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(57) **Abrégé/Abstract:**

Non-vein irritating pharmaceutical formulations (e.g., oil-in-water emulsions, frozen formulations, and lyophilized formulations) of vancomycin and clarithromycin are provided. Also provided are methods for preparing and using such formulations.



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(57) Abstract: Non-vein irritating pharmaceutical formulations (e.g., oil-in-water emulsions, frozen formulations, and lyophilized formulations) of vancomycin and clarithromycin are provided. Also provided are methods for preparing and using such formulations.



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PHARMACEUTICAL COMPOSITIONS FOR VEIN IRRITATING DRUGS

BACKGROUND

Technical Field

The present invention relates generally to the field of pharmaceutical formulations for intravenous administration of vein irritating drugs. Specifically, the present invention relates to formulations for delivering vein irritating antibiotic drugs, such as vancomycin and clarithromycin.

Description of the Related Art

It is well known that many intravenously injected drugs cause vein irritation or phlebitis at the injection site. Vancomycin is one of them. Vancomycin is an important antibiotic drug that is active against most gram-positive bacteria, and is particularly effective in clinically precarious settings, including against methicillin-resistant *Staphylococcus aureus* and other multidrug-resistant organisms, against staphylococcal and streptococcal infections in penicillin- and cephalosporin-allergic patients, and against *Clostridium difficile* in pseudomembranous colitis. Vancomycin is not absorbed well when given orally, and intravenous injection is the main route of administration used for systemic infections. It is widely reported that vancomycin causes phlebitis, which is a severe form of vein irritation and inflammation (Clin Pharm. 1988 Oct; 7(10):720-1), with incidence occurred in up to 13% of patients (Archives of Pathology and Laboratory Medicine, 2000 Dec; 124(2)322-3). The prevention and treatment of vancomycin associated phlebitis add significantly, as much as 45%, to the total cost of vancomycin treatment (Pharmacotherapy, 1994 Jul-Aug; 14(4):438-45).

The current intravenous vancomycin products are available in two formulations. The first formulation is listed in the United State Pharmacopoeia (USP) as Sterile Vancomycin Hydrochloride, USP. It is provided in vials containing lyophilized (freeze-dried) sterile powder of vancomycin hydrochloride equivalent to either 500 mg or 1 g vancomycin activity. The formulation may also contain hydrochloric acid and/or sodium hydroxide for pH adjustment. When reconstituted with Sterile Water for Injection, USP, it forms a clear solution with pH of about 4.0 (2.5 to 4.5). The second formulation is provided as a frozen, iso-osmotic sterile, non-pyrogenic premixed 100 mL or 200 mL solution containing 500 mg or 1 g Vancomycin, USP, respectively, as vancomycin hydrochloride. Each 100 mL of solution contains approximately 5 g of Dextrose Hydrus, USP. The pH of the

solution has been adjusted with hydrochloric acid and/or sodium hydroxide. Thawed solutions have a pH in the range of 3.0 to 5.0. After thawing to room temperature, this solution is available for intravenous use. This formulation is packaged in a plastic container (e.g., VANCOCIN® HCl in GALAXY Plastic Container (PL2040) for intravenous use Only), also listed in the USP..

Since vancomycin is sensitive to oxidation and hydrolysis degradation in solution, it must be either lyophilized or frozen to provide sufficiently long shelf life. In solution, it is more stable in acidic than neutral or alkaline environments, therefore both the lyophilized and the frozen formulations are adjusted to about pH 4.

While these simple solution formulations are able to preserve the chemical integrity of vancomycin during storage, they are incapable of preventing the phlebitis caused by vancomycin. Vancomycin in its current formulations must be given slowly as a diluted solution, and the sites of infusion need be rotated to reduce frequency and severity of the vein irritation caused by vancomycin (Product Description for Sterile Vancomycin Hydrochloride, USP).

Clarithromycin is another vein irritating antibiotic when administered intravenously. The currently available intravenous clarithromycin formulation, KLARICID® by Abbott Labs, is approved only in the United Kingdom and certain other European countries, and is not licensed in the United States. Local tolerability of intravenous clarithromycin formulation was reported as problematic. For example, Zimmerman *et al.* (Clinical Drug Investigation 21: 527-36, 2001) reported various adverse events at the injection sites from the intravenous clarithromycin (KLARICID®) administration, including phlebitis (50%), vein inflammation (75%), and vein irritation (100%).

BRIEF SUMMARY

Both freeze-stable and lyophilizable oil-in-water emulsions of vancomycin are provided. In addition, frozen or lyophilized vancomycin formulations that are stable upon storage and capable of being reconstituted to sub-micron size emulsions are also provided. Methods of preparing the oil-in-water emulsions and frozen or lyophilized formulations of vancomycin are further provided. Similar methods may be used to prepare oil-in-water emulsions and frozen or lyophilized formulations of clarithromycin. The resulting vancomycin and clarithromycin formulations may be used in treating or reducing infection and other diseases.

In one aspect, a freeze-stable oil-in-water emulsion is provided that comprises: (i) vancomycin at a concentration of about 0.1% to about 3% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 2% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water.

In certain embodiments, the one or more liquid oils of the freeze-stable vancomycin oil-in-water emulsion comprise soybean oil.

In certain embodiments, the one or more liquid oils of the freeze-stable oil-in-water vancomycin emulsion comprise a vegetable oil and a medium chain triglyceride.

In certain embodiments, the one or more phospholipids of the freeze-stable vancomycin oil-in-water emulsion comprise lecithin.

In certain embodiments, the freeze-stable oil-in-water emulsion comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil at a concentration of about 1% to about 2% by weight, (3) medium chain triglyceride at a concentration of about 1% to about 2% by weight, (4) lecithin at a concentration of about 2% to about 4% by weight, and (5) dextrose at a concentration of about 5% to about 6% by weight.

In certain embodiments, the freeze-stable oil-in-water emulsion comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1, (3) lecithin at a concentration of about 2% by weight, and (4) dextrose at a concentration of about 5% by weight.

In certain embodiments, the average size of the oil droplets in the freeze-stable vancomycin oil-in-water emulsion is no more than about 200 nm, and the PFAT5 is less than about 0.05.

In certain embodiments, the freeze-stable oil-in-water vancomycin emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion.

In certain embodiments, less than about 30% of vancomycin is in the oil droplets of the freeze-stable oil-in-water emulsion.

In another aspect, a frozen composition is provided that comprises:
(i) vancomycin at a concentration of about 0.5% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one
5 or more phospholipids at a total concentration of about 1% to about 5% by weight; wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water; wherein when thawed, the composition forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm and a PFAT of less than about
10 0.05.

In certain embodiments, the one or more liquid oils of the frozen vancomycin composition comprise a vegetable oil and a medium chain triglyceride.

In certain embodiments, the frozen vancomycin composition does not further comprise a compound that increases the amount of vancomycin in the oil
15 droplets of the emulsion formed by thawing the frozen vancomycin composition.

In certain embodiments, when the frozen vancomycin composition is thawed to form an oil-in-water emulsion, less than about 30% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

In another aspect, a method for treating or reducing infection is provided that comprises administering to a patient in need thereof a
20 pharmaceutically effective amount of the freeze-stable vancomycin oil-in-water emulsion described herein.

In a related aspect, a method for treating or reducing infection is provided that comprises administering to a patient in need thereof a
25 pharmaceutically effective amount of an oil-in-water vancomycin emulsion formed by thawing the frozen vancomycin composition described herein.

In another aspect, a freeze-stable oil-in-water emulsion is provided that comprises: (i) clarithromycin at a concentration of at least about 0.5% by weight or a pharmaceutically acceptable salt or ester of clarithromycin at an
30 equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water.

35 In certain embodiments, the one or more liquid oils of the freeze-stable clarithromycin oil-in-water emulsion comprise soybean oil.

In certain embodiments, the one or more liquid oils of the freeze-stable clarithromycin oil-in-water emulsion comprise a vegetable oil and a medium chain triglyceride.

5 In certain embodiments, the one or more phospholipids of the freeze-stable clarithromycin oil-in-water emulsion comprise lecithin.

In certain embodiments, the freeze-stable clarithromycin oil-in-water emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

10 In certain embodiments, less than about 30% of clarithromycin is in the oil droplets of the freeze-stable clarithromycin oil-in-water emulsion.

In certain embodiments, the freeze-stable oil-in-water emulsion comprises: (1) clarithromycin at a concentration of about 1% to about 5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, 15 the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1; (3) lecithin at a concentration of about 2% by weight; and (4) dextrose at a concentration of about 5% by weight.

20 In certain embodiments, the average size of the oil droplets in the freeze-stable oil-in-water clarithromycin emulsion is no more than about 200 nm, and the PFAT5 is less than about 0.05.

In another aspect, a frozen composition is provided that comprises: (i) clarithromycin at a concentration of at least about 0.5% by weight or a pharmaceutically acceptable salt or ester of clarithromycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to 25 about 4% by weight; (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water; wherein when thawed, the composition forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 30 200 nm and a PFAT5 of less than 0.05.

In certain embodiments, the one or more liquid oils of the frozen clarithromycin composition comprise a vegetable oil and a medium chain triglyceride.

35 In another aspect, a method for treating or reducing infection is provided that comprises administering to a patient in need thereof a pharmaceutically effective amount of the freeze-stable oil-in-water clarithromycin emulsion as described herein.

In another aspect, a method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water clarithromycin emulsion formed by thawing the frozen clarithromycin composition as described herein.

5 In one aspect, the present invention provides a lyophilizable oil-in-water emulsion comprising: (i) at least about 15 mg/ml vancomycin or a pharmaceutically acceptable salt or analog thereof, (ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight, (iii) one or more phospholipids at a total concentration of about 1% to about 10% by weight, and (iv)
10 dextrose at a concentration of at least about 10% by weight.

In certain embodiments, the one or more liquid oils of the lyophilizable vancomycin oil-in-water emulsion comprise soybean oil.

In certain embodiments, the one or more phospholipids of the lyophilizable vancomycin oil-in-water emulsion comprise lecithin.

15 In certain embodiments, the lyophilizable oil-in-water emulsion comprises vancomycin hydrochloride at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a concentration of about 1% to about 4% by weight, and dextrose of
20 about 15% to about 25% by weight.

In certain embodiments, the pH of the lyophilizable vancomycin oil-in-water emulsion is about 3 to about 8.

In certain embodiments, the average size of the oil droplets in the lyophilizable vancomycin oil-in-water emulsion is less than about 250 nm.

25 In certain embodiments, the average size of the oil droplets in the lyophilizable vancomycin oil-in-water emulsion is less than about 200 nm and the PFAT5 of the emulsion is less than about 0.05.

In certain embodiments, the lyophilizable vancomycin oil-in-water emulsion does not further comprise a compound that increases the amount of
30 vancomycin in the oil droplets of the emulsion.

In certain embodiments, less than about 30% of vancomycin is present in the oil droplets of the lyophilizable vancomycin oil-in water emulsion.

In another aspect, the present invention provides a lyophilized composition comprising vancomycin or a pharmaceutically acceptable salt or
35 analog thereof, liquid oil(s), phospholipid(s), and dextrose, wherein the composition is prepared by removal of water from the oil-in-water emulsion described herein, the composition can be rehydrated with water to form an

emulsion suitable for injection, and the average diameter of the re-formed emulsion droplets is no greater than about 1 micron.

In certain embodiments, the average diameter of the reformed emulsion droplets is no greater than about 400 nm.

5 In another aspect, the present invention provides a lyophilized composition comprising: (i) vancomycin or a pharmaceutically acceptable salt or analog thereof at a concentration of about 5% to about 10% by weight, (ii) one or more liquid oils at a total concentration of about 10% to about 20% by weight, (iii) one or more phospholipids at a total concentration of about 10% to about 20% by
10 weight, and (iv) dextrose at a concentration 50% to about 80% by weight.

In certain embodiments, the lyophilized vancomycin composition forms an oil-in-water emulsion when rehydrated with water, and the average diameter of the emulsion droplets is no greater than about 1 micron.

15 In certain embodiments, the lyophilized vancomycin composition does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion reconstituted from the lyophilized vancomycin composition.

In certain embodiments, when the lyophilized vancomycin composition is rehydrated with water to form an oil-in-water emulsion, less than
20 about 30% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

In certain embodiments, the composition forms an oil-in-water emulsion when rehydrated with water, the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

25 In another aspect, the present invention provides a method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the lyophilizable oil-in-water emulsion of vancomycin described herein.

30 In a related aspect, the present invention provides a method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by rehydrating the lyophilized vancomycin composition described herein.

In another aspect, the present invention provides a lyophilizable oil-in-water emulsion comprising: (i) clarithromycin or a pharmaceutically acceptable
35 salt or ester thereof at a concentration of at least about 1% by weight, (ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight, (iii)

one or more phospholipids at a total concentration of about 1% to about 10% by weight, and (iv) dextrose at a concentration of at least about 10% by weight.

In certain embodiments, the lyophilizable oil-in-water emulsion comprises clarithromycin or its pharmaceutically acceptable salt or ester at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a concentration of about 1% to 10% by weight, and dextrose of about 15% to 25% by weight.

In certain embodiments of the lyophilizable oil-in-water emulsion of clarithromycin, the average size of the oil droplets in the emulsion is less than about 250 nm.

In certain embodiments of the lyophilizable oil-in-water emulsion of clarithromycin, the average size of the oil droplets in the emulsion is less than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

In certain embodiments of the lyophilizable oil-in-water emulsion of clarithromycin, the emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

In certain embodiments of the lyophilizable oil-in-water emulsion of clarithromycin, less than about 30% of clarithromycin is in the oil droplets of the emulsion.

In another aspect, the present invention provides a lyophilized composition comprising clarithromycin or a pharmaceutically acceptable salt or ester thereof, liquid oil(s), phospholipid(s), and dextrose, wherein the composition is prepared by removal of water from the oil-in-water emulsion of clarithromycin described herein, the composition can be rehydrated with water to form an emulsion suitable for injection, and the average diameter of the re-formed emulsion droplets is no greater than about 1 micron.

In certain embodiments, the average diameter of oil droplets in the emulsion reconstituted from the lyophilized clarithromycin composition is no greater than about 200 nm.

In a related aspect, the present invention provides a lyophilized composition comprising: (i) clarithromycin or a pharmaceutically acceptable salt or ester thereof at a concentration of about 2% to about 8% by weight, (ii) liquid oil at a concentration of about 10% to about 20% by weight, (iii) one or more phospholipids at a concentration of about 10% to about 20% by weight, and (iv) dextrose at a concentration about 50% to about 80% by weight.

In certain embodiments, the lyophilized clarithromycin composition as described herein forms an oil-in-water emulsion when rehydrated with water, and the average diameter of the emulsion droplets is no greater than about 200 nm.

5 In certain embodiments, the lyophilized clarithromycin composition as described herein forms an oil-in-water emulsion when rehydrated with water, and the PFAT of the emulsion is less than about 0.05.

10 In certain embodiments, the lyophilized clarithromycin composition as described herein forms an oil-in-water emulsion when rehydrated with water, the average diameter of the emulsion droplets is no greater than about 200 nm, and the PFAT of the emulsion is less than about 0.05.

In certain embodiments, the lyophilized clarithromycin composition does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion reconstituted from lyophilized composition.

15 In certain embodiments, the lyophilized clarithromycin composition as described herein forms an oil-in-water emulsion when rehydrated with water, and less than about 30% of clarithromycin is in the oil droplets of the emulsion.

20 In another aspect, the present invention provides a method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the lyophilizable oil-in-water emulsion of clarithromycin described herein.

25 In a related aspect, the present invention provides a method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by rehydrating the lyophilized composition of clarithromycin described herein.

DETAILED DESCRIPTION

30 Both freeze-stable and lyophilizable oil-in-water emulsions are provided for the vein irritating antibiotics vancomycin and clarithromycin. Methods for preparing the oil-in-water emulsions and frozen or lyophilized formulations are also provided. Methods for using the oil-in-water emulsions directly prepared or reconstituted from frozen or lyophilized formulations in treating or reducing infection are further provided.

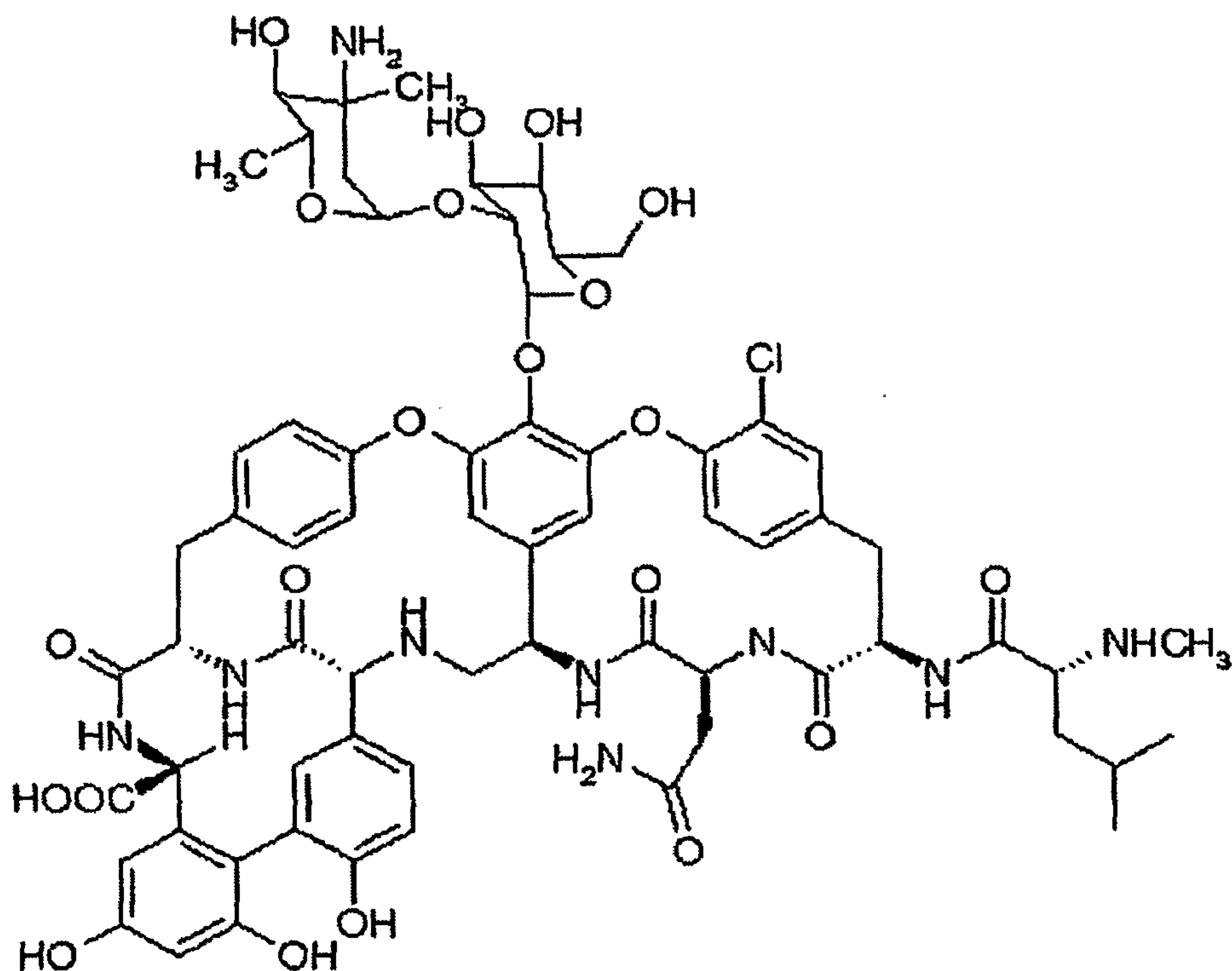
A term used in one subsection of this specification has the same meaning in another subsection unless otherwise noted.

Freeze-stable Oil-in-Water Emulsions and Frozen Formulations

In one aspect, freeze-stable oil-in-water emulsions are provided for vancomycin and clarithromycin. Such emulsions may have one or more of the following advantages: (1) they may be frozen for storage and remain stable during storage, (2) they contain sub-micron oil droplets and may be filter sterilized, (3) the frozen emulsions may be thawed to re-form oil-in-water emulsions with sub-micron oil droplets, and the re-formed emulsions may also be filter sterilized, (4) the emulsions that are either directly prepared or re-formed from the frozen emulsions are isotonic and ready for administration to a patient in need of such a treatment, (5) the oil-in-water emulsions that are either directly prepared or re-formed from the frozen emulsions are non-vein irritating; and (6) the oil-in-water emulsions do not contain any additional compounds (e.g., stabilizers) that increase the amount of vancomycin or clarithromycin in the oil droplets, which avoids any side effects of these additional compounds.

Vancomycin Freeze-Stable and Frozen Formulations

Vancomycin is a tricyclic glycopeptide (whose structure is shown below). In an aqueous solution, it has limited stability and is most stable at pH about 4.0-4.5; so as to maximize its stability, the currently marketed formulation (Sterile Vancomycin Hydrochloride, USP) is formulated at pH 4.0 to 4.5 in a lyophilized form. Vancomycin is moderately soluble in water (to about 1% to about 5%). It is more soluble in an acidic or basic than a pH neutral environment. Its solubility reaches a minimum at about pH 7. As the pH changes from pH 4.0-4.5 (*i.e.*, the formulation pH) to pH 7 (*i.e.*, blood pH), the solubility of vancomycin is reduced by about 40%. Thus, there is a potential for a partial drug precipitation in the vein upon an intravenous injection where the acidic formulation solution is mixed with the pH neutral blood. Such a partial drug precipitation might be a factor that contributes to the vein irritation caused by the currently marketed formulation.



The oil-in-water emulsions provided herein are a safe and effective formulation option for intravenous delivery of vancomycin. Although not wishing to be bound, it is hypothesized that the oil droplets of vancomycin oil-in-water emulsions prevent or reduce vein irritation of vancomycin by (1) interfering with the binding of vancomycin to the endothelium of the vein, (2) confining a portion of vancomycin molecules in the emulsion oil droplets, thus reducing direct contact with vein endothelium, and/or (3) improving the vancomycin solubility by allowing vancomycin to dissolve in the oil droplets and reducing the possibility of vancomycin precipitation in the blood stream and depositing or binding to the vein at the injection site.

In one aspect, a freeze-stable oil-in-water emulsion is provided that comprises: (i) vancomycin at a concentration of about 0.1% to about 3% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 2% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water.

An "oil-in-water emulsion," as used herein, refers to a colloidal dispersion system in which liquid oil is dispersed in small droplets (the discrete

phase, also referred to as "the oil phase") in an aqueous medium (the continuous phase, also referred to as "the aqueous phase").

"Pharmaceutically acceptable salts or analogs," as used herein, refers to salts or structurally related chemicals, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and effective for their intended use in treating or preventing infections. Pharmaceutically acceptable salts of vancomycin include hydrochloride, sulfate, mesylate, acetate, citrate, ascorbate, aspartate, besylate, benzoate, decanoate, hexanoate, octanoate, cyclamate, laurylsulfate, formate, fumarate, glucoheptonate, glucuronate, glutamate, glutarate, glycolate, hydrobromate, lactate, lactobionate, maleate, malonate, nicotinate, nitrate, oleate, orotate, oxalate, palmitate, pamoate, phosphate, stearate, succinate, tartarate, etc. Pharmaceutically acceptable analogs of vancomycin refer to glycopeptide chemicals having a structure and biological activities similar to vancomycin. Examples of such analogs include LY333328 and BI 397 (Malabarba A, Ciabatti R. Glycopeptide derivatives. *Curr Med Chem.* 2001; 8:1759-1773), Teicoplanin (formerly known as teichmycin A2(1), Salaria M. Teicoplanin. *Indian Pediatr.* 2001;38:372-375). Telavancin (TLV) (Douchin K, Shaw J, Spencer E, Seroogy J, Barriere S, Wilbraham D. Single dose pharmacokinetics (PK) of telavancin (TLV) in healthy elderly subjects. *Clin Microbiol Infect.* 2004;10:275), Oritavancin (Internet press release from Biospace Beat. Biotechnology and Pharmaceutical News), Targocid (<http://home.intekom.com/pharm/rousseau/targocid.html>), and norvancomycin.

"Concentration by weight," as used herein, refers to the ratio (in percentage) of the weight of a component (e.g., vancomycin) of a composition (e.g., a vancomycin oil-in-water emulsion) to the total weight of the composition.

A pharmaceutically acceptable salt of vancomycin is at a concentration "equivalent" to a specified concentration of vancomycin if at that concentration, the vancomycin salt contains the same amount of vancomycin free base as vancomycin at the specified concentration. For example, 5.16 mg/g vancomycin hydrochloride is equivalent to 5.0 mg/g vancomycin free base.

A pharmaceutically acceptable analog of vancomycin is at a concentration "equivalent" to a specified concentration of vancomycin if at that concentration, the vancomycin analog is as effective as vancomycin at the specified concentration in treating or preventing infection.

In the freeze-stable oil-in-water emulsions provided herein, vancomycin is present at a concentration of about 0.1% to about 3% by weight, including any value from 0.09% to 3.3%.

5 The term "about," as used in the present disclosure, refers to any value in the range of 90% to 110% of a specified value. For example, about 0.1% refers to any percentage from 0.09% to 0.11%.

10 The term "liquid oil" is used in the present disclosure in a general sense to identify hydrocarbon derivatives, carbohydrate derivatives, or similar organic compounds that are liquid at body temperatures, *i.e.*, about 37°C, and are pharmacologically acceptable in injectable formulations. This class includes vegetable oils, animal fats, and synthetic oils, as well as various liquids that are obtained by chemical treatment of such oils and fats.

The term "oil component" refers to an oil, or a combination of multiple oils in an oil-in-water emulsion.

15 In certain embodiments, the oil component of oil-in-water emulsions provided herein comprises a monoglyceride, a diglyceride, a triglyceride, or a mixture thereof. In certain embodiments, the oil component comprises an ester formed between one or more fatty acids and an alcohol other than glycerol.

20 "Vegetable oil" refers to oil derived from plant seeds or nuts. Exemplary vegetable oils include, but are not limited to, almond oil, borage oil, black currant seed oil, corn oil, safflower oil, soybean oil, cottonseed oil, peanut oil, olive oil, rapeseed oil, coconut oil, palm oil, canola oil, *etc.* In certain embodiments, the one or more liquid oils of the oil-in-water emulsion comprise soybean oil.

25 Vegetable oils are typically "long-chain triglycerides," formed when three fatty acids (usually about 14 to about 22 carbons in length, with unsaturated bonds in varying numbers and locations, depending on the source of the oil) form ester bonds with the three hydroxyl groups on glycerol. In certain embodiments, vegetable oils of highly purified grade (also called "super refined") are generally used to ensure safety and stability of oil-in-water emulsions.

30 "Medium chain triglycerides" (MCT's) is another class of triglyceride oil that can be either naturally derived or synthetic. MCT's are made from fatty acids that are usually about 6 to about 12 carbons in length. Like vegetable oils, MCT's have been used extensively in emulsions designed for injection as a source of calories, for patients requiring parenteral nutrition. Such oil is commercially available as Miglyol 812 from SASOL GmbH, Germany, CRODAMOL GTCC-PN from Croda Inc. of Parsippany, New Jersey, or Neobees M-5 oil from PVO

International, Inc., of Boonton, New Jersey. Other low-melting medium chain oils may also be used in the emulsions provided herein.

“Animal fat” refers to oil derived from an animal source. It also comprises triglycerides, but the lengths of, and unsaturated bonds in, the three
5 fatty acid chains vary, compared to vegetable oils. Animal fats from sources that are solid at room temperature (such as tallow, lard, *etc.*) can be processed to render them liquid if desired. Other types of animal fats that are inherently liquid at room temperature include various fish oils, *etc.*

The freeze-stable oil-in-water emulsions provided herein contain one
10 or more liquid oils at a total concentration of about 2% to about 4% by weight, including any values from 1.8% to 4.4%.

In certain embodiments, combinations of vegetable oil and MCT oil are used in the emulsions provided herein. Such combinations generally have a long record of safe use in combination in injectable emulsions and provide superior
15 stability for the emulsions of this invention. The specific type of vegetable oil used (*i.e.*, soy bean oil, corn oil, or safflower oil, *etc.*) is not critical, so long as it is safe, well tolerated, pharmaceutically acceptable, chemically stable, and provides emulsion droplets having a desired size range. Generally, MCT oil is limited to at most 50% by weight in the combinations of vegetable oil and MCT.

20 A “phospholipid,” as used herein, refers to a triester of glycerol with two fatty acids and one phosphate ion. Exemplary phospholipids useful in the emulsions provided herein include, but are not limited to, phosphatidyl chlorine, lecithin (a mixture of choline ester of phosphorylated diacylglyceride), phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid with about 4 to
25 about 22 carbon atoms, and more generally from about 10 to about 18 carbon atoms and varying degrees of saturation. The phospholipid component of the emulsions of the present invention can be either a single phospholipid or a mixture of several phospholipids.

The phospholipids useful in the emulsions provided herein can be of
30 natural origin. Naturally occurring lecithin is a mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine, and can be obtained from a variety of sources such as eggs and soy beans. Soy lecithin and egg lecithin (including hydrogenated versions of these compounds) have a long history of safety, possess combined
35 emulsification and solubilization properties, and tend to be broken down into innocuous substances more rapidly than most synthetic surfactants. Commercially available soya phospholipids are the Centrophase and Centrolex products

marketed and sold by Central Soya, Phospholipon from Phospholipid GmbH, Germany, Lipoid by Lipoid GmbH, Germany, and EPIKURON by Degussa.

Phospholipids useful in the present invention can also be synthesized. Exemplary common synthetic phospholipids are listed below:

5 Diacylglycerols

- 1,2-Dilauroyl-sn-glycerol (DLG)
- 1,2-Dimyristoyl-sn-glycerol (DMG)
- 1,2-Dipalmitoyl-sn-glycerol (DPG)
- 1,2-Distearoyl-sn-glycerol (DSG)

10 Phosphatidic Acids

- 1,2-Dimyristoyl- sn-glycero-3-phosphatidic acid, sodium salt (DMPA,Na)
- 1,2-Dipalmitoyl- sn-glycero-3-phosphatidic acid, sodium salt (DPPA,Na)
- 1,2-Distearoyl- sn-glycero-3-phosphatidic acid, sodium salt (DSPA,Na)

Phosphocholines

- 15 1,2-Dilauroyl-sn-glycero-3-phosphocholine (DLPC)
- 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC)
- 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)
- 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)
- 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
- 20 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)

Phosphoethanolamines

- 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE)
- 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE)
- 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE)
- 25 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)

Phosphoglycerols

- 1,2-Dilauroyl-sn-glycero-3-phosphoglycerol, sodium salt (DLPG)
- 1,2-Dimyristoyl-sn-glycero-3-phosphoglycerol, sodium salt (DMPG)
- 1,2-Dimyristoyl-sn-glycero-3-phospho- sn-1-glycerol, ammonium salt
- 30 (DMP-sn-1-G,NH₄)
- 1,2-Dipalmitoyl- sn-glycero-3-phosphoglycerol, sodium salt (DPPG,Na)
- 1,2-Distearoyl- sn-glycero-3-phosphoglycerol, sodium salt (DSPG,Na)

1,2-Distearoyl- sn-glycero-3-phospho- sn-1-glycerol, sodium salt (DSP-sn-1G,Na)

Phosphoserines

1,2-Dipalmitoyl- sn-glycero-3-phospho-L-serine, sodium salt (DPPS,Na)

Mixed Chain Phospholipids

- 5 1-Palmitoyl-2-oleoyl- sn-glycero-3-phosphocholine (POPC)
 1-Palmitoyl-2-oleoyl- sn-glycero-3-phosphoglycerol, sodium salt (POPG,Na)
 1-Palmitoyl-2-oleoyl- sn-glycero-3-phosphoglycerol, ammonium salt (POPG,NH₄)

Lysophospholipids

- 1-Palmitoyl-2-lyso- sn-glycero-3-phosphocholine (P-lyso-PC)
 10 1-Stearoyl-2-lyso- sn-glycero-3-phosphocholine (S-lyso-PC)

Pegylated Phospholipids

- N-(Carbonyl-methoxypolyethyleneglycol 2000)- MPEG-2000-DPPE
 1,2-dipalmitoyl- sn-glycero-3-phosphoethanolamine, sodium salt
 N-(Carbonyl-methoxypolyethyleneglycol 5000)- MPEG-5000-DSPE
 15 1,2-distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt
 N-(Carbonyl-methoxypolyethyleneglycol 5000)- MPEG-5000-DPPE
 1,2-dipalmitoyl- sn-glycero-3-phosphoethanolamine, sodium salt
 N-(Carbonyl-methoxypolyethyleneglycol 750)- MPEG-750-DSPE
 1,2-distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt
 20 N-(Carbonyl-methoxypolyethyleneglycol 2000)- MPEG-2000-DSPE
 1,2-distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt

In certain embodiments, the one or more phospholipids of the freeze-stable oil-in-water emulsion comprise lecithin, such as soy lecithin or egg lecithin.

- 25 The freeze-stable oil-in-water emulsion provided herein comprises one or more phospholipids at a total concentration of about 2% to about 5% by weight (including any value between 1.8% and 5.5%).

- The weight ratio of the total phospholipid(s) to the total liquid oil(s) in the freeze-stable oil-in-water emulsion provided herein is at least 0.5:1. In certain
 30 embodiments, the weight ratio of the total phospholipid(s) to the total liquid oil(s) is 1:1.

The freeze-stable oil-in-water emulsion provided herein comprises about 5% to about 6% dextrose by weight.

In most embodiments, the freeze-stable oil-in-water emulsion provided herein is "isotonic" (used interchangeably with "iso-osmotic"). An oil-in-water emulsion is isotonic when its measured osmotic pressure equals to that of normal saline (0.9% sodium chloride), which is about 296 mOsm. Typical measurement variability for an emulsion sample is about $\pm 10\%$; therefore, an emulsion with a measured osmotic pressure between 266 and 326 mOsm is regarded as iso-osmotic or isotonic.

In certain embodiments, the oil droplets of the freeze-stable oil-in-water emulsions are of sub-micron size. A "sub-micron size droplet," as used herein, refers to an oil droplet in an oil-in-water emulsion having an average diameter of less than 1 micron as measured by conventional sizing techniques such as laser light scattering spectrometry. Oil droplets of sub-micron size are desired for the safe passage of these droplets in capillary blood vessel circulation. Droplets of greater than 5 micron in diameter are believed to be unsafe for intravenous injection since they may block capillary blood vessels resulting in pulmonary embolism.

In certain embodiments, the oil droplets of the freeze-stable oil-in-water emulsions have an average diameter of less than 500, 450, 400, 350, 300, or 250 nm.

In certain embodiments, the oil droplets of the freeze-stable formulations have an average diameter of less than 0.2 micron (200 nm) so that the emulsion may be sterilized by filtering through a 0.2 micron rated filter membrane. In certain embodiments, the oil droplets of the compositions of the present invention have an average diameter of less than about 175, 150, 125, 100, or 75 nm.

In certain embodiments, the freeze-stable oil-in-water emulsions also have a PFAT5 value of less than 0.05. "PFAT5" refers to the volume percent of fat or oil droplets in diameter greater than 5 μm . A PFAT5 of less than 0.05% is preferred for an intravenous emulsion (Todd Canada, "Pathological Consequences From the Infusion of Unstable Lipid Emulsion Admixtures in Guinea Pigs" *Nutrition in Clinical Practice*, Vol. 21, No. 6, 2006 636-637). A PFAT5 value can be measured by the method of single-particle optical sensing (SPOS), also called optical particle counting (OPC) such as *AccuSizer 780 by Particle Sizing System*.

In certain embodiments, the freeze-stable oil-in-water emulsion has an average size of the oil droplets of no more than about 200 nm and a PFAT5 less than about 0.05. The low PFAT5 reduces or eliminates the potential for large

oil droplets to block the capillary circulation. The small average size of the oil droplets allows the emulsion be filter sterilized, which is particularly preferred for vancomycin due to its heat, light and oxygen sensitivities. Such sensitivities render other sterilization methods, such as autoclave, gamma radiation, or UV exposure, infeasible or less preferred.

An oil-in-water emulsion is "freeze-stable" if after one cycle of freeze (at -20°C) – thaw (at 4°C or 25°C), the average diameter of the oil droplets in the emulsion does not increase by more than 50%.

In certain embodiments, the freeze-stable oil-in-water emulsions provided herein do not increase their average diameters of the oil droplets by more than 50% after 2, 3, 4, or 5 freeze-thaw cycles.

In certain embodiments, the average diameters of the oil droplets of the freeze-stable oil-in-water emulsions provided herein do not increase by more than 40%, 30%, 30%, 20%, or 10% after 1, 2, 3, 4, or 5 freeze-thaw cycles.

In certain embodiments, the freeze-stable oil-in-water emulsion retains its average oil droplet size of no more than about 200 nm and a PFAT5 of less than about 0.05 after 1, 2, 3, 4, or 5 freeze-thaw cycles.

The freeze-stable oil-in-water emulsions disclosed herein are stable when stored at a frozen state (e.g., at -20°C) for an extended period of time (e.g., for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) as described in more detail below. The freeze-stable oil-in-water emulsions disclosed herein when stored at a frozen state are also referred to as "frozen compositions," "frozen emulsions," or "frozen formulations."

In certain embodiments, the pH of the freeze-stable oil-in-water emulsions of vancomycin is about 3 to about 8. In certain embodiments, the pH is about 4 to about 7.

In certain embodiments, the freeze-stable oil-in-water emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the oil-in-water emulsion. Examples of such compounds include fatty acids, cholesterol sulfate, riboflavin-5-phosphate, vitamin E succinate, and a mixture of two or more of the above-listed agents. The answer is "no" according to Andrew.

In certain other embodiments, although the freeze-stable oil-in-water emulsion may further comprise a compound that increases the amount of vancomycin in the oil droplets, the stability (physical and/or chemical stability) of the emulsion does not require the presence of such a compound.

In certain embodiments, less than about 70% of vancomycin is in the oil droplets of the freeze-stable oil-in-water emulsion. In certain embodiments, less than about 60%, 50%, 40%, 30%, or 20% of vancomycin is in the oil droplets of the freeze-stable oil-in-water emulsion.

5 In certain embodiments, some or all of the components other than vancomycin in the freeze-stable oil-in-water emulsion (e.g., an oil component and a phospholipid) are safe, well tolerated, and acceptable by the FDA for intravenous injection.

10 A component of oil-in-water emulsions is regarded as "safe" if it does not cause undesired systemic reactions such as anaphylactic shock in patients.

A component of oil-in-water emulsions is regarded as "well tolerated" if it does not result in substantially adverse effects at the injection site, such as phlebitis, vein inflammation or vein irritation.

15 A component of oil-in-water emulsions is regarded as "acceptable by the FDA" if it has been approved by the FDA for intravenous injection as of the filing date of the present application, and is being used at a concentration comparable to those used in FDA approved products.

20 In certain embodiments, some or all of the components other than the vancomycin in the freeze-stable oil-in-water emulsion (e.g., an oil component and a phospholipid) are generally regarded as safe for use in intravenous injections by a drug regulatory authority.

25 A component of oil-in-water emulsions is "generally regarded as safe for use in intravenous injections by a drug regulatory authority" if it has been used in intravenous injection products approved by the FDA or a drug regulatory authority in Europe as of the filing date of the present application, and is being used at a concentration comparable to that used in the products approved by the FDA in the United States or by a drug regulatory authority in Europe.

30 In certain embodiments, the freeze-stable oil-in-water emulsions are vein non-irritable. "Vein non-irritable" refers to the property of a compound or composition, when administered intravenously, that does not cause substantial irritation at the injection site, as evident by, for example, thickened skin, necrotic skin, local redness, local swelling, venous dilation with blood clot formation, or venous embolism with subcutaneous inflammation. This term is used interchangeable with "non-vein irritable", "non-vein irritating" or the like.

35 In certain embodiments, the freeze-stable oil-in-water emulsion or its component(s) is injectable. "Injectable" refers to acceptance of an ingredient by a drug authority agent (e.g., the US FDA) by allowing it for use in an injection drug.

In certain embodiments, the freeze-stable oil-in-water emulsion or its component(s) is biocompatible. "Biocompatible" refers to the capability of performing functions within or upon a living organism in an acceptable manner, *i.e.*, without undue toxicity or harmful physiological or pharmacological effects.

5 An exemplary freeze-stable oil-in-water emulsion of the present invention comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil at a concentration of about 1% to about 2% by weight, (3) medium chain triglyceride at a concentration of about 1% to about 2% by weight, (4) lecithin at a concentration of about 2% to about 4% by weight, and
10 (5) dextrose at a concentration of about 5% to about 6% by weight.

Another exemplary freeze-stable oil-in-water emulsion of the present invention comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight,
15 the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1, (3) lecithin at a concentration of about 2% by weight, and (4) dextrose at a concentration of about 5% by weight.

The present invention also provides methods for preparing freeze-stable oil-in-water emulsions of vancomycin described herein. Such emulsion
20 compositions may be prepared by (a) forming a mixture that comprises (i) one or more liquid oils (*e.g.*, a vegetable oil, or a combination of a vegetable oil and a medium chain triglyceride) and (ii) one or more phospholipids, (b) forming a mixture that comprises (i) a pharmaceutically effective amount of vancomycin or a pharmaceutically acceptable salt or analog thereof, (ii) dextrose, and (iii) water,
25 and (c) forming an oil-in-water emulsion with the mixtures of step (a) and (b).

In certain embodiments, step (a) may be performed by dissolving the liquid oil(s) and phospholipid(s) in ethanol, and then removing ethanol (*e.g.*, via vacuum) until the residual ethanol is less than 1% of the dry weight to obtain a clear oil solution.

30 In certain embodiments, step (c) may be performed by adding the aqueous solution of step (b) to the mixture of step (a) to form a primary emulsion. The aqueous solution may further contain buffer and/or tonicity modifier(s). The formation of the primary emulsion may be performed or facilitated by the use of mechanical homogenization (*e.g.*, high shear mixing, high pressure extrusion, and
35 microfluidization) or other suitable techniques. In certain embodiments, the pH of the primary emulsion is adjusted to about 4. The above-described primary emulsion may be further refined by cycling through a microfluidizer homogenizer or

a similar apparatus to obtain a stable emulsion having fairly uniform oil droplet sizes. The resulting refined emulsion may be filter sterilization, for example, through a 0.22-micron sterile filter.

5 An exemplary method of preparing an oil-in-water emulsion of vancomycin hydrochloride is provided in Examples 3 and 6.

Besides being ready-to-use oil-in-water emulsions, the freeze-stable vancomycin compositions of the present invention can be frozen for storage and thawed at a later date before administration. The frozen formulations prevent or reduce the rapid degradation of vancomycin by hydrolysis.

10 In one aspect, the present application provides a frozen composition that comprises vancomycin or a pharmaceutically acceptable salt or analog thereof, liquid oil(s), phospholipid(s), dextrose, and water. The compositions may be prepared by freezing the freeze-stable oil-in-water emulsions provided herein. The resulting compositions may be thawed to form an oil-in-water emulsion
15 suitable for administration (e.g., injection).

"Frozen emulsion" is an emulsion that is stored at a sub-ambient temperature (e.g., -20°C to -10°C) at which the aqueous phase of the emulsion is completely or partially crystallized (e.g., forms ice).

20 An exemplary frozen composition comprises: (i) vancomycin at a concentration of about 0.5% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1;
25 (iv) about 5% to about 6% dextrose by weight; and (v) water.

Another exemplary frozen composition comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil at a concentration of about 1% to about 2% by weight, (3) medium chain triglyceride at a concentration of about 1% to about 2% by weight, (4) lecithin at a concentration
30 of about 2% to about 4% by weight, and (5) dextrose at a concentration of about 5% to about 6% by weight.

A further exemplary frozen composition comprises: (1) vancomycin hydrochloride at a concentration of about 0.5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, the weight ratio of soybean oil to
35 medium chain triglyceride is between 2:1 to 1:1, (3) lecithin at a concentration of about 2% by weight, and (4) dextrose at a concentration of about 5% by weight.

In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm.

5 In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with a PFAT5 of less than about 0.05.

In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm and a PFAT5 of less than about 0.05.

10 In certain embodiments, the frozen formulation is physically stable, chemically stable, or both physically and chemically stable at room temperature for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months.

A frozen formulation is "physically stable" if it may be stored in the frozen state for a defined period of time without increase in average droplet size of the oil-in-water emulsion thawed from the frozen formulation after storage by more
15 than 50%, or evidence of phase separation or oil droplet aggregation (coalescence) of the thawed emulsion. In certain embodiments, the average size of oil droplets of the emulsion re-formed from a frozen formulation of the present invention after being stored in the frozen state for at least 1, 2, 3, 4, 5, 6, 7, 8, 9,
20 10, 11, or 12 months does not increase or does not increase by more than about 10%, 20%, 25%, 30%, or 40% compared with that of the freeze-stable oil-in-water emulsion from which the frozen formulation has been prepared.

A frozen formulation is "chemically stable" if the vancomycin concentration in the formulation does not change by about 20% under appropriate storage conditions for a defined period of time. In certain embodiments, the
25 vancomycin concentration in an emulsion re-formed from the frozen formulation does not change or does not change by about 5%, 10%, 15% or 20% in the frozen state compared with that of the freeze-stable oil-in-water emulsion from which the frozen formulation has been prepared for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months.

30 In certain embodiments, the one or more liquid oils of the frozen composition comprise a vegetable oil and a medium chain triglyceride.

In certain embodiments, the frozen composition does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion formed by thawing the frozen composition.

35 In certain embodiments, when the frozen composition is thawed to form an oil-in-water emulsion, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

In a related aspect, oil-in-water emulsions of vancomycin re-formed by thawing the frozen formulations described herein are also provided.

In certain embodiments, the re-formed oil-in-water emulsions have the same chemical and physical characteristics as described above for the freeze-stable oil-in-water emulsions. For example, in certain embodiments, the re-formed oil-in-water emulsion has an average diameter of oil droplets no more than about 200 nm, and/or a PFAT5 of less than about 0.05. In certain embodiments, the re-formed oil-in-water emulsion is isotonic and ready for use. In certain embodiments, the re-formed oil-in-water emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the re-formed emulsion. In certain embodiments, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is present in the oil droplets in the re-formed oil-in-water emulsion.

The vancomycin formulations described herein may be used to treat or prevent (*i.e.*, reduce or eliminate the risk of) infection for which vancomycin is effective, including treating or preventing gram-positive infection, treating peritoneal dialysis-associated peritonitis in patients with end-stage renal disease, treating pseudomembranous colitis due to *Clostridium difficile* or *Staphylococcus aureus* enterocolitis, surgical prophylaxis in patients allergic to penicillin or other beta-lactam antibiotics, bacterial endocarditis prophylaxis in patients undergoing gastrointestinal/genitourinary procedures and allergic to ampicillin, amoxicillin, penicillin, or other beta-lactam antibiotics, treatment of meningitis or ventriculitis, nosocomial bacteremia prophylaxis in neonates receiving total parenteral nutrition.

The vancomycin oil-in-water formulations of the present invention (either directly prepared or re-formed from frozen formulations) may be administered to a subject (*e.g.*, human or other mammals) in need thereof at a pharmaceutically effective amount by various routes, including but not limited to, intravenous, intramuscular, intra-arterial, intrathecal, intraocular, subcutaneous, intraarticular, intra-peritoneal, oral, topical, intravaginal, and ophthalmic administration.

"Pharmaceutically effective amount" refers to an amount of an antibiotic (*i.e.*, vancomycin or clarithromycin) oil-in-water emulsion that is sufficient for treating infection.

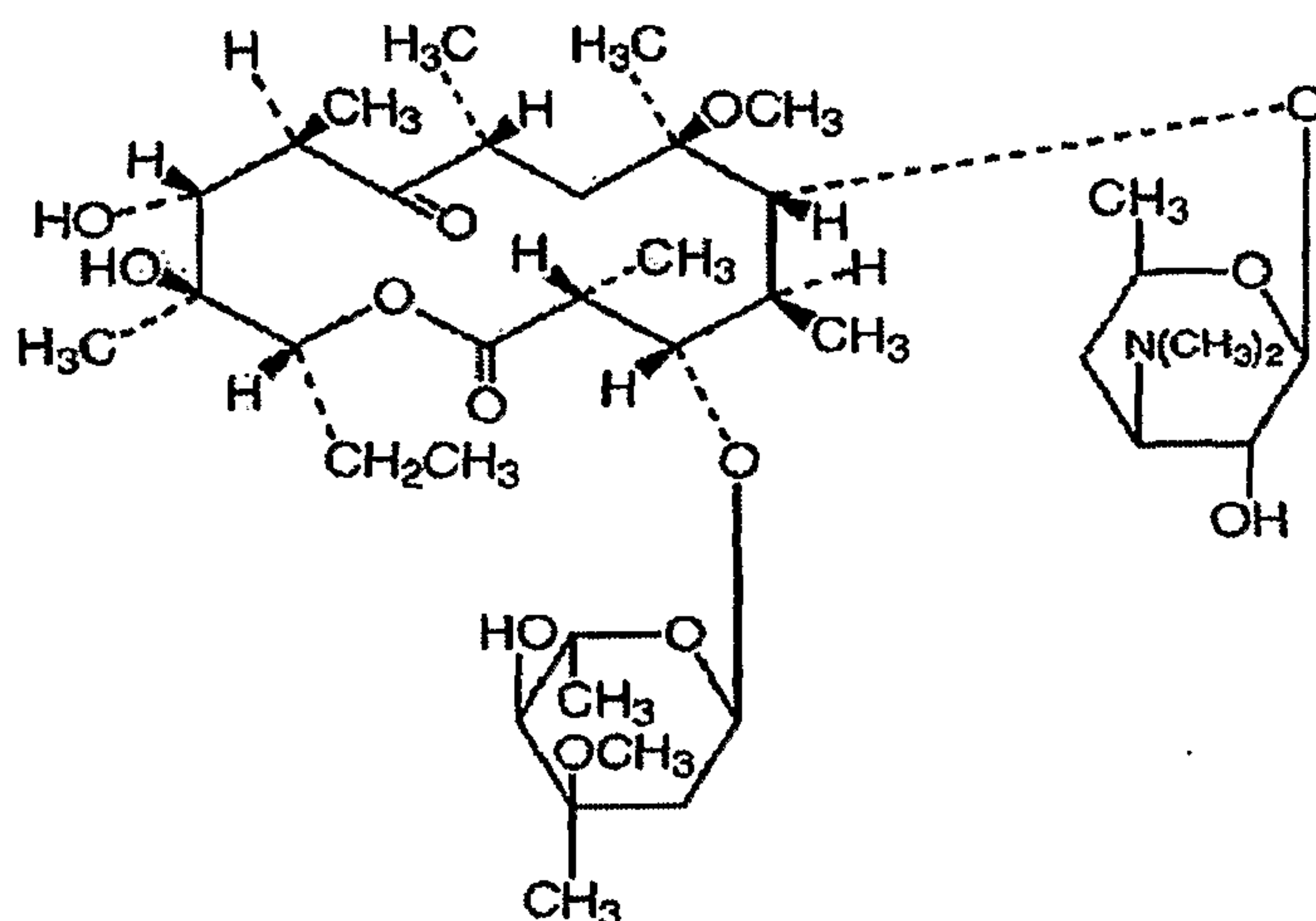
The vancomycin oil-in-water emulsions provided herein can be administered in a single daily dosage or in multiple doses per day. Other periodic treatment protocols may also be adopted. The treatment may require administration over extended periods of time, such as for several days or for from

5 principles of treatment well known in the antibiotic art.

10 the oil-in-water emulsions provided herein include about 5 mg to 10 mg of vancomycin per kg of body weight every six hours or about 10 mg to 20 mg of vancomycin per kg of body weight every twelve hours.

Clarithromycin Freeze-Stable or Frozen Formulations

15 No. 4,331,803) with a structure shown below



20 clarithromycin (e.g., pharmaceutically acceptable salts and esters of clarithromycin).

25 clarithromycin at an equivalent concentration; (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight

ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water.

“Pharmaceutically acceptable salts and esters” refers to salts and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and effective for their intended use in the chemotherapy and prophylaxis of antimicrobial infections. Among the more common pharmaceutically acceptable salts and esters of clarithromycin are acetate, estolate (lauryl sulfate salt of the propionate ester), ethyl succinate, gluceptate (glucoheptonate), lactobionate, stearate, and hydrochloride forms. Other acid salts used in the pharmaceutical art are the following: adipate, alginate, aspartate, benzoate, benzene-sulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, gluconate, glycerophosphate, hemisulfate, heptaonate, hexanoate, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, pamoate, pantothenate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

A pharmaceutically acceptable salt of clarithromycin is at a concentration “equivalent” to a specified concentration of clarithromycin if at that concentration, the clarithromycin salt contains the same amount of clarithromycin free base as clarithromycin at the specified concentration.

A pharmaceutically acceptable ester of clarithromycin is at a concentration “equivalent” to a specified concentration of clarithromycin if at that concentration, the clarithromycin ester is as effective as clarithromycin at the specified concentration in treating or preventing infection.

In the freeze-stable oil-in-water emulsions provided herein, clarithromycin is present at a concentration of at least about 0.5%. In certain embodiments, clarithromycin is present at a concentration of at least about 1%, 2%, or 3%.

The freeze-stable oil-in-water clarithromycin emulsions provided herein contain one or more liquid oils at a total concentration of about 2% to about 4% by weight, including any values from 1.8% to 4.4%.

5 In certain embodiments, the oil component of the oil-in-water clarithromycin emulsions provided herein comprises a monoglyceride, a diglyceride, a triglyceride, or a mixture thereof. In certain embodiments, the oil component comprises an ester formed between one or more fatty acids and an alcohol other than glycerol.

10 In certain embodiments, the one or more liquid oils of the oil-in-water clarithromycin emulsions comprise a vegetable oil, such as soybean oil.

In certain embodiments, combinations of vegetable oil and MCT oil are used in the present invention. Generally, MCT oil is limited to at most 50% by weight in the combinations of vegetable oil and MCT.

15 In certain embodiments, the one or more phospholipids of the freeze-stable oil-in-water clarithromycin emulsions comprise lecithin, such as soy lecithin or egg lecithin.

The freeze-stable oil-in-water clarithromycin emulsions provided herein comprise one or more phospholipids at a total concentration of about 2% to about 5% by weight (including any value between 1.8% and 5.5%).

20 The weight ratio of the total phospholipid(s) to the total liquid oil(s) in the freeze-stable oil-in-water clarithromycin emulsions provided herein is at least 0.5:1. In certain embodiments, the weight ratio of the total phospholipid(s) to the total liquid oil(s) is 1:1.

25 The freeze-stable oil-in-water clarithromycin emulsions provided herein comprise about 5% to about 6% dextrose by weight.

In most embodiments, the freeze-stable oil-in-water clarithromycin emulsion provided herein is isotonic and thus ready for use.

30 In certain embodiments, the oil droplets of the freeze-stable oil-in-water clarithromycin emulsions are of sub-micron size. In certain embodiments, the oil droplets of the freeze-stable oil-in-water clarithromycin emulsions have an average diameter of less than about 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, or 75 nm.

In certain embodiments, the freeze-stable oil-in-water clarithromycin emulsions also have a PFAT5 value less than about 0.05.

35 In certain embodiments, the freeze-stable oil-in-water clarithromycin emulsion has an average size of the oil droplets of no more than about 200 nm and a PFAT5 less than about 0.05.

In certain embodiments, the freeze-stable oil-in-water clarithromycin emulsions provided herein do not increase their average diameters of the oil droplets by more than about 50% after 1, 2, 3, 4, or 5 freeze-thaw cycles.

5 In certain embodiments, the freeze-stable oil-in-water clarithromycin emulsions provided herein do not increase their average diameters of the oil droplets by more than about 40%, 30%, 30%, 20%, or 10% after 1, 2, 3, 4, or 5 freeze-thaw cycles.

10 In certain embodiments, the freeze-stable oil-in-water clarithromycin emulsion retains its average oil droplet size of no more than about 200 nm and a PFAT5 of less than about 0.05 after 1, 2, 3, 4, or 5 freeze-thaw cycles.

The freeze-stable oil-in-water clarithromycin emulsions disclosed herein are stable when stored at a frozen state (e.g., at -20°C) for an extended period of time (e.g., for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) as described in more detail below.

15 In certain embodiments, the pH of the freeze-stable oil-in-water emulsions of clarithromycin is about 3 to about 8 (e.g., about 6 to about 8). In certain embodiments, the pH is about 4 or about 7.

20 In certain embodiments, the oil-in-water emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of a clarithromycin oil-in-water emulsion. Examples of such compounds include fatty acids, N-methyl pyrrolidone, and benzyl alcohol.

In certain embodiments, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is present in the oil droplets of the freeze-stable oil-in-water clarithromycin emulsion.

25 In certain embodiments, some or all of the components other than clarithromycin in the freeze-stable oil-in-water emulsion (e.g., an oil component and a phospholipid) is safe, well tolerated, and acceptable by the FDA for intravenous injection.

30 In certain embodiments, some or all of the components other than the clarithromycin in the freeze-stable oil-in-water emulsion (e.g., an oil component and a phospholipid) is generally regarded as safe for use in intravenous injections by a drug regulatory authority.

In certain embodiments, the freeze-stable oil-in-water emulsions are vein non-irritable, injectable, and/or biocompatible.

35 An exemplary freeze-stable oil-in-water clarithromycin emulsion comprises: (1) clarithromycin at a concentration of about 1% to about 5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total

concentration of soybean oil and medium chain triglyceride is about 2% by weight, and the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1, (3) lecithin at a concentration of about 2% by weight, and (4) dextrose at a concentration of about 5% to about 6% by weight.

5 Another exemplary freeze-stable oil-in-water clarithromycin emulsion comprises: (1) clarithromycin at a concentration of about 5% by weight, (2) soybean oil at a concentration of about 1% by weight, (3) a medium chain triglyceride at a concentration of about 1% by weight, (4) lecithin at a concentration of about 2% by weight, and (5) dextrose at a concentration of about 5% by weight.

10 The present invention also provides methods for preparing freeze-stable oil-in-water emulsions of clarithromycin described herein. Such emulsion compositions may be prepared by (a) forming a mixture that comprises (i) one or more liquid oils (e.g., a vegetable oil, or a combination of a vegetable oil and a medium chain triglyceride) and (ii) one or more phospholipids, (b) forming a
15 mixture that comprises (i) a pharmaceutically effective amount of clarithromycin or a pharmaceutically acceptable salt or ester thereof, (ii) dextrose, and (iii) water, and (c) forming an oil-in-water emulsion with the mixtures of step (a) and (b).

In certain embodiments, step (a) may be performed by dissolving the liquid oil(s) and phospholipid(s) in ethanol, and then removing ethanol (e.g., via
20 vacuum) until the residual ethanol is less than 1% of the dry weight to obtain a clear oil solution.

In certain embodiments, step (c) may be performed by adding the aqueous solution of step (b) to the mixture of step (a) to form a primary emulsion. The aqueous solution may further contain buffer and/or tonicity modifier(s). The
25 formation of the primary emulsion may be performed or facilitated by the use of mechanical homogenization (e.g., high shear mixing, high pressure extrusion, and microfluidization) or other suitable techniques. In certain embodiments, the pH of the primary emulsion is adjusted to about 5 to about 9 (e.g., about 7). The above-described primary emulsion may be further refined by cycling through a
30 microfluidizer homogenizer or a similar apparatus to obtain a stable emulsion having fairly uniform oil droplet sizes. The resulting refined emulsion may be filter sterilization, for example, through a 0.22-micron sterile filter.

An exemplary method of preparing an oil-in-water emulsion of clarithromycin is provided in Example 9.

35 Besides being ready-to-use oil-in-water emulsions, the freeze-stable clarithromycin compositions of the present invention can be frozen for storage and thawed at a later date before injection.

In one aspect, the present application provides a frozen composition that comprises clarithromycin or a pharmaceutically acceptable salt or ester thereof, liquid oil(s), phospholipid(s), dextrose, and water. The compositions may be prepared by freezing the freeze-stable oil-in-water emulsions provided herein.

5 The resulting compositions may be thawed to form an oil-in-water emulsion suitable for injection.

An exemplary frozen composition comprises: (i) clarithromycin at a concentration of at least about 0.5% by weight or a pharmaceutically acceptable salt or ester of clarithromycin at an equivalent concentration; (ii) one or more liquid
10 oils at a total concentration of about 2% to about 4% by weight; (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1; (iv) about 5% to about 6% dextrose by weight; and (v) water.

Another exemplary frozen composition comprises: clarithromycin at a
15 concentration of about 1% to about 5% by weight, (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, and the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1, (3) lecithin at a concentration of about 2% by weight, and (4) dextrose at a concentration of about 5% to about 6% by weight.

20 A further exemplary frozen composition comprises: (1) clarithromycin at a concentration of about 5% by weight, (2) soybean oil at a concentration of about 1% by weight, (3) a medium chain triglyceride at a concentration of about 1% by weight, (4) lecithin at a concentration of about 2% by weight, and (5) dextrose at a concentration of about 5% by weight.

25 In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm.

In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with a PFAT5 less than about 0.05.

30 In certain embodiments, when thawed, the frozen composition re-forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm and a PFAT5 less than about 0.05.

In certain embodiments, the frozen formulation is physically stable, chemically stable, or both physically and chemically stable at room temperature for
35 at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months.

In certain embodiments, the average size of oil droplets of the emulsion re-formed from a frozen formulation disclosed herein after being stored in

the frozen state for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months does not increase or does not increase by more than about 10%, 20%, 25%, 30%, or 40% compared with that of the freeze-stable oil-in-water emulsion from which the frozen formulation has been prepared.

5 In certain embodiments, the clarithromycin concentration in an the emulsion re-formed from a frozen formulation disclosed herein after being stored in the frozen state for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months does not change or does not change by about 5%, 10%, 15% or 20% in the frozen state compared with that of the freeze-stable oil-in-water emulsion from which the frozen
10 formulation has been prepared.

In certain embodiments, the one or more liquid oils of the frozen composition comprise a vegetable oil and a medium chain triglyceride.

In certain embodiments, the frozen composition does not further comprise a compound that increases the amount of vancomycin in the oil droplets
15 of the emulsion.

In certain embodiments, when the frozen composition is thawed to form an oil-in-water emulsion, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of clarithromycin is present in the oil droplets of the oil-in-water emulsion.

In a related aspect, oil-in-water emulsions of clarithromycin re-formed
20 by thawing the frozen formulations described herein are also provided.

In certain embodiments, the re-formed oil-in-water emulsions have the same chemical and physical characteristics as described above for the freeze-stable oil-in-water emulsions. For example, in certain embodiments, the re-formed oil-in-water emulsion has an average diameter of oil droplets no more than about
25 200 nm, and/or a PFAT5 less than about 0.05. In certain embodiments, the re-formed oil-in-water emulsion is isotonic and ready for use. In certain embodiments, the re-formed oil-in-water emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the re-formed emulsion. In certain embodiments, no more than about 70%, 60%, 50%,
30 40%, 30%, or 20% of clarithromycin is present in the oil droplets in the re-formed oil-in-water emulsion.

The clarithromycin formulations provided herein may be used to treat or reduce the risk of infection for which clarithromycin is effective, including infections caused by bacterial, such as pneumonia, bronchitis, and ear, lung,
35 sinus, stomach, skin and throat infections.

The clarithromycin oil-in-water formulations of the present invention (either directly prepared or re-formed from frozen formulations) may be

administered to a subject (e.g., human or other mammals) in need thereof at a pharmaceutically effective amount by various routes, including but not limited to, intravenous, intramuscular, intra-arterial, intrathecal, intra-ocular, subcutaneous, intra-articular, oral, topical, intravaginal and intra-peritoneal administration.

5 The clarithromycin oil-in-water emulsions provided herein can be administered in a single daily dosage or in multiple doses per day. Other periodic treatment schemes may also be used. The treatment may require administration over extended periods of time, such as for several days or for from about one to four weeks. The amount per administered dose or the total amount administered
10 will depend on various factors such as the route and frequency of administration, the nature and severity of the infection, the age, sex, weight, and general health of the patient, and can be determined by a physician according to principles of treatment well known in the antibiotic art. For example, in certain embodiments, the oil-in-water emulsions provided herein may be administered intravenously to a
15 human adult patient at a dose of about 250 mg to about 750 mg every 12 hours.

Lyophilizable Oil-in-Water Emulsions and Lyophilized Formulations

In another aspect of the present invention, lyophilizable oil-in-water emulsions are provided for vancomycin and clarithromycin. Such emulsions may have one or more of the following advantages: (1) they may be lyophilized for
20 storage and remain stable during storage, (2) they contain sub-micron oil droplets and may be filter sterilized, (3) the lyophilized emulsions may be reconstituted to oil-in-water emulsions with sub-micron oil droplets, and the reconstituted emulsions may also be filter sterilized, (4) the oil-in-water emulsions that are either directly prepared or reconstituted from the lyophilized emulsions are non-vein
25 irritating, and (5) the oil-in-water emulsions do not contain any additional compounds (e.g., stabilizers), which avoids any side effects of such compounds.

The word "reformed" is used interchangeably with "reconstituted" in connection with describing oil-in-water emulsions formed from lyophilized compositions.

30 Vancomycin Lyophilizable and Lyophilized Formulations

In one aspect, the present invention provides a lyophilizable oil-in-water emulsion that comprises: (i) at least 15 mg/ml vancomycin or a pharmaceutically acceptable salt or analog thereof, (ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight, (iii) one or more

phospholipids at a total concentration of about 1% to about 10% by weight, and (iv) dextrose at a concentration of at least about 10% by weight.

In certain embodiments, vancomycin or a pharmaceutically acceptable salt or analog is present in the oil-in-water emulsion at a concentration
5 at least about 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50 mg/ml.

The amount of the total oil component in the lyophilizable vancomycin emulsions provided herein may be within a range of about 1% to about 20% (e.g., about 2% to about 10%) by weight. In certain embodiments, the total concentration of the oil component is about 2%, 3%, 4%, 5%, 6%, 7%, 8%,
10 9%, 10%, 12%, 15%, 18%, or 20% by weight.

In certain embodiments, the weight ratio of vegetable oil to MCT oil in the oil-in-water vancomycin emulsion is within a range of about 9:1 to about 1:1 by weight. In certain embodiments, the weight ratio of the vegetable oil to MCT oil is about 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1 or 1:1.

15 The amount of phospholipids, by weight, in the vancomycin emulsions provided herein may be within a range of about 1% to about 10%. In certain embodiments, the phospholipids in the emulsions are at a concentration, by weight, about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10%.

The lyophilizable oil-in-water emulsions of vancomycin also comprise
20 dextrose at a concentration of at least about 10% by weight. In certain embodiments, the concentration of dextrose in the oil-in-water emulsions is about 12%, 14%, 15%, 18%, 20%, 22%, 24%, 25%, 28%, or 30% by weight.

The presence of dextrose in the oil-in-water emulsions prevents the droplets from forming aggregates or phase separation during lyophilization and
25 reconstitution, and allows the resulting lyophilized formulations to be reconstituted with water quickly (e.g., within about 5 minutes or less) to re-form oil-in-water emulsions with average diameter of droplets no greater than about 1 micron. In addition, because vancomycin is a high dose drug, a relatively large amount of cryoprotectants is required in the oil-in-water emulsions to ensure that the
30 formulations after being lyophilized may be reconstituted to re-form oil-in-water emulsions with micron size or sub-micron size droplets. Using dextrose as the cryoprotectant avoids the safety or biological activity concerns associated with other cryoprotectants such as mannitol when administered intravenously in a relatively large quantity.

35 In certain embodiments, the average size of oil droplets of a lyophilizable emulsion provided herein does not increase by more than about 10%, 20%, 25%, 30%, 40%, 50%, 75%, 100%, 125%, 150%, 175%, or 200% under

appropriate storage conditions (e.g., at 2-8°C) for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 20, 25, or 30 days.

In certain embodiments, the vancomycin concentration in a lyophilizable emulsion of the present invention does not change by about 5%, 10%, 15% or 20% under appropriate storage conditions (e.g., at 2-8°C) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days.

In certain embodiments, the oil droplets of the lyophilizable compositions provided herein have an average diameter of less than about 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, or 50 nm.

10 In certain embodiments, the oil-in-water emulsion has a PFAT5 of less than about 0.05.

In certain embodiments, the oil-in-water emulsion has an average diameter of oil droplets of less than about 200 nm and a PFAT5 of less than about 0.05.

15 In certain embodiments, the oil-in-water emulsion is sterilized. For instance, the oil-in-water emulsion with an average oil droplet diameter of no more than about 200 nm may be sterilized via a 0.2 µm filter.

In certain embodiments, the pH of the oil-in-water emulsions of vancomycin is about 3 to about 8). In certain embodiments, the pH is about 7 or about 7.5.

20 In certain embodiments, the lyophilizable oil-in-water emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion.

In certain other embodiments, although the lyophilizable oil-in-water emulsion may further comprise a compound that increases the amount of vancomycin in the oil droplets, the stability (physical and/or chemical stability) of the emulsion does not require the presence of such a compound.

In certain embodiments, less than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is in the oil droplets of the oil-in-water emulsions.

30 "Lyophilizable oil-in-water emulsion" refers to an oil-in-water emulsion ("original oil-in-water emulsion") that can be lyophilized to form a lyophile, and the average oil droplet size of the oil-in-water emulsion reconstituted from the lyophile does not increase by 50% compared to that of the original oil-in-water emulsion.

In certain embodiments, the lyophilizable oil-in-water emulsion retains its average oil droplet size of no more than about 200 nm and a PFAT5 of less than about 0.05 after being lyophilized to form a lyophile and then reconstituted from the lyophile.

Another exemplary lyophilizable oil-in-water emulsion comprises: vancomycin hydrochloride at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a concentration of about 1% to 4% by weight, and dextrose of about 15% to 25% by weight.

The present invention also provides methods for preparing lyophilizable oil-in-water emulsions of vancomycin described herein. Such emulsion compositions may be prepared by (a) forming a mixture that comprises (i) one or more liquid oils (e.g., a vegetable oil, or a combination of a vegetable oil and a medium chain triglyceride) and (ii) one or more phospholipids, (b) forming a mixture that comprises: (i) a pharmaceutically effective amount of vancomycin or a pharmaceutically acceptable salt or analog thereof, (ii) dextrose, and (iii) water, and (c) forming an oil-in-water emulsion with the mixtures of step (a) and (b).

In certain embodiments, step (a) may be performed by dissolving the liquid oil(s) and phospholipid(s) in ethanol, and then removing ethanol (e.g., via vacuum) until the residual ethanol is less than 1% of the dry weight to obtain a clear oil solution.

In certain embodiments, step (c) may be performed by adding the aqueous solution of step (b) to the mixture of step (a) to form a primary emulsion. The aqueous solution may further contain buffer, stabilizer(s) and/or tonicity modifier(s). The formation of the primary emulsion may be performed or facilitated by the use of mechanical homogenization (e.g., high shear mixing, high pressure extrusion, and microfluidization) or other suitable techniques. In certain embodiments, the pH of the primary emulsion is adjusted to about 6 to about 8 (e.g., about 7.4). The above-described primary emulsion may be further refined by cycling through a microfluidizer homogenizer or a similar apparatus to obtain a stable emulsion having fairly uniform oil droplet sizes. The resulting refined emulsion may be filter sterilization, for example, through a 0.22-micron sterile filter.

An exemplary method of preparing an oil-in-water emulsion of vancomycin hydrochloride is provided in Example 1.

Besides being ready-to-use oil-in-water emulsions, the lyophilizable vancomycin compositions provided herein can also be lyophilized and then reconstituted at a later date, prior to injection, by dilution with water, to reform the oil-in-water emulsion. As a lyophile, the formulations of vancomycin in accordance with the invention prevent the rapid degradation of vancomycin by hydrolysis, which occurs in the presence of water.

In another aspect, the present application provides a lyophilized composition that comprises vancomycin or a pharmaceutically acceptable salt or analog thereof, liquid oil(s), phospholipid(s), and dextrose. The compositions may be prepared by removal of water from the above-described oil-in-water emulsions.

5 The resulting compositions may be rehydrated with water or a buffer solution to form an oil-in-water emulsion suitable for injection. The average diameter of the re-formed emulsion droplets is no greater than about 1 micron.

In certain embodiments, the average diameter of the re-formed emulsion droplets is no greater than about 1000, 900, 800, 700, 600, 500, 450,
10 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, or 50 nm.

In certain embodiments, the average size of oil droplets of the emulsion reconstituted from a lyophilized formulation of the present invention after the lyophilized formulation is stored under appropriate storage conditions (e.g., at –20°C) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24
15 months does not increase by more than about 10%, 20%, 25%, 30%, 40%, 50%, 75%, 100%, 125%, 150%, 175%, or 200% compared with that of the lyophilizable oil-in-water emulsion from which the lyophilized formulation has been prepared.

In certain embodiments, the lyophilized formulation does not further comprise a compound that increases the amount of vancomycin in the oil droplets
20 of the emulsion reconstituted from the lyophilized formulation.

In certain embodiments, when the lyophilized formulation is reconstituted to form an oil-in-water emulsion, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

25 In certain embodiments, the vancomycin concentration in the emulsion reconstituted from a lyophilized formulation provided herein does not change by about 5%, 10%, 15% or 20% after the lyophilized formulation has been stored under appropriate storage conditions (e.g., at –20°C) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24 months compared with that of the
30 lyophilizable oil-in-water emulsion from which the lyophilized formulation has been prepared.

In certain embodiments, the present application provides a lyophilized composition comprising: (i) vancomycin or a pharmaceutically acceptable salt or analog thereof at a concentration of about 5% to 10% by weight,
35 (ii) one or more liquid oils at a total concentration of about 10% to 20% by weight, (iii) one or more phospholipids at a total concentration of about 10% to 20% by weight, and (iv) dextrose at a concentration 50% to 80% by weight.

The lyophilized vancomycin formulations of the present invention may be prepared by lyophilizing the oil-in-water emulsions as described herein via any appropriate lyophilization technique (e.g., via a shelf freeze-dryer).

5 "Lyophilization" or "freeze drying" is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes: freezing, primary drying (sublimation), and secondary drying (desorption).

10 The lyophilized formulation may be reconstituted with an appropriate amount of an aqueous solution (e.g., water, a buffer solution, or an aqueous solution with other additives such as tonicity modifiers) to re-form an oil-in-water emulsion that comprises vancomycin or a pharmaceutically acceptable salt or analog thereof at a pharmaceutically effective concentration. "Pharmaceutically effective concentration" refers to a concentration of vancomycin or its
15 pharmaceutically acceptable salt or analog in an oil-in-water emulsion that is sufficient in treating infections or other diseases that vancomycin or its pharmaceutically acceptable salt or analog is effective when the oil-in-water emulsion is administered.

20 In certain embodiments, the average oil droplet size of the reconstituted oil-in-water emulsion does not increase by more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 70%, 80%, 90%, or 100% for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days under appropriate storage condition (e.g., at 2-8°C).

25 In certain embodiments, the concentration of vancomycin in the reconstituted oil-in-water emulsion does not change by 5%, 10%, 15%, or 20% for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days under appropriate storage condition (e.g., at 2-8°C).

In certain embodiments, the reconstituted oil-in-water emulsion is non-vein irritating.

30 In certain embodiments, the reconstituted oil-in-water emulsion has a pH of about 6 to about 8 (e.g., about 7 or about 7.5).

In certain embodiments, the reconstituted oil-in-water emulsions have the same chemical and physical characteristics as described above for the lyophilizable oil-in-water emulsions. For example, in certain embodiments, the
35 reconstituted oil-in-water emulsion has an average diameter of oil droplets no more than about 200 nm, and/or a PFAT5 of less than about 0.05. In certain embodiments, the reconstituted oil-in-water emulsion is isotonic and ready for use.

In certain embodiments, the reconstituted oil-in-water emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the reconstituted emulsion. In certain embodiments, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of vancomycin is present in the oil droplets in the reconstituted oil-in-water emulsion.

The lyophilizable vancomycin formulations as well as oil-in-water emulsions reconstituted from lyophilized formulations provided herein may be used to treat or prevent infection for which vancomycin is effective. More specifically, they may be administered to a subject (e.g., human or other mammals) in need thereof at a pharmaceutically effective amount by various routes, including but not limited to, intravenous, intramuscular, intra-arterial, intrathecal, intraocular, subcutaneous, intra-articular, intra-peritoneal, oral, topical, intravaginal and ophthalmic administration.

Clarithromycin Lyophilizable and Lyophilized Formulations

In another aspect, a lyophilizable oil-in-water emulsion is provided that comprises: (i) clarithromycin at a concentration of at least about 1% by weight or a pharmaceutically acceptable salt or ester thereof at an equivalent concentration, (ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight, (iii) one or more phospholipids at a total concentration of about 1% to about 10% by weight, and (iv) dextrose at a concentration of at least about 10% by weight.

In certain embodiments, clarithromycin or a pharmaceutically acceptable salt or ester thereof is present in the oil-in-water emulsion at a concentration at least about 0.5% by weight. In certain embodiment, the concentration of clarithromycin or a pharmaceutically acceptable salt or ester thereof in the emulsion is about 1%, 1.5%, 2%, 2.5%, 3%, 4%, or 5%.

The content of the total oil component in the lyophilized clarithromycin emulsions provided herein may be within a range of about 1% to about 20% (e.g., about 2% to about 10%) by weight. In certain embodiments, the total concentration of the oil component is about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 15%, 18%, or 20% by weight.

In certain embodiments, the weight ratio of vegetable oil to MCT oil in the oil-in-water emulsion is within a range of about 9:1 to about 1:1, by weight. In certain embodiments, the weight ratio of the vegetable oil to MCT oil is about 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1 or 1:1.

The amount of phospholipids, by weight, in the lyophilized clarithromycin emulsions provided herein may be within a range of about 1% to about 10%. In certain embodiments, the phospholipids in the emulsions are at a concentration, by weight, about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10%.

5 The lyophilized oil-in-water emulsions of clarithromycin also comprise dextrose at a concentration of at least about 10% by weight. In certain embodiments, the concentration of dextrose in the oil-in-water emulsions is about 12%, 14%, 15%, 18%, 20%, 22%, 24%, 25%, 28%, or 30% by weight.

10 In certain embodiments, some or all of the components other than clarithromycin or its pharmaceutically acceptable salt or ester in the oil-in-water emulsion (*e.g.*, an oil component, a phospholipid, a stabilizer, and a tonicity modifier) is safe, well tolerated, and acceptable by the FDA for intravenous injection.

15 In certain embodiments, some or all of the components other than clarithromycin or its pharmaceutically acceptable salt or ester in the oil-in-water emulsion (*e.g.*, an oil component, an emulsifier, a stabilizer, and a tonicity modifier) is generally regarded as safe for use in intravenous injections by a drug regulatory authority.

20 In certain embodiments, the lyophilizable oil-in-water clarithromycin emulsions provided herein are vein non-irritable, injectable, and/or biocompatible.

 In certain embodiments, the lyophilizable oil-in-water clarithromycin emulsions provided herein are stable physically, chemically, or both chemically and physically.

25 In certain embodiments, the average size of oil droplets of a lyophilizable oil-in-water clarithromycin emulsions provided herein does not increase by more than about 10%, 20%, 25%, 30%, 40%, 50%, 75%, 100%, 125%, 150%, 175%, or 200% under appropriate storage conditions (*e.g.*, at -20°C or $2-8^{\circ}\text{C}$) for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 20, 25, or 30 days.

30 In certain embodiments, the clarithromycin concentration in a lyophilizable oil-in-water clarithromycin emulsions provided herein does not change by about 5%, 10%, 15% or 20% under appropriate storage conditions (*e.g.*, at -20°C or $2-8^{\circ}\text{C}$) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days.

35 In certain embodiments, the oil droplets of the lyophilizable oil-in-water clarithromycin emulsions provided herein have an average diameter of less than about 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, or 50 nm.

 In certain embodiments, the lyophilizable oil-in-water clarithromycin emulsion is sterilized. For instance, the oil-in-water emulsion with an average oil

droplet diameter of no more than about 200 nm may be sterilized via a 0.2 μ m filter.

In certain embodiments, the pH of the lyophilizable oil-in-water clarithromycin emulsions is about 3 to about 8. In certain embodiments, the pH is
5 about 7 or about 7.5.

In certain embodiments, the lyophilizable oil-in-water emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

In certain embodiments, no more than about 70%, 60%, 50%, 40%,
10 30%, or 20% of clarithromycin is present in the oil droplets of the lyophilizable oil-in-water emulsion.

In certain embodiments, the lyophilizable oil-in-water emulsion retains its average oil droplet size of no more than about 200 nm and a PFAT5 of less than about 0.05 after being lyophilized to form a lyophilized formulation and
15 then reconstituted from the lyophilized formulation.

In certain embodiments, the lyophilizable oil-in-water emulsion comprises clarithromycin at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a
20 concentration of about 1% to 10% by weight, and dextrose of about 15% to 25% by weight.

The present invention also provides methods for preparing lyophilizable oil-in-water emulsions of clarithromycin described herein. Such emulsion compositions may be prepared by (a) forming a mixture that comprises
25 (i) one or more liquid oils (*e.g.*, a vegetable oil, or a combination of a vegetable oil and a medium chain triglyceride) and (ii) one or more phospholipids, (b) forming a mixture that comprises (i) a pharmaceutically effective amount of clarithromycin or a pharmaceutically acceptable salt or ester thereof, (ii) dextrose, and (iii) water, and (c) forming an oil-in-water emulsion with the mixtures of step (a) and (b).

In certain embodiments, step (a) may be performed by dissolving the
30 liquid oil(s) and phospholipid(s) in ethanol, and then removing ethanol (*e.g.*, via vacuum) until the residual ethanol is less than 1% of the dry weight to obtain a clear oil solution.

In certain embodiments, step (c) may be performed by adding the
35 aqueous solution of step (b) to the mixture of step (a) to form a primary emulsion. The aqueous solution may further contain buffer, stabilizer(s) and/or tonicity modifier(s). The formation of the primary emulsion may be performed or facilitated

by the use of mechanical homogenization (e.g., high shear mixing, high pressure extrusion, and microfluidization) or other suitable techniques. In certain embodiments, the pH of the primary emulsion is adjusted to about 6 to about 8 (e.g., about 7.4). The above-described primary emulsion may be further refined by

5 cycling through a microfluidizer homogenizer or a similar apparatus to obtain a stable emulsion having fairly uniform oil droplet sizes. The resulting refined emulsion may be filter sterilization, for example, through a 0.22-micron sterile filter.

An exemplary method of preparing a clarithromycin oil-in-water emulsion is provided in Example 2.

10 The lyophilizable clarithromycin compositions of the present invention can also be prepared as a lyophilized formulation that can be reconstituted at a later date and diluted with water to reform the oil-in-water emulsion before injection.

In one aspect, the present application provides a lyophilized

15 composition that comprises clarithromycin or a pharmaceutically acceptable salt or ester thereof, liquid oil(s), phospholipid(s), and dextrose. The compositions may be prepared by removal of water from the oil-in-water emulsions as described above. The resulting compositions may be rehydrated with water or a buffer solution to form an oil-in-water emulsion suitable for injection. The average

20 diameter of the re-formed emulsion droplets is no greater than about 1 micron.

In certain embodiments, the average diameter of the re-formed emulsion droplets is no greater than about 1000, 900, 800, 700, 600, 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, or 50 nm.

In certain embodiment, the lyophilized formulation is physically

25 stable, chemically stable, or both physically and chemically stable at room temperature for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24 months.

In certain embodiments, the average size of oil droplets of the clarithromycin emulsion reconstituted from a lyophilized formulation provided

30 herein after the lyophilized formulation has been stored under appropriate storage conditions (e.g., at -20°C) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24 months does not increase by more than about 10%, 20%, 25%, 30%, 40%, 50%, 75%, 100%, 125%, 150%, 175%, or 200% compared with that of the lyophilizable oil-in-water emulsion from which the lyophilized formulation has been

35 prepared.

In certain embodiments, the lyophilized formulation does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the reconstituted emulsion.

5 In certain embodiments, when the lyophilized formulation is thawed to form an oil-in-water emulsion, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of clarithromycin is present in the oil droplets of the oil-in-water emulsion.

10 In certain embodiments, the clarithromycin concentration in an oil-in-water emulsion reconstituted from a lyophilized formulation provided herein after the lyophilized formulation has been stored under appropriate storage conditions (e.g., at -20°C) for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, or 24 months does not change by about 5%, 10%, 15% or 20% compared with that of the lyophilizable oil-in-water emulsion from which the lyophilized formulation has been prepared.

15 In certain embodiments, the present invention provides a lyophilized composition comprising: (i) clarithromycin or a pharmaceutically acceptable salt or ester thereof at a concentration of about 2% to 8% by weight, (ii) liquid oil at a concentration of about 10% to 20% by weight, (iii) one or more phospholipids at a concentration of about 10% to 20% by weight, and (iv) dextrose at a concentration 50% to 80% by weight.

20 The lyophilized clarithromycin formulation may be reconstituted with an appropriate amount of an aqueous solution (e.g., water, a buffer solution, or an aqueous solution with other additives such as tonicity modifiers) to re-form an oil-in-water emulsion that comprises clarithromycin or a pharmaceutically acceptable salt or ester thereof at a pharmaceutically effective concentration. In certain 25 embodiments, the re-formed oil-in-water emulsion is physically, chemically, or both physically and chemically stable for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days under appropriate storage condition (e.g., at $2-8^{\circ}\text{C}$).

In certain embodiments, the re-formed oil-in-water clarithromycin emulsion is non-vein irritating.

30 In certain embodiments, the re-formed oil-in-water clarithromycin emulsion has a pH of about 6 to about 8 (e.g., about 7 or about 7.5).

In certain embodiments, the reconstituted oil-in-water emulsions have the same chemical and physical characteristics as described above for the lyophilizable oil-in-water emulsions. For example, in certain embodiments, the 35 reconstituted oil-in-water emulsion has an average diameter of oil droplets no more than about 200 nm, and/or a PFAT5 of less than about 0.05. In certain embodiments, the reconstituted oil-in-water emulsion is isotonic and ready for use.

In certain embodiments, the reconstituted oil-in-water emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the reconstituted emulsion. In certain embodiments, no more than about 70%, 60%, 50%, 40%, 30%, or 20% of clarithromycin is present in the oil droplets in the reconstituted oil-in-water emulsion.

The clarithromycin formulations of the present invention may be used to treat or reduce the risk of infection for which clarithromycin is effective. More specifically, the lyophilizable clarithromycin oil-in-water formulations or oil-in-water emulsions reconstituted from lyophilized formulations may be administered to a subject (e.g., human or other mammals) in need thereof at a pharmaceutically effective amount by various routes, including but not limited to, intravenous, intramuscular, intra-arterial, intrathecal, intraocular, subcutaneous, intra-articular, oral, topical, intravaginal and intra-peritoneal administration.

EXAMPLES

EXAMPLE 1

PREPARATION OF LYOPHILIZABLE AND LYOPHILIZED VANCOMYCIN EMULSIONS

A 1000 g batch of vancomycin emulsion was prepared in the following composition:

Component	Suppliers	% (w/w)	g/1000 g
Vancomycin hydrochloride, USP	Hospira Inc.	2	20
Soy lecithin, EP	American lecithin company	4	40
Medium chain triglyceride, USP	Sasol	1.5	15
Soybean oil, USP	Corda	2.5	25
Dextrose, USP	Roquette	20	200
Water, de-ionized to add to		100	1000

The emulsion was prepared in the following steps:

- (1) Weighed out and combined soy lecithin, medium chain triglyceride and soybean oil in a compounding vessel;
- (2) Added an appropriate amount of ethanol to dissolve all components to obtain a clear solution;
- (3) Applied vacuum to remove ethanol until the residual ethanol is less than 1% the dry weight to obtain a clear oil solution;
- (4) Added vancomycin HCl, dextrose and water in another container, mixed well to dissolve the solids to obtain a clear aqueous solution;
- (5) Added the aqueous solution to the oil solution and applied a high-shear homogenizer, *e.g.*, an IKA Ultra Turrax mixer, to obtain a primary emulsion (oil-in-water);
- (6) Adjusted pH of the primary emulsion to 7.4 ± 0.1 ;
- (7) Passed the primary emulsion through a high-pressure homogenizer (*e.g.*, Microfluidizer 110L operating a 100 psi inlet air pressure) for 3-5 passes to obtain a sub-micron emulsion with average droplet size of about 77 nanometers;
- (8) Passed the emulsion through a 0.2-micron sterilizing filter (Nalgene) to obtain the lyophilizable emulsion;
- (9) Filled 25 g of the sterilized emulsion into each 50 mL sterile vial (500 mg vancomycin HCl per vial); and

(10) Lyophilized using a shelf freeze-dryer (e.g., Advantage model by Virtis) to obtain the lyophilized vancomycin emulsion.

The lyophilized vancomycin emulsion was tested as follow:

Lyophile appearance

5 The lyophilized emulsion in the vials was observed as off-white, uniform cake-like, porous mass.

Reconstitution

10 Each vial of lyophilized emulsion was reconstituted with 15.4 g water with gentle mixing for about 1-5 minutes to obtain a white, uniform, and translucent to opaque emulsion ("reformed emulsion").

The reformed emulsion

15 The reformed emulsion was observed under an optical microscope at 400x magnification, no crystals, visible droplets, or solid matter was observed. pH of the reformed emulsion was measured to be 7.1. Average droplet size of the reformed emulsion was determined by a laser light scattering spectrometer (Model 770 by Particle Sizing Systems) to be 82 nm. The amount and integrity of vancomycin HCl in the reformed emulsion was confirmed by HPLC.

Stability of the reformed emulsion

20 The reformed emulsion was diluted to 10 mg/mL with water and further diluted to 1 mg/mL with 5% dextrose solution and tested for stability for 7 days. At -20°C, 5°C and 25°C, the 1 mg/mL diluted emulsion was found to be stable for at least 1 days and the 10 mg/mL emulsion stable for at least 7 days.

Vein irritation

25 The reformed vancomycin emulsion was tested for vein irritation using rabbit marginal ear vein model by slow infusion at 5 mg/mL and 10 mL/kg daily for 7 consecutive days. Appearance and histopathological examinations did not reveal any abnormality in vein tissues compared to a negative control (5% dextrose solution). It was concluded that the vancomycin emulsion was non-vein irritating.

EXAMPLE 2

PREPARATION OF LYOPHILIZABLE AND LYOPHILIZED CLARITHROMYCIN EMULSIONS

A 1000 g batch of vancomycin emulsion was prepared in the following composition:

5

Component	Suppliers	% (w/w)	g/1000 g
Clarithromycin, USP	Teva	1.5	15
Soy lecithin, EP	American lecithin company	4	40
Medium chain triglyceride, USP	Sasol	1.5	15
Soybean oil, USP	Corda	2.5	25
Dextrose, USP	Roquette	20	200
Water, de-ionized to add to		100	1000

The emulsion was prepared in the following steps:

- (1) Weighed out and combined soy lecithin, medium chain triglyceride and soybean oil in a compounding vessel;
- 10 (2) Added an appropriate amount of ethanol to dissolve all components to obtain a clear solution;
- (3) Applied vacuum to remove ethanol until the residual ethanol is less than 1% the dry weight to obtain a clear oil solution;
- (4) Added clarithromycin, dextrose and water in another
15 container, mixed well and added hydrochloric acid to about pH 2.3 to dissolve the solids to obtain a clear aqueous solution;
- (5) Added the aqueous solution to the oil solution and applied a high-shear homogenizer, e.g., an IKA Ultra Turrax mixer, to obtain a primary emulsion;
- 20 (6) Adjusted pH of the primary emulsion to 6.0 – 6.2;
- (7) Passed the primary emulsion through a high-pressure homogenizer (e.g., Microfluidizer 110L operating a 100 psi inlet air pressure) for 5 passes to obtain a sub-micron emulsion with average droplet size of about 170 nanometers;
- 25 (8) Passed the emulsion through a 0.2-micron sterilizing filter (Millipak-20 by Millipore) to obtain the lyophilizable emulsion;
- (9) Filled 16.7 g of the sterilized emulsion into each 50 mL sterile vial (250 mg clarithromycin per vial); and
- (10) Lyophilized using a shelf freeze-dryer (e.g., Advantage model
30 by Virtis) to obtain the lyophilized clarithromycin emulsion.

The lyophilized clarithromycin emulsion was tested as follow:

Lyophile appearance

The lyophilized emulsion in the vials was observed as off-white, uniform cotton-candy-like porous mass.

Reconstitution

- 5 Each vial of lyophilized emulsion was reconstituted with 11.78 g water with gentle mixing for about 2-5 minutes to obtain a white, uniform, and opaque emulsion ("reformed emulsion").

The reformed emulsion

- 10 The reformed emulsion was observed under an optical microscope at 400x magnification, no crystals, visible droplets, or solid matter was observed. pH of the emulsion was measured to be 6.4.

Average droplet size of the emulsion was determined by a laser light scattering spectrometer (Model zetasizer by Malvern Instruments) to be 157-180 nm.

- 15 The amount of clarithromycin in the reformed emulsion was confirmed by HPLC.

EXAMPLE 3

**DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND
SUB-MICRON VANCOMYCIN EMULSIONS**

- 20 A 1 g batch of each vancomycin emulsion was prepared in the following composition:

Mg/g	F30	F31	F32	F33	F34	F35	F36	F37
Vancomycin HCl	5.16*	5.16	5.16	5.16	5.16	5.16	5.16	5.16
Soy lecithin, EP	10	10	10	10	10	10	10	10.00
Soybean oil, USP	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Medium chain triglyceride, USP	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Dextrose, USP	50	60	70	80	90	100	50	60
Glycerin, USP							4.5	
Deionized water qs to	1000	1000	1000	1000	1000	1000	1000	1000
pH	4	4	4	4	4	4	4	7.00
Total oil	10	10	10	10	10	10	10	10
Lecithin to oil ratio	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

* Equivalent to 5.0 mg/g vancomycin free base

- 25 The emulsion was prepared in the following steps:

(1) Weighed out and combined soy lecithin, soybean oil and medium chain triglyceride in a suitable container;

(2) Added an appropriate amount of ethanol to dissolve all components to obtain a clear solution;

5 (3) Applied vacuum to remove ethanol until the residual ethanol is less than 2% the dry weight to obtain a clear oil solution;

(4) Added vancomycin HCl, dextrose, glycerin and water in another container, mixed well to dissolve the solids to obtain a clear aqueous solution;

10 (5) Added the aqueous solution to the oil solution;

(6) Agitated the mixture of aqueous and oil solutions vigorously using mini-beadbeater for 10 seconds to form a primary emulsion;

(7) Recorded pH and adjusted pH to 4.0 +/- 0.2 or 7.0 +/- 0.2 with 0.1N HCl/NaOH if needed;

15 (8) Agitated the primary emulsion for 200 seconds using the same mini-beadbeater to obtain a final emulsion;

(9) Passed the emulsion through a 0.2-micron filter (Spin-X); and

(10) Froze the filtered emulsion at - 20°C.

The frozen emulsions were tested as follow:

20

pH and Osmotic Pressure

Formulation	Osmotic pressure (mOsm)	pH
F30	261.8	3.80
F31	314.5	4.00
F32	357.0	3.95
F33	415.7	3.90
F34	471.8	3.94
F35	522.3	3.96
F36	325.6	4.07
F37	315.0	6.98

Average Droplet Diameter by Laser Light Scattering (nm) by a Malevern

Zetasizer Particle Sizing Instrument

25

Formulation	Initial	1.5 days			6 days		
		- 20°C (one freeze-thaw cycle)	5°C	25°C	- 20°C (two freeze-thaw cycles)	5°C	25°C
F30	143	141	141	143	149	138	146
F31	166	149	153	168	173	150	151

F32	140	135	191	173	137	140	147
F33	218	146	149	150	222	158	149
F34	184	149	160	155	157	146	155
F35	155	152	152	157	151	161	152
F36	160	157	158	160	150	151	160
F37	147	143	145	157	141	159	141

The above results show that: (1) dextrose concentration at about 5% and about 6% provided iso-osmotic emulsion (F30, F31, F36 and F37); (2) F30, F31, F36 and F37 also showed no significant change in droplet size after two cycles of freeze-thaw; and (3) it appears that sub-micron emulsions can be prepared with about 0.5% vancomycin, about 1% oil, about 1% lecithin, about 5% or about 6% dextrose at either pH 4 or 7, and such emulsions are freeze-stable.

EXAMPLE 4

DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND SUB-MICRON VANCOMYCIN EMULSIONS

Another set of vancomycin emulsions were prepared in the following composition:

mg/g	F-30	F38	F39	F40	F41	F42	F43	F44	F45	F46	F47	F48	F49
Vancomycin HCl	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16
Soy lecithin, EP	10	20	30	50	20	30	50	20	30	50	20.0	30	50
Soybean oil, USP	6.25	12.5	18.75	31.25	12.5	18.75	31.25	12.5	18.75	31.25	12.5	18.75	31.25
MCT, USP	3.75	7.5	11.25	18.75	7.5	11.25	18.75	7.5	11.25	18.75	7.5	11.25	18.75
Dextrose, USP	50	50	50	50	60	60	60	50	50	50	60	60	60
Glycerin, USP								4.5	4.5	4.5			
Deionized water qs to	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
pH		4	4	4	4	4	4	4	4	4	7	7	7
Total oil	10	20	30	50	20	30	50	20	30	50	20	30	50
Lecithin to oil ratio	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

The emulsion was prepared and tested according the procedure and methods described in Example 3.

Average Droplet Diameter by Laser Light Scattering (nm)

Sample Name	Time-0	2-day	2-day	2-day
		-20°C (2 freeze-thaw cycles)	5°C	25°C
F-30	133.7	138.7	135.7	137.0
F-38	91.5	96.1	90.0	94.7
F-39	105.3	89.4	82.6	85.2
F-40	112.0	108.3	92.7	105.7

F-41	99.0	87.5	136.0	100.0
F-42	133.3	107.7	92.6	107.0
F-43	106.3	108.3	93.3	109.0
F-44	104.3	108.0	93.4	106.0
F-45	107.0	108.0	93.8	107.3
F-46	112.3	113.0	99.1	111.0
F-47	106.0	109.0	97.4	107.3
F-48	90.7	93.1	87.1	92.0
F-49	93.4	130.7	87.6	94.3

The results show that formulations at a lecithin to oil ratio of 1:1 with about 1% to about 5% oil, about 1% to about 5% soy lecithin, and about 5% to about 6% dextrose, or about 5% dextrose with about 0.45% glycerol at pH 4 or 7 formed sub-micron emulsions that are freeze-stable.

EXAMPLE 5

DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND SUB-MICRON VANCOMYCIN EMULSIONS

Another set of vancomycin emulsions were prepared in the following composition:

mg/g	F-50	F-51	F-52	F-53	F-54	F-55	F-56	F-57	F-58	F-59	F-60	F-61
Vancomycin HCl	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16	5.16
Egg lecithin	12			12			12			12		
Soy lecithin by Lipoid		12			12			12			12	
Soy lecithin by Phospholipid Co.			12			12			12			12
Soybean oil, USP	100	100	100	75	75	75	50	50	50	50	50	50
Dextrose, USP	50	50	50	50	50	50	50	50	50	50	50	50
Deionized H ₂ O qs to	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
pH	4	4	4	4	4	4	4	4	4	7	7	7
Total oil	100	100	100	75	75	75	50	50	50	50	50	50
Lecithin to oil ratio	0.12:1	0.12:1	0.12:1	0.16:1	0.16:1	0.16:1	0.24:1	0.24:1	0.24:1	0.24:1	0.24:1	0.24:1

The emulsion was prepared and tested according the procedure and methods described in Example 3.

15 Appearance and Microscopic Observation for Visible Droplets

Formulation	Appearance	Microscopic observation
F50	No emulsion formed	
F51	No emulsion formed	
F52	No emulsion formed	

F53	Coarse emulsion	A lot visible drops (>5 μm)
F54	Coarse emulsion	A lot visible drops (>5 μm)
F55	Coarse emulsion	A lot visible drops (>5 μm)
F56	Coarse emulsion	A lot visible drops (>5 μm)
F57	Coarse emulsion	A lot visible drops (>5 μm)
F58	Coarse emulsion	A lot visible drops (>5 μm)
F59	Coarse emulsion	A lot visible drops (>5 μm)
F60	Coarse emulsion	A lot visible drops (>5 μm)
F61	Coarse emulsion	A lot visible drops (>5 μm)

The results show that no sub-micron emulsion was formed with about 0.5% vancomycin, about 1.2% lecithin, and about 10% soybean oil using the method described in Example 3. The compositions tested in this study are similar to the conventional fat emulsion, *i.e.*, with oil of about 5% to about 10% and lecithin about 1.2%. Their failure to form a sub-micron emulsion suggested that high oil concentration (> about 5%) does not favor the formation of sub-micron emulsion, and the lecithin to oil ratio of greater than 0.24:1 is required for the formation for sub-micron emulsion.

10

EXAMPLE 6

DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND SUB-MICRON VANCOMYCIN EMULSIONS

A 16 g batch of each vancomycin emulsion was prepared according to following compositions:

15

Mg/g	F-62	F-63	F-64	F-65
Vancomycin HCl	5.16	5.16	5.16	5.16
Egg lecithin, EP	8.26	12.38	16.51	20.12
Soybean oil, USP	50	100	100	100
Dextrose, USP	50	50	50	50
Deionized water qs to	1000	1000	1000	1000
pH	4	4	4	4
Total oil	50	100	100	100
Lecithin to oil ratio	0.17:1	0.12:1	0.17:1	0.20:1

The emulsion was prepared in the following steps:

(1) Weighed out and combined egg lecithin and soybean oil in a suitable container;

20

(2) Added an appropriate amount of ethanol to dissolve all components to obtain a clear solution;

(3) Applied vacuum to remove ethanol until the residual ethanol is less than 2% the dry weight to obtain a clear oil solution;

(4) Added vancomycin HCl, dextrose and water in another container, mixed well to dissolve the solids to obtain a clear aqueous solution;

5 (5) Added the aqueous solution to the oil solution;

(6) Recorded pH and adjusted pH to 4.0 +/- 0.2 with 0.1N HCl/NaOH if needed;

(7) Agitated the mixture of aqueous and oil solutions by hand shaking;

10 (8) Recorded pH and adjusted pH to 4.0 +/- 0.2 or 7.0 +/- 0.2 with 0.1N HCl/NaOH if needed;

(9) Applied a high-shear homogenizer, e.g., an IKA Ultra Turrax mixer, to obtain a primary emulsion (oil-in-water);

15 (10) Passed the primary emulsion through a high-pressure homogenizer (e.g., Microfluidizer 110L operating at 100 psi inlet air pressure) for 3-5 passes to obtain a sub-micron emulsion.

(11) Passed the emulsion through a 0.2-micron sterilizing filter (Sartorius, CE); and

(12) Froze the sterilized emulsion at -20°C.

20 The frozen emulsions were tested as follow:

Average Droplet Diameter by Laser Light Scattering (nm)

Formulation	Before filtration	After filtration	-20°C, 1 day (One freeze-thaw cycle)	25°C, 1 day
F62	192.5	171	185	216
F63	186.8	186	195	184
F64	191	177	208	184
F65	167	164	178	162

Observation under microscope for visible droplets (>5 µm)

Formulation	Before filtration	After filtration	-20°C, 1 day (One freeze-thaw cycle)	25° C, 1 day
F62	No	No	Yes	Yes
F63	Yes	Yes	Yes	Yes
F64	Yes	Yes	Yes	Yes
F65	Yes	Yes	Yes	Yes

This study demonstrated that it is possible to produce a sub-micron emulsion with about 5% oil at lecithin-to-oil ratio of 0.17:1 (F62) using the preparation method described in Example 6. However, this emulsion was not freeze-stable.

5 The presence of large droplets ($> 5 \mu\text{m}$) demonstrated that a high % of oil (about 10%) accompanied with a low lecithin to oil ratio (0.12:1, 0.17:1 or 0.2:1) did not favor the formation of a sub-micron emulsion.

EXAMPLE 7

DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND SUB-MICRON VANCOMYCIN 10 EMULSIONS

A 16 g batch of each vancomycin emulsion was prepared according to following compositions:

mg/g	F66	F67	F68	F69	F70
Vancomycin HCl	5.16	5.16	5.16	5.16	5.16
Egg lecithin, EP	8.26	12.38	16.51	20.12	
Soy lecithin, EP					12.38
Medium chain triglyceride, USP	25.0	50.0	50.0	50.0	50.0
Soybean oil, USP	25.0	50.0	50.0	50.0	50.0
Dextrose, USP	50.0	50.0	50.0	50.0	50.0
Deionized water qs to	1000	1000	1000	1000	1000
PH	4	4	4	4	4
Total oil	50	100	100	100	100
Lecithin to oil ratio	0.17:1	0.12:1	0.17:1	0.20:1	0.12:1

15 The emulsion was prepared and tested according the procedure and methods described in Example 6.

Observation Under Microscope for Large Droplets ($> 5 \mu\text{m}$)

Formulation	Before filtration	After filtration	-20°C, 1 day (One freeze-thaw cycle)	25°C, 1 day
F66	Yes	Yes	Yes	Yes
F67	Yes	Yes	Yes	Yes
F68	Yes	Yes	Yes	Yes
F69	Yes	Yes	Yes	Yes
F70	Yes	Yes	Yes	Yes

20 This study confirmed that an about 5 mg/mL vancomycin composition with a high oil concentration ($\geq$ about 5%) accompanied with a low lecithin-to-oil

ratio (< 0.2:1) does not favor formation of a sub-micron emulsion - for either soybean oil alone or a combination of soybean oil and medium chain triglyceride, or for egg lecithin or soy lecithin.

EXAMPLE 8

5 DEVELOPMENT OF FREEZE-STABLE, ISOTONIC, AND SUB-MICRON VANCOMYCIN EMULSIONS

A 16 g batch of each vancomycin emulsion was prepared according to following compositions:

mg/g	F-38	F-71	F-72	F-73
Vancomycin HCl	5.16	5.16	5.16	5.16
Soy lecithin, EP	20	20	20	20
Soybean oil, USP	12.5	18.8	25.0	10.0
Medium chain triglyceride, USP	7.5	11.3	15.0	10.0
Dextrose, USP	50	50	50	50
Deionized water qs to	1000	1000	1000	1000
pH	4	4	4	4
Total oil	20	30	40	20
Lecithin to oil ratio	1:1	0.67:1	0.5:1	1:1

10

The emulsion was prepared and tested according the procedure and methods described in Example 6.

pH

Formulation	Time-0	- 20°C (One freeze-thaw cycle)				25°C		
		1 day	2 day	3 day	42 day	1 day	2 day	3 day
F38	3.99	Not tested	3.97	4.05	4.05	Not tested	4.04	4.05
F71	4.16		4.12	4.11	4.15		4.31	4.33
F72	4.08		4.06	4.14	4.06		4.2	4.2
F73	4.06		4.11	4.09	3.93		4.19	4.26

15

Average Droplet Diameter by Laser Light Scattering (nm)

Formulation	Time-0	- 20°C (One freeze-thaw cycle)				25°C		
		1 day	2 day	3 day	42 day	1 day	2 day	3 day
F38	113	123	117	115	127	112	112	108
F71	190	130	141	149	129	128	131	140

F72	190	141	138	139	146	185	136	136
F73	127	116	121	124	136	114	127	116

Observation Under Microscope for Large Droplets (> 5 μ m)

Formulation	Time-0	- 20°C (One freeze-thaw cycle)				25°C		
		1 day	2 day	3 day	42 day	1 day	2 day	3 day
F38	None	None	Few	Few	Few	None	Few	Few
F71	None	None	Few	Few	Few	None	Few	Few
F72	None	None	Few	Few	Few	None	Few	Few
F73	None	None	Few	Few	Few	None	None	None

Percentage of Fat Greater Than 5 Micrometers at Time-0 (i.e., PFAT5)
by Accusizer 380

5

(%)	F-38	F-71	F-72	F-73
AVG	0.002	0.003	0.004	0.003
Std Dev	0.001	0.001	0.002	0.003

10 The results show that submicron and freeze-stable emulsions were obtained with the oil concentration no more than about 4% and lecithin-to-oil ratio of greater than about 0.5:1 using microfluidization process. No significant change in pH or particle size was observed for all four formulations after 3 days storage at either -20°C or 25°C. F38 and F73 appeared to be better formulations based average droplet size and on the microscope observation where fewer large droplets were seen in F38 and F73 than the others.

EXAMPLE 9

15

PREPARATION OF A FROZEN ISOTONIC CLARITHROMYCIN EMULSION

A 16 g batch of each vancomycin emulsion is prepared according to following compositions:

mg/g	F-74	F-75
Clarithromycin	5.0	5.0
Soy lecithin, EP	20	20
Soybean oil, USP	12.5	10.0
Medium chain triglyceride, USP	7.5	10.0

Dextrose, USP	50	50
Deionized water qs to	1000	1000
pH	7	7
Total oil	20	20
Lecithin to oil ratio	1:1	1:1

The emulsion is prepared in the following steps:

- (1) Weigh out and combine soy lecithin, soybean oil and medium chain triglyceride in a suitable container;
- 5 (2) Add an appropriate amount of ethanol to dissolve all components to obtain a clear solution;
- (3) Apply vacuum to remove ethanol until the residual ethanol is less than 2% the dry weight to obtain a clear oil solution;
- (4) Add clarithromycin, dextrose and water in another container, mixed well to dissolve the solids to obtain a clear aqueous solution;
- 10 (5) Add the aqueous solution to the oil solution;
- (6) Record pH and adjust pH to 7.0 +/- 2 with 0.1N HCl/NaOH if needed;
- (7) Agitate the mixture of aqueous and oil solutions by hand shaking;
- 15 (8) Record pH and adjust pH to 7.0 +/- 2 with 0.1N HCl/NaOH if needed;
- (9) Apply a high-shear homogenizer, *e.g.*, an IKA Ultra Turrax mixer, to obtain a primary emulsion (oil-in-water);
- 20 (10) Pass the primary emulsion through a high-pressure homogenizer (*e.g.*, Microfluidizer 110L operating at 100 psi inlet air pressure) for 3-5 passes to obtain a sub-micron emulsion;
- (11) Pass the emulsion through a 0.2-micron sterilizing filter (Sartorius, CE); and
- 25 (12) Freeze the sterilized emulsion at -20°C.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all
5 possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

AMENDED CLAIMS
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1. An oil-in-water emulsion comprising:
 - (i) vancomycin at a concentration of about 0.1% to about 3% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration;
 - (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight;
 - (iii) one or more phospholipids at a total concentration of about 2% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1;
 - (iv) about 5% to about 6% dextrose by weight; and
 - (v) water,wherein the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.
2. The emulsion of claim 1, wherein the one or more liquid oils comprise soybean oil.
3. The emulsion of claim 1, wherein the one or more liquid oils comprise a vegetable oil and a medium chain triglyceride.
4. The emulsion of any one of claims 1 to 3, wherein the one or more phospholipids comprise lecithin.
5. The emulsion of claim 1, comprising:
 - (1) vancomycin hydrochloride at a concentration of about 0.5% by weight,
 - (2) soybean oil at a concentration of about 1% to about 2% by weight,
 - (3) medium chain triglyceride at a concentration of about 1% to about 2% by weight;
 - (4) lecithin at a concentration of about 2% to about 4% by weight; and
 - (5) dextrose at a concentration of about 5% to about 6% by weight.

6. The emulsion of claim 1, comprising:
- (1) vancomycin hydrochloride at a concentration of about 0.5% by weight,
 - (2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, and the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1;
 - (3) lecithin at a concentration of about 2% by weight; and
 - (4) dextrose at a concentration of about 5% by weight.
7. The emulsion of any one of claims 1 to 6, wherein the emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion.
8. The emulsion of any one of claims 1 to 6, wherein less than about 30% of vancomycin is in the oil droplets of the emulsion.
9. A frozen composition comprising:
- (i) vancomycin at a concentration of about 0.1% to about 3% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration;
 - (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight;
 - (iii) one or more phospholipids at a total concentration of about 2% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1;
 - (iv) about 5% to about 6% dextrose by weight; and
 - (v) water;
- wherein when thawed, the composition forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm and a PFAT of less than about 0.05.

10. The composition of claim 9, comprising vancomycin at a concentration of about 0.5% by weight or a pharmaceutically acceptable salt or analog of vancomycin at an equivalent concentration.

11. The composition of claim 9 or claim 10, wherein the one or more liquid oils comprise a vegetable oil and a medium chain triglyceride.

12. The composition of any one of claims 9 to 11, wherein the composition does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion.

13. The composition of any one of claims 9 to 11, wherein when thawed, less than about 30% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

14. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the emulsion of any one of claims 1 to 8.

15. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by thawing the frozen composition of any one of claims 9 to 13.

16. An oil-in-water emulsion comprising:

- (i) clarithromycin at a concentration of at least about 0.5% by weight or a pharmaceutically acceptable salt or ester of clarithromycin at an equivalent concentration;
- (ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight;
- (iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1;
- (iv) about 5% to about 6% dextrose by weight; and
- (v) water;

wherein the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

17. The emulsion of claim 16, wherein the one or more liquid oils comprise soybean oil.

18. The emulsion of claim 16, wherein the one or more liquid oils comprise a vegetable oil and a medium chain triglyceride.

19. The emulsion of any one of claims 16 to 18, wherein the one or more phospholipids comprise lecithin.

20. The emulsion of any one of claims 16 to 19, wherein the emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

21. The emulsion of any one of claims 16 to 19, wherein less than about 30% of clarithromycin is in the oil droplets of the emulsion.

22. The emulsion of claim 16, comprising:

(1) clarithromycin at a concentration of about 1% to about 5% by weight,

(2) soybean oil and medium chain triglyceride, wherein the total concentration of soybean oil and medium chain triglyceride is about 2% by weight, the weight ratio of soybean oil to medium chain triglyceride is between 2:1 to 1:1;

(3) lecithin at a concentration of about 2% by weight; and

(4) dextrose at a concentration of about 5% by weight.

23. A frozen composition comprising:

(i) clarithromycin at a concentration of at least about 0.5% by weight or a pharmaceutically acceptable salt or ester of clarithromycin at an equivalent concentration;

(ii) one or more liquid oils at a total concentration of about 2% to about 4% by weight;

(iii) one or more phospholipids at a total concentration of about 1% to about 5% by weight, wherein the weight ratio of the total phospholipid(s) to the total liquid oil(s) is at least 0.5:1;

(iv) about 5% to about 6% dextrose by weight; and

(v) water;

wherein when thawed, the composition forms an oil-in-water emulsion with an average diameter of oil droplets no more than about 200 nm and a PFAT5 of less than about 0.05.

24. The composition of claim 23, wherein the one or more liquid oils comprise a vegetable oil and a medium chain triglyceride.

25. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the emulsion of any one of claims 16 to 22.

26. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by thawing the frozen composition of claim 23 or claim 24.

27. An oil-in-water emulsion comprising:

(i) at least about 15 mg/ml vancomycin or a pharmaceutically acceptable salt or analog thereof at an equivalent concentration,

(ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight,

(iii) one or more phospholipids at a total concentration of about 1% to about 10% by weight, and

(iv) dextrose at a concentration of at least about 10% by weight.

28. The oil-in-water emulsion of claim 27 wherein the one or more liquid oils comprise soybean oil.

29. The oil-in-water emulsion of claim 27 wherein the one or more phospholipids comprise lecithin.

30. The oil-in-water emulsion of claim 27 comprising vancomycin hydrochloride at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a concentration of about 1% to about 4% by weight, and dextrose at a concentration of about 15% to about 25% by weight.

31. The oil-in-water emulsion of claim 27 wherein the pH of the emulsion is about 3 to about 8.

32. The oil-in-water emulsion of any one of claims 27 to 31 wherein the average size of the oil droplets in the emulsion is less than 250 nm.

33. The oil-in-water emulsion of claim 32, wherein the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

34. The oil-in-water emulsion of any one of claims 27 to 33, wherein the emulsion does not further comprise a compound that increases the amount of vancomycin in the oil droplets of the emulsion.

35. The oil-in-water emulsion of any one of claims 27 to 33, wherein no more than about 30% of vancomycin is present in the oil droplets of the oil-in-water emulsion.

36. A lyophilized composition comprising vancomycin or a pharmaceutically acceptable salt or analog thereof, liquid oil(s), phospholipid(s), and dextrose, wherein

the composition is prepared by removal of water from the oil-in-water emulsion of any one of claims 27 to 35,

the composition can be rehydrated with water to form an emulsion suitable for injection, and

the average diameter of the re-formed emulsion droplets is no greater than about 1 micron.

37. The lyophilized composition of claim 36 wherein the average diameter of the reformed emulsion droplets is no greater than about 400 nm.

38. A lyophilized composition comprising:

(i) vancomycin at a concentration of about 5% to about 10% by weight or a pharmaceutically acceptable salt or analog thereof at an equivalent concentration,

(ii) one or more liquid oils at a total concentration of about 10% to about 20% by weight,

(iii) one or more phospholipids at a total concentration of about 10% to 20% by weight, and

(iv) dextrose at a concentration about 50% to about 80% by weight.

39. The lyophilized composition of claim 38, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and the average diameter of the oil droplets in the oil-in-water emulsion is no greater than about 1 micron.

40. The lyophilized composition of claim 38 or claim 39, wherein the composition does not further comprise a compound that increases the amount of vancomycin in the oil droplets of an oil-in-water emulsion formed by rehydrating the composition with water.

41. The lyophilized composition of claim 38 or claim 39, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and less than about 30% of vancomycin is in the oil droplets of the emulsion.

42. The lyophilized composition of any one of claims 38 to 41, wherein the composition forms an oil-in-water emulsion when rehydrated with water, the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

43. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the oil-in-water emulsion of any one of claims 27 to 35.

44. A method for treating or reducing infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by rehydrating the lyophilized composition of any one of claims 36 to 42.

45. An oil-in-water emulsion comprising:

(i) clarithromycin at a concentration of at least about 1% by weight or a pharmaceutically acceptable salt or ester thereof at an equivalent concentration,

(ii) one or more liquid oils at a total concentration of about 2% to about 10% by weight,

(iii) one or more phospholipids at a total concentration of about 1% to about 10% by weight, and

(iv) dextrose at a concentration of at least about 10% by weight.

46. The oil-in-water emulsion of claim 45 comprising clarithromycin at a concentration of about 1% to about 3% by weight, medium chain triglyceride at a concentration of about 1% to about 5% by weight, vegetable oil at a concentration of about 1% to about 5% by weight, lecithin at a concentration of about 1% to about 10% by weight, and dextrose of about 15% to about 25% by weight.

47. The oil-in-water emulsion of claim 45 or claim 46 wherein the average size of the oil droplets in the emulsion is less than about 250 nm.

48. The oil-in-water emulsion of claim 47, wherein the average size of the oil droplets in the emulsion is no more than about 200 nm, and the PFAT5 of the emulsion is less than about 0.05.

49. The oil-in-water emulsion of any one of claims 45 to 48, wherein the emulsion does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

50. The oil-in-water emulsion of any one of claims 45 to 48, wherein no more than 30% of clarithromycin is in the oil droplets of the emulsion.

51. A lyophilized composition comprising clarithromycin or a pharmaceutically acceptable salt or ester thereof, liquid oil(s), phospholipid(s), and dextrose, wherein

the composition is prepared by removal of water from the oil-in-water emulsion of any one of claims 45 to 50,

the composition can be rehydrated with water to form an emulsion suitable for injection, and

the average diameter of the re-formed emulsion droplets is no greater than about 1 micron.

52. The lyophilized composition of claim 51 wherein the average diameter of the re-formed emulsion droplets is no greater than about 200 nm.

53. A lyophilized composition comprising:

(i) clarithromycin at a concentration of about 2% to about 8% by weight or a pharmaceutically acceptable salt or ester thereof at an equivalent concentration,

(ii) liquid oil at a concentration of about 10% to about 20% by weight,

(iii) one or more phospholipids at a concentration of about 10% to about 20% by weight, and

(iv) dextrose at a concentration about 50% to about 80% by weight.

54. The lyophilized composition of claim 53, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and the average diameter of the emulsion droplets is no greater than about 200 nm.

55. The lyophilized composition of claim 54, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and the PFAT5 of the emulsion is less than about 0.05.

56. The lyophilized composition of any one of claims 53 to 55, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and the composition does not further comprise a compound that increases the amount of clarithromycin in the oil droplets of the emulsion.

57. The lyophilized composition of any one of claims 53 to 55, wherein the composition forms an oil-in-water emulsion when rehydrated with water, and less than about 30% of clarithromycin is in the oil droplets of the emulsion.

58. A method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of the oil-in-water emulsion of any one of claims 45 to 50.

59. A method for treating or reducing the risk of infection comprising administering to a patient in need thereof a pharmaceutically effective amount of an oil-in-water emulsion formed by rehydrating the lyophilized composition of any one of claims 51 to 57.