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(54) Title: ORAL FORMULATIONS FOR PICOPLATIN

(57) Abstract: The invention provides formulations for the organoplatinum anticancer drug picoplatin. Self emulsifying compositions, stabilized nanoparticulate compositions, solid dispersions, and nanoparticulate suspensions in oils are provided, along with methods for preparation of the formulations. The formulations can provide improved oral availability of picoplatin relative a to a simple solution of picoplatin such as in water or normal saline solution and can be used in combination therapy.

ORAL FORMULATIONS FOR PICOPLATIN

BACKGROUND

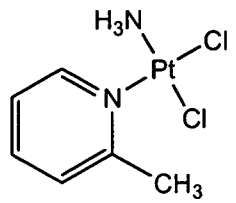
Cross Reference to Related Applications:

This application claims priority to U.S. Provisional Applications Serial Nos. 60/950,033, filed July 16, 2007, and 61/043,962 filed April 10, 2008, both entitled "Oral Formulations for Picoplatin", both of which are incorporated by reference in their entireties herein.

Background

Picoplatin is a new-generation organoplatinum drug that has promise for treatment of various types of malignancies, including those that have developed resistance to earlier organoplatinum drugs such as cisplatin and carboplatin. Picoplatin has shown promise in the treatment of various kinds of cancer or tumor, including small cell lung cancer, colorectal cancer, and hormone-refractory prostate cancer.

Structurally, picoplatin is:

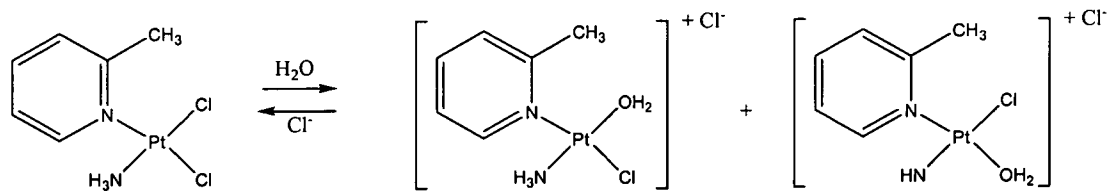


and is named cis-amminedichloro(2-methylpyridine)platinum(II), or alternatively [SP-4-3]-ammine(dichloro)(2-methylpyridine)platinum(II). The compound is a square planar complex of divalent platinum that is tetracoordinate and has three different ligand types. Two ligands are anionic, and two are neutral; therefore as the platinum in picoplatin carries a +2 charge, picoplatin is itself a neutral compound and no counterions need be present. The name "picoplatin", referring to the presence of α-picoline (2-methylpyridine) in the molecule, is the United States Adopted Name (USAN), the British Approved Name (BAN), and the International Nonproprietary Name (INN) for this material. Picoplatin is also referred to in the literature as NX473, ZD0473, and

AMD473, and is disclosed in U.S. Pat. Nos. 5,665,771, 6,518,428, and U.S. Serial No. 10/276,503.

Picoplatin is been provided to patients in solution by intravenous (IV) administration. Picoplatin under standard conditions is a solid, and has only sparing solubility in water. The relatively low solubility of picoplatin in water (about 1 mg/mL) necessitates that substantial volumes of liquid be delivered intravenously to provide a patient with total doses in the range of 100 mg and more (i.e., at a concentration of 0.5 mg/mL, some 200 mL of liquid must be introduced by IV infusion to provide a 100 mg dose). As typical human dosages for cancer patients can be on the order of several hundred milligrams per administration, and may be repeated every few weeks, substantial volumes of liquid must be delivered to the patient for each administration of the substance by the IV route. Intravenous administration is thus undesirable due to the need for needle insertion into a vein, and the relatively prolonged periods over which the patient must be immobile to allow for infusion of the relatively large volumes of the picoplatin solutions. Picoplatin is orally bioavailable, but its low solubility in water poses an obstacle to the preparation of effective oral dosage forms.

Picoplatin has also been found to be hydrolytically unstable, particularly under certain storage conditions, undergoing conversion to two isomeric species designated Aquo 1 and Aquo 2, the structures of which are shown below:



Picoplatin Aquo 1 Aquo 2

SUMMARY

The present invention provides formulations for picoplatin adapted for oral administration to a cancer patient. The formulations comprise (a) a self-emulsifying formulation containing picoplatin, (b) a plurality of stabilized picoplatin nanoparticles, (c) a picoplatin solid dispersion in a water-dispersible matrix material, (d) a nanoparticulate picoplatin suspension in a medium chain triglyceride or a fatty ester, or any combination thereof. The formulation can

provide improved oral availability of the picoplatin relative to an equivalent dose of solid picoplatin such as in a tablet, or to an equivalent dose of picoplatin in a simple solution such as in water or normal saline solution, that is orally ingested.

An embodiment of the invention concerns a self-emulsifying formulation of picoplatin. The self-emulsifying formulation includes picoplatin, an oil and an emulsifier, and, optionally, a first solvent. Examples of the oil include a medium chain triglyceride, a fatty ester, or an edible vegetable oil, such as peanut oil, cottonseed oil, or soybean oil. The emulsifier can be a lecithin, a polyethylene glycol (PEG), or a surfactant, or any combination thereof.

In another embodiment according to the invention, a method of preparing a self-emulsifying formulation of picoplatin using a solvent method is provided. The method includes dissolving picoplatin in a first solvent other than DMSO to provide a picoplatin solution, then adding an oil, and an emulsifier comprising a lecithin, a PEG, or a surfactant, or any combination thereof; then, adding a second solvent to dissolve the picoplatin solution, the oil, and the emulsifier, providing a substantially homogeneous second solution; then, evaporating at least the second solvent and, optionally, the first solvent, from the homogeneous solution to provide the self-emulsifying formulation.

Another embodiment of the invention concerns a formulation that includes a plurality of stabilized picoplatin nanoparticles. The picoplatin nanoparticles, having an average particle diameter of less than about one micron, are stabilized to inhibit aggregation, and can be stabilized with casein, a caseinate, or lecithin, or any combination thereof.

In another embodiment, a method of preparation of a formulation of stabilized picoplatin nanoparticles is provided, the method comprising mixing a stabilizer and an aqueous medium under high-shear conditions or microfluidization conditions to obtain a uniform dispersion, then adding solid picoplatin, and then mixing until an average particle size of the solid picoplatin is less than about one micron or until crystalline particles are substantially absent, or both, to provide a suspension of the stabilized picoplatin nanoparticles. The suspension can further be dried, such as by freeze-drying, to obtain a substantially dry picoplatin formulation.

Another embodiment of the invention concerns a picoplatin solid dispersion in a water-dispersible matrix material. The water-dispersible matrix material can comprise a PEG-ylated mono- or diglyceride.

In another embodiment, a method of preparing a picoplatin solid dispersion in a water-dispersible matrix material using a melt method is provided, wherein the picoplatin is dissolved in a melt of the matrix material, which is then cooled to provide the solid dispersion.

In another embodiment, a nanodispersion of picoplatin in medium chain triglyceride (MCT) oil or in a fatty ester, for example ethyl oleate, is provided. In an embodiment, a method of preparing the picoplatin nanodispersion in an MCT oil or in a fatty ester is provided.

In another embodiment, an oral picoplatin formulation comprising a substantially water-soluble capsule shell, the shell enclosing a formulation comprising a substantially dry, finely particulate material comprising, in admixture, about 10 to 60 wt% picoplatin, wherein the picoplatin is, in physical form, particulates of less than about 10 microns average particle diameter, in admixture with a substantially water-soluble, water-dispersible, or water-absorbing carbohydrate and an effective amount of up to about 5 wt% of a lubricant (or "glidant"), is provided.

In another embodiment, an oral picoplatin formulation, wherein the dosage form comprises a solid core comprising about 10 to 60 wt% particulate picoplatin wherein the picoplatin is a particulate of less than about 10 microns average particle diameter, about 40-80 wt% of a filler comprising a substantially water-soluble, water-dispersible, or water-absorbing carbohydrate, and an effective amount of up to about 5 wt% of a lubricant, and optionally a dispersant; and a continuous coating on the outer surface of the core; wherein the core and/or the coating are substantially free of redox-active metal salts, is provided.

In various embodiments, the present invention provides a method of treating cancer comprising administering an oral formulation of the invention or an oral formulation prepared by a method of the invention to a patient afflicted by cancer, in an amount, at a frequency, and for a duration of treatment effective to provide a beneficial effect to the patient. The patient can be chemotherapy-naïve or the patient can have previously received chemotherapy and/or radiation therapy.

In various embodiments, the cancer can be lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer, renal cancer, stomach and other gastrointestinal (GI) cancers, mesothelioma, melanoma, peritoneal lymphoepithelioma, endometrial cancer, glioblastoma, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, esophageal cancer, uterine cancer, endometrial cancer, prostate cancer, thymic cancer, breast cancer, head and neck cancer, liver cancer, sarcomas, including Kaposi's sarcoma, carcinoid tumors, other solid tumors, lymphomas (including non-Hodgkins lymphoma, NHL), leukemias, bone-associated cancers and other cancers disclosed in the patents and patent applications cited herein.

In various embodiments, an embodiment of the oral formulation can be administered repeatedly to a patient suffering from cancer, at a dose, in a frequency, and for a duration sufficient to provide a beneficial effect to the patent. The oral picoplatin formulation can be administered in conjunction with a second anticancer agent or anticancer therapy. For example, the oral formulation can be administered in conjunction with radiotherapy such as X-ray or γ-ray irradiation, particle beam irradiation, brachytherapy, or radioisotope therapy, for treatment of the cancer.

In various embodiments, the oral formulation can be administered with a second anticancer agent comprising a molecular entity such as a small molecule or a protein. The second anticancer agent can be included in the oral formulation and thus administered in a combination with the picoplatin, or the second anticancer agent can be administered separately from the picoplatin. If administered separately, it can be administered substantially concurrently, prior to, or after administration of the oral formulation. The second anticancer agent can be administered orally or parenterally, for example intravenously. Examples are provided hereinbelow, and can be termed non-platinum containing anti-cancer agents or platinum-containing anti-cancer agents. The second anticancer agent can be provided at doses, frequencies of administration, and over a duration of time in combination with picoplatin doses, frequencies of administration, and over a duration of time effective to provide a beneficial effect to the patient.

In another embodiment of the invention, the present formulation is provided as a kit; i.e., enclosed in packaging with instruction materials, such as paper labeling, a tag, a compact disk, a DVD, a cassette tape and the like, regarding administration of the formulation to a patient. For example, the instruction materials can comprise labeling describing/directing a use of the formulation that has been approved by a government agency responsible for the regulation of drugs.

Brief Description of the Figures

Figure 1 shows an HPLC calibration curve for picoplatin.

Figure 2 shows an HPLC trace of 0.5 mg/mL picoplatin standard solution in normal saline.

Figure 3 shows an HPLC trace of 0.5 mg/mL picoplatin solution stored in deionized water at 40 deg C for 2 days.

Figure 4 shows HPLC traces of, from the bottom up, 0.5 mg/mL picoplatin solution in pH 2, 3, 4, 5, 6 buffers, normal saline and deionized water, each stored for 2 days at 40°C.

Figure 5 is a graph showing the solubility of picoplatin in neutral water and in buffers of various pH values.

Figure 6 shows picoplatin recovery (% over initial) at 25°C after 0, 1 and 2 days.

Figure 7 shows picoplatin recovery (% over initial) at 40°C after 0, 1 and 2 days.

Figure 8 shows the stability over time of picoplatin in dimethylsulfoxide (DMSO) with added buffers at various pH values.

Figure 9 shows representative chromatograms of picoplatin in N-methyl-pyrrolidone (NMP) at 25° C for 4 hours. From top down: 0.5 mg/mL in 100% NMP, 0.5 mg/mL in 80% NMP in normal saline, 0.5 mg/mL in 50% NMP in normal saline, 0.5 mg/mL in 20% NMP in normal saline, and 0.5 mg/mL standard in normal saline.

Figure 10 shows HPLC chromatograms of Picoplatin in reconstituted solutions. The reconstituted solutions were obtained by adding normal saline to lyophilized picoplatin from various NMP solvents. From top down: from 100%

"Miglyol 812" (Sasol Germany GmbH, Witten, Germany) refers to a medium chain triglyceride wherein the acid moieties are caprylic and capric acid. Miglyol is a trademark identifying the source of this and other varieties of MCT oil.

"Administering" or "administration" refers to providing a medicinal compound to a patient in need thereof. A "dose" is the amount of the active pharmaceutical ingredient (API), in this case picoplatin, that is provided in a single administration. A "frequency" of administration refers to how often the medication is given when repeated doses are prescribed; for example, the medication can be administered daily. A "duration" refers to the period of time over which repeated doses are administered; for example, the picoplatin can be administered for a duration of two weeks.

A "second medicament comprising an anticancer medicament" can include, without limitation, a taxane (e.g.: paclitaxel (Taxol®) or docetaxel (Taxotere®), a tyrosine kinase and/or a growth factor receptor inhibitor such as a VEGFR inhibitor (e.g.: monoclonal antibodies such as: bevacizumab (Avastin®), trastuzumab (Herceptin®), panitumumab (Vectibix®) or cetuximab (Erbitux®)); a cephalotaxine analog (e.g.: topotecan (Hycamtin®); irinotecan; 9-aminocamptothecin; Rubitecan®; Exatecan®; XR-5000, XR-11576); an anti-metabolite (e.g.: capecitabine (Xeloda), gemcitabine, 5-FU with or without leucovorin, S1 (gimeracil / oteracil /tegafur), tegafur/uracil, methotrexate, or a thymidylate synthease inhibitor (Tomudex®, ZA9331, LY231514 (pemetrexed))); a protein kinase inhibitor (e.g.: sorafenib (Nexavar®), dasatinib (Sprycel®), gefitnib (ZD1839, Iressa®), imatinib (Gleevac®), lapatinib (Tykerb®), cediranib, also known as AZD2171 (Recentin®), erlotinib (Tarceva®) or sunitinib (Sutent®)); an anthracyclin (e.g.: amrubicin, doxorubicin, liposomal doxorubicin, epirubicin, idarubicin, Doxil®); a *Vinca* alkaloid (e.g.: vinorelbine (Navelbine®), vincristine, vinblastine, vindesine); a podophyllotoxin analog (e.g.: etoposide, teniposide); a growth factor inhibitor (e.g.: inhibitor of PDGF, endothelial GF, VEGF, EGF, or hepatocyte GF; for example an GF-binding antibody or a GF receptor-binding antibody); an inhibitor of cell cycle kinases (such as CDK-2, CDK-4, or CDK-6); a cytostatic agent (Tamoxifen, Toremifene, Raloxifene, Droloxifene, Iodoxyfene; megestrol acetate; an aromatase inhibitor such as Anastrozole (ZD1033), Letrazole, Vorazole,

NMP, from 80% NMP in normal saline, from 50% NMP in normal saline, from 20% NMP in normal saline, and from normal saline.

Figure 11 shows a thermogravimetric / differential thermal analysis (TG/DTA) scan of micronized picoplatin powder.

Figure 12 shows a thermogravimetric / differential thermal analysis (TG/DTA) scan of TG/DTA of F50 Picoplatin nanoparticles in sodium caseinate.

Figure 13 shows representative HPLC chromatograms of picoplatin nanoparticles. From the top down: 0.5 mg/mL nanoparticles in normal saline and 0.5 mg/mL picoplatin standard in normal saline. One unknown peak at 5.5 min (not Aquo #1).

Figure 14 shows representative HPLC Chromatograms after hot melt in Gelucire 50/15. From top down: 0.5 mg/mL picoplatin standard in normal saline and 0.5 mg/mL F51 in normal saline.

Figure 15 shows a representative DSC for Picoplatin in Gelucire 50/15 hot melt. From top down: Gelucire 50/15, 5% picoplatin in Gelucire 50/15 hot melt, and picoplatin API.

Figure 16 shows a representative DSC for Picoplatin in hot melt. From top down: 5% picoplatin in Gelucire 50/15, 6% picoplatin in Gelucire 50/15 and 5% in Compritol 888 ATO.

Figure 17 shows HPLC traces, from the top down: 0.5 mg/mL standard in neutral saline, F73- picoplatin in MCT, F74- picoplatin in MCT and PL90G, and F75- picoplatin in MCT and Polysorbate 80.

Figure 18 shows zoomed-in views of the HPLC traces of Figure 17. From the top down: 0.5 mg/mL standard in normal saline, F73- picoplatin in MCT, F74- picoplatin in MCT and PL90G, and F75- picoplatin in MCT and Polysorbate 80.

Figure 19 shows representative HPLC chromatograms From top down: 0.5 mg/mL standard in normal saline, F77- picoplatin in Ethyl Oleate and PL90, F80- picoplatin in MCT, PL90G and normal saline.

Figure 20 shows representative HPLC chromatograms, enlarged. From top down: 0.5 mg/mL standard in neutral saline, F77- picoplatin in Ethyl Oleate and PL90, F80- picoplatin in MCT, PL90G and normal saline.

Figure 21 shows representative HPLC Chromatograms. From top down: 0.5 mg/mL picoplatin standard in normal saline and 0.5 mg/mL F81-picoplatin in PL90 and EO in normal saline.

Figure 22 shows representative HPLC chromatograms, enlarged. From top down: 0.5 mg/mL picoplatin standard in normal saline and 0.5 mg/mL F81-picoplatin in PL90 and EO in normal saline.

Definitions:

As the term is used herein, "picoplatin" refers to the organoplatinum anticancer drug, the structure of which is provided above, including any solvate, hydrate, or crystalline polymorph thereof, in solid form, or in solution or dispersion.

A "formulation" as the term is used herein is a composition of matter including picoplatin and other components, such as excipients, stabilizers, dispersants, surfactants, and the like.

"Self-emulsifying" refers to a property of a formulation wherein upon contacting the formulation with an aqueous medium, such as in the gastro-intestinal tract of a patient, the formulation spontaneously forms an emulsion.

"Nanoparticles" are solid particles of an average particle diameter of less than about 1 micron (micrometer, μm). One micron is 1,000 nanometers (nm).

"Stabilized" nanoparticles are picoplatin nanoparticles coated with a stabilizing material and having a reduced tendency for aggregation and loss of dispersion with respect to nanoparticles of picoplatin without a stabilizing coating.

"Casein" is a milk-derived protein that typically is globular in aqueous dispersion, as is well known in the art. A "caseinate" is a salt form of casein wherein carboxylate groups in the protein are present in ionized form, such as the sodium salts ("sodium caseinate").

"Microfluidization" is a technique for preparing dispersions of fine particles in a liquid medium wherein coarser particles are comminuted in the presence of the liquid medium.

"High-shear mixing" is a technique for preparing dispersions of fine particles in a liquid medium wherein high-shear conditions comminute coarser particles into finer ones in the presence of the liquid medium.

A "solid dispersion" as the term is used herein refers to a dispersion of solid picoplatin in a solid or semi-solid matrix. The solid dispersion can be formed in a liquid or melt phase wherein the final mixture solidifies into the solid or semi-solid form.

"Water-dispersible" means that a solid or semi-solid material can be suspended in an aqueous medium and does not spontaneously phase separate from the aqueous medium. "Water-dispersible" includes "water-soluble", referring to a solid or semi-solid material that completely dissolves in the aqueous medium to form a homogeneous solution. A "matrix" as the term is used herein refers to an organic material, that is at least dispersible in water, that is solid at about room temperature or about human body temperature, in which picoplatin can be dispersed.

An "oil" as the term is used herein refers to an organic liquid, which is water-insoluble, or at least only partially water-soluble, that can form a separate phase in the presence of water. An example of an "oil" is a glyceride such as a medium chain triglyceride, or a medium chain mono- or di-glyceride, or castor oil. Another example of an oil is a fatty ester. A fatty ester refers to an alkyl ester of a fatty acid. An example is ethyl oleate. "MCT oil" refers to medium chain triglyceride oil. Examples include the MCT oil sold under the Miglyol trademark, such as Miglyol 912, a caprylate/caprate (octanoate/decanoate triglyceride).

A "nanodispersion" is a dispersion of picoplatin particles of less than 1 μm average particle diameter in a liquid, for example in MCT oil or in a fatty ester.

A "lecithin" as the term is used herein is a mixture of triglycerides, glycolipids, and phospholipids such as phosphatidylcholine, as is well-known in the art. Lecithins can be derived from eggs or from soy beans. A high-phosphatidylcholine lecithin is a lecithin with a relatively high phosphatidyl-choline (PC) content. A low-phosphatidylcholine lecithin is accordingly a lecithin with a relatively low PC content.

A "surfactant" as the term is used herein is a substance that reduces interfacial surface tension between immiscible liquids such as oil and water, reduces surface tension of a water drop, and exhibits other surface-active properties as are well known in the art.

The term "weight average molecular weight" is well known in the art and characterizes an average molecular weight of a polydisperse sample of a polymer.

A "PEG" or a "polyethyleneglycol" is a polymeric material composed of repeating $-CH_2CH_2O-$ units, wherein there are two or more units. Thus, diethyleneglycol and all higher polymers are polyethyleneglycols within the meaning herein. A polyethyleneglycol can have a free OH group at either terminus or at both termini, or can alternatively include other groups such as an ether group at one or both ends, for example a methyl ether $CH_3O-(CH_2CH_2O)_n-OCH_3$. Such an ether-terminated PEG can also be referred to as a "polyethyleneglycol ether". PEG-400 is a PEG with a weight average molecular weight of about 400 DA. PEG-8000 is a PEG with a weight average molecular weight of about 8000 DA. A compound can be "PEG-ylated", meaning that it bears at least one PEG group, which can be introduced in a variety of ways, such as by polymerization of ethylene glycol initiated by the compound, or coupling of the compound with a preformed PEG. For example, Gelucire® is a PEG-ylated fatty acid monoglyceride, meaning that a glycerol moiety bears a single fatty acid moiety and PEG moieties on one or both of the remaining free hydroxyl groups.

A "dipolar aprotic solvent" is a solvent not containing a source of protons in aqueous solution (an example of a protic solvent is ethanol) that also is polar in character and is typically at least partially soluble in water. Examples of aprotic solvents are DMF, NMP, DMSO, DMAC, and the like. "DMSO" is dimethylsulfoxide. "NMP" is N-methylpyrrolidone. "DMF" is N,N-dimethyl-formamide. "DMAC" is N,N-dimethylacetamide.

"Labrasol®" is a mixture composed of about 30% mono-, di-, and triglycerides of C8 and C10 fatty acids, 50% of mono- and di-esters of polyethyleneglycol (PEG 400), and 20% of free PEG 400. Labrasol® has surfactant properties.

"Cremophor RH 40®" is a nonionic solubilizer and emulsifying agent obtained by reacting 45 moles of ethylene oxide with 1 mole of hydrogenated castor oil. The main constituent of Cremphor RH 40® is glycerol polyethylene glycol oxystearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate.

"Cremophor ELP®" is a nonionic solubilizer made by reacting castor oil with ethylene oxide in a molar ratio of 1 : 35.

"Gelucire®" including Gelucire 44/14 (CAS RN 121548-04-7) and Gelucire 50/13 (CAS RN 121548-05-8) are fatty acid glycerides bearing polyethyleneglycol (PEG) groups. For example, Gelucire 44/14 is a PEG-ylated glyceride of lauric acid; Gelucire 50/13 is a PEG-ylated glyceride of stearic acid. The numbers after the word Gelucire refer to the melting point in °C and the hydrophilic-lipophilic balance (HLB) value respectively. Gelucire compounds are PEG-ylated with PEG 1500 (polyethyleneglycol of weight average molecular weight 1500 DA).

"Polysorbate 80" refers to sorbitan mono-9-octadecanoate poly(oxy-1,2-ethanediyl) derivatives; they are well known as complex mixtures of polyoxyethylene ethers used as emulsifiers or dispersing agents in pharmaceuticals.

"Phospholipon 90G" or "PL90G" (American Lecithin Products, Oxford, CT) is a tradename for lecithin, minimum 94% phosphatidylcholine for the manufacture of liposomes. "Phospholipon 90H" or "PL90H" is a hydrogenated PL90G. The term "PL90" refers to either one of these materials.

"Vitamin E TPGS" refers to the compound D-alpha-tocopheryl polyethylene glycol 1000 succinate.

"Compritol 888" refers to glyceryl behenate. A "behenate" is an ester of docosanoic acid, as is well known in the art.

"Poloxamer 188" (CAS RN 9003-11-6) is a Polyethylene-Polypropylene Glycol copolymer of the formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ with a weight average molecular weight of about 8400

"SPAN 60" refers to sorbitan monostearate.

"Kollidon K90" (Hoechst, Germany) refers to a polyvinylpyrrolidone with a molecular weight of about 90,000.

Exemestane; an antiandrogen such as Flutamide, Nulutamide, Bicalutamide, Cyproterone acetate; an LHRH agonist or antagonist such as Foserelin acetate or Luprolide; an inhibitor of testosterone dihyhdroreductase such as Finasetide, a metalloproteinase inhibitor such as Marimastat or a uPAR inhibitor); an alkylating agent (e.g.: melphalan, cyclophosphamide, ifosphamide, nitrosourea, carmustine, lomustine); or radiation therapy (e.g.: X-ray, γ-ray, particle beam, brachytherapy, radioisotope).

Alternatively, the additional medicament is a non-platinum containing agent, can be selected to treat a complication of the cancer, or to provide relief to a subject from at least one symptom of the cancer, for example, sirolimus or rapamycin (Rapamune®), dexamethasone (Decadron®), palonosetron HCl (Aloxi®), aprepitant (Emend®), ondansetron (Zofran®), or granisetron (Kytril®).

Examples of anti-cancer medicaments that can be orally administered are listed in Table 1, below.

Table 1. Orally Administrable Agents

altretamine	exemestane	lapatinib	tamoxifen
anagrelide	fadrozole	lenalidomide	tegafur/uracil
anastrozole (ZD1033)	finasteride	letrozole	temozolomide
bexarotene	fludarabine	osaterone	thalidomide
bicalutamide	gefitinib	polysaccharide K	topotecan
capecitabine	GMDP	prednimustine	toremifene
clodronic acid	HMPL 002	S1 (gimeracil/oteracil/tegafur)	treosulfan
cytarabine ocfosfate	hydroxycarbamide	sobuzoxane	trilostane
dasatinib	ibandronic acid	sorafenib	ubenimex
dutasteride	idarubicin	sunitinib	vinorelbine
erlotinib	imatinib	tamibarotene	vorinostat

Orally active anticancer agents that can be administered include altretamine (Hexalen®), an alkylating agent; capecitabine (Xeloda®), an anti-metabolite; dasatinib (Sprycel®), a TK inhibitor; erlotinib (Tarceva®), an EGF receptor antagonist; gefitinib (Iressa®), an EGF inhibitor; imatinib (Gleevec®), a TK inhibitor; lapatinib (Tykerb®), an EGFR inhibitor; lenalidomide,

(Revlimid®), a TNF antagonist; sunitinib (Sutent®), a TK inhibitor; S-1 (gimeracil/oteracil/tegafur), an anti-metabolite; sorafenib (Nexavar®), an angiogenesis inhibitor; tegafur/uracil (UFT®, Uftoral®), an anti-metabolite; temozolomide (Temodar®), an alkylating agent; thalidomide (Thalomid®), an angiogenesis inhibitor; topotecan (Hycamtin® for injection or Oral Hycamtin®), vinorelbine (Navelbine®), an anti-mitotic; cediranib (AZD2171, Recentin®), a VEGF inhibitor; and/or vorinostat (Zolinza®), a histone deacetylase inhibitor.

As the term is used herein, "radiation" or "radiotherapy" refers to the treatment of cancer patients with various forms of ionizing radiation, which acts to a great extent on dividing cells by interfering with DNA replication and cell division. The three main types of radiotherapy are external beam radiotherapy (EBRT or XBRT) or teletherapy, brachytherapy or sealed source radiotherapy and unsealed source radiotherapy. The differences relate to the position of the radiation source; external is outside the body, while sealed and unsealed source radiotherapy has radioactive material delivered internally. External beam radiotherapy can involve beams of photons, such as X-rays, or beams of particles, such as protons. External beam radiotherapy can involve either total body irradiation or the use of multiple focussed beams to concentrate the energy in a defined volume of body tissue. Brachytherapy involves implantation of sealed sources of various radioisotopes within body tissues, such that the sources can be removed after a period of time. The type of radiation emitted depends on the identity of the radioisotope included in the sealed source, and can be photon (X-ray) or particle (e.g., beta particle). When unsealed sources are used, e.g., radiolabeled antibodies or the like, the nature of the radiation again depends on the identity of the radioisotope used, but due to the fact that there is no containment, particles of shorter range such as alpha particle and Auger electrons can be used effectively. However, since unsealed sources typically cannot be removed surgically, the radioisotopic form must be one that can be excreted, or else decays, within an appropriate time frame. Examples of useful isotopes include ^{90}Y, ^{131}I, and ^{177}Lu.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns formulations of the anticancer drug picoplatin adapted for oral administration to a cancer patient, and to methods of

preparation of the formulations. In an embodiment of the invention, a self-emulsifying formulation provides the picoplatin dissolved in a one-phase oleaginous vehicle, which forms an emulsion upon exposure to an aqueous medium in the gastrointestinal tract, and delivers picoplatin in emulsified oil droplets with a potential for better intestinal absorption into the bloodstream. A self-emulsifying formulation can include an oil (oleaginous vehicle) along with dispersants and surfactants that assist in the self-emulsification properties of the formulation. Once orally ingested by a patient, the formulation can emulsify in the gastrointestinal tract. The formulation can provide improved oral availability of the picoplatin relative to an equivalent dose of solid picoplatin such as in a tablet, or to an equivalent dose of picoplatin in a simple solution such as in water or normal saline solution, that is orally ingested.

An embodiment of the self-emulsifying picoplatin formulation can include an oil, and an emulsifier including a lecithin, a surfactant, a PEG, or any combination thereof. Preferably, the self-emulsifying formulation includes at least about 10% w/w of the picoplatin, although it can include lesser amounts of picoplatin, for example, 5% w/w of the picoplatin. The inventive self-emulsifying formulation can also include a first solvent in which picoplatin is at least sparingly soluble, provided that the first solvent is not DMSO. As disclosed hereinbelow, picoplatin is unstable in DMSO, perhaps due to oxidation of the picoplatin by the DMSO. The first solvent can be a dipolar aprotic solvent, a polyethylene glycol, or a polyethyleneglycol ether, a polyethyleneglycol derivative of a mono- or a di-glyceride, or any combination thereof. The dipolar aprotic solvent can be NMP. Preferably the dipolar aprotic solvent, particularly if it is NMP, is substantially free of amine contaminants.

For example, the first solvent can be a polyethyleneglycol derivative of a mono- or a di-glyceride, such as Gelucire 40/14® or Gelucire 50/13®. The picoplatin can be dissolved in the Gelucire held above Gelucire's melting point, i.e., 40°C for Gelucire 40/14, or 50°C for Gelucire 50/13. The solution of the picoplatin in the melted Gelucire can then be mixed with other components in the second solvent to form a substantially homogenous second solution. The Gelucire (polyethyleneglycol derivative of a mono-glyceride, i.e., a PEG-ylated monoglyceride) is itself a surfactant; thus mixing the Gelucire solution of the picoplatin with the oil in the second solvent, followed by removal of the second

solvent, can provide the self-emulsifying formulation of the invention, wherein the Gelucire serves both as the first solvent and as the emulsifier. Alternatively, lecithin, PEG, another surfactant, or any combination thereof, can also be mixed with the second solvent to provide a substantially homogeneous solution, from which the second solvent is removed to provide the present self-emulsifying formulation.

The self-emulsifying formulation includes an oil, wherein the oil is a medium chain triglyceride, castor oil, a medium chain mono-glyceride, a medium chain di-glyceride, an edible vegetable oil such as peanut oil, cottonseed oil, or soybean oil, or any combination thereof. Alternatively, the oil can be other than a glyceride; for example, the oil can be a hydrocarbon oil or a silicone oil.

The self-emulsifying formulation includes an emulsifier. For example, the emulsifier can contain a lecithin. The lecithin can be a high phosphatidyl-choline content lecithin, a low phosphatidylcholine content lecithin, or any combination thereof.

The emulsifier can also include a surfactant, such as Labrasol® (a mixture of glycerides and PEG-ylated materials), Cremophor RH40® (a PEG-ylated glyceride), Cremophor ELP® (a PEG-ylated glyceride), Gelucire 44/14® (a PEG-ylated glyceride), Polysorbate 80 HP® (a PEG-ylated fatty ester of sorbitan), or Vitamin E TPGS (a PEG-ylated tocopherol succinate), or any combination thereof. Gelucire can be both the first solvent and the emulsifier of the inventive self-emulsifying formulation.

The present self-emulsifying formulation can contain a PEG, such as PEG-400. PEG compounds are typically water-soluble, but also can stabilize hydrophobic materials in aqueous media.

A method of preparation of the self-emulsifying formulation is likewise provided as an embodiment of the invention herein. For example, the formulation can be prepared by dissolving picoplatin in a first solvent other than DMSO to provide a picoplatin solution, then adding an oil, and an emulsifier comprising a lecithin, a PEG, or a surfactant, or any combination thereof; then, adding a second solvent to dissolve the picoplatin solution, the oil, and the emulsifier, providing a substantially homogeneous second solution; then,

evaporating at least the second solvent and, optionally, the first solvent, from the homogeneous solution to provide the self-emulsifying formulation.

The first solvent can be a dipolar aprotic solvent, a polyethylene glycol, or a polyethyleneglycol ether, a polyethyleneglycol derivative of a mono- or di-glyceride, or any combination thereof. The dipolar aprotic solvent can be NMP. Preferably the dipolar aprotic solvent, particularly if NMP, is substantially free of amine contaminants. DMSO is not suitable as the first solvent, due to the instability of picoplatin in DMSO. A solution of a preselected amount of picoplatin for the batch formulation being prepared is dissolved in the first solvent, then the emulsifier is added. The emulsifier can include a lecithin, a PEG, a surfactant, or any combination thereof. The oil can be a medium chain triglyceride, castor oil, a medium chain mono-glyceride, a medium chain di-glyceride, or any combination thereof. The lecithin can be a high phosphatidylcholine content lecithin, a low phosphatidylcholine content lecithin, or any combination thereof. The PEG can be PEG-400. The surfactant can be Labrasol, Cremophor RH40, Cremophor ELP, Gelucire 44/14, Polysorbate 80 HP, or Vitamin E TPGS, or any combination thereof.

Then, a second solvent is added to provide a substantially homogenous second solution, at or near room temperature, although some heating can be used to assist dissolution of all components. Then, the second solvent is removed from the homogenous solution. A suitable second solvent is ethanol, which can be removed under reduced pressure at or near room temperature, although elevated temperatures can also be used. The evaporation can continue such that the first solvent is also removed, although the first solvent or portions of it can remain in the formulation. The residue is a self-emulsifying formulation of the invention, which can be liquid, solid or semi-solid. This material can be filled into hard or soft gelatin capsules for administration to a patient. The self-emulsifying formulation is adapted to aid in dissolution of the picoplatin in the gastrointestinal (GI) tract of the patient, and thus provide for enhanced uptake into the bloodstream compared to the same dose of picoplatin administered as a pure solid.

In another embodiment of the invention, a stabilized nanoparticle preparation of picoplatin is provided that possesses a greatly increased surface area and thus an improved dissolution rate relative to solid crystalline picoplatin.

The picoplatin nanoparticles are stabilized with organic materials. For example, the picoplatin nanoparticles can be stabilized with casein, a caseinate, or lecithin, or any combination thereof. Casein and caseinates are proteins found in milk that serve to stabilize butterfat droplets in the aqueous medium. In the present stabilized nanoparticle formulation, the casein or caseinates, or both, can stabilize the sub-micron size picoplatin particles and inhibit re-aggregation of the particles. Also, lipid compositions such as lecithin can be used to stabilize the picoplatin nanoparticles. Preferably, the formulation contains at least about 10% w/w of the picoplatin on a dry weight basis, although the formulation can include a lesser amount of picoplatin, for example, at least about 5% w/w of picoplatin, on a dry weight basis, or an intermediate weight. The formulation can provide improved oral availability of the picoplatin relative to an equivalent dose of solid picoplatin such as in a tablet, or to an equivalent dose of picoplatin in a simple solution such as in water or normal saline solution, that is orally ingested.

The picoplatin nanoparticles can be prepared by a process comprising high-shear mixing or microfluidization. Solid picoplatin, for example picoplatin in crystalline form, can be mixed in an aqueous medium with a stabilizer such as casein, using microfluidization conditions or high-shear conditions, until the average particle diameter of the solid picoplatin is less than about one micron as determined by laser light scattering spectroscopy, or, alternatively, until crystalline picoplatin is observed to be largely absent using an optical microscope with a polarized light filter lens. The average particle diameter can be even smaller; for example the picoplatin nanoparticles can have an average particle diameter of less than about 0.5 micron; of less than about 0.25 micron; or of less than about 0.15 micron.

An embodiment of the invention also provides a method of preparation of the stabilized picoplatin nanoparticles. The method includes mixing a stabilizer and an aqueous medium under high-shear conditions or microfluidization conditions to obtain a uniform dispersion, then adding solid picoplatin, and then continuing mixing under these conditions until an average particle size of the picoplatin is less than about one micron or until crystalline particles are substantially absent, or both, to provide a suspension of the stabilized picoplatin nanoparticles. The stabilizer can be casein, a caseinate, or a lecithin. The

average picoplatin particle diameter can be less than about 1 micron, or less than about 0.5 micron, or less than about 0.25 micron, or less than about 0.15 micron.

The suspension of stabilized picoplatin nanoparticles can then be dried to provide a solid material, for example by freeze-drying, to provide a substantially dry solid. By this method, a solid formulation that can be filled into gelatin capsules for oral administration to a patient can be obtained. The picoplatin content of the substantially dry solid can be at least about 10% w/w, or at least about 5% w/w.

In another embodiment of the invention, a dispersion of solid picoplatin in a solid water-dispersible material (matrix) is provided. The inventive solid dispersion can be prepared by a process comprising dispersing of the picoplatin in a melt of the water-dispersible matrix material that then is cooled and solidified. Preferably, the formulation contains at least about 10% w/w of the picoplatin, although the formulation can include a lesser amount of picoplatin, for example, at least about 5% w/w of picoplatin. The water-dispersible matrix material can include Gelucire 50/13, Gelucire 44/14, Poloxamer 188, SPAN 60, PEG-8000, Kollidon K-90, Vitamin E TPGS, or Compritol 888, or any combination thereof, definitions of which are provided herein. The Gelucire and Compritol materials are PEG-ylated glycerides of fatty acids. Poloxamer is a polyethyleneglycol-polypropyleneglycol copolymer. Span is a monostearate ester of sorbitan, and Kollidon is a poly-vinylpyrrolidone. Vitamin E TPGS is a PEG-ylated toxopherol succinate.

The water-dispersible matrix material is at least dispersible in water, not phase-separating spontaneously, and can be completely water-soluble. The matrix material is preferably a solid at about 20°C to about 37°C. The melt of the water-dispersible matrix material can be held at a temperature of about 40°C to about 160°C during dispersion of the solid picoplatin. The step of dispersing the picoplatin in the melt can involve dissolving the picoplatin in the melt to provide a homogenous melt. The homogeneous melt can include Gelucire 50/13, Gelucire 44/14, Compritol 888, or Vitamin E TPGS. The melt is then cooled and solidified to provide the inventive solid dispersion. The formulation can provide improved oral availability of the picoplatin relative to an equivalent dose of solid picoplatin such as in a tablet, or to an equivalent dose of picoplatin

in a simple solution such as in water or normal saline solution, that is orally ingested.

In an embodiment of the invention, a nanoparticulate picoplatin suspension in a medium chain triglyceride (MCT oil) or in a fatty ester is provided. The nanoparticulate picoplatin comprises picoplatin particles of less than 1 micron average particle diameter, suspended in the MCT oil or fatty ester. The nanoparticulate picoplatin can make up about 20% up to about 70% by weight of the composition. The MCT oil can be a triglyceride ester of a medium chain fatty acid, or of a combination of different medium chain fatty acids. For example, the MCT oil can be tricaprylglyceride (trioctanoylglyeride) or can be a mixed caprylic / capric (octanoyl / decanoyl) glyceride. All three glycerin hydroxyl groups are acylated in the MCT oil. An example of an MCT oil is a Miglyol brand (Sasol) MCT oil, such as Miglyol 812). Alternatively, the nanoparticulate picoplatin suspension can include a fatty ester. An example is ethyl oleate. The suspension can further contain a lecithin, i.e., a phospholipid. An example is the brand Phospholipon 90G (American Lecithin). The suspension can further contain a sugar ester surfactant, such as a sorbitan ester. An example is sorbitan mono-9-octadecanoate PEG ether (sold under the brand name Sorbate 80).

An embodiment of the invention provides a method of preparation of the nanoparticulate picoplatin suspension comprising contacting the picoplatin in bulk form and the MCT oil or fatty ester, then mixing under high shear conditions until the average picoplatin particle diameter is 1 micron or less. A lecithin, a Sorbate-type surfactant, or both can also be present during the high shear mixing, or can be added subsequently. In an embodiment, following the high shear mixing, the solid picoplatin nanoparticulate form can be allowed to settle, or can be settled by centrifugation, and a portion of the supernatant liquid removed to provide a nanoparticulate picoplatin suspension with a higher picoplatin content than prior to removal of some of the supernatant liquid.

In another embodiment, an oral picoplatin formulation comprising a substantially water-soluble capsule shell, the shell enclosing a formulation comprising a substantially dry, finely particulate material comprising, in admixture, about 10 to 60 wt% picoplatin, wherein the picoplatin is, in physical form, particulates of less than about 10 microns average particle diameter, in

admixture with a substantially water-soluble, water-dispersible, or water-absorbing carbohydrate and an effective amount of up to about 5 wt% of a lubricant (or "glidant"), is provided. The capsule shell is preferably composed of a biodegradable and/or digestible material, such as hard or soft gelatin, PVA, polylactides, polyglycolic acids, and the like. The picoplatin preferably is a particulate having an average particle diameter of 1-5 microns. The picoplatin particulate can be micronized, for example by jet-milling, or can be a microcrystalline material, such as can be prepared by precipitation, or can be a particulate formed by a lyophilization process, or any combination of the three processes. The picoplatin particulate can be dispersed within substantially every particle of the powder of the formulation. The oral picoplatin formulation, can comprise a substantially dry powder comprising about 20 to 55 wt% picoplatin wherein the picoplatin is particulates of less than about 10 microns average particle diameter, a substantially water-soluble, water-dispersible, or water-absorbing carbohydrate, and an effective amount of up to about 5 wt% of a lubricant, enclosed within a substantially water-soluble capsule shell. The formulation can also comprise an effective amount of a dispersing agent.

In another embodiment, an oral picoplatin formulation, wherein the dosage form comprises a solid core comprising about 10 to 60 wt% particulate picoplatin wherein the picoplatin is a particulate of less than about 10 microns average particle diameter, about 40-80 wt% of a filler comprising a substantially water-soluble, water-dispersible, or water-absorbing carbohydrate, and an effective amount of up to about 5 wt% of a lubricant, and optionally a dispersant; and a continuous coating on the outer surface of the core; wherein the core and/or the coating are substantially free of redox-active metal salts, is provided. Preferably both the coating and the core are free of amounts of redox-active metals that can be deleterious to the picoplatin *in vivo* or *in vitro* (e.g., in storage). The coating forms a protective covering for the core, both protecting the contents from environmental degradation by oxygen, light, and reactive chemicals, and protecting persons handling the dosage form from the cytotoxic picoplatin. The coating can comprise gelatin, either hard or soft; a polymer, for example hydroxypropyl methyl cellulose; a sugar, for example sucrose; or any other non-toxic, water soluble material suitable for human consumption. The picoplatin particulate that has an average particle diameter of less than about 10

microns, preferably has an average particle diameter of less than about 7 microns, and more preferably has a particle size distribution such that about 90% of the individual particulates have a diameter of less than about 5 microns.

In various embodiments, the present invention provides a method for treating cancer comprising administering an inventive oral formulation or an oral formulation prepared by an inventive method to a patient afflicted by cancer, in an amount, at a frequency, and for a duration of treatment effective to provide a beneficial effect to the patient. The patient can be chemotherapy-naïve or the patient can have previously received chemotherapy.

The dose, dosage form, frequency, and duration of administration can be determined by the attending physician, based upon his or her knowledge and experience, the body weight, skin area, disease state, and physical condition of the patient, and any other factors that the physician may decide are relevant to selection of a dose, frequency of administration, and duration of time over which the formulation is administered to the patient.

In various embodiments, the cancer can be lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer, renal cancer, stomach and other gastrointestinal (GI) cancers, mesothelioma, melanoma, peritoneal lymphoepithelioma, endometrial cancer, glioblastoma, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, esophageal cancer, uterine cancer, endometrial cancer, prostate cancer, thymic cancer, breast cancer, head and neck cancer, liver cancer, sarcomas, including Kaposi's sarcoma, carcinoid tumors, other solid tumors, lymphomas (including non-Hodgkins lymphoma, NHL), leukemias, bone-associated cancers and other cancers disclosed in the patents and patent applications cited herein.

In another embodiment of the invention, the picoplatin compositions of the invention used to prepare medicaments that are used in combination with an effective amount of a second medicament, such as an non-platinum containing anticancer agent. The latter agent can be co-administered to a patient in conjunction with administration of an embodiment of the present oral formulation

The anticancer drug can be a non-platinum based anticancer agent, or can be a platinum-based anticancer agent. Examples of a second anticancer agent or

therapy comprising a molecular entity are provided above in Table 1, above. For example, a second anticancer agent can be a non-platinum based anticancer agent, or can be a platinum-based anticancer agent.

By "a non-platinum based anticancer agent" is meant a compound with anticancer and/or anti-cell proliferation activity that does not contain platinum, for example, a compound or drug can be selected from one of the following classes:

1. A compound of the camptothecin analogue class, i.e. any tumour cell growth inhibiting compound which is structurally related to camptothecin, and inhibits topoisomerase I; or a compound of the podophyllotoxin analogue class which inhibits topoisomerase II; or is a compound of the camptothecin analogue class which is an inhibitor of both topoisomerase I and II. Suitable compounds of the camptothecin analogue class include, but are not limited to, pure topoisomerase I inhibitors such as Topotecan, Irinotecan, 9-Aminocamptothecin, Rubitecan and Exatecan (DX-8951f); mixed topoisomerase I and topoisomerase II inhibitors such as XR-5000 and XR-11576; and suitable compounds of the podophyllotoxin analogue class which are pure topoisomerase II inhibitors include, but are not limited to, Etoposide and Teniposide. Such compounds also include, but are not limited to, any tumour cell growth inhibiting camptothecin analogue claimed or described in WO 93/09782 and the references cited therein (which are hereby incorporated herein by reference). The preparation of Topotecan (including pharmaceutically acceptable salts, hydrates and solvates thereof) as well as the preparation of oral and parenteral pharmaceutical compositions comprising topotecan and an inert, pharmaceutically acceptable carrier or diluent, is extensively described in U.S. Patent 5,004,758 and European Patent Application Publication Number EP 0,321,122.

2. A taxane, such as Taxol (Paclitaxel) or Taxotere® (Docetaxel).

3. A growth-factor receptor inhibitor such as a growth factor receptor - protein-kinase inhibitor, including an epidermal growth factor receptor - class I tyrosine kinase inhibitor, for example, Iressa® (ZD1839 or Gefitinib) or Tarceva® (or Erlotinib)), and other inhibitors of growth factor function. Such growth factors include, for example, platelet derived growth factor, endothelial growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor and hepatocyte growth factor and such inhibitors include growth factor

antibodies and growth factor receptor antibodies, such as, e.g., Avastin® or Bevacizumab, and Erbitux® or Cetuximab, as well as serine/threonine kinase inhibitors. Also included are inhibitors of cell cycle kinases such as CDK-2, CDK-4 and CDK-6. Inhibitors of endothelial growth factor or vascular endothelial growth factor may act, at least in part, by inhibiting tumor angiogenesis.

4. An anti-metabolite such as 5-FU, S1, UFT, Capecitabine; a thymidylate synthase inhibitor such as Tomudex or ZD9331, or LY231514 (MTA, pemetrexed disodium) or Gemcitabine, or an antifolate such as Methotrexate.

5. A *Vinca* alkaloid such as Vinolrebine (Navelbine), Vincristine, Vinblastine or Vindesine.

6. An anti-angiogenic compound such as described in International Patent Application Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856, WO 98/13354, WO 00/21955 and WO 00/47212.

7. An alkylating agent such as Melphalan, Cyclophosphamide, Ifosphamide or a nitroso-urea, such as Carmustine or Lomustine.

8. An Anthracyclin such as Doxrubicin, Epiribicin, Idarubicin, Amrubicin or Doxil®.

9. An anti-HER-neu compound, such as Herceptin (Trastuzumab).

10. A cytostatic agent such as an antioestrogen (for example, Tamoxifen, Toremifene, Raloxifene, Droloxifene, Iodoxyfene), a progestogen (for example, Megestrol Acetate), an aromatase inhibitor (for example, Anastrozole, Letrazole, Vorazole, Exemestane), an antiprogestogen, an antiandrogen (for example, Flutamide, Nilutamide, Bicalutamide, Cyproterone Acetate), LHRH agonists and antagonists (for example, Goserelin acetate, Luprolide), an inhibitor of testosterone 5α-dihydroreductase (for example, Finasteride) and an anti-invasion agent (for example, metalloproteinase inhibitors like Marimastat and inhibitors of urokinase plasminogen activator receptor function).

11. Antimitotics, natural and synthetic.

12. Interleukins and cytokines such as TNF.

13. Vaccines.

14. Uptake/efflux modulators such as mdr2.

15. Rescue agents.

16. Ca antagonists.

Potentiation agents, e.g., Leucovorin, that do not possess anti-cancer activity *per se*, can also be used in the present method.

A "platinum-based anticancer agent" can include other platinum agents, such as BBR3464, Satraplatin, Cisplatin, Carboplatin, Nedaplatin, Heptaplatin or Oxaliplatin, with a different mode of action or useful profile, may also be used with picoplatin.

These categories are provided as a summary of art-recognized classes of anti-cancer agents or other classes of active agent or adjuvant and not meant to be exclusive.

The second anticancer agent can be administered in an effective amount to the patient, concurrently with the oral picoplatin formulation, prior to administration of the oral picoplatin formulation, or subsequent to the oral picoplatin formulation, on a similar or diverse schedule of administration, provided that the second anticancer agent is administered at a dose, in a frequency, and for a duration of time sufficient to provide a beneficial effect to the patient when administered with the oral picoplatin formulation. The picoplatin oral formulation can be administered with (before, after or concurrently with) at least one platinum or non-platinum anticancer agent, which can be administered orally or parenterally. Preferably the picoplatin is administered concurrently (simultaneously or overlapping) or prior to the administration of the second anticancer agent. The second anticancer agent can be administered prior to the picoplatin. If it is a taxane it is preferably administered less than 10-20 hours to about 5 minutes prior to the picoplatin, e.g., about 1 hour to 15 minutes prior to the picoplatin.

Additive effects between the picoplatin and the additional anticancer agent can be observed, wherein the therapeutic effect of each agent is summed to provide a proportional increase in effectiveness. Synergistic effects between the picoplatin and the additional anticancer agent can be observed, wherein the combined effectiveness of the treatment is greater than the summed effectiveness of the two agents.

In various embodiments of the present invention the ionizing radiation employed may be X-radiation, γ-radiation, or β-radiation. The dosages of ionizing radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include, for example, the use of γ-rays, X-rays,

and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. It is most likely that all of these factors effect a broad range of damage to DNA, to the precursors of DNA, to the replication and repair of DNA, and to the assembly and maintenance of chromosomes. For example, X-rays may be dosed in daily doses of 1.8-2.0 Gy, 5 days per week for 5-6 weeks. Normally, a fractionaed dose will lie in the range 45-60 Gy. Single larger doses, for example 5-10 Gy, may be administered as part of a course of radiotherapy. Dosage ranges for radioisotopes vary widely, and depend upon the half-life of the isotope, the type and energy of the radiation emitted, and the rate of uptake by cells.

This application is related to Application No. PCT/US2008/008076, filed June 27, 2008, entitled "Stabilized Picoplatin Dosage Form"; Application No. PCT/US2008/001746, filed Feb. 8, 2008, entitled "Encapsulated Picoplatin"; Application No. PCT/US2008/001752, filed Feb. 8, 2008, entitled "Stabilized Picoplatin Oral Dosage Form"; U.S. Serial No. 10/276,503, filed September 4, 2003, entitled "Combination Chemotherapy"; U.S. Serial No. 11/982,841, filed November 5, 2007, entitled "Use of Picoplatin to Treat Colorectal Cancer"; U.S. Serial No. 11/935,979, filed November 6, 2007, entitled "Use of Picoplatin to Treat Prostate Cancer"; U.S. Serial No. 11/982,839, filed November 5, 2007, entitled "Use of Picoplatin to Treat Small Cell Lung Cancer"; WO/98/045331, filed Apr. 3, 1998, entitled "Anti-VEGF Antibodies"; WO/96/040210, filed June 7, 1996, entitled "Antibody and Antibody Fragments for Inhibiting the Growth of Tumors"; all of the above being incorporated by reference in their entireties herein.

This application is also related to U.S. Ser. No. 61/027,387, filed February 8, 2008, entitled "Use of Picoplatin and Bevacizumab to Treat Colorectal Cancer"; U.S. Ser. No. 61/027,382, filed February 8, 2008, entitled "Use of Picoplatin and Cetuximab to Treat Colorectal Cancer"; U.S. Ser. No. 61/027,360, filed February 8, 2008, entitled "Picoplatin and Amrubicin to Treat Lung Cancer"; and U.S. Serial No. 61/034,410, filed Mar. 6, 2008, entitled "Use of Picoplatin and Liposomal Doxorubicin Hydrochloride to Treat Ovarian Cancer"; all of the above being incorporated by reference in their entireties herein.

Furthermore, U.S. Pat. No. 7,060,808, issued June 13, 2006, entitled "Humanized anti-EGF receptor monoclonal antibody"; and U.S. Pat. No. 4,673,668, issued June 16, 1987, entitled "Aminonaphthacene derivatives"; are also incorporated herein by reference.

These patents and applications disclose, *inter alia*, useful agents for administration with picoplatin, methods of treatment, dosing regimens, and compositions.

EXAMPLES

Example 1: HPLC method for picoplatin.

Conditions:

Column:	Luna 5u C18(2) 250x 4.6 mm 00G-4252-E0 (Phenomenex)
Mobile phase A:	0.2% TFA (v/v) in deionized water ("di-water")
Mobile phase B:	Methanol HPLC grade
Flow rate:	1.0 mL/min
Detection wavelength:	267 nm
Column temperature:	35 deg C
Sample temperature:	25 deg C
Run time:	25 min
Sample diluent:	Normal saline

TABLE I - Gradient

Time (min)	% B
0	5
4	5
13	35
14	100
18	100
19	5
25	5

Example 2: Determination of the solubility of picoplatin at various pH values.

The objective of this study was to determine the solubility of picoplatin in aqueous solutions and to measure the effect of pH on picoplatin solubility.

TABLE II - pH Buffers

Vial	pH	Buffer
1	2	50 mM sodium phosphate
2	3	50 mM sodium phosphate
3	4	50 mM sodium acetate
4	5	50 mM sodium acetate
5	6	50 mM sodium citrate
6	7	50 mM sodium phosphate
7	8	50 mM sodium phosphate
8	9	50 mM sodium bicarbonate
9	10	50 mM sodium bicarbonate
10	Record	di-water

Procedure:

Picoplatin (10 mg) was weighed into 0.5 mL Eppendorf vials, for a total 10 vials, then 250 μL of buffer or water was added to the picoplatin. The vials were mixed for one minute. For each vial, the pH was measured. The vials were then placed on a shaker at 25 deg C for 16 hr in dark and the pH was measured again. The solutions were filtered centrifugally through 0.45 uM Spin-X filters, then 50 mg of each filtrate was transferred into a respective HPLC vial. 1.5 mL of 0.9% NaCl solution (normal saline) was added to the HPLC vials, then HPLC analysis was performed immediately to determine the concentration of each sample.

TABLE III - pH of Picoplatin in Buffer Solutions

Buffer	Initial pH	Final pH (filtrate)	Solubility (mg/mL)*
50mM sodium phosphate pH2	1.83	2.05	0.74
50mM sodium phosphate pH3	3.51	3.82	0.98
50mM sodium acetate pH4	3.81	4.01	0.77
50mM sodium acetate pH5	4.88	4.97	0.84
50mM sodium citrate pH6	6.29	6.54	0.78
50mM sodium phosphate pH7	7.02	6.80	1.10
50mM sodium phosphate pH8	8.28	7.81	0.97
50mM sodium bicarbonate pH9	8.92	8.76	0.67
50mM sodium bicarbonate pH10	10.45	10.07	0.60
Deionized H_2O	5.24	4.66	1.23

* Assuming the density of the saturated solution is 1 g/mL

Example 3: Determination of the pH-stability profile of picoplatin.

The objective of this study was to determine the effects of pH on stability of picoplatin in aqueous solution and to assess the overall stability of picoplatin in an aqueous solution.

TABLE IV - pH Buffers

Vial	pH	Buffer/Solvent
1	2	50 mM sodium phosphate
2	3	50 mM sodium phosphate
3	4	50 mM sodium acetate
4	5	50 mM sodium acetate
5	6	50 mM sodium citrate
6	Record	di-water
7	Record	Normal Saline (NS)

Procedure:

Picoplatin (10 mg (+/- 0.1 mg) was weighed into a 5 mL volumetric flask, then normal saline was added to the 5 mL volumetric mark and the sample mixed by inversion to dissolve all solid and obtain a 2 mg/mL stock solution.

Then, to 1.125 mL buffer of specified pH or deionized water or normal saline in an HPLC vial was added 0.375 mL of the stock solution, which was mixed by vortex for 10 sec to obtain a 0.5 mg/mL test solution. Two vials were made up for each pH, which was checked.

The samples were then injected for HPLC analysis, analyzing each vial once in the following sequence: pH 6, pH 5, pH 4, pH 3, pH 2, deionized water, normal saline.

Then, one of each pair of vials for each solution was transferred to a 40°C stability chamber, and the other to a 25°C chamber.

The injection sequence was repeated after the elapse of 1 and 3 days, or until the samples were at least 20% degraded.

Results:

The results are shown below in TABLES V – XIII

TABLE V - Picoplatin Recovery (% over initial) at 25 and 40°C After 0, 1 and 2 Days

At 25°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	100	99.79	94.85
pH 3, 50 mM sodium phosphate buffer	3.48	100	68.86	65.59
pH 4, 50 mM sodium acetate buffer	3.93	100	96.60	90.65
pH 5, 50 mM sodium acetate buffer	4.89	100	73.97	63.63
pH 6, 50 mM sodium citrate buffer	6.20	100	24.85	12.21
Normal Saline	5.54	100	102.67	97.45
Deionized water	5.59	100	29.87	25.43

* Based on peak area of picoplatin ONLY

TABLE VI - Picoplatin Recovery (% over initial) at 25 and 40°C After 0, 1 and 2 Days

At 25°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	100	106.29	100.95
pH 3, 50 mM sodium phosphate buffer	3.48	100	95.35	101.32
pH 4, 50 mM sodium acetate buffer	3.93	100	103.18	96.96
pH 5, 50 mM sodium acetate buffer	4.89	100	84.99	73.82
pH 6, 50 mM sodium citrate buffer	6.20	100	51.08	46.51
Normal Saline	5.54	100	113.71	109.15
Deionized water	5.59	100	100.59	94.68

* Based on combined peak area of picoplatin, Aquo 1 and Aquo 2.

TABLE VII - Picoplatin Recovery (% over initial) at 25 and 40°C After 0, 1 and 2 Days

At 40°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	100	101.72	94.46
pH 3, 50 mM sodium phosphate buffer	3.48	100	71.13	70.96
pH 4, 50 mM sodium acetate buffer	3.93	100	88.65	81.91
pH 5, 50 mM sodium acetate buffer	4.89	100	49.59	43.84
pH 6, 50 mM sodium citrate buffer	6.20	100	1.43	0.93
Normal Saline	5.54	100	103.79	102.59
Deionized water	5.59	100	29.58	31.41

* Based on peak area of picoplatin ONLY

TABLE VIII - Picoplatin Recovery (% over initial) at 25 and 40°C After 0, 1 and 2 Days

At 40°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	100	108.39	100.68
pH 3, 50 mM sodium phosphate buffer	3.48	100	113.45	167.66
pH 4, 50 mM sodium acetate buffer	3.93	100	95.58	88.04
pH 5, 50 mM sodium acetate buffer	4.89	100	62.23	53.01
pH 6, 50 mM sodium citrate buffer	6.20	100	28.32	38.77
Normal Saline	5.54	100	116.58	113.36
Deionized water	5.59	100	109.26	103.81

* Based on combined peak area of picoplatin, Aquo 1 and Aquo 2.

TABLE IX - Picoplatin purity (% over total peak area) at 25 and 40 deg C after 0, 1 and 2 days

At 25°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	97.9	90.2	88.0
pH 3, 50 mM sodium phosphate buffer	3.48	97.8	61.3	60.7
pH 4, 50 mM sodium acetate buffer	3.93	98.6	87.4	84.6
pH 5, 50 mM sodium acetate buffer	4.89	98.4	67.6	58.6
pH 6, 50 mM sodium citrate buffer	6.20	98.8	23.9	12.1
Normal Saline	5.54	95.3	90.4	89.2
Deionized water	5.59	98.9	29.5	25.6

* Based on peak area of picoplatin ONLY

TABLE X - Picoplatin purity (% over total peak area) at 25 and 40 deg C after 0, 1 and 2 days

At 25°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	97.9	97.0	94.7
pH 3, 50 mM sodium phosphate buffer	3.48	97.8	94.1	93.7
pH 4, 50 mM sodium acetate buffer	3.93	98.6	93.3	90.5
pH 5, 50 mM sodium acetate buffer	4.89	98.4	77.6	68.0
pH 6, 50 mM sodium citrate buffer	6.20	98.8	49.0	46.1
Normal Saline	5.54	95.3	100.0	100.0
Deionized water	5.59	98.9	98.1	95.4

* Based on combined peak area of picoplatin, Aquo 1 and Aquo 2.

TABLE XII - Picoplatin purity (% over total peak area) at 25 and 40 deg C after 0, 1 and 2 days

At 40°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	97.9	91.5	88.7
pH 3, 50 mM sodium phosphate buffer	3.48	97.8	57.4	58.0
pH 4, 50 mM sodium acetate buffer	3.93	98.6	77.8	74.7
pH 5, 50 mM sodium acetate buffer	4.89	98.4	44.6	41.0
pH 6, 50 mM sodium citrate buffer	6.20	98.8	2.0	0.9
Normal Saline	5.54	95.3	89.2	90.5
Deionized water	5.59	98.9	25.6	28.2

* Based on peak area of picoplatin ONLY

TABLE XIII - Picoplatin purity (% over total peak area) at 25 and 40 deg C after 0, 1 and 2 days

At 40°C	Initial pH	Initial (T=0)	Day 1	Day 2
pH 2, 50 mM sodium phosphate buffer	2.78	97.9	98.5	95.6
pH 3, 50 mM sodium phosphate buffer	3.48	97.8	91.5	114.3
pH 4, 50 mM sodium acetate buffer	3.93	98.6	83.5	80.3
pH 5, 50 mM sodium acetate buffer	4.89	98.4	55.9	49.6
pH 6, 50 mM sodium citrate buffer	6.20	98.8	38.6	37.1
Normal Saline	5.54	95.3	100.0	100.0
Deionized water	5.59	98.9	94.3	93.1

* Based on combined peak area of picoplatin, Aquo 1 and Aquo 2.

Example 4: Determination of solubility of picoplatin in organic solvents.

The purpose of this study was to search for a solvent that can be used to facilitate dissolution of picoplatin into self-emulsifying vehicles.

Solvent selection criteria:

- Dissolve picoplatin to > 20% w/w or 200 mg/mL
- Volatile – removable by vacuum drying
- Class 3 or injectable
- Chemically compatible with picoplatin

TABLE XIV - Composition

mg/g	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Acetonitrile	180						
Tetrachloroethylene		180					
Acetone			180				
Methanol				180			
THF					180		
Isopropanol						180	
Methylene chloride							180
Picoplatin	20	20	20	20	20	20	20
Total	200	200	200	200	200	200	200

Procedure:

Picoplatin (20+/-2 mg) was weighed into a series of 2 mL Eppendorf vials, 100 mg of each solvent was added respectively, then each sample was sonicated to mix and dissolve the picoplatin. If the picoplatin did not dissolve, additional aliquots of 100 mg solvent were added (to a maximum of 1.5 g), and the suspensions sonicated, until all of the solid did dissolve. Each sample was then dried on a Speedvac on low heat overnight to evaporate the solvent, then 200 mg deionized water was added to each vial. The supernatant (500 mg) was transferred from each vial into a respective HPLC vial, then 0.5 mL of the solvent used was added.

Results:

The results are shown below in TABLE XV.

TABLE XV

Solvent	Solubility (mg/g)
Acetonitrile	1.30
Tetrachloroethylene	0.00
Acetone	0.14
Methanol	0.61
THF	1.81
Isopropanol	0.15
Methylene chloride	0.00
DMSO	> 200 (degradation)
N-methylpyrrolidone	> 200 (peak shifted)
Benzyl benzoate	< 5
Benzyl alcohol	< 5

Example 5: Determination of the solubility of picoplatin in self-emulsifying vehicles.

The purpose of this study was to find an oil: surfactant system(s) capable of dissolving Picoplatin to 10% w/w. The composition of the various samples is shown in TABLE XVI.

TABLE XVI - Composition

mg/g	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
Labrasol	200								
Cremophor RH40		200							
Cremophor ELP			200						
Gelucire 44/14				200					
Polysorbate 80, HP					200				
Vitamin E TPGS						200	200	200	200
PEG400	100	100	100	100	100	100	100	100	100
Soy lecithin (high PC content)	200	200	200	200	200	200		200	200
Soy lecithin (low PC content)							200		
Medium chain triglyceride	300	300	300	300	300	300	300		
Castor oil								300	
Medium chain mono- & di-glycerides									300
Picoplatin	200	200	200	200	200	200	200	200	200
Total	1000	1000	1000	1000	1000	1000	1000	1000	1000

Procedure:

Picoplatin was weighed out to within +/-5% of the target weight, then solvent (e.g. DMSO USP) was added to dissolve. Then, oil, lecithin, PEG400 and a surfactant were mixed to within +/-5-10% of the target weight, then ethanol was added to homogeneity. The two solutions were combined, then vacuum dried until the residual solvent was less than 1% of the dry weight. The dry formulation was examined under a microscope for crystals. If crystals were present, the sample was centrifuged to the pellet the crystals. Then 10 mg of the supernatant was removed and 5g normal saline added . The drug concentration was analyzed by HPLC.

TABLE XVII

Result	**F-8**	**F-9**	**F-10**	**F-11**	**F-12**	**F-13**	**F-14**	**F-15**	**F-16**
Appearance of the dry formulations	Free of crystalline particles								
Form	Liquid	Liquid	Liquid	Semi-solid	Liquid	Semi-solid	Semi-solid	Semi-solid	Liquid
pH	4.28	5.18	5.5	4.83	5.86	5.67	4.96	4.67	5.23
Picoplatin Conc. (% w/w)	0.67	0.42	0.19	0.19	0.36	0.33	0.18	3.99	0.40
Picoplatin Purity (Area%)	42.4	6.2	7.3	6.3	11.5	7.3	6.6	73.2	19.8

Example 6: Degradation of picoplatin in DMSO and pH buffers at 25°C.

The purpose of this study was to obtain a profile of picoplatin in DMSO and pH buffers or water.

TABLE XVIII - Materials

mg/mg	F-28	F-29	F-30	F-31	F-32	F-33	F-34
Picoplatin	0.5	0.5	0.5	0.5	0.5	0.5	0.5
DMSO	950	950	950	950	950	950	500
glacial acetic acid	50						
Normal saline		50					500
pH 2 buffer			50				
pH 4 buffer				50			
pH 6 buffer					50		
Di-water						50	
Total	1000	1000	1000	1000	1000	1000	1000

Procedure :

Picoplatin (0.5 mg +/- 0.01) was weighed out into a 1.5 mL HPLC vials for a total of 7 vials. DMSO and the 2nd solvent were weighed out in a separate 2 mL Eppendorf vial and mixed well. Then, 1 mL of the DMSO mixture with solvent was transferred into the HPLC vial containing picoplatin, then mixed by vortex for 10 sec to make sure all solid was dissolved.

The samples were then analyzed by HPLC, running the sequence 4-5 times, or until at least 20% of the picoplatin had degraded

Example 7: Preparation of picoplatin nanoparticles

The purpose of this study was to generate nanometer sized and preferably non-crystalline particles of picoplatin.

TABLE XIX

Compound	%w/w
Picoplatin	2.5
Soy lecithin	5
deionized water	92.5
Total	100

Procedure:

Soy lecithin and deionized water were weighed out, then mixed with a high-shear mixer to obtain a uniform dispersion. Picoplatin was added and mixed well, the suspension being microfluidized until the particle size reached a minimum by laser light scattering or disappearance of crystalline particles. Then, the nanosuspension was freeze-dried to obtain a dry powder.

Results:

The results are shown below in TABLE XX.

TABLE XX

In-process sample	Particle size by LLS	Purity by HPLC	Crystalline particles
Pre-microfluidization	10-20 micron	94.4%	A lot
Post-microfluidization	643 nm	93.8%	Not seen
Post-lyophilization	584 nm	95.1%	A few

A significant size reduction from about 10 to 0.5 micron in diameter corresponding to about 400-fold increase in particle surface area was obtained by microfluidization. It was found that picoplatin retains its integrity (purity) after the microfluidization and lyophilization process. Also, a reduction in crystallinity was apparent.

Example 8: Determination of picoplatin stability in NMP.

The purpose of this study was to develop a profile of picoplatin in N-methyl-pyrrolidone at 25°C and at 5°C

TABLE XXI - Composition

mg/g	F-45	F-46	F-47	F-48	F-49
Picoplatin	0.5	0.5	0.5	0.5	0.5
NMP	1000	800	500	200	
NS		200	500	800	1000
Total	1000.5	1000.5	1000.5	1000.5	1000.5

TABLE XXII - Composition

mg/g	F-45	F-46	F-47	F-48	F-49
Stock	200	200	200	200	HPLC Std
NMP	800	600	300		
NS		200	500	800	
Total	1000	1000	1000	1000	

Procedure:

In a 2 mL Eppendorf vial, 2.000 mg picoplatin was weighed out, 800 mg NMP added, and the mixture vortexed to dissolve picoplatin to obtain a stock solution, of which 200 mg was transferred into Eppendorf vials for total of 4 vials. An appropriate amount of normal saline was added and mixed well by vortex for approximately 10 seconds, then 500 mg was transferred into an HPLC vial, and an HPLC analysis run. Then, the remainder of the solution was dried in a lyophilizer until all the liquid was gone and 500 mg normal saline was added to each vial and mixed well by vortex for 20 seconds, transferred 500 mg into an HPLC vial. Ran HPLC with a 0.5 mg/mL standard.

Results:

Representative HPLC chromatograms are shown in Figures 9 and 10.

Example 9: Optimization of picoplatin nanoparticle formulations.

The purpose of this study was to prepare and compare stability of nanoparticles using various stabilizers by microfluidization.

TABLE XXIII – Composition (%w/w)

Composition (% w/w)

Compound	F-37	F-38	F-39	F-40	F-41	F-42	F-43
Picoplatin	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Soy lecithin S-45	5						
Soy lecithin S-75		5					
Soy lecithin PL-90			5				
Soy lecithin PL-90H				5			
Vitamin E Succinate, pH7 5% pre-made dispersion in NS					97.5		
Oleic acid (Croda), pH 7, 5% pre-made dispersion in water						97.5	
Sodiumcaseinate, pH 7, 5% pre-made dispersion in water							97.5
Di-water	92.5	92.5	92.5	92.5			
Total	100	100	100	100	100	100	100

Composition (mg/10 g)

Compound	F-37	F-38	F-39	F-40	F-41	F-42	F-43
Picoplatin	25	25	25	25	25	25	25
S-45	50	0	0	0	0	0	0
S-75	0	50	0	0	0	0	0
PL-90	0	0	50	0	0	0	0

PL-90H	0	0	0	50	0	0	0
VES pH7 5% pre-made dispersion in water	0	0	0	0	975	0	0
Oleic acid (Croda), pH 7, 5% pre-made dispersion in water	0	0	0	0	0	975	0
Sodium caseinate, pH 7, 5% pre-made dispersion in water	0	0	0	0	0	0	975
Di-water	925	925	925	925	0	0	0
Total	1000	1000	1000	1000	1000	1000	1000

*Added additional 10 g of di-water to each.

Procedure

Lecithin PL, picoplatin and deionized water were weighed out into a 50 mL falcon tube and mixed by high-shear mixer at 8000 RPM for 2 minutes until all of the solid was uniformly dispersed. A micro fluidizer with a Z-chamber was set up and the sample was processed for about 1100 strokes. 1 g each was transferred into 3 mL glass vial for a total of ~15 vials, which were freeze-dried to obtain a "lyophilizate".

One vial of the lyophilizate was reconstituted by adding di-water and mixing well to form a suspension. "Post-lyo"

For all samples, the following tests were performed at (T=0):

Micrograph at 200 x, laser light scattering (LLS),

HPLC (dilute to 0.5 mg/mL with NS) for post lyophilization sample only

Results

The results are shown below in TABLE XXIV.

TABLE XXIV – Results

	F-37	F-38	F-39	F-40	F-41	F-42	F-43
Microscopic examination after 1100 passes	+	++	++	+	+++	+++	+
Microscopic examination after keeping the suspension at 5°C for 24 hr	++	Not tested	Not tested	+++	Not tested	Not tested	+
Microscopic examination after keeping the suspension at 5°C for 72 hr	++	Not tested	Not tested	+++	Not tested	Not tested	+
Microscopic examination after keeping the suspension at 25°C for 24 hr	++	Not tested	Not tested	+++	Not tested	Not tested	+
Microscopic examination after keeping the suspension at 25°C for 72 hr	++	Not tested	Not tested	+++	Not tested	Not tested	+
Microscopic examination after reconstitution of the lyophile	++	Not tested	Not tested	++	Not tested	Not tested	+
Microscopic examination after reconstitution of the lyophile at 25°C for 72 hr	+++	Not tested	Not tested	+++	Not tested	Not tested	++ Protein precipitate

+++ A large number of visible crystals in 1-5 micron
++ Some crystalline particles
+ Few crystalline particles

TABLE XXV – Particle diameter by Laser Light Scattering (LLS) in nm

Sample ID	F-37	F-40	F-43
After 1100 passes	746	3386	136
After keeping the suspension at 5°C for 24 hr	844	1630	188
After keeping the suspension at 25°C for 24 hr	1406	758	228
Reconstituted suspension at 25° C for 72 hr	1126	1740	1104

TABLE XXVI – HPLC analysis for picoplatin in nanoparticles

Sample ID	Concentration (mg/mL)*	Purity
F37 reconstituted suspension (fresh)	0.36	97.3
F40 reconstituted suspension (fresh)	0.48	94.8
F43 reconstituted suspension (fresh)	0.59	94.5

Based picoplatin peak only

Sample ID	Concentration (mg/mL)*	Purity
F37 reconstituted suspension (fresh)	0.36	100.0
F40 reconstituted suspension (fresh)	0.50	100.0
F43 reconstituted suspension (fresh)	0.60	97.7

Based on combination of pico, Aquo 1 and Aquo 2 peaks

* The target concentration is 0.5 mg/mL

Example 10: Preparation of a second batch of picoplatin nanoparticles in 5% Sod. Caseinate dispersion.

The purpose of this study was to reproduce the results from the previous experiment and to try using a rotary evaporator to remove water.

TABLE XXVII – Composition:

Composition (% w/w)	
Compound	F-50
Picoplatin	1.25
Sodiumcaseinate, pH 7, 5% pre-made dispersion in water	2.5
Di-water	QS
Total	100

Composition (mg/40 g)	
Compound	F-50
Picoplatin	500
Sodiumcaseinate, pH 7, 5% pre-made dispersion in water	19500
Di-water	20000
Total	40000

Procedure

100 g of a 5% sodium caseinate dispersion and 100g of deionized water were weighed into an Erlenmeyer flask, and the pH adjusted to 6 using HCl/NaOH. The solution was sparged with Nitrogen gas for 10 minutes, then 39.5g of the dispersion transferred into a 100 mL Erlenmeyer flask. 500 mg picoplatin was added and mixed under high shear conditions at 8000 RPM for 5 minutes. A 500 mg sample was processed in a microfluidizer with a Z-chamber for 2200 strokes and the pH recorded. The remainder of the sample was dried at 40°C on a rotary evaporator for 2 hr, then vacuum dried at 25°C and 150 mTorr for 16 hr. The residue was ground into a fine powder, then the moisture content determined by TG/DTA along with a picoplatin standard. A moisture uptake study was performed by placing 10 mg in 3 HPLC vials and keeping them at 25 deg C/60%RH, 30 deg C

/65%RH and 40 deg C /75%RH respectively, exposed overnight. An HPLC analysis and a microscopic examination were performed.

Results

Figure 11 shows a thermogravimetric / differential thermal analysis (TG/DTA) scan of micronized picoplatin powder.

Figure 12 shows a thermogravimetric / differential thermal analysis (TG/DTA) scan of TG/DTA of F50 Picoplatin nanoparticles in sodium caseinate.

Particle size in the reconstituted suspension could not be measured due to presence of large non-crystalline caseinate agglomerates, which interfered with the laser light scattering measurement. However, microscopic examination revealed that there was few crystalline particles in the micron size range, indicating that picoplatin remained in nanometer size (possibly less than 300-400 nm).

TABLE XXVIII – Hygroscopicity Data

Temperature/Humidity Conditions	**% Weight Gain**
25° C/60% RH overnight	0.36
30° C/65% RH overnight	0.73
40° C/75% RH overnight	3.6

TABLE XXIX – HPLC Results

Lot: 69-1-68	**Assay (mg/g) ***	**% Peak area**
Picoplatin	569.0	93.9
Aqua 1	761.7	1.7
Aqua 2	848.4	1.15
Total	573.7	96.75

*Theoretical assay value = 333.3 mg/g or 33.3% w/w. The higher-than-theoretical assay value may be due to presence of volatile components (e.g. water) in the sodium caseinate starting material.

Figure 13 shows a representative HPLC chromatogram of picoplatin nanoparticles. From the top down: 0.5 mg/mL picoplatin nanoparticles in normal

saline and 0.5 mg/mL picoplatin standard in normal saline. One unknown peak at 5.5 min (not Aquo #1).

Example 11: Solid dispersion of picoplatin using hot melt method.

The purpose of this study was to determine if it is possible to dissolve picoplatin in a molten solution of a solid matrix excipient without decomposition of picoplatin. The second purpose of this study is to verify the solid matrix form for crystallinity by DSC.

TABLE XXX – Composition (mg)

Component, grade	MP	F-51	F-52	F-53	F-54	F-57
Gelucire 50/13	45	950				
poloxamer 188	52		950			
PEG 8000	60			950		
Sorbitan monostearate (SPAN 60)	57				950	
Kollidon K-90	150					950
Picoplatin		50	50	50	50	50

Procedure:

The selected excipient was weighed out into a 3 mL glass vial, then warmed up to a temperature of about 5-10° C above the melting point of the matrix material using a hot plate. Picoplatin was added and the mixture stirred at about 100°C for 1 hr, or for the sorbitan monostearate sample, at about 150°C. The samples were then cooled quickly on a chilled metal block.

Observations:

Picoplatin dissolved in molten Gelucire 50/13 and in SPAN 60, but not in PEG, poloxamer or Kollidon, suggesting picoplatin is more soluble in lipids. The Gelucire 50/13 picoplatin mixture appeared to contain intact picoplatin, but the SPAN 60 picoplatin mixture turned brown on heating

Example 12-1: Solid dispersion of picoplatin using hot melt method.

The purpose of this study is to determine the solubility of picoplatin in Gelucire 50/13 and to try two more low MP lipids

TABLE XXXI – Composition (mg)

Component, supplier, grade	MP	F-59	F-60	F-61	F-62	F-63	F-64	F-65	F-66
Gelucire 50/13	45	90	80	70	60	50	40		
Gelucire 44/14	44							70	
Vitamin E TPGS	40								70
Picoplatin		10	20	30	40	50	60	30	30

Procedure

The selected excipient and the picoplatin (+/- 2 mg) were weighed into a HPLC glass vial, and vortexed to mix. The mixture was heated to 60°C to form a complete melt, and stirred and observed to determine if complete dissolution of the picoplatin occurred. The sample was heated at 60 deg C for 1 hour for F-59 to F-66, and F-61 to F-66 received additional 30 min heating at 80 deg C. The samples were then cooled immediately by placing the vial in a chilled metal block.

Example 12-2: Solubility of picoplatin in Gelucire 50/13.

The purpose of this study was to determine the solubility of picoplatin in Gelucire 50/13 at less than 10% and to test one more lipid (Compritol 888 ATO) at 5%

TABLE XXXII – Composition (mg)

Component, supplier, grade	MP	F-67	F-68	F-69	F-70	F- 71
Gelucire 50/13	45	95	94	93	92	
Compritol 888 ATO	70					95
Pico		5	6	7	8	5

Procedure:

The lipid and picoplatin (+/- 2mg) were weighed into a HPLC glass vial, then vortexed to mix. Then, a glass beaker with Miglyol oil and placed it on a hot plate set to 100°C. All mixtures were heated for 2 hours (100 deg C) and vortexed from time to time. After heating, all samples were cooled rapidly by placing the vial in a chilled metal block.

Observations:

All turned clear. The solutions of F-67 and F-68 appeared slightly clearer than the others. The results of Samples F-51 to F-71 are shown below in Tables XXXIII and XXXIV.

TABLE XXXIII – Results of Examples 12-1 and 12-2

Matrix	**F-51**	**F-52**	**F-53**	**F-54**	**F-57**	**F- 59**	**F-60**	**F-61**	**F-62**
Gelucire 50/13	YTO*					YTO	YTO	YQC	YQC
Poloxamer 188		YQC							
PEG 8000			YQC						
SPAN 60				BTO*					
Kollidon K-90					N				
Gelucire 44/14									
Vitamin E TPGS									
Compritol 888 ATO									

Characterization of picoplatin-matrix mixture upon heating

Key: Y= yellow
B= brown
O= oily
C= creamy
T= translucent
Q= opaque
N= never melted
*= No DSC peak

TABLE XXXIV – Results of Examples 12-1 and 12-2

Matrix	**F-63**	**F-64**	**F-65**	**F-66**	**F-67**	**F-68**	**F-69**	**F-70**	**F-71**
Gelucire 50/13	YQC	YQC			YTO*	YTO	YTO	YTO	
Poloxamer 188									
PEG 8000									
SPAN 60									
Kollidon K-90									
Gelucire 44/14			YTO						
Vitamin E TPGS				YTO					
Compritol 888 ATO									YTO

Characterization of picoplatin-matrix mixture upon heating

Key: Y= yellow
B= brown
O= oily
C= creamy
T= translucent
Q= opaque
N= never melted
*= No DSC peak

TABLE XXXV – Concentration of Picoplatin in Gelucire 50/15 hot melt (F-51, 5% load)

	Concentration (mg/g)*	Purity (% peak area)
5% picoplatin in Gelucire 50/15	68.7	96.95

* Theoretical concentration is 50 mg/g (5% w/w)

Figure 14 shows a representative HPLC trace of picoplatin in Gelucire 50/15.

Figure 15 shows a representative DSC for Picoplatin in Gelucire 50/15 hot melt. From top down: Gelucire 50/15, 5% picoplatin in Gelucire 50/15 hot melt, and picoplatin API.

Figure 16 shows a representative DSC for Picoplatin in hot melt. From top down: 5% picoplatin in Gelucire 50/15, 6% picoplatin in Gelucire 50/15 and 5% in Compritol 888 ATO.

TABLE XXXVI – Heat of Fusion for 5% picoplatin in Gelucire 50/15, 6% picoplatin in Gelucire 50/15 and 5% picoplatin in Compritol 888 ATO.

Sample	Heat of Fusion (mJ/mg) for the endothermic peak at 220-250°C
Picoplatin API	54.9
F51- 5% picoplatin in Gelucire 50/15	10.0
F68- 6% picoplatin in Gelucire 50/15	31.7
F71- 5% picoplatin in Compritol 888 ATO	36.3

Example 13: Preparation of 50% w/w picoplatin suspension in medium chain triglyceride (MCT) oil.

Objective:

To prepare 50% w/w picoplatin nano-suspension in MCT oil

TABLE XXXVII – Materials

Composition (% w/w)

Compound	F-73	F-74	F-75
Picoplatin	5	5	5
Miglyol 812	95	90	90
Phospholipon 90G		5	
Polysorbate 80			5
Total	100	100	100

Composition (g/30 g)

Compound	F-73	F-74	F-75
Picoplatin	1.5	1.5	1.5
Miglyol 812	28.5	27	27
Phospholipon 90G		1.5	1.5
Polysorbate 80			
Total	30	30	30

Procedure:

Picoplatin was weighted out into a 50 mL Falcon tube, MCT oil was added to the tube (final picoplatin concentration was 5% w/w). PL-90 or Polysorbate 80 was then added, and mixed using a high shear mixer (IKA @ 5 setting for 3 minutes), then microfluidized using M110EH at 25000 psi and a Z-chamber to obtain submicron particles. Chill the chamber with ice. Maintain the suspension during processing at below 40-50 deg C.

Samples were removed and average size determined by laser light scattering. Allow the suspension settle down and remove supernatant to obtain about 50% w/w suspension. Store at 2-8°C. Observe under microscope and measure size at T-0 and Day-1. Run HPLC (diluted in normal saline to 0.5 mg/mL) at Day-7

Results

TABLE XXXVIII – Process and Size

	F-73	F-74	F-75
Passes	200	200	200
Size at T0	430 nm	482.33	807 nm
Size at Day 1	638 nm	602.7 nm	576 nm
Size at Day 7	474 nm	485 nm	186 nm
Observation under microscope	Aggregated particles	Uniformly separated particles	Aggregated particles and phase separated

TABLE XXXIX – HPLC (Method #1)

Peak Area (% of total)	**RT (min)**	**Std (0.5 mg/mL in NS)**	**F-73**	**F-74**	**F-75**
Picoplatin		91.7	90.18	88.98	80.13
Aqua 1	4.6	4.9	5.59	6.12	9.81
Aqua 2	9.09	3.4	4.23	4.70	9.62
Unk#1	5.7	0	0	0.24	0
Unk#2	6.2	0	0	0	0.88
Total		100.0	100.01	100.03	100.43

*Oil phase (supernatent) contained no picoplatin, as determined by HPLC.

Figure 17 shows HPLC traces, from the top down: 0.5 mg/mL standard in normal saline, F73- picoplatin in MCT, F74- picoplatin in MCT and PL90G, and F75- picoplatin in MCT and Polysorbate 80.

Figure 18 shows zoomed-in views of the HPLC traces of Figure 17 From the top down: 0.5 mg/mL standard in NS, F73- picoplatin in MCT, F74- picoplatin in MCT and PL90G, and F75- picoplatin in MCT and Polysorbate 80.

Example 14: Preparation of 50% w/w picoplatin suspension in MCT and oils.

Objective:

%To prepare final concentration of 50% w/w picoplatin suspension in oils. To compare microfluidization efficiency in oils with different viscosity

TABLE XL – Materials

Composition (% w/w)

Compound	F-76	F-77	F-78	F-79
Picoplatin	10	10	10	10
Miglyol MCT	85			
Ethly oleate		85		
Capmul MCM			85	
Soybean oil, super refined				85
PL-90	5	5	5	5
Normal saline	10			
Total	110	100	100	100

Composition (g/tube)

Compound	F-76	F-77	F-78	F-79
Picoplatin	3	3	3	3
Miglyol MCT	25.5	0	0	0
Ethyl oleate	0	25.5	0	0
Capmul MCM	0	0	25.5	0
Soybean oil, super refined	0	0	0	25.5
PL-90	1.5	1.5	1.5	1.5
Normal saline	3	0	0	0
Total	33	30	30	30

Procedure:

Weigh out Picoplatin into a 50 mL Falcon tube. Record weight. Add oil and PL90. Record weight. Mix using a high shear mixer, IKA @ 5 setting for 3 minutes

Microfluidize using Z-chamber for 200 passes. Record the pass# and final particle size. Let the sample settle down and remove 90% of sample weight of supernatant to obtain 50% w/w suspension. HPLC for purity. Store at 2-8°C.

Results:

F76 formed large aggregates and was not able to be microfludized. However, small amount of sample with additional amount of PL90 added (double amount) was tested and it appeared to have smaller particle size and possibly can be microfludized. It will be tested in the next study.

F79 formed large aggregates and was not able to be microfludized.

F78 became a waxy semi-solid and therefore, could not be processed by either high-shear or microfluidization.

F77 was the only formulation that could be microfludized. The particle size after microfluidization for 200 passes is 919 nm by LLS.

TABLE XLI – Purity% by HPLC (Method #1) for F77

Peak Area (% of total)	**RT (min)**	**Std (0.5 mg/mL in NS)**	**F-77**
Picoplatin	7.6	91.9	77.1
Aqua 1	4.7	3.5	10.6
Aqua 2	10.3	4.4	10.8
Unk#1	4.3	0.2	1.5
Total		100.0	100.0

Example 15: Preparation of 50% w/w picoplatin suspension in MCT oil.

Objective

To prepare final concentration of 50% w/w picoplatin suspension in oil. To test microfluidization efficiency with normal saline

TABLE XLII – Materials:

Composition (% w/w)	
Compound	**F-80**
Picoplatin	10
Miglyol MCT	80
PL-90	10
Normal saline	10
Total	110

Composition (g/tube)	
Compound	**F-80**
Picoplatin	3
Miglyol MCT	24
PL-90	3
Normal saline	3
Total	33

Procedure:

Weigh out Picoplatin into a 50 mL Falcon tube. Record weight.

Add oil, PL90, and N.S. Record weight.

Mix using a high shear mixer, IKA @ 5 setting for 3 minutes

Microfluidize using Z-chamber for 200 passes. Record final particle size

Let the sample settle down and remove 90% of sample weight of supernatant to obtain 50% w/w suspension.

HPLC for purity

Store at 2-8°C.

Results:

F80 was able to be microfluidized. The particle size after microfluidization for 200 passes is 554 nm by LLS.

TABLE XLIII – Purity% by HPLC (Method #1) for F80

Peak Area (% of total)	**RT (min)**	**Std (0.5 mg/mL in NS)**	**F-80**
Picoplatin	7.6	91.9	72.6
Aqua 1	4.7	3.5	12.2
Aqua 2	10.3	4.4	13.1
Unk#1	4.3	0.2	2.0
Total		100.0	99.9

Figure 19 shows representative HPLC chromatograms. From top down: 0.5 mg/mL standard in normal saline, F77- picoplatin in Ethyl Oleate and PL90, F80- picoplatin in MCT, PL90G and normal saline.

Figure 20 shows representative HPLC chromatograms, enlarged. From top down: 0.5 mg/mL standard in normal saline, F77- picoplatin in Ethyl Oleate and PL90, F80- picoplatin in MCT, PL90G and normal saline.

Example 16: Preparation of 50% w/w picoplatin suspension in Ethyl Oleate.

Objective

To prepare final concentration of 50% w/w picoplatin suspension in ethyl oleate at pico:PL90 ratio of 1:1 (wt).

TABLE XLIV – Materials

Composition (% w/w)		
Compound	**Supplier Grade**	**F-81**
Picoplatin		10
Ethyl oleate		80
PL-90		10
Total		100

Composition (g/tube)		
Compound	**lot**	**F-81**
Picoplatin		3
Ethyl oleate		24
PL-90		3
Total		30

Procedure:

Weigh out Picoplatin into a 50 mL Falcon tube. Record weight. Add oil and PL90. Record weight. Mix using a high shear mixer, IKA @ 5 setting for 3 minutes.

Microfluidize using Z-chamber for 2000 strokes. Record the pass# and final particle size. Let the sample settle down and remove 21 g (90% of sample weight) of supernatant to obtain 50% w/w suspension. HPLC for purity Store at 2-8°C.

Results:

F81 can be microfluidized. The particle size after microfluidization for 200 passes is 586 nm by LLS.

TABLE XLV – Purity% by HPLC for F81

Peak Area (% of total)	RT (min)	Std (0.5 mg/mL in NS)	F-81
Picoplatin	7.8	94.8	86.5
Aqua 1	4.7	2.2	6.7
Aqua 2	10.3	2.9	6.6
Unk#1	4.3	0.0	0.3
Unk#2	16.5	0.1	0.0
Total		100.0	100.01

Figure 21 shows representative HPLC Chromatograms. From top down: 0.5 mg/mL picoplatin standard in normal saline and 0.5 mg/mL F81-picoplatin in PL90 and EO in normal saline.

Figure 22 shows representative HPLC chromatograms, enlarged. From top down: 0.5 mg/mL picoplatin standard in normal saline and 0.5 mg/mL F81-picoplatin in PL90 and EO in normal saline.

TABLE XLVI – Picoplatin Oil Nano-Suspension Summary

	PL90:Pico	Pass#	Size (nm)	Observation
F74 in MCT	1:1	200	482	Uniformly separated particles
F77 in EO	1:2	200	919	Uniformly separated particles.
F80 in MCT w/ NS	1:1	200	554	Uniformly separated particles
F81 in EO	1:1	200	586	Uniformly separated particles.

All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that

the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

Claims

What is claimed is:

1. A formulation for picoplatin adapted for oral administration of the picoplatin, the formulation comprising:
(a) a self-emulsifying formulation containing picoplatin wherein the picoplatin is in a nanoparticulate or microparticulate form,
(b) a plurality of stabilized picoplatin nanoparticles,
(c) a picoplatin solid dispersion in a water-dispersible matrix material, or
(d) a nanoparticulate picoplatin suspension in an oil,
or any combination thereof.

2. The formulation of claim 1, the formulation comprising the self-emulsifying formulation containing picoplatin, wherein the self-emulsifying formulation is prepared by a solvent method; the plurality of picoplatin nanoparticles, wherein the nanoparticles are stabilized with casein or a caseinate and are prepared by microfluidization or high-shear mixing; the picoplatin solid dispersion in a water-dispersible matrix material, wherein the dispersion is prepared by a hot melt method; or the nanoparticulate picoplatin suspension in oil, wherein the oil comprises a medium chain triglyceride or in a fatty ester, or any combination thereof.

3. The formulation of claim 1 or 2 comprising a self-emulsifying formulation containing picoplatin.

4. The formulation of claim 3 wherein the self-emulsifying formulation is prepared by a solvent method.

5. The formulation of claim 3 wherein the self-emulsifying formulation comprises an oil, and an emulsifier comprising a lecithin, a surfactant, a PEG, or any combination thereof.

6. The formulation of any one of claims 3-5 wherein the self-emulsifying formulation comprises at least about 10% w/w, or at least about 5% w/w, of the picoplatin.

7. The formulation of any one of claims 3-5 further comprising a first solvent.

8. The formulation of claim 7, wherein the first solvent comprises a dipolar aprotic solvent, a polyethylene glycol, a polyethyleneglycol ether, a polyethyleneglycol derivative of a mono- or di-glyceride, or any combination thereof.

9. The formulation of claim 7 wherein the first solvent comprises a polyethyleneglycol derivative of a mono- or di-glyceride.

10. The formulation of claim 5 wherein the oil comprises a medium chain triglyceride, castor oil, a medium chain mono-glyceride, a medium chain di-glyceride, an edible vegetable oil, peanut oil, cottonseed oil, or soybean oil, or any combination thereof.

11. The formulation of claim 5 wherein the lecithin comprises a high phosphatidylcholine content lecithin, a low phosphatidylcholine content lecithin, or any combination thereof.

12. The formulation of claim 5 wherein the PEG comprises PEG-400.

13. The formulation of claim 5 wherein the surfactant comprises Labrasol, Cremophor RH40, Cremophor ELP, Gelucire 44/14, Polysorbate 80 HP, Phospholipon 90G, or Vitamin E TPGS, or any combination thereof.

14. A method of preparation of the formulation of any one of claims 3-5, comprising dissolving picoplatin in a first solvent other than DMSO to provide a

picoplatin solution, then, adding an oil and an emulsifier, wherein the emulsifier comprises a lecithin, a PEG, or a surfactant, or any combination thereof; then, adding a second solvent to dissolve picoplatin solution, the oil and the emulsifier, providing a substantially homogeneous second solution; then, evaporating at least the second solvent and, optionally, the first solvent, from the substantially homogeneous second solution to provide the self-emulsifying formulation.

15. The method of claim 14, wherein the first solvent comprises a dipolar aprotic solvent, a polyethylene glycol, a polyethyleneglycol ether, a polyethyleneglycol derivative of a mono- or di-glyceride, or any combination thereof.

16. The method of claim 14 wherein the first solvent comprises a polyethyleneglycol derivative of a mono- or di-glyceride.

17. The method of claim 14 wherein the second solvent comprises a lower alkanol, such as ethanol.

18. The method of claim 14 wherein the oil comprises a medium chain triglyceride, castor oil, a medium chain mono-glyceride, a medium chain di-glyceride, an edible vegetable oil, peanut oil, cottonseed oil, or soybean oil, or any combination thereof.

19. The method of claim 14 wherein the lecithin comprises a high phosphatidyl-choline content lecithin, a low phosphatidylcholine content lecithin, or any combination thereof.

20. The method of claim 14 wherein the PEG comprises PEG-400.

21. The method of claim 14 wherein the surfactant comprises Labrasol, Cremophor RH40, Cremophor ELP, Gelucire 44/14, Gelucire 50/13, Polysorbate 80 HP, or Vitamin E TPGS, or any combination thereof.

22. The method of claim 14 wherein the picoplatin comprises at least about 10% w/w, or at least about 5% w/w, of the self-emulsifying formulation.

23. A method of treating cancer in a patient in need thereof, comprising administering to the patient the self-emulsifying formulation of any one of claims 1-13, or the formulation prepared by the method of any one of claims 14-22, in a dose, at a frequency, and for a period of time sufficient to provide a beneficial effect to the patient.

24. The formulation of claim 1 or 2 comprising a plurality of stabilized picoplatin nanoparticles.

25. The formulation of claim 24 wherein the picoplatin nanoparticles are stabilized with casein, a caseinate, or lecithin, or any combination thereof.

26. The formulation of claim 24 wherein the picoplatin nanoparticles are prepared by a process comprising high-shear mixing or microfluidization.

27. The formulation of any one of claims 24-26 comprising at least about 10% w/w of the picoplatin on a dry weight basis.

28. The formulation of any one of claims 24-26 wherein the picoplatin nanoparticles have an average particle diameter of less than about 1 micron.

29. The formulation of any one of claims 24-26 wherein the picoplatin nanoparticles have an average particle diameter of less than about 0.5 micron.

30. The formulation of any one of claims 24-26 wherein the picoplatin nanoparticles have an average particle diameter of less than about 0.25 micron.

31. The formulation of any one of claims 24-26 wherein the picoplatin nanoparticles have an average particle diameter of less than about 0.15 micron.

32. A method of preparation of the formulation of claim 24, comprising mixing a stabilizer and an aqueous medium under high-shear conditions or microfluidization conditions, or both, to obtain a uniform dispersion, then adding solid picoplatin and then mixing until an average particle size of the picoplatin is less than about one micron or until crystalline particles are substantially absent, or both, to provide a suspension of the stabilized picoplatin nanoparticles.

33. The method of claim 32 wherein the stabilizer comprises casein or a caseinate, or lecithin.

34. The method of claim 33 wherein the caseinate comprises sodium caseinate.

35. The method of claim 32 further comprising freeze-drying the suspension to obtain a substantially dry powder of the stabilized picoplatin nanoparticles.

36. The method of claim 35 wherein the picoplatin comprises at least about 10% w/w of the substantially dry powder.

37. A method of treating cancer in a patient in need thereof, comprising administering to the patient the formulation comprising stabilized picoplatin nanoparticles of any one of claims 1, 2, or 24-31, or the formulation prepared by the method of any one of claims 32-36, in a dose, at a frequency, and for a period of time sufficient to provide a beneficial effect to the patient.

38. The formulation of claim 1 or 2 comprising a picoplatin solid dispersion in a water-dispersible matrix material.

39. The formulation of claim 38 prepared by a process comprising dispersing of the picoplatin in a melt of the water-dispersible matrix material that then is cooled and solidified.

40. The formulation of claim 38 or 39 comprising at least about 10% w/w picoplatin.

41. The formulation of claim 38 or 39 wherein the water-dispersible matrix material comprises Gelucire 50/13, Gelucire 44/14, Poloxamer 188, SPAN 60, PEG-8000, Kollidon K-90, Vitamin E TPGS, or Compritol 888, or any combination thereof.

42. The formulation of claim 38 or 39 wherein the matrix material is a solid up to temperatures of at least about 20°C or at least about 37°C.

43. The formulation of claim 39 wherein the melt of the water-dispersible matrix material is at a temperature of about 40°C to about 160°C.

44. The formulation of claim 39 wherein the step of dispersing the picoplatin in the melt comprises dissolving the picoplatin in the melt.

45. The formulation of claim 44 wherein the matrix material comprises Gelucire 50/13, Gelucire 44/14, Compritol 888, or Vitamin E TPGS.

46. A method of preparation of the formulation of claim 38 or 39, comprising melting a water-dispersible matrix material at an elevated temperature, then, dispersing solid picoplatin in the melt to provide a dispersed picoplatin composition, then, cooling the composition to provide the picoplatin solid dispersion.

47. The method of claim 46 wherein the step of dispersing the picoplatin in the matrix comprises dissolving the picoplatin in the matrix.

48. The method of claim 46 wherein the formulation comprises at least about 10% w/w of picoplatin.

49. The method of claim 46 wherein the elevated temperature is about 40°C to about 160°C.

50. The method of claim 46 wherein dispersing comprises vortex mixing.

51. The method of claim 46 wherein the cooling the composition comprises cooling the composition to about room temperature or to about human body temperature.

52. A method of treating cancer in a patient in need thereof, comprising administering to the patient the picoplatin solid dispersion in a water-dispersible matrix material of any one of claims 1, 2, or 38-45, or the formulation prepared by the method of any one of claims 46-51, in a dose, at a frequency, and for a period of time sufficient to provide a beneficial effect to the patient.

53. The formulation of claim 1 or 2 comprising a nanoparticulate suspension of picoplatin in a medium chain triglyceride or in a fatty ester.

54. The formulation of claim 53 comprising about 20% to about 70% w/w picoplatin.

55. The formulation of claim 53 prepared by a process comprising microfluidization of the picoplatin in the medium chain triglyceride or the fatty ester by high shear mixing.

56. The formulation of claim 53 wherein the medium chain triglyceride is a triglyceride of capric acid, caprylic acid, or a combination thereof.

57. The formulation of claim 53 wherein the medium chain triglyceride is Miglyol MCT.

58. The formulation of claim 53 further comprising a lecithin.

59. The formulation of claim 58 wherein the lecithin is Phospholipon 90G.

60. The formulation of claim 53 further comprising sorbitan mono-9-octadecanoate PEG ether.

61. The formulation of claim 53 further comprising Polysorbate 80.

62. A method of preparation of the formulation of claim 53, comprising combining solid picoplatin and a medium chain triglyceride or a fatty ester, then, under conditions comprising high shear mixing, dispersing the picoplatin in the medium chain triglyceride or fatty ester, wherein the picoplatin comprises about 20% to about 70% w/w of the medium chain triglyceride or fatty ester, to provide the nanoparticulate dispersion.

63. The method of claim 62 comprising further combining a lecithin.

64. The method of claim 62 comprising further combining a sorbitan mono-9-octadecanoate PEG ether.

65. The method of claim 62 further comprising, after high shear mixing, allowing the dispersion to settle for a period of time, then removing supernatant liquid to provide a concentrated nanoparticulate dispersion of picoplatin.

66. A method of treating cancer in a patient in need thereof, comprising administering to the patient the picoplatin solid dispersion in a water-dispersible matrix material of any one of claims 53-61, or the formulation prepared by the method of any one of claims 62-65, in a dose, at a frequency, and for a period of time sufficient to provide a beneficial effect to the patient.

67. The method of any one of claims 23, 37, 52, or 66, wherein the cancer is lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer, renal cancer, stomach and other gastrointestinal (GI) cancers, mesothelioma, melanoma, peritoneal lymphoepithelioma, endometrial cancer, glioblastoma, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, esophageal cancer, uterine cancer, endometrial cancer, prostate cancer, thymic cancer, breast cancer, head and neck cancer, liver cancer, sarcomas, including Kaposi's sarcoma, carcinoid tumors, other solid tumors, lymphomas (including non-Hodgkins lymphoma, NHL), leukemias, or a bone-associated cancer.

68. The method of claim 67 further comprising administration of an effective amount of a second anticancer agent to the patient.

69. The method of claim 68 wherein the second anticancer agent comprises a taxane, a tyrosine kinase and/or a growth factor receptor inhibitor, a cephalotaxine analog, an anti-metabolite, a protein kinase inhibitor, an anthracyclin, a *Vinca* alkaloid, a podophyllotoxin analog, a growth factor inhibitor, an inhibitor of cell cycle kinases, a cytostatic agent, an alkylating agent, or radiation, or a combination thereof.

70. The use of a formulation of any one of claims 1, 2, 3, 24, 38, or 53, or a formulation prepared by any one of the methods of claims 14, 32, 46, or 62, in the treatment of cancer in a patient in need thereof.

71. The use of claim 70 wherein the cancer comprises lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer, renal cancer, stomach and other gastrointestinal (GI) cancers, mesothelioma, melanoma, peritoneal lymphoepithelioma, endometrial cancer, glioblastoma, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, esophageal cancer, uterine cancer, endometrial cancer, prostate cancer, thymic cancer, breast cancer, head and neck cancer, liver cancer, sarcomas, including Kaposi's sarcoma, carcinoid tumors, other solid tumors, lymphomas (including non-Hodgkins lymphoma, NHL), leukemias, or a bone-associated cancer.

72. The use of claim 70 or 71 wherein the patient is administered a second anticancer agent.

73. The use of claim 72 wherein the second anticancer agent comprises a taxane, a tyrosine kinase and/or a growth factor receptor inhibitor, a cephalotaxine analog, an anti-metabolite, a protein kinase inhibitor, an anthracyclin, a *Vinca* alkaloid, a podophyllotoxin analog, a growth factor inhibitor, an inhibitor of cell cycle kinases, a cytostatic agent, an alkylating agent, or radiation, or a combination thereof.

74. An oral formulation comprising picoplatin and a carrier, wherein the formulation is selected from the group consisting of:

(a) a self-emulsifying formulation containing picoplatin wherein the picoplatin is in a nanoparticulate or microparticulate form,

(b) a plurality of stabilized picoplatin nanoparticles,

(c) a picoplatin solid dispersion in a water-dispersible matrix material,

(d) a nanoparticulate picoplatin suspension in an oil, and

(e) a substantially water-soluble capsule shell, the capsule shell enclosing a formulation comprising a substantially dry powder comprising about 10 to 60 wt% particulate picoplatin, a substantially water-soluble, water-dispersible, or water-

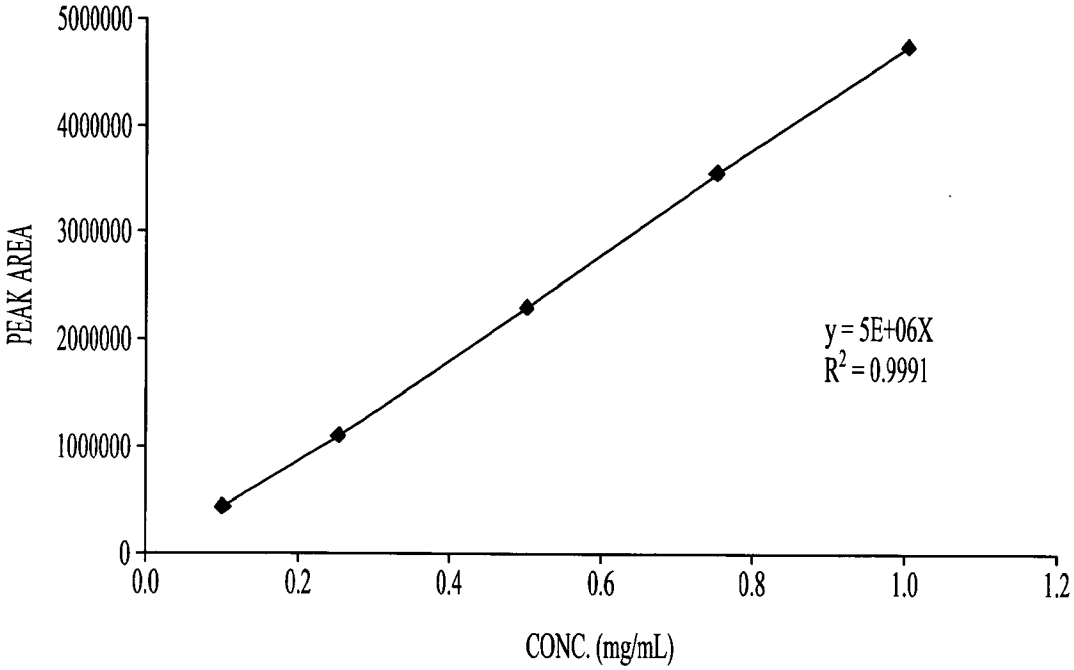
absorbing carbohydrate, and an effective amount of up to about 5 wt% of a lubricant,

for use in combination with an effective amount of a second anticancer agent in the treatment of cancer in a patient in need thereof.

75. The oral formulation of claim 74, wherein the cancer comprises lung cancer including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), kidney cancer, bladder cancer, renal cancer, stomach and other gastrointestinal (GI) cancers, mesothelioma, melanoma, peritoneal lymphoepithelioma, endometrial cancer, glioblastoma, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, esophageal cancer, uterine cancer, endometrial cancer, prostate cancer, thymic cancer, breast cancer, head and neck cancer, liver cancer, sarcomas, including Kaposi's sarcoma, carcinoid tumors, other solid tumors, lymphomas (including non-Hodgkins lymphoma, NHL), leukemias, or a bone-associated cancer.

76. The oral formulation of claim 74 or 75, wherein the second anticancer agent comprises a taxane, a growth factor receptor inhibitor, a cephalotaxine analog, an anti-metabolite, a protein kinase inhibitor, an anthracyclin, a *Vinca* alkaloid, a podophyllotoxin analog, an alkylating agent, or radiation, or a combination thereof.

77. The oral formulation of claim 74 or 75, wherein the second anticancer agent comprises Topotecan, Irinotecan, etoposide, paclitaxel, docetaxel, bevacizumab, cetuximab, erlotinib, sunitinib, gemcitabine, 5-fluorouracil with or without leucovorin, vinorelbine, amrubicin, doxorubicin, liposomal doxorubicin, Doxil®, radiation, or a combination thereof.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PEAK AREA
y = 5E+06X
R2 = 0.9991
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0.2
0.4
0.6
0.8
1.0
1.2
CONC. (mg/mL)

FIG. 1

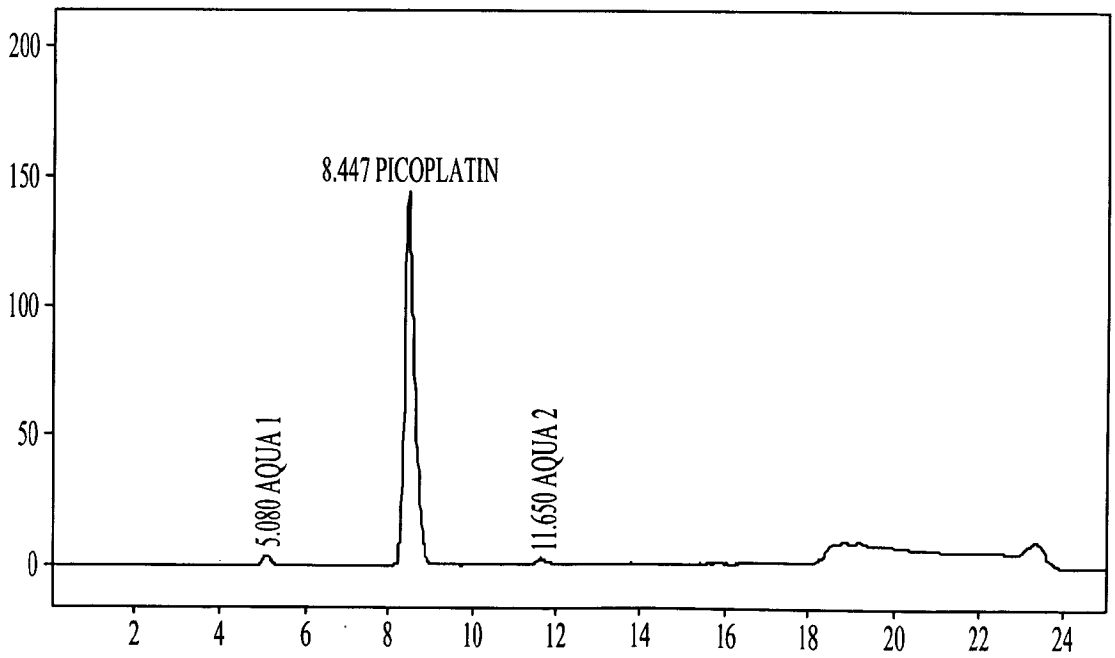
200
150
100
50
0
8.447 PICOPLATIN
5.080 AQUA 1
11.650 AQUA 2
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 2

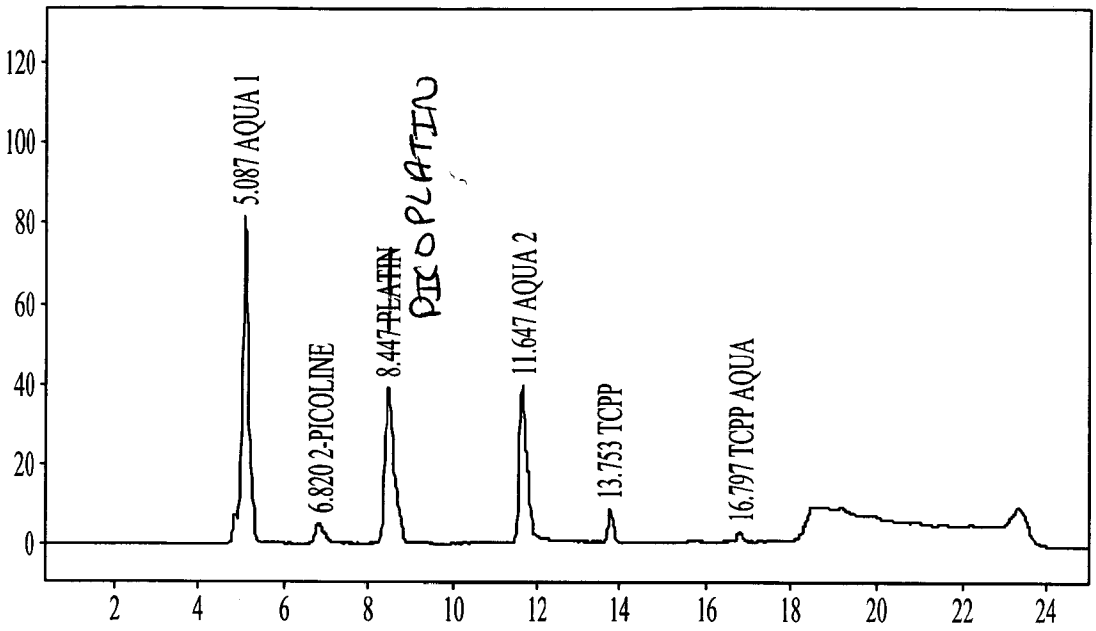
5.087 AQUA 1
6.820 2-PICOLINE
8.447 PICOPLATIN
11.647 AQUA 2
13.753 TCPP
16.797 TCPP AQUA

FIG. 3

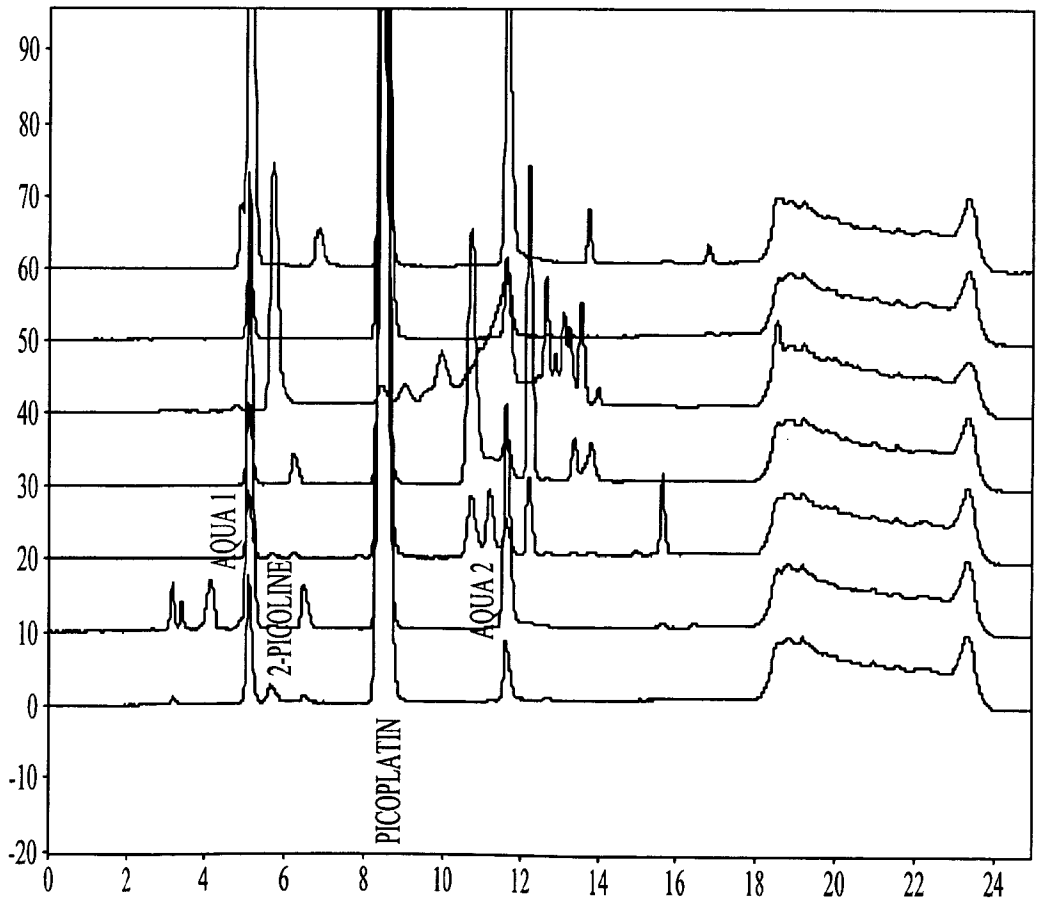
AQUA 1
2-PICOLINE
PICOPLATIN
AQUA 2

FIG. 4

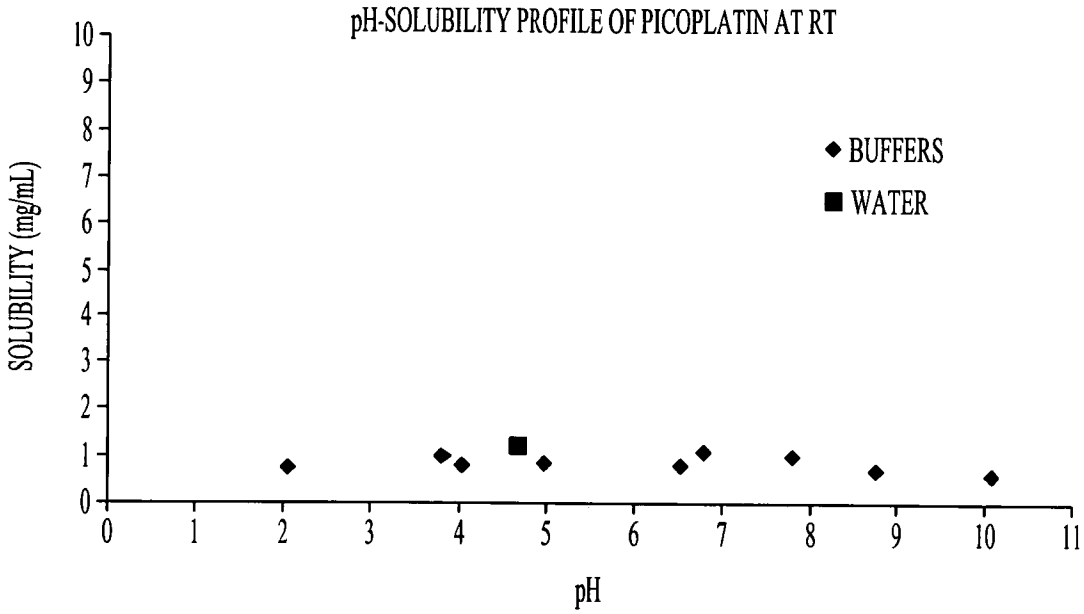
pH-SOLUBILITY PROFILE OF PICOPLATIN AT RT
SOLUBILITY (mg/mL)
pH
BUFFERS
WATER
0
1
2
3
4
5
6
7
8
9
10
11

FIG. 5

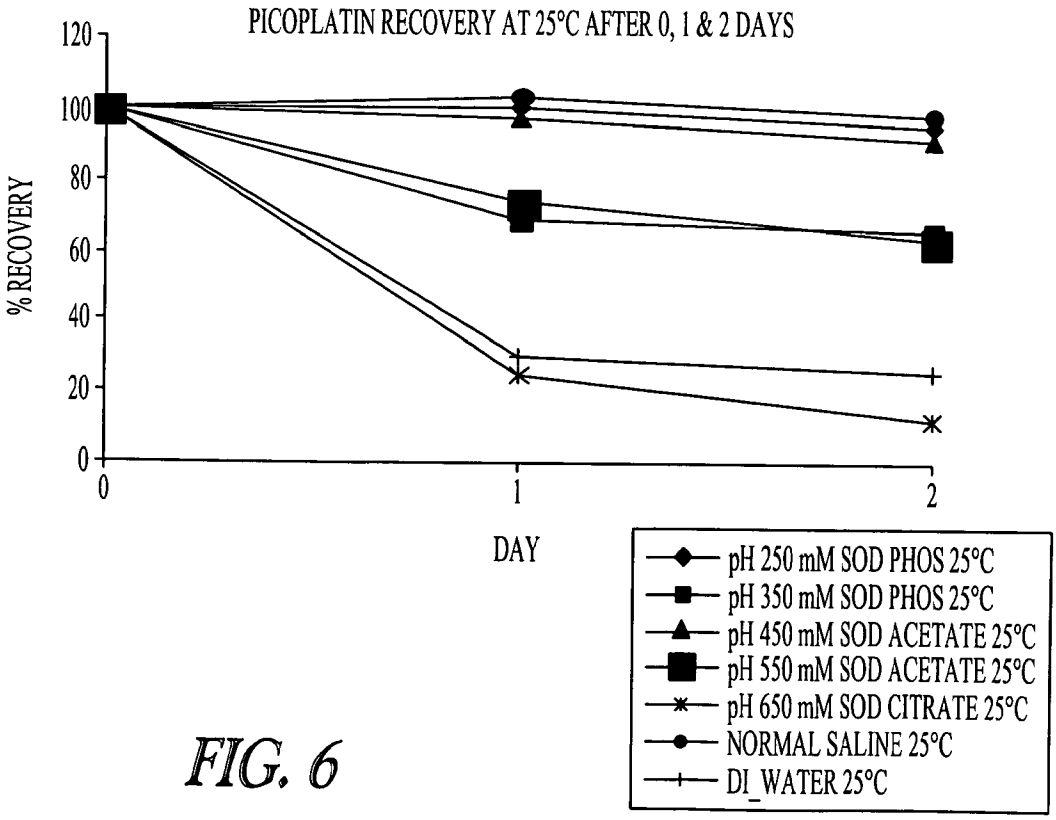
PICOPLATIN RECOVERY AT 25°C AFTER 0, 1 & 2 DAYS
% RECOVERY
DAY
pH 250 mM SOD PHOS 25°C
pH 350 mM SOD PHOS 25°C
pH 450 mM SOD ACETATE 25°C
pH 550 mM SOD ACETATE 25°C
pH 650 mM SOD CITRATE 25°C
NORMAL SALINE 25°C
DI_WATER 25°C

FIG. 6

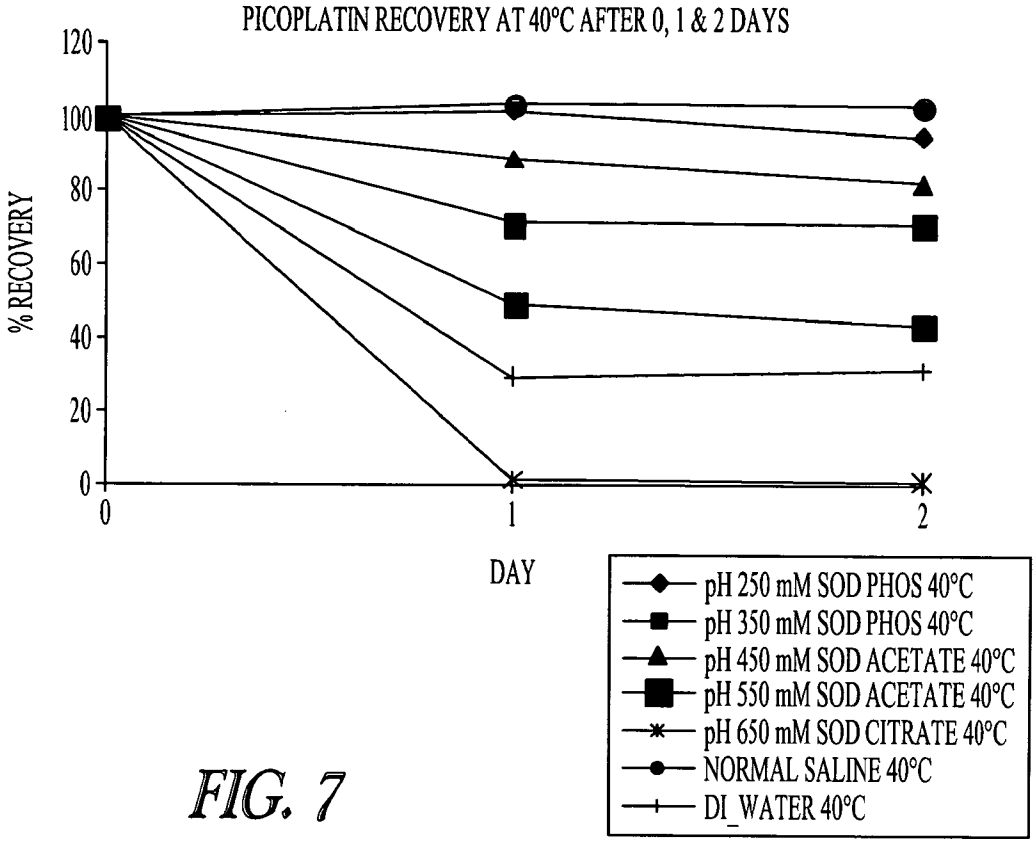
PICOPLATIN RECOVERY AT 40°C AFTER 0, 1 & 2 DAYS
% RECOVERY
120
100
80
60
40
20
0
0
1
2
DAY
pH 250 mM SOD PHOS 40°C
pH 350 mM SOD PHOS 40°C
pH 450 mM SOD ACETATE 40°C
pH 550 mM SOD ACETATE 40°C
pH 650 mM SOD CITRATE 40°C
NORMAL SALINE 40°C
DI_WATER 40°C

FIG. 7

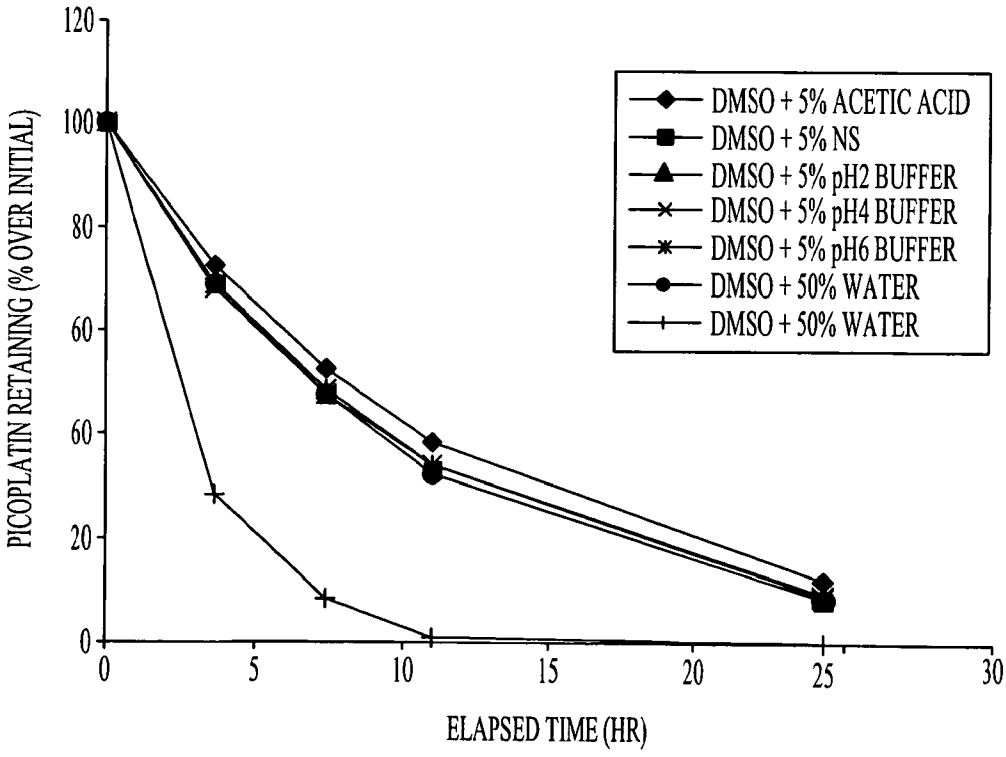
PICOPLATIN RETAINING (% OVER INITIAL)
120
100
80
60
60
20
0
0
5
10
15
20
25
30
ELAPSED TIME (HR)
DMSO + 5% ACETIC ACID
DMSO + 5% NS
DMSO + 5% pH2 BUFFER
DMSO + 5% pH4 BUFFER
DMSO + 5% pH6 BUFFER
DMSO + 50% WATER
DMSO + 50% WATER

FIG. 8

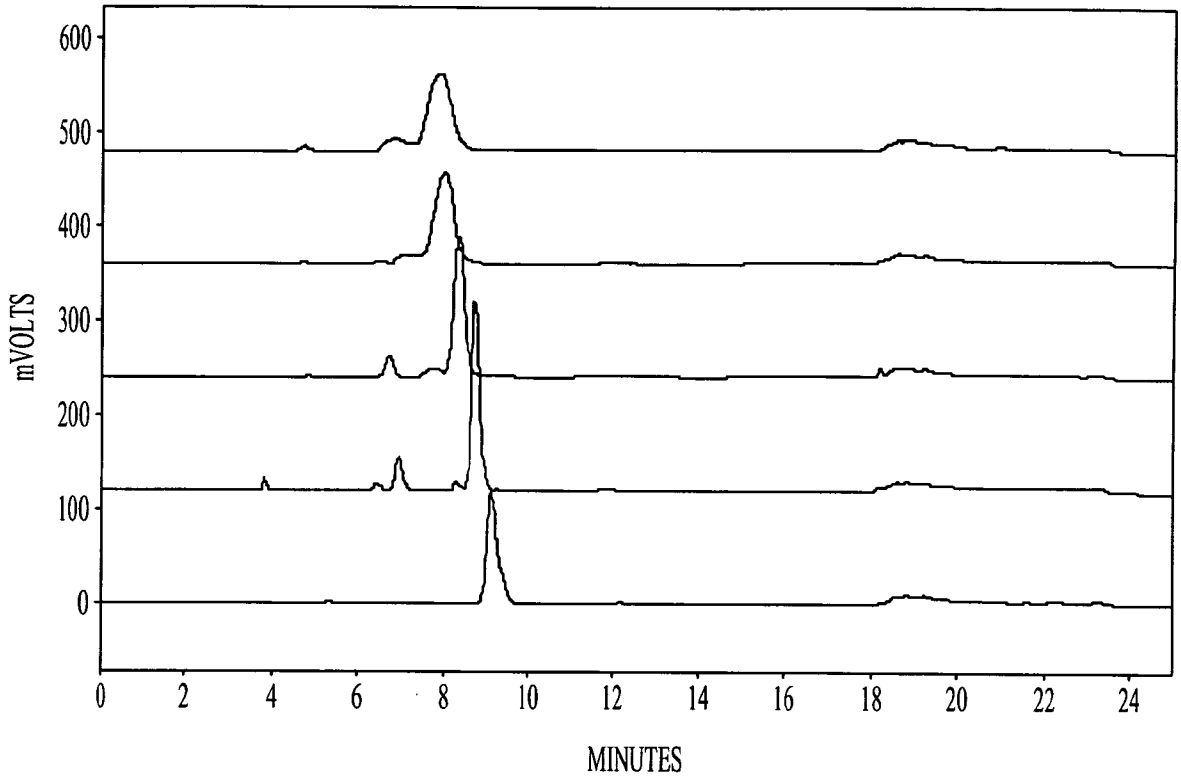
600
500
400
300
200
100
0
mVOLTS
0 2 4 6 8 10 12 14 16 18 20 22 24
MINUTES

FIG. 9

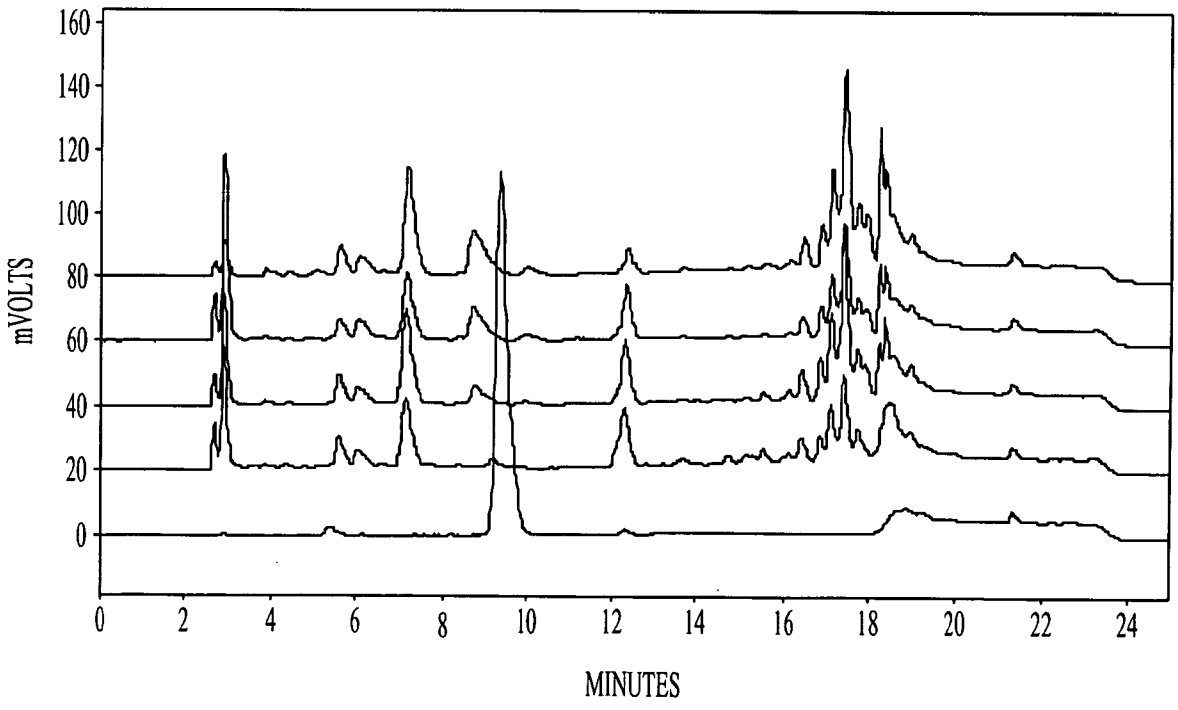
160
140
120
100
80
60
40
20
0
mVOLTS
0 2 4 6 8 10 12 14 16 18 20 22 24
MINUTES

FIG. 10

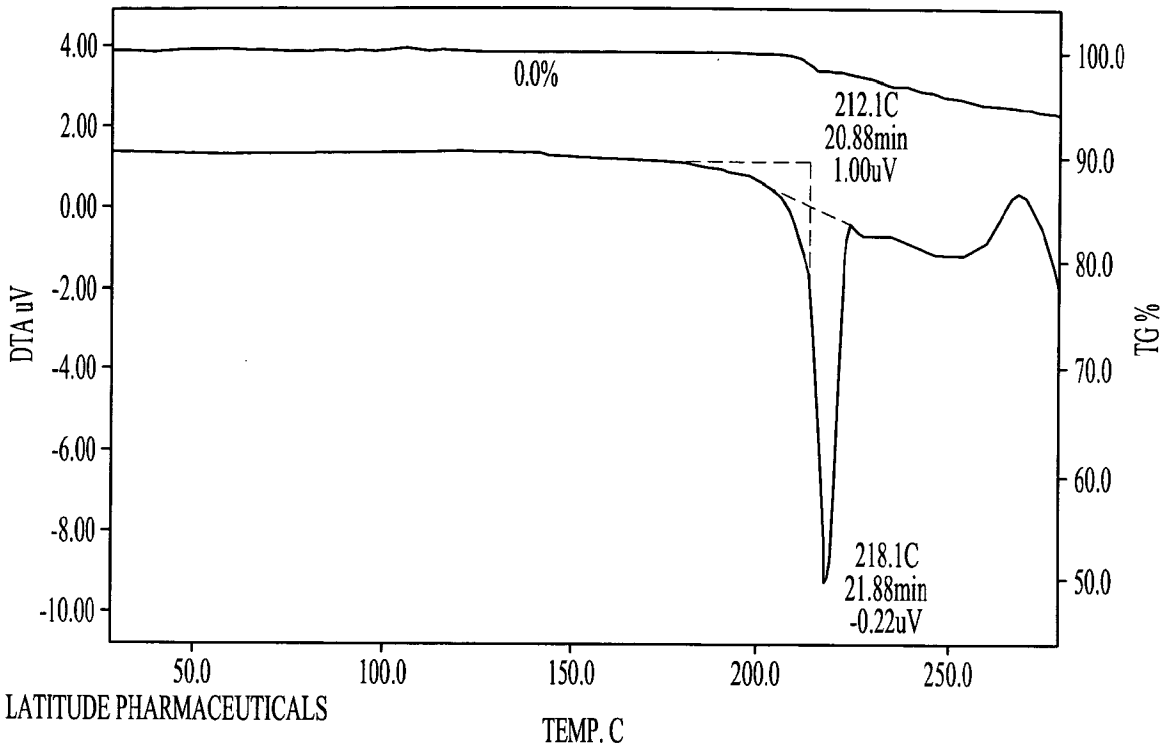
4.00
2.00
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
DTA uV
100.0
90.0
80.0
70.0
60.0
50.0
TG %
0.0%
212.1C
20.88min
1.00uV
218.1C
21.88min
-0.22uV
50.0
100.0
150.0
200.0
250.0
LATITUDE PHARMACEUTICALS
TEMP. C

FIG. 11

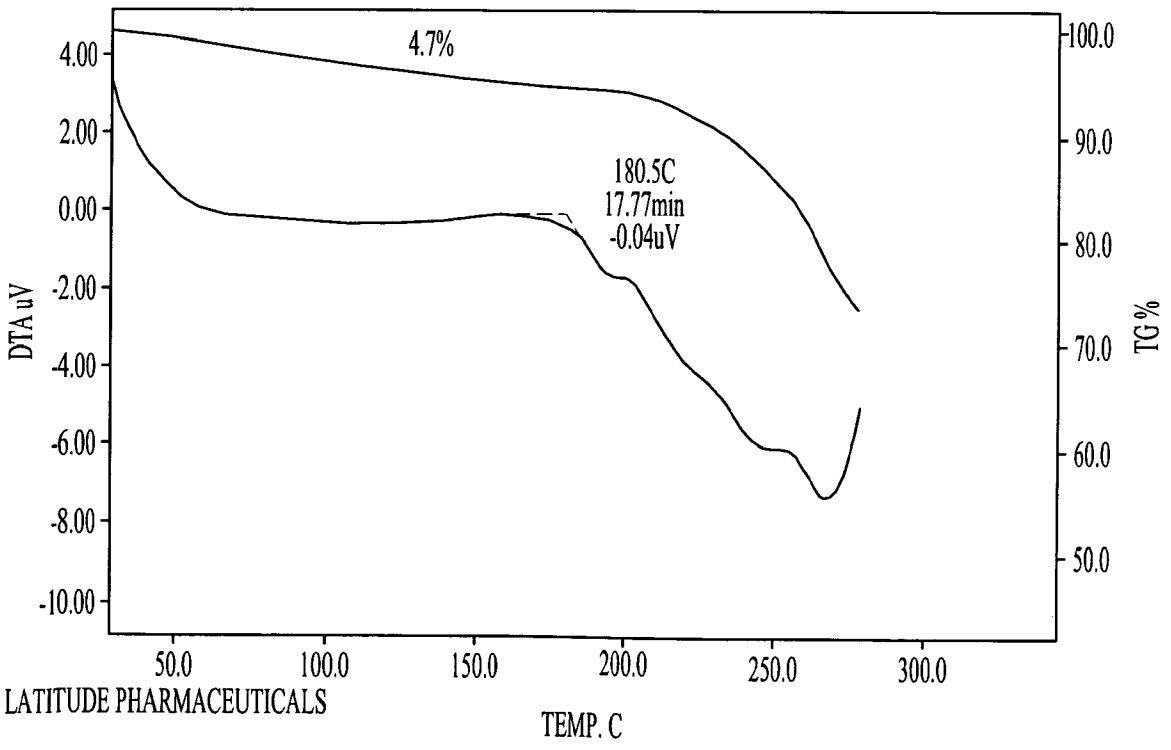
4.00
2.00
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
DTA uV
100.0
90.0
80.0
70.0
60.0
50.0
TG %
4.7%
180.5C
17.77min
-0.04uV
50.0
100.0
150.0
200.0
250.0
300.0
LATITUDE PHARMACEUTICALS
TEMP. C

FIG. 12

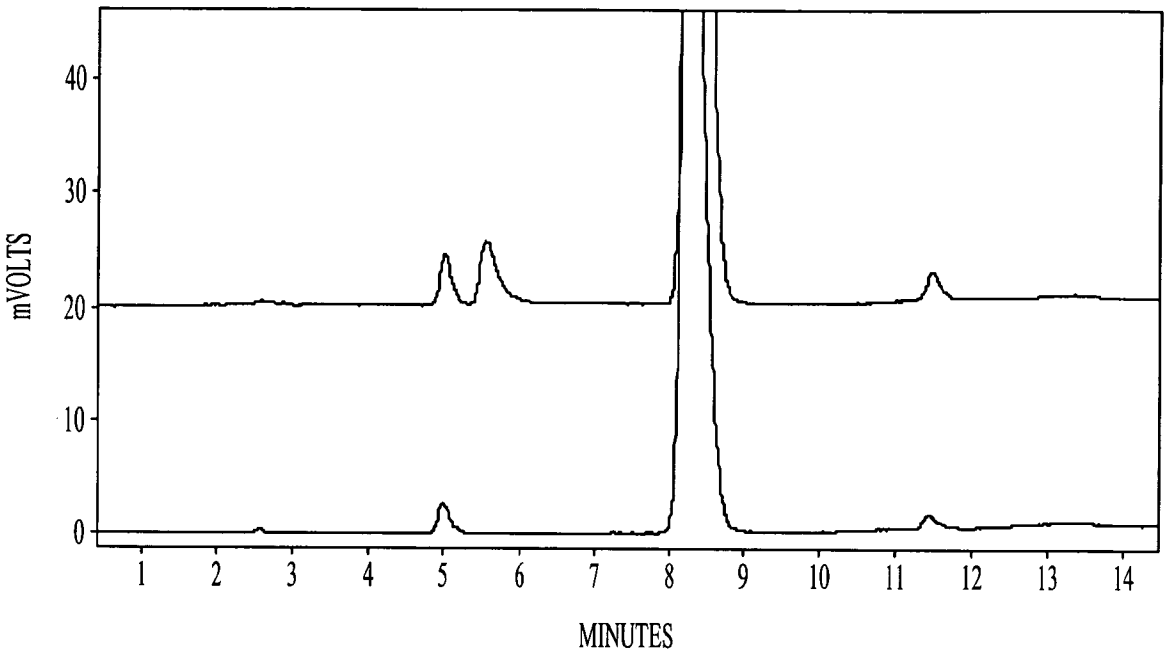
mVOLTS
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
MINUTES

FIG. 13

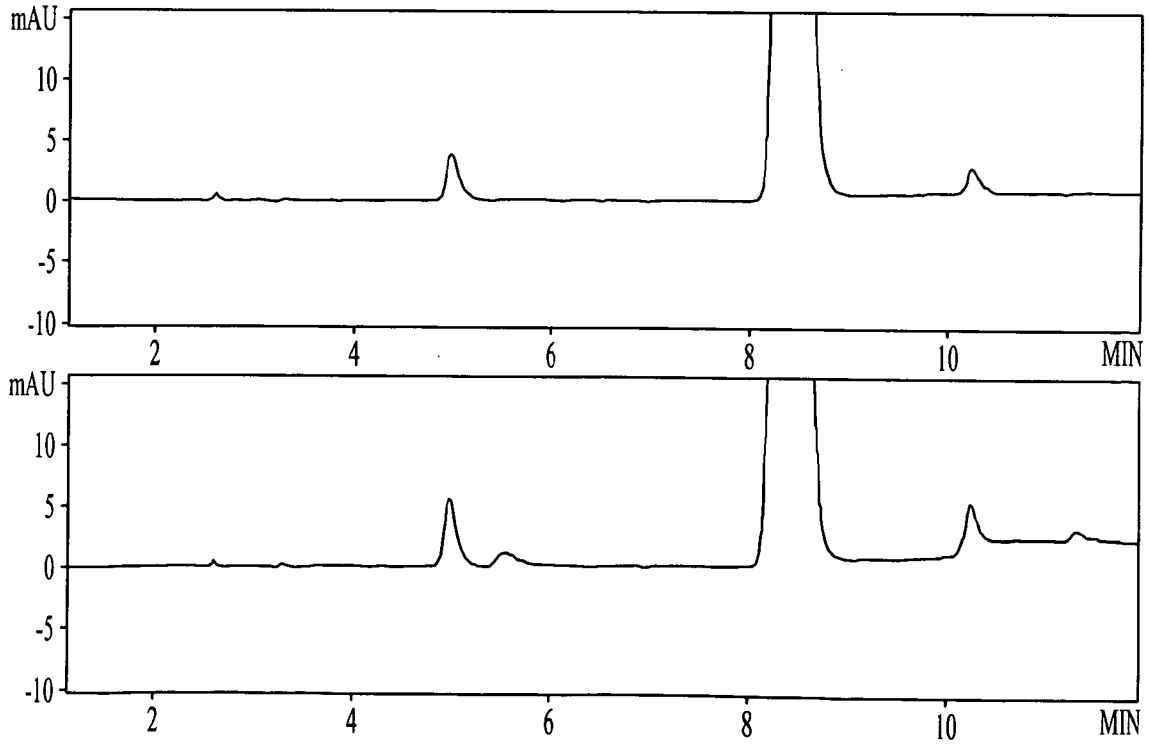
mAU
10
5
0
-5
-10
2 4 6 8 10
MIN
mAU
10
5
0
-5
-10
2 4 6 8 10
MIN

FIG. 14

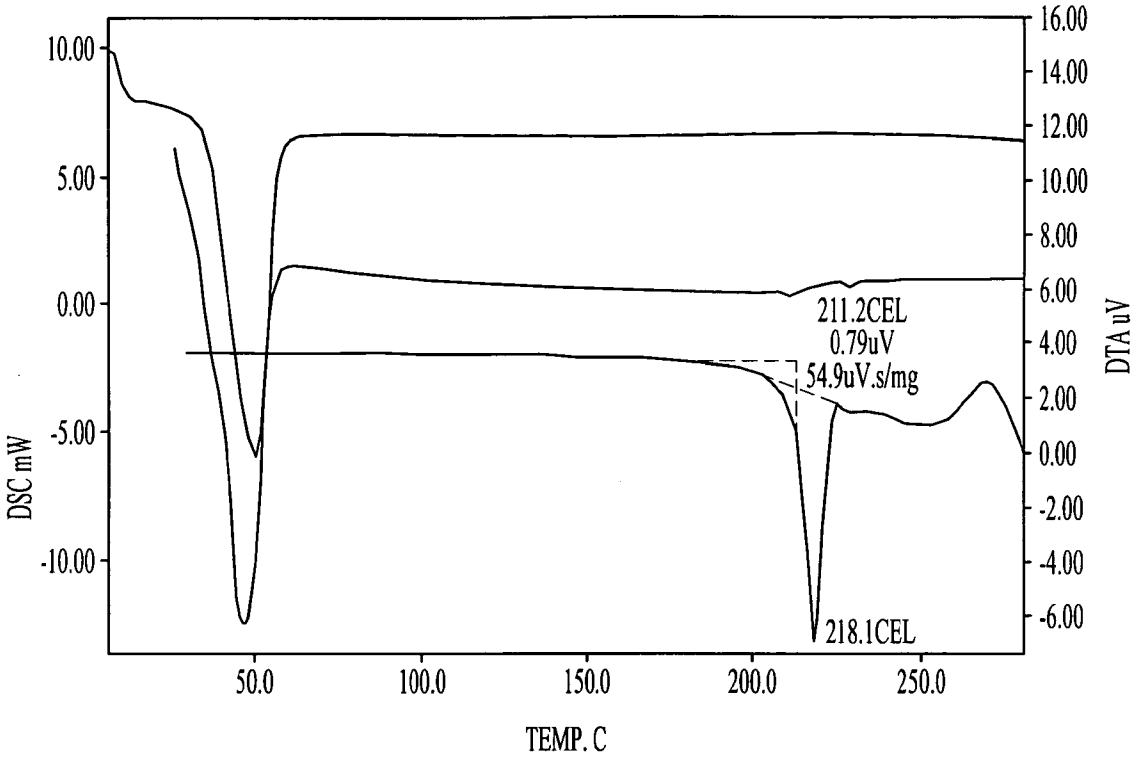
10.00
5.00
0.00
-5.00
-10.00
DSC mW
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
-2.00
-4.00
-6.00
DTA uV
211.2CEL
0.79uV
54.9uV.s/mg
218.1CEL
50.0
100.0
150.0
200.0
250.0
TEMP. C

FIG. 15

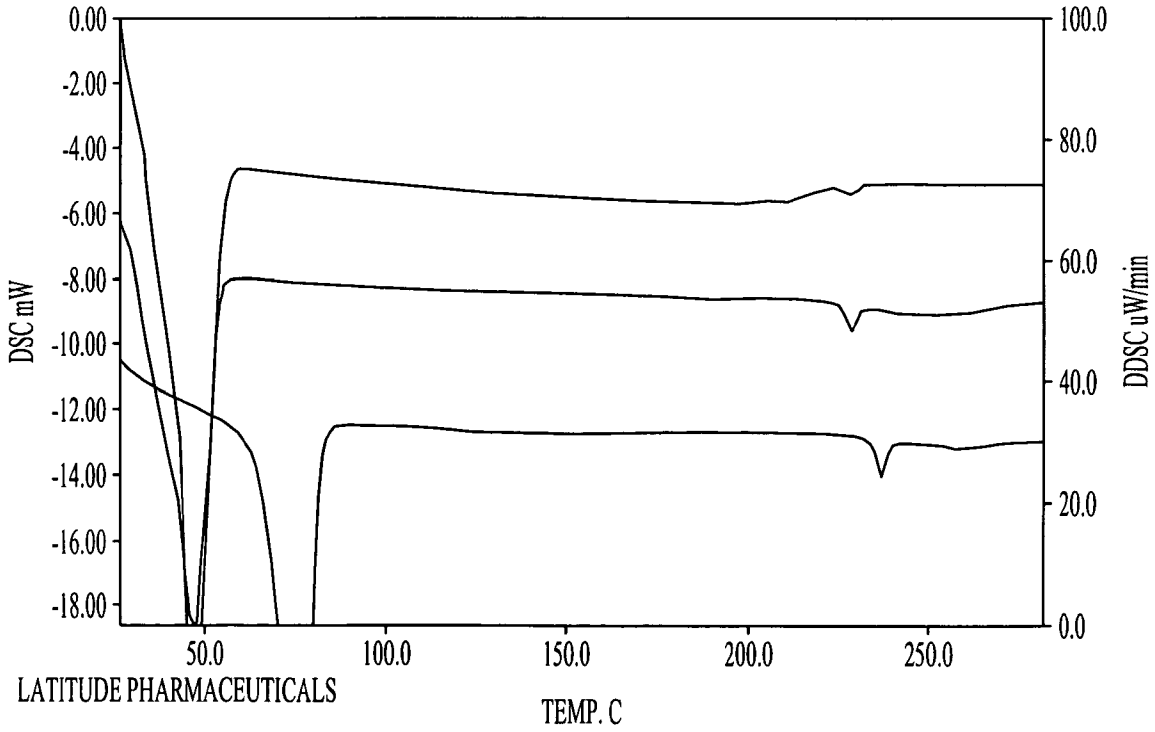
0.00
-2.00
-4.00
-6.00
-8.00
-10.00
-12.00
-14.00
-16.00
-18.00
DSC mW
100.0
80.0
60.0
40.0
20.0
0.0
DDSC uW/min
50.0
100.0
150.0
200.0
250.0
LATITUDE PHARMACEUTICALS
TEMP. C

FIG. 16

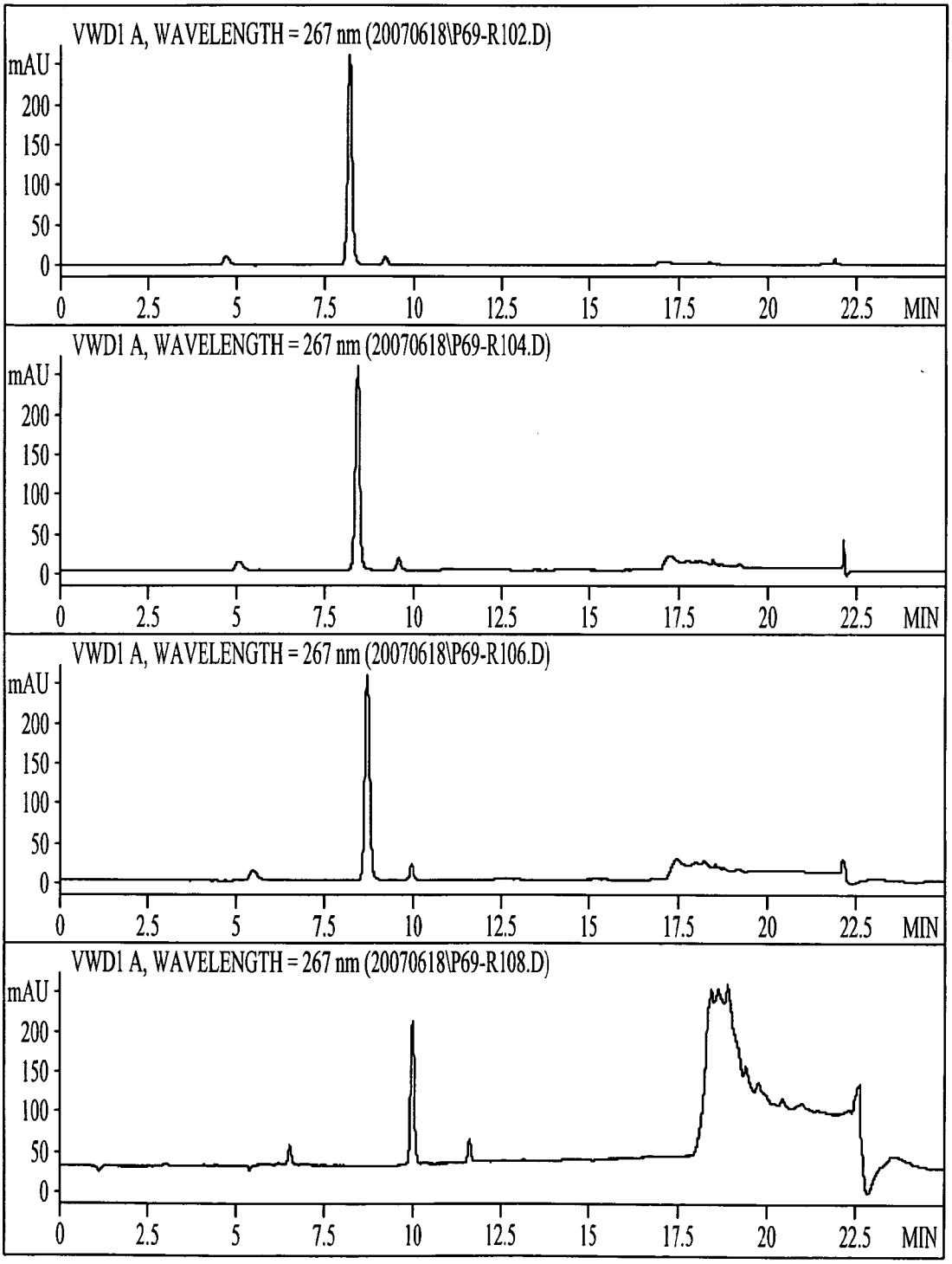
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R102.D)
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R104.D)
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R106.D)
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R108.D)
mAU
200
150
100
50
0
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
MIN

FIG. 17

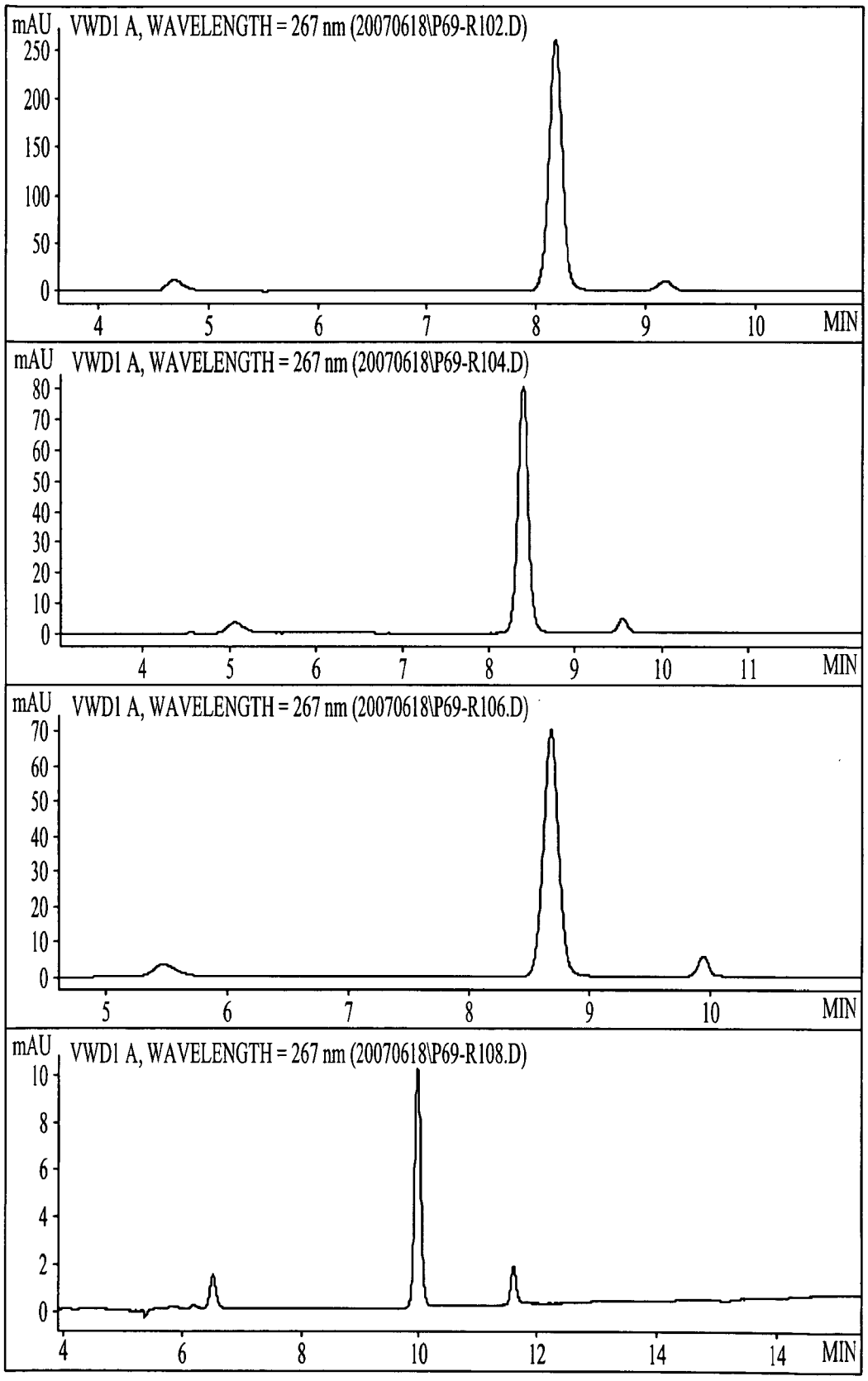
mAU
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R102.D)
250
200
150
100
50
0
4
5
6
7
8
9
10
MIN
mAU
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R104.D)
80
70
60
50
40
30
20
10
0
4
5
6
7
8
9
10
11
MIN
mAU
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R106.D)
70
60
50
40
30
20
10
0
5
6
7
8
9
10
MIN
mAU
VWD1 A, WAVELENGTH = 267 nm (20070618\P69-R108.D)
10
8
6
4
2
0
4
6
8
10
12
14
14
MIN

FIG. 18

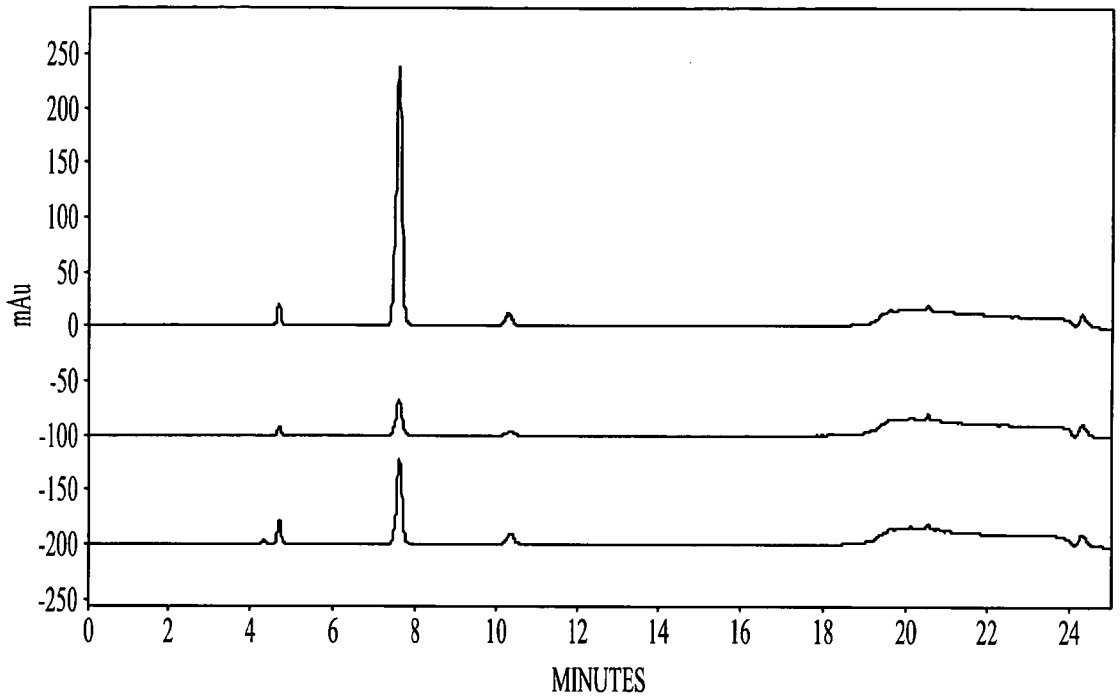
250
200
150
100
50
0
-50
-100
-150
-200
-250
mAu
0
2
4
6
8
10
12
14
16
18
20
22
24
MINUTES

FIG. 19

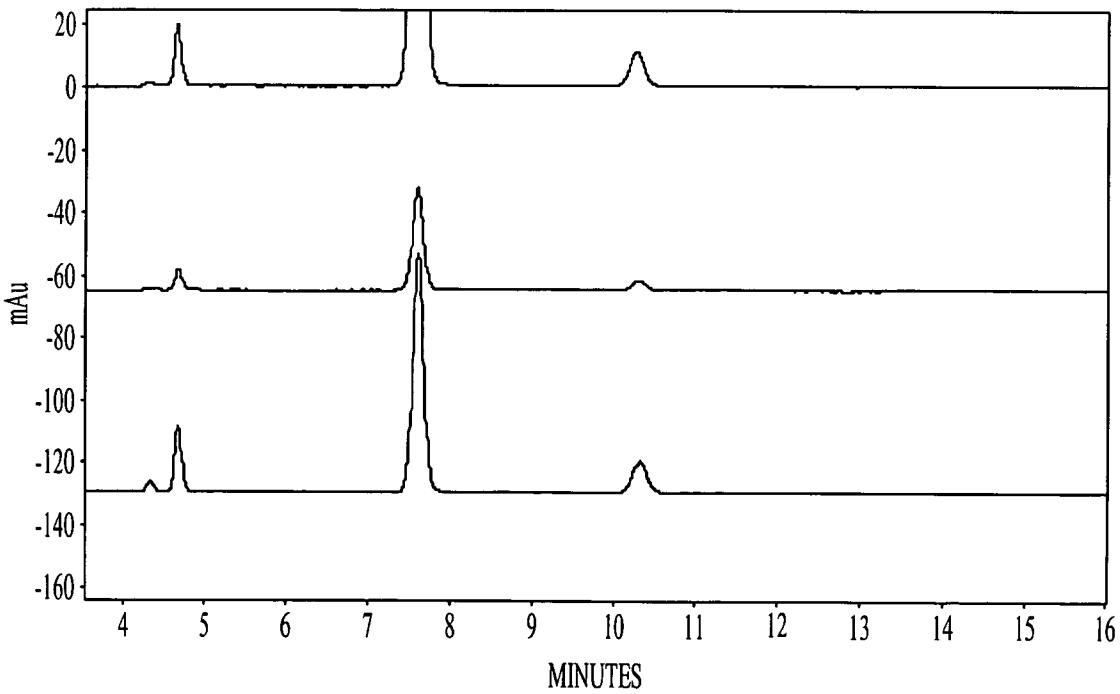
20
0
-20
-40
-60
-80
-100
-120
-140
-160
mAu
4
5
6
7
8
9
10
11
12
13
14
15
16
MINUTES

FIG. 20

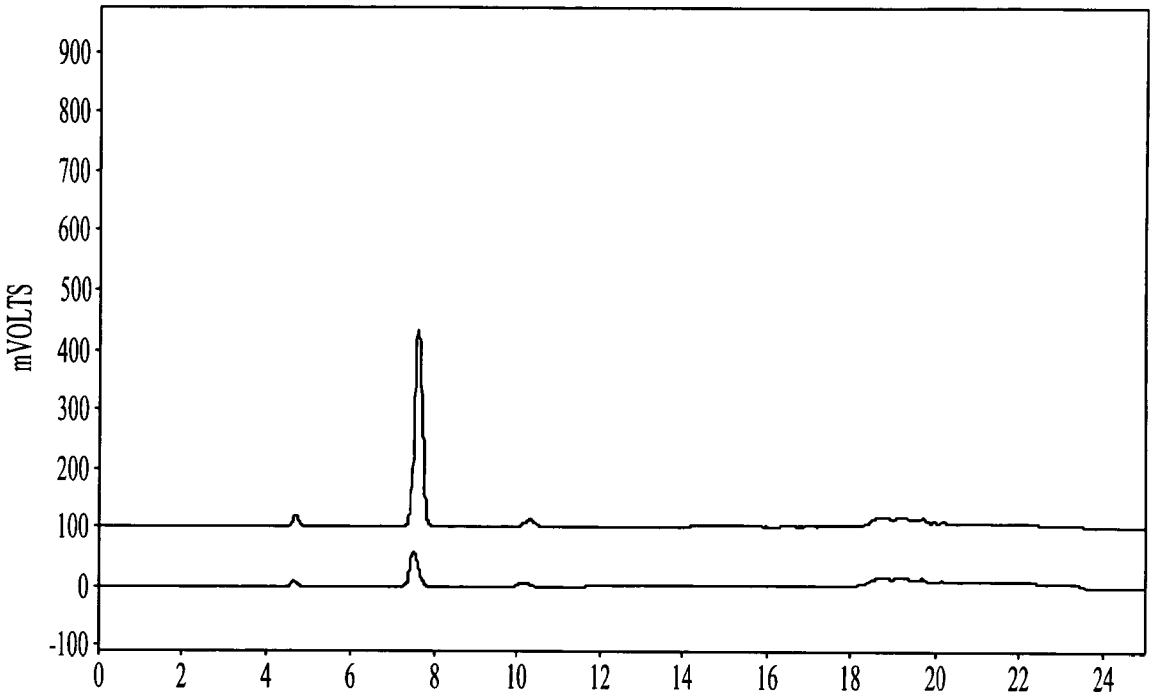
mVOLTS
900
800
700
600
500
400
300
200
100
0
-100
0 2 4 6 8 10 12 14 16 18 20 22 24

FIG. 21

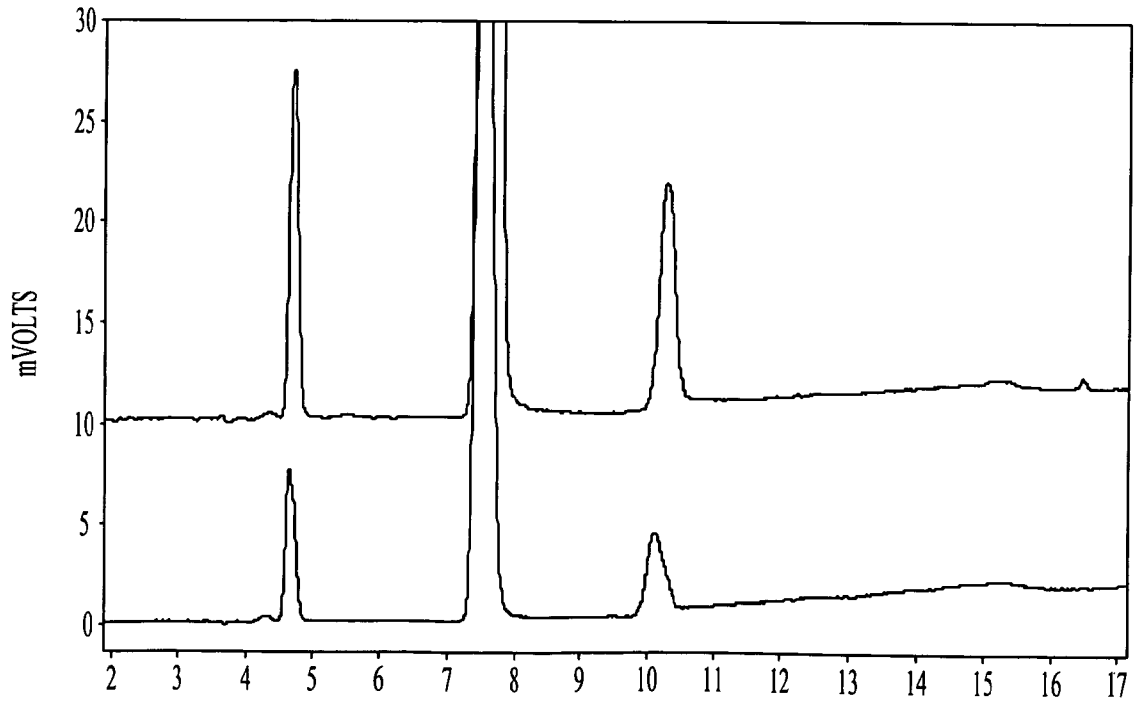
mVOLTS
30
25
20
15
10
5
0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

FIG. 22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/08669

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07F 15/00 (2008.04)
USPC - 556/137
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07F 15/00 (2008.04)
USPC - 556/137

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C07F 17/02; A01N 55/02; A61K 31/28, 31/555 (2008.04)
USPC - 556/136; 514/184,188,492; 546/2

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google
Search Terms Used:
picoplatin, zd0473, amd473, water dispersible matrix, self-emulsifying, caprylic acid, nanoparticulate, microfluidization, Gelucire matrix

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPENLEHAUER et al. "Formation and characterization of cisplatin loaded poly(d,l-lactide) microspheres for Chemoembolization" Clinical Cancer Research. 01 November 1997 (01.11.1997), Vol 3, Issue 11, pages 2063-2074	1-5, 10-13, 24-26, 38-39, 43-45, 53-65, 74-77
Y	RAYNAUD et al. "cis-Amminedichloro(2-methylpyridine) Platinum(II) (AMD473), a Novel Sterically Hindered Platinum Complex: In Vivo Activity, Toxicology, and Pharmacokinetics in Mice" Journal of Pharmaceutical Sciences. August 1986 (08.1986), Vol 75, Issue 8, abstract	1-5, 10-13, 24-26, 38-39, 43-45, 53-65, 74-77
Y	US 5,976,577 A (GREEN et al.) 02 November 1999 (02.11.1999), col 3, 5	2-5, 10-13, 24-26, 53-65
Y	US 5,082,655 A (SNIPES et al.) 21 January 1992 (21.01.1992), col 4	39 and 43-45
Y	US 2006/0078618 A1 (CONSTANTINIDES et al.) 13 April 2006 (13.04.2006), para [0007-0044]	53-65 and 74-77
Y	US 2005/0232952 A1 (LAMBERT et al.) 20 October 2005 (20.10.2005), abstract	3-5 and 10-13
Y	US 2007/0082838 A1 (DE et al.) 12 April 2007 (12.04.2007), para [0129]	24-26
Y	US 7,201,913 B1 (MUGGETTI et al.) 10 April 2007 (10.04.2007), col 8, Table 2	45
Y	US 2002/0102301 A1 (SCHWARZ) 01 August 2002 (01.08.2002), para [0002-0010]	11 and 12
Y	US 2005/0009908 A1 (HEDBERG et al.) 13 January 2005 (13.01.2005), para [0037-0051]	57 and 62-65
Y	US 6,245,349 B1 (YIV et al.) 12 June 2001 (12.06.2001), col 11, ln 52-53	59
Y	WO 2003/103596 A2 (ROMANOWSKI et al.) 18 December 2003 (18.12.2003), para [0086]	60 and 64

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
05 October 2008 (05.10.2008)

Date of mailing of the international search report
09 OCT 2008

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:
Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/08669

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-9, 14-23, 27-37, 40-42, 46-52, and 66-73
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.