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(54) Title: FORMULATIONS OF L-ORNITHINE PHENYLACETATE

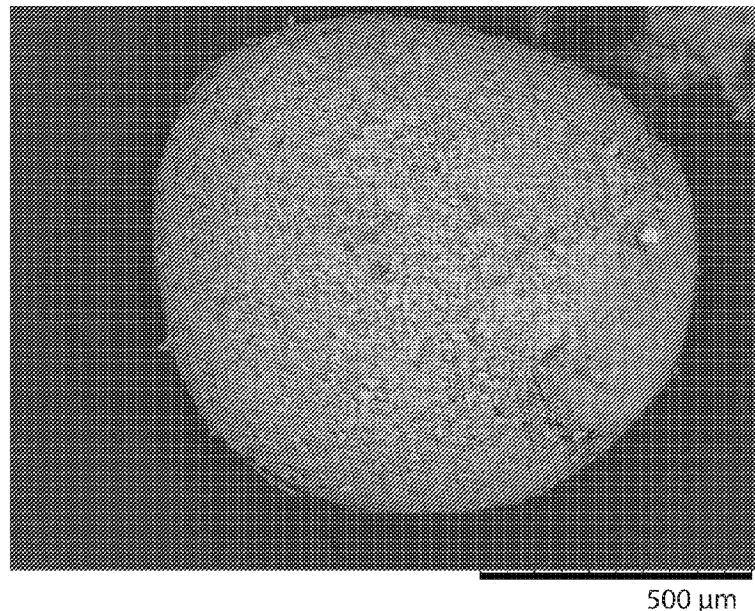


FIG. 1A

(57) Abstract: Some embodiments of the present application are directed to oral formulations of L-ornithine phenylacetate and methods of preparing the same. These oral formulations offer alternative administration route than the standard intravenous

[Continued on next page]

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## FORMULATIONS OF L-ORNITHINE PHENYLACETATE

### INCORPORATION BY REFERENCE TO PRIORITY APPLICATIONS

**[0001]** The present application claims the benefit of priority to U.S. Provisional Patent Application No. 62/150,238, filed April 20, 2015; U.S. Provisional Patent Application No. 62/150,676, filed April 21, 2015; U.S. Provisional Patent Application No. 62/211,619, filed August 28, 2015; U.S. Provisional Patent Application No. 62/255,300, filed November 13, 2015; and U.S. Provisional Patent Application No. 62/276,754, filed January 8, 2016; all which are hereby expressly incorporated by reference in their entireties.

### BACKGROUND

**[0002]** The present application relates to pharmaceutical compositions comprising oral formulations of L-ornithine phenylacetate and methods of administration and the use for treating hyperammonemia in patients having various acute and chronic liver diseases and disorders, for example, acute liver failure, liver cirrhosis, liver decompensation, portal hypertension, hepatic encephalopathy, or patients with urea cycle disorders.

**[0003]** Chronic liver disease is characterized by the gradual destruction of liver tissue over time, whereby healthy and regenerating liver tissue is slowly replaced with scar and necrotic tissue. This is known as liver cirrhosis. Normal liver function is impaired and the scar tissue progressively diminishes blood flow through the liver. As normal regenerating liver tissue is lost, nutrients, hormones, drugs and toxins are no longer effectively processed. This can result in symptoms including abnormal clearance of proteins absorbed through the intestinal tract, leading to accumulation of ammonia; abnormal excretion, leading to an accumulation of bilirubin in the blood, producing jaundice; increased sinusoidal pressure, leading to fluid accumulation in the abdomen (ascites); and portal hypertension (and portosystemic shunting) wherein scarred liver tissue acts as a barrier to blood flow, leading to increased portal blood pressure and oesophageal varices.

**[0004]** Patients with chronic liver disease can be in a fairly stable clinical state and exhibit few or no symptoms. However, such patients are at risk of an abrupt deterioration in their condition which can lead to acute-on-chronic liver failure. This transition from a “compensated” state, where the liver is able to function, albeit at a reduced level, to a “decompensated” state, where liver function fails, involves the effect of precipitating events.

Precipitating events associated with chronic liver disease include gastrointestinal bleeding, infection (sepsis), portal vein thrombosis and dehydration.

**[0005]** Hepatic encephalopathy (HE) is a common complication of decompensated cirrhosis; it has a significant negative effect on survival even after liver transplantation and is associated with irreversible impairment in cognitive function. An estimated 60–70% of cirrhotic subjects have at least subtle signs of neurocognitive impairment, and HE is the principal diagnosis in hospitalized subjects. Overt HE has a prevalence of approximately 30% in the cirrhotic population, and accounts for about 150,000 hospitalizations annually in the United States.

**[0006]** Hepatic encephalopathy (HE) is a complex neuropsychiatric disorder that occurs in diverse clinical situations such as acute or chronic liver disease and spontaneous portosystemic venous shunting. In the early stages of hepatic encephalopathy subtle mental changes occur such as poor concentration, confusion and disorientation. In severe cases, hepatic encephalopathy can lead to stupor, coma, brain swelling (cerebral edema) and death. In the case of patients who develop HE as a result of chronic liver disease, the onset of HE is often the result of a clinically precipitating event such as gastrointestinal bleeding, sepsis (infection), portal vein thrombosis or dehydration.

**[0007]** Gastrointestinal bleeding and portosystemic shunting allows toxic substances, which are usually metabolized by the liver, to bypass the liver, enter the systemic circulation and cross the blood-brain barrier to exert direct or indirect neurotoxic effects on the central nervous system. Ammonia accumulation is thought to play an important role in the progression of hepatic encephalopathy and multiorgan failure (respiratory failure, cardiovascular failure, kidney failure). In addition to ammonia, septicaemia (or bacterial peritonitis) which develops soon after a gastrointestinal bleed is also likely to be a contributing factor to hepatic encephalopathy.

**[0008]** Liver decompensation can then lead to multi-organ failure and hepatic encephalopathy. In the early stages of hepatic encephalopathy subtle mental changes such as poor concentration or the inability to construct simple objects occurs. In severe cases, hepatic encephalopathy can lead to stupor, coma, brain swelling and death.

**[0009]** Urea cycle disorder or urea cycle defect is a genetic disorder caused by a deficiency of one of the enzymes in the urea cycle which is responsible for removing ammonia from the blood stream. Normally, the urea is transferred into the urine and removed from the body. In urea cycle disorders, the nitrogen accumulates in the form of ammonia, a toxic substance, and is not removed from the body. It has been reported that sodium phenylbutyrate

may be used in the management of this condition. *See, for example, Batshaw, M. L. et al., "Alternative pathway therapy for urea cycle disorders: twenty years later," J. Pediatr. (2001) 138 (1 Suppl): S46-S55.*

**[0010]** A common therapy for patients with hepatic encephalopathy involves strategies to reduce the concentration of ammonia. These include restriction of dietary protein intake; administration of lactulose, neomycin, L-ornithine L-aspartate (LOLA), or sodium benzoate; and cleansing enemas. There are currently marketed products that contain phenylacetic acid (e.g., AMMONUL®) or prodrugs of phenylacetic acid, e.g., phenylbutyrate (BUPHENYL®) or glycerol phenylbutyrate (RAVICTI®) as the ammonia scavenger (binding agent) for the treatment of hyperammonemia due to urea cycle disorder (UCDs). RAVICTI® has also been evaluated in clinical trials and shown preliminary efficacy for the treatment of hepatic encephalopathy. *See, for example, Rockey D. et al., "Randomized, Double-Blind, Controlled Study of Glycerol Phenylbutyrate in Hepatic Encephalopathy," Hepatology, 2014, 59(3):1073-1083.* In addition, L-ornithine phenylacetate has been reported to be an effective treatment of hyperammonemia and hepatic encephalopathy. Jalan *et al.*, reported a clinical study where the data showed that L-ornithine phenylacetate is useful in ammonia lowering. *See Jalan et al., "L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy," Med Hypotheses 2007; 69(5):1064-69.* *See also, U.S. Publication Nos. 2008/0119554, 2010/0280119, and 2013/0211135, each of such is hereby incorporated by reference in its entirety.*

**[0011]** Currently, L-ornithine phenylacetate is under a double-blind placebo-controlled Phase 2b clinical trial for the treatment of acute hepatic encephalopathy. The Interim analysis suggested a promising treatment effect with L-ornithine phenylacetate and a reduction in time to recovery for patients with acute hepatic encephalopathy. *See April 1, 2015 Ocera Therapeutics, Inc. Press Release.*

**[0012]** Typically, L-ornithine phenylacetate has excellent solubility in water or aqueous solution. In all the known clinical studies of L-ornithine phenylacetate for treating acute or chronic liver diseases, L-ornithine phenylacetate is administered by intravenous infusion over a period of time, for example, from 1 day or up to five days in human studies. There exists a need to develop alternative administration routes to improve patient convenience.

## SUMMARY

**[0013]** The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

**[0014]** Some embodiments of the present application relate to oral pharmaceutical formulations, comprising L-ornithine phenylacetate at an oral dosage of about 2.0 g to about 10.0 g, and one or more pharmaceutically acceptable excipients or carriers. In some embodiments, the formulation provides an immediate release profile of L-ornithine phenylacetate upon oral administration. In some embodiment, the oral dosage of L-ornithine phenylacetate is from about 5.0 g to about 8.0 g.

**[0015]** Some embodiments of the present application relate to oral pharmaceutical formulations comprising an effective amount of L-ornithine phenylacetate, and one or more pharmaceutically acceptable excipients or carriers, wherein upon oral administration, the formulation has a controlled release profile of L-ornithine and phenylacetate. In some embodiments, the oral pharmaceutical formulation comprises a core and one or more controlled release coating layers on the core, where the core comprises L-ornithine phenylacetate and the controlled release coating layers comprise one or more polymers.

**[0016]** Some embodiments of the present application relate to methods of treating hyperammonemia comprising administering to a subject in need thereof an oral pharmaceutical formulation comprising L-ornithine phenylacetate. In some embodiments, the oral pharmaceutical formulation of L-ornithine phenylacetate provides a controlled release of L-ornithine phenylacetate after administration. In some other embodiments, the oral pharmaceutical formulation of L-ornithine phenylacetate provides an immediate release of L-ornithine phenylacetate after administration. 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 embodiments, the subject has hepatic encephalopathy. In still some embodiments, the subject has portal hypertension.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** **FIGs. 1A and 1B** are microscopic images of a particle of the controlled-release oral pharmaceutical formulation of L-ornithine phenylacetate with smooth, spherical and consistent coating produced by the extrusion spheronization process.

**[0018]** **FIG. 2** is a line chart depicting the *in vitro* dissolution profile of phenylacetate for various coated extrudates.

**[0019]** **FIG. 3** is a bar chart depicting the *in vivo* pharmacokinetic profiles of L-ornithine (ORN), phenylacetate metabolites phenylacetic acid (PAA) and phenylacetylglutamine (PAGN) after oral administration of controlled-release L-ornithine phenylacetate of Formulations 3, 5 and 6 and an immediate-release L-ornithine phenylacetate solution.

[0020] **FIG. 4** is a line chart depicting the *in vivo* pharmacokinetic profiles of phenylacetic acid (PAA) in beagle dogs after oral administration of controlled-release L-ornithine phenylacetate of Formulations 3, 5 and 6 and an immediate-release L-ornithine phenylacetate solution.

[0021] **FIG. 5** is a line chart depicting the *in vivo* surrogate pharmacodynamic profiles of phenylacetylglutamine (PAGN) in beagle dogs after oral administration of controlled-release L-ornithine phenylacetate of Formulations 3, 5 and 6 and an immediate-release L-ornithine phenylacetate solution.

[0022] **FIG. 6A** is a line chart depicting the comparison of *in vitro* dissolution profile of Formulation D with Formulation A using USP Apparatus 2 Paddle Method.

[0023] **FIG. 6B** is a line chart depicting the comparison of *in vitro* dissolution profile of Formulation E with Formulation C using USP Apparatus 2 Paddle Method

[0024] **FIGs. 7A** and **7B** are Scanning Electron Micrographs (SEM) images of the small pellets of Formulation D. **FIGs. 7C** and **7D** are Scanning Electron Micrographs (SEM) images of the small pellets of Formulation E.

[0025] **FIG. 8** is a line chart depicting the *in vivo* plasma pharmacokinetic profiles of phenylacetic acid (PAA) in humans after administration of controlled-release Formulations A, B, and C, RAVICTI®, and an immediate-release oral formulation of L-ornithine phenylacetate.

[0026] **FIG. 9** is a line chart depicting the *in vivo* surrogate plasma pharmacodynamic profiles of phenylacetylglutamine (PAGN) in humans after administration of controlled-release Formulations A, B, and C, RAVICTI®, and an immediate-release oral formulation of L-ornithine phenylacetate.

#### DETAILED DESCRIPTION OF THE EMBODIMENTS

[0027] Some embodiments of the present application are directed to oral formulations of L-ornithine phenylacetate. Some embodiments, provide a low dose formulation, using much lower doses of equivalent phenylacetate as compared to RAVICTI®. Some such embodiments are an immediate release formulation. Other embodiments provide a multi-particulate controlled release system. This system provides less variability in GI transit time and release profile. It also minimizes effects on high local drug concentrations as the drug load is more dispersed. Additional advantages of the multi-particulate controlled release system include dose flexibility, and the ease to administer high doses or loadings of L-ornithine phenylacetate.

Low Dose Formulations

**[0028]** Some embodiments of the present application relate to pharmaceutical formulations, comprising L-ornithine phenylacetate at an dosage of about 2.0 g to about 10.0 g, and one or more pharmaceutically acceptable excipients or carriers. In some embodiments, the formulation provides an immediate release profile of L-ornithine phenylacetate upon administration (for example, an IV formulation or an immediate-release oral formulation in the form of a liquid solution). Other embodiments provide a controlled-release profile, such as by using the controlled release oral formulation described below. 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). For example, where an oral dosage is about 5.0 g, it may be provided in the form of four or five tablets, each containing about 1.25 g or 1.0 g of L-ornithine phenylacetate. In some embodiments, the unit dosage form is a tablet, a capsule, a pill, pellets, free-flowing powder, or liquid. In some embodiments, the formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, or greater than about 90%. In some further embodiments, the formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 80%.

**[0029]** The low dose pharmaceutical formulations described herein may be administered by any suitable route, for example, it may be administered by oral, intravenous, intragastric, intraperitoneal or intravasular routes. In a preferred embodiment, the pharmaceutical formulation of L-ornithine is an oral dosage form. In another embodiment, the pharmaceutical formulation is an intravenous dosage form.

Controlled Release Formulations

**[0030]** Some embodiments of the present application relate to oral pharmaceutical formulations comprising an effective amount of L-ornithine phenylacetate, and one or more pharmaceutically acceptable excipients or carriers, wherein upon oral administration, the formulation has a controlled release profile of L-ornithine and phenylacetate. In some embodiments, the oral pharmaceutical formulation comprises a core and one or more coating

layers on the core, where the core comprises L-ornithine phenylacetate and the coating layer comprises one or more polymers.

**[0031]** In some embodiments, the polymer is selected from alkyl cellulose, hydroxyalkyl cellulose, carboxyalkyl cellulose, alkylvinyl polymers, acrylic acid polymers or copolymers, acrylate polymers or copolymers, or natural or synthetic gums. In some such embodiments, the polymer is an alkyl cellulose, for example, methyl cellulose or ethyl cellulose. In one embodiment, the polymer is ethyl cellulose. In some other embodiments, the polymer is selected from acrylic acid polymers or copolymers, for example, the Eudragit® polymers. In one embodiment, the Eudragit® polymer is Eudragit® NM 30 D, which is a neutral copolymer of ethyl acrylate and methyl methacrylate.

**[0032]** In some embodiments, the controlled release oral pharmaceutical formulation of L-ornithine phenylacetate is in the form of a tablet, a capsule, a pill, pellets or free-flowing powder. In some further embodiments, L-ornithine phenylacetate is in the form of pellets. The average size of the pellets are between about 100  $\mu\text{m}$  to about 1000  $\mu\text{m}$  in diameter, preferably between about 200  $\mu\text{m}$  to about 900  $\mu\text{m}$ , more preferably between about 200  $\mu\text{m}$  to about 800  $\mu\text{m}$ . In one embodiment, the average size of the pellets is between about 200  $\mu\text{m}$  to about 600  $\mu\text{m}$  in diameter. In one embodiment, the average size of the pellets is between about 200  $\mu\text{m}$  to about 400  $\mu\text{m}$  in diameter. In another embodiment, the average size of the pellets is between about 300  $\mu\text{m}$  to about 600  $\mu\text{m}$  in diameter. In yet another embodiment, the average size of the pellets is between about 500  $\mu\text{m}$  to about 800  $\mu\text{m}$  in diameter. In some embodiments, the pellets or free-flowing powder are provided in a sachet. In some embodiments, the controlled release pharmaceutical formulation is in a single unit dosage form. In some other embodiments, the controlled release pharmaceutical formulation is in two or more unit dosage forms.

**[0033]** In some embodiments, the controlled release oral pharmaceutical formulation comprises about 0.1 g to about 25.0 g L-ornithine phenylacetate. In some further embodiments, the formulation comprises about 1.0 g to about 20.0 g L-ornithine phenylacetate. In some further embodiments, the formulation comprises about 2.0 g to about 15.0 g L-ornithine phenylacetate. In still some further embodiments, the formulation comprises about 4.0 g to about 10.0 g L-ornithine phenylacetate. In still some further embodiments, the formulation comprises about 5.0 g to about 8.0 g L-ornithine phenylacetate. In one embodiment, the formulation comprises about 20.0 g L-ornithine phenylacetate. In one embodiment, the formulation comprises about 15.0 g L-ornithine phenylacetate. In one embodiment, the formulation comprises about 10 g L-ornithine phenylacetate.

**[0034]** The oral pharmaceutical formulation described herein provides a controlled release profile of L-ornithine phenylacetate. In some embodiments, L-ornithine phenylacetate has an *in vitro* dissolution profile as measured by USP Apparatus 2 Paddle Method of between about 5% and about 30% L-ornithine phenylacetate release in 2 hours. In some embodiments, L-ornithine phenylacetate has an *in vitro* dissolution profile as measured by USP Apparatus 2 Paddle Method of between about 15% and about 80% L-ornithine phenylacetate release in 4 hours. In some further embodiments, L-ornithine phenylacetate has an *in vitro* dissolution profile as measured by USP Apparatus 2 Paddle Method of between about 50% and about 95% of L-ornithine phenylacetate release in 6 hours.

**[0035]** In some embodiments, the controlled-release formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, or greater than about 90%. In some further embodiments, the controlled-release formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 80%.

#### Methods of Treatment

**[0036]** Some embodiments of the present application relate to methods of treating hyperammonemia comprising orally administering to a subject in need thereof a pharmaceutical formulation comprising an effective amount of L-ornithine phenylacetate. 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 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.

**[0037]** In some embodiments, L-ornithine phenylacetate is administered in a dose ranging from about 10 mg/kg to about 1000 mg/kg, from about 20 mg/kg to about 900 mg/kg, from about 30 mg/kg to about 800 mg/kg, from about 40 mg/kg to about 700 mg/kg, or from about 50 mg/kg to about 600 mg/kg. In some further embodiments, L-ornithine phenylacetate is administered in a dose ranging from about 50 mg/kg to about 500 mg/kg. In still some further embodiments, L-ornithine phenylacetate is administered in a dose ranging from about 100 mg/kg to about 250 mg/kg. In one embodiment, L-ornithine phenylacetate is administered in a dose of about 50 mg/kg. In another embodiment, L-ornithine phenylacetate is administered in a dose of about 200 mg/kg.

**[0038]** In some embodiments, L-ornithine phenylacetate is administered in an amount from about 0.1 g to about 50.0 g per day, from about 1.0 g to about 40.0 g per day, from about 5.0 g to about 30.0 g per day, from about 10.0 g to about 25.0 g per day, or from about 15.0 g to about 25.0 g per day. In some embodiments, the pharmaceutical formulation is for administration at least once a day. In some further embodiments, the pharmaceutical formulation is for administration 2 or 3 times a day. In one embodiment, the formulation is for thrice daily oral administration.

**[0039]** In some embodiments, L-ornithine phenylacetate is administered as a single dose in an amount from about 2.0 g to about 10.0 g. In some further embodiments, L-ornithine phenylacetate is administered as a single dose in an amount from about 5.0 g to about 8.0 g. In some such embodiments, the pharmaceutical formulation containing such amount of L-ornithine phenylacetate is in two or more unit dosage forms. For example, some embodiments comprise administering 3 to 6 unit dosage forms each comprising from about 0.75 g to about 2.0 g of L-ornithine phenylacetate, or about 3 to 5 unit dosage forms each comprising from about 1.0 g to about 1.5 g of L-ornithine phenylacetate. Some embodiments comprise administering 4 unit dosage forms each comprising about 1.25 g of L-ornithine phenylacetate. Some embodiments comprise administering 5 unit dosage forms each comprising about 1.0 g of L-ornithine phenylacetate. In one embodiment, the pharmaceutical formulation is administered three times a day. For example, where multiple unit dosage forms are administered at a time, the multiple unit dosage administration is repeated three time a day.

**[0040]** In some embodiments, the plasma Cmax of L-ornithine is from about 10 mg/L to about 60 mg/L, from about 12 mg/L to about 50 mg/L, or from about 15 mg/L to about 40 mg/L. In some further embodiments, the plasma Cmax of L-ornithine is from about 18.0 mg/L to about 35.0 mg/L.

**[0041]** In some embodiments, the plasma Cmax of metabolite phenylacetic acid ranges from about 15 mg/L to about 120 mg/L. In some such embodiments, the plasma Cmax of metabolite phenylacetic acid is from about 15 mg/L to about 55 mg/L. In some such embodiments, the plasma Cmax of metabolite phenylacetic acid is from about 20 mg/L to about 100 mg/L. In some such embodiments, the plasma Cmax of metabolite phenylacetic acid is from about 40 mg/L to about 90 mg/L. In some further embodiments, the plasma Cmax of metabolite phenylacetic acid is from about 50 mg/L to about 90 mg/L.

**[0042]** In some embodiments, the plasma Cmax of metabolite phenylacetylglutamine ranges from about 15 mg/L to about 75 mg/L. In some such embodiments, the plasma Cmax of metabolite phenylacetylglutamine is from about 15 mg/L to about 35 mg/L. In some such

embodiments, the plasma Cmax of metabolite phenylacetylglutamine is from about 20 mg/L to about 60 mg/L. In some such embodiments, the plasma Cmax of metabolite phenylacetylglutamine is from about 25 mg/L to about 50 mg/L. In some further embodiments, the plasma Cmax of metabolite phenylacetylglutamine is from about 30 mg/L to about 45 mg/L.

**[0043]** In some embodiments, the pharmaceutical formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, or greater than about 90%. In some further embodiments, the pharmaceutical formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 80%.

### Definitions

**[0044]** 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.

**[0045]** As used herein, common organic abbreviations are defined as follows:

AUC              Area under the curve

AUC<sub>0→t</sub>              Area under the concentration *vs.* time curve from time = 0 (zero) to time of last quantifiable concentration

AUC<sub>0→∞</sub>              Area under the plasma concentration with time curve extrapolated to infinite time

C<sub>12</sub>              Drug concentration at 12 hr after drug administration

CL              Coat Level

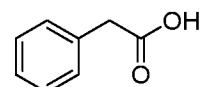
Cmax              Maximum plasma concentration

HPMC	Hydroxypropylmethylcellulose
hr	Hour(s)
IR	Immediate release
MCC	Microcrystalline cellulose
ORN	Ornithine
PAA	Phenylacetic acid (or the conjugate base phenylacetate)
PAGN	Phenylacetylglutamine
PD	Pharmacodynamic
PK	Pharmacokinetic
SEM	Scanning Electron Micrographs

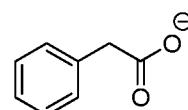
**[0046]** The term “immediate release” as used herein, has its ordinary meaning as understood by those skilled in the art and thus includes, by way of non-limiting example, release of a drug from a dosage form in a relatively brief period of time after administration.

**[0047]** 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.

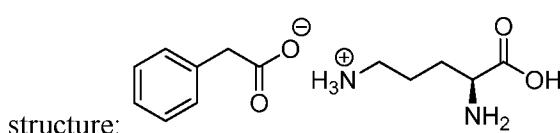
**[0048]** The term “phenylacetic acid” as used herein, is also known as benzeneacetic acid or 2-phenylacetic acid). It has the following chemical structure:



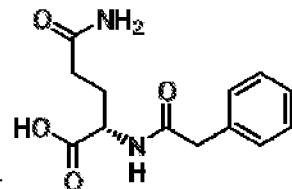
**[0049]** The term “phenylacetate” as used herein, refers to the anionic form of phenylacetic acid with the following chemical structure:



**[0050]** 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:



**[0051]** The term “phenylacetylglutamine” as used herein, refers to the product formed by the conjugation of phenylacetic acid and glutamine. It is a common metabolite that



can be found in human urine. It has the following chemical structure:

**[0052]** The term “percentage of coat level” as used herein, refers to the weight percentage of a particle coating in the total mass of the finished particle. For example, 15% CL extrudate means the coating of the particle constitutes about 15% by weight of the total mass of the finished particle.

**[0053]** As used herein, the term “percent conversion of phenylacetate to phenylacetylglutamine over 24 hours” refers to the mass percent of phenylacetate administered to a patient that is converted to phenylacetylglutamine collected over 24 hours in the urine.

**[0054]** 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.

**[0055]** 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 bases 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).

**[0056]** “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.

**[0057]** “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 liver disease, whereby the treatment reduces the likelihood that the patient will develop a liver disease. The term “therapeutic treatment” refers to administering treatment to a patient already suffering from a liver disease.

**[0058]** The compositions or formulations described herein are preferably provided in unit dosage form. As used herein, a “unit dosage form” is a composition/formulation containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single administration, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy, or that the unit dosage form contains all of the dose to be administered at a single time. Such dosage forms are contemplated to be administered once, twice, thrice or more per day, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. In addition, multiple unit dosage forms may be administered at substantially the same time to achieve the full dose intended (e.g., two or more tablets may be swallowed by the patient to achieve a complete dose). The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of

therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

#### Methods of Manufacturing

**[0059]** The key challenges in the development of the oral formulation of L-ornithine phenylacetate include the high dose of the API (for example, about 20 g/day); the high API solubility; the short API half-life (for example, phenylacetic acid has a short half-life of about 90 minutes); the taste/odor masking, the palatability and alcohol resistance. In particular, the high solubility of L-ornithine phenylacetate renders the controlled release formulation very challenging due to the fast dissolution of the API. Extreme high osmotic pressures build up inside the coating and can rupture the coating membrane if it is not strong enough to withstand the forces.

**[0060]** As discussed herein, embodiments of the present application relates to the use of a multi-particulate controlled release oral formulation system to address some or all of the key challenges. The system comprises a core and one or more coating layers on the core.

#### Core Composition and Processes

**[0061]** The core comprises the API - L-ornithine phenylacetate and one or more excipients. In some embodiments, L-ornithine phenylacetate is mixed with the core excipient(s) to form granules. In some other embodiments, L-ornithine phenylacetate is applied to an inert core (consists of excipients only) as a layer, for example, by spray layering. In some other embodiments, L-ornithine phenylacetate is combined with ion exchange resins in particle form.

**[0062]** The granulation process includes the step of combining L-ornithine phenylacetate with excipients in fluid bed or high-shear granulator. This process yields rough, porous, irregular-shaped particles. The use of Glatt specialty granulation technology offers an improvement to the standard granulation process, resulting in the formation of uniform spherical granules with a high drug load.

**[0063]** Alternatively, an extrusion spheronization process can be used, including the steps of combining L-ornithine phenylacetate and excipients to make plastic dough, extruding, spheronizing the extrudate. This process results in the yield of somewhat spherical particles.

**[0064]** The spray layering process includes the step of building up a layer of L-ornithine phenylacetate on an inert spherical core via fluid bed coating operation. This process yields spherical particles. In some embodiments, L-ornithine phenylacetate is first dissolved in a solvent optionally comprising a hydrophilic polymer to form L-ornithine phenylacetate coating solution. Then, such coating solution is sprayed on an inert core. Non-limiting examples of

hydrophilic polymers includes compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums. In one embodiment, the hydrophilic polymer is hydroxypropylmethylcellulose (HPMC). Non-limiting examples of the inert core described herein includes microcrystalline cellulose spheres such as Celphere™ from Asahi-Kasei and sugar/starch spheres such as SUGLETS® from Colorcon.

**[0065]** The melt-spray-congeal process includes the step of embedding L-ornithine phenylacetate in a molten waxy matrix; spraying and cooling to yield the spherical particles.

**[0066]** In some embodiments, the granules produced by the standard granulation process may not be an adequate substrate for coating. Particles produced by granulation are inherently porous, irregularly shaped particles with a rough surface. In these cases, processes such as spray layering and extrusion spheroidization may be used to provide more uniform core granules. *See FIGs. 1A and 1B.* FIG. 1B shows that the final particle with a coating thickness between 122  $\mu\text{m}$  and 126  $\mu\text{m}$ .

**[0067]** **FIG. 2** illustrates the dissolution profile of phenylacetate of the various coated ethyl cellulose extrudates. Specifically, “% l.c.” refers to percent label claim. It is the percentage of the total dose that is dissolved at a given time in the dissolution vessel. The dissolution test was carried out as described in the USP, General Chapter 711, using Apparatus 2 Paddle Method. **FIG. 2** shows the dissolution profiles of four different coated extrudates with different percentage of coat level (CL) – 15% CL, 25% CL, 30% CL and 35% CL extrudate. The dissolution profiles suggest that the higher the percentage of coating used, the slower the release rate is. These *in vitro* data suggest that the BID dosing profile is feasible.

#### Coating Composition and Processes

**[0068]** As discussed herein, the multi-particulate controlled release oral formulation system comprises one or more coating layers on the core. In some embodiments, the coating composition comprises a cellulose derivative, for example, ethyl cellulose to provide controlled-release. Alternatively, polymethacrylates (Eudragits) can also be used either in dispersions or solvent based. Other polymers may be used in the present application include, but not limited to alkyl cellulose, hydroxyalkyl cellulose, carboxyalkyl cellulose, cellulose acetate, alkylvinyl polymers, acrylic acid polymers or copolymers, polyvinyl pyrrolidine, polyvinyl acetate, polymethacrylate, natural or synthetic gums.

**[0069]** In some embodiments, aqueous-based coating formulation may be problematic. Because of the high water solubility of L-ornithine causes the API to dissolve in

the coating during the coating process, effectively increasing the coating porosity. A solvent-based coating is a good alternative approach.

**[0070]** The coating layer can be applied to the core via various processes. The fluid bed coating process includes the step of recirculating particles in streams of air; spraying coating agent onto particles to gradually build up the coating. The spray step can be performed via top-spray, bottom-spray, tangential spray, etc. Alternatively, the coating layer can be applied on the core via Wurster coating process. The Wurster coating process is a variant of bottom-spray fluid bed coating and is widely used in pharmaceutical applications.

**[0071]** In some embodiments, two or more coating layers may be used. The multi coating layers may include a seal coating, a control coating, and/or an enteric coating. The additional coating may add or augment the product properties, for example, improving alcohol resistance. For example, the enteric coating may comprise, for example, acrylic and methacrylic acids polymers (Eudragit®) or copolymer or cellulose derivatives, such as cellulose acetophthalate.

**[0072]** Other factors that may affect final product properties include, but not limited to coating thickness, plasticizer type and concentration, pore former or other additives and process variables (spray rate, drying time, temperatures, etc.). In some embodiments, the average coating thickness is from about 10  $\mu\text{m}$  to about 500  $\mu\text{m}$ , from about 25  $\mu\text{m}$  to about 250  $\mu\text{m}$ , or from about 50  $\mu\text{m}$  to about 125  $\mu\text{m}$ .

**[0073]** In some embodiments, the controlled release oral formulation may be prepared by combining L-ornithine phenylacetate particles with different coatings. This facilitates the adjustment of the pharmacokinetics profile of the final controlled release formulation to achieve the desired sustainable exposure.

**[0074]** Some examples of substances that can serve as pharmaceutically-acceptable carriers or excipients thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

**[0075]** Non-limiting examples of oral formulation tablet excipients or carriers comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above.

**[0076]** In some embodiments, the oral formulation can also be in the form of pellets or free-flow powders. In particular, the pellets or free-flow powder can be further packed into sachets for oral administration. In some embodiments, the pellets or free-flow powder can be administered in conjunction with food and/or beverage in order to improve patient compliance and tolerability. For example, the pellets or powder in the sachet can be mixed with a beverage such as juice or water to form a suspension. Alternatively, the pellets or powder in the sachet can be mixed with food. Preferably, the size of particles is not too granular such that it is undesirable to be administered orally. The palatable oral sachet formulation may also comprise conventional pharmaceutical compatible adjuvants, excipients or carriers, including those commonly used in the oral tablet formulation as discussed herein.

**[0077]** In some embodiments, the oral formulation described herein provides for lower doses than previously expected. For example, RAVICTI® (glycerol phenylbutyrate, a pre-prodrug of phenylacetate) was found in clinical studies at a dose of 6 mL (delivering about 1.02 g/mL of phenylbutyrate) twice daily to lower the incidence of hepatic encephalopathy events. Both the immediate release and the controlled release oral pharmaceutical formulations of L-ornithine phenylacetate described herein provide similar percentage of PAGN urinary excretion, permitting use of substantially lower API doses, compared to RAVICTI® or other phenylacetate formulations.

## EXAMPLES

**[0078]** 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 - Preparation of Coated Controlled Release Formulations

**[0079]** Three controlled release oral pharmaceutical formulations of L-ornithine phenylacetate (Formulations 3, 5 and 6) were prepared. Formulations 3 and 6 comprise sugar spheres (“Suglets”) onto which a mixture of L-ornithine phenylacetate and hydroxypropylmethylcellulose (HPMC) in aqueous solution has been spray-layered up to an approximate weight percentage of 35%. After drying, these spray-layered beads or pellets were further coated using a solution of ethyl cellulose (“ETHOCEL™”) dissolved in organic solvents. By adjusting the amount of ethyl cellulose coating applied, the release properties of the pellets may be adjusted to yield the desired release profile. This profile may be measured *in vitro*, such as by the dissolution results, and also may be assessed by *in vivo* techniques in which the pharmacokinetic profile of the drug in plasma (or other biological locations, such as urine) is assessed. Formulation 3 is described as a 25% coat level bead, and Formulation 6 as a 15% coat level bead. The excipient talc may also be added to the ethyl cellulose.

**[0080]** The preparation of Formulation 5 began in a similar fashion to Formulations 3 and 6, except that instead of an ethyl cellulose coating, a coating comprised of Eudragit NM 30 D was applied using an aqueous dispersion of the NM 30 D polymer. Eudragit NM 30 D is a neutral copolymer based on ethyl acrylate and methyl methacrylate. The amount of coating was approximately 70% weight gain over the original weight of the drug-layered bead. In addition to the Eudragit polymer, talc was used in the coating dispersion to yield a product with suitable properties.

Example 2 – Pharmacokinetic Studies in Dogs

**[0081]** A pharmacokinetic study of the controlled-release oral formulations of L-ornithine phenylacetate was conducted in dogs. 6 dogs in two sets of three were used in the study. The controlled-release formulations (Formulations 3, 5 and 6 as described in Example 1) were administered orally at a dose of 200 mg/kg. An immediate release formulation of L-ornithine phenylacetate in water was administered orally at the dose of 50 mg/kg. The AUC and plasma Cmax of analyte L-ornithine and phenylacetate metabolites phenylacetylglutamine (PAGN) and phenylacetic acid (PAA) are illustrated in **FIG. 3**. All the controlled-release formulations produced comparable PAGN and ORN pharmacokinetics and the ratio of plasma Cmax to AUC is equal for the controlled release formulations with respect to PAA and PAGN.

**[0082]** *In vivo* PK data of metabolite PAA and *in vivo* surrogate PD data of metabolite PAGN in animal models were collected and demonstrated in **FIGs. 4 and 5** where the three controlled-release formulations (Formulations 3, 5 and 6) were administered at a dose of

200 mg/kg and two immediate-release formulations were administered at the dose of 50 mg/kg and 200 mg/kg respectively.

Example 3 - Preparation of Large Pellets of Coated Controlled Release Formulations

**[0083]** Three controlled release oral pharmaceutical formulations of L-ornithine phenylacetate (Formulations A, B and C) were prepared following similar procedure described in Example 1. Sugar spheres with an average diameter between 500 and 600  $\mu\text{m}$  were used as core. Then, a mixture of L-ornithine phenylacetate and hydroxypropylmethylcellulose (HPMC) in aqueous solution has been spray-layered onto the sugar spheres. In each case, the excipient talc was also used in forming the layered core pellets.

**[0084]** After drying, these layered core pellets were further coated with an extended release polymer selected from ethyl cellulose or Eudragit NM 30 D. The components of Formulations A, B, and C are summarized in Table 1 below. The final pellets in Formulations A, B, and C contain 15%, 30% or about 41% extended release coating respectively, relative to the total weight of the pellets. The average diameter of the final large pellets is between about 650  $\mu\text{m}$  and 950  $\mu\text{m}$ , for example, about 800  $\mu\text{m}$ .

**Table 1.**

Component	Quantity (g/dose)		
	Formulation A	Formulation B	Formulation C
<b>Drug Layered Core Pellets (g)</b>			
L-ornithine phenylacetate	10.00	10.00	10.00
Sugar Spheres (500-600 $\mu\text{m}$ )	17.57	17.57	17.57
Talc	0.50	0.50	0.50
Hydroxypropylmethylcellulose	0.50	0.50	0.50
Total (Dry weight) Core Pellets	28.57	28.57	28.57
<b>Extended Release Coating (g)</b>			
Ethyl cellulose	4.54	11.02	NA
Dibutyl Sebacate	0.50	1.22	NA
Eudragit NM 30D	NA	NA	11.42
Talc	NA	NA	8.57
Total Dry Weight per Unit Dose	33.6	40.8	48.6

Example 4 - Preparation of Small Pellets of Coated Controlled Release Formulations

**[0085]** A large scale preparation of two controlled release oral pharmaceutical formulations of L-ornithine phenylacetate (Formulations D and E) were carried out, following similar procedures described in Example 1. First, a HPMC solution was prepared by dissolving 0.765 kg HPMC in 27.4 kg water. Then, 15.2 kg L-ornithine phenylacetate was dissolved in this

HPMC aqueous solution. 0.765 kg Talc was then suspended into this mixture. The resulting L-ornithine phenylacetate coating suspension was sprayed onto 5 kg microcrystalline cellulose spheres with the average diameter between 100  $\mu\text{m}$  and 200  $\mu\text{m}$  using a fluid bed coating process to form the core pellets. The final core pellets comprises about 70% w/w of L-ornithine phenylacetate. Interestingly, during the spraying process, it was observed that a crystalline form of L-ornithine phenylacetate was precipitating out of the L-ornithine phenylacetate coating suspension. The crystalline structure of the precipitate was determined by X-Ray Powder Diffraction (XRPD) analysis and the result confirmed it was Form II, previously reported in PCT Pub. No. WO2010/115055 A1.

**[0086]** To prepare Formulation D, ethyl cellulose coating was applied to a polymer weight gain of 80% w/w. For example, if the core pellets for a batch weighed 1000 g, 800 g of ethyl cellulose would be sprayed onto the core pellets. To prepare Formulation E, Eudragit NM 30 D coating was applied to a polymer weight gain of 185% w/w. For example, if the core pellets for a batch weighed 1000 g, 1850 g of Eudragit NM 30 D would be sprayed onto the core pellets. Two batches of Formulation D smaller pellets were prepared.

**[0087]** The components of Formulations D and E are summarized in Table 2 below. The average diameter of the final small pellets is between about 300  $\mu\text{m}$  and about 600  $\mu\text{m}$ , for example, between about 300  $\mu\text{m}$  and about 425  $\mu\text{m}$  for pellets of Formulation D and between 425  $\mu\text{m}$  and about 500  $\mu\text{m}$  for pellets of Formulation E.

<b>Table 2.</b>		
Component	Formulation D	Formulation E
<b>Core Pellet (g)</b>		
L-Ornithine Phenylacetate	10	10
Microcrystalline Cellulose Spheres (Celphene CP102, 100-200 $\mu\text{m}$ )	3.3	3.3
Talc	0.5	0.5
Hydroxypropyl Methylcellulose (E5)	0.5	0.5
Total (Dry weight) Core Pellets	14.3 g	14.3 g
<b>Extended Release Pellets (g)</b>		
Ethyl cellulose (80% polymer weight gain)	11.4	NA
Dibutyl Sebacate	1.3	NA
Eudragit NM 30 D (185% polymer weight gain)	NA	26.5
Talc	NA	19.9
Total (Dry Weight) of Coated Pellets	27 g	60.7 g

**[0088]** **FIG. 6A** illustrates the dissolution profiles of two batches of small pellets of Formulation D and the large pellets of Formulation A, all of which utilized ethyl cellulose for providing the extended release. The dissolution test was carried out as described in the USP, General Chapter 711, using Apparatus 2 Paddle Method, 75 rpm at 37°C in water. It was observed that the release profile of L-ornithine phenylacetate in Formulation D small pellets was about 18% to 20% in 2 hours, about 76% to 78% in 4 hours, and about 91% to 93% in 6 hours. In comparison, the release profile of L-ornithine phenylacetate in Formulation A large pellets was about 27% in 2 hours, about 54% in 4 hours, and about 68% in 6 hours.

**[0089]** **FIG. 6B** illustrates the dissolution profiles of small pellets of Formulation E and the large pellets of Formulation C, both of which utilized Eudragit NM 30 D for providing the extended release. The dissolution test was carried out as described in the USP, General Chapter 711, using Apparatus 2 Paddle Method, 75 rpm at 37°C in water. It was observed that the release profile of L-ornithine phenylacetate in Formulation E small pellets was about 8% in 2 hours, about 20% in 4 hours, and about 82% in 6 hours. In comparison, the release profile of L-ornithine phenylacetate in Formulation C large pellets was less than about 5% in 2 hours, about 32% in 4 hours, and about 58% in 6 hours.

**[0090]** The Scanning Electron Micrographs (SEM) images of the small pellets of Formulation D are illustrated in **FIGs. 7A** and **7B** in different magnitudes. The Scanning Electron Micrographs (SEM) images of the small pellets of Formulation E are illustrated in **FIGs. 7C** and **7D** in different magnitudes.

#### Example 5 – Pharmacokinetic Studies in Humans

**[0091]** An open-label, five-treatment, five-period single-dose crossover Phase 1 human clinical study was conducted to evaluate the pharmacokinetics of phenylacetic acid and phenylacetylglutamine after a single dose of three extended-release oral dosage forms of L-ornithine phenylacetate in comparison to RAVICTI® (glycerol phenylbutyrate), a prodrug of phenylacetic acid. The study also compared the pharmacokinetics and safety of single doses of the three extended-release oral dosage forms of L-ornithine phenylacetate in comparison to a single dose of an immediate release oral solution of L-ornithine phenylacetate.

**[0092]** The five treatments are listed as follows: each of Treatment A, B, and C refers to a single oral dose of 10 g Formulations A, B and C (each is an equivalent of about 5 g PAA); Treatment D refers to a single oral dose of 6 mL RAVICTI® (equivalent of about 5 g PAA); Treatment E refers to a single oral dose of an immediate release formulation of 5 g L-ornithine phenylacetate (equivalent of about 2.5 g PAA).

**[0093]** The primary objective is to assess the plasma profiles and pharmacokinetics of phenylacetic acid (a potent ammonia scavenger), ornithine and phenylacetylglutamine (the end-product responsible for clearing ammonia) following a single oral dose of three extended-release formulations of L-ornithine phenylacetate in comparison to an oral solution of L-ornithine phenylacetate and a prodrug of phenylacetic acid (glycerol phenylbutyrate, RAVICTI®) in healthy human subjects. The secondary objective is to determine the safety, tolerability, and palatability of three extended-release formulations in healthy subjects.

**[0094]** Eligible male or female adult healthy subjects were enrolled to first receive four treatments (Treatments A-D) over 4 dosing periods in a crossover fashion using a balanced 4x4 Latin Square design with an at least 7-day washout interval between treatments followed by receiving Treatment E for all subjects in the fifth (last) dose period after a minimum 7-day washout interval. Following dosing in each dose period, subjects underwent serial blood and urine sampling up to 24 hrs post dose for PK assessment.

*PK Assessments*

**[0095]** In the dose periods where Treatment A, B, C, or D was administered (the ER formulations of OCR-002 or RAVICTI®), venous blood samples (5 mL each) were collected at the following time points: immediately (within 15 mins) prior to dosing, and then at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hrs post dose. In the dose period where the immediate release formulation of L-ornithine phenylacetate was administered (Period 5), venous blood samples (5 mL each) were collected at the following time points: immediately (within 15 mins) prior to dosing, and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hrs post-dose.

**[0096]** In addition, urine samples were collected at the following time intervals: within 1 hour prior to dosing (spot sample), and then cumulatively over the intervals of 0-4, 4-8, 8-12, and 12-24 hrs post dose. Plasma samples were separated by centrifugation within 1 hour of blood collection and stored at approximately -80 °C until analyzed. The total urine volume for each collection interval were measured and recorded and aliquots of urine were stored at approximately -80 °C until analyzed.

*Bioanalytical Methods*

**[0097]** Plasma samples were analyzed for concentrations of phenylacetic acid (PAA), phenylacetylglutamine (PAGN) and ornithine (ORN) using a validated LC-MS/MS method. All urine samples were analyzed for concentrations of PAGN using a validated LC-MS/MS method.

Endpoints

**[0098]** Pharmacokinetics: Plasma concentration *vs.* time profiles of phenylacetate, ornithine, and phenylacetylglutamine following a single oral dose of each of the study drug were analyzed by noncompartmental PK methods. Pharmacokinetic parameters that were determined include  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{12}$  and  $t_{1/2}$ . The amount of PAGN excreted in urine and the percent of PAA dose excreted in urine as PAGN over each collection interval and the entire 24 hr interval were also determined.

**[0099]** **FIG. 8** and **FIG. 9** illustrate the mean plasma profiles of PAA and PAGN, respectively, from this Phase 1 study. **FIG. 8** demonstrates the Mean Plasma PAA concentration *vs.* time curves following administration of a single oral dose of the controlled-release formulations in comparison to the immediate-release solution and glycerol phenylbutyrate. **FIG. 9** demonstrates the Mean Plasma PAGN concentration *vs.* time curves following administration of a single oral dose of the controlled-release formulations in comparison to the immediate-release solution and glycerol phenylbutyrate.

**[0100]** The mean maximum concentration ( $C_{max}$ ) of plasma PAA from three extended-release formulations ranged from approximately 50 to 90  $\mu\text{g}/\text{mL}$  occurring at various time points over 4 to 9 hours after dosing. For comparison, RAVICTI® produced a mean plasma PAA  $C_{max}$  of approximately 10  $\mu\text{g}/\text{mL}$  at 4 to 6 hours after dosing. The plasma PAA data after a single oral dose of 6mL RAVICTI® are consistent with published data in healthy subjects. In addition, PAA exposure with the extended-release formulations of L-ornithine phenylacetate showed lower inter-subject variability than RAVICTI®.

**[0101]** Plasma profiles of PAGN, the end-product of ammonia scavenging, also demonstrated a similar pattern as the PAA profiles. The mean  $C_{max}$  of plasma PAGN from the three extended-release formulations of L-ornithine phenylacetate ranged from approximately 30 to 45  $\mu\text{g}/\text{mL}$  occurring at various time points over 4 to 10 hours after dosing. For comparison, RAVICTI® produced a mean plasma PAGN  $C_{max}$  of about 20 to 25 $\mu\text{g}/\text{mL}$  at approximately 5 hours. These data are also consistent with the published data in healthy subjects.

**[0102]** The total urinary excretion data of PAGN over 24 hours is summarized in Table 3 below. The mean PAGN excretion amount was comparable for Treatment A through C, each with about 80% PAA converted to PAGN excretion over 24 hours. In contrast, Treatment D with RAVICTI® only showed about 40% conversion efficiency compared to Treatment A through C at approximately the same molar PAA dose (in the case of RAVICTI®, PAA is provided from the glycerol phenylbutyrate prodrug). It was surprisingly observed that the immediate release formulation Treatment E also exhibited about 80% conversion efficiency,

which provided a similar mean PAGN excretion amount at approximately half the molar dose of PAA administered in the RAVICTI® arm.

**Table 3.**

Treatment	Statistics	Total PAGN Amount Excreted over 24 hours (G)	PAA Equivalents Excreted over 24 hours (G)	Percent PAA Dose Excreted over 24 hours (%)
<b>A</b>	N	12	12	12
	Mean	8.26	4.26	83.8
	Median	8.47	4.37	86.0
	%CV	14.7	14.7	14.7
<b>B</b>	N	12	12	12
	Mean	7.77	4.00	78.9
	Median	7.77	4.00	78.8
	%CV	10.7	10.7	10.8
<b>C</b>	N	12	12	12
	Mean	8.53	4.39	86.6
	Median	8.39	4.33	85.3
	%CV	11.3	11.3	11.3
<b>D</b>	N	12	12	12
	Mean	4.11	2.12	42.7
	Median	4.06	2.09	42.1
	%CV	24.9	24.9	24.9
<b>E</b>	N	12	12	12
	Mean	4.01	2.07	81.5
	Median	4.14	2.13	84.0
	%CV	15.2	15.1	15.1

**[0103]** Conclusion: The controlled-release and immediate release formulations were well tolerated throughout the study, with no toxicities or serious adverse events observed. The results showed a robust, extended-release pattern for all three extended-release formulations with mean plasma PAA concentrations exceeding those achieved with RAVICTI® (glycerol phenylbutyrate) at all time points for at least 24 hours post dose. In addition, mean plasma PAGN concentrations and urinary PAGN excretion were greater for all three extended-release dosage forms than for RAVICTI® at approximately the same molar PAA dose. It also demonstrated that urinary PAGN excretion for the immediate release formulation of L-ornithine phenylacetate was approximately twice as efficient as for RAVICTI®.

WHAT IS CLAIMED IS:

1. An oral pharmaceutical formulation, comprising L-ornithine phenylacetate at an oral dosage of about 2.0 g to about 10.0 g, and one or more pharmaceutically acceptable excipients or carriers.
2. The oral pharmaceutical formulation of Claim 1, wherein the formulation provides an immediate release profile of L-ornithine phenylacetate upon oral administration.
3. The oral pharmaceutical formulation of Claim 1, wherein the formulation provides a controlled release profile of L-ornithine phenylacetate upon oral administration.
4. The oral pharmaceutical formulation of Claim 1, wherein the oral dosage is about 5.0 g.
5. The oral pharmaceutical formulation of Claim 1, wherein the oral dosage is about 7.5 g.
6. The oral pharmaceutical formulation of any one of Claims 1 to 5, wherein the formulation is in a single unit dosage form.
7. The oral pharmaceutical formulation of any one of Claims 1 to 5, wherein the formulation is in two or more unit dosage forms.
8. The oral pharmaceutical formulation of Claims 6 or 7, wherein the unit dosage form is a tablet, a capsule, a pill, pellets, free-flowing powder, or liquid.
9. The oral pharmaceutical formulation of any one of Claims 1 to 8, wherein the formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 30%.
10. The oral pharmaceutical formulation of Claim 9, wherein the formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 50%.
11. The oral pharmaceutical formulation of Claim 10, wherein the formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 80%.
12. An oral pharmaceutical formulation, comprising an effective amount of L-ornithine phenylacetate, and one or more pharmaceutically acceptable excipients or carriers, wherein upon oral administration, the formulation has a controlled release profile of L-ornithine and phenylacetate.
13. The oral pharmaceutical formulation of Claim 12, comprising a core and one or more controlled release coating layers on the core, wherein the core comprises L-ornithine phenylacetate and said controlled release coating layers comprise one or more polymers.

14. The oral pharmaceutical formulation of Claim 13, wherein the polymer is selected from alkyl cellulose, hydroxyalkyl cellulose, carboxyalkyl cellulose, alkylvinyl polymers, acrylic acid polymers or copolymers, acrylate polymers or copolymers, or natural or synthetic gums.

15. The oral pharmaceutical formulation of Claim 13 or 14, wherein the polymer is alkyl cellulose.

16. The oral pharmaceutical formulation of Claim 13 or 14, wherein the polymer is selected from acrylic acid polymers or copolymers.

17. The oral pharmaceutical formulation of Claim 16, wherein the acrylic acid polymers or copolymers are selected from Eudragit polymers.

18. The oral pharmaceutical formulation of any one of Claims 13 to 17, comprising two or more coating layers.

19. The oral pharmaceutical formulation of any one of Claims 12 to 18, wherein the formulation is in the form of a tablet, a capsule, a pill, pellets or free-flowing powder.

20. The oral pharmaceutical formulation of any one of Claims 12 to 19, comprising about 0.1 g to about 25.0 g L-ornithine phenylacetate.

21. The oral pharmaceutical formulation of any one of Claims 12 to 20, comprising about 1.0 g to about 20.0 g L-ornithine phenylacetate.

22. The oral pharmaceutical formulation of any one of Claims 12 to 21, comprising about 2.0 g to about 15.0 g.

23. The oral pharmaceutical formulation of any one of Claims 12 to 22, comprising about 4.0 g to about 10.0 g.

24. The oral pharmaceutical formulation of any one of Claims 12 to 23, comprising about 5.0 g to about 8.0 g L-ornithine phenylacetate.

25. The oral pharmaceutical formulation of any one of Claims 12 to 24, wherein said L-ornithine phenylacetate has an in vitro dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method of between about 5% and 30% of L-ornithine phenylacetate released in 2 hours.

26. The oral pharmaceutical formulation of Claim 25, wherein said L-ornithine phenylacetate has an in vitro dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method of between about 15% and 80% of L-ornithine phenylacetate released in 4 hours.

27. The oral pharmaceutical formulation of Claim 26, wherein said L-ornithine phenylacetate has an in vitro dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method of between about 50% and 95% of L-ornithine phenylacetate released in 6 hours.

28. A method for treating hyperammonemia, comprising orally administering to a subject in need thereof a pharmaceutical formulation comprising L-ornithine phenylacetate.

29. The method of Claim 28, wherein the subject has acute liver failure or chronic liver disease.

30. The method of Claim 29, wherein the subject has liver cirrhosis or liver decompensation.

31. The method of Claim 28, wherein the subject has hepatic encephalopathy.

32. The method of Claim 28, wherein the subject has portal hypertension.

33. The method of Claim 28, wherein the subject has a urea cycle disorder.

34. The method of any one of Claims 28 to 33, wherein L-ornithine phenylacetate is administered in a dose ranging from about 10 mg/kg to about 1000 mg/kg.

35. The method of Claim 34, wherein L-ornithine phenylacetate is administered in a dose ranging from about 50 mg/kg to about 500 mg/kg.

36. The method of Claim 35, wherein L-ornithine phenylacetate is administered in a dose ranging from about 100 mg/kg to about 250 mg/kg.

37. The method any one of Claims 28 to 36, wherein L-ornithine phenylacetate is administered in an amount from about 0.1 g to about 50.0 g per day.

38. The method of any one of Claims 28 to 37, wherein L-ornithine phenylacetate is administered in an amount from about 1.0 g to about 40.0 g per day.

39. The method of any one of Claims 28 to 38, wherein L-ornithine phenylacetate is administered in an amount from about 5.0 g to about 30.0 g per day.

40. The method of any one of Claims 28 to 39, wherein L-ornithine phenylacetate is administered in an amount from about 10.0 g to about 25.0 g per day.

41. The method of any one of Claims 28 to 40, wherein said pharmaceutical formulation is administered at least once a day.

42. The method of any one of Claims 28 to 41, wherein said pharmaceutical formulation is administered 2 to 3 times a day.

43. The method of any one of Claims 28 to 36, wherein L-ornithine phenylacetate is administered in a dose ranging from about 2.0 g to about 10.0 g.

44. The method of Claim 43, wherein the dose is administered in two or more unit dosage forms.

45. The method of Claim 43 or 44, wherein the dose is administered three times a day.

46. The method of any one of Claims 28 to 45, wherein the plasma Cmax of L-ornithine is from about 18 mg/L to about 35 mg/L.

47. The method of any one of Claims 28 to 45, wherein the plasma Cmax of phenylacetic acid is from about 15 mg/L to about 120 mg/L.

48. The method of Claim 47, wherein the plasma Cmax of phenylacetic acid is from about 50 mg/L to about 90 mg/L.

49. The method of any one of Claims 28 to 45, wherein the plasma Cmax of phenylacetylglutamine is from about 15 mg/L to about 75 mg/L.

50. The method of Claim 49, wherein the plasma Cmax of phenylacetylglutamine is from about 30 mg/L to about 45 mg/L.

51. The method of any one of Claims 28 to 50, wherein said pharmaceutical formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 30%.

52. The method of Claim 51, wherein said pharmaceutical formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 50%.

53. The method of Claim 52, wherein said pharmaceutical formulation provides conversion of phenylacetate to phenylacetylglutamine over 24 hours of greater than about 80%.

54. The method of Claim 28, comprising orally administering 3 to 6 unit dosage forms each comprising from about 0.75 g to about 2.0 g of L-ornithine phenylacetate.

55. The method of Claim 54, comprising orally administering 3 to 5 unit dosage forms each comprising from about 1.0 g to about 1.5 g of L-ornithine phenylacetate.

56. The method of Claim 54 or 55, wherein said administration is repeated 3 times per day.

57. The method of any one of Claims 28 to 53, wherein said pharmaceutical formulation is selected from the oral pharmaceutical formulation of Claims 1 to 27.

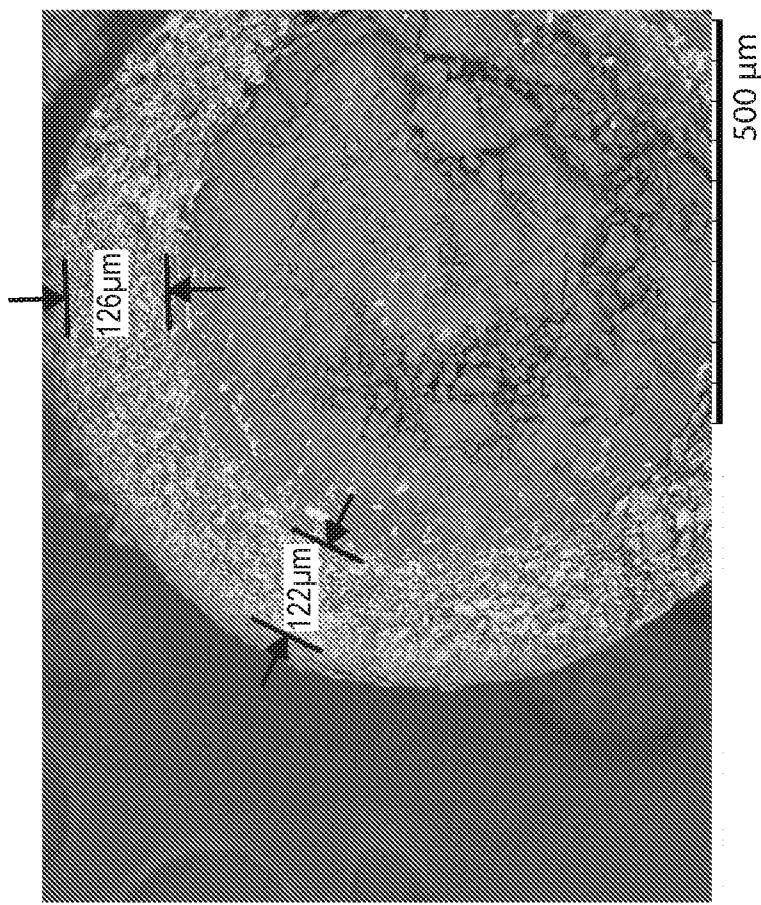


FIG. 1B

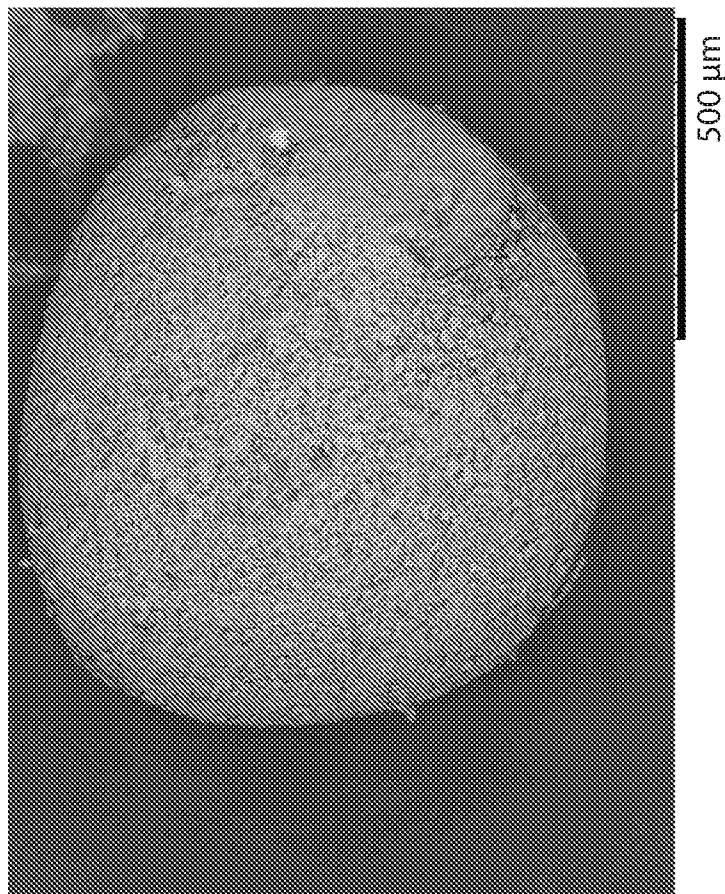


FIG. 1A

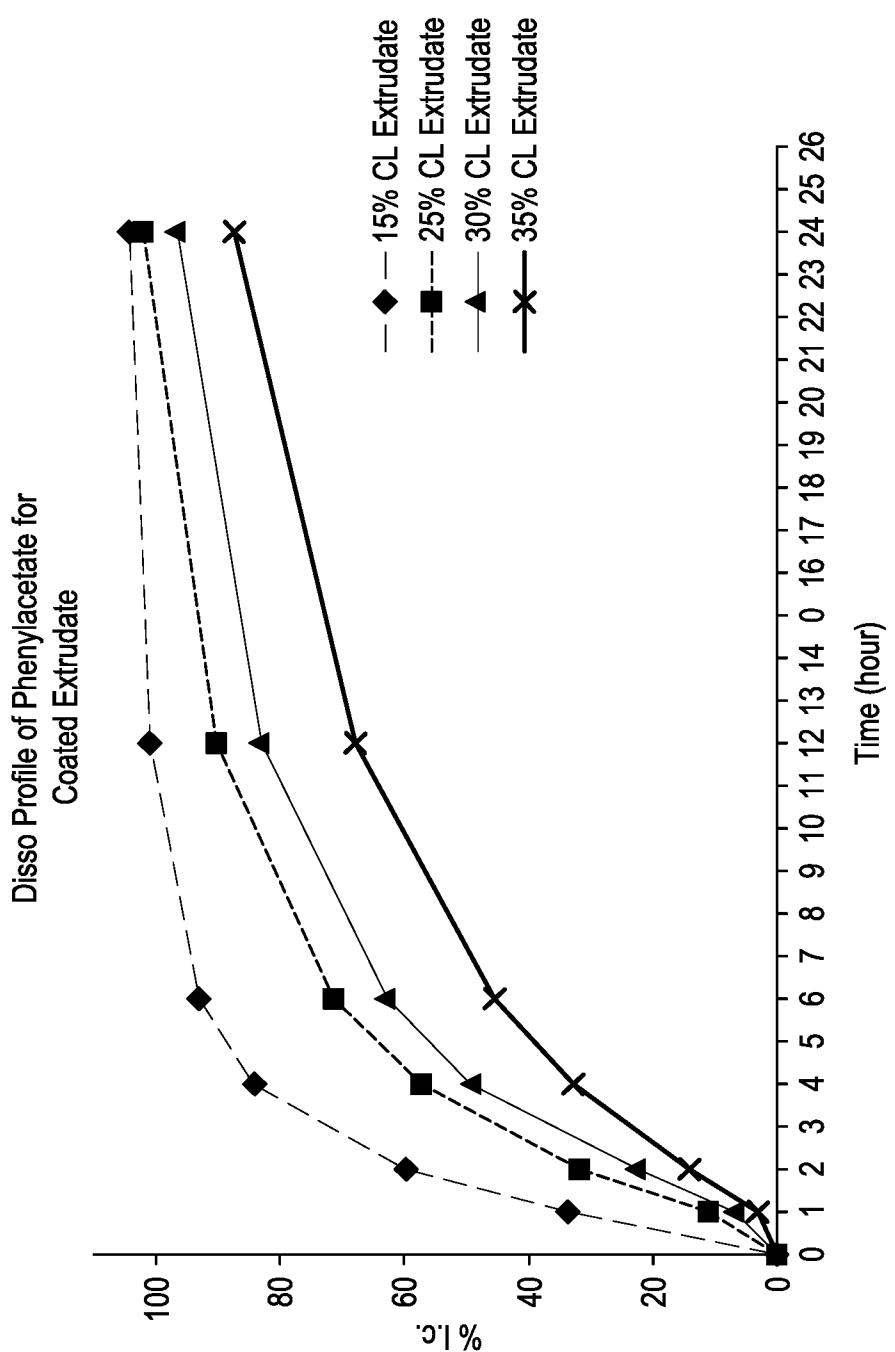


FIG. 2

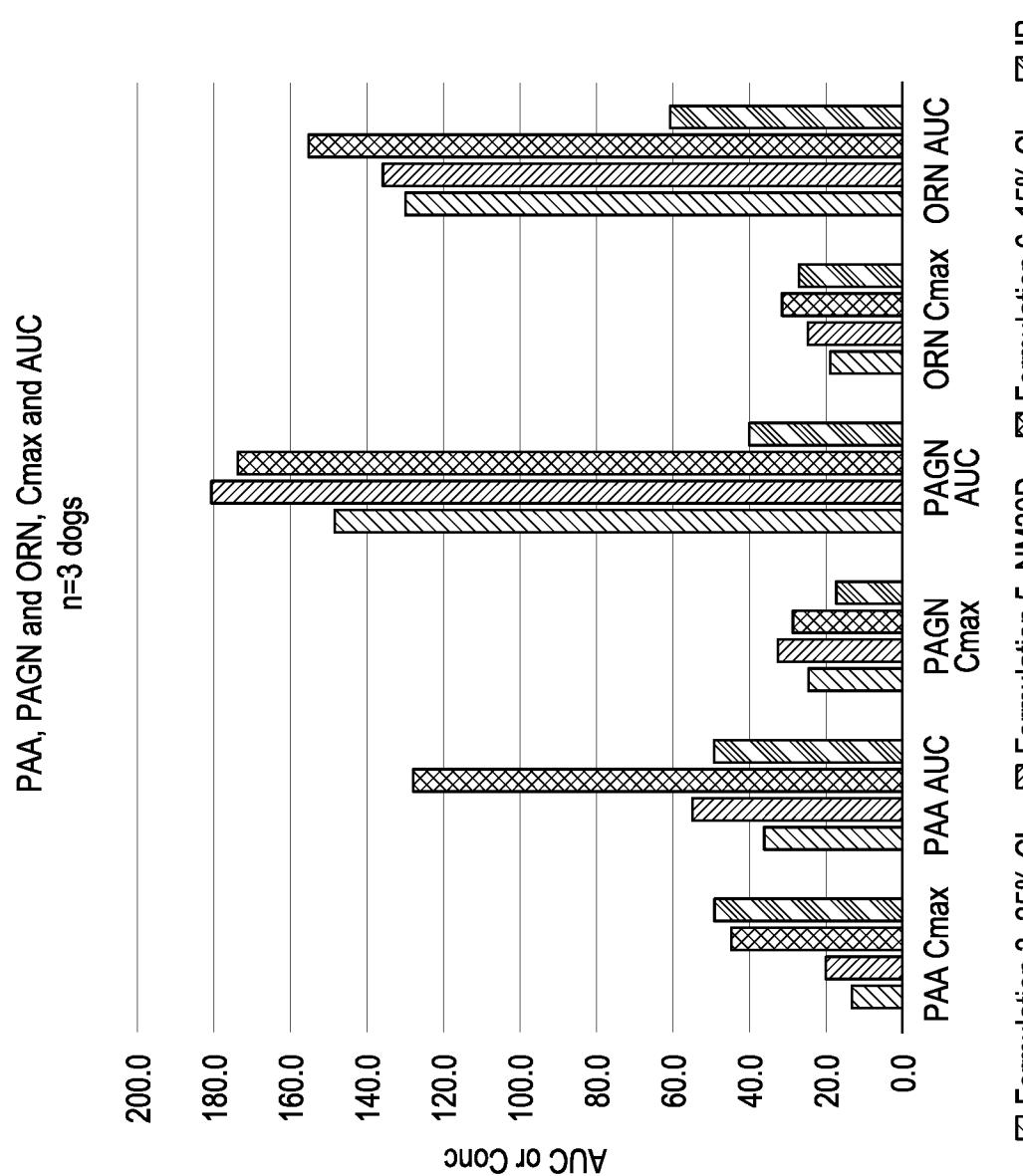


FIG. 3

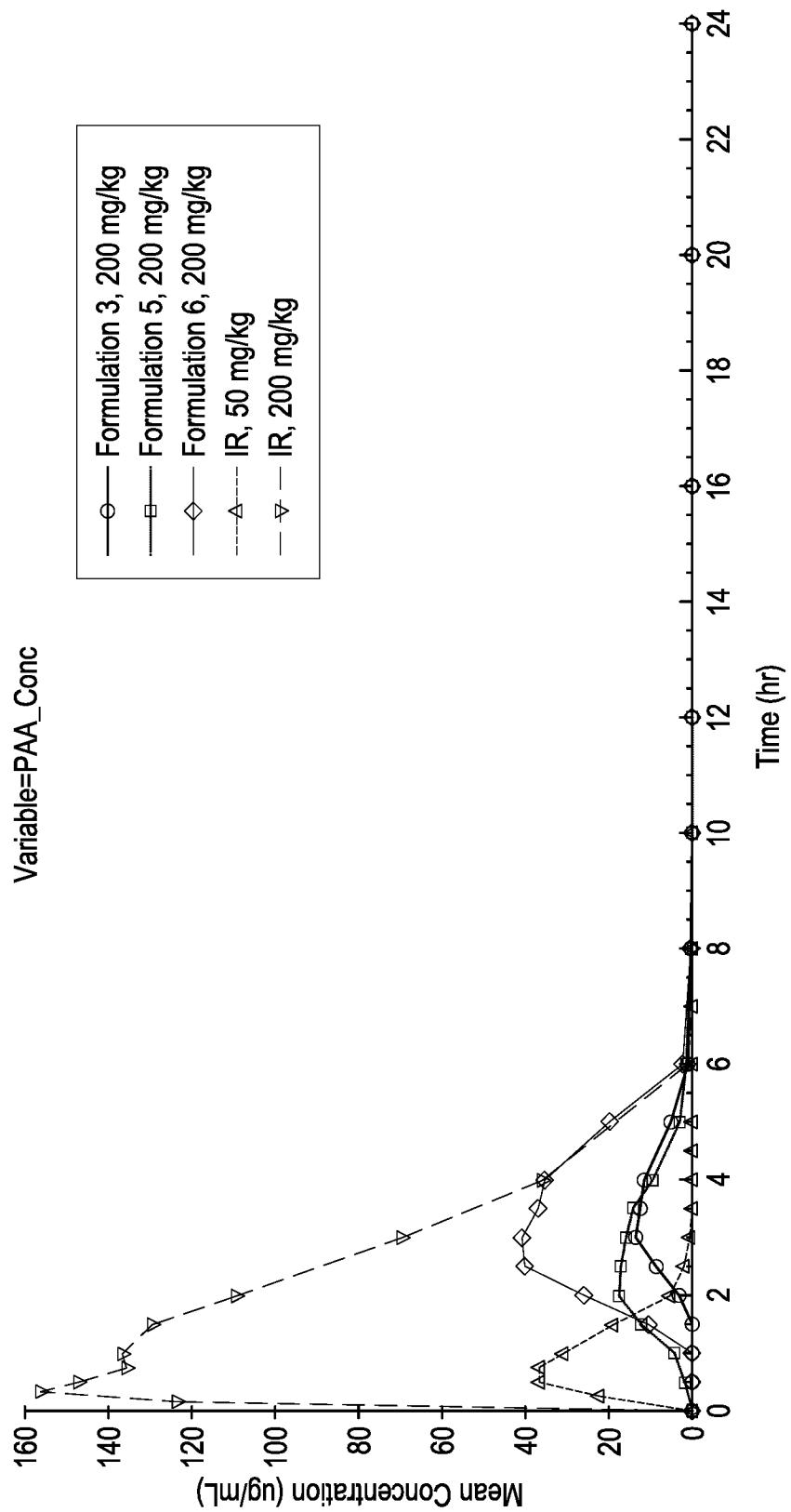


FIG. 4

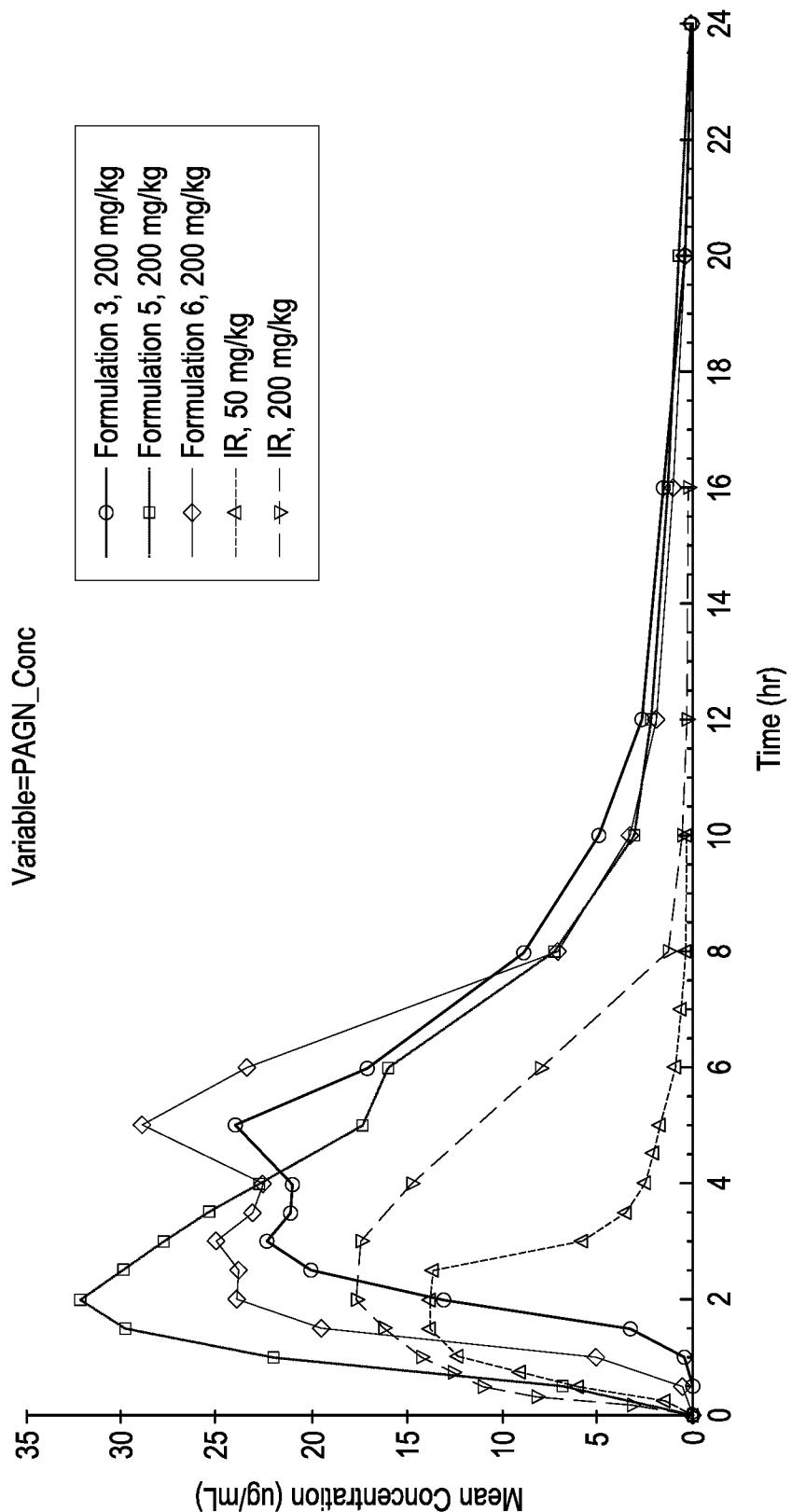


FIG. 5

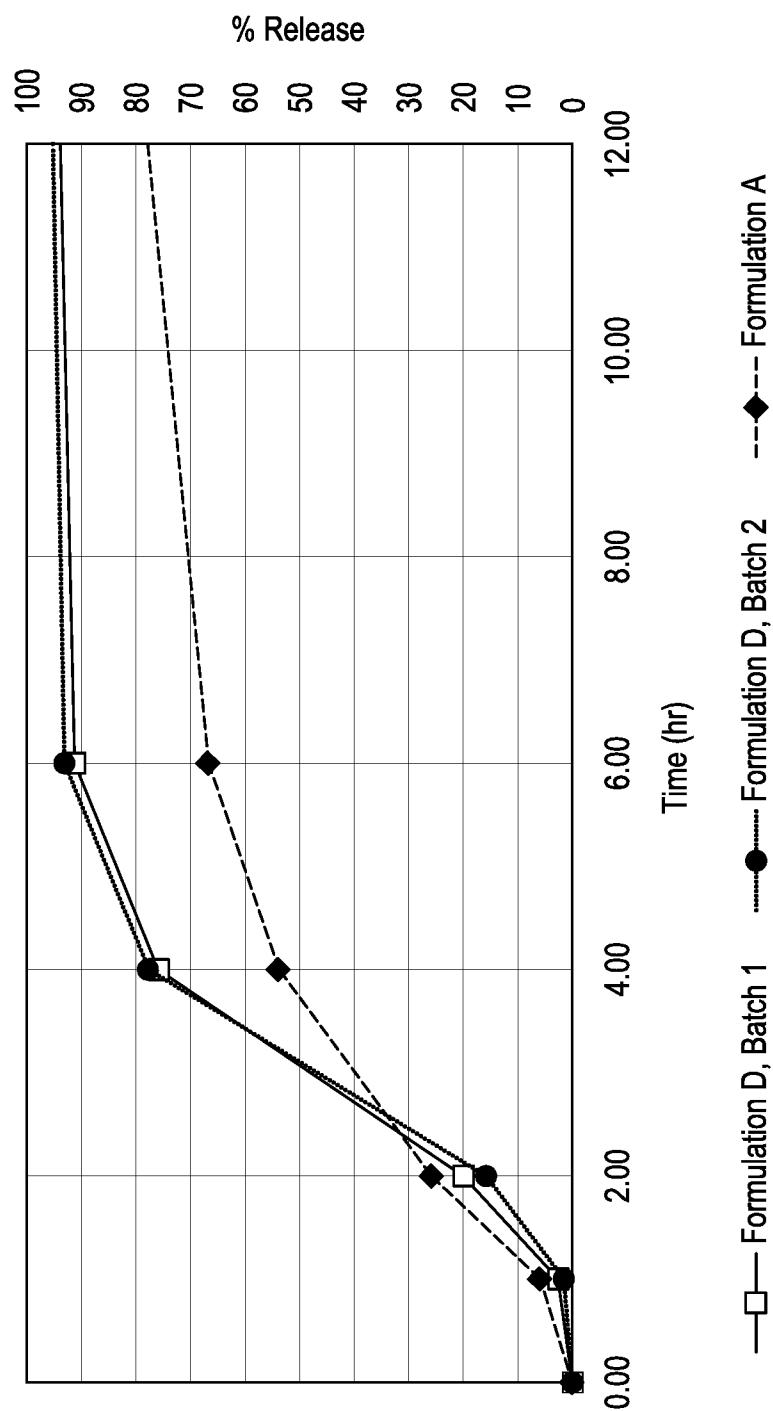


FIG. 6A

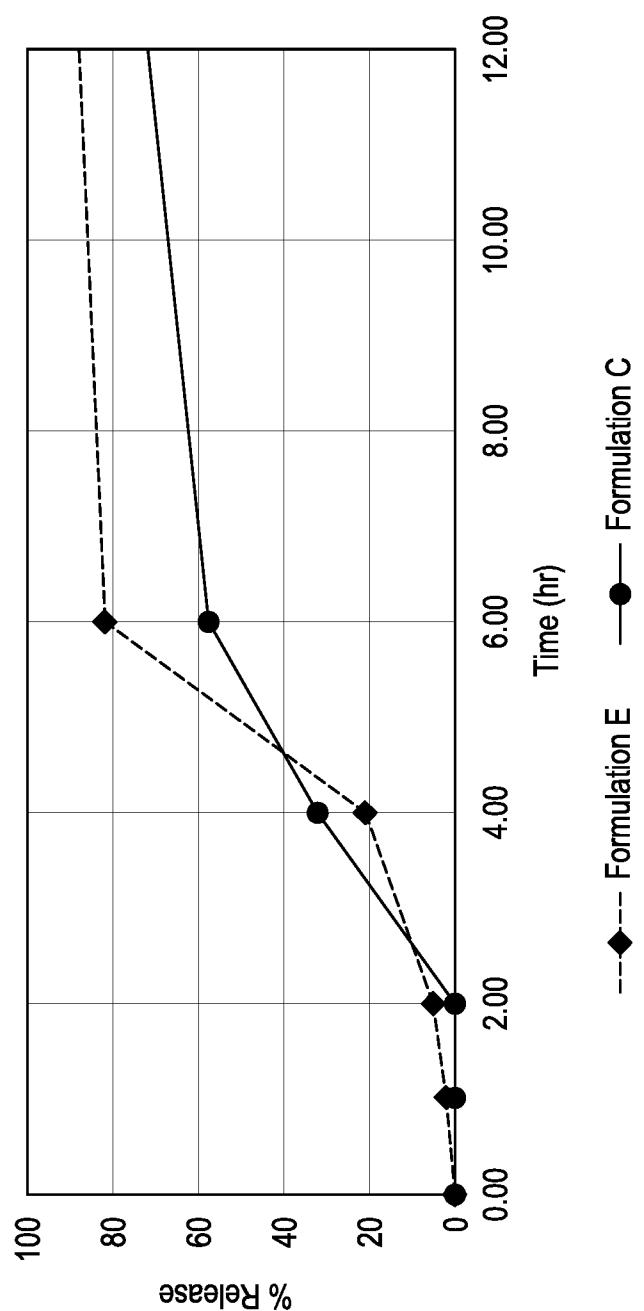


FIG. 6B

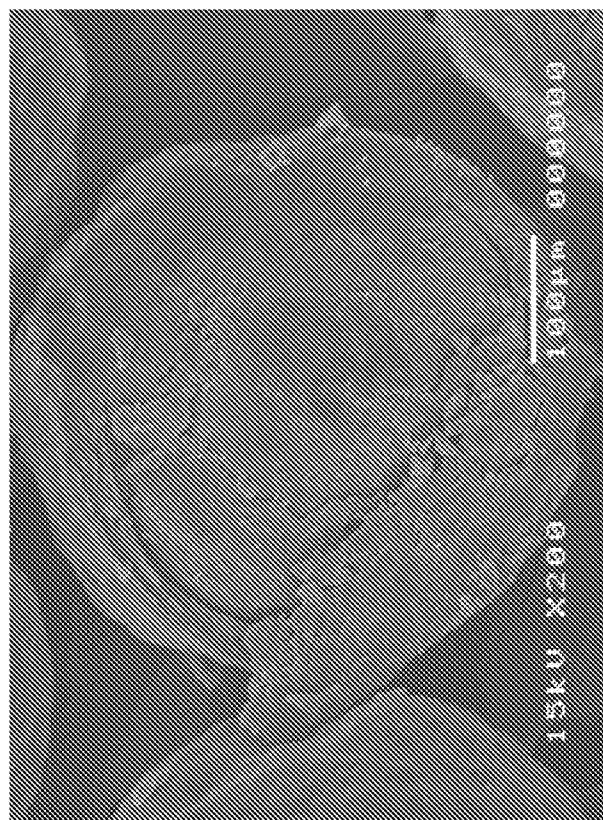


FIG. 7B

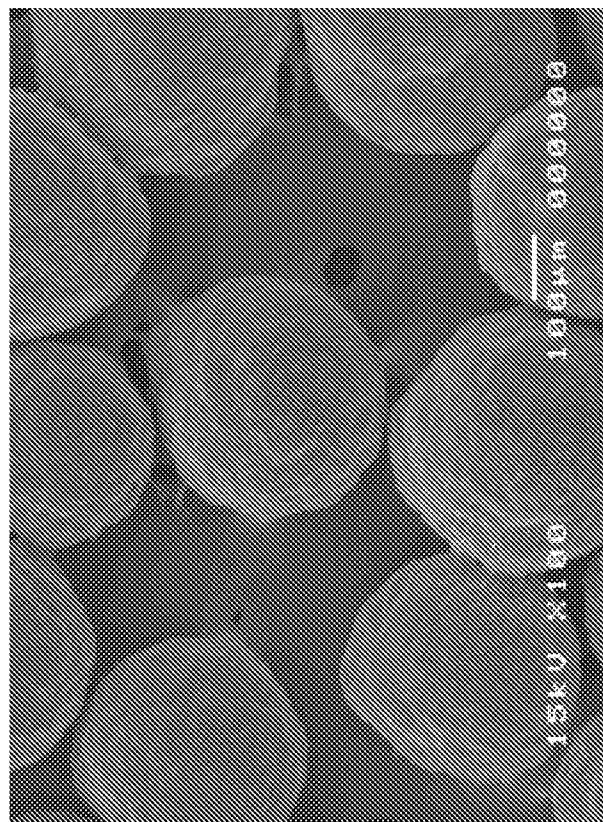


FIG. 7A

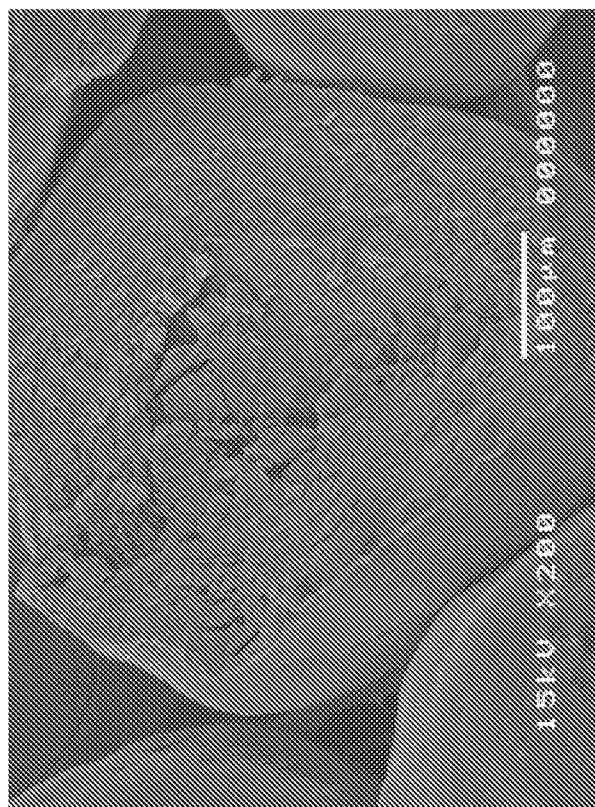


FIG. 7D

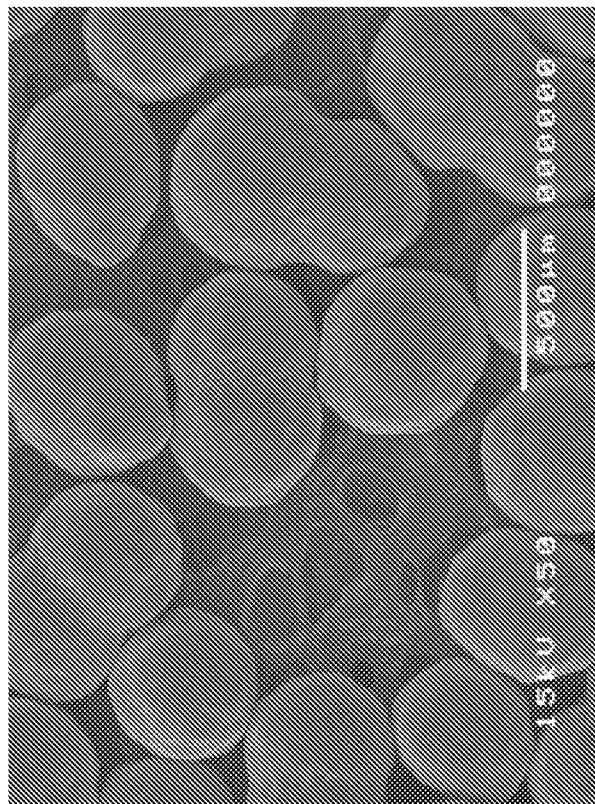


FIG. 7C

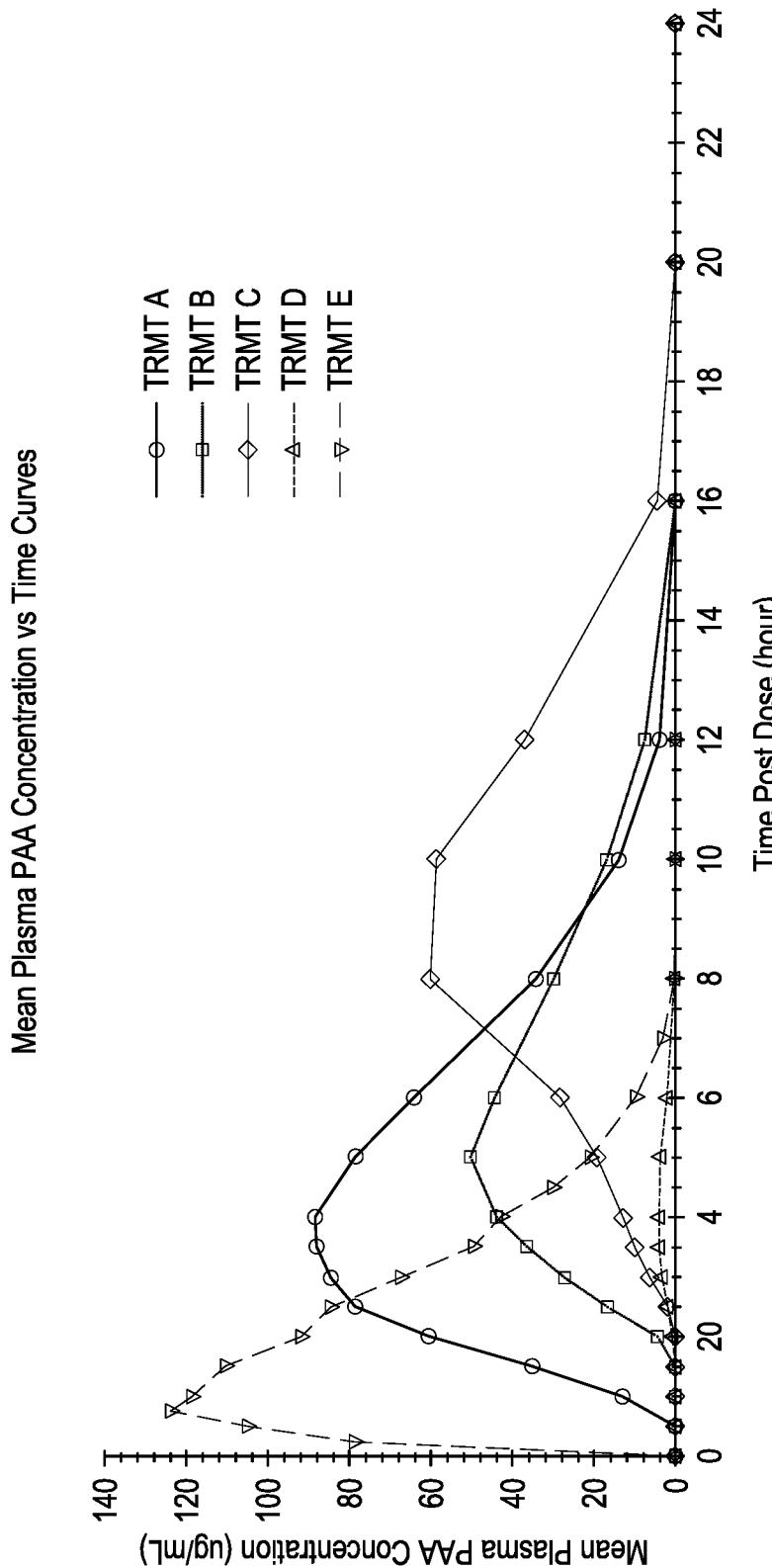


FIG. 8

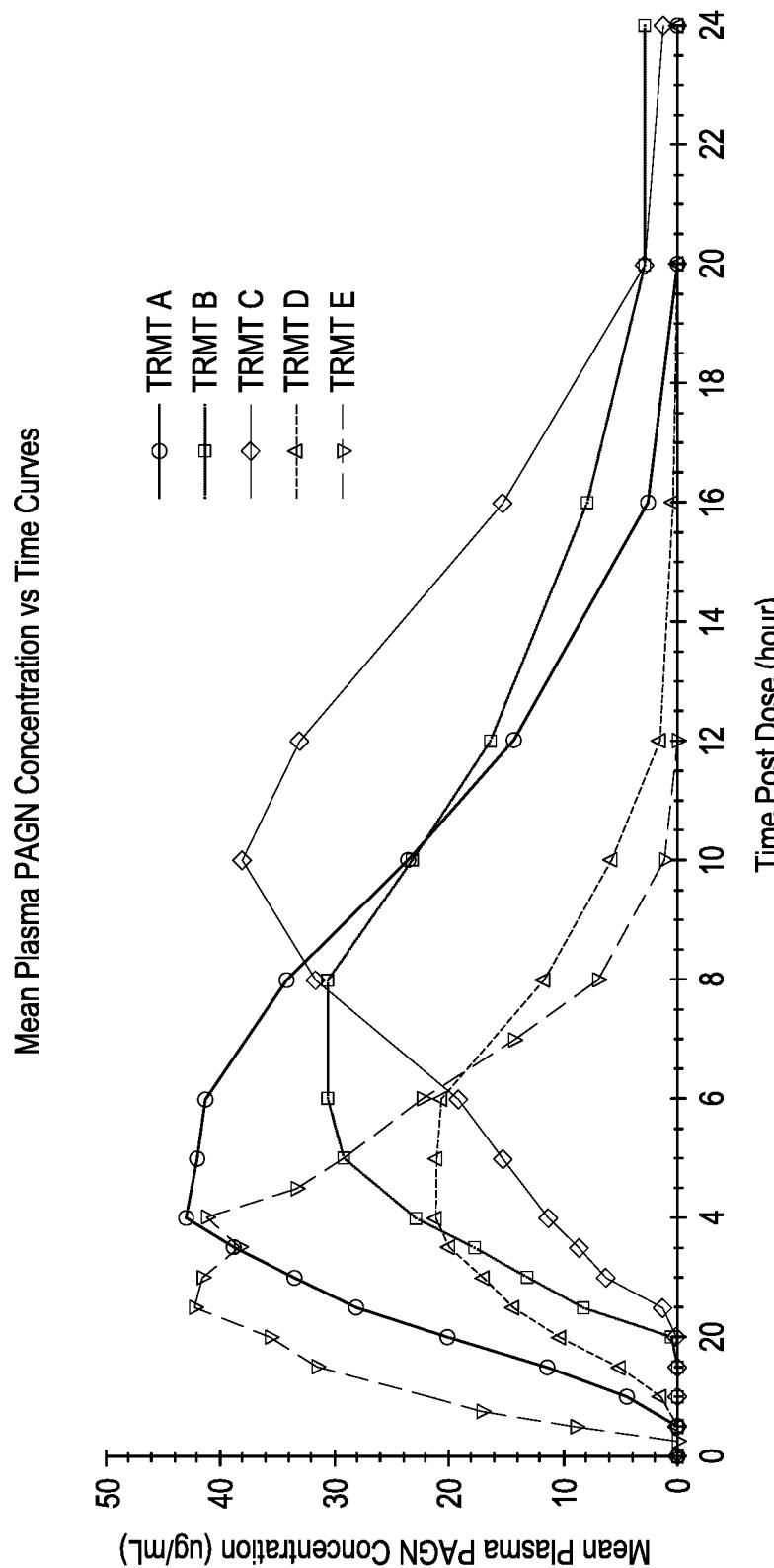


FIG. 9

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/028298

## A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/198 (2006.01) A61K 31/192 (2006.01) A61K 31/195 (2006.01) A61P 1/16 (2006.01) C07C 57/32 (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)

**MEDLINE, WPIAP, EPODOC:** keyword search - L-ornithine phenylacetate, diaminopentanoic acid, benzeneacetate, phenylacetic acid, benzeneacetic acid, 2-phenylacetic acid, ammonium, phenylbutyrate, buphenyl, glycerol phenylbutyrate, ravicti, alpha-tolue acid, phenylethanoic acid, hyperammonemia, urea cycle disorder, ammonia, hepatic encephalopathy, portal hypertension, cirrhosis, decompensation, liver failure, control release, immediate release, coat, polymer, core, oral, tablet, capsule, pill, pellet, powder, liquid, syrup.

**Internal databases provided by IP Australia, AusPat, Patentscope, PubMed:** Applicant/Inventors and keywords 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	

Further documents are listed in the continuation of Box C

See patent family annex

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"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search  
30 May 2016

Date of mailing of the international search report  
30 May 2016

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(ISO 9001 Quality Certified Service)  
Telephone No. 0262256130

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).		DOCUMENTS CONSIDERED TO BE RELEVANT
		PCT/US2016/028298
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/144498 A2 (UCL BUSINESS PLC et al.) 16 December 2010 See abstract, [0005], [0033], [0034], [0043], [0061], [0071], [0086], [0087], [0090], [0107].	1-57
Y	As above.	34-40, 42, 44, 45 and 54-56
X	AU 2014250643 A1 (OCERA THERAPEUTICS, INC. et al.) 06 November 2014 See abstract, [0005], [0033], [0034], [0043], [0061], [0071], [0086], [0087], [0090], [0107].	1-57
Y	As above.	34-40, 42, 44, 45 and 54-56
X	WO 2006/056794 A1 (UCL BIOMEDICA PLC) 01 June 2006 See abstract, page 2, lines 4-6, page 9, lines 12-14, page 10, lines 16-17, page 11, lines 21-33, page 11, line 33-page 12, line 5, page 14, lines 17-26, page 17, lines 4-7 and lines 18-20.	1-57
X	WO 2012/048043 A1 (OCERA THERAPEUTICS, INC.) 12 April 2012 See [0003], [0005], [0102], [0103], [0113], [0114], [0117].	1-33, 41, 43, 46-53 and 57
Y	As above.	34-40, 42, 44, 45 and 54-56
X	WO 2010/115055 A1 (OCERA THERAPEUTICS, INC.) 07 October 2010 See [0034], [0035], [0092], [0102], [0103], [0106], [0151], [0157], [0158].	1-57
A	VENTURA-COTS, M. et al., 'Safety of ornithine phenylacetate in cirrhotic decompensated patients: an open-label, dose-escalating, single-cohort study', Journal of Clinical Gastroenterology. 2013, Vol. 47, No. 10, pages 881-887 See abstract.	28-33
A	JALAN, R. et al., 'L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy', Medical Hypotheses. 2007, Vol. 69, No. 5, pages 1064-1069 See abstract, Figure 5.	28-33
A	JOVER-COBOS, M. et al., 'Ornithine phenylacetate revisited', Metabolic Brain Disease. 2013, Vol. 28, No. 2, pages 327-331 See abstract, subheading 'Clinical Studies'.	28-33
P,X	AU 2015221466 A1 (OCERA THERAPEUTICS, INC.) 24 September 2015 See [0034], [0035], [0092], [0102], [0103], [0106], [0151], [0157], [0158].	1-57

<b>INTERNATIONAL SEARCH REPORT</b> Information on patent family members		International application No. <b>PCT/US2016/028298</b>	
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.			
<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2010/144498 A2	16 December 2010	WO 2010144498 A2	16 Dec 2010
		AU 2010258888 A1	02 Feb 2012
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		CA 2764587 A1	16 Dec 2010
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		EA 018007 B1	30 Apr 2013

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

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/028298**

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<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
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<b>INTERNATIONAL SEARCH REPORT</b> Information on patent family members		International application No. <b>PCT/US2016/028298</b>	
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<b>Patent Document/s Cited in Search Report</b>		<b>Patent Family Member/s</b>	
Publication Number	Publication Date	Publication Number	Publication Date
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Patent Document/s Cited in Search Report		Patent Family Member/s
Publication Number	Publication Date	Publication Number
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		29 Jan 2015
		04 Nov 2010
		08 May 2012
		16 Aug 2012
		23 Jul 2013
		07 Nov 2013
		22 Jul 2014
		25 Sep 2014
		19 May 2015
		10 Sep 2015
<b>End of Annex</b>		
<small>Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.  Form PCT/ISA/210 (Family Annex)(July 2009)</small>		

## 摘要

本申请的一些实施方案涉及 L-鸟氨酸苯乙酸盐的口服制剂及制备 L-鸟氨酸苯乙酸盐的方法。这些口服制剂提供 L-鸟氨酸苯乙酸盐的标准静脉内给药的替代给药途径，以治疗患有各种急慢性肝脏疾病和病症如急性肝衰竭、肝硬化、肝失代偿、门静脉高血压、肝性脑病的患者的高氨血症，或尿素循环障碍患者的高氨血症。

