NON-AQUEOUS TAXANE PRO-EMULSION FORMULATIONS AND METHODS OF MAKING AND USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 U.S.C. § 119 (e), this application claims priority to the filing dates of: United States Provisional Patent Application Serial No. 61/330,705 filed on May 3, 2010; the disclosure of which application is herein incorporated by reference.

INTRODUCTION

Taxanes constitute a family of naturally occurring diterpene compounds including paclitaxel. Paclitaxel, originally isolated from the bark of the Pacific Yew tree (Taxus brevifolia), and its semi-synthetic analogue, docetaxel, are two examples of taxane compounds. Taxanes are active agents that block cell growth by stopping mitosis via microtubule interference.

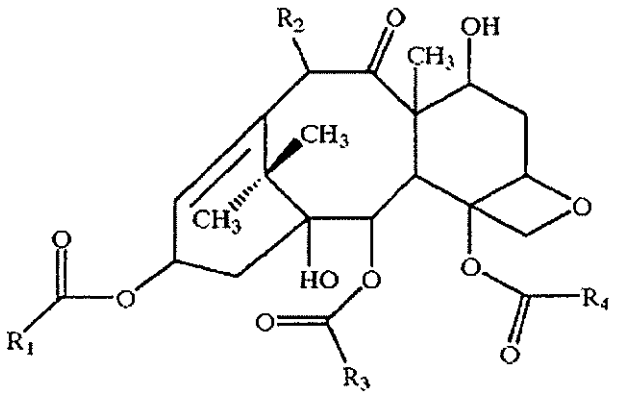
Taxanes can be used effectively to treat a variety of cancers and have been reported to have therapeutic effects in treating certain inflammatory diseases. Paclitaxel, for example, has been found to have activity against ovarian and breast cancers, as well as against malignant melanoma, colon cancer, leukemias and lung cancer (see, e.g., Borman, Chemical & Engineering News, Sep. 2, 1991, pp. 11-18; The Pharmacological Basis of Therapeutics (Goodman Gilman et al., eds.), Pergamon Press, New York (1990), p. 1239: Suffness, Antitumor Alkaloids, in: "The Alkaloids, Vol. XXV," Academic Press, Inc. (1985), Chapter 1, pp. 6-18: Rizzo et al., J. Pharm. & Biomed. Anal. 8(2):159-164 (1990); and Biotechnology 9:933-938 (October, 1991).

Formulation of taxanes in therapeutically useful carriers, so as to enable the taxanes to be administered to animals, is made difficult by the nature of the taxane molecule, which can be poorly soluble in both aqueous and lipid carriers.

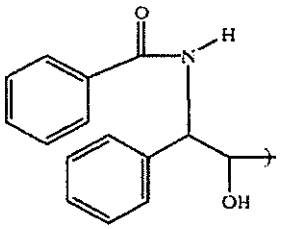
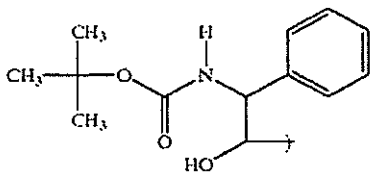
SUMMARY

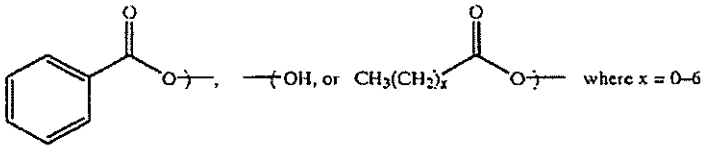
Non-aqueous taxane pro-emulsion formulations are provided. Pro-emulsion formulations include a taxane, an oil component, a surfactant component and, optionally, a non-aqueous solvent component. Also provided are methods of making and using the pro-emulsion formulations, as well as kits that include the pro-emulsion formulations.

Aspects of the invention include non-aqueous taxane liquid pro-emulsion formulations comprising: a taxane; an oil component; and a surfactant component. In some instances, the taxane is described by the formula:



where:

R_1 =  ,  , alkyl of 1 to 6 carbons or phenyl

R_2 = 

R_3 = alkyl of 1 to 6 carbons or phenyl; and

R_4 = alkyl of 1 to 6 carbons or phenyl. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some instances, the oil component is present in an amount ranging from 0.1 to 10% w/w, such as from 0.3 to 5% w/w. In some instances, the oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof, e.g., the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof. In some instances, the amounts of the taxane and oil components differ by 50% w/w or less, such as wherein the amounts of the taxane and oil components differ by 10% w/w or less. In some instances, the surfactant component is present in an amount ranging from 10 to 98 % w/w. The surfactant component may comprise a non-ionic surfactant, and in some instances the non-ionic surfactant is polysorbate 80. In some some instances, the formulation further includes a non-aqueous solvent component. In some instances, the non-aqueous solvent component is present in an amount ranging from 0.1 to 75 % w/w, such as in an amount ranging from 15 to 65 % w/w. In some instances, the non-aqueous solvent component is selected from the group consisting of proplyene glycol, glycerin, polyethylene glycol, and combinations thereof. In some instances, the formulation further includes an organic acid component, e.g., a lactic acid/sodium lactate component, which in some instances is present in an amount ranging from 0.3 to 3 % w/w.

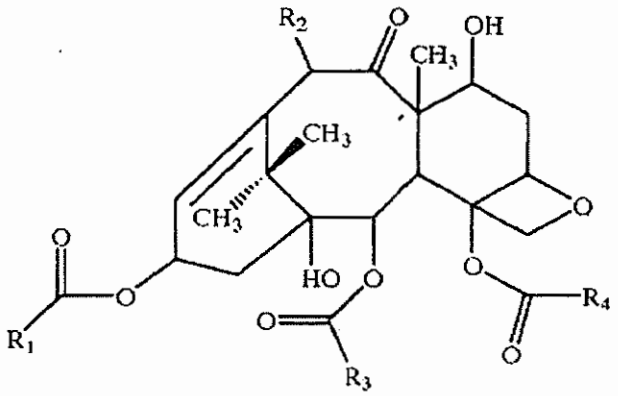
Of interest in certain embodiments is A non-aqueous taxane pro-emulsion formulation consisting essentially of: a taxane; soybean oil or MCT(medium chain triglyceride) oil; polysorbate 80; and propylene glycol or polyethylene glycol having an average molecular weight of 1,000 or less; wherein: the soybean oil or MCT oil is present in an amount that is 10 % w/w or less of the formulation. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some instances, the the soybean oil or MCT oil is present in an amount ranging from 0.5 to 5% w/w. In some instances, the polysorbate 80 is

present in an amount of 30 % w/w or more. In some instances, the propylene glycol or polyethylene glycol is present in an amount of 70 % w/w or less.

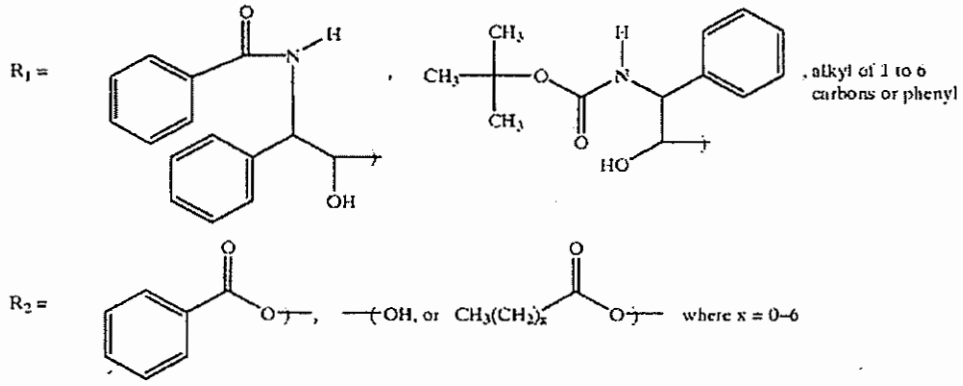
Aspects of the invention include a non-aqueous taxane pro-emulsion formulation consisting of: a taxane selected from the group consisting of paclitaxel, docetaxel and docetaxel trihydrate in an amount ranging from 0.4 to 5% w/w; an oil selected group consisting of soybean oil and MCT oil in an amount ranging from 0.4 to 5% w/w; polysorbate 80 in an amount of 30 % w/w or more; and a non-aqueous solvent selected from the group consisting of propylene glycol and polyethylene glycol having an average molecular weight of1,000 daltons or less in an amount of 70 % w/w or less.

Aspects of the invention include a non-aqueous taxane pro-emulsion formulation consisting of: a taxane selected from the group consisting of paclitaxel, docetaxel and docetaxel trihydrate in an amount ranging from 0.5 to 5% w/w; an oil selected group consisting of soybean oil and MCT oil in an amount ranging from 0.4 to 5% w/w; polysorbate 80 in an amount of 30 % w/w or more; a non-aqueous solvent selected from the group consisting of propylene glycol and polyethylene glycol having an average molecular weight of1,000 daltons or less in an amount of 70 % w/w or less; and a lactic acid/sodium lactate component in an amount ranging from 0.3 to 3% w/w.

Aspects of the invention further include methods of administering a taxane to a subject, the methods comprising: combining a taxane pro-emulsion formulation, e.g., as described above, with an aqueous medium to produce a taxane emulsion; and administering the taxane emulsion to the subject. In some instances, the taxane is described by the formula:



where:



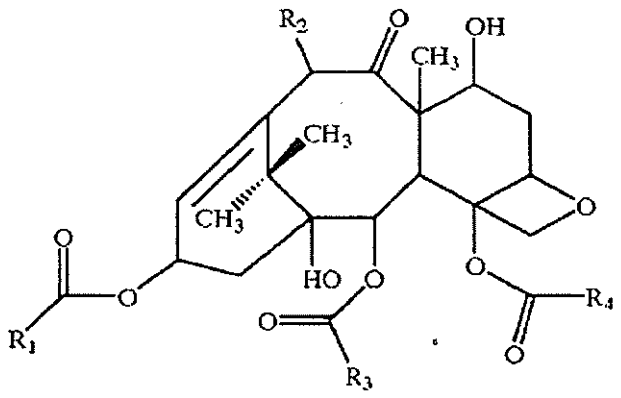
R_3 = alkyl of 1 to 6 carbons or phenyl; and

R_4 = alkyl of 1 to 6 carbons or phenyl. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some instances, the oil component is present in an amount ranging from 0.1 to 10% w/w, such as from 0.3 to 5% w/w. In some instances, the oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof, e.g., the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof. In some instances, the amounts of the taxane and oil

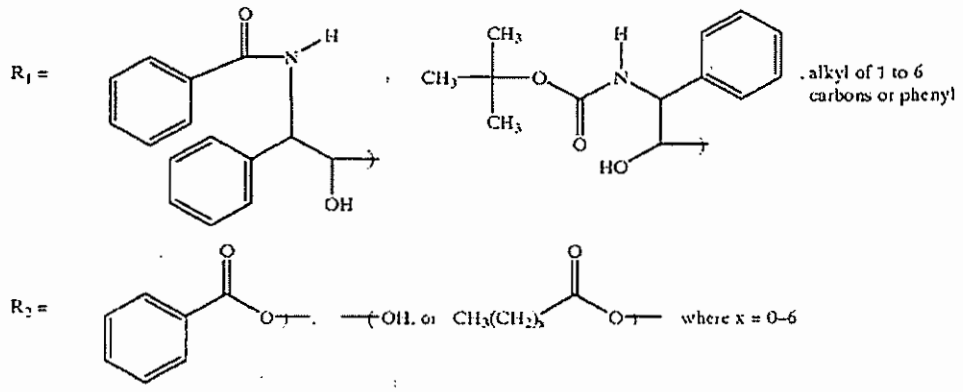
components differ by 50% w/w or less, such as wherein the amounts of the taxane and oil components differ by 10% w/w or less. In some instances, the surfactant component is present in an amount ranging from 10 to 98 % w/w. The surfactant component may comprise a non-ionic surfactant, and in some instances the non-ionic surfactant is polysorbate 80. In some some instances, the formulation further includes a non-aqueous solvent component. In some instances, the non-aqueous solvent component is present in an amount ranging from 0.1 to 75 % w/w, such as in an amount ranging from 15 to 65 % w/w. In some instances, the non-aqueous solvent component is selected from the group consisting of proplyene glycol, glycerin, polyethylene glycol, and combinations thereof. In some instances, the formulation further includes an organic acid component, e.g., a lactic acid/sodium lactate component, which in some instances is present in an amount ranging from 0.3 to 3 % w/w.

In some instances the methods, the methods comprise storing the taxane pro-emulsion formulation for 1 day or longer before contacting the pro-emulsion formulation with the aqueous medium. In some instances, the subject suffers from a cellular proliferative disease.

Also of interest are taxane emulsion compositions produced by combining a pro-emulsion composition, e.g., as described above, with an aqueous medium. In some instances, the taxane is described by the formula:



where:

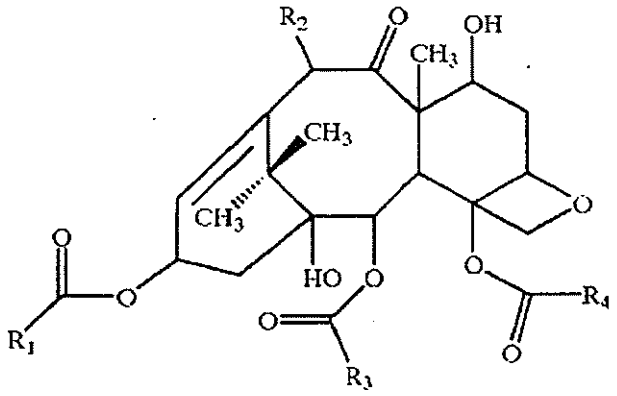


R_3 = alkyl of 1 to 6 carbons or phenyl; and

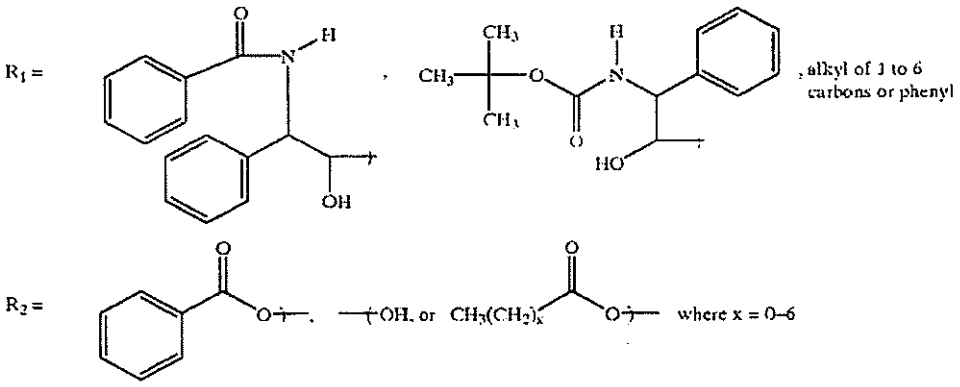
R_4 = alkyl of 1 to 6 carbons or phenyl. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some instances, the oil component is present in an amount ranging from 0.1 to 10% w/w, such as from 0.3 to 5% w/w. In some instances, the oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof, e.g., the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof. In some instances, the amounts of the taxane and oil components differ by 50% w/w or less, such as wherein the amounts of the taxane and oil components differ by 10% w/w or less. In some instances, the surfactant component is present in an amount ranging from 10 to 98 % w/w. The surfactant component may comprise a non-ionic surfactant, and in some instances the non-ionic surfactant is polysorbate 80. In some some instances, the formulation further includes a non-aqueous solvent component. In some instances, the non-aqueous solvent component is present in an amount ranging from 0.1 to 75 % w/w, such as in an amount ranging from 15 to 65 % w/w. In some instances, the non-aqueous solvent component is selected from the group consisting of proplyene glycol, glycerin, polyethylene glycol, and combinations thereof. In some instances, the formulation further includes an organic acid component, e.g., a lactic acid/sodium

lactate component, which in some instances is present in an amount ranging from 0.3 to 3 % w/w.

Aspects of the invention further include kits comprising: a taxane pro-emulsion formulation, e.g., as described above, and an aqueous medium. In some instances, the taxane is described by the formula:



where:

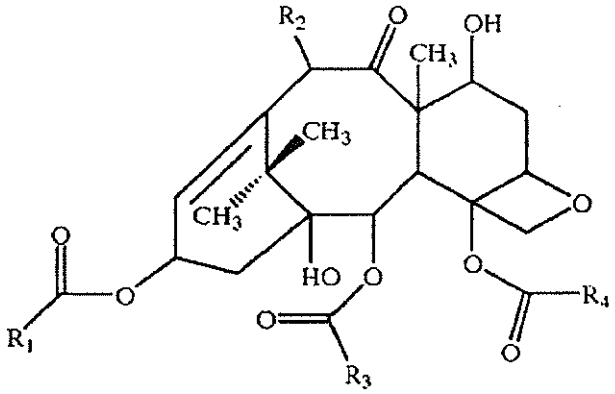


R_3 = alkyl of 1 to 6 carbons or phenyl; and

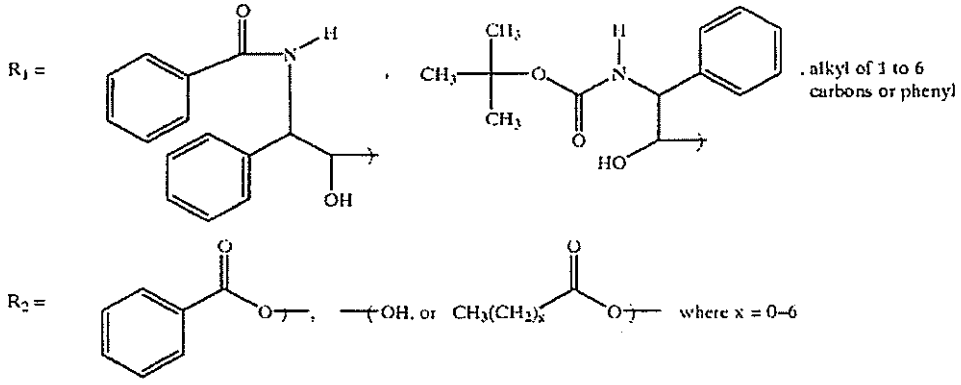
R_4 = alkyl of 1 to 6 carbons or phenyl. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some

instances, the oil component is present in an amount ranging from 0.1 to 10% w/w, such as from 0.3 to 5% w/w. In some instances, the
oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof, e.g., the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof. In some instances, the amounts of the taxane and oil components differ by 50% w/w or less, such as wherein the amounts of the taxane and oil components differ by 10% w/w or less. In some instances, the surfactant component is present in an amount ranging from 10 to 98 % w/w. The surfactant component may comprise a non-ionic surfactant, and in some instances the non-ionic surfactant is polysorbate 80. In some some instances, the formulation further includes a non-aqueous solvent component. In some instances, the non-aqueous solvent component is present in an amount ranging from 0.1 to 75 % w/w, such as in an amount ranging from 15 to 65 % w/w. In some instances, the non-aqueous solvent component is selected from the group consisting of proplyene glycol, glycerin, polyethylene glycol, and combinations thereof. In some instances, the formulation further includes an organic acid component, e.g., a lactic acid/sodium lactate component, which in some instances is present in an amount ranging from 0.3 to 3 % w/w.

Aspects of the invention further include methods of making a taxane pro-emulsion formulation, e.g., as described above, where the methods comprise combining a taxane, an oil component, a surfactant component, and a non-aqueous solvent in a manner sufficient to produce a taxane pro-emulsion. In some instances, the taxane is described by the formula:



where:



R_3 = alkyl of 1 to 6 carbons or phenyl; and

R_4 = alkyl of 1 to 6 carbons or phenyl. Taxanes of interest include, but are not limited to: anhydrous paclitaxel or a hydrate thereof and anhydrous docetaxel or a hydrate thereof, where in some instances the taxane is docetaxel trihydrate. In some instances, the oil component is present in an amount ranging from 0.1 to 10% w/w, such as from 0.3 to 5% w/w. In some instances, the oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof, e.g., the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof. In some instances, the amounts of the taxane and oil

components differ by 50% w/w or less, such as wherein the amounts of the taxane and oil components differ by 10% w/w or less. In some instances, the surfactant component is present in an amount ranging from 10 to 98 % w/w. The surfactant component may comprise a non-ionic surfactant, and in some instances the non-ionic surfactant is polysorbate 80. In some some instances, the formulation further includes a non-aqueous solvent component. In some instances, the non-aqueous solvent component is present in an amount ranging from 0.1 to 75 % w/w, such as in an amount ranging from 15 to 65 % w/w. In some instances, the non-aqueous solvent component is selected from the group consisting of proplyene glycol, glycerin, polyethylene glycol, and combinations thereof. In some instances, the formulation further includes an organic acid component, e.g., a lactic acid/sodium lactate component, which in some instances is present in an amount ranging from 0.3 to 3 % w/w.

In some embodiments of these methods, the combining step occurs in the presence of elevated temperatures. In some instances, the method comprises combining the taxane, oil component, surfactant component and non-aqueous solvent with an aqueous fluid in a manner sufficient to produce an initial emulsion composition andthen separating water from the initial emulsion composition to produce a taxane pro-emulsion formulation. In some instances, the separating comprises modulating pressure and/or temperature of the emulsion. In some instances, the method further comprises filtering the pro-emulsion formulation.

DETAILED DESCRIPTION

Non-aqueous taxane pro-emulsion formulations are provided. Pro-emulsion formulations include a taxane, an oil component, a surfactant component and, optionally, a non-aqueous solvent component. Also provided are methods of making and using the pro-emulsion formulations, as well as kits that include the pro-emulsion formulations.

Before the present invention is described in greater detail, it is to be understood that this invention is not limited to particular embodiments described, as

such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Certain ranges are presented herein with numerical values being preceded by the term "about." The term "about" is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure

prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

It is noted that, as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

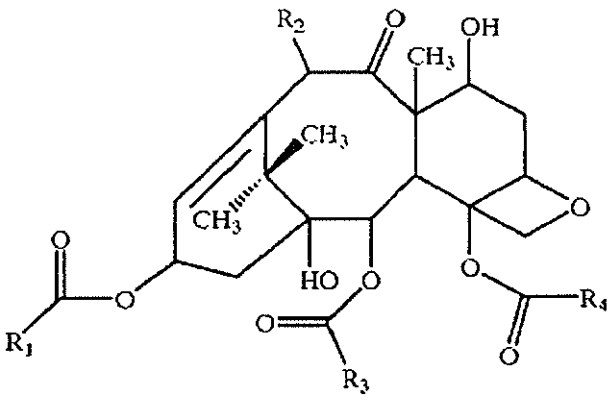
As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

In the following sections, the pro-emulsion formulations and emulsions prepared therefrom, as well as methods using the same, are described first in greater detail, followed by a review of methods for preparing the pro-emulsion formulations and emulsions, as well as kits that may include the formulations.

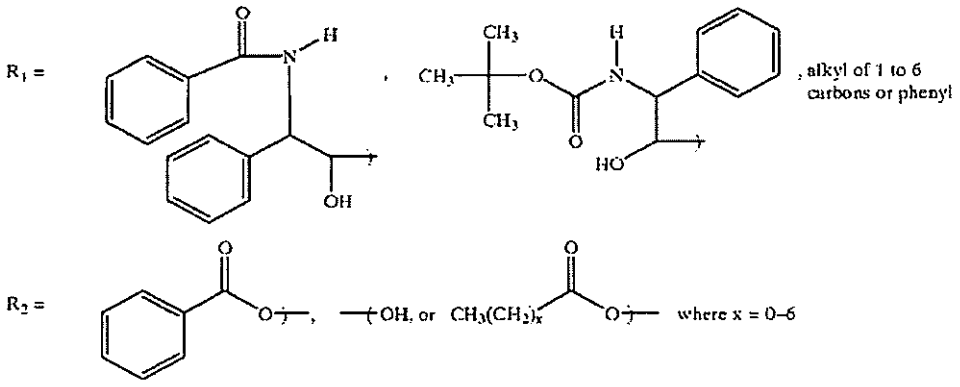
TAXANE PRO-EMULSION FORMULATIONS

Aspects of the invention include taxane pro-emulsion formulations. In some instances, the pro-emulsion formulations are non-aqueous liquid compositions that, upon combination with an aqueous medium, produce a taxane emulsion. The non-aqueous liquid pro-emulsion formulations of embodiments of the invention include at least a taxane, an oil component, a surfactant component and, optionally, a non-aqueous solvent component.

Taxanes of interest are diterpene compounds. In some instances, taxanes are compounds described by the formula:



where:



R_3 = alkyl of 1 to 6 carbons or phenyl; and

R_4 = alkyl of 1 to 6 carbons or phenyl.

Of interest are anhydrous taxanes as well as hydrates thereof, e.g., mono, di, tri, tetra and penta hydrates, etc. In certain embodiments, the taxane is paclitaxel or docetaxel or a hydrate thereof, e.g., docetaxel trihydrate, paclitaxel trihydrate, etc. Taxanes of interest also include, but are not limited to: 7-epitaxol, 7-acetyl taxol, 10-desacetyl-taxol, 10-desacetyl-7-epitaxol, 7-xylosyltaxol, 10-desacetyl-7-glutaryltaxol,

7-N,N-dimethylglycyltaxol, 7-L-alanyltaxol, SB-T-1011, etc. The taxane may be present as a free base or salt.

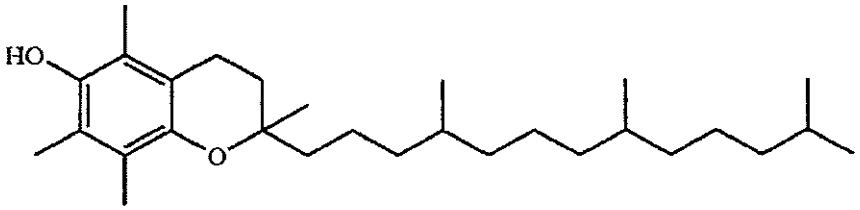
Pro-emulsion formulations include an effective amount of a taxane. By effective amount is meant a dosage sufficient to provide the desired result, e.g., inhibition of cellular proliferation. The effective amount of taxane may vary depending on the particular taxane employed, and in certain embodiments ranges from 0.05 to 5% by weight, such as 0.5 to 5 % by weight and including 0.3 to 3% by weight. In certain embodiments, the pro-emulsion formulations include an effective amount of paclitaxel or paclitaxel trihydrate. In certain embodiments, paclitaxel or paclitaxel trihydrate is present in the pro-emulsion formulation in an amount ranging from 0.05 to 5.0% w/w, such as 0.5 to 5.0% w/w, and including 0.3 to 3.0% w/w, where in some instances the amount ranges from 0.3 to 5.0% w/w, such as 0.3 to 3.0% w/w, e.g., 0.4 to 2.5% w/w, e.g., 0.5 to 2.0% w/w, and including 1.0 to 1.5% w/w. In certain embodiments, the pro-emulsion formulations include an effective amount of docetaxel or docetaxel trihydrate. In certain embodiments, docetaxel or docetaxel trihydrate is present in the pro-emulsion formulation in an amount ranging from 0.1 to 5% w/w, such as 0.5 to 5% w/w and including 0.5 to 3% w/w.

Also present in the pro-emulsion formulations is an oil component made up of one or more oils. Oils of interest are physiologically acceptable and include, but are not limited to: simple lipids, derived lipids, complex lipids that are derived from natural vegetable oil and fat, animal oil and fat, and mineral oil, or mixtures thereof, where the oils may be naturally occurring or synthetic.

In certain embodiments, the oil includes, but is not limited to soybean oil, olive oil, sesame oil, castor oil, corn oil, peanut oil, safflower oil, grape seed oil, eucalyptus oil, medium-chain fatty acid esters, low-chain fatty acid esters, and the like. Animal oils and fat of interest include, but are not limited to, cod-liver oil, seal oil, sardine oil, docosahexiaenoic acid, and eicosapentaenoic acid. Mineral oils of interest include, but are not limited to, liquid paraffins (e.g. oils derived from *n*-alkanes), naphthenic oils (e.g. oils based on cycloalkanes), and aromatic oils (e.g. oil based on aromatic hydrocarbons). One or a combination of more than one of these types of oils can be used. For example, some embodiments of the subject emulsion

formulations include soybean oil, olive oil, sesame oil, or combinations thereof. Other embodiments include soybean oil, olive oil, or combinations thereof. Highly refined oils and fats are employed in certain embodiments.

Oils of interest also include tocopherols. Tocopherols are a family of natural and synthetic compounds, also known by the generic names tocols or Vitamin E. α-tocopherol is the most abundant and active form of this class of compounds and it has the following chemical structure (Scheme I):



Other members of this class include α-, β-, γ-, and δ-tocotrienols, and α-tocopherol derivatives such as tocopherol acetate, phosphate, succinate, nitotinate and linoleate. Any convenient tocopherol may be present, as desired, including the specific tocopherols listed above.

Oils of interest also include polyol esters of medium chain fatty acids. The term "polyol esters of medium chain fatty acids" is intended to include esters and mixed esters of glycerol, propylene glycol or other open chain polyols such as polyethylene glycol, reacted with medium chain fatty acids, e.g., where the acid has a chain length between 6 and 12 carbon atoms. In some instances, the polyol esters of medium chain fatty acids are triglycerides or diglycerides of the C_8 -C_{10} fatty acids, e.g., as may be commercially available from the fractionation of coconut oil. Commercially available products of this description are sold under the trade names "Miglyol" and "Captex 300" which are described as having a typical composition of about 68% C_8 fatty acid (caprylic) triglyceride and about 28% C_{10} fatty acid (capric) triglyceride with minor levels of C_6 and C_{14} fatty acid triglycerides.

In certain embodiments, the oil component is 10 % w/w or less of the formulation. In some instances, the amount of oil in the pro-emulsion formulation

ranges from 0.05 to 10% w/w, such as 0.1 to 10% or 0.1 to 8% w/w, and including 0.5 to 5% w/w or 5 to 10% w/w. In some instances, the amount of oil by weight is the same as the amount of taxane by weight.

Also present in certain embodiments of the subject pro-emulsion formulations is a surfactant component, which may include one or more surfactants. Surfactants of interest include any type of surfactant that can be used for pharmaceutical formulations. Nonionic surfactants of interest include, but are not limited to, polyoxyalkylene copolymer, and sorbitan fatty acid esters. In some embodiments, the sorbitan fatty acid ester is a polyoxyethylene sorbitan fatty acid ester (e.g., Polyoxyethylene sorbitan tristearate (Tween 65); Polyoxyethylene sorbitan trioleate (Tween 85); Polyethylene glycol 400 monostearate; Polysorbate 60; (Tween 60); Polyoxyethylene monostearate (Myrj 49); Polysorbate 80 (Tween 80); Polysorbate 40 (Tween 40); and Polysorbate 20 (Tween 20)) or sorbitan fatty acid esters (e.g., Sorbitan trioleate (Span 85); Sorbitan tristearate (Span 65); Sorbitan sesquioleate (Arlacel 83); Glyceryl monostearate; Sorbitan monooleate (Span 80); Sorbitan monostearate (Span 60); Sorbitan monopalmitate (Span 40); Sorbitan monolaurate (Span 20)). The amount of surfacant in the pro-emulsion formulation may vary. In some instances, the amount of surfactant in the pro-emulsion formulation is 10 % w/w or more, such as 20 % w/w or more, 30 % w/w or more, 40 % w/w or more, or 45 % w/w or more. In some instances, the amount of surfactant in the pro-emulsion formulation ranges from 10 to 98% w/w, such as 20 to 98% w/w and including 30 to 98% w/w, e.g., 45 to 98 % w/w. In some instances, the amount of surfactant in the pro-emulsion formulation ranges from 30 to 70% w/w, such as 30 to 60% w/w, e.g., 35 to 55 % w/w, and including 30 to 50% w/w, e.g., 30 to 40 % w/w. The combination ratio by weight of the oil and the surfactant in the subject pro-emulsion formulations may vary, ranging in some instances from 1/1000 to 1/5, such as 1/100 to 1/8, 1/80 to 1/10, 1/50 to 1/16, 1/40 to 1/16, or 1/35 to 1/20.

In some instances, pro-emulsion formulations of the invention further include a non-aqueous solvent component, which may include one or more non-aqueous solvents. Non-aqueous solvents of interest include, but are not limited to: propylene glycol, polypropylene glycol, polyethylene glycol (such as PEG300, 400, 600, 800,

1000, etc., where in certain embodiments polyethylene glycols, when employed, have an average molecular weight of 1000 or less), glycerin, ethanol, triacetin, dimethyl isosorbide, glycofurol, propylene carbonate, dimethyl acetamide or a mixture thereof. The non-aqueous solvent, when present, may be present in varying amounts, and in some instances ranges from 0.1 to 90% by weight, such as 10 to 70% by weight and including 20 to 65% by weight, e.g., 30 to 60 %, 35 to 55%, or 40-50% by weight. In some instances, the non-aqueous solvent, when present, may be present in an amount by weight that is 70% or less, such as 60% or less, 50% or less, 40% or less, 30% or less or 20% or less. The combination ratio by weight of the oil and the non-aqueous solvent in the subject pro-emulsion formulations may vary, and in some instances is 1/1000 or greater, such as 1/200 or greater. In some instances, the combination ratio by weight of the oil and the non-aqueous solvent ranges from 1/200 to 1/2, such as 1/100 to 1/2, 1/100 to 1/6, 1/100 to 1/20, 1/80 to 1/30, or 1/60 to 1/40.

In some instances, the pro-emulsion formulation may include an organic acid component. An organic acid component may include an organic acid and/or its conjugate base (or salt thereof), wherein in some instances the organic acid component may include an organic acid and a salt of its conjugate base. Organic acids of interest upon which the organic acid component may be based include lactic acid, acetic acid, citric acid, etc. In some instances, the organic acid component is a lactic acid/sodium lactate component, such that the component includes both lactic acid and sodium lactate. In some instances, the lactic acid/sodium lactate component is present in an amount ranging from about 0.3 to 3% w/w.

METHODS OF PREPARING TAXANE PRO-EMULSION FORMULATIONS

Pro-emulsion formulations may be prepared according to any convenient protocol. As such, the components of the desired pro-emulsion may be combined under conditions sufficient to produce the desired pro-emulsion. Accordingly, an amount of one or more taxanes, one or more oils, one or more surfactants and one or more non-aqueous solvents may be combined under conditions sufficient to

produce a pro-emulsion. The components may be combined in any convenient order. The components may be combined at any convenient temperature, e.g., room temperature or elevated temperatures, such as temperatures ranging from 30 to 95 °C, e.g., 50 to 60 °C. Certain of the components may be combined with each other, and then combined with the aqueous medium, or all of the components may be combined at substantially the same time. Combination may include various manners of agitation, e.g., stirring, sonication, etc., in order to produce the desired precursor emulsion. Depending on the particular preparation method, an aqueous solvent, e.g., water, etc. may or may not be employed during preparation of the pro-emulsion compositions.

In one embodiment, a pro-emulsion is prepared without an aqueous solvent. In these embodiments, the components of the pro-emulsion, e.g., taxane, oil, surfactant and non-aqueous solvent, are combined, e.g., as described above, Where desired, heat may be employed to facilitate mixing. This resultant pro-emulsion is translucent e.g., as described above.

As indicated above, in some instances, the pro-emulsion preparation protocol includes use of an aqueous solvent, e.g., pure water. In these instances, an initial emulsion composition is prepared that includes a taxane, an oil component, a surfactant component, a non-aqueous solvent component and an aqueous solvent, e.g., water, etc. In certain embodiments, the initial emulsion composition is clear. By clear is meant that the emulsion is a translucent, if not transparent liquid, i.e., the liquid is pellucid. As such, the initial preparation is not cloudy, e.g., as a suspension may appear. Further details regarding the pro emulsions that may be prepared from the taxane initial composition precursors are provided below. In some instances, the particle size of the initial composition ranges from 3 to 70 nm, such as 5 to 50 nm and including 7 to 30 nm, such as 8 to 15 nm. Of interest in certain embodiments are initial compositions that are clear (e.g., as described above) and have a particle size of 70nm or less, such as 50 nm or less, including 30 nm or less, including 25 nm or less, 20 nm or less and 15 nm or less. In these embodiments, as a final step, water may be removed from the initial emulsion composition to produce a final, non-aqueous pro-emulsion. Removal of water may be accomplished using any

convenient protocol, e.g., via a combination of pressure and/or temperature modulation, such as heating.

The preparation methods can be carried out at room temperature or at a temperature lower than room temperature. Specific examples of protocols for preparing pro- emulsions are provided in the Experimental section, below.

Where desired, an amount of the pro-emulsion may be loaded into an individual dosage container, e.g., vial, which holds the pro-emulsion and keeps it sterile during shipping, storage, and handling. Before or during the loading stage, the pro-emulsion can be passed through a sub-micron sterilizing filter, e.g., a 0.2 μ hydrophilic filter) which has a sufficiently small pore size to remove any bacteria or viruses. As used herein, the term "vial" refers to any stiff-walled container that is used to hold the pro-emulsion formulation. Nearly all pharmaceutical vials are made of clear glass, which allows several advantages, including visual inspection of the enclosed drug (to ensure that it is still in a clean, non-caramelized, non-collapsed form, when it is ready for use) and of the container itself (to ensure that it does not have a hairline crack in one of the walls, which could jeopardize or destroy sterility of the enclosed drug). Various types of pharmaceutical vials are known. Single-chamber vials can be sealed with rubber or plastic plugs that will allow a hypodermic needle to be pushed through the rubber seal. Alternately, a single-chamber vial can be made of a brittle and easily breakable material, inside a sealed bag that can contain an aqueous solution (such as physiological saline or a dextrose solution, in an intravenous infusion bag); if this type of vial is broken, it will release its contents into the still-sealed bag, for mixing. In yet other embodiments, two-chamber vials or analogous structures, e.g., as described in Published United States Application Publication No. 20030099674 and U.S. Patent no. 4,781,354 may be employed.

TAXANE PRODUCT EMULSION FORMULATIONS AND METHODS OF USE

Following preparation of the pro-emulsion formulation, e.g., as described above, at the time of desired administration to a subject, a dosage amount of the pro-emulsion may be combined with an aqueous medium to prepare a product

emulsion formulation that is suitable for use. The dosage amount of the pro-emulsion formulation may be combined with any suitable aqueous medium, where aqueous mediums of interest include, but are not limited to: deinionized water, USP water for injection (WFI), salines, transfusion solutions, physiological solutions, etc. The liquids to pro-emulsion (high viscous liquid) ratio employed during preparation of the product emulsion may vary, and in certain embodiments ranges from 0.5 to 300, such as 1 to 100, 2 to 50 or 2 to 20, and including 2 to 10. In some instances, the dosage amount of pro-emulsion formulation that is combined with the aqueous medium ranges from 100 to 1200g, such as 300 to 600g and the amount of aqueous medium that is combined with the dosage amount ranges from 100 to 1200 ml, such as 250 to 600 ml.

The emulsions prepared from the pro-emulsion formulations are liquid preparations that are a suspension of small particles (i.e., globules) of one liquid in a second liquid with which the first liquid will not mix. In certain embodiments, the product emulsions prepared from pro-emulsion formulations of the invention are emulsions of oil and water. As the formulations are emulsions, they are mixtures of two immiscible (e.g., unblendable) fluids, where one fluid (e.g., an oil or water) (the dispersed phase) is dispersed in the other fluid (e.g., the other of the oil or water) (the continuous phase). The water present in the emulsions may be any convenient water, including deinionized water, USP water for injection (WFI), etc.

The product emulsions include a taxane, an oil component, a surfactant component, a non-aqueous solvent component and water. In certain embodiments, the product emulsions are clear. By clear is meant that the emulsion is a translucent, if not transparent liquid, i.e., the liquid is pellucid. As such, the emulsion is not cloudy, e.g., as a suspension may appear. Further details regarding the product emulsions that may be prepared from the taxane pro-emulsion precursors are provided below. In some instances, the particle size of the final emulsion ranges from 3 to 70 nm, such as 5 to 50 nm and including 7 to 30 nm, such as 8 to 15 nm. Of interest in certain embodiments are product emulsions that are clear (e.g., as described above) and have a particle size of 70nm or less, such as 50 nm or less, including 30 nm or less, including 25 nm or less, 20 nm or less and 15 nm or less. In

some instances, any difference in particle size between the pro and product emulsions is minimal, such that the particle sizes in the pro and product emulsions are substantially the same. In some instances, any difference in particle size between the pro and product emulsions is 30 nm or less, such as 20 nm or less, 10 nm or less, 5 nm or less, 4 nm or less, 3 nm or less, 2 nm or less, including 1 nm or less.

Where desired, the pro-emulsion formulation may be stored for a period of time prior to combination with the aqueous medium. This storage time of the pro-emulsion composition may vary, where storage times may be 1 year or more, such as 2 years or more, including 3 years or more. While the storage conditions may vary, in certain instances the storage conditions are characterized by a temperature ranging from 5 to 60 °C, e.g., 5 °C, such as 8 to 40 °C, e.g., 25 °C. The activity of the taxane active agent is preserved during the storage period, such that the pro-emulsion formulations are storage stable. As such, the activity of the taxane active agent in the reconstituted product emulsion following storage is substantially the same as that in the precursor emulsion prior to being dried, where the magnitude of any difference in activity between the precursor and final emulsion may be 15 % or less, such as 10 % or less, including 5 % or less, e.g., as measured according to HPLC performed as summarized in the following table.

Measurement Wavelength	UV=230nm
Column	MERCK Lichrospher RP-18 5μ 4.0mm ϕ ×125mmL (ODS type)
Column temperature	40ºC
Mobile phase	Methanol/Water 65/35 vol.%
Sample volume	20μl
Measurement time	PAC 13 min. DOC 20 min.
Internal reference	PAC butyl benzoate 0.1mg/ml DOC isopentyl benzoate 0.1mg/ml

The combination protocol may vary, where agitation may be employed, e.g., by stirring, by kneading a bag that includes both the emulsion and the aqueous medium, etc.

The product taxane emulsion formulations that are produced upon reconstitution of the pro-emulsion formulation with the aqueous medium can have a

physiologically acceptable pH. In certain embodiments, the pH of the emulsion formulations ranges from 2.5 to 8, such as from 3 to 7, including from 3.5 to 6. The product taxane emulsion formulations are clear formulations. The concentration of the taxane in the product emulsion may vary, ranging in some embodiments from 0.05 to 10 mg/ml, such as 0.2 to 3 mg/ml.

Methods of using the product taxane emulsion formulations include administering an effective amount of the taxane emulsion formulation to a subject in order to treat the subject for a target condition of interest. By "treating" or "treatment" is meant at least a suppression or an amelioration of the symptoms associated with the condition afflicting the subject, where suppression and amelioration are used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom, associated with the condition being treated, such as pain. As such, treatment also includes situations where the condition is completely inhibited, e.g., prevented from happening, or stopped, e.g., terminated, such that the subject no longer experiences the condition. As such, treatment includes both preventing and managing a condition.

In practicing the methods, the emulsion formulations disclosed herein can be parenterally administered to a subject. By "parenteral administration" is meant administration by a protocol that delivers a quantity of the emulsion formulation to the subject, e.g., a patient suffering from a cellular proliferative disease, by a route other than the digestive tract. Examples of parenteral administration include, but are not limited to, intramuscular injection, intravenous injection, transdermal absorption, inhalation, and the like. In certain embodiments, parenteral administration is by injection using an injection delivery device. The amount of emulsion formulation that is administered to the subject may vary depending on a number of factors, such as patient specifics, nature of condition, nature of taxane active agent, etc. In certain embodiments, the volume of emulsion that is administered to a subject may range from 100 to 1000 ml, such as 200 to 600 ml. The time period over which this volume is administered may vary, ranging from 0.5 to 6 hr, such as from 1 to 3 hr. Dosages administered to a subject during a given procedure may also vary, ranging in some instances from 20 to 500 mg/m^2, such as from 50 to 300 mg/m^2.

In certain embodiments, the subject methods include a diagnostic step. Individuals may be diagnosed as being in need of the subject methods using any convenient protocol. In addition, individuals may be known to be in need of the subject methods, e.g., they are suffering from a target disease condition (e.g., cellular proliferative disease, prior to practicing the subject methods. Diagnosis or assessment of target condition can be performed using any convenient diagnostic protocol.

Methods of the invention may further include assessing the efficacy of the treatment protocol that includes administration of the taxane emulsion formulation. Assessing the efficacy of treatment may be performed using any convenient protocol.

Taxane emulsion formulations of the invention may be administered to a variety of different types of subjects. Subjects of interest include, but are not limited to: mammals, both human and non-human, including the orders carnivore (e.g., dogs and cats), rodentia (e.g., mice, guinea pigs, and rats), lagomorpha (e.g. rabbits) and primates (e.g., humans, chimpanzees, and monkeys). In certain embodiments, the subjects, e.g., patients, are humans.

In determining whether to administer the emulsion to a particular given subject, care will be taken to ensure that the formulation is not contraindicated for that subject. As such, symptoms of the subject may be assessed to ensure that administration of the emulsion will not have adverse effects that outweigh any benefit that that emulsion may provide.

UTILITY

The subject emulsion formulations and methods find use in a variety of applications, including the treatment of subjects suffering from cellular proliferative disease conditions. Cellular proliferative diseases that may be treated with compositions of the invention include, but are not limited to: carcinomas, myelomas, neuroblastomas, or sarcomas, of the brain, breast, lung, colon, prostate or ovaries, as well as leukemias or lymphomas. Specific disease conditions of interest include,

but are not limited to, human ovarian cancer, breast cancer, malignant lymphoma, lung cancer, melanoma, and Kaposi's sarcoma.

KITS

Also provided are kits that find use in practicing the subject methods, as described above. For example, kits for practicing the subject methods may include a quantity of the pro-emulsion formulation, present in unit dosages, e.g., vials, or a multi-dosage format. As such, in certain embodiments, the kits may include one or more unit dosages (e.g., vials) of the pro-emulsion formulation. The term "unit dosage", as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of the subject pro-emulsion formulation calculated in an amount sufficient to produce the desired effect. The amount of the unit dosage of the subject emulsion formulation depends on various factors, such as the particular active agent employed, the effect to be achieved, and the pharmacodynamics associated with the active agent in the subject. In yet other embodiments, the kits may include a single multi-dosage amount of the emulsion formulation.

In certain embodiments, the kits may further include an amount of an aqueous medium suitable for use in reconstitution of the production taxane emulsion. The aqueous medium may be any convenient aqueous medium, such as described above, present in any suitable container, e.g., an IV bag.

In addition to the above components, the subject kits may further include instructions for practicing the subject methods. These instructions may be present in the subject kits in a variety of forms, one or more of which may be present in the kit. One form in which these instructions may be present is as printed information on a suitable medium or substrate, e.g., one or more pieces of paper on which the information is printed, in the packaging of the kit, in a package insert, etc. The instructions may be present on a computer readable medium, e.g., diskette, CD, DVD, etc., on which the information has been recorded. The instructions may be present on a website, which may be used via the internet to access the information

at a removed site. Other convenient means are possible and may be included in the kits.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

EXPERIMENTAL

I. Paclitaxel Formulations

A. Working Example 1 (Lot. 7)

200 mg of paclitaxel, 200 mg of soybean oil, 16g of polysorbate 80, and 4g of propylene glycol were placed into a 300 ml beaker. The beaker was heated to 50ºC and the ingredients were almost completely dissolved in an ultrasonic disperser. The beaker was then placed in a water bath with the temperature setting at 60ºC. The contents were agitated with a high-speed mixer (8,000rpm × 5 min.) while adding about 50 ml of warm water at 60ºC. The contents were agitated more (10,000rpm × 10 min.) to obtain a uniform solution.

16g of propylene glycol were then added to this emulsion. The emulsion was gently stirred for more uniformity and sufficient pure water was added to make the emulsion volume be 200 ml. The pH of this solution was adjusted to around 4 with 1N hydrochloric acid or 0.1N hydrochloric acid.

The resultant solution was poured into each 50 ml vial tube while applying nitrogen and the tube was sealed. High-pressure steam sterilization (121ºC ×

10min.) was then applied. In a clean room, 50 ml of this solution was taken from the vial and poured into a 200ml flask. The water was removed by evaporation at 60ºC to obtain a non-aqueous composition.

362mg of the resultant non-aqueous composition was then placed into a test tube. 2ml of pure water were added and the tube was shaken by hand for about 10 seconds to obtain a clear solution. When the particle size was measured via a particle size distribution in dynamic light scattering measurement protocol, the average size was observed to be 11.4 nm, which almost matches the average size of 11.7 nm in the solution before turning into the non-aqueous form. Regeneration of the non-aqueous composition is completed.

B. Additional Working Examples:

Additional formulations and the above formulation are summarized below in Table 1.

Table 1

Lot.	1	2	3	4
Drug [mg]	PAC 1	PAC 1	PAC 2	PAC 1
Oil [mg]	Soybean oil 1	Soybean oil 1	Soybean oil 2	Soybean oil 1
Surfactant [mg]	Polysorbate 80	Polysorbate 80	Polysorbate 100	Polysorbate 80
Non-Aqueous solvent [mg]	PG 100	GLY 122	PG 122	PG 80
Before φ [nm]	8.1	9.3	9.6	9.7
After φ [nm]	11.4	16.0	12.3	10.9

Lot.	5	6	7	8	9
Drug [mg]	PAC 1	PAC 1	PAC 1	PAC 1	PAC 1
Oil [mg]	Soybean oil 1	Soybean oil 1	Soybean oil 1	MCT 1	VE 1
Surfactant [mg]	Polysorbate	Polysorbate	Polysorbate	Polysorbate	Polysorbate

Lot.	5	6	7	8	9
	80	80	80	80	80
Non Aqueoussolvent [mg]	PG 20	0	PG 100	PG 100	PG 100
Before φ [nm]	9.7	9.7	11.7	11.1	11.6
After φ [nm]	10.1	10.7	11.4	11.6	11.6

In the Tables:
PAC refers to paclitaxel
Polysorbate refers to "polysorbate 80"
MCT refers to medium chain triglyceride
VE refers to Vitamin E or Tocopherol
PG refers to propylene glycol
GLY refers to glycerin
φ refers to particle size

C. Working Example 2 (Lot. 24)

400 mg of paclitaxel, 200 mg of MCT, 3.2g of polysorbate 80, 2g of polyethylene glycol 300 (average molecule weight = 300) and 160 mg of lactic acid mixture (=128mg of lactic acid and 32mg of 70% sodium lactate) were placed into a 50 ml beaker. The beaker was heated to 50ºC and the ingredients were almost completely dissolved in an ultrasonic disperser.

The resultant solution was poured into a 5 ml vial tube through a 0.2 μ filter while applying nitrogen and the tube was sealed. The resultant solution was then heated to 95ºC for 30min. to produce a non-aqueous composition.

30mg of the resultant non-aqueous composition was then placed into a test tube. 4ml of pure water were added and the tube was shaken by hand for about 20 seconds to obtain a clear solution. When the particle size was measured via a particle size distribution in the dynamic light scattering measurement protocol, the average size was observed to be 20.4 nm.

D. Additional Working Examples:

Additional formulations and the above formulation are summarized below in Table 2, below:

Table 2

Lot.	21	22	23	24
Drug [mg]	PAC 2	PAC 2	PAC 2	PAC 2
Oil [mg]	MCT 10	MCT 10	MCT 10	MCT 1
Surfactant [mg]	Polysorbate 80	Polysorbate 80	Polysorbate 80	Polysorbate 16
Non Aqueous solvent [mg]	PG 60	PG 120	PEG400 20	PEG300 10
Lactic acid mixture [mg]	0.8	0.8	0.8	0.8
Water [mg]	0	10	0	0

PEG—polyethylene glycol

II. Docetaxel Formulations

A. Working Example 1 (Lot. 16)

150mg of docletaxel, 150mg of MCT, 5g of polysorbate 80, and 3.5g of propylene glycol were placed into a 200 ml beaker. The beaker was heated to 50ºC and the ingredients dissolved almost completely in an ultrasonic disperser. The beaker was placed in a water bath with the temperature setting at 60ºC. The contents were then agitated with a high-speed mixer (7,000rpm × 2 min.) while adding about 35 ml of warm water at 60ºC. The contents were then agitated more (10,000rpm × 5 min.) to get a uniform solution.

2.5g of propylene glycol were added to this uniform solution. The solution was then gently stirred for more uniformity and sufficient pure water was added to

make the volume 50 ml. The pH of this solution was adjusted to 4 with 1N hydrochloric acid or 0.1N hydrochloric acid.

This solution was poured into each 50 ml vial tube while applying nitrogen and the tube was sealed. High-pressure steam sterilization (121ºC × 10min.) was then applied. In a clean room, 50 ml of this solution was removed from the vial and poured into a 200ml flask. The water was removed by evaporation at 60ºC to obtain a non-aqueous composition.

452mg of the obtained non-aqueous composition was placed into a test tube.2ml of pure water was then added and the resultant composition shaken by hand for about 10 seconds to obtain a clear solution. When the particle size was measured using a particle size distribution in dynamic light scattering measurement protocol, the average size was observed to be 11.6nm, which almost matches the average size of 11.8nm in the solution before turning into the non-aqueous form. Regeneration of the non-aqueous composition is completed.

B. Additional Working Examples

Additional formulations and the above formulation are summarized in Table 3.

Table 3

Lot.	11	12	13	14
Drug [mg/ml]	DOC 1	DOC 1	DOC 3	DOC 3
Oil [mg/ml]	MCT 1	MCT 1	MCT 3	Tocopherol 3
Surfactant [mg/ml]	Polysorbate 100	Polysorbate 80	Polysorbate 100	Polysorbate 100
Non Aqueous solvent [mg/ml]	PG 122	PG 80	PG 120	PG 120
Before φ [nm]	11.1	11.0	11.3	14.0
After φ [nm]	13.6	10.5	11.6	12.5

Lot.	15	16	17
Drug [mg/ml]	DOC 3	DOC 3	DOC 3
Oil [mg/ml]	Soybean oil 3	MCT 3	Tocopherol acetate 3
Surfactant [mg/ml]	Polysorbate 100	Polysorbate 100	Polysorbate 100
Non Aqueous solvent [mg/ml]	PG 120	PG 120	PG 120
Before φ	12.6	11.8	12.1
After φ	11.9	11.6	11.6

DOC-docetaxel

C. Working Example 2 (Lot.33)

400 mg of docetaxel trihydrate, 400 mg of MCT, 9.5 g of polysorbate 80, 7 g of polyethylene glycol 300 (average molecule weight = 300) and 100 mg of lactic acid mixture (=80mg of lactic acid and 20mg of 70% sodium lactate) were placed into a 50 ml beaker. The beaker was heated to 50ºC and the ingredients were almost completely dissolved in an ultrasonic disperser

The resultant solution was poured into a 5 ml vial tube through a 0.2 μ filter while applying nitrogen and the tube was sealed. Steam treatment (95ºC × 30min.) was then applied.

174 mg of the resultant non-aqueous composition was then placed into a test tube. 25 ml of 5% glucose solution were added and the tube was shaken by hand for about 20 seconds to obtain a clear solution. When the particle size was measured via a particle size distribution in the dynamic light scattering measurement protocol, the average size was observed to be 19.4 nm.

D. Additional Working Examples:

Additional formulations and the above formulation are summarized below in Table 4:

Table 4

Lot.	31	32	33	34
Drug [mg]	DOC 4	DOC-3W 4	DOC-3W 4	DOC-3W 4
Oil [mg]	MCT 4	MCT 4	MCT 4	MCT 4
Surfactant [mg]	Polysorbate 100	Polysorbate 95	Polysorbate 95	Polysorbate 95
Non Aqueous solvent [mg]	PEG300 40 PEG400 10	PEG300 85	PEG300 70	PEG300 70
Lactic acid mixture [mg]	1	1	1	1
Heated treatment	95℃×30min.	95℃×30min.	95℃×30min.	No treatment

DOC-3W –docetaxel trihydrate

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

That which is claimed:

1. A non-aqueous docetaxel liquid pro-emulsion formulation comprising:

an anhydrous docetaxel or a hydrate thereof;

an oil component in an amount ranging from 0.3 to 5% w/w;

an organic acid component;

a surfactant component; and

a non-aqueous solvent component in an amount ranging from 15 to 65 % w/w, which is polyethylene glycol;

wherein the amounts of the docetaxel and oil components differ by 50% w/w or less.

2. The pro-emulsion formulation according to Claim 1, wherein the oil is selected from the group consisting of synthetic oils, vegetable oils, tocopherols and combinations thereof.

3. The pro-emulsion formulation according to any of the preceding claims, wherein the surfactant component is present in an amount ranging from 10 to 98 % w/w.

4. The pro-emulsion formulation according to Claim 1, wherein the surfactant is polysorbate 80.

5. The pro-emulsion formulation according to any of Claims 1 to 4, wherein the organic acid component is selected from the group consisting of acetic acid, lactic acid, and citric acid.

6. The pro-emulsion formulation according to any of Claims 1 to 4, wherein the organic acid component is lactic acid.

7. The pro-emulsion formulation according to any of Claims 1 to 4, wherein the oil is selected from the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof.

8. A docetaxel emulsion composition produced by combining a pro-emulsion composition according to any of Claims 1 to 7 with an aqueous medium.

9. A kit comprising:

(a) a docetaxel pro-emulsion formulation according to any of Claims 1 to 4; and
(b) an aqueous medium.

10. A method of making a docetaxel pro-emulsion formulation according to any of Claims 1 to 4, the method comprising combining docetaxel, an oil component, a surfactant component, and a non-aqueous solvent in a manner sufficient to produce a docetaxel pro-emulsion according to any of Claims 1 to 4.

11. The pro-emulsion formulation according to claim 1, comprising:

an anhydrous docetaxel or a hydrate thereof;

an oil component, selected from the group consisting of soybean oil, olive oil, sesame oil, corn oil, a medium chain triglyceride, a tocopherol or derivative thereof, and combinations thereof, in an amount ranging from 0.3 to 5% w/w;

an organic acid component;

a surfactant component, which is polysorbate 80, in an amount ranging from 10 to 98% w/w; and

a non-aqueous solvent component in an amount ranging from 15 to 65 % w/w, which is polyethylene glycol;

wherein the amounts of the docetaxel and oil components differ by 50% w/w or less.