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SEÑORES
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y CC
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SUPERINDUSTRIA Y COMERCIO
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Trámite : 002 PATENTES D 1 REGISTRO/ 329 COMPLETEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

COD 01

RE SOLICITUD N° 01003856
FECHA SOLICITUD Enero 19, 2001
PATENTE PURIFICACIÓN DE ACEITES DE CASTOR POLIOXIETILADOS
CON CARBÓN ACTIVADO
SOLICITANTE BAKER NORTON PHARMACEUTICALS, INC

ASUNTO PRESENTACIÓN PRIORIDAD

DILIA RODRIGUEZ D ALEMAN, en mi condición de apoderada de la sociedad solicitante, en esta oportunidad por el presente escrito me permito presentar

- Copia certificada de la prioridad Estadounidense reivindicada N° 60/177,459 de Enero 20 de 2 000
- Traducción al Español de la mencionada prioridad

Esta prioridad está siendo presentada dentro del término de 3 meses que exige el Convenio de París, toda vez que la solicitud fué radicada el 19 de Enero de 2 001

Ruego a usted continuar con el presente trámite

Señor Jefe,

DILIA RODRIGUEZ D ALEMAN
CCR/brr
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PA 377084



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

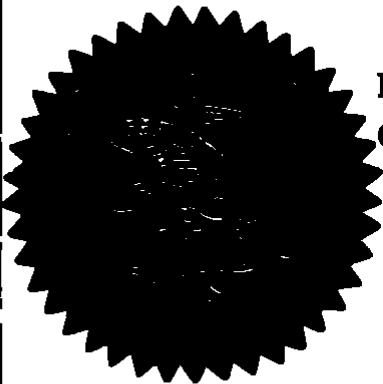
United States Patent and Trademark Office

March 15, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
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OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111

APPLICATION NUMBER 60/177,459

FILING DATE January 20, 2000



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS


H. PHILLIPS
Certifying Officer

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10490 U.S. PTO

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. 1.53(b)(2).

Docket No.		INFORM-P	Type a plus sign (+) in this box	+
INVENTOR(S)/APPLICANT(S)				
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY & EITHER STATE OR FOREIGN COUNTRY)	
ZHANG	KAI		12700 SW 127 CT MIAMI, FL. 33156	
SMITH	GREGORY	A.	14025 NW 3RD AVE N MIAMI FL. 33186	
TITLE OF THE INVENTION				
METHOD FOR STABILIZATION OF PACLITAXEL IN CREMOPHOR EL/ETHANOL SOLUTION				
CORRESPONDENCE ADDRESS				
Simona A. Levi-Minzi, Ph.D. BAKER NORTON PHARMACEUTICALS, INC 4400 Biscayne Boulevard Miami, FL 33137 Telephone (305) 575-6061 Facsimile (305) 575-6064				
ENCLOSED APPLICATION PARTS (check all that apply)				
☒ Specification Number of Pages <u>3</u> ☐ Small Entity Statement				
☐ Drawing(s) Number of Sheets <u>1</u> ☐ Other (specify) _____				
METHOD OF PAYMENT (check one)				
☐ A check or money order is enclosed to cover the Provisional Filing Fee			Provisional Filing Fee Amount	
☒ The Commissioner is hereby authorized to charge the filing fee to Deposit Account Number: 30-0943			\$150.00	

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01/20/00

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government

☒ No

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Simona A. Levi-Minzi DATE: January 21, 2000

TYPED or PRINTED NAME Simona A. Levi-Minzi, Ph.D. REGISTRATION NO: 43,730

☐ Additional inventors are being named on separately numbered sheets attached hereto

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

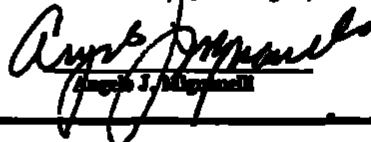
In re Application of: Kai Zhang and Gregory A. Smith
Serial No: To be assigned
Filing Date: HEREWITH
Title: METHOD FOR STABILIZATION OF PACLITAXEL
IN CREMOPHOR EL/ETHANOL SOLUTION
Attorney Docket No.: BNP0206-P

CERTIFICATION UNDER 37 C.F.R. 1.10

I hereby certify that the attached papers are being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Service under 37 C.F.R. 1.10 on January 21, 2000 and is addressed to BOX PROVISIONAL PATENT APPLICATION, Assistant Commissioner for Patents, Washington, D.C. 20231

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Joseph J. Minzelli

BOX PROVISIONAL PATENT APPLICATION
Assistant Commissioner for Patents
Washington DC 20231

Dear Sir:

Enclosed herewith for filing with the United States Patent and Trademark Office in the above-identified application are the following documents

- 1 Provisional Application Cover Sheet (one page)
- 2 Provisional Patent Application (5 pages comprising 5 pages of specification only) and
- 3 Return Postcard

Respectfully Submitted,

BAKER NORTON PHARMACEUTICALS, INC


Simon A. Levi-Minzi Ph.D
Registration No 43 750
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Method for Stabilization of Paclitaxel in Cremophor EL/Ethanol Solution

The present invention provides a new process to treat Cremophor EL with low content of carboxylate salts and lower pH value. This treated Cremophor EL can be then utilized to prepare stabilized pharmaceutical compositions especially, a formulation of paclitaxel.

There is no mention in the published literature or patents on the use of this process to lower the content of carboxylate salts and decoloring of polyethoxylated castor oil. Nor there is any reference for the use of this treated polyethoxylated castor oil to prepare paclitaxel solution. The treatment of Cremophor EL with aluminum oxide and magnesium silicates, for the removal of carboxylate anions, is the subject of major patents held by both BASF (the manufacturer of Cremophor) and BMS (for their preparation of Taxol™). The suppression of carboxylic acid ionization to carboxylate anions - catalysts in the degradation of Paclitaxel - by the addition of Bronsted acids is described in patent documents from BMS, NaPro BioTherapeutics, Inc. and F H Faulding, Ltd. A method pre-treat Cremophor EL with strong cationic exchange resin to lower the cation content was invented by Nikolayev, Schein Pharmaceuticals, inc.

It is well known that activated charcoal is widely used for purification in the organic synthesis process. With relative large surface area, charcoal can absorb polar compounds, such as water, carboxylate salts and color.

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stuff which we think as the source of degradation of paclitaxel in this invention composition

Results

Sample	% Paclitaxel remaining (80 °C for 48 hours)
Charcoal treated Cremophor EL	98.2
Untreated Cremophor EL	42.2

The pH value of the samples was measured following 1:10 dilution with water. The potassium concentration of samples was analyzed. The color of the samples also was measured as shown in following

Sample	K (ppm)	pH	Color (Vis 425 nm, AU)
Charcoal treated Cremophor EL	137.5	4.27	0.0381
Untreated Cremophor EL	398.7	6.06	0.0516

Process Optimization Plan

In order to achieve the most stable formulation and scale up to commercial batch, we are currently working on optimization of process parameters and quality control testing method. Key parameters for treated Cremophor EL include

- K content 40 –80 ppm
- Na content 20 – 40 ppm
- Water less than 1.5%

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Color less than 0.04 AU at 425 nm (1.0 cm cell)

pH 4.2 – 4.6 (1:10 dilution with water)

Formulation stability Recover no less than 98.5% of paclitaxel after storage at 60 °C for one week

References

US patent documents

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- 2 Sampedro, F., Partika, J., Santalo, P., Molins-Pujol, A. M., Bonal, J., and Perez-Soler, R., Short Communication - Liposomes as Carriers of Different New Lipophilic Antitumour Drugs: A Preliminary Report, *J. Microencapsulation*, 1993, Vol. 11, No. 3, 309-318
- 3 Balasubramanian, S. V., Alderfer, J. L., and Straubinger, R. M., Solvent- and Concentration—Dependent Molecular Interactions of Taxol (Paclitaxel), *Journal of Pharmaceutical Sciences*, Vol. 83, No. 10, October 1994
- 4 Merisko-Liversidge, E., Sarpotdar, P., Bruno, J., Hajj, S., Wei, L., Peltier, N., Rake, J., Shaw, J. M., Pugh, S., Polin, L., Jones, J., Corbett, T., Cooper, E., and Liversidge, G. G., Formulation and

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- 5 **Sharma, A , and Straubinger, R M , Novel Taxol Formulations: Preparation and Characterization of Taxol-Containing Liposomes, *Pharmaceutical Research*, Vol 11, No 6, 1994**
- 6 **Adams, J D , Flora, K P , Goldspiel, B R , Wilson, J W , Arbuck, S G , Finley, R , Taxol. A History of Pharmaceutical Development and Current Pharmaceutical Concerns, *J Natl Cancer Inst Monogr* , 15, 141, 1993**
- 7 **Dordunoo, S K , and Burt, H M , Solubility and Stability of Taxol: Effects of Buffers and Cyclodextrins, *International Journal of Pharmaceutics* 133 (1996) 191-201**
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- 9 **Kingston D G I , The Chemistry of Taxol, *Pharma Ther* , Vol 52, pp 1-34, 1991**
- 10 **Wenk, M R , Fahr, A , Reszka, R., and Seelig, J , Paclitaxel Partitioning into Lipid Bilayers, *Journal of Pharmaceutical Sciences*, Vol 85, No 2, February 1996**

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Procedure

Put certain amount of charcoal into a oven at 120 °C for about 16 hours

To certain amount of activated charcoal, add Cremophor EL to make a 10 % charcoal (w/w) Cremophor EL slurry solution, heat the solution to 45 °C with a hot plate for 3 hours with mechanical stirring, then, naturally cool down to room temperature, keeping stirring for 2 more hours. The slurry solution is then filtered twice using a 10 µm filter and a 0.45 µm filter.

The paclitaxel formulation was prepared by dissolving 6 mg/mL of paclitaxel in 50/50 (v/v) commercial or pre-treated Cremophor EL and dehydrate ethanol. Two mL of the formulation solution was placed in a 6 cc glass vial. The vials were sealed with teflon faced cap and stored for certain period time at 80 °C, then analyzed by HPLC for the concentration of paclitaxel.

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TRADUCCIÓN**ESTADOS UNIDOS DE AMÉRICA -**

A quien corresponda

DEPARTAMENTO DE COMERCIO - OFICINA DE PATENTES Y MARCAS

15 de marzo de 2001

CERTIFICO QUE ADJUNTA A LA PRESENTE SE ENCUENTRA UNA COPIA FIEL DE LOS REGISTROS EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE REUNIAN LOS REQUISITOS PARA LA ASIGNACIÓN DE UNA FECHA DE PRESENTACIÓN EN VIRTUD DE 35 USC 111

SOLICITUD NUMERO 60 /177 459

FECHA DE DEPÓSITO 20 de enero de 2000

En nombre del COMISARIO DE PATENTES Y MARCAS

(Firmado) H PhillipsCertificaciones

(La presente certificación se encuentra unida en forma inviolable a sus adjuntos y lleva una oblea dorada que dice) OFICINA DE PATENTES Y MARCAS - ESTADOS UNIDOS DE NORTEAMÉRICA.

(Adjuntos)

Carátula para la Presentación de una Solicitud de Patente Provisional Esta solicitud es para presentación de una SOLICITUD DE PATENTE PROVISIONAL bajo el CRF 37, art 1 53 (b)(2)

Expediente BNP0206-P

INVENTORES SOLICITANTE/S

Apellido, Nombre e Inicial	Residencia (Ciudad y Estado o País Extranjero)
ZHANG, KAY	12700 SW 127 CT MIAMI, FL 33156
SMITH, GREGORY A.	14025 NW 3RD AVE N MIAMI, FL 33186

Titulo de la invención METODO PARA ESTABILIZAR PACLITAXEL EN UNA SOLUCION DE CREMOFOR EL/ETANOL

Dirección Postal Rogamos dirigir toda la correspondencia relacionada con esta Solicitud a

SIMONA A. LEVI-MINZI, PH D

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Adjuntos

Memoria descriptiva 3 Páginas

Se autoriza al Comisario a cobrar los aranceles de presentación a través de la cuenta Numero 50-0943 Arancel \$150

La invención no fue hecha por una dependencia del Gobierno de los Estados Unidos ni por contrato con una dependencia del Gobierno de los Estados Unidos

Atentamente, firmado SIMONA A. LEVI-MINZI, PH D , Registro 34750

Fecha 21 de enero de 2000

EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

SOLICITUD DE KAI ZHANG Y GREGORY A SMITH

NUMERO A SER ASIGNADO,

FECHA DE PRESENTACIÓN ADJUNTA A LA PRESENTE

TITULO METODO PARA ESTABILIZAR PACLITAXEL EN UNA SOLUCION DE CREMOFOR EL/ETANOL

Expediente BNP0206-P

Certificado de despacho por expreso EK062989721US con fecha 21 de enero de 2000 firmado por Angelo Mignanelli

Casilla de Solicitudes de Patente Provisionales

Washington, DC 20231

De mi consideración

Adjuntamos para su presentación en la Oficina de Patentes y Marcas de los Estados Unidos los siguientes documentos

- 1 Caratula de Solicitud Provisional (1 página)
- 2 Solicitud de Patente Provisional (5 páginas incluyendo 5 páginas de memoria descriptiva)
- 3 Aviso de Retorno

BAKER NORTON PHARMACEUTICALS, INC

SIMONA A. LEVI-MINZI, Ph D

Registro 43750, Abogado de los solicitantes

21 de enero de 2000

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METODO PARA ESTABILIZAR PACLITAXEL EN UNA SOLUCION DE CREMOPHOR EL/ETANOL

La presente invención provee un proceso novedoso para tratar Cremofor EL con bajo contenido de sales de carboxilato y bajo valor pH. Este Cremofor EL tratamiento puede ser utilizado para preparar composiciones farmacéuticas estabilizadas, especialmente una formulación de paclitaxel. El tratamiento de Cremofor EL con óxido de aluminio y silicatos de magnesio para la remoción de aniones de carboxilato, es el tema de patentes importantes de BASF (fabricante de Cremofor) y BMS (Para su preparación de Taxol (MR)). La supresión de la ionización de ácido carboxílico de aniones carboxilato – catalizadores en la degradación de Paclitaxel- por agregado de ácidos Bronsted tal como se describe en la patente de BMS, Na Pro Bio Therapeutics, Inc y F. H. Faulding, Ltd. Un método para pre-tratar Cremophor EL con resina de intercambio catiónico fuerte para disminuir el contenido catiónico, inventada por Nikolayev, Schein Pharmaceuticals, Inc.

Se sabe que el carbón activado es ampliamente utilizado para purificación en el proceso de síntesis orgánica. Con un área de superficie grande, el carbono puede absorber compuestos polares, tales como agua, sales carboxiladas y sustancias colorantes lo cual pensamos sea la causa de la degradación de paclitaxel en esta composición de la invención.

Resultados

TABLA

Muestra	% Paclitaxel restante (80°C durante 48 horas)
Cremophor EL® Tratado con Carbón	98,2
Cremophor EL® sin tratar	42,2

El valor del pH de las muestras se midió luego de una dilucion con agua 1 10 Se analizó la concentración de potasio en las muestras El color de las muestras también se midió segun se muestra a continuación

Muestra	K ⁺ (ppm)	pH	Color (Vis 425nm, AU)
Cremophor EL® Tratado con Carbon	137,5	4,27	0,0381
Cremophor EL® Sin tratar	398,7	6,06	0,0516

Plan de Optimización del Proceso

A fin de lograr una formulación más estable para uso comercial, se esta trabajando actualmente en la optimización de los parámetros del l proceso y método de testeo de control de calidad Los parámetros clave para Cremophor EL tratado incluyen

Contenido K 40 – 80 ppm

Contenido Na 20 – 40 ppm

Agua menos de 1,5%

color menos de 0,04 AU nm (célula 1,0cm)

pH 4,2 – 4,6 (1 10 dilución con agua)

Estabilidad de la formulación Recuperar no menos de 98,5% de paclitaxel luego del almacenamiento a 60°C durante una semana

Referencias

Documentos de Patentes de los EE UU

5,504 102 4/96 Agharkar

5 925 776 7799 Nikolayev

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8 Tarr, B D y Yalkowsky S H , A New Parenteral Vehicle for the Administration of Some Poorly Water Soluble Anti–Cancer Drugs, Journal of Parenteral Science & Technology 41(1) (1987)

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Procedimiento

Se colocó cierta cantidad de carbón en un horno a 120°C durante aproximadamente 16 horas, se agregó Cremophor El para obtener para hacer una suspensión lechosa de Cremophor El, de carbón 10%(p/p), la solución se calentó a 45°C con una placa caliente durante tres horas con agitación mecánica, se enfrió naturalmente a temperatura ambiente, manteniendo la agitación durante dos horas adicionales. Luego se filtró la solución lechosa dos veces usando filtros de 10µm y de 0,45µm

Se preparó la formulación de paclitaxel disolviendo 6 mg/ml de paclitaxel en Cremophor EL y etanol deshidratado comercial o pretratado 50/50 (v/v). Se pusieron dos mililitros de la solución de formulación en un vial de vidrio de 6 cm³. Los viales se sellaron con una tapa con una cara de Teflon y se almacenaron durante un cierto periodo a 80°C, se analizaron por HPLC para determinar la concentración de paclitaxel

PURIFYING POLYOXYETHYLATED CASTOR OILS WITH ACTIVATED CHARCOAL TECHNICAL FIELD

The present invention relates to the removal of impurities from polyethoxylated castor oils, and formulations containing the treated castor oils and active agents

BACKGROUND OF THE INVENTION

Polyethoxylated castor oils are commonly used as solubilizing and/or dispersing agents for a variety of pharmaceutically active agents that are substantially insoluble in water. Impurities tend to catalyze the decomposition of the pharmaceutically active agents, particularly anti-neoplastic agents such as paclitaxel. In particular it has been found that pharmaceutical compositions of paclitaxel in a co-solvent system containing dehydrated ethyl alcohol and commercial grade Cremophor EL® exhibit a loss of potency of greater than 60% after storage for 12 weeks at 50°C, the loss of which is attributable to the decomposition of paclitaxel during storage. In addition to the impurities such as colorants and dopants that are contained in the castor oil solution that is used to prepare the pharmaceutical composition, other impurities are formed during storage of the ultimate pharmaceutical formulation. Such impurities include fibrous precipitate of unknown composition and which also cause loss of potency of the active agent.

U S Patent 5 504,101 to Agharkar, *et al*, teaches a method for treating a polyoxyethylated castor oil with an acid or contacted with alumina to reduce carboxylate anion content, thereby extending shelf life and lower amounts of degradation by-products. U S Patent 5 925 776 to Nikolayev, *et al* teaches methods of reducing cation contents of polyoxyethylated castor oils by pre-treating the castor oil with a strong cationic exchange resin such as styrene divinyl benzene. International publication number WO 00/23070 to Ben Venue teaches a method for purifying polyoxyethylated castor oils by contacting a solution of castor oil and an alcohol with a column containing activated carbon, followed by contact with an ion exchange resin column to remove residual amounts of carbon.

SUMMARY OF THE INVENTION

Applicants have devised a method for removing impurities from polyethoxylated castor oils without requiring cumbersome chromatographic procedures.

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Hence, one aspect of the present invention is directed to a polyoxyethylated castor oil produced by the steps of preparing a suspension of activated charcoal in a polyoxyethylated castor oil (e.g., a commercial grade castor oil), and separating the activated charcoal from the polyoxyethylated castor oil. In preferred embodiments, the suspension is heated prior to separating and the separation of the activated charcoal from the castor oil is performed while the suspension is still heated. In a more preferred embodiment, impurities are removed by preparing a suspension of activated charcoal and a polyoxyethylated castor oil wherein the activated charcoal has a median surface area of about 900 m²/g, and is present in the suspension in an amount of from 3 to about 20% (w/w) heating said suspension at a temperature of from about 30°C to about 60°C for a period of time of from about 1 to about 6 hours and filtering the heated suspension to separate the activated charcoal from the castor oil. The castor oils of the present invention have reduced impurities (e.g., colorants and alkali metal cations including K⁺ and Na⁺) relative to castor oils not having undergone the processes described herein.

Another aspect of the present invention is directed to the purification process *per se*, which entails preparing a suspension of activated charcoal in the polyoxyethylated castor oil under conditions of time and temperature so as to allow the impurities to be removed from the castor oil.

Another aspect of the present invention is directed to compositions and formulations containing a polyoxyethylated castor oil treated in accordance with the aforementioned process, and an active agent. The agent is soluble or dispersible in the castor oil. In preferred embodiments, the active agent is an anti-neoplastic agent, more preferably a taxane such as paclitaxel. More preferred compositions also contain, in addition to the paclitaxel, dehydrated ethanol and citric acid. Processes of making the compositions are also provided.

BEST MODE OF CARRYING OUT THE INVENTION

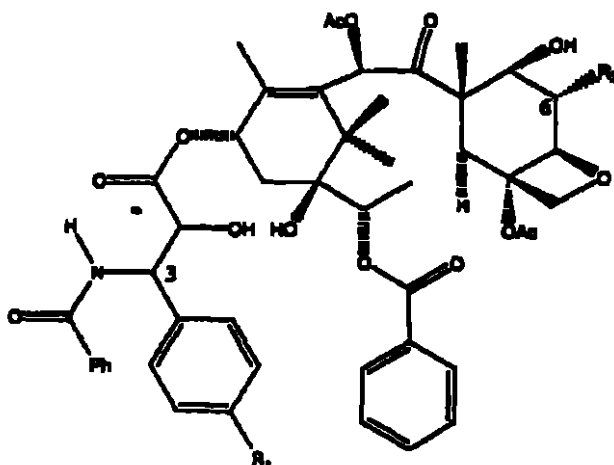
Polyoxyethylated castor oils are produced by condensation of castor oil with ethylene oxide. Preferred oils are commercially available under the trade names Cremophor EL® and Cremophor EL-P (BASF). Other preferred castor oils include polyoxyl 35 castor oil and Cremophor RH60. Alternatively, Cremophor may be prepared in accordance with the methods disclosed in U.S. Patent 3,070,499.

Activated charcoal is commercially available from several sources *e.g.* Calgon (Pittsburg, PA) and Spectrum Chemical Manufacturing Corp. (Gardena, CA). Alternatively, charcoal may be activated in accordance with standard procedures, notably by chemical treatment, or steam or some other heat source, charcoal can be "activated". Bonhomme-Pauvre *et al.*, *Life Sci* 66(9) 817-827 (2000), for example, discloses pinewood charcoal LSM (CECA-SA, 92 La Défense) and peat charcoal SX4 (Norit 93, Le Blanc Mesnil), activated by steam and washed with phosphoric acid. The surface absorption for pinewood charcoal is 1,000 m²/g and 650 m²/g for peat charcoal. In general, the activated charcoal has a surface area ranging from about 500 to about 1300 m²/g, and preferably a median surface area range of about 900 m²/g.

To reduce the impurities in a given polyoxylated castor oil, a predetermined amount of the oil is added together with activated charcoal to produce a suspension of the charcoal in the oil. In general, the charcoal is present in the suspension in an amount of from 3 to about 20% (w/w), preferably from about 5 to about 10 % (w/w). The castor oil and activated charcoal are allowed to remain in contact under conditions and for a period of time suitable to allow removal or capture of impurities by the charcoal. Although not intending to be bound by any particular theory of operation, it is believed that the activated charcoal adsorbs the impurities. In preferred embodiments, the suspension is heated, generally at a temperature of from about 30°C to about 60°C, and for a period of time from about 1 to about 6 hours. It is believed that the heating enhances absorption of impurities and thus facilitates their removal from the castor oil. It is also preferred to stir the suspension, at least periodically. The activated charcoal is then separated from the castor oil. This separation is conveniently performed by at least one filtration step. In the event that two or more filtration steps are used, filters having successively smaller apertures are used. In preferred embodiments the heated suspension is filtered while it is still heated. It is believed that the lesser viscosity of the heated suspension facilitates filtration. In less preferred embodiments, the heated suspension is allowed to cool to about room temperature, optionally with stirring.

The treatment or purification process removes impurities from the castor oil. The main impurities removed include colorants (*e.g.*, naturally occurring color-stuffs contained in castor oils, and dopants and other chemical additives that are included in the final commercial product) and alkali metal cations such as K⁺ and Na⁺. In preferred

embodiments, the thus-treated castor oil has a color content of no greater than about 0.045 absorbance units (AU), measured at 425 nm/1cm cell. In more preferred embodiments, the castor oil has a color content of no more than about 0.038 AU. With respect to cations, the castor oils of the present invention have a K^+ content is no more than about 80 ppm, more preferably no more than about 50 ppm, and a Na^+ content no more than about 10 ppm. In other preferred embodiments, the castor oil has a water content of no greater than about 2.5%. The polyoxyethylated castor oil of the present invention disperse or solubilize a wide variety of active agents, including pharmaceutical agents *e.g.* anesthetics (*e.g.*, benzocaine), immunosuppressive agents, anti-fungal agents (*e.g.*, miconazole and clotrimazole), anti-bacterial agents (*e.g.*, hexidine), non-steroidal anti-inflammatory agents (*e.g.*, diclofenac), vitamins (*e.g.* A, D, E and K), cosmetics (*e.g.* deodorant and antiperspirant actives such as aluminum zirconium chloride, aluminum chloride and sodium bicarbonate) and feedstuff, and other agents such as excipients (*e.g.* solvents, thickeners, colors, dyes, flow aids, lubricants and non-volatile silicones such as cyclomethicone and clays *e.g.*, bentonite). In preferred embodiments, the active agent is an anti-neoplastic agent. Suitable anti-neoplastic agents include teniposide, a semi-synthetic derivative of podophyllotoxin having the chemical name 4-demethylepodophyllotoxin 9-(4,6-O-2-thenylidene- β -D-glucopyranoside), camptothecin, a compound isolated from the stemwood of the Chinese tree, and taxanes (*e.g.* obtainable from the bark of Pacific yew trees). In more preferred embodiments, the anti-neoplastic agent is a taxane. Suitable taxanes include paclitaxel and its prodrugs (*e.g.* docetaxel), derivatives, pharmaceutically acceptable salts and metabolites thereof. Docetaxel (N-debenzoyl-N-tert-butoxycarbonyl 10-deacetyl paclitaxel) is commercially available under the trade name TAXOTERE® (Rhone-Poulenc Rohrer S.A.). Taxol analogs and derivatives are disclosed in the literature, *e.g.* U.S. Patents 6,103,698 and 6,136,990 WO 94/03093 Kingston, DGI Taxol: the chemistry and structure-activity relationships of a novel anticancer agent. Trends Biotechnology 12: 222-227 (1994), and Alder JD *et al.* Preclinical *in vivo* efficacy of two dihydrotaxane analogues against human and murine tumors. Br J Cancer 73: 560-564 (1996). Other than docetaxel, other prodrugs include the 2'-onium salts of paclitaxel and docetaxel, particularly the 2-methylpyridinium mesylate (2-MPM) salts. Preferred metabolites of paclitaxel designated A, B and C, are represented by the following formula



In the formula, metabolite A. $R_1 = H$ and $R_2 = OH$, metabolite B $R_1 = OH$ and $R_2 = H$ and metabolite C $R_1 = H$ and $R_2 = H$.

In the case of taxanes, it is particularly preferred that the castor oil is contained in admixture with an alcohol such as dehydrated ethanol. A 50:50 mixture (w/w) is preferred. Stabilizers may also be added. Citric acid is a preferred stabilizer.

The products and methods of the present invention are further illustrated by the following example. The presentation of this example is by no way intended to limit applicants' invention in any way. Unless otherwise specified, all percentages are by weight.

EXAMPLE

One hundred grams of charcoal were placed in an oven at 120°C for about 16 hours. Nine hundred grams Cremophor EL® were added to make a 10% charcoal (w/w) Cremophor EL® slurry solution. The solution was heated to 45°C with a hot plate for three hours with mechanical stirring, followed by cooling to room temperature, followed by stirring for two additional hours. The slurry solution was then filtered twice using a $10\mu\text{m}$ filter and a $0.45\mu\text{m}$ filter.

The paclitaxel formulation was prepared by dissolving 6 mg/ml of paclitaxel in 50/50 (v/v) commercial or pre-treated Cremophor EL® and dehydrated ethanol. Two ml of the formulation solution were placed in a 6 cc glass vial. The vials were sealed with a Teflon faced cap and stored for 48 hours at 80°C . They were analyzed by HPLC for the concentration of paclitaxel. The results were as follows. It was found that 98.2% of the

paclitaxel remained in the sample treated with charcoal whereas 42.2% of the paclitaxel remained in the untreated sample. Thus, the processes of the present invention and the formulations produced thereby possess greater storage stability, particularly compared to identical formulations made without the treatment or purification of the present invention.

The pH value of both samples was measured following 1:10 dilution with water. The potassium concentration and the color of the samples were analyzed as well. The results are shown in the Table below.

TABLE

Sample	% Paclitaxel remaining (80°C for 48 hours)
Charcoal Treated Cremophor EL®	98.2
Untreated Cremophor EL®	42.2

The pH value of the samples was measured following 1:10 dilution with water. The potassium concentration of samples was analyzed. The color of the samples also was measured as shown in following:

Sample	K (ppm)	pH	Color (Vis 425 nm, AU)
Charcoal Treated Cremophor EL®	137.5	4.27	0.0381
Untreated Cremophor EL®	398.7	6.06	0.0516

PUBLICATIONS

1. MacEachern-Keith *et al*, Anal Chem 69 72-77 (1997)
2. Sampietro *et al*, J Microencapsulation 11(3):309-318 (1993)
3. Balasubramanian, *et al*, Solvent- and Concentration-Dependent Molecular Interactions of Taxol (Paclitaxel), Journal of Pharmaceutical Sciences 83(10) (1994)
4. Mensko-Liversidge, *et al*, Formulation and Antitumor Activity Evaluation of Nanocrystalline Suspensions of Poorly Soluble Anticancer Drugs, Pharmaceutical Research 13(2)(1996)
5. Sharma, *et al*, Novel Taxol Formulations: Preparation and Characterization of Taxol Containing Liposomes, Pharmaceutical Research 11(6) (1994)
6. Adams, *et al*, J Natl Cancer Inst Monogr 15,141 (1993)
7. Dordunoo, *et al*, International Journal of Pharmaceutics 133 191-201 (1996).

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- 8 Tarr, *et al* *A New Parenteral Vehicle for the Administration of Some Poorly Water Soluble Anti-Cancer Drugs*, *Journal of Parenteral Science & Technology* 41(1) (1987)
- 9 Kingston, *Pharma. Ther* 52 1-34 (1991)
- 10 Wenk, *et al.*, *Partitioning into Lipid Bilayers*, *Journal of Pharmaceutical Sciences* 85(2) (1996)

INDUSTRIAL APPLICABILITY

The present invention is useful the preparation of compositions, particularly pharmaceutical compositions containing polyethoxylated castor oils.

All patent and non-patent publications cited in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated as being incorporated herein by reference.

CLAIMS

- 1 A polyoxyethylated castor oil produced by
preparing a suspension of activated charcoal and a polyoxyethylated castor oil,
and
separating the activated charcoal from the polyoxyethylated castor oil.
- 2 The castor oil of Claim 1 wherein the charcoal is present in the suspension in an
amount of from 3 to about 20% (w/w)
- 3 The castor oil of Claim 1 wherein the activated charcoal is present in the suspension
in an amount of from about 5 to about 10 % (w/w)
- 4 The castor oil of Claim 1 wherein the activated charcoal has a surface area ranging
from about 500 m²/g to about 1300 m²/g.
- 5 The castor oil of Claim 1 further comprising heating the suspension prior to said
separating
- 6 The castor oil of Claim 5 wherein said heating is conducted at a temperature of from
about 30°C to about 60°C
- 7 The castor oil of Claim 6 wherein said heating is conducted for a period of time of
from about 1 to about 6 hours
- 8 The castor oil of Claim 1 wherein said separating comprises filtering the suspension
- 9 The castor oil of Claim 8 wherein said filtering comprises at least two filtration steps
using filters with successively smaller apertures
- 10 The castor oil of Claim 1 which is Cremophor EL[®]
- 11 A formulation comprising the castor oil of Claim 1 and an active agent.
- 12 The composition of Claim 11 wherein said active agent is an anti-neoplastic agent.
- 13 The composition of Claim 12 wherein said anti-neoplastic agent is a taxane
- 14 The composition of Claim 13 wherein said taxane is paclitaxel.
- 15 The composition of Claim 13 further comprising an alcohol
- 16 The composition of Claim 15 wherein said alcohol comprises dehydrated ethanol
- 17 The composition of Claim 13 further comprising an acid.
- 18 The composition of Claim 17 wherein said acid is citric acid.
- 19 A polyoxyethylated castor oil produced by

preparing a suspension of activated charcoal and a polyoxyethylated castor oil wherein the activated charcoal has a median surface area of about 900 m²/g, and is present in the suspension in an amount of from 3 to about 20% (w/w),

heating said suspension at a temperature of from about 30°C to about 60°C for a period of time of from about 1 to about 6 hours and

filtering the heated suspension to separate the activated charcoal from the castor oil

20 A polyoxyethylated castor oil formulation produced by

preparing a suspension of activated charcoal and a polyoxyethylated castor oil wherein the activated charcoal has a median surface area of about 900 m²/g, and is present in the suspension in an amount of from 3 to about 20% (w/w);

heating said suspension at a temperature of from about 30°C to about 60°C for a period of time of from about 1 to about 6 hours;

filtering the heated suspension to separate the activated charcoal from the castor oil and

adding an active agent to the filtered castor oil

21 The formulation of claim 20 wherein the active agent is a taxane

22 The formulation of claim 21 wherein the taxane is paclitaxel

23 The formulation of claim 22 wherein said adding further comprises adding dehydrated ethanol

24 The formulation of claim 23 wherein said adding further comprises adding citric acid.

25 The formulation of claim 24 wherein said castor oil is Cremophor EL[®]

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ABSTRACT

Purifying Polyalkoxyethylated Castor Oils with Activated Charcoal

Disclosed are polyoxyethylated castor oils produced by preparing a suspension of activated charcoal and a polyoxyethylated castor oil, and separating the activated charcoal from the polyoxyethylated castor oil. Also disclosed are compositions containing the treated castor oil and an active agent such as a pharmaceutical agent.