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(54) Title: PROCESSES OF MAKING L-ORNITHINE PHENYLACETATE

(57) Abstract: Embodiments of the present disclosure are related to improved processes for making L-ornithine phenylacetate without using any silver salts or forming any L-ornithine intermediate salts, such as a benzoate salt. The present processes may be used in the commercial scale manufacturing of L-ornithine phenylacetate with high yields and low impurities.

PROCESSES OF MAKING L-ORNITHINE PHENYLACETATE

BACKGROUND

Field

[0001] The present disclosure relates to the fields of pharmaceutical chemistry, biochemistry, and medicine. In particular, it relates to processes of making L-ornithine phenylacetate, compositions and methods of using the same.

Description

[0002] Hyperammonemia is a hallmark of liver disease and is characterized by an excess of ammonia in the bloodstream. Hepatic encephalopathy is a primary clinical consequence of progressive hyperammonemia and is a complex neuropsychiatric syndrome, which may complicate acute or chronic hepatic failure. It is characterized by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor signs of altered brain function to overt psychiatric and/or neurological symptoms, or even deep coma. The accumulation of unmetabolized ammonia has been considered as the main factor involved in the pathogenesis of hepatic encephalopathy, but additional mechanisms may be associated.

[0003] L-Ornithine monohydrochloride and other L-ornithine salts are available for their use in the treatment of hyperammonemia and hepatic encephalopathy. For example, U.S. Publication No. 2008/0119554, which is hereby incorporated by reference in its entirety, describes compositions of L-ornithine and phenylacetate for the treatment of hepatic encephalopathy. L-ornithine has been prepared by enzymatic conversion methods. For example, U.S. Patent Nos. 5,405,761 and 5,591,613, both of which are hereby incorporated by reference in their entirety, describe enzymatic conversion of arginine to form L-ornithine salts. Sodium phenylacetate is commercially available, and also available as an injectable solution for the treatment of acute hyperammonemia. The injectable solution is marketed as AMMONUL.

[0004] Although salt forms may exhibit improved degradation properties, certain salts, particularly sodium or chloride salts, may be undesirable when treating patients having diseases associated with the liver disease, such as hepatic encephalopathy. For example, a high sodium intake may be dangerous for cirrhotic patients prone to ascites, fluid overload and electrolyte imbalances. Similarly, certain salts are difficult to administer intravenously because of an increased osmotic pressure, i.e., the solution is hypertonic. High concentrations of excess salt may require diluting large volumes of solution for intravenous administration which, in turn, leads to excessive fluid overload. Accordingly, there exists a need for the preparation of L-

ornithine and phenylacetate salts which are favorable for the treatment of hepatic encephalopathy or other conditions where fluid overload and electrolyte imbalance are prevalent.

SUMMARY

[0005] Some embodiments of the present disclosure include a process of making L-ornithine phenylacetate, comprising: intermixing L-ornithine hydrochloride and potassium hydroxide in a first solvent to form a first reaction mixture; adding a second solvent to said first reaction mixture, isolating potassium chloride from said first reaction mixture; intermixing phenylacetic acid with said first reaction mixture to form a second reaction mixture; and isolating a composition comprising L-ornithine phenylacetate from said second reaction mixture. In some embodiments, the process further comprises stirring the first reaction mixture. In some embodiments, the process further comprises cooling said first reaction mixture before isolating potassium chloride. In some embodiments, the process further comprises recrystallizing the composition comprising L-ornithine phenylacetate.

[0006] Some embodiments of the present disclosure include a composition comprising L-ornithine phenylacetate prepared by the process disclosed herein.

[0007] Some embodiments of the present disclosure include a composition comprising L-ornithine phenylacetate having a chloride content of less than about 1.5% by weight, wherein the composition is free of silver ion, benzoic acid or salts thereof. In some embodiments, the composition is free of L-ornithine cyclization or dimerization side products.

DETAILED DESCRIPTION

[0008] Disclosed herein are processes of making L-ornithine phenylacetate, and in particular, large scale and high efficiency processes of making L-ornithine phenylacetate. These processes permit large-scale production of pharmaceutically acceptable forms of L-ornithine phenylacetate using economical processes. Moreover, the processes of making L-ornithine phenylacetate have the added benefit of having low amounts of impurities.

Definitions

[0009] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0010] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not

limiting. The use of the term "having" as well as other forms, such as "have", "has," and "had," is not limiting. As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the above terms are to be interpreted synonymously with the phrases "having at least" or "including at least." For example, when used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition, formulation, or device, the term "comprising" means that the compound, composition, formulation, or device includes at least the recited features or components, but may also include additional features or components.

[0011] As used herein, common organic abbreviations are defined as follows:

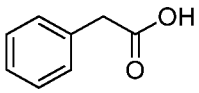
hr	Hour(s)
IPC	In-process control
IR	Immediate release
KCl	Potassium chloride
KOH	Potassium hydroxide
ORN	Ornithine
PAA	Phenylacetic acid
PAGN	Phenylacetylglutamine

[0012] The term "immediate release" as used herein, has its ordinary meaning as understood by those skilled in the art and thus includes, by way of non-limiting example, release of a drug from a dosage form in a relatively brief period of time after administration.

[0013] The term "controlled release" and the term "extended release" as used herein, each has its ordinary meaning as understood by those skilled in the art and thus includes, by way of non-limiting example, controlled release of a drug from a dosage form over an extended period of time. For example, in some embodiments, controlled release or extended release formulations are those that have a release rate that is substantially longer than that of a comparable immediate release form. The two terms can be used interchangeably.

[0014] The term "about" as used herein, refers to a quantity, value, number, percentage, amount, or weight that varies from the reference quantity, value, number, percentage, amount, or weight by a variance considered acceptable by one of ordinary skill in the art for that type of quantity, value, number, percentage, amount, or weight. In various embodiments, the term "about" refers to a variance of 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1% relative to the reference quantity, value, number, percentage, amount, or weight.

[0015] The term "oral dosage form" as used herein, has its ordinary meaning as understood by those skilled in the art and thus includes, by way of non-limiting examples, a formulation of a drug or drugs in a form orally administrable to a human, including pills, tablets, cores, capsules, caplets, loose powder, liquid solution or suspension.

[0016] The term "phenylacetic acid" as used herein, is also known as benzeneacetic acid or 2-phenylacetic acid). It has the following chemical structure: 

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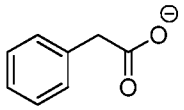
[0017] The term "phenylacetate" as used herein, refers to the anionic form of phenylacetic acid with the following chemical structure: 

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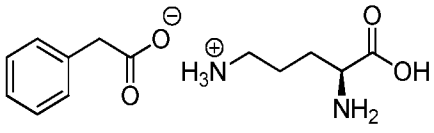
[0018] The term "L-ornithine phenylacetate" as used herein, refer to a compound consisting of L-ornithine cation and phenylacetate anion. It has the following chemical structure: 

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[0019] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions or formulations is contemplated. Supplementary active ingredients can also be incorporated into the compositions or formulations. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

[0020] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds of the preferred embodiments and, which are not biologically or otherwise undesirable. In many cases, the compounds of the preferred embodiments are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid,

nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic cations from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0021] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0022] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition/formulation for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a patient who is not yet suffering from a disease, but who is susceptible to, or otherwise at risk of, a particular disease, whereby the treatment reduces the likelihood that the patient will develop a disease. The term "therapeutic treatment" refers to administering treatment to a patient already suffering from a disease.

Processes of Manufacturing L-ornithine Phenylacetate

[0023] Some embodiments of the present disclosure relate to processes of making L-ornithine phenylacetate. The processes can be used in the large scale manufacturing of L-ornithine phenylacetate, and easily scalable without significant amounts of impurities, such as chloride ions, or side products, such as L-ornithine cyclization or dimerization side products. Additionally, the processes advantageously eliminate the use of costly purification techniques, such as azeotropic distillation or chromatography. Accordingly, the present processes of making L-ornithine phenylacetate allow for greater economy and purity in the large scale production of L-ornithine phenylacetate.

[0024] Some embodiments of the present disclosure relate to compositions of L-ornithine phenylacetate with low concentrations of impurities and side products. Impurities and

side products in an L-ornithine phenylacetate salt composition may limit the commercial availability of the composition, due their harmful or dangerous effects in some patients. Impurities may be derived from salts used in the process of making L-ornithine phenylacetate, such as chloride ion, benzoate, silver ion, etc. Side products may be due to cyclization or dimerization reactions, such as cyclization or dimerization of L-ornithine. Accordingly, the present compositions of L-ornithine phenylacetate provide significant improvements, and allow for their medical use in broader patient populations.

[0025] Some embodiments of the present disclosure include a process of making L-ornithine phenylacetate, comprising: intermixing L-ornithine hydrochloride and potassium hydroxide in a first solvent to form a first reaction mixture; adding a second solvent to said first reaction mixture, isolating potassium chloride from said first reaction mixture; intermixing phenylacetic acid with said first reaction mixture to form a second reaction mixture; and isolating a composition comprising L-ornithine phenylacetate from said second reaction mixture.

[0026] In some embodiments, the process further comprises stirring the first reaction mixture. In some such embodiments, the stirring step is performed for less than about 90, 80, 70, 60, 50, 40, 30, 20, or 10 minutes, or in a range defined by any two preceding values (for example, between about 10 to about 90 minutes, about 20 to about 80 minutes, about 30 to about 70 minutes, or about 40 to about 60 minutes). In one embodiment, the stirring step is performed for about 60 to 90 minutes. As another non-limiting example, stirring may be performed before and/or after cooling of the first reaction mixture, and before and/or after adding a second solvent to the first reaction mixture. In some embodiments, the stirring time is selected to avoid re-dissolution of precipitated KCl (e.g., a stirring time of sufficiently short duration is selected).

[0027] In some embodiments, the process further comprises cooling the first reaction mixture before isolating potassium chloride. In some such embodiments, the first reaction mixture is cooled to less than about 10 °C. In one embodiment, the first reaction mixture is cooled to about 0 to 5 °C.

[0028] In some embodiments of the process described herein, the first solvent comprises or is water. In one embodiment, L-ornithine hydrochloride is added to an aqueous solution of potassium hydroxide. Other non-limiting examples of the first solvent include a mixture of water and one or more polar organic solvents, for example, an alcohol or polyol such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol, ethylene glycol, propylene glycol, or glycerol.

[0029] In some embodiments of the process described herein, the second solvent comprises or is an alcohol. In some such embodiments, the second solvent comprises or is ethanol. Other non-limiting examples of the second solvent include an alcohol or polyol such as

methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol, ethylene glycol, propylene glycol, or glycerol, or combinations thereof. In addition, the second solvent may also comprise water.

[0030] In some embodiments of the process described herein, the first reaction mixture after addition of the second solvent comprises about 1:1 (v/v) to about 1:8 (v/v) first solvent to second solvent. In some such embodiments, the first reaction mixture comprises about 1:1 (v/v) to about 1:8 (v/v) H_2O to ethanol. In particular, the H_2O to ethanol ratio may be selected from about 1:1 (v/v), about 1:2 (v/v), about 1:3 (v/v), about 1:4 (v/v), about 1:5 (v/v), about 1:6 (v/v), about 1:7 (v/v), or about 1:8 (v/v), or in a range defined by any of the two preceding values (for example, about 1:1 (v/v) to about 1:8 (v/v), about 1:2 (v/v) to about 1:7 (v/v), about 1:3 (v/v) to about 1:6 (v/v), or about 1:4 (v/v) to about 1:5 (v/v)). In some embodiments, the ratio of water to ethanol is selected to maintain L-ornithine in solution while minimizing dissolution of KCl. In one embodiment, the water to ethanol ratio is about 1:4.3 (v/v).

[0031] In some embodiments of the process described herein, phenylacetic acid is dissolved in a third solvent before intermixing with the first reaction mixture. In some such embodiments, the third solvent comprises or is ethanol. Other non-limiting examples of the third solvent include an alcohol or polyol such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, tert-butanol, ethylene glycol, propylene glycol, or glycerol, or combinations thereof. In addition, the third solvent may also comprise water.

[0032] In some embodiments of the process described herein, the molar ratio of potassium hydroxide to L-ornithine hydrochloride is at least about 1.1:1, at least about 1.15:1, at least about 1.2:1, at least about 1.3:1, at least about 1.4:1, or at least about 1.5:1, or in a range defined by any of the two preceding values. In one embodiment, the molar ratio of potassium hydroxide to L-ornithine hydrochloride is about 1.1:1. In another embodiment, the molar ratio of potassium hydroxide to L-ornithine hydrochloride is about 1.15:1. In still another embodiment, the molar ratio of potassium hydroxide to L-ornithine hydrochloride is about 1.2:1.

[0033] In some embodiments of the process described herein, the chloride content of the isolated composition comprising L-ornithine phenylacetate is less than about 2.5%, 2.4%, 2.3%, 2.2%, 2.1%, 2.0%, 1.9%, 1.8%, 1.7%, 1.6%, 1.5%, 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% by weight, or in a range defined by any of the two preceding values (for example, between about 2.5% to about 0.1%, about 2.0% to about 0.5%, or about 1.5% to about 1.0%). Without being bound to any particular theory, it was surprisingly discovered that chloride content of the isolated composition comprising L-ornithine phenylacetate can affect the purification (e.g., recrystallization) of L-ornithine phenylacetate.

Specifically, when the L-ornithine phenylacetate composition after initial isolation comprises a chloride content of over about 2.5% to 2.8% by weight, the recrystallization was less efficient. In addition, disproportionation of the organic salt and increase in chloride content (i.e., Cl^-) can occur. In one embodiment, the chloride content of the composition prepared by the process described herein is less than about 2.5% by weight. In another embodiment, the chloride content of the composition is less than about 1.5% by weight. In yet another embodiment, chloride content of the composition is less than about 1.0% by weight.

[0034] In some embodiments of the process described herein, the process further comprises recrystallizing the composition comprising L-ornithine phenylacetate. Recrystallization may be achieved using a single solvent, or a solvent mixture, for example, a mixture of water with one or more polar solvents such as alcohols and/or polyols. As a non-limiting example, the composition is recrystallized from a solvent mixture of water and methanol. In some further embodiments, the volume ratio of water and methanol used in the recrystallization is from about 1:1 to about 1:10, for example, about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10, or a range defined by any two of the preceding values. In one embodiment, the volume ratio of water and methanol is about 1:8. In some embodiments of the process described herein, the chloride content of the recrystallized composition is less than about 0.1% by weight, less than about 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02% or 0.01% by weight, or in a range defined by any two preceding values (for example, between about 0.01% to about 0.1%, about 0.02% to about 0.09%, about 0.03% to about 0.08%, or about 0.04% to about 0.07%).

[0035] In some embodiments of the process described herein, the isolated composition of L-ornithine phenylacetate comprises less than about 5.0%, 4.0%, 3.0%, 2.0%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% L-ornithine cyclization or dimerization side products, or a range defined by any two of the preceding values. Certain side products may be formed during the manufacturing of L-ornithine phenylacetate. For example, cyclization of L-ornithine lead to the formation of a lactam (i.e., (*S*)-3-aminopiperidin-2-one), which is known to be a significant side product in preparation protocols that involve elevated temperatures. In addition, it is known that amino acids like L-ornithine can dimerize under certain conditions, such as in basic condition at elevated temperature where two molecules of L-ornithine can undergo intermolecular condensation. The process described herein eliminate the need of using any distillation at elevated temperature to isolate L-ornithine phenylacetate, thereby reducing or preventing the formation of any L-ornithine cyclization or dimerization side products. In some embodiments, the isolated composition comprises less than about 1.0% L-

ornithine cyclization or dimerization side products. In some further embodiments, the isolated composition is substantially free or free of L-ornithine cyclization or dimerization side products.

Pharmaceutical Compositions of L-Ornithine Phenylacetate

[0036] Some embodiments disclosed herein include a composition comprising L-ornithine phenylacetate, in particular a composition prepared by the process described herein. In some embodiments, the composition has a chloride content of less than about 1.5% by weight, and in some embodiments, the composition is free of silver ion, benzoic acid or salts thereof. In some further embodiments, the composition has a chloride content less than about 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, or 0.01% by weight, or in a range defined by any two of the preceding values (for example, between about 1.5% and about 0.01%, about 1.2% to about 0.05%, or about 1.0% to about 0.1%). In one embodiment, the composition has a chloride content of less than about 0.1% by weight. In some embodiments, the composition comprises less than about 1.0% L-ornithine cyclization or dimerization side products. In some further embodiments, the composition comprises less than about 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% L-ornithine cyclization or dimerization side products. In some further embodiments, the composition is substantially free or free of L-ornithine cyclization or dimerization side products.

[0037] In some embodiments, the composition comprises one or more crystalline forms of L-ornithine phenylacetate, or combinations thereof. Various crystalline forms of L-ornithine phenylacetate have been disclosed in U.S. Publication No. 2010/0280119, which is incorporated by reference. In particular, crystalline forms of L-ornithine phenylacetate include Form I (exhibiting XRPD characteristic peaks at approximately 4.9°, 13.2°, 17.4°, 20.8° and 24.4° 2θ), Form II (exhibiting XRPD characteristic peaks at approximately 6.0°, 13.9°, 14.8°, 17.1°, 17.8° and 24.1° 2θ), or Form III (exhibiting XRPD characteristic peaks at approximately 5.8°, 14.1°, 18.6°, 19.4°, 22.3° and 24.8° 2θ). As is well understood in the art, because of the experimental variability when X-ray diffraction patterns are measured on different instruments, the peak positions are assumed to be equal if the two theta (2θ) values agree to within 0.2° (i.e., ± 0.2°).

[0038] The compositions of L-ornithine phenylacetate of the present disclosure may be formulated for administration to a subject (*e.g.*, a human). L-Ornithine phenylacetate, and accordingly the compositions disclosed herein, may be formulated for administration with a pharmaceutically acceptable carrier or diluent. L-ornithine phenylacetate may thus be formulated as a medicament with a standard pharmaceutically acceptable carrier(s) and/or

excipient(s) as is routine in the pharmaceutical art. The exact nature of the formulation will depend upon several factors including the desired route of administration. Typically, L-ornithine phenylacetate is formulated for oral, intravenous, intragastric, subcutaneous, intravascular or intraperitoneal administration.

[0039] The pharmaceutical carrier or diluent may be, for example, water or an isotonic solution, such as 5% dextrose in water or normal saline. Solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, gum arabic, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical compositions. Such pharmaceutical preparations may be manufactured in known manners, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes. The solid oral forms may provide immediate release or controlled release of L-ornithine phenylacetate.

[0040] Liquid dispersions for oral administration may be syrups, emulsions or suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol. Suspensions and emulsions may contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

[0041] The pharmaceutical composition may consist essentially of L-ornithine phenylacetate and a pharmaceutically acceptable carrier. Such a pharmaceutical composition therefore contains substantially no other amino acids in addition to L-ornithine and phenylacetate. Furthermore, such a pharmaceutical composition contains insubstantial amounts of other salts in addition to L-ornithine phenylacetate.

[0042] Oral formulations may generally include dosages of L-ornithine phenylacetate in the range of about 500 mg to about 50 g. In some embodiments, L-ornithine phenylacetate is in a low dosage of about 0.1 g to about 10 g. In some embodiments, the L-ornithine phenylacetate is in a dosage of about 2.0 g, about 2.5 g, about 3.0 g, about 3.5 g, about 4.0 g, about 4.5 g, about 5.0 g, about 5.5 g, about 6.0 g, about 6.5 g, about 7.0 g, about 7.5 g, about 8.0 g, about 8.5 g, about 9.0 g, about 9.5 g, or about 10.0 g, or in a dosage range defined by any of the two preceding values (for example, 5.0 g to 8.0 g). In some embodiments, the pharmaceutical formulation is in a single unit dosage form. In some other embodiments, the pharmaceutical formulation is in two or more unit dosage forms (i.e., a divided dose). In one

embodiment, the oral dosage is about 2.5 g. In another embodiment, the oral dosage is about 5 g.

[0043] Intravenous formulations may also generally include dosages of L-ornithine phenylacetate in the range of about 500 mg to about 50 g (preferably about 1 g to about 25 g, about 2.0 g to about 20 g, or about 2.5 g to about 10 g). In some embodiments, the intravenous formulation has a concentration of about 5 to about 300 mg/mL of L-ornithine phenylacetate (preferably about 25 to about 200 mg/mL, and more preferably about 40 to about 60 mg/mL).

[0044] The pharmaceutical composition may optionally be placed is sealed packaging. The sealed packaging may reduce or prevent moisture and/or ambient air from contacting the composition or medicament. In some embodiments, the packaging includes a hermetic seal. In some embodiments, the packaging sealed under vacuum or with an inert gas (*e.g.*, argon) within the sealed package. Accordingly, the packaging can inhibit or reduce the rate of degradation for the composition or medicament stored within the packaging. Various types of sealed packaging are known in the art. For example, U.S. Patent Number 5,560,490, is hereby incorporated by reference in its entirety, discloses an exemplary sealed package for medicaments.

[0045] The composition, in some embodiments, may further include a sufficiently low chloride content. As a non-limiting example, the chloride content of the composition comprising L-ornithine phenylacetate may be less than about 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, or 0.01%, by weight. In addition, the pharmaceutical composition can be free of silver ions, benzoic acid or salts thereof, or L-ornithine cyclization or dimerization side product.

Methods of Treatment

[0046] Some embodiments of the present disclosure relate to methods of treating or ameliorating hyperammonemia comprising orally administering to a subject in need thereof a pharmaceutical composition comprising an effective amount of L-ornithine phenylacetate as described herein. In some embodiments, the subject has acute liver failure or chronic liver diseases. In some embodiments, the subject has liver cirrhosis or liver decompensation. In some such embodiments, the chronic liver disease or liver cirrhosis has a classification of Child-Pugh class A, B or C. In some embodiments, the subject has hepatic encephalopathy. In still some embodiments, the subject has portal hypertension. In some embodiments, the subject has a urea cycle disorder.

[0047] In some embodiments, L-ornithine phenylacetate is administered in an amount from about 0.1 g to about 50 g per day, from about 0.5 g to about 45 g per day, from

about 1 g to about 40 g per day, from about 1.5 g to about 35 g per day, from about 2 g to about 30 g per day, from about 2.5 g to about 25 g per day, from about 3 g to about 20 g per day, or from about 5 g to about 15 g per day. In some embodiments, the pharmaceutical composition is for administration at least once a day. In some further embodiments, the pharmaceutical composition is for administration two or more times per day.

EXAMPLES

[0048] The following examples, including experiments and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present application.

Example 1: Large-scale Batch Process to Produce Crude L-Ornithine Phenylacetate

[0049] A first reactor was charged with 4.05 kg (61.38 moles) of KOH, which was dissolved in 10.4 L (10.4 kg) H_2O and stirred until a clear solution was formed. Subsequently, 9.00 kg (53.37 moles) of L-ornithine HCl was added to the KOH solution in two portions at about 15-25 °C to create a suspension. Subsequently, 45.0 L (35.5 kg) ethanol was added to the suspension at 15-25 °C, and stirred for approximately 15-20 minutes. The suspension was then cooled to about 0-5 °C and stirred at that temperature for at least 60 minutes, but no longer than 90 minutes. Separately, 8.72 kg (64.05 mol) of phenylacetic acid (PAA) was dissolved in 36.0 L (28.4 kg) of ethanol and stirred at 15-25 °C until full dissolution occurred in a second reactor. The cold suspension of the first reactor was filtered into the solution of PAA through depth filtration to remove the precipitated KCl, and the filter cake was washed with about 18.0 L (14.2 kg) of ethanol at 0-5 °C. The reaction mixture was stirred at 15-25 °C for about 15-30 minutes and a thick white suspension formed. The reaction mixture was concentrated in vacuo at 45-55 °C (azeotropic distillation) to reach a final volume of about 90 L, which was stirred for at least 2 hours at 15-25 °C. The suspension was filtered to obtain the crude L-ornithine phenylacetate, which was then washed with 36.0 L (28.4 kg) of ethanol, and dried *in vacuo* at approximately 50 °C for at least 12 hours. Yield: 88.4% (14.00 kg) calculated based on the assay data from chloride titration.

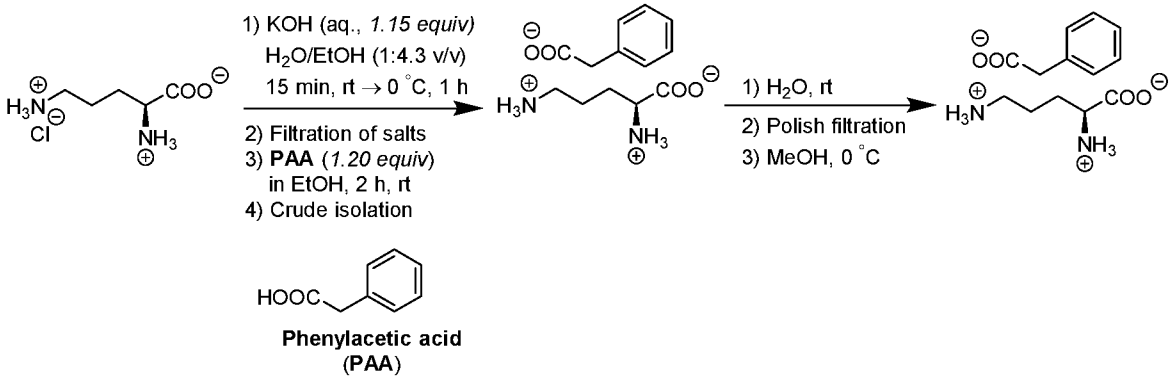
[0050] In this process, azeotropic distillation on scale performed poorly, giving approx. 10% H_2O in the mother liquor of the suspension after the first cycle. After the second distillation the mixture was stirred overnight. It was observed that the water level was relatively low and that significant precipitation of salts (shown by the high Cl^- level in filtered and dried product) had occurred during that time. Adjustment of the water level in the slurry by addition of extra water did not restore the desired chloride distribution in the system and the crude product

was isolated afterwards. It is presumed that the combination of the low water level (3% vs. 8%) and the longer stirring time (16 hours vs. 2 hours) was responsible for the precipitation of KCl. Surprisingly, the high salt content in the crude product did not affect its stoichiometry (determined by 1H-NMR in D_2O – 1.000:1.002 (PAA/L-ORN)). Laboratory experiments with material derived from IPC samples revealed that a reduction of the chloride level in the crude product by conventional recrystallization was not successful as the chloride content of the crude product was 4.57% by weight. Hence, the batch was not recrystallized on scale.

Example 2: Improved Large-scale Batch Process to Produce Crude L-Ornithine Phenylacetate

[0051] A first reactor (100 L) was charged with 4.05 kg (61.38 moles) of KOH, which was dissolved in 10.4 L (10.4 kg) H_2O and stirred until a clear solution was formed. Subsequently, 9.00 kg (53.37 moles) of L-ornithine HCl was added to the KOH solution in two portions at about 15-25 °C to create a suspension. Subsequently, 45.0 L (35.5 kg) ethanol was added to the suspension at 15-25 °C, and stirred for approximately 15-20 minutes. The suspension was then cooled to about 0-5 °C and stirred at that temperature for at least 60 minutes, but no longer than 90 minutes. Separately, 8.72 kg (64.05 mol) of phenylacetic acid (PAA) was dissolved in 36.0 L (28.4 kg) of ethanol and stirred at 15-25 °C until full dissolution occurred in a second reactor (450 L). The cold suspension of the first reactor was filtered into the solution of PAA through depth filtration to remove the precipitated KCl, and the filter cake was washed with about 36.0 L (28.4 kg) of ethanol at 0-5 °C. The reaction mixture was stirred for approximately 2 hours at 15-25 °C, and a thick, white suspension was formed. The suspension was isolated with a centrifuge to obtain the crude L-ornithine phenylacetate, which was then washed with 36.0 L (28.4 kg) of ethanol, and dried *in vacuo* at approximately 50 °C for at least 10 hours. Yield: 95.1% (13.62 kg); not corrected for assay. The crude L-ornithine phenylacetate contained about 1.28% by weight of chloride (Cl^-).

The process of Example 2 is illustrated in the scheme below:



Example 3: Recrystallization of L-Ornithine Phenylacetate

[0052] 13.12 kg (48.89 moles) of the crude L-ornithine phenylacetate of Example 2 was added followed by addition of 32.8 L (32.8 kg) of H_2O in a first container, and stirred for approximately 15-30 minutes at 15-25 °C until full dissolution. The resulting solution was then filtered through a particle filter (0.2 µm) into a second container. The particle filter was washed with 262.4 L (207.8 kg) methanol into the second container and a suspension forms. The suspension was cooled to 0-5 °C and stirred for approximately 60 minutes at 0-5 °C, but stirred no longer than 90 minutes. A crystalline solid (L-ornithine phenylacetate) precipitated after cooling. The precipitate was isolated by centrifuge and washed with 52.5 L (42.6 kg) of methanol. The final product was dried *in vacuo* at approximately 50 °C for at least 10 hours. The dried product was delumped via milling (sieve of 1.0 mm). Yield: 70.5% overall (9.72 kg) (74.1% yield for recrystallization only). The recrystallized L-ornithine phenylacetate contained about 0.08% by weight of chloride-(Cl^-).

WHAT IS CLAIMED IS:

1. A process of making L-ornithine phenylacetate, comprising:

intermixing L-ornithine hydrochloride and potassium hydroxide in a first solvent to form a first reaction mixture;

adding a second solvent to said first reaction mixture;

isolating potassium chloride from said first reaction mixture;

intermixing phenylacetic acid with said first reaction mixture to form a second reaction mixture; and

isolating a composition comprising L-ornithine phenylacetate from said second reaction mixture.

2. The process of claim 1, further comprising stirring said first reaction mixture.

3. The process of claim 1 or 2, further comprising cooling said first reaction mixture before isolating potassium chloride.

4. The process of claim 3, wherein said first reaction mixture is cooled to about 0 to 5 °C.

5. The process of any one of claims 1 to 4, wherein said first solvent is water.

6. The process of any one of claims 1 to 5, wherein said second solvent comprises an alcohol.

7. The process of claim 6, wherein said second solvent comprises ethanol.

8. The process of any one of claims 1 to 7, wherein the first reaction mixture after addition of the second solvent comprises about 1:1 (v/v) to 1:8 (v/v) H_2O to ethanol.

9. The process of any one of claims 1 to 8, wherein phenylacetic acid is dissolved in a third solvent before intermixing with said first reaction mixture.

10. The process of claim 9, wherein said third solvent comprises ethanol.

11. The process of any one of claims 1 to 10, wherein the molar ratio of potassium hydroxide to L-ornithine hydrochloride is at least about 1.1:1.

12. The process of any one of claims 1 to 11, wherein the molar ratio of phenylacetic acid to L-ornithine hydrochloride is at least about 1.2:1.

13. The process of any one of claims 1 to 12, wherein the chloride content of the composition comprising L-ornithine phenylacetate is less than about 2.5% by weight.

14. The process of claim 13, wherein the chloride content of the composition comprising L-ornithine phenylacetate is less than about 1.5% by weight.

15. The process of any one of claims 1 to 14, further comprising recrystallizing the composition comprising L-ornithine phenylacetate.

16. The process of claim 15, wherein the composition is recrystallized from a solvent mixture of water and methanol.

17. The process of claim 16, wherein the volume ratio of water and methanol used in the recrystallization is from about 1:1 to about 1:10.

18. The process of any one of claims 15 to 17, wherein the chloride content of the recrystallized composition is less than about 0.1% by weight.

19. The process of any one of claims 1 to 18, wherein said composition comprises less than about 5.0% L-ornithine cyclization or dimerization side products.

20. The process of claim 19, wherein said composition comprises less than about 1.0% L-ornithine cyclization or dimerization side products.

21. The process of any one of claims 1 to 20, wherein said composition is free of L-ornithine cyclization or dimerization side products.

22. A composition prepared according to the process of any one of claims 1 to 21.

23. A composition comprising L-ornithine phenylacetate, having a chloride content of less than about 1.5% by weight, wherein said composition is free of silver ion, benzoic acid or salts thereof.

24. The composition of claim 23, wherein the chloride content is less than about 0.1% by weight.

25. The composition of claim 23 or 24, comprising less than about 1.0% L-ornithine cyclization or dimerization side products.

26. The composition of claim 25, wherein said composition is free of L-ornithine cyclization or dimerization side products.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/031405

A. CLASSIFICATION OF SUBJECT MATTER

C07C 227/16 (2006.01) ***C07C 227/40 (2006.01)*** ***C07C 227/42 (2006.01)*** ***C07C 229/26 (2006.01)*** ***C07C 57/46 (2006.01)***

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)

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

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

STN: Chemical Abstracts Registry and CAplus – search using CAS RNs 952154-79-9, 3184-13-2, 20724-48-5, 6211-16-1, 103-82-2, 70-26-8, 616-07-9 and 348-66-3 (corresponding to L-ornithine phenylacetate, isomers of ornithine and phenylacetate and forms of L-ornithine hydrochloride);

STN: Casreact - search using CAS RN 952154-79-9 (L-ornithine phenylacetate);

Keyword search in Espacenet – ornithine phenylacetate in the title or abstract;

Espacenet and Patentscope: applicant and inventor search;

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] 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

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

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"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
1 August 2018	01 August 2018

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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2018/031405**
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X	WO 2010/115055 A1 (OCERA THERAPEUTICS, INC.) 07 October 2010 Paragraph [0090], [0096] and [0100], Scheme 4, Examples 1-6 and 12	1-26
X	CN 102993037 A (NANJING TECH UNIVERSITY) 27 March 2013 Examples 1-3, Claims 1-10.	22-26
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/031405**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/031405**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/031405**

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End of Annex

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