FORMULATIONS CONTAINING DEUTERATED DOMPERIDONE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/750,491, filed October 25, 2018, which is incorporated by reference herein.

TECHNICAL FIELD

[0002] This disclosure relates to pharmaceutical formulations containing d_4-domperidone.

BACKGROUND

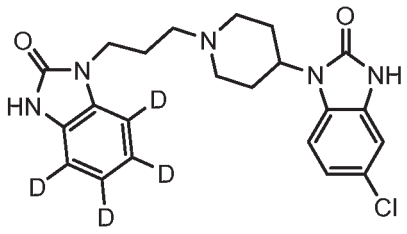
[0003] Gastroparesis is a condition where motility of the stomach does not function or does not function properly, which prevents the stomach from emptying and interferes with digestion. Treatment of gastroparesis requires medications, *e.g.*, metoclopramide, erythromycin, or cisapride, to stimulate the stomach muscles. Metoclopramide poses serious side effects, such as development of movement disorders or adverse interactions with other medications; erythromycin is susceptible to loss of efficacy as patient drug tolerance increases; and cisapride has limited accessibility.

[0004] Medications to control nausea and vomiting, *e.g.*, prochlorperazine, thiethylperazine, diphenhydramine, or ondansetron, may also be administered to treat gastroparesis. The symptoms of gastroparesis also may be treated surgically, such as installing jejunostomy tubes, gastric venting tubes, or feeding tubes.

[0005] Domperidone, in both deuterated and non-deuterated forms, is an effective dopamine antagonist that does not readily cross the blood-brain barrier and may be used to treat gastroparesis. Safe and efficacious formulations of domperidone are needed.

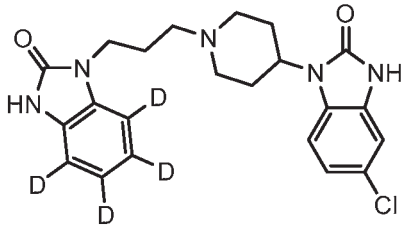
SUMMARY

[0006] In some embodiments, the disclosure provides pharmaceutical formulation comprising d_4-domperidone of the formula (I):



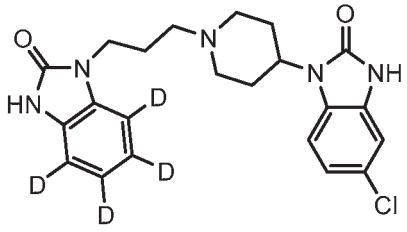
(I) or a pharmaceutically acceptable salt thereof; a glyceryl stearate, and a medium chain triglyceride.

[0007] In other embodiments, the disclosure provides pharmaceutical formulations comprising d_4-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride.

[0008] In further embodiments, the disclosure provides pharmaceutical formulations comprising d_4-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

[0009] In still other embodiments, the disclosure provides methods for treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient, comprising administering to the patient a formulation described herein. In some aspects, the disorder is gastroparesis. In other aspects, the disorder is gastroesophageal reflux disease. In further aspects, the disorder is insufficient lactation.

[00010] Other aspects and embodiments of the invention will be readily apparent from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[00011] The present application is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the subject matter, there are shown in the drawings exemplary embodiments of the subject matter; however, the presently disclosed subject matter is not limited to the specific compositions, methods, devices, and systems disclosed. In addition, the drawings are not necessarily drawn to scale.

[00012] FIG. 1 is a line graph showing the resulting plasma levels of d_4-domperidone after administration of Formulations A-F.

[00013] FIG. 2 is an expanded section of FIG. 1.

[00014] FIG. 3 is a line graph showing the mean concentration of domperidone or d_4-domperidone after a 1 mg/kg dog as described in Example 3.

[00015] FIG. 4 is an extension of Figure 3 which further illustrates the C_{max} and AUC of domperidone and d_4-domperidone in a bar graph format.

[00016] FIG. 5 is a line graph comparing the plasma levels of d_4-domperidone after administration of Formulation A, B, or F to a dog as described in Example 4.

[00017] FIG. 6 is a line graph showing a pharmacokinetic profile of domperidone and d_4-domperidone dosed in dogs at 1 mg/kg dose.

[00018] FIG. 7 is a flowchart for the fill compounding of the d_4-domperidone placebo and the 5 mg and 10 mg domperidone samples.

[00019] FIG. 8 is a line graph showing the C_{max} and AUC for suspension formulations containing d_4-domperidone and domperidone.

[00020] FIG. 9 is a line graph showing the corrected QT_c – absolute values for the d_4-domperidone samples of Example 3.

[00021] FIG. 10 is a line graph showing the corrected QT_c values – absolute for the non-deuterated domperidone samples of Example 3.

[00022] FIG. 11 is a bar graph showing the C_{max} % change from the vehicle for the d_4-domperidone and non-deuterated domperidone samples of Example 3.

[00023] FIG. 12 is a bar graph showing the C_{max} % change from the vehicle relative to dose for the d_4-domperidone and non-deuterated domperidone samples of Example 3.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[00024] In the disclosure, the singular forms "a,", "an," and "the" include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to "a material" is a reference to at least one of such materials and equivalents thereof known to those skilled in the art, and so forth.

[00025] When a value is expressed as an approximation by use of the descriptor "about" it will be understood that the particular value forms another embodiment. In general, use of the term "about" indicates approximations that can vary depending on the desired properties sought to be obtained by the disclosed subject matter and is to be interpreted in the specific context in which it is used, based on its function. The person skilled in the art will be able to interpret this as a matter of routine. In some cases, the number of significant figures used for a particular value may be one non-limiting method of determining the extent of the word "about." In other cases, the gradations used in a series of values may be used to determine the intended range available to the term "about" for each value. Where present, all ranges are inclusive and combinable. That is, references to values stated in ranges include every value within that range.

[00026] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list and every combination of that list is to be interpreted as a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

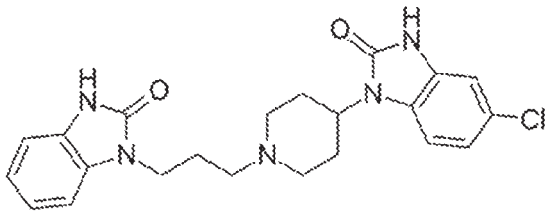
[00027] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. It is further noted that the claims may be drafted to exclude an optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation. Finally,

while an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself.

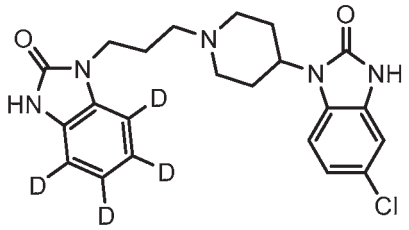
[00028] The terms "subject" and "patient" are used interchangeably and typically refer to mammals. In some embodiments, the patient or subject is a human. In other embodiments, the patient or subject is a veterinary or farm animal, a domestic animal or pet, or animal used for conducting clinical research.

[00029] "Treating" or variations thereof refers to eliminating or reducing at least one physical parameter of the disease or disorder.

[00030] "Domperidone" as referenced herein refers to 5-chloro-1-(1-[3-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)propyl]piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one, which has the following structure:



[00031] "D_4-domperidone" as referenced herein refers to 1-{3-[4-(5-chloro-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)piperidin-1yl]propyl}-2,3-dihydro(4,5,6,7-D4)-1H-1,3-benzodiazol-2-one, which has the following structure:



[00032] Any reference to d_4-domperidone may also include, where noted, pharmaceutically acceptable salts, esters, hydrates, solvates, prodrug forms, and derivatives of these, which are broadly defined as d_4-domperidone compounds that are modified or partially substituted, examples include but are not limited to adding a single atom, adding a reactive group, adding a functional group, forming a dimer or multimer, conjugating to another molecule such as an antibody, etc.

[00033] "Pharmaceutically acceptable" refers to properties and/or substances that are acceptable to the patient from a pharmacological/toxicological vantage, and to the

manufacturing pharmaceutical chemist from a physical/chemical vantage regarding composition, formulation, stability, patient acceptance, and bioavailability.

[00034] A pharmaceutically acceptable salt includes salts with a pharmaceutically acceptable acid or base, e.g., inorganic acids, e.g., hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic, cyclohexylsulfamic (cyclamic) or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal, e.g. sodium or potassium, and alkali earth metal, e.g. calcium or magnesium, hydroxides, and organic bases, e.g., alkyl amines, arylalkyl amines and heterocyclic amines.

[00035] The abbreviation "D," as used herein, refers to a stable isotope of hydrogen that is deuterium (heavy hydrogen or ^{2}H). Such instances of "D" include an amount of deuterium that is above the naturally occurring distribution of deuterium. In some embodiments, D has deuterium enrichment of no less than about 1%. In other embodiments, D has a deuterium enrichment of no less than about 5%. In further embodiments, D has a deuterium enrichment of no less than about 10%. In still other embodiments, D has a deuterium enrichment of no less than about 20%. In still other embodiments, D has a deuterium enrichment of no less than about 30%. In still other embodiments, D has a deuterium enrichment of no less than about 40%. In yet further embodiments, D has a deuterium enrichment of no less than about 50%. In still other embodiments, D has a deuterium enrichment of no less than about 60%. In other embodiments, D has a deuterium enrichment of no less than about 70%. In further embodiments, D has a deuterium enrichment of no less than about 80%. In yet other embodiments, D has a deuterium enrichment of no less than about 90%. In still further embodiments, D has a deuterium enrichment of no less than about 98% of deuterium. In still further embodiments, D has a deuterium enrichment of no less than about 99% of deuterium. In still further embodiments, D has a deuterium enrichment of at least 99% of deuterium.

[00036] It has now been discovered that formulations of non-deuterated domperidone exhibited corrected QT (QT_c) prolongation, which can have potentially deadly effects. Without wishing to be held to any particular theory, it is speculated that the QT prolongation might be associated with the relatively high C_{max} that was also observed with those non-deuterated domperidone formulations.

[00037] Pharmaceutical formulations containing d_4-domperidone described herein exhibit a variety of unexpected effects when administered to *in vivo*. In some embodiments, these pharmaceutical formulations result in a reduced C_{max} as compared to formulations containing domperidone. In other embodiments, these pharmaceutical formulations result in a lowering of the AUC as compared to formulations containing domperidone. In further embodiments, these pharmaceutical formulations result in a reduced C_{max} and a comparable AUC. In addition, as disclosure herein, the described d_4-domperidone formulations have much higher bioavailability as compared to non-deuterated domperidone.

[00038] The pharmaceutical formulations contain about 1 to about 20% (w/w), based on the weight of the formulation, of d_4-domperidone. In some embodiments, the pharmaceutical formulations contain about 2 to about 19% (w/w), about 3 to about 18% (w/w), about 4 to about 17% (w/w), about 5 to about 16% (w/w), about 6 to about 15% (w/w), about 7 to about 15% (w/w), about 8 to about 14% (w/w), about 9 to about 13% (w/w), about 10 to about 12% (w/w), about 5 to about 15% (w/w), about 5 to about 14% (w/w), about 5 to about 13% (w/w), about 5 to about 12% (w/w), about 5 to about 11% (w/w), about 5 to about 10% (w/w), about 5 to about 9% (w/w), about 1 to about 15% (w/w), or about 1 to about 10% (w/w) of d_4-domperidone. In other embodiments, the pharmaceutical formulations contain about 5 to about 12% (w/w) of d_4-domperidone. In further embodiments, the pharmaceutical formulations contain about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, or about 20% (w/w) of d_4-domperidone. In still other embodiments the pharmaceutical formulations contain about 10% (w/w) of d_4-domperidone.

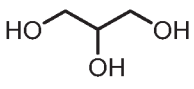
[00039] The amount of d_4-domperidone in the pharmaceutical formulations may also be expressed by way of an amount. In some embodiments, the pharmaceutical formulations contain about 1 to about 50 mg of d_4-domperidone. In other embodiments, the pharmaceutical formulations contain about 5 to about 45 mg, about 10 to about 40 mg, about 15 to about 35 mg, about 20 to about 30 mg, about 1 to about 45 mg, about 1 to about 40 mg, about 1 to about 35 mg, about 1 to about 30 mg, about 1 to about 25 mg, about 1 to about 20 mg, about 1 to about 15 mg, about 5 to about 50 mg, about 5 to about 40 mg, about 5 to about 35 mg, about 5 to about 30 mg, about 5 to about 25 mg, about 5 to about 20 mg, about 5 to about 15 mg, about 10 to about 50 mg, about 20 to about 50 mg, about 30 to about 50 mg, or about 40 to about 50 mg of d_4-domperidone. In further embodiments, the pharmaceutical

formulations contain about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, or about 50 mg of d_4-domperidone.

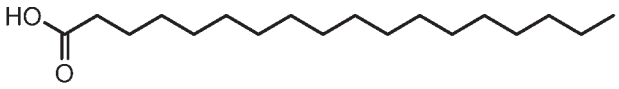
[00040] D_4-Domperidone Formulations Containing a Glyceryl Stearate and Medium Chain Triglyceride

[00041] In some embodiments, the present disclosure provides pharmaceutical formulations comprising d_4-domperidone or a pharmaceutically acceptable salt thereof, a glyceryl stearate, and a medium chain triglyceride.

[00042] As one component, the pharmaceutical formulations contain a glyceryl stearate. The term "glyceryl stearate" as used herein refers to a compound having glyceryl and stearate components as shown below, where the components are bound together to form a chemically stable molecule.



glyceryl



stearate

[00043] In some embodiments, the glyceryl stearate is a glyceryl palmitostearate. In other embodiments the glyceryl stearate is a glycerol distearate. In further embodiments, the glyceryl stearate is a glyceryl distearate. In yet other embodiments, the pharmaceutical formulation may contain combinations of glyceryl stearates. Thus, the pharmaceutical formulation may contain 1, 2, 3, 4, or more glyceryl stearates. In some embodiments, the pharmaceutical formulations contain glyceryl palmitostearate and glycerol distearate. In other embodiments, the pharmaceutical formulations contain glyceryl palmitostearate and glyceryl distearate. In further embodiments, the pharmaceutical formulations contain glycerol distearate and glyceryl distearate. In yet other embodiments, the pharmaceutical formulations contain glyceryl palmitostearate, glycerol distearate, and glyceryl distearate. In still other embodiments, the glyceryl stearate is Precirol® ATO 5.

[00044] The pharmaceutical formulations contain about 2 to about 20% (w/w), based on the weight of the formulation, of the glyceryl stearate. In some embodiments, the pharmaceutical

formulations contain about 5 to about 15% (w/w) of the glyceryl stearate. In further embodiments, the pharmaceutical formulations contain about 6 to about 14% (w/w), about 7 to about 13% (w/w), about 8 to about 12% (w/w), about 9 to about 11% (w/w), or 5 to about 15% (w/w) of the glyceryl stearate. In other embodiments, the pharmaceutical formulations contain about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15% (w/w) of the glyceryl stearate. In yet further embodiments, the pharmaceutical formulations contain about 9% (w/w) of the glyceryl stearate. In still other embodiments, the pharmaceutical formulations contain about 10% (w/w) of the glyceryl stearate.

[00045] The term "medium chain triglyceride" as used herein refers to triglycerides where the fatty acid moiety has an aliphatic tail of about 6 to about 12 carbon atoms. In some embodiments, the fatty acid moiety has an aliphatic tail of 6, 7, 8, 9, 10, 11, or 12 carbon atoms. In further embodiments, the fatty acid aliphatic tails are the same. In other embodiments, the fatty acid aliphatic tails are different. In still further embodiments, the fatty acid has an aliphatic tail of 6 carbon atoms, *i.e.*, the medium chain triglyceride is caproic acid. In yet other embodiments, the fatty acid has an aliphatic tail of about 8 carbon atoms, *i.e.*, the medium chain triglyceride is caprylic acid. In other embodiments, the fatty acid has an aliphatic tail of about 10 carbon atoms, *i.e.*, the medium chain triglyceride is capric acid. In further embodiments, the fatty acid has an aliphatic tail of about 12 carbon atoms, *i.e.*, the medium chain triglyceride is lauric acid.

[00046] The medium chain triglyceride is present in the pharmaceutical formulation at about 70 to about 90% (w/w), based on the weight of the formulation. In some embodiments, the pharmaceutical formulations contains about 72 to about 88% (w/w), about 74 to about 86 % (w/w), about 76 to about 84 % (w/w), about 78 to about 82% (w/w), about 70 to about 85% (w/w), about 70 to about 80% (w/w), about 75 to about 90% (w/w), about 75 to about 85% (w/w), about 75 to about 80% (w/w), about 80 to about 90% (w/w), about 80 to about 85% (w/w), or about 80 to about 90% (w/w) of the medium chain triglyceride. In further embodiments, the pharmaceutical formulations contain about 80 to about 85% (w/w) of the medium chain triglyceride. In other embodiments, the pharmaceutical formulations contain about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, or about 90% (w/w) of the medium chain triglyceride. In yet further

embodiments, the pharmaceutical formulations contain about 90% (w/w) of the medium chain triglyceride. In still other embodiments, the pharmaceutical formulations contain about 91% (w/w) of the medium chain triglyceride.

[00047] In some aspects, the pharmaceutical formulations contain about 1 to about 20% (w/w), of d_4-domperidone or a pharmaceutically acceptable salt thereof, about 2 to about 20% (w/w) of the glyceryl stearate and about 70 to about 90% (w/w) of the medium chain triglyceride. In other aspects, the pharmaceutical formulations contain about 5 to about 15% (w/w) of d_4-domperidone or a pharmaceutically acceptable salt thereof, about 5 to about 15% (w/w) of the glyceryl stearate, and about 80 to about 85% (w/w) of the medium chain triglyceride. In further aspects, the pharmaceutical formulations contain about 10% (w/w) of the glyceryl stearate and about 90% (w/w) of the medium chain triglyceride.

[00048] D_4-Domperidone Formulation Containing a Stearoyl Polyoxyl Glyceride, Nonionic Poly(ethylene oxide) Polymer, and Medium Chain Triglyceride

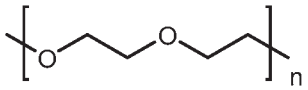
[00049] The present disclosure also provides pharmaceutical formulations comprising d_4-domperidone or a pharmaceutically acceptable salt thereof, a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride.

[00050] As a first component, the pharmaceutical formulations contain a stearoyl polyoxyl glyceride. The term "stearoyl polyoxyl glyceride" as used herein refers to a mixture of glycerol esters and polyethylene glycol. Typically, the polyethylene glycol has a mean molecular weight (M_n) of about 350 to about 1700. In some embodiments, the polyethylene glycol has a M_n of about 400 to about 1500, about 500 to about 1400, about 600 to about 1300, about 700 to about 1200, about 800 to about 1100, about 400 to about 1300, about 400 to about 1100, about 400 to about 900, about 400 to about 700, about 500 to about 1500, about 700 to about 1500, about 900 to about 1500, about 1100 to about 1500, or about 1300 to about 1500. In other embodiments the polyethylene glycol has a M_n of about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, about 1000, about 1050,about 1100, about 1150, about 1200, about 1250, about 1300, about 1350, about 1400, about 1450, about 1500, about 1550, about 1600, about 1650, or about 1700. In further embodiments, the polyethylene glycol has a M_n of about 1450 to about 1550. In still other embodiments, the mixture of polyethylene glycol and glycerol esters is a Gelucire® product (available from Gattefosse) such as Gelucire® 44/14

(containing mono, di- and triglycerides and PEG-32 (molecular weight of about 1450 to about 1550) mono- and diesters of lauric acid (C_{12}) having a melting range of about 42.5 to about 47.5°C, or critical micelle concentration (CMC) of 72 ± 53g/mL at about 25°C), Gelucire® 50/13 (containing mono, di- and triglycerides and PEG-32 (M_n of about 1450 to about 1550) mono- and diesters of palmitic (C_{16}) and stearic (C_{18}) acids, a melting range of about 46 to about 51°C, hydrophile-lipophile balance (HLB) of about 13, CMC of about 100 mg/L at about 25°C), Gelucire® 43/01 (containing mono-, di- and triglyceride esters of fatty acids (C_{8-18}), a melting range of about 42 to about 46°C, and/or HLB of about 1), or Gelucire® 48/16 (containing PEG-32 (molecular weight of about 1450 to about 1550) esters of fatty acids, a melting range of about 46 to about 50°C, HLB of about 16, and/or CMC of 153 ± 31 mg/L at about 25°C). In some embodiments, a stearoyl polyoxyl glyceride contains monoesters, diesters, and triesters of glycerol. In other embodiments, a stearoyl polyoxyl glyceride contains monoesters and diesters of polyethylene glycols. In further embodiments, the stearoyl polyoxyl glyceride contains (i) monoesters, diesters, and/or triesters of glycerol and (ii) monoesters and/or diesters of polyethylene glycols. In yet other embodiments, the stearoyl polyoxyl glyceride is a stearoyl polyoxyl-32 glyceride (containing 32 repeating oxyethylene units). In still further embodiments, the stearoyl polyoxyl glyceride is Gelucire® 50/13.

[00051] The pharmaceutical formulations contain about 3 to about 15% (w/w), based on the weight of the formulation, of the stearoyl polyoxyl glyceride. In some embodiments, the pharmaceutical formulations contain about 4 to about 14% (w/w), about 5 to about 13% (w/w), about 6 to about 12% (w/w), about 7 to about 11% (w/w), about 8 to about 10% (w/w), about 5 to about 12% (w/w), about 5 to about 10% (w/w), or about 6 to about 8% (w/w) of the stearoyl polyoxyl glyceride. In other embodiments, the pharmaceutical formulations contain about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15% (w/w) of the stearoyl polyoxyl glyceride. In further embodiments, the pharmaceutical formulations contain about 7% (w/w) of the stearoyl polyoxyl glyceride.

[00052] The pharmaceutical formulation also contains a nonionic poly(ethylene oxide) polymer. The term "nonionic poly(ethylene oxide)" as used herein refers to a polymer having the following structure that is a liquid at room temperature.



In some embodiments, n is about 2,000 to about 100,000. In other embodiments, n is about 2,000 to about 90,000; about 2,000 to about 80,000; about 2,000 to about 60,000; about 2,000 to about 40,000; about 2,000 to about 20,000; about 2,000 to about 10,000; about 2,000 to about 8,000; about 2,000 to about 6,000; about 2,000 to about 4,000; about 4,000 to about 100,000; about 8,000 to about 100,000; about 10,000 to about 100,000; about 20,000 to about 100,000; about 40,000 to about 100,000; about 60,000 to about 100,000; about 80,000 to about 100,000; about 4,000 to about 80,000; about 6,000 to about 60,000; about 8,000 to about 40,000; about 10,000 to about 20,000. In further embodiments, n is about 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; 10,000; 15,000; 20,000; 25,000; 30,000; 35,000; 40,000; 45,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000, 95,000; or 100,000.

[00053] In some embodiments, the nonionic poly(ethylene oxide) polymer has a molecular weight (M_w) of about 400,000 to about 8,000,000. In other embodiments, the nonionic poly(ethylene oxide) has a M_w of about 500,000 to about 8,000,000, about 600,000 to about 8,000,000, about 700,000 to about 8,000,000, about 800,000 to about 8,000,000, about 900,000 to about 8,000,000, about 1,000,000 to about 8,000,000, about 2,000,000 to about 8,000,000, about 3,000,000 to about 8,000,000, about 4,000,000 to about 8,000,000, about 5,000,000 to about 8,000,000, about 6,000,000 to about 8,000,000. In further embodiments, the nonionic poly(ethylene oxide) polymer has a M_w of about 500,000, about 600,000, about 700,000, about 800,000, about 900,000, about 1,000,000, about 2,000,000, about 3,000,000, about 4,000,000, about 5,000,000, about 6,000,000, about 7,000,000, or about 8,000,000. In yet other embodiments, the nonionic poly(ethylene oxide) has a M_w of about 7,000,000. In yet other embodiments, the nonionic poly(ethylene oxide) is polyethylene oxide 303. In still further embodiments, the nonionic poly(ethylene oxide) is POLYOX™ WSR 303.

[00054] The nonionic poly(ethylene oxide) polymer is present in the pharmaceutical formulations at about 5 to about 40% (w/w), based on the weight of the formulation. In some embodiments, the pharmaceutical formulations contain about 10 to about 35% (w/w), about 15 to about 30% (w/w), about 20 to about 25% (w/w), about 5 to about 35% (w/w), about 5 to about 30% (w/w), about 5 to about 25% (w/w), about 5 to about 20% (w/w), about 5 to about 15% (w/w), about 5 to about 10% (w/w), about 10 to about 40% (w/w), about 10 to about

30% (w/w), about 10 to about 20% (w/w), about 10 to about 25% (w/w), about 5 to about 35 % (w/w), about 5 to about 30% (w/w), about 5 to about 25% (w/w), or about 5 to about 20% (w/w) of the nonionic poly(ethylene oxide) polymer. In other embodiments, the pharmaceutical formulations contain about 12 to about 25% (w/w) of the nonionic poly(ethylene oxide) polymer. In other embodiments, the pharmaceutical formulations contain about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% (w/w) of the nonionic poly(ethylene oxide) polymer. In further embodiments, the pharmaceutical formulations contain about 19% (w/w) of the nonionic poly(ethylene oxide) polymer.

[00055] The pharmaceutical formulations further contain a medium chain triglyceride as defined above. In some embodiments, the fatty acid moiety has an aliphatic tail of about 6, 7, 8, 9, 10, 11, or 12 carbon atoms. In further embodiments, the medium chain triglyceride is caproic acid. In other embodiments, the medium chain triglyceride is caprylic acid. In yet further embodiments, the medium chain triglyceride is capric acid. In still other embodiments, the medium chain triglyceride is lauric acid.

[00056] The medium chain triglyceride is present in the pharmaceutical formulation at about 40 to about 80% (w/w), based on the weight of the formulation. In some embodiments, the pharmaceutical formulations contains about 45 to about 75% (w/w), about 50 to about 70% (w/w), about 55 to about 65% (w/w), about 50 to about 80% (w/w), about 60 to about 80% (w/w), about 70 to about 80% (w/w), about 40 to about 70% (w/w), about 40 to about 60% (w/w), or about 50 to about 70% (w/w) of the medium chain triglyceride. In further embodiments, the pharmaceutical formulations contain about 50 to about 68% (w/w) of the medium chain triglyceride. In other embodiments, the pharmaceutical formulations contain about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 51, about 52, about 53, about 54, about 55, about 56, about 57, about 58, about 59, about 60, about 61, about 62, about 63, about 64, about 65, about 66, about 67, about 68, about 69, about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, or about 80% (w/w) of the medium chain triglyceride. In still further embodiments, the pharmaceutical formulations contain about 64% (w/w) of the medium chain triglyceride.

[00057] In some aspects, the pharmaceutical formulations contain about 1 to about 20% (w/w), based on the weight of the formulation, of d_4-domperidone or a pharmaceutically

acceptable salt thereof, about 3 to about 15% (w/w) stearoyl polyoxyl glyceride, about 5 to about 40% (w/w) of the nonionic poly(ethylene oxide) polymer, and about 40 to about 80% (w/w) of the medium chain triglyceride. In other aspects, the pharmaceutical formulations contain about 5 to about 10% (w/w), based on the weight of the formulation, of d_4-domperidone or a pharmaceutically acceptable salt thereof, about 5 to about 10% (w/w) stearoyl polyoxyl glyceride, about 12 to about 25% (w/w) of the nonionic poly(ethylene oxide) polymer, and about 50 to about 68% (w/w) of the medium chain triglyceride.

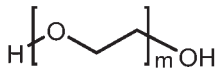
[00058] D_4-Domperidone Formulation Containing a Nonionic Poly(ethylene oxide) Polymer and Polyethylene Glycol

[00059] In further embodiments, the present disclosure provides pharmaceutical formulations comprising d_4-domperidone or a pharmaceutically acceptable salt thereof, a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

[00060] As one component, the pharmaceutical formulations contain a nonionic poly(ethylene oxide) polymer as defined above. In some embodiments, the nonionic poly(ethylene oxide) is polyethylene oxide 303. In further embodiments, the nonionic poly(ethylene oxide) is POLYOX™ WSR 303.

[00061] The nonionic poly(ethylene oxide) polymer is present in the pharmaceutical formulations at about 5 to about 30% (w/w), based on the weight of the formulation. In some embodiments, the pharmaceutical formulations contain about 10 to about 30% (w/w), about 15 to about 30% (w/w), about 20 to about 25% (w/w), about 5 to about 30% (w/w), about 5 to about 25% (w/w), about 5 to about 20% (w/w), about 5 to about 15% (w/w), about 5 to about 10% (w/w), about 10 to about 20% (w/w), about 10 to about 25% (w/w), or about 5 to about 20% (w/w) of the nonionic poly(ethylene oxide) polymer. In other embodiments, the pharmaceutical formulations contain about 10 to about 20% (w/w) of the nonionic poly(ethylene oxide) polymer. In further embodiments, the pharmaceutical formulations contain about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, or about 30% (w/w) of the nonionic poly(ethylene oxide) polymer. In still other embodiments, the pharmaceutical formulations contain about 15% (w/w) of the nonionic poly(ethylene oxide) polymer.

[00062] The pharmaceutical formulations also contain polyethylene glycol. The term "polyethylene glycol" as used herein refers to chemical compound having the following structure that is a liquid at room temperature, wherein m is about 7 to about 20.



In some embodiments, m is about 7 to about 15, about 7 to about 10, about 8 to about 15, about 8 to about 10, about 9 to about 15, or about 9 to about 13. In other embodiments, m is about m is about 8 to 9. In further embodiments, m is about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or about 20. In yet further embodiments, m is about 8. In still other embodiments, m is about 9. The polyethylene glycol has also a molecular weight (M_w) of about 300 to about 1,000. In some embodiments, the polyethylene glycol has a M_w of about 400 to about 900, about 500 to about 800, about 600 to about 700, about 300 to about 900, about 300 to about 800, about 300 to about 700, about 300 to about 600, about 300 to about 500, about 400 to about 1,000, about 500 to about 1,000, about 600 to about 1,000, about 700 to about 1,000, about 800 to about 1,000, or about 900 to about 1,000. In further embodiments, the polyethylene glycol has a M_w of about 400, about 450, about 500, about 550, 6 about 00, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1,000. In yet other embodiments, the polyethylene glycol has a M_w of about 400. In yet other embodiments, the polyethylene glycol is polyethylene glycol 400.

[00063] The pharmaceutical formulations contain about 70 to about 90% (w/w), based on the weight of the formulation, of the polyethylene glycol. In some embodiments, the pharmaceutical formulations contain about 70 to about 85% (w/w), about 70 to about 80% (w/w), about 70 to about 75% (w/w), about 75 to about 90% (w/w), about 80 to about 90% (w/w), or about 85 to about 90% (w/w) of the polyethylene glycol. In other embodiments, the pharmaceutical formulations contain about 70, about 71, about 72, about 73, about 74, about 75, about 76, about 77, about 78, about 79, about 80, about 81, about 82, about 83, about 84, about 85, about 86, about 87, about 88, about 89, or about 90% (w/w). In further embodiments, the pharmaceutical formulations contain about 75% (w/w) of the polyethylene glycol.

[00064] In some aspects, the pharmaceutical formulations contain about 1 to about 20% (w/w), based on the weight of the formulation, of d_4-domperidone or a pharmaceutically acceptable salt thereof, about 5 to about 30% (w/w) of the nonionic poly(ethylene oxide)

polymer and about 70 to about 90% (w/w) of the polyethylene glycol. In other aspects, the pharmaceutical formulations contain about 5 to about 10% (w/w), based on the weight of the formulation, of d_4-domperidone or a pharmaceutically acceptable salt thereof, about 10 to about 20% (w/w) of the nonionic poly(ethylene oxide) polymer and about 70 to about 80% (w/w) of the polyethylene glycol.

[00065] The pharmaceutical formulations described herein may also contain one or more antioxidants. In some embodiments, the pharmaceutical formulations contain one antioxidant. In other embodiments, the pharmaceutical formulations contain two antioxidants. In further embodiments, the pharmaceutical formulations contain three antioxidants. The antioxidant may be selected by those skilled in the art. In some embodiments, the antioxidant is ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, potassium metabisulfite, sodium metabisulfite, sodium thiosulfate, or vitamin E. In other embodiments, the antioxidant is BHA. In further embodiments, the antioxidant is BHT. In still other embodiments, the antioxidant is BHA and BHT.

[00066] The total amount of antioxidant in the pharmaceutical formulation is about 0.01 to about 0.5% (w/w), of the total weight of the formulation. In some embodiments, amount of one or more antioxidant in the pharmaceutical formulation is about 0.01 to about 0.4, about 0.01 to about 0.3, about 0.01 to about 0.2, about 0.01 to about 0.1, about 0.01 to about 0.05, about 0.05 to about 0.4, about 0.05 to about 0.3, about 0.05 to about 0.2, about 0.05 to about 0.1% (w/w). In other embodiments, the pharmaceutical formulations contain about 0.01, about 0.02, about 0.03, about 0.04, about 0.05, about 0.06, about 0.07, about 0.08, about 0.09, about 0.10, about 0.11, about 0.12, about 0.013, about 0.014, about 0.015, about 0.016, about 0.017, about 0.018, about 0.019, about 0.20, about 0.21, about 0.22, about 0.23, about 0.24, about 0.25, about 0.26, about 0.27, about 0.28, about 0.29, about 0.30, about 0.31, about 0.32, about 0.33, about 0.34, about 0.35, about 0.36, about 0.37, about 0.38, about 0.39, about 0.40, about 0.41, about 0.42, about 0.43, about 0.44, about 0.45, about 0.46, about 0.47, about 0.48, about 0.49, or about 0.50% (w/w). In further embodiments, the pharmaceutical formulations contain about 0.1% (w/w) of the antioxidant. In still other embodiments, the pharmaceutical formulations contain about 0.05% (w/w) of the antioxidant. In yet further embodiments, the pharmaceutical formulations contain about 0.15% (w/w) of the antioxidant. In other embodiments, the pharmaceutical formulations contain about 0.1% (w/w) BHA. In further

embodiments, the pharmaceutical formulations contain about 0.05% (w/w) of BHT. In yet other embodiments, the pharmaceutical formulations contain about 0.1% (w/w) BHA and 0.05% (w/w) of BHT.

[00067] The d_4-domperidone formulations described herein are useful in a variety of treatment methods including, without limitation, methods for treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, nausea and/or vomiting associated with chemotherapy, or a combination thereof. The methods include administering to the patient a pharmaceutical formulation described herein. In some embodiments, the methods are useful for treating gastroparesis. In other embodiments, the methods are useful for treating nausea apart from gastroparesis. In further embodiments, the methods are useful for treating vomiting apart from gastroparesis. In yet other embodiments, the methods are useful for treating nausea associated with gastroparesis. In still further embodiments, the methods are useful for treating vomiting associated with gastroparesis. In other embodiments the methods are useful for treating gastroesophageal reflux disease. In further embodiments, the methods are useful for treating insufficient lactation. In still other embodiments, the methods are useful for treating nausea and/or vomiting associated with chemotherapy.

[00068] The pharmaceutical formulations may be administered by any route that would be acceptable for administered of non-deuterated domperidone. In some embodiments, the pharmaceutical formulations the administration is oral, transdermal, parenteral, or a combination thereof. In further embodiments, administration is oral.

[00069] The pharmaceutical formulations may be formulated for administration in solid or liquid forms. In some embodiments, the pharmaceutical formulations are formulated in the form of a tablet, caplet, capsule, powder, softgel, suspension or liquid, or a combination thereof. In other embodiments, the pharmaceutical formulations are formulated in the form of a tablet. In further embodiments, the pharmaceutical formulations are formulated in the form of a caplet. In yet other embodiments, the pharmaceutical formulations are formulated in the form of a capsule. In still further embodiments, the pharmaceutical formulations are formulated in the form of a powder. In other embodiments, the pharmaceutical formulations are formulated in the form of a softgel. In further embodiments, the pharmaceutical

formulations are formulated in the form of suspension. In yet other embodiments, the pharmaceutical formulations are formulated in the form of a liquid.

[00070] The following Examples are provided to illustrate some of the concepts described within this disclosure. While each Example is considered to provide specific individual embodiments of formulations, methods of preparation and use, none of the Examples should be considered to limit the more general embodiments described herein.

[00071] In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C; C_{max} = maximum plasma concentration; t_{max} = time of maximum plasma concentration; MRT_{last} = mean residence time, calculated to the last observable time point; AUC_{last} = area under the curve, calculated to the last observable time point.

EXAMPLES

Example 1: Formulation Preparation

[00072] Five formulations, *i.e.*, A-E, containing d_4-domperidone were prepared by combining the components identified in Table 1.

Table 1

Ingredient	Formulation (%)				
	A	B	C	D Tablet	E
d_4-Domeridone	10.0	9.6	10.0	2.5	4.6
Precirol ATO 5	9.75	0	0	0	0
Gelucire 50/13	0	7.2	0	0	0
Cremophor RH40	0	0	0	0	13.9
PEO 303	0	19.4	15.0	20.0	0
PEG 400	0	0	75.0	0	6.9
Avicel PH 102	0	0	0	77.5	0
Compritol ATO 888	0	0	0	0	10.0
Oleic acid	0	0	0	0	64.6
MCT	80.25	63.8	0	0	0
Fill/Tablet Weight (mg)	100.0	104.0	100.0	400.0	217.0

[00073] Formulations A-C and E were formulated as liquid or semi solid and filled into capsules and formulation D was compressed to form a tablet using a single station carver press.

Example 2: Dog PK study with d_4-Domperidone Formulations

[00074] In this study, the oral exposure of domperidone and d_4-domperidone was evaluated in male Beagle dogs following oral administration of various capsule or tablet formulations of d_4-domperidone as shown in Example 1 and a suspension formulation of domperidone prepared by combining 0.5% Methocel™ cellulose ether, 0.2% polysorbate 80 (Tween® 80), and 0.72% lactic acid.

[00075] Each d_4-domperidone formulation was dosed orally (PO) at 10 mg/dog, and the domperidone formulation was dosed orally at 1 mg/kg. Blood samples were collected up to 24 hours post-dose and plasma concentrations of domperidone or domperidone-d_4 were determined by LCMS/MS. Pharmacokinetic parameters were determined using Phoenix WinNonlin (v8.0) software. Average plasma concentrations and pharmacokinetic parameters are summarized in Table 2.

Table 2

Measurement	Formulation					
	A	B	C	D	E	F
Weight Dosed (mg)	10	10	10	10	10	10
Dose (mg/kg)	0.8	0.9	0.9	0.8	0.9	1
C_{max} (ng/mL)	23.7	38.5	55.1	7.09	165	100
t_{max} (hr)	3	3	2	3	0.8	1
MRT_{last} (hr)	7.9	6.46	4.64	10.2	3.1	3.34
AUC_{last} (hr ng/mL)	332	415	359	130	641	475

[00076] Table 2 provides the measured C_{max}, t_{max}, MRT_{last}, and AUC_{last} and illustrate that Formulations A-C showed a significant reduction in C_{max}, a longer MRT and comparable AUC as compared to Formulation F. Formulation D showed much lower C_{max} and AUC and a much higher MRT compared to Formulation F. However, Formulation E showed a much higher C_{max} and AUC compared to Formulation F. See, FIGs. 1-2.

Example 3: Dog Cardiovascular Study Showing QT_c Minimizing Using d_4-Domperidone

[00077] The potential cardiovascular effects of non-deuterated domperidone and d_4-domperidone were evaluated in beagle dogs. Oral suspensions were administered via gavage for comparison purposes.

[00078] In one study the non-deuterated domperidone was evaluated using a formulation of 0.5% Methocel™ (hydroxy propyl methylcellulose), 0.2% polysorbate 80 (Tween® 80), and 0.72% lactic acid in sterile water for injection. USP. The d_4-domperidone formulation was Formulation A, Example 1. For the non-deuterated domperidone, formulations were prepared

by mixing the appropriate amount of vehicle with the appropriate amount of non-deuterated domperidone to achieve a nominal concentration of 0.2, 1 and 4 mg/mL Beagle dogs were dosed at a volume of 5 mL/kg by gavage to provide doses of 1, 5 and 20 mg/kg and a vehicle control. See Table 3. One animal/treatment was dosed each week with at least a 2-day washout period between administrations until each animal received all treatments. The same 4 animals received treatments according to a Latin square design. Systolic blood pressure, diastolic blood pressure, heart rate and Lead II electrocardiogram were continuously recorded. The measurements started 1.5 hrs prior to the dose administration and all parameters were continuously recorded 24 hrs following the end of dosing of the last animal.

Table 3

Treatment Number	Route of Administration	Dose Level (mg/kg)	Number of Male Animals
1	Gavage	0	4
2	Gavage	1	4
3	Gavage	5	4
4	Gavage	20	4

[00079] The individual animal correction (QT_cVdW) was calculated using Van de Water formula. When corrected with the Van de Water formula, QT_cVdW was increased up to 23 and 21 msec at doses of 5 and 20 mg/kg, respectively after dosing with the non-deuterated domperidone.

[00080] Table 4 indicates the change (% and ms) from the appropriate time-matched control for each non-deuterated domperidone treatment.

Table 4: QT_c Percent Change

Treatment	Segment 1 (0-6 hours)	Segment 2 (7-24 hours)	Maximum % Change/Time	Duration of Effect (hours post dose)
1 mg/kg	+6% (13 ms)	+2% (4 ms)	6% (2 hours)	1 - 2
5 mg/kg	+11% (23 ms)	+7% (15 ms)	11% (2 hours)*	0.5 - 6
20 mg/kg	+10% (21 ms)	+7% (16 ms)	10% (2 hours)*	0.5 – 4
ms – milliseconds * – statistically significant				

[00081] For the deuterated domperidone, male dogs were, independently, orally administered the vehicle (0 mg; capsule) and capsules containing d_4-domperidone at dose levels of 20, 110, or 385 mg. One animal/treatment was dosed each week with at least a 3-day washout period between administrations until each animal received all treatments. See, Table

5. The same 5 animals received all treatments according to a Latin square design with at least a 3-day washout between treatments. Body temperature, blood pressure, heart rate, and the electrocardiogram (ECG) were monitored continuously for at least 2 hours prior to dosing and for at least 24 hours post dose.

Table 5

Treatment Number	Route of Administration	Dose Level	Number of Male Animals
1	Capsule	0 mg	5
2	Capsule	20 mg	5
3	Capsule	110 mg	5
4	Capsule	385 mg	5

[00082] Three days prior to the study, the animals were continuously monitored for at least 24 hours for body temperature and cardiovascular endpoints while on the stock colony (10 days prior to the first administration). These data were collected in 1-minute intervals. The first 24 hours of the data were used in the calculation of the QTc interval. Body temperature, blood pressure, heart rate (derived from blood pressure and ECG), and the ECG were monitored continuously from at least 2 hours predose until at least 24 hours post dose. Data were collected and analyzed in 1-minute intervals and are reported in 15-minute intervals. The QT_c interval was calculated using a procedure based on the method described by Spence ("The heart rate corrected QT interval of conscious beagle dogs: a formula based on analysis of covariance," Toxicol Sci, 1998; 45:247 258) and modified by Miyazaki and Tagawa ("Rate-correction technique for QT interval in long term telemetry ECG recording in beagle dogs," Exp. Anim., 2002; 51:465 475). Blood samples (approximately 1 mL) were collected via jugular vein and 8 and 24 hours post dose to confirm exposure.

[00083] There was a time-dependent increase in QT_c interval following the 110 mg and 385 mg, treatments which were of a similar magnitude between treatments. Individual time intervals from 9 to 20 hours following the 110 mg and 385 mg treatments achieved statistical significance with a maximum increase of up to 13% (30 ms) compared with the time-matched vehicle treatment. Table 6 indicates the change (% and ms) from the appropriate time-matched control for each d_4-domperidone treatment.

Table 6: QT_c Percent Change				
Treatment	**Segment 1 (0-6 hours)**	**Segment 2 (7-24 hours)**	**Maximum % Change/Time**	**Duration of Effect (hours post dose)**
20 mg	+1% (3 ms)	+0% (1 ms)	4% (3.5 hours)	1.5-12
110 mg	+5% (12 ms)	+1% (2 ms)	10% (5 hours)*	0.5-12
385 mg	+8% (17 ms)	+6% (13 ms)	13% (6 hours)*	0.5-24+
ms – milliseconds * – statistically significant				

[00084] FIGs. 9 and 10 illustrate the effect of different doses of d_4-domperidone and non-deuterated domperidone on QT_c change. The graphs demonstrate that at lower doses of the non-deuterated formulation there is a greater effect on QT_c change as compared to the higher doses of the deuterated formulation. This is also graphically represented in Figs. 11 and 12 which shows the effect of QT_c change at the maximal plasma concentration.

Example 4: Comparison of PK parameters for suspension formulations of d_4-domperidone and domperidone

[00085] The C_{max} and AUC values of domperidone and d_4-domperidone dosed at different doses in dogs were compared. The data for non-deuterated domperidone was obtained as described in Heykants, "On the pharmacokinetics of domperidone in animals and man I. Plasma levels of domperidone in rats and dogs. Age related absorption and passage through the blood brain barrier in rats," European J. of Drug Metabolism and Pharmacokinetics, 1981, 6(1):27-36, which is hereby incorporated by reference, where dogs were dosed capsules containing different amounts of domperidone.

[00086] The d_4-domperidone suspension formulation was prepared and contained 0.5% Methocel, 0.1% polysorbate 80 and 0.72% lactic acid. The d_4-domperidone suspension was then administered to dogs as described in Example 2 or 3 at the different doses shown in Table 7.

Table 7				
Dose (mg/kg)	**d_4-Domperidone Suspension**	**Domperidone Suspension**	**D_4-Domperidone Suspension**	**Domperidone Suspension**
	C_{max}		**AUC**	
2.5	-	94	-	700
3	356	-	1440	-
10	1570	322	6760	2600
40	5610	975	34200	8900

[00087] The data as shown in Table 7 and Fig. 8 show that d_4-domperidone provides a significantly higher bioavailability, including a higher C_{max} (4 to 5 fold) and AUC (2 to 4 fold) compared to domperidone.

Example 5: Dog PK study for blunting C_{max}

[00088] In this study, the oral exposure of domperidone and d_4-domperidone was evaluated in male Beagle dogs following oral administration of capsules independently containing Formulations A and B of d_4-domperidone of Example 1and a suspension formulation of domperidone prepared by combining 0.5% Methocel™ cellulose ether, 0.2% polysorbate 80 (Tween® 80), and 0.72% lactic acid. The compositions of the d_4-domperidone formulations (A and B) are repeated in Table 8.

Table 8

Ingredient	Amount (%)
Formulation A	
d_4-domperidone	10.0
Precirol ATO 5	9.75
Medium Chain Triglycerides	80.25
Total	100.0
Formulation B	
d_4-domperidone	9.6
Gelucire 50/13	7.2
PEO 303	19.4
Medium Chain Triglycerides	63.8
Total	100.0

[00089] The d_4-domperidone formulation was dosed orally (PO) at 10 mg/dog and the domperidone formulation was dosed orally at 1 mg/kg. Blood samples were collected up to 24 hours post-dose and plasma concentrations of domperidone or d_4-domperidone were determined by LCMS/MS. Pharmacokinetic parameters were determined using Phoenix WinNonlin (v8.0) software. Average plasma concentrations and pharmacokinetic parameters are summarized in Table 9.

Table 9

	Formulation A	Formulation B	Formulation F (domperidone)
Weight Dosed (mg)	10	10	10
Dose (mg/kg)[1]	0.8	0.9	1
C_{max} (ng/mL)	23.7	38.5	39.2
t_{max} (hr)	3	3	0.67
MRT_{last} (hr)	7.9	6.46	2.57
AUC_{last} (hr·ng/mL)	350[1]	415[1]	129

[1] dose normalized to 1 mg/kg

[00090] See, FIG. 5. These data illustrate that Formulation A showed a significant reduction in C_{max} compared to the non-deuterated domperidone and both Formulation A and B showed a significant increase in AUC mean residence time compared to non-deuterated domperidone.

Example 6: Dog PK study with Formulation A

[00091] In this study, the oral exposure of domperidone and a d_4-domperidone formulation was evaluated in male Beagle dogs. A capsule formulation of d_4-domperidone ("Formulation A" from Example 1) as repeated in Table 10 and a suspension formulation of domperidone prepared by combining 0.5% Methocel™ cellulose ether, 0.2% polysorbate 80 (Tween® 80), and 0.72% lactic acid were, independently, prepared.

Table 10: Formulation A

Ingredient	**Amount (%)**
d_4-domperidone	10.0
Precirol ATO 5	9.75
Medium Chain Triglycerides	80.25
Total	100.0

[00092] The d_4-domperidone formulation was dosed orally (PO) at 10 mg/dog, and the domperidone formulation was dosed orally at 1 mg/kg. Blood samples were collected up to 36 hours post dose and plasma concentrations of domperidone or d_4-domperidone were determined by LCMS/MS. Pharmacokinetic parameters were determined using Phoenix WinNonlin (v8.0) software. Average plasma concentrations and pharmacokinetic parameters are summarized in Table 11.

Table 11

	Domperidone	**d_4-domeridone (Formulation A)**	**Change**
C_{max} (ng/mL)	52.7 (0.656)	14.3 (3.9)	-72.87%
MRT_{last} (hr)	5.00 (0.327)	14.8 (2.88)	2.96 x
AUC_{∞} (hr·ng /mL)	335	315	-5.97%

[00093] See, FIG. 6. These data illustrate that Formulation A shows similar AUC, significant reduction in C_{max} and increase in mean residence time compared to non-deuterated domperidone.

Example 7: Use of Anti-Oxidants

[00094] A study was conducted to evaluate the effect of antioxidants on the degradation of d_4-domperidone. Samples were prepared and analyzed initially and stored at 60°C and analyzed again after 28 days. A reversed phase HPLC method was used for the determination of impurities of d_4-domperidone. Gradient HPLC analysis was performed using a Waters Atlantis dC_{18} (or equivalent) column, methanol containing ammonium acetate mobile phase and UV detection. The formulation is shown in Table 12 and the results for formulations with and without antioxidants is provided in Table 13.

Table 12

Ingredient	%	mg/capsule
d_4-domperidone	10.00%	10.00
Precirol ATO 5	9.75%	9.75
Butylatedhydroxyanisole (BHA)	0.10%	0.10
Butylatedhydroxytoluene (BHT)	0.05%	0.05
Medium Chain Triglycerides (MCT)	80.1%	80.10
Total		**100.0 mg**

Table 13: Summary of Impurity Results

Impurity Peak	% Impurity		
	Formulation without BHT/BHA T=0	Formulation without BHT/BHA T=28	Formulation with BHT/BHA
RRT 0.45	0.040	0.039	0.051
RRT 0.76	1.548	1.682	0.045
RRT 0.93	0.034	0.033	0.053
RRT 1.09	0.123	0.108	0.155
RRT 1.12	0.144	0.140	0.146
RRT 1.14	0.373	0.352	0.381
RRT 1.26	0.508	0.461	0.515
Total Impurities	2.77	2.82	1.35

[00095] These data illustrate that the formulations containing antioxidant resisted oxidation under 60°C heat condition. However, samples lacking antioxidant, under the same heating conditions, showed significant amount of oxidation.

Example 8

[00096] D_4-domperidone pharmaceutical formulations were prepared and encapsulated on a GMP encapsulation machine using the amounts noted in Tables 14-16. Specifically, the compounding activities were conducted under a nitrogen blanket and yellow light. See, FIG. 7. The batches were then encapsulated using the 2C Oval die and 0.040" hole single bottom

shot wedge at a temperature of about 38.7 to 51.7°C. Capsules were hand polished with a medium chain triglyceride/lecithin mixture (97% MCT/3%lecithin).

Table 14: Formulation for d_4-Domperidone Placebo Softgels Fill

Ingredient	Theoretical Quantity/capsule (mg)	Theoretical Quantity (g)
Medium Chain Triglycerides	90.1	4505.0
Glyceryl Distearate	9.75	487.5
Butylated Hydroxyanisole, NF	0.1	5.0
Butylated Hydroxytoluene, NF	0.05	2.5
Total	100.0	5000.0

Table 15: Formulation for d_4-Domperidone 5 mg Softgels Fill

Ingredient	Theoretical Quantity/capsule (mg)	Theoretical Quantity (g)
d_4-Domperidone	5.0	100.00
Medium Chain Triglycerides	85.1	1702.00
Glyceryl Distearate	9.75	195.00
Butylated hydroxyanisole, NF	0.1	2.00
Butylated hydroxytoluene, NF	0.05	1.00
Total	100.0	2000.00

Table 16: Formulation for d_4-Domperidone 10 mg Softgels Fill

Ingredient	Theoretical Quantity/capsule (mg)	Theoretical Quantity (g)
d_4-Domperidone	10.0	200.00
Medium Chain Triglycerides	80.1	1602.00
Glyceryl Distearate	9.75	195.00
Butylated Hydroxyanisole, NF	0.1	2.00
Butylated Hydroxytoluene, NF	0.05	1.00
Total	100.0	2000.00

[00097] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description and the examples that follow are intended to illustrate and not limit the scope of the invention. It will be understood by those skilled in the art that various changes may be made, and equivalents may be substituted without departing from the scope of the invention, and further that other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. In addition to the embodiments described herein, the present invention contemplates and claims those inventions resulting from the combination of features of the

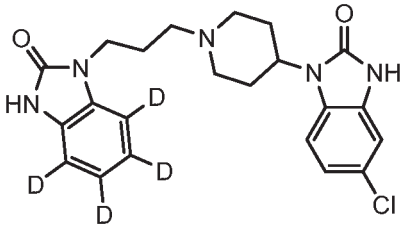
invention cited herein and those of the cited prior art references which complement the features of the present invention. Similarly, it will be appreciated that any described material, feature, or article may be used in combination with any other material, feature, or article, and such combinations are considered within the scope of this invention.

[00098] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, each in its entirety, for all purposes.

What is Claimed is:

1. A pharmaceutical formulation comprising:

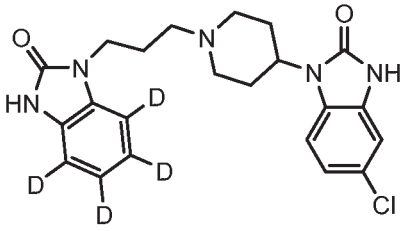
(i) deuterated d_4-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a glyceryl stearate, and a medium chain triglyceride;

or

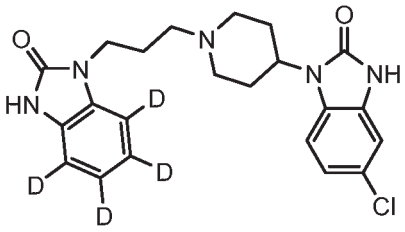
(ii) deuterated d_4-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride;

or

(iii) deuterated d_4-domperidone of the formula (I):



(I) or a pharmaceutically acceptable salt thereof; a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

2. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a glyceryl stearate, and a medium chain triglyceride.

3. The pharmaceutical formulation of claim 1 or 2, wherein the glyceryl stearate is a glyceryl palmitostearate, a glycerol distearate, a glyceryl distearate, or a combination thereof.

4. The pharmaceutical formulation of any one of the preceding claims, comprising about 2 to about 20% (w/w), based on the weight of the formulation, of the glyceryl stearate, preferably about 5 to about 15% (w/w), or more preferably about 10% (w/w).

5. The pharmaceutical formulation of any one of the preceding claims, comprising about 70 to about 90% (w/w), based on the weight of the formulation, of the medium chain triglyceride, or preferably about 80 to about 85% (w/w).

6. The pharmaceutical formulation of any one of the preceding claims, wherein the glyceryl stearate is Precirol® ATO 5.

7. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a stearoyl polyoxyl glyceride, a nonionic poly(ethylene oxide) polymer, and a medium chain triglyceride.

8. The pharmaceutical formulation of claim 7, comprising about 3 to about 15% (w/w), based on the weight of the formulation, of the stearoyl polyoxyl glyceride, preferably about 5 to about 10% (w/w), or more preferably about 7% (w/w).

9. The pharmaceutical formulation of claim 7 or 8, comprising about 5 to about 40% (w/w), based on the weight of the formulation, of the nonionic poly(ethylene oxide) polymer, preferably about 12 to about 25% (w/w), or more preferably about 19% (w/w).

10. The pharmaceutical formulation of any one of claims 7 to 9, comprising about 40 to about 80% (w/w), based on the weight of the formulation, of the medium chain triglyceride, preferably about 50 to 68% (w/w), or more preferably about 64% (w/w).

11. The pharmaceutical formulation of any one of claims 7 to 10, wherein the stearoyl polyoxyl glyceride is Gelucire® 50/13.

12. The pharmaceutical formulation of any one of claims 7 to 11, wherein the nonionic poly(ethylene oxide) polymer is polyethylene oxide 303.

13. The pharmaceutical formulation of claim 1, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, a nonionic poly(ethylene oxide) polymer, and a polyethylene glycol.

14. The pharmaceutical formulation of claim 13, comprising about 5 to about 30% (w/w), based on the weight of the formulation, of the nonionic poly(ethylene oxide) polymer, preferably about 10 to about 20% (w/w), or more preferably about 15% (w/w).

15. The pharmaceutical formulation of claim 13 , comprising about 70 to about 90% (w/w), based on the weight of the formulation, of the polyethylene glycol, preferably about 70 to about 80% (w/w), or more preferably about 75% (w/w).

16. The pharmaceutical formulation of any one of claims 13 to 15, wherein the nonionic poly(ethylene oxide) polymer has a M_w of about 400,000 to about 8,000,000.

17. The pharmaceutical formulation of any one of claims 13 to 16, wherein the nonionic poly(ethylene oxide) polymer has a M_w of about 7,000,000.

18. The pharmaceutical formulation of any one of claims 13 to 17, wherein the polyethylene glycol has a M_w of about 300 to about 1000.

19. The pharmaceutical formulation of any one of claims 13 to 18, wherein the polyethylene glycol has a M_w of about 400.

20. The pharmaceutical formulation of any one of the preceding claims, further comprising an antioxidant.

21. The pharmaceutical formulation of claim 20, wherein the antioxidant is ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, potassium metabisulfite, sodium metabisulfite, sodium thiosulfate, or vitamin E, or preferably butylated hydroxyanisole or butylated hydroxytoluene.

22. The pharmaceutical formulation of any one of the preceding claims, comprising about 1 to about 20% (w/w), based on the weight of the formulation, of d_4-domperidone, preferably about 5 to about 12% (w/w), or more preferably about 10% (w/w).

23. The pharmaceutical formulation of any one of the preceding claims, comprising about 1 to about 50 mg of d_4-domperidone.

24. A method for treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient, comprising administering to the patient the formulation of any one of claims 1 to 23.

25. The method of claim 24, wherein the administration is oral, transdermal, parenteral, or a combination thereof.

26. The method of claim 24 or 25, wherein the administration is oral.

27. The method of any one of claims 24 to 26, wherein the formulation is in the form of a tablet, capsule, softgel, suspension, liquid, or combination thereof.

28. The method of any one of claims 24 to 27, wherein the disorder is gastroparesis.

29. The method of any one of claims 24 to 27, wherein the disorder is gastroesophageal reflux disease.

30. The method of any one of claims 24 to 27, wherein the disorder is insufficient lactation.

31. A pharmaceutical formulation of any one of claims 1 to 23 for use in treating a disorder that is gastroparesis, nausea apart from gastroparesis, vomiting apart from gastroparesis, nausea associated with gastroparesis, vomiting associated with gastroparesis, gastroesophageal reflux disease, insufficient lactation, or a combination thereof in a patient.

32. The pharmaceutical composition of claim 31, wherein the formulation is in the form of a tablet, capsule, softgel, suspension, liquid, or combination thereof.

33. The pharmaceutical composition of claim 31 or 32, wherein the disorder is gastroparesis.

34. The pharmaceutical composition of claim 31 or 32, wherein the disorder is gastroesophageal reflux disease.

35. The pharmaceutical composition of claim 31 or 32, wherein the disorder is insufficient lactation.