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CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-120944- -00004-0000
Fecha: 2008-05-15 14:42:38 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 538 PETICION Folios: 2

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. **06.120.944**

Solicitud del examen de patentabilidad correspondiente a la Patente PCT Entrada en Fase Nacional, para:

"FORMULACION DE IRINOTECAN"

Solicitante: **KABUSHIKI KAISHA YAKULT HONSHA**

SOLICITUD EXAMEN DE PATENTABILIDAD

(CAPITULO I)

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago **No. 08-38.519** de **Mayo 14 de 2008,** correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente PCT Entrada en Fase Nacional, y se continúe con su tramitación.

Señor Jefe,

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C. S. J.
Calle 94 A No. 7 A-09 - Bogotá, D.C.
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Bogotá,
MCA/gcb/P1425

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-120944- -00004-0000

Fecha: 2008-05-15 14:42:38 Dep: 2020 NUECREACIONE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 38,519
FECHA : MAYO 14 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	106619	14/05/2008	6,964,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

177

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-120944

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/041681 A2

(54) Title: LIPID CARRIER COMPOSITIONS WITH ENHANCED BLOOD STABILITY

(57) Abstract: Liposomes that contain at least 10 mol % of a negatively charged lipid coupled to an non-zwitterionic moiety are stable in the blood. Liposomes containing at least 1 mol % of such lipids may be frozen safely.

LIPID CARRIER COMPOSITIONS WITH ENHANCED BLOOD STABILITY

Cross-Reference to Related Applications

[0001] This application claims benefit of U.S. Serial No. 60/394,271, filed 9 July 2002, and of U.S. Serial No. 60/331,248, filed 13 November 2001. The contents of these applications are incorporated herein by reference.

Technical Field

[0002] The present invention relates to liposomal compositions having long lifetime in circulation. These liposomes include the incorporation of negatively charged lipids that do not include zwitterions.

Background Art

[0003] Liposomes are delivery vehicles prepared from aqueous dispersions of amphipathic lipids arranged in one or more bilayers around a central aqueous core. Solutes may be entrapped in the internal aqueous compartment thereby protecting them from reaction with blood components. In order to effectively deliver an entrapped agent to a target site, it is desirable that a liposome exhibits optimal circulation longevity and retention of an encapsulated agent.

[0004] The pharmacological properties of liposomes may be varied by changing the types of lipids incorporated in the membrane. Liposomes composed of neutral (no net charge) lipids are commonly employed as such liposomes are stable upon exposure to the numerous protein, carbohydrate and lipid components present in the blood compartment. Incorporating negatively charged lipids such as phosphatidylserine in liposomal compositions has resulted in increased recognition and clearance of liposomes from the circulation. Kirby, *et al.*, *Biochem. J.* (1980) 186:591-598. Thus, drug delivery to disease sites is reduced. Allen, *et al. Proc. Natl. Acad. Sci. USA* (1998) 85:8061-8071.

[0005] A comparison of the circulation lifetimes of liposomes containing phosphatidylinositol, phosphatidylglycerol, cardiolipin and phosphatidylserine revealed that phosphatidylserine liposomes were eliminated quickly from the circulation whereas cardiolipin, phosphatidylglycerol and phosphatidylinositol liposomes were eliminated at a reduced rate in rats (Kao, Y, *et al., J. Pharm. Sci.* (1980) 69:1338-1349).

be frozen, they will contain about 1-30 mol % of one or more hydrophilic polymer-conjugated lipids and up to about 99 mol % of one or more vesicle-forming lipids, and substantially no cholesterol. Preferably, the hydrophilic polymer-lipid conjugate is a PEG lipid conjugate. The liposomes may also contain cryoprotectants such as trehalose, maltose, sucrose, glucose, lactose, dextran or aminoglycosides. Particularly preferred is glucose.

[0020] The liposomes may be frozen to about -5°C, preferably below about -10°C and more preferably below about -20°C. They may be lyophilized when frozen.

Brief Description of the Drawings

[0021] Figure 1A is a graph showing the percent injected lipid remaining in the blood after intravenous administration of daunorubicin-loaded liposomes containing DSPC/DSPG at mole ratios of 90:10 (filled circles), 80:20 (open circles) and 70:30 (inverted triangles).

[0022] Figure 1B is a graph showing the percent injected daunorubicin remaining in the blood after intravenous administration of daunorubicin-loaded liposomes containing DSPC/DSPG at mole ratios of 90:10 (filled circles), 80:20 (open circles) and 70:30 (inverted triangles).

[0023] Figure 2 is a graph showing the FUDR-to-lipid ratio at various time points after intravenous administration of DSPC/DSPG (80:20 mole ratio) and DSPC/Chol (55:45 mole ratio) liposomes passively entrapped with FUDR.

[0024] Figure 3 is a graph showing the effect of cholesterol content on the percent initial FUDR-to-lipid ratio at various time points after intravenous administration of DSPC/DSPG liposomes co-loaded with FUDR and irinotecan. The liposomes contained cholesterol at 5 mole % (filled circles), 10 mole % (open circles), 15 mole % (inverted, filled triangles) and 20 mole % (open, inverted triangles) and DSPG levels were held constant at 20 mole %.

[0025] Figure 4 is a graph showing the percent injected lipid remaining in the blood after intravenous administration of liposomes containing DSPC/DPPG at mole ratios of 90:10 (filled circles), 80:20 (open circles) and 70:30 (inverted triangles).

[0026] Figure 5 is a graph showing percent injected lipid remaining in the blood after intravenous administration of liposomes containing DSPC/PI (hydrogenated plant) at molar ratios of 90:10 (filled circles), 80:20 (open circles) and 70:30 (inverted triangles).

[0027] Figure 6A is a histogram showing the size of DSPC/DSPG (80:20 mole ratio) liposomes co-loaded with FUDR and irinotecan before freezing after loading of both drugs, after

(R1)

[0071] The liposomes of the invention will be useful in delivering drugs and will thus be formulated to contain a biologically active agent.

[0072] A wide variety of agents may be encapsulated in the liposomes of the present invention. Liposomes of this invention may also be frozen with agent encapsulated or the agent may be encapsulated subsequent to the freezing. The term "agent" refers to chemical moieties that may be used in therapeutic and diagnostic applications. The terms "therapeutic agent" and "drug" as used herein refer to chemical moieties used in therapy and for which liposome-based drug delivery is desirable. The liposomes of this invention may be encapsulated with therapeutic agents such as anti-neoplastic agents, anti-viral agents and anti-microbial agents. The terms "anti-microbial agent" and "anti-viral agent" as used herein refers to chemical moieties having an effect on the growth, proliferation and survival of microbes and viruses respectively. Anti-microbial agents include, but are not limited to penicillin G, streptomycin, ampicillin, penicillin, carbenicillin, tetracycline, streptomycin, amphotericin B, vancomycin and floxacin and derivatives floxacin such as ciprofloxacin, norfloxacin, gatrifloxacin, levofloxacin, moxifloxacin and trovafloxacin. Anti-viral agents include AZT. The term "anti-neoplastic agent" as used herein refers to chemical moieties having an effect on the growth, proliferation, invasiveness or survival of neoplastic cells or tumours. Anti-neoplastic therapeutic agents include alkylating agents, antimetabolites, cytotoxic antibiotics and various plant alkaloids and their derivatives.

[0073] Agents may be encapsulated inside liposomes of the present invention by passive loading techniques known in the art. Passive methods of encapsulating therapeutic agents in liposomes involve encapsulating the agent during the synthesis of the liposomes. In this method, the agent may be membrane associated or encapsulated within an entrapped aqueous space. This includes a passive entrapment method described by Bangham, *et al.*, *J. Mol. Biol.* (1965) 12:238 where the aqueous phase containing the agent of interest is put into contact with a film of dried vesicle-forming lipids deposited on the walls of a reaction vessel. Upon agitation by mechanical means, swelling of the lipids will occur and multilamellar vesicles (MLVs) will form. Using extrusion, the MLVs can be converted to large unilamellar vesicles (LUVs) or small unilamellar vesicles (SUVs) following sonication. Another method of passive loading that may be used includes that described by Deamer, *et al.*, *Biochim. Biophys. Acta* (1976) 443:629. This method involves dissolving vesicle-forming lipids in ether and, instead of first evaporating the ether to form a thin film on a surface, this film being thereafter put into contact with an

aqueous phase to be encapsulated, the ether solution is directly injected into said aqueous phase and the ether is evaporated afterwards, whereby liposomes with encapsulated agents are obtained. A further method that may be employed is the Reverse Phase Evaporation (REV) method described by Szoka, *et al., P.N.A.S.* (1978) 75:4194 in which a solution of lipids in a water insoluble organic solvent is emulsified in an aqueous carrier phase and the organic solvent is subsequently removed under reduced pressure.

[0074] Other methods of passive entrapment that may be used include subjecting liposomes to successive dehydration and rehydration treatment, or freezing and thawing. This technique is disclosed by Kirby, *et al., Biotechnology* (1984) 979-984. Also, Shew, *et al., Biochim. Biophys. Acta* (1985) 816:1-8 describe a method wherein liposomes prepared by sonication are mixed in aqueous solution with the solute to be encapsulated, and the mixture is dried under nitrogen in a rotating flask. Upon rehydration, large liposomes are produced in which a significant fraction of the solute has been encapsulated.

[0075] Agents may be encapsulated using active methods of encapsulation. Active loading involves the use of transmembrane gradients across the liposome membrane to induce uptake of a therapeutic agent after the liposome has been formed. This can involve a gradient of one or more ions including Na+, K+, H+, and/or a protonated nitrogen moiety. Active loading techniques that may be used in accordance with this invention include pH gradient loading, charge attraction, and drug shuttling by an agent that can bind to the drug. (R 2)

[0076] Liposomes may be loaded according to the pH gradient loading technique. According to this technique, liposomes are formed which encapsulate an aqueous phase of a selected pH. Hydrated liposomes are placed in an aqueous environment of a different pH selected to remove or minimize a charge on the drug or other agent to be encapsulated. Once the drug moves inside the liposome, the pH of the interior results in a charged drug state, which prevents the drug from permeating the lipid bilayer, thereby entrapping the drug in the liposome.

[0077] To create a pH gradient, the original external medium is replaced by a new external medium having a different concentration of protons. The replacement of the external medium can be accomplished by various techniques, such as, by passing the lipid vesicle preparation through a gel filtration column, *e.g.*, a Sephadex column, which has been equilibrated with the new medium (as set forth in the examples below), or by centrifugation, dialysis, or related techniques. The internal medium may be either acidic or basic with respect to the external medium.

[0078] After establishment of a pH gradient, a pH gradient loadable agent is added to the mixture and encapsulation of the agent in the liposome occurs as described above.

[0079] Loading using a pH gradient may be carried out according to methods described in U.S. patent Nos. 5,616,341, 5,736,155 and 5,785,987 incorporated herein by reference.

[0080] Therapeutic agents that may be loaded using pH gradient loading comprise one or more ionizable moieties such that the neutral form of the ionizable moiety allows the drug to cross the liposome membrane and conversion of the moiety to a charged form causes the drug to remain encapsulated within the liposome. Ionizable moieties may comprise, but are not limited to comprising, amine, carboxylic acid and hydroxyl groups. Agents that load in response to an acidic interior may comprise ionizable moieties that are charged in response to an acidic environment whereas drugs that load in response to a basic interior comprise moieties that are charged in response to a basic environment. In the case of an basic interior, ionizable moieties including but not limited to carboxylic acid or hydroxyl groups may be utilized. In the case of an acidic interior, ionizable moieties including but not limited to primary, secondary and tertiary amine groups may be used. Preferably, the pH gradient loadable agent is a therapeutic agent and most preferably an anti-neoplastic agent, antimicrobial agent or an anti-viral agent. Examples of therapeutic agents that can be loaded into liposomes by the pH gradient loading method and therefore may be used in this invention include, but are not limited to anthracycline antibiotics such as doxorubicin, daunorubicin, mitoxantrone, epirubicin, aclarubicin and idarubicin; anti-neoplastic antibiotics such as mitomycin, bleomycin and dactinomycin; vinca alkaloids such as vinblastine, vincristine and navelbine; purine derivatives such as 6-mercaptopurine and 6-thioguanine; purine and pyrimidine derivatives such as 5-fluorouracil; camptothecins such as topotecan, irinotecan, lurtotecan, 9-aminocamptothecin, 9-nitrocamptothecin and 10-hydroxycamptothecin; cytarabines such as cytosine arabinoside; antimicrobial agents such as ciprofloxacin and salts thereof. This invention is not to be limited to those drugs currently available, but extends to others not yet developed or commercially available, and which can be loaded using the transmembrane pH gradients.

[0081] Various methods may be employed to establish and maintain a pH gradient across a liposome. This may involve the use of ionophores that can insert into the liposome membrane and transport ions across membranes in exchange for protons (see, for example, U.S. patent No. 5,837,282). Buffers encapsulated in the interior of the liposome that are able to shuttle protons across the liposomal membrane and thus set up a pH gradient (see, for example, U.S.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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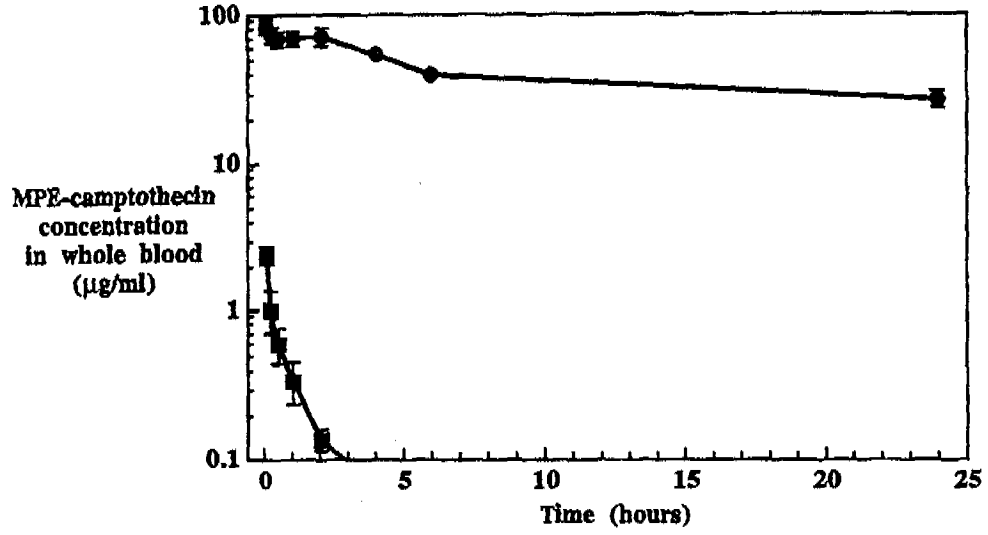
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LIPOSOME-ENTRAPPED TOPOISOMERASE INHIBITORS



(57) Abstract

A composition for administration of a therapeutically effective dose of a topoisomerase inhibitor I or topoisomerase I/II inhibitor is described. The composition includes liposomes having an outer surface and an inner surface defining aqueous liposome compartment, and being composed of a vesicle-forming lipid and of a vesicle-forming lipid derivatized with a hydrophilic polymer to form a coating of hydrophilic polymer chains on both the inner and outer surfaces of the liposomes. Entrapped in the liposomes is the topoisomerase inhibitor at a concentration of at least about 0.10 µmole drug per µmole lipid.

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this method of preparation it is difficult to achieve a sufficient drug load in the liposomes for clinical efficacy.

Accordingly, there is still a need in the art for a liposome formulation which (i) includes a topoisomerase inhibitor, such as camptothecin and its analogues; (ii) remains in the bloodstream for a prolonged period of time; (iii) retains antitumor activity; and (iv) includes a sufficient drug load for clinical relevance.

Summary of the Invention

Accordingly, it is an object of the invention to provide a topoisomerase inhibitor composition for improved cancer therapy.

It is another object of the invention to provide a liposome composition for administration of a topoisomerase inhibitor for antitumor therapy.

In one aspect, the invention includes a composition for treating a tumor in a subject, comprising liposomes composed of a vesicle-forming lipid and between about 1-20 mole percent of a vesicle-forming lipid derivatized with a hydrophilic polymer. The liposomes are formed under conditions that distribute the polymer on both sides of the liposomes' bilayer membranes. Entrapped in the liposomes is a topoisomerase I inhibitor or a topoisomerase I/II inhibitor at a concentration of at least about 0.10 μmole drug per μmole lipid. The liposomes have an inside/outside ion gradient sufficient to retain the topoisomerase I inhibitor or topoisomerase I/II inhibitor within the liposomes at the specified concentration.

In one embodiment, the topoisomerase inhibitor is a topoisomerase I inhibitor selected from the group consisting of camptothecin and camptothecin derivatives. For example, the camptothecin derivative can be 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methlyenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin or 9-chloro-10,11-methylenedioxycamptothecin. In other embodiments, the camptothecin derivative is irinotecan, topotecan, (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin or 7-(2-(N-isopropylamino)ethyl)-(20S)-camptothecin.

In another embodiment, the topoisomerase inhibitor is a topoisomerase I/II inhibitor, such as 6-[[2-(dimethylamino)-ethyl]amino]-3-hydroxy-7H-indeno[2,1-

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ethanol:lipid:ammonium sulfate hydration mixture was mixed continuously for at least one hour while maintaining the temperature using a 65°C water bath to form oligolamellar ethanol hydration liposomes.

The oligolamellar liposomes were size reduced using a Lipex thermobarrel extruder to pass the hydration mixture through polycarbonate membranes with known pore size dimensions. The mixture was passed 5 times through a 0.20 μm pore diameter membrane, followed by 10 passes through a 0.10 μm pore diameter membrane. The extruded liposomes contained ammonium sulfate within the interior aqueous compartment(s) of the liposomes, as well as in the exterior aqueous bulk phase medium in which they are suspended. The sized liposomes were stored in the refrigerator until diafiltration preceding the remote loading procedure.

100 mg of a selected topoisomerase inhibitor, MPE-camptothecin, CKD-602 or topotecan, was dissolved in 40 mL 10% sucrose solution to yield a concentration of 2.5 mg/mL. After dissolution, the solution was passed through a 0.20 μm filter to remove insoluble particulates.

B. Remote Loading of Liposomes

Ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to remote loading by hollow fiber tangential flow diafiltration with a 100KDa nominal molecular weight cutoff cartridge. Constant feed volume was maintained, and at least seven exchange volumes were used resulting in liposomes suspended in an exterior aqueous phase comprised of 10% sucrose.

After diafiltration, the liposomes were mixed with a selected drug solution at a ratio (drug solution:liposomes) of 1:4 (vol/vol) and rapidly warmed to 65°C using a pre-equilibrated jacketed vessel containing water. The temperature of the mixture was maintained at 65°C for 40 to 60 minutes, after which the mixture was rapidly cooled in an ice-water bath. After remote loading, a sample of the liposomes was taken to check for the presence of crystals, to determine percent encapsulation and to measure the mean particle diameter.

Unencapsulated drug was removed from the bulk phase medium by hollow fiber tangential flow diafiltration using a 100 kDa nominal molecular weight cutoff cartridge. At least eight exchange volumes were used, resulting in liposomally encapsulated drug suspended in an external aqueous phase comprised of 10% sucrose 10 millimolar

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IT IS CLAIMED:

1. A composition for treating a tumor in a subject, comprising

liposomes composed of a vesicle-forming lipid and between about 1-20 mole percent of a vesicle-forming lipid derivatized with a hydrophilic polymer, said liposomes being formed under conditions that distribute the polymer on both sides of the liposomes' bilayer membranes; and

entrapped in the liposomes, a topoisomerase inhibitor at a concentration of at least about 0.10 μmole drug per μmole lipid, said liposomes having an inside/outside ion gradient sufficient to retain the topoisomerase inhibitor within the liposomes at the specified concentration.

2. The composition of claim 1, where the topoisomerase inhibitor is a topoisomerase I inhibitor selected from the group consisting of camptothecin and camptothecin derivatives.

3. The composition of claim 2, wherein the camptothecin derivative is selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methlyenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, irinotecan, topotecan, (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin.

4. The composition of claim 1, wherein the topoisomerase inhibitor is a topoisomerase I/II inhibitor selected from the group consisting of 6-[[2-(dimethylamino)-ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one dihydrochloride, azotoxin and 3-methoxy-11H-pyrido[3',4'-4,5]pyrrolo[3,2-c]quinoline-1,4-dione.

5. The composition of claim 1, wherein the hydrophilic polymer is polyethyleneglycol having a molecular weight between 500-5,000 daltons.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado:
MARGARITA CASTELLANOS ABONDANO

ASUNTO:	Radicación No.	06 12 0944
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	
	Folios	3077

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 7 a 122 como se radicó inicialmente.

Reivindicaciones: Folios 123 a 124 como se radicó inicialmente.

Prioridad: JP 2004-163742 (2004-06-01)

Objeto de la Invención

Titulo de la invención: "Formulación de irinotecan"

Problema Técnico Planteado: "Necesidad de una formulación que contenga suficiente activos como para alcanzar un efecto clínico y cuyas características mantengan la concentración de SN-38 en el plasma por un periodo de tiempo prolongado"

Solución: "Proporcionar una preparación de irinotecan que comprende vesículas cerradas formadas de una membrana de lípido en donde el irinotecan y/o una sal del mismo se sellan en una concentración de al menos 0.07 mol activo/mol de lípidos totales"

IPC: A61K 31/4745 AC; A61K 9/127 AC; A61K 47/4 AC; A61K 47/18 AC; A61K 47/24 AC; A61K 47/30 AC; A61P 35/0

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de prioridad 2004-06-01y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO03041681	*Lipid carrier compositions with enhanced blood stability*	22.05.2003
D2	WO2002/036203	*Liposome-entrapped topoisomerase inhibitors*	27.04.2000

Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 revela una formulación de irinotecan caracterizado porque incluye una vesícula cerrada formada por una membrana de lípidos, en la que el irinotecan y/o una sal del mismo están encapsulados en una concentración de por lo menos 0.07 mol/mol (mol de fármaco/mol de lípido total de la membrana).

D1 presenta liposomas que contienen fosfolípidos, y sistemas que contienen irinotecan (pagina 5, párrafo 27), enseña que una gran variedad de agentes activos que pueden estar en el liposoma y que puede estar asociado con la membrana o encapsulado en un espacio acuoso dentro de la vesícula (página 15). Sugiere gradientes de iones y residuos de nitrógeno protonados para fines de cargar la vesícula, y para lograr dicho efecto revela el uso de residuos ionizables como aminas primarias, secundarias, terciarias (página 17)

La solicitud se diferencia de D1 en la relación fármaco/lípido total de membrana.

El Efecto Técnico que logra la diferencia es la prolongación de la concentración del metabolito SN-38 en el plasma sanguíneo.

El Problema Técnico Objetivo de esta solicitud es la necesidad de composiciones y formulaciones alternativas para la administración de irinotecan.

D2 revela composiciones para administrar dosis terapéuticamente efectivas de inhibidores de topoisomerasa, la cual contiene liposomas que tienen una superficie interna y una superficie externa que definen el compartimento acuoso del liposoma, que están conformados por un lípido formador de vesícula con un polímero hidrofílico para formar una cubierta de cadenas poliméricas hidrofilicas sobre ambos superficies de los liposomas, en donde la concentración revelada es cercana a 0.1. micromolar de medicamentos por micromol de lípido(portada, página 3). Revela que el derivado de inhibores de topoisomerasa es irinotecan.

El experto en la materia, teniendo en cuenta las enseñanzas de D2, habría podido tomar la relación micromolar existente entre el ingrediente activo y el lípido revelada por D1 y la habría podido llevar a limites como el 0.10 micromolar de activo/micromolar de lípidos, valor que es sugerido por D2. El experto en la materia además habría sido capaz de ajustar ensayos por debajo y por encima de la relación 0.10 y de este modo lograría llegar a la solución propuesta por la presente solicitud.

Se concluye que las reivindicaciones independientes 9 no poseen nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03041681	1-9	Nivel inventivo
D2	WO2002/036203	1-9	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TECNICO NUMERO: 562	EXAMINADOR TÉCNICO Código:202092