a minute.

[00071] Next, for the Ursodiol solution (50 mg/ml), propylene glycol based formulation (formula 1), withdrawn from the refrigerator is shown in **Figure 3**. **Figure 3(A)** is still samples just retrieved from the refrigerator and **Figure 3(B)** shows samples after vortexing for a minute.

[00072] Referring to **Figure 4** which shows the Ursodiol solution (50 mg/ml), ethanol based formulation (formula 2), previously stored in the refrigerator. **Figure 4(A)** shows still samples just retrieved from the refrigerator and **Figure 4(B)** shows samples after vortexing for a minute.

[00073] After shaking the plastic containers retrieved from the stability chamber, the contents were poured into a 50-ml glass beaker. The type of container did not have an effect on the final physical appearance, but in order to keep consistency only the product poured from HDPE bottles is shown. The appearance for the extemporaneous preparations is shown in **Figure 5**. **Figure 5(A)** shows Ursodiol suspension (20 mg/ml) prepared with Ora-plus: Ora Sweet (1:1) (v/v) and **Figure 5(B)** shows Ursodiol suspension (50 mg/ml) prepared from Sugar syrup NF.

[00074] Next, the appearance for the prepared Ursodiol solutions (50 mg/ml) is shown in **Figure 6** after pouring from HDPE bottles retrieved from the environmental chamber. **Figure 6(A)** shows Ursodiol solution (50 mg/ml) propylene glycol based formulation (formula 1), and **Figure 6(B)** Ursodiol solution (50 mg/ml) ethanol based formulation (formula 2).

[00075] Table 1 shows assayed Ursodiol concentrations for extemporaneous preparations made with 20 mg/ml and 50 mg/ml Ursodiol. The assayed values were determined using HPLC on samples retrieved from the environmental chamber. The values represent the "Area under the curve" or "AUC". The assayed concentration values were obtained from the ratio of At/Ar where At is the AUC for the extemporaneous preparations and Ar is the AUC for the propylene glycol based formulation. The ratio

is expressed as a percentage. For the 20 mg/ml extemporaneous preparations, the injection volume was doubled (so the theoretical value would have been equivalent to 40 mg/ml).

[00076] Table 1. Assayed values estimated for formulations retrieved from the environmental chamber.

Replicate #	EXTEMPORANEOUS PREPARATIONS*		PROPYLENE GLYCOL BASED FORMULATION*
	URSODIOL SUSPENSION (20 mg/ml)**	URSODIOL SUSPENSION (50 mg/ml)	URSODIOL SOLUTION (50 mg/ml)
1	15,288,525	17,950,663	31,948,070
2	16,325,575	16,128,518	28,439,901
3	14,401,512	13,219,044	23,559,619
MEAN	15,338,537	15,766,075	27,982,530
STD. DEV.	786,291	1,948,603	3,439,808
RSD	5.13%	12.36%	12.29%
Notes: (*) Comparison from products stored in HDPE bottles (**) Area from twice the extraction volume			
CONCENTRATIONS ESTIMATED FROM THE SOLUTION (50mg/ml)			
ASSAYED CONCENTRATION	20 mg/ml suspension	50 mg/ml suspension	
	13.7	28.17	
% OF LABEL CLAIM	68.50%	56.30%	

Replicate #	EXTEMPORANEOUS PREPARATIONS*		PROPYLENE GLYCOL BASED FORMULATION*
	URSODIOL SUSPENSION (20 mg/ml)**	URSODIOL SUSPENSION (50 mg/ml)	URSODIOL SOLUTION (50 mg/ml)
1	16,725,241	19,811,238	29,788,626
2	16,277,065	17,003,021	35,299,793
3	13,518,493	14,747,299	30,205,924
MEAN	15,506,933	17,187,186	31,764,781
STD. DEV.	1,417,894	2,071,442	2,505,430
RSD	9.14%	12.05%	7.89%
Notes: (*) Comparison from products stored in PET bottles (**) Area from twice the extraction volume			
CONCENTRATIONS ESTIMATED FROM THE SOLUTION (50mg/ml)			
ASSAYED CONCENTRATION	20 mg/ml suspension	50 mg/ml suspension	
	12.2	27.05	
% OF LABEL CLAIM	61.00%	54.10%	

[00077] **Discussion and conclusions**: samples prepared as a suspension and stored in the refrigerator (prior art_extemporaneous formulations) led to an evident physical instability. The Ursodiol comparative formulations showed a coral shade with two clear phases when stored for a few days in the refrigerator; neither gentle agitation nor vortex allowed the liquid to distribute uniformly. Refrigeration is specified after first administration; but, it is evident that the product will lose uniformity after few days at these conditions. (Nahata et al., 2011)

[00078] Prior art Ursodiol suspension (50 mg/ml) showed a three-phase liquid; a gentle shake did not lead to the distribution of all three layers to form a homogeneous suspension. Vortexing helped in the inclusion of the upper layer but still the precipitate did not distribute with the remaining of the liquid.

[00079] The advantage of the inventive solutions is apparent since there is a continuous phase for both formulations prepared. No crystals or solids were apparent that may be the result of unstable solutions evident when the product is placed at low temperature (less than 5 °C). These liquids were prepared from the mixture of different components with water as the major component; therefore during rigorous vortexing some bubbles were formed that slowly ascended to the surface before breaking.

[00080] Physical appearance from samples retrieved from the environmental chamber (40 °C no more than 20 % of relative humidity) showed an apparent uniformity in the comparative example Ursodiol suspension (20 mg/ml); however some of the solid was settled at the bottom of the container even after shaking. The comparative (correct?) Ursodiol suspension (50 mg/ml) prepared with Sugar syrup in the comparative example decreased the viscosity of the liquid, showing the uneven distribution of the active through the vehicle. The solutions showed a slight darkening in color; the formulation is still a continuous phase.

[00081] HDPE containers showed a slightly higher assay value (expressed as percentage of the theoretical claim) for the extemporaneous preparations as compared to those tested from PET bottles. The assay range for a product to be approved is 85 to 115 %. None of the prior art extemporaneous preparations were within this limit, mainly because of the physical instability of the formulation; a

significant amount of solids were found at the bottom of the container that could not be effectively resuspended leading to a sub therapeutic dose. The inventive Ursodiol composition showed physical stability for up to about 6 months at 4°C and up to about 3 months at 40 °C and relative humidity of no more than 20 %.

[00082] After prior art extemporaneous preparations are dispensed into the appropriate container and first administered, subsequent doses will be inadequate because of the inefficient distribution of the drug in the liquid. The continuous phase provided by the inventive compositions as described herein allow the appropriate dose as specified on the prescription to be given on a repeated basis.

[00083] **EXAMPLE 2**

[00084] This study provides solubility data for ursodeoxycholic acid (Ursodiol).

[00085] Method: in this example, product was magnetically stirred at room temperature (22 ± 4 °C), unless otherwise mentioned. A total incorporation of the solids to form a continuous phase was considered fully soluble.

[00086] **Preformulation studies – Ursodiol (initial tests at 200 mg/ml)**

SOLVENT	HLB[A]	DESCRIPTION
Ethanol	12.55	Freely soluble.
Benzyl alcohol	12.31	Freely soluble, the mixture is not as clear as ethanol.
Propylene glycol	14.00	A grayish dispersion, solids are still apparent in the liquid.
Deionized water	23.40	Insoluble.
Buffer solution pH 4.0		Insoluble.
Buffer solution pH 10.0		Insoluble.

NOTE: [A] Hydrophilic-Lipophilic Balance (HLB).

Active was tested at this concentration (200 mg/ml) in Sorbitol solution 70 %, it was not dispersed because of the high viscosity of the vehicle.

[00087] **Preformulation studies – Ursodiol (50 mg/ml) dosage form concentration**

SOLVENT	HLB	DESCRIPTION
Propylene glycol (Room Temp.)	14.00	Few solids are still remaining.

Propylene glycol (40 °C)		Soluble. It did not settle when placed in the refrigerator.
Transcutol® HP	4.2[A]	Completely soluble.
Labrasol®	14[B]	Light gray uniform suspension.
Labrafil® M 2125	4[B]	Insoluble, it led to a dark colored suspension.
Maisine® 35-1	4[B]	Insoluble, led to a two-phase dark yellow system.

NOTES: [A]Ref: Afr. J. Pharm Pharmacol 7 (22): 1482-1500 (2013).

[B]Data from: Gattefosse "Regulatory Summary Table Oral Excipients"; no significant figures are shown for HLB values.

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6838484 January 2005 Mitchell et al.

INCORPORATIONS BY REFERENCE

[00089] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

1. A composition, comprising: a liquid vehicle having an intermediate hydrophilic-lipophilic balance (HLB), and an effective amount of Ursodiol.

2. The composition of claim 1, further comprising a hydrophilic solvent.

3. The composition of claim 2, wherein the hydrophilic solvent is water.

4. The composition of claim 1, further comprising a surfactant.

5. The composition of claim 1, further comprising a preservative.

6. The compositing of claim 1, further comprising a sweetener.

7. The composition of claim 1, further comprising an alkalinizing agent.

8. The composition of claim 2, wherein the hydrophilic solvent is included in the composition at concentration from about 65% to about 85% weight percentage of the composition.

9. The composition of claim 1, wherein the hydrophilic-lipophilic balance of the vehicle ranges from about 12.5 to about 16.5.

10. The composition of claim 1, wherein the vehicle having the intermediate hydrophilic-lipophilic balance is at concentration of about 2.0% to 10.0% by weight of the composition.

11. The composition of claim 1, wherein the surfactant has a hydrophilic-lipophilic balance ranges from about 14.0 to about 17.0.

12. The composition of claim 11, wherein the surfactant comprises about 2.0% to about 9.0% by weight of the composition.

13. The composition of claim 1, wherein the Ursodiol is included in the composition at a concentration of about 40.0 mg/ml to about 60.0 mg/ml.

14. The composition of claim 5, wherein the preservative is included in the composition at a concentration of about 0.15% to about 0.30% by weight of the composition.

15. The composition of claim 5, wherein the preservative is effective at a pH about 8.0.

16. The composition of claim 6, wherein the sweetener is included in the composition at a concentration of about 0.25% to about 0.50% by weight of the composition.

17. The composition of claim 1, wherein the pH of the composition ranges from about 7.7 to about 8.6.

18. The composition of claim 1, wherein the hydrophilic-lipophilic balance of the vehicle ranges from about 11.0 to about 15.0.

19. The composition of claim 1, wherein the vehicle having the intermediate HLB vehicle is included in the composition at concentration of about 1.0% to about 6.0% by weight of the composition.

20. The composition of claim 11, wherein the surfactant is about 6.0% to about 9.0% by weight in the composition.

21. A method of treating liver disease in a subject in need thereof, comprising: administering to the subject the composition of claim 1.

22. The method of claim 23, wherein the subject is a human.

23. A method of producing an aqueous pharmaceutical composition containing Ursodiol, comprising the steps of:

preparing a liquid solution at about 35°C to about 55°C, comprising the steps of:

adding a hydrophilic solvent at initial concentration of about 65% to about 85% by weight of the composition,

adding a vehicle with an intermediate hydrophilic-lipophilic balance (HLB) of about 12.5 to about 16.5 and at concentration of about 4.0 to about 7.0 % by weight of the composition, and

adding a surfactant to be used in a high HLB vehicle composition having a HLB ranging from about 14.0 to about 17.0 and at concentration of about 2.5 to about 5.5 % by weight of the composition;

adding and dissolving solids comprising the steps of:

adding an therapeutically effective amount of Ursodiol at concentration of about 40.0 to about 60.0 mg/ml,

adding a preservative at concentration of about 0.15 to about 0.30 %, by weight of the composition,

adding a sweetener in a concentration of about 0.25 to about 0.50 %, by weight of the composition, and

adding an alkalinizing agent to adjust the final pH between about 7.7 and about 8.6; and

adding a hydrophilic solvent to make up the remaining volume.

24. The method of claim 23, wherein the aqueous pharmaceutical composition is a clear and slightly yellow solution.

25. A method of producing an aqueous pharmaceutical composition containing Ursodiol, comprising the steps of:

preparing a liquid solution at about 35°C to about 55 °C, comprising the steps of:

adding a hydrophilic solvent at initial concentration of about 65% to about 85% by weight of the composition,

adding a vehicle with an intermediate hydrophilic-lipophilic balance (HLB) of about 11.0 to about 15.0 and at concentration of about 1.0% to about 3.0% by weight of the composition, and

adding a surfactant with a HLB of about 14.0 to about 17.0 and at a concentration of about 6.0 to about 9.0 % by weight of the final composition;

adding and dissolving solids, comprising the steps of:

adding a therapeutically effective amount of Ursodiol at concentration of about 40.0 to about 60.0 mg/ml,

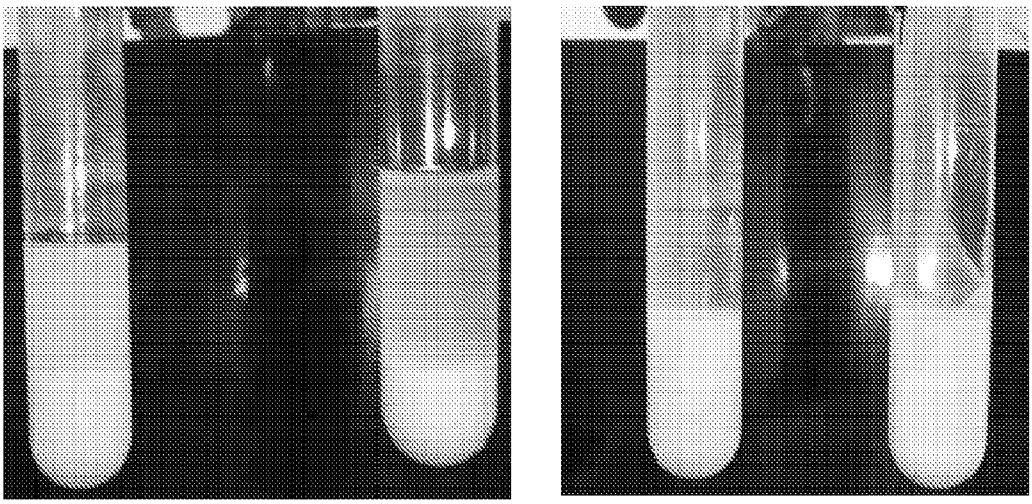
adding a preservative of about 0.15% to about 0.30% by weight of the final composition,

adding a sweetener in a concentration of about 0.25 to about 0.50 % by weight of the final composition,

adding an alkalinizing agent to adjust the final pH between about 7.7 and about 8.6; and

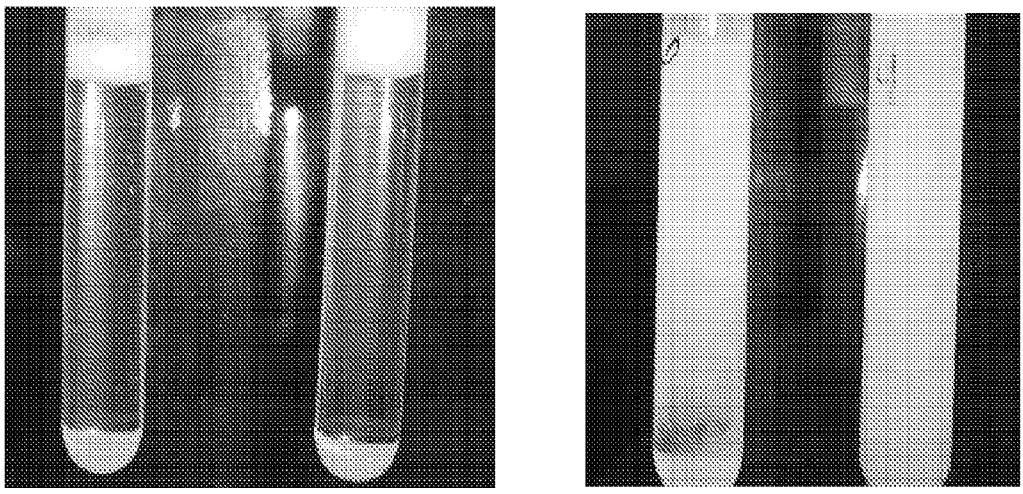
adding the hydrophilic solvent to make up the remaining volume.

26. The method of claim 25, wherein the aqueous pharmaceutical composition is a clear and slightly yellow solution.



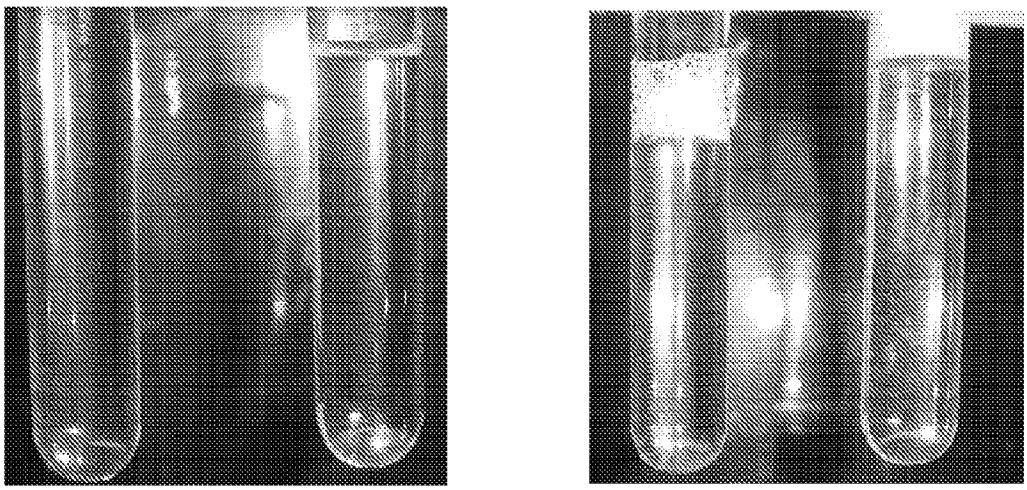
A. B.

Figure 1.



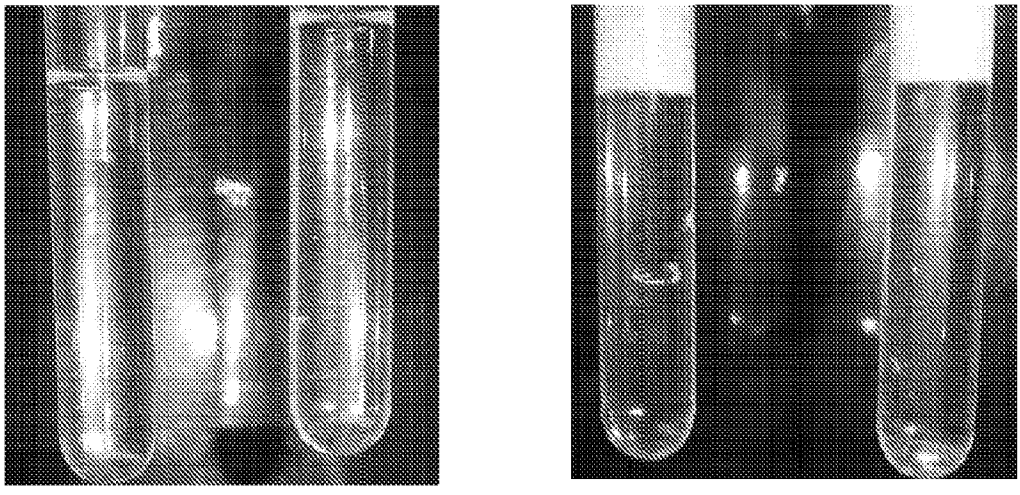
A. B.

Figure 2.



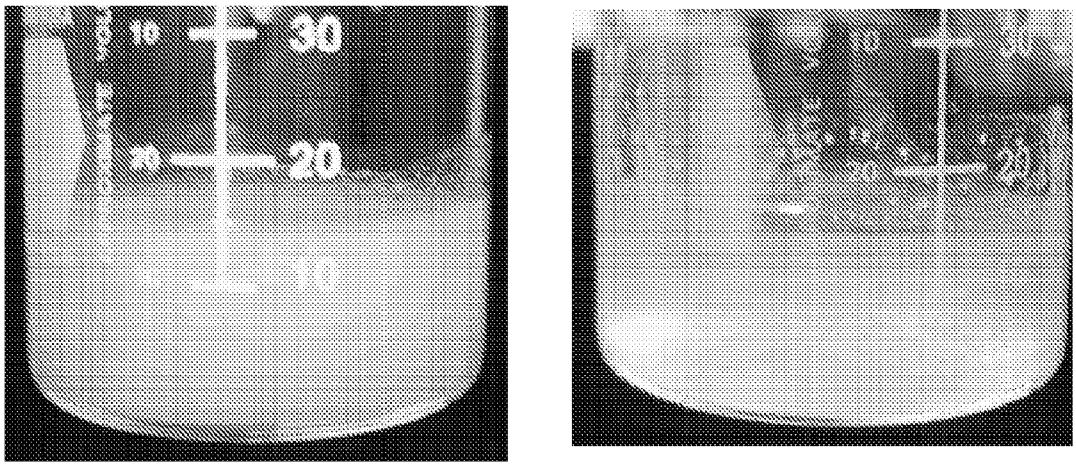
A. B.

Figure 3.



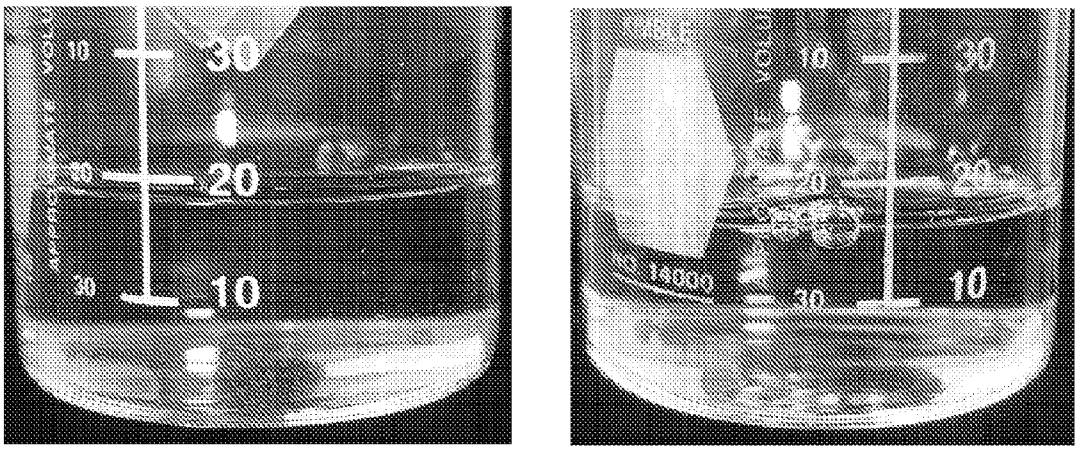
A. B.

Figure 4.



A. B.

Figure 5.



A. B.

Figure 6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/42746

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/575; A61P 1/16; A61K 9/10 (2015.01)
CPC - A61K 31/575; A61K 9/10; A61K 9/107
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)
IPC(8): A61K 31/575; A61P 1/16; A61K 9/10 (2015.01)
CPC: A61K 31/575; A61K 9/10; A61K 9/107

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/182; 514/772; 514/785; 514/975 (key word limited; see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar
Search terms used: ursodiol, formulation, liquid, hydrophilic solvent, glycol, surfactant, HLB, liver disease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,534,505 A (Widauer) 09 July 1996 (09.07.1996); col 1 ln 8-11, 60-62; col 2 ln 20-31, 35-38, 50-52, 57-58, 64-65; col 3 ln 3, 7-15, 28, 32-37, 40-42, 44-46; col 4 ln 9-20	1-23, 25 --------- 24, 26
Y	US 2002/0031558 A1 (Yoo) 14 March 2002 (14.03.2002); para [0067], [0101], [0105]	24, 26
A	US 2012/0156263 A1 (Choy et al.) 21 June 2012 (21.06.2012); entire document	1-26

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
02 October 2015 (02.10.2015)	29 OCT 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)