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DIVISION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación: 00007997 00000002

Folios: 2

Fecha (AMB): 2002-09-06 17:02:14

Trámite : 002 PATENTES Y REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

TRÁMITE : 002

EVENTO : 001

ACTUACIÓN : 538

Referencia : Expediente No. 00-007997

Asunto : Solicitud de patente para VEHÍCULOS VISCOSOS DE FASE SIMPLE NO ACUOSOS ESTABLES Y FORMULACIONES QUE UTILIZAN DICHS VEHICULOS

Solicitante : ALZA CORPORATION

Fecha de solicitud : 08 de febrero de 2000

Publicada en : la Gaceta No. 514 del 22 de Marzo de 2002

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 02-56,212 por valor de \$318.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44691 del 31 de diciembre de 2001.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 6 SEP 2002
Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

COLO 03981 801 011 6

MRE/JFR/ID-000124/WPCL3981



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Industria y Comercio
SUPERINTENDENCIA

1.4
1.4

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 00007997 00000002 Folios: 2
Fecha (AMB): 2002-09-06 17:02:14
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 56,212
FECHA : AGOSTO 26 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3344171	26/08/2002	34,463,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
	TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 2007

Colo 03981-001-011-6

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N° 00012119

REFERENCIA	Radicación	00 07997
	Trámite	002
	Evento	001
	Actuación	430
	Folios	030

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 07997, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 2-40
- . Ejemplos: folios 40-52
- . Capítulo reivindicatorio estudiado: folios 92-97
- . Se reivindica prioridad presentada en Estados Unidos, el 08.02.99, bajo el número 60/119170

Objeto de la invención

Según las reivindicaciones 1 a 35 de la presente solicitud, se refiere a vehículos no acuosos estables de fase simple y formulaciones que contienen dichos vehículos. Las formulaciones comprenden un agente de beneficio uniformemente suspendido en el vehículo, la formulación es capaz de ser almacenada a temperaturas que van desde el frío hasta la temperatura corporal por largos periodos de tiempo.

Clasificación internacional de patentes A 61 K 9/00

Claridad de la solicitud

El artículo 30 de la decisión 486 de la comisión de la comunidad andina establece que:
"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"

Teniendo en cuenta lo anterior, las reivindicaciones se relacionan con un número extremadamente grande de posibles combinaciones de compuestos, debido a que tales compuestos se definen con términos vagos como "vehículo viscoso", "disolvente", "tensioactivos" o "polímeros", los cuales abarcan un gran número de posibilidades. Se le recuerda al solicitante que las reivindicaciones deben ser claras por sí mismas y que una composición se define por sus componentes específicos y la proporción de los mismos para que se diferencie de las existentes en el estado de la técnica

Favor hacer las aclaraciones y correcciones del caso.

Excepciones a la patentabilidad

El art. 20d de la decisión 486 establece que *"no serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 30-35, que trata de "Un método para tratar un sujeto que sufre de una condición...", no es patentable.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 08.02.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	US 5071642	"Composiciones que contienen dihidropiridina"	10.12.91
2	WO 9827962	"Composición en gel de depósito inyectable y método para preparar la composición"	02.07.98
3	WO 9827963	"Composición en gel y métodos"	02.07.98
4	US 5385738	"Inyección de liberación sostenida"	31.06.95
5	US 5756450	"Monoésteres solubles en agua como solubilizadores para compuestos farmacológicamente activos y excipientes farmacéuticos y formas galénicas de ciclosporina novedosas"	26.05.98
6	US 4734284	"Preparaciones de etoposido"	29.03.88
7	WO 9639142	"Composiciones farmacéuticas que comprenden un inhibidor de proteinasa y un monoglicérido"	12.12.96

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina,

se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El art. 16 de la Decisión 486 contempla *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La patente US 5071642 presenta en sus ejemplos 1-4 composiciones que contienen polímeros y disolventes junto con nifedipina

La publicación WO 9827962 presenta composiciones que comprenden un polímero, un solvente y un emulsificante, junto con un agente de beneficio

La publicación WO 9827963 presenta composiciones que comprenden un polímero, un solvente y un emulsificante, junto con un agente de beneficio

La patente US 5385738 publica en sus ejemplos 12, 14 y 15 que contienen una proteína, un tensioactivo y un disolvente

La patente US 5756450 revela en sus ejemplos 13-22 composiciones que comprenden ciclosporina, un tensioactivo, un disolvente y/o un polímero

La patente US 4734284, en su ejemplo 4, revela composiciones que contiene etoposido, solvente y un polímero

La solicitud WO 9639142 publica composiciones que contienen un agente de beneficio, un disolvente, un polímero y un tensioactivo

Comparando elemento por elemento, las composiciones que se pretenden proteger son iguales a las reveladas en los documentos citados y pueden afectar la novedad de la presente solicitud.

Evaluación del NIVEL INVENTIVO

El art. 18 de la Decisión 486 contempla *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

La patente US 5071642 presenta en sus ejemplos 1-4 composiciones que contienen polímeros y disolventes junto con nifedipina

La publicación WO 9827962 presenta composiciones que comprenden un polímero, un solvente y un emulsificante, junto con un agente de beneficio

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La patente US 5756450 revela en sus ejemplos 13-22 composiciones que comprenden ciclosporina, un tensioactivo, un disolvente y/o un polímero

La patente US 4734284, en su ejemplo 4, revela composiciones que contiene etoposido, solvente y un polímero

La solicitud WO 9639142 publica composiciones que contienen un agente de beneficio, un disolvente, un polímero y un tensioactivo

Teniendo en cuenta el objeto de la solicitud, el cual es proporcionar composiciones que contienen un agente benéfico, un solvente, un tensioactivo y un polímero, es una derivación evidente del estado de la técnica ya que los documentos citados enseñan composiciones similares que tienen el mismo propósito.

Una persona versada en la materia utilizaría las enseñanzas de los documentos citados y fabricaría las composiciones que se pretenden proteger.

Finalmente, no se presentan ventajas de las composiciones que se pretenden proteger en relación con las del estado de la técnica.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5071642	1-13	Novedad
		1-29	Nivel Inventivo
2	WO 9827962	1-13	Novedad
		1-29	Nivel Inventivo
3	WO 9827963	1-13	Novedad
		1-29	Nivel Inventivo
4	US 5385738	1-13	Novedad
		1-29	Nivel Inventivo
5	US 5756450	1-13	Novedad
		1-29	Nivel Inventivo
6	US 5734284	1-13	Novedad
		1-29	Nivel Inventivo
7	WO 9639142	1-13	Novedad
		1-29	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 sesenta días contados a partir de la fecha de la 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 5 del título primero de la Circular Única N° 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 17 FEB. 2005

CONCEPTO TÉCNICO Número 0189	EXAMINADOR TÉCNICO Código 202024
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United States Patent [19]**Lahr et al.**[11] **Patent Number:** **5,071,642**[45] **Date of Patent:** **Dec. 10, 1991**[54] **DIHYDROPYRIDINE CONTAINING COMPOSITIONS**[75] **Inventors:** Wolfgang Lahr, Laupheim; Hans Köhne, Obersulmetingen; Frank Musculus, Achstetten; Helm-Uwe Schmersahl, Linscham, all of Fed. Rep. of Germany[73] **Assignee:** Dr. Rentschler Arzneimittel GmbH & Co., Laupheim, Fed. Rep. of Germany[21] **Appl. No.:** 111,623[22] **Filed:** Oct. 21, 1987[30] **Foreign Application Priority Data**

Oct. 23, 1986 [DE] Fed. Rep. of Germany 3636123

[51] **Int. Cl.³** A61K 31/485[52] **U.S. Cl.** 424/474; 514/19; 514/356; 514/302[58] **Field of Search** 514/19, 302, 356; 424/78[56] **References Cited****U.S. PATENT DOCUMENTS**4,562,069 12/1985 Hegazy et al. 514/356
4,703,038 10/1987 Garthoff et al. 514/19**FOREIGN PATENT DOCUMENTS**

0248548 12/1987 European Pat. Off. .

Primary Examiner—Prince E. Willis*Assistant Examiner*—John F. McNally*Attorney, Agent, or Firm*—Cohen, Pontani & Lieberman[57] **ABSTRACT**

Solid drug formulations for oral administration containing one or more dihydropyridines in doses of between 10 and 240 mg and suitable to be administered as a single dose per day for the treatment of circulatory disorders and high blood pressure.

11 Claims, No Drawings

EXAMPLE 1

Nifedipine	10.0 g
Polyethylene glycol (average molecular weight 200)	80.0 g
Polyethylene glycol (average molecular weight 4,000)	30.0 g
Stearyl alcohol	30.0 g
Polyvinylpyrrolidone	5.0 g

The two polyethylene glycols are mixed together with heating and the nifedipine is dissolved therein with stirring. The stearyl alcohol is added to the melt and also melted. After addition of the polyvinylpyrrolidone the still-liquid mass is poured into hard gelatin capsules, size 3, in an amount of 310 mg, corresponding to 20 mg of nifedipine.

EXAMPLE 2

Nifedipine	10 g
Polyethylene glycol (average molecular weight 200)	90 g
Polyethylene glycol (average molecular weight 20,000)	25 g
Stearyl alcohol	30 g

The preparation is effected in a manner similar to Example 1. The melt is filled into hard gelatin capsules, size 1, in an amount of 465 mg, corresponding to 30 mg of nifedipine.

EXAMPLE 3

Nifedipine	10 g
Polyethylene glycol (average molecular weight 200)	90 g
Octyl alcohol	15 g

The nifedipine is stirred into the molten polyethylene glycol and dissolved. The fatty alcohol is then added. The melt is poured into hard gelatin capsules, size 0, in an amount of 620 mg, corresponding to 40 mg of nifedipine.

EXAMPLE 4

Nifedipine	40 g
Polyethylene glycol (average molecular weight 6,000)	440 g
Stearyl alcohol	120 g
Polyvinylpyrrolidone	20 g

The melt is prepared in the manner indicated in Example 1. The melt is then poured out and after hardening is comminuted by means of a screening machine to an upper particle size of 1.0 mm.

The ground powder is mixed with 1% by weight each of magnesium stearate and colloidal silica. The mixture is compacted to form oblong tablets containing 60 mg nifedipine.

EXAMPLE 5

Nifedipine	60.0 g
Polyethylene glycol (average molecular weight 2,000)	450.3 g
Stearyl alcohol	112.6 g

-continued

Polyoxyethylene stearic acid ester (Myrj ® 59)	75.1 g
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The preparation of the melt and of the tablets having a content of 60 mg of nifedipine per tablet is effected in a manner similar to Example 4.

EXAMPLE 6

Nifedipine	40.0 g
Polyethylene glycol (average molecular weight 2,000)	262.5 g
Stearyl alcohol	75.0 g
Polyoxyethylene sorbitan fatty acid ester (polysorbate 80)	87.5 g

The melt is prepared in a manner similar to Example 5. The melt is filled into hard gelatin capsules, size 1, with a nifedipine content of 40 mg.

In Vitro Liberation Rates

The liberation behavior of the active substance from the drug forms was tested in accordance with the US Pharmacopoeia. The pH of the liberation medium was maintained constant at 1.5 (values given in % of the amount of active substance present in each case).

As comparison there was used an ordinary commercial retard tablet (Adalat ® retard, 20 mg).

TABLE 1

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Control
	%	%	%	%	%	%	%
1 h	13	13	19	21.5	12	23	23
2 h	22	23	25	41	17	31	45
3 h	34.5	28	36	55	24	40	57
4 h	48	34	47	65	28	46	66
5 h	60	44	56	72	34	51	71
6 h	69	53	68	77	37	55	74
7 h	81	62	79	81	40	59	76

Examples 1 to 6 show no substantial differences from the control in liberation behavior which demonstrates that blood levels are maintained for a longer period than heretofore produced in vivo in the prior art.

The formulations of the present invention were tested as to their bioavailability on test subjects.

EXAMPLE 7

The drug form in accordance with Example 1 was tested on each of four healthy volunteers of an age of between 18 and 40 years. They received 2 capsules of 20 mg each as single dose corresponding to 40 mg nifedipine, or 3 capsules of 20 mg each as single dose corresponding to 60 mg nifedipine. At given time intervals, blood was taken from the antecubital vein and the plasma examined for nifedipine by selective HPLC determination.

Results

Time (hours)	0.5	1	2	3	4	6	9	12	24	36
40 mg average of N = 4 (ng/ml)	4.5	6.9	8.3	6.3	6.5	4.7	5.8	6.6	4.6	1.8
60 mg average of N = 4 (ng/ml)	6.9	10.4	12.6	9.9	8.6	11.1	8.7	10.1	7.7	2.5

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 9/00, 47/34		(11) International Publication Number: WO 98/27962								
A2		(43) International Publication Date: 2 July 1998 (02.07.98)								
(21) International Application Number: PCT/US97/23341 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). SHINN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHUEY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, HU, IL, 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, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GI, GM, KE, LS, MW, SD, SZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NI, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>								
(54) Title: INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF PREPARING THE COMPOSITION <table border="1"><caption>Disposition Force (g) Data</caption><thead><tr><th>Formulation</th><th>Disposition Force (g)</th></tr></thead><tbody><tr><td>60% TRICACETIN 40% PLGA 502</td><td>~39</td></tr><tr><td>60% NMP 40% PLGA 502</td><td>~7</td></tr><tr><td>EMULSIFIED WITH 10% ETHANOL IN WATER</td><td>~1</td></tr></tbody></table>			Formulation	Disposition Force (g)	60% TRICACETIN 40% PLGA 502	~39	60% NMP 40% PLGA 502	~7	EMULSIFIED WITH 10% ETHANOL IN WATER	~1
Formulation	Disposition Force (g)									
60% TRICACETIN 40% PLGA 502	~39									
60% NMP 40% PLGA 502	~7									
EMULSIFIED WITH 10% ETHANOL IN WATER	~1									
(57) Abstract An injectable depot gel composition containing a polymer, a solvent that can dissolve the polymer and thereby form a viscous gel, a beneficial agent; and an emulsifying agent in the form of a dispersed droplet phase in the viscous gel. The injectable depot gel composition can be prepared by mixing the polymer and the solvent so that the solvent dissolves the polymer and forms a viscous gel. The beneficial agent is dissolved or dispersed in the viscous gel and the emulsifying agent is mixed with the beneficial agent containing viscous gel. The emulsifying agent forms a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition. The injectable depot gel composition can deliver a beneficial agent to a human or animal with a desired release profile.										

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1 DESCRIPTION OF THE PREFERRED EMBODIMENTS

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3 As explained above, one aspect of the present invention relates to an
4 injectable depot gel composition comprising:

5 A) a biocompatible polymer;

6 B) a solvent that dissolves the biocompatible polymer and forms a viscous
7 gel;

8 C) a beneficial agent; and

9 D) an emulsifying agent in the form of a dispersed droplet phase in the
10 viscous gel.

11 The polymer, solvent and emulsifying agents of the invention must be
12 biocompatible, that is they must not cause irritation or necrosis in the environment
13 of use. The environment of use is a fluid environment and may comprise a
14 subcutaneous or intramuscular portion or body cavity of a human or animal.

15 Polymers that may be useful in the invention may be biodegradable and may
16 include, but are not limited to polylactides, polyglycolides, polycaprolactones,
17 polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters,
18 polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates,
19 polyphosphazenes, succinates, poly(malic acid), poly(amino acids),
20 polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan,
21 and copolymers, terpolymers and mixtures thereof.

22 The polymer may be a polylactide, that is, a lactic acid-based polymer that
23 can be based solely on lactic acid or can be a copolymer based on lactic acid and
24 glycolic acid which may include small amounts of other comonomers that do not
25 substantially affect the advantageous results which can be achieved in accordance
26 with the present invention. As used herein, the term "lactic acid" includes the
27 isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term
28 "glycolic acid" includes glycolide. The polymer may have a monomer ratio of
29 lactic acid/glycolic acid of from about 100:0 to about 15:85, preferably from about

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1 60:40 to about 75:25 and an especially useful copolymer has a monomer ratio of
2 lactic acid/glycolic acid of about 50:50.

3 The lactic acid-based polymer has a number average molecular weight of
4 from about 1,000 to about 120,000, preferably from about 10,000 to about 30,000
5 as determined by gas phase chromatography. As indicated in aforementioned U.S.
6 Patent No. 5,242,910, the polymer can be prepared in accordance with the
7 teachings of U.S. Patent No. 4,443,340. Alternatively, the lactic acid-based
8 polymer can be prepared directly from lactic acid or a mixture of lactic acid and
9 glycolic acid (with or without a further comonomer) in accordance with the
10 techniques set forth in U.S. Patent No. 5,310,865. The contents of all of these
11 patents are incorporated by reference. Suitable lactic acid-based polymers are
12 available commercially. For instance, 50:50 lactic acid:glycolic acid copolymers
13 having molecular weights of 10,000, 30,000 and 100,000 are available from
14 Boehringer Ingelheim (Petersburg, VA).

15 The biocompatible polymer is present in the composition in an amount
16 ranging from about 5 to about 80% by weight, preferably from about 20 to about
17 50% by weight and often 35 to 45% by weight of the viscous gel, the viscous gel
18 comprising the combined amounts of the biocompatible polymer and the solvent.
19 Once in place in the environment of use, the solvent will diffuse slowly away from
20 the depot and the polymer will slowly degrade by hydrolysis.

21 The solvent must be biocompatible and is selected so as to dissolve the
22 polymer to form a viscous gel that can maintain particles of the beneficial agent
23 dissolved or dispersed and isolated from the environment of use prior to release.
24 Illustrative solvents which can be used in the present invention include but are not
25 limited to triacetin, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl
26 acetate, benzyl benzoate, ethyl acetate, methyl ethyl ketone, dimethylformamide,
27 dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid,
28 and 1-dodecylazacyclo-heptan-2-one and mixtures thereof. The preferred solvents
29 are triacetin and N-methyl-2-pyrrolidone. Triacetin provides a high level of

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1 emulsifying agent and (c) beneficial agent. Prior to use the beneficial agent is mixed
2 with the emulsifying agent, and that solution or suspension is mixed with the
3 polymer/solvent mixture to prepare the injectable depot implant for use.

4 The emulsifying agent is present in an amount ranging from about 5 to about
5 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based
6 on the amount of the injectable depot gel composition, that is the combined amounts
7 of polymer, solvent, emulsifying agent and beneficial agent. Illustrative
8 emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones,
9 aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols,
10 propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures
11 thereof. Especially preferred are water, ethanol, and isopropyl alcohol and
12 solutions and mixtures thereof. The type of emulsifying agent affects the size of the
13 dispersed droplets. For instance, ethanol will provide droplets that have average
14 diameters that can be on the order of ten times larger than the droplets obtained with
15 an isotonic saline solution containing 0.9% by weight of sodium chloride at 21°C.

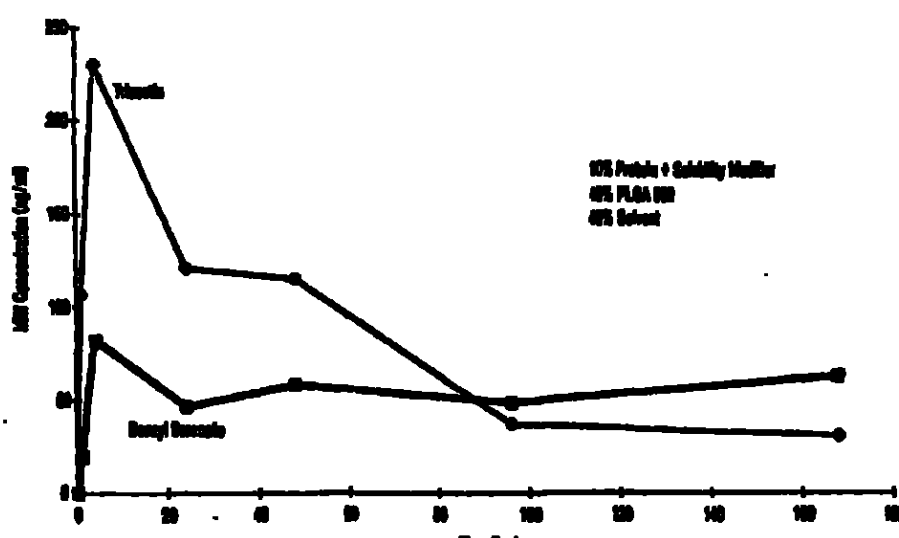
16 While normally no other components are present in the composition, to the
17 extent that conventional optional ingredients are desired, such as polyethylene
18 glycol, hygroscopic agents, stabilizing agents and others, they are used in an
19 amount that does not substantially affect the advantageous results which can be
20 attained in accordance with the present invention.

21 To illustrate various aspects of the invention further, Figure 3 shows the
22 viscosities at different shear rates using water alone and an aqueous mixture
23 containing 10% by volume of ethanol at a weight ratio of 2:1 (gel:emulsifying
24 agent) using a viscous gel formed from 50% by weight of a 50:50 lactic
25 acid:glycolic acid copolymer and 50% by weight of triacetin compared to the
26 viscosities of the viscous gel without emulsifying agent.

27 It is to be understood that the emulsifying agent of the present invention does
28 not constitute a mere diluent that reduces viscosity by simply decreasing the
29 concentration of the components of the composition. The use of conventional



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(21) International Application Number: PCT/US97/23659 (22) International Filing Date: 18 December 1997 (18.12.97) (30) Priority Data: 60/033,439 20 December 1996 (20.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODBECK, Kevin, J. [US/US]; 2383 South Court Street, Palo Alto, CA 94301 (US). GAYNOR-DUARTE, Ann, T. [US/US]; 13063 Broadway Terrace, Oakland, CA 94611 (US). SHEN, Theodore, T. [US/US]; 18 Dockside Circle, Redwood City, CA 94065 (US). (74) Agents: DHURY, John, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, 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, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, MC, NI, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	
(54) Title: GEL COMPOSITION AND METHODS  (57) Abstract Methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject are described, and include, for example, compositions having burst indices of 8 or less for systemic applications and systems releasing 10 % or less of the total dose of beneficial agent in the first 24 hours after implantation for local applications. The compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent.		

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1 used herein means that 7% or less by weight of the solvent is soluble in or
2 miscible with water. For the purposes of this disclosure, solubility values of
3 solvent in water are considered to be determined at 20°C. Since it is
4 generally recognized that solubility values as reported may not always be
5 conducted at the same conditions, solubility limits recited herein as percent
6 by weight miscible or soluble with water as part of a range or upper limit may
7 not be absolute. For example, if the upper limit on solvent solubility in water
8 is recited herein as "7% by weight", and no further limitations on the solvent
9 are provided, the solvent "triacetin", which has a reported solubility in water of
10 7.17 grams in 100 ml of water, is considered to be included within the limit of
11 7%. A solubility limit in water of less than 7% by weight as used herein does
12 not include the solvent triacetin or solvents having solubilities in water equal
13 to or greater than triacetin.

14 The polymer, solvent and other agents of the invention must be
15 biocompatible; that is they must not cause irritation or necrosis in the
16 environment of use. The environment of use is a fluid environment and may
17 comprise a subcutaneous or intramuscular portion or body cavity of a human
18 or animal.

19 Polymers that may be useful in the invention may be biodegradable
20 and may include, but are not limited to polylactides, polyglycolides,
21 polycaprolactones, polyanhydrides, polyamines, polyurethanes,
22 polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals,
23 polycarbonates, polyorthocarbonates, polyphosphazenes, succinates,
24 poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol,

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1 polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and
2 mixtures thereof.

3 Presently preferred polymers are polylactides, that is, a lactic acid-
4 based polymer that can be based solely on lactic acid or can be a copolymer
5 based on lactic acid and glycolic acid which may include small amounts of
6 other comonomers that do not substantially affect the advantageous results
7 which can be achieved in accordance with the present invention. As used
8 herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid,
9 DL-lactic acid and lactide while the term "glycolic acid" includes glycolide.
10 Most preferred are poly(lactide-co-glycolide)copolymers, commonly referred
11 to as PLGA. The polymer may have a monomer ratio of lactic acid/glycolic
12 acid of from about 100:0 to about 15:85, preferably from about 60:40 to about
13 75:25 and an especially useful copolymer has a monomer ratio of lactic
14 acid/glycolic acid of about 50:50.

15 The lactic acid-based polymer has a number average molecular weight
16 of from about 1,000 to about 120,000, preferably from about 5,000 to about
17 30,000 as determined by gas phase chromatography. As indicated in
18 aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in
19 accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively,
20 the lactic acid-based polymer can be prepared directly from lactic acid or a
21 mixture of lactic acid and glycolic acid (with or without a further comonomer)
22 in accordance with the techniques set forth in U.S. Patent No. 5,310,885.
23 The contents of all of these patents are incorporated by reference. Suitable
24 lactic acid-based polymers are available commercially. For instance, 50:50

1 20°C, and weighed, and a candidate solvent is added dropwise. The solution
2 is swirled to observe phase separation. When the saturation point appears to
3 be reached, as determined by observation of phase separation, the solution
4 is allowed to stand overnight and is re-checked the following day. If the
5 solution is still saturated, as determined by observation of phase separation,
6 then the percent (w/w) of solvent added is determined. Otherwise more
7 solvent is added and the process repeated. Solubility or miscibility is
8 determined by dividing the total weight of solvent added by the final weight of
9 the solvent/water mixture. When solvent mixtures are used, for example 20%
10 triacetin and 80% benzyl benzoate, they are pre-mixed prior to adding to the
11 water.

12 Solvents useful in this invention are generally less than 7% water
13 soluble by weight as described above. Solvents having the above solubility
14 parameter may be selected from the lower alkyl and aralkyl esters of aryl
15 acids such as benzoic acid, the phthalic acids, salicylic acid, lower alkyl
16 esters of citric acid, such as triethyl citrate and tributyl citrate and the like, and
17 aryl, aralkyl and lower alkyl ketones. Among preferred solvents are those
18 having solubilities within the foregoing range selected from (i) compounds
19 having the following structural formulas :



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1 and (i)



4 in which R₁ is aryl or aralkyl, R₂ is lower alkyl or aralkyl, and R₁ and R₂ are
5 optionally the same or different, with the proviso that when each of R₁ and R₂
6 are lower alkyl, the total carbon atoms in R₁ and R₂ combined are 4 or more,
7 and (ii) lower alkyl and aralkyl esters of phthalic acid, isophthalic acid and
8 terephthalic acid and (iii) lower alkyl and aralkyl esters of citric acid. For the
9 purposes hereof, lower alkyl means straight or branched chain hydrocarbons
10 having 1-6 carbon atoms, optionally substituted with non-interfering
11 substituents; aralkyl means (lower alkyl)phenyl, e.g., benzyl, phenethyl, 1-
12 phenylpropyl, 2-phenylpropyl, and the like wherein the alkyl moiety contains
13 from 1-6 carbon atoms; and aryl means phenyl, optionally substituted by non-
14 interfering substituents. Many of the solvents useful in the invention are
15 available commercially (Aldrich Chemicals, Sigma Chemicals) or may be
16 prepared by conventional esterification of the respective arylalkanoic acids
17 using acid halides, and optionally esterification catalysts, such as described in
18 US Patent No. 5,556,805, which is incorporated herein by reference, and in
19 the case of ketones, oxidation of their respective secondary alcohol
20 precursors.

21 Art recognized benzoic acid derivatives from which solvents having the
22 requisite solubility may be selected include: 1,4-cyclohexane dimethanol
23 dibenzoate, diethylene glycol dibenzoate, dipropylene glycol dibenzoate,

1 polypropylene glycol dibenzoate, propylene glycol dibenzoate, diethylene
2 glycol benzoate and dipropylene glycol benzoate blend, polyethylene glycol
3 (200) dibenzoate, iso decyl benzoate, neopentyl glycol dibenzoate, glyceryl
4 tribenzoate, pentaerythritol tetrabenzoate, cumylphenyl benzoate, trimethyl
5 pentanediol dibenzoate.

6 Art recognized phthalic acid derivatives from which solvents having the
7 requisite solubility may be selected include: Alkyl benzyl phthalate, bis-
8 cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate,
9 dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate,
10 butyl octyl phthalate, diisoheptyl phthalate, butyl octyl phthalate, diisononyl
11 phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-iso octyl phthalate,
12 dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear
13 heptyl, nonyl, phthalate, linear heptyl, nonyl, undecyl phthalate, linear nonyl
14 phthalate, linear nonyl undecyl phthalate, linear dinonyl, didecyl phthalate
15 (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate,
16 undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and
17 didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

18 Preferred solvents include the lower alkyl and aralkyl esters of the aryl
19 acids described above. Representative acids are benzoic acid and the
20 phthalic acids, such as phthalic acid, isophthalic acid, and terephthalic acid.
21 Most preferred solvents are derivatives of benzoic acid and include, but are
22 not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl
23 benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, tert-butyl

1 benzoate, isoamyl benzoate and benzyl benzoate, with benzyl benzoate
2 being most especially preferred. Preferred solvent mixtures are those in
3 which benzyl benzoate is the primary solvent, and mixtures formed of benzyl
4 benzoate and either triacetin, tributyl citrate, triethyl citrate or N-methyl-2-
5 pyrrolidone. Preferred mixtures are those in which benzyl benzoate is
6 present by weight in an amount of 50% or more, more preferably 60% or
7 more and most preferably 80% or more of the total amount of solvent present.
8 Especially preferred mixtures are those of 80/20 mixtures by weight of benzyl
9 benzoate/triacetin and benzyl benzoate/N-methyl-2-pyrrolidone.

10 It has been surprisingly found that the solvents described above
11 having a miscibility in water of less than 7% by weight may be mixed with one
12 or more additional miscible solvents ("component solvents"). Component
13 solvents compatible and miscible with the primary solvent may have a higher
14 miscibility with water and the resulting mixtures may still exhibit significant
15 restriction of water uptake into the implant. Such mixtures will be referred to
16 as "component solvent mixtures." Useful component solvent mixtures may
17 exhibit solubilities in water greater than the primary solvents themselves,
18 typically between 0.1 weight percent and up to and including 50 weight
19 percent, preferably up to and including 30 weight percent, and most
20 preferably up to an including 10 weight percent, without detrimentally
21 affecting the restriction of water uptake exhibited by the implants of the
22 invention. Especially preferred are component solvent mixtures having a
23 solubility in water of about 0.1% to about 7% by weight.

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1 Component solvents useful in component solvent mixtures are those
2 solvents that are miscible with the primary solvent or solvent mixture, and
3 include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate,
4 tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides,
5 triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene,
6 silicone fluid, glycerin, ethylene glycol, polyethylene glycol, octanol, ethyl
7 lactate, propylene glycol, propylene carbonate, ethylene carbonate,
8 butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-
9 pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl
10 ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam,
11 decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one, and
12 mixtures thereof.

13 In an especially preferred embodiment, the primary solvent is selected
14 from lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-
15 acid based polymer, most preferably PLGA, having a number average
16 molecular weight of between about 8,000 to about 13,000, preferably about
17 10,000. Presently, the most preferred solvents are benzyl benzoate and the
18 lower alkyl esters of benzoic acid. The benzoic acid esters may be used
19 alone or in a mixture with other miscible solvents, e.g., triacetin, as described
20 herein. Implants are prepared as viscous gels in which the beneficial agent is
21 dissolved or dispersed substantially throughout, and such compositions are
22 useful both for systemic and local administration of beneficial agent, whether
23 or not initial burst is an important consideration. Additionally, use of esters of
24 benzoic acid provides increased control of water migration resulting in

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1 viscosity, to permit a reasonable force to dispense the viscous gel from a
2 needle, and the potential burst effect. Highly viscous gels enable the
3 beneficial agent to be delivered without exhibiting a significant burst effect,
4 but may make it difficult to dispense the gel through a needle. In those
5 instances, an emulsifying agent may optionally be added to the composition.
6 Also, since the viscosity may generally be lowered as the temperature of the
7 composition increases, it may be advantageous in certain applications to
8 reduce the viscosity of the gel by heating to provide a more readily injectable
9 composition.

10 For instance, as shown in Figure 1, a gel prepared from 40% by weight
11 of a 50:50 lactic acid:glycolic polymer and 60% by weight of triacetin required
12 about 40 psig to dispense the gel through a standard 20 gauge needle at 2
13 cc/min while a gel prepared from the same amount of polymer with 60% by
14 weight of N-methyl-2-pyrrolidone required only about 8 psig. Figure 1 further
15 shows that when the emulsifying agent (in this case 33% by weight of a 10%
16 ethanol solution) is added to the viscous gel according to the invention, the
17 dispense force needed is only about 2 psig. The shear thinning
18 characteristics of the depot gel compositions of the present invention allow
19 them to be readily injected into an animal including humans using standard
20 gauge needles without requiring undue dispensing pressure.

21 When the emulsifying agent is mixed with the viscous gel formed from
22 the polymer and the solvent using conventional static or mechanical mixing
23 devices, such as an orifice mixer, the emulsifying agent forms a separate
24 phase composed of dispersed droplets of microscopic size that typically have

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1 an average diameter of less than about 100 microns. The continuous phase
2 is formed of the polymer and the solvent. The particles of the beneficial agent
3 may be dissolved or dispersed in either the continuous phase or the droplet
4 phase. In the resulting thixotropic composition, the droplets of emulsifying
5 agent elongate in the direction of shear and substantially decrease the
6 viscosity of the viscous gel formed from the polymer and the solvent. For
7 instance, with a viscous gel having a viscosity of from about 5,000 to about
8 50,000 poise measured at 1.0 sec^{-1} at 25°C , one can obtain a reduction in
9 viscosity to less than 100 poise when emulsified with a 10% ethanol/water
10 solution at 25°C as determined by Haake Rheometer.

11 When used, the emulsifying agent typically is present in an amount
12 ranging from about 5 to about 80%, preferably from about 20 to about 60%
13 and often 30 to 50% by weight based on the amount of the injectable depot
14 gel composition, that is the combined amounts of polymer, solvent,
15 emulsifying agent and beneficial agent. Emulsifying agents include, for
16 example, solvents that are not fully miscible with the polymer solvent or
17 solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols,
18 esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred
19 emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol,
20 water, and solutions and mixtures thereof. Especially preferred are water,
21 ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type
22 of emulsifying agent affects the size of the dispersed droplets. For instance,
23 ethanol will provide droplets that have average diameters that can be on the

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1 order of ten times larger than the droplets obtained with an isotonic saline
2 solution containing 0.9% by weight of sodium chloride at 21°C.

3 Figure 3 shows the viscosities at different shear rates using water
4 alone and an aqueous mixture containing 10% by volume of ethanol at a
5 weight ratio of 2:1 (gel:emulsifying agent) using a viscous gel formed from
6 50% by weight of a 50:50 lactic acid:glycolic acid copolymer and 50% by
7 weight of triacetin compared to the viscosities of the viscous gel without
8 emulsifying agent.

9 It is to be understood that the emulsifying agent does not constitute a
10 mere diluent that reduces viscosity by simply decreasing the concentration of
11 the components of the composition. The use of conventional diluents can
12 reduce viscosity, but can also cause the burst effect mentioned previously
13 when the diluted composition is injected. In contrast, the injectable depot
14 composition of the present invention can be formulated to avoid the burst
15 effect by selecting the solvent and emulsifying agent so that once injected
16 into place, the emulsifying agent has little impact on the release properties of
17 the original system.

18 Since the implant systems of the present invention preferably are
19 formed as viscous gels, the means of administration of the implants is not
20 limited to injection, although that mode of delivery may often be preferred.
21 Where the implant will be administered as a leave-behind product, it may be
22 formed to fit into a body cavity existing after completion of surgery or it may
23 be applied as a flowable gel by brushing or palleting the gel onto residual

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United States Patent [19]
Yamahira et al.

[11] Patent Number: 5,385,738
[45] Date of Patent: * Jan. 31, 1995

- [34] SUSTAINED-RELEASE INJECTION
- [75] Inventors: Yoshiya Yamahira, Kobe; Keiji Fujitaka, Amagasaki; Shigeji Sato, Ibaraki; Yoshihiro Takada, Takatsuki, all of Japan
- [73] Assignee: Sumitomo Pharmaceuticals Company, Ltd., Osaka, Japan
- [*] Notice: The portion of the term of this patent subsequent to Sep. 27, 2005 has been disclaimed.
- [21] Appl. No.: 844,929
- [22] Filed: Mar. 4, 1992

Related U.S. Application Data

- [63] Continuation of Ser. No. 488,531, Feb. 28, 1990, abandoned, which is a continuation of Ser. No. 849,968, Apr. 10, 1986, abandoned, which is a continuation-in-part of Ser. No. 660,044, Oct. 12, 1984, abandoned.

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- [31] Int. Cl.⁴ A61K 9/14; A61K 9/50; A61F 2/02; B01J 13/02
- [32] U.S. Cl. 424/489; 424/423; 424/424; 424/426; 424/499; 428/402.2; 428/402.24; 514/801; 514/953; 514/963; 514/964; 514/965; 264/4.1
- [58] Field of Search 424/85.4, 85.5, 85.6, 424/85.7, 422, 423, 424, 426, 489, 499; 514/801, 953, 963, 964, 965; 264/4.1; 428/402.2, 402.24

[36] References Cited

U.S. PATENT DOCUMENTS

2,518,510	8/1950	Welch et al.	424/78
3,016,895	1/1962	Sato	
3,857,932	12/1974	Shepherd et al.	
4,181,731	1/1980	Yoshida et al.	

4,191,741	3/1980	Hudson et al.	424/19
4,245,635	1/1981	Kontos	
4,347,234	8/1982	Wahlig et al.	
4,376,765	3/1983	Troust et al.	514/12
4,442,051	4/1984	Rowe et al.	
4,465,622	8/1984	Nobuhara et al.	424/85
4,474,753	10/1984	Hadam et al.	424/85
4,503,035	3/1985	Paska et al.	424/85
4,507,281	3/1985	Ascalai et al.	424/85
4,536,387	8/1985	Sakamoto et al.	
4,604,284	8/1986	King et al.	530/351
4,609,346	9/1986	Hirataki	424/85
4,855,134	8/1989	Yamahira et al.	424/85.7

FOREIGN PATENT DOCUMENTS

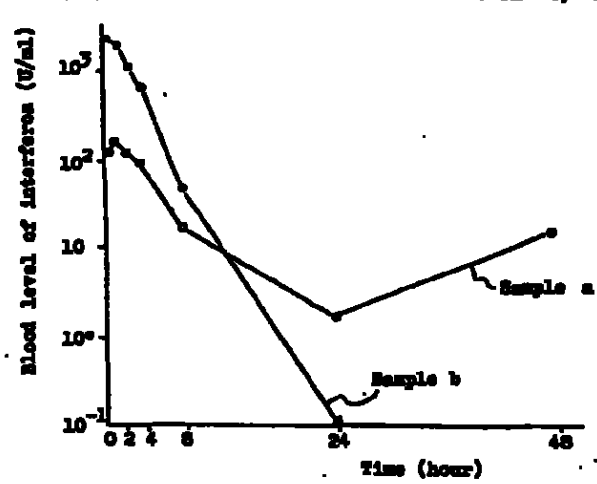
0094157	11/1983	European Pat. Off.	
0098110	1/1984	European Pat. Off.	
0134289	3/1985	European Pat. Off.	
102519	8/1980	Japan	
642385	11/1950	United Kingdom	
1567503	5/1980	United Kingdom	
2042882	10/1980	United Kingdom	
2067072	7/1981	United Kingdom	
2091554	1/1982	United Kingdom	
83/01198	4/1983	WIPO	

Primary Examiner—G. S. Kishore
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Attorney, Agent, or Firm—Birch, Stewart, Kolach & Birch

[57] ABSTRACT

The present invention relates to a sustained-release injection, which comprises a suspension of a powder comprising an active ingredient and a pharmaceutically acceptable biodegradable carrier (e.g. proteins, polysaccharides and synthetic high molecular compounds, preferably collagen, atelocollagen, gelatin, and a mixture thereof) in a viscous solvent for injection (e.g. vegetable oils, polyethylene glycol, propylene glycol, silicone oil, and medium-chain fatty acid triglycerides). The sustained-release injection can release the active ingredient at an effective level for a long period of time when injected.

33 Claims, 1 Drawing Sheet



sesame oil to give an oily suspension type, sustained-release preparation.

EXAMPLE 10

Gelatin (10 g) is dissolved in distilled water (100 ml) and thereto are added indomethacin (0.5 g), arginine (0.292 g) and 37% formaldehyde (1 ml). The mixture is lyophilized and pulverized at a low temperature using liquid nitrogen. The pulverized product thus obtained is suspended in sesame oil to give an oily suspension type, sustained-release preparation.

EXAMPLE 11

Gelatin (10 g) is dissolved in distilled water (100 ml). To the solution (5 ml) is added hGRF(1-44)NH₂ (i.e. human GRF consisting of 44 amino acids) (20 mg), and the mixture is lyophilized. The lyophilized product is pulverized at a low temperature using liquid nitrogen to obtain a powder of GRF - gelatin composite. The powdery composite (100 mg) is suspended in sesame oil (3 ml) to give a sustained-release oily suspension.

EXAMPLE 12

IGF-I (1 mg) is dissolved in a phosphate buffer containing 2% atelocollagen (2 ml), and the solution is lyophilized. The composite thus obtained is pulverized at a low temperature using liquid nitrogen and then suspended in polyethylene glycol (3 ml) to give a sustained-release oily suspension.

EXAMPLE 13

B-HGH (biosynthetic human growth hormone containing glycine 800 mg) (100 IU) is dissolved in 10% aqueous gelatin solution (3 ml) and the solution is lyophilized. The composite thus obtained is pulverized at a low temperature using liquid nitrogen and then suspended in sesame oil (10 ml) to give a sustained-release oily suspension.

EXAMPLE 14

IGF-I (1 mg) is dissolved in a phosphate buffer containing 2% atelocollagen (2 ml), and the solution is lyophilized. The composite thus obtained is pulverized at a low temperature using liquid nitrogen and then suspended in cotton seed oil (5 ml) to give a sustained-release oily suspension.

EXAMPLE 15

B-HGH (biosynthetic human growth hormone containing glycine 800 mg) (100 IU) is dissolved in 10% aqueous gelatin solution (3 ml) and the solution is lyophilized. The composite thus obtained is pulverized at a low temperature using liquid nitrogen, and the pulverized product (100 mg) is suspended in polyethylene glycol (5 ml) to give a sustained-release oily suspension.

What is claimed is:

1. A sustained-release preparation, which comprises a suspension of a powder in an injectable viscous solvent, said powder comprising a pharmaceutically effective amount of an active ingredient and a pharmaceutically acceptable biodegradable carrier selected from the group consisting of proteins, polysaccharides and synthetic high molecular compounds.

2. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of indomethacin, bio-hormones, interferons, interleukins, tumor necrosis factor, and other cytokines, and the carrier is selected from the group consisting of proteins,

polysaccharides, polyglycolic acid, polylactic acid, and polyglutamic acid.

3. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of indomethacin, bio-hormones, interferons, interleukins, tumor necrosis factor, and other cytokines, and the carrier is selected from the group consisting of collagen, gelatin, albumin, chitin, polyglycolic acid, and polylactic acid.

4. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of bio-hormones, interferons, interleukins, tumor necrosis factor, and other cytokines.

5. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of growth hormone, growth hormone releasing factor, somatomedines, and calcitonin.

6. The preparation according to claim 1, wherein the biodegradable carrier is polyalanine and the active ingredient is interferon.

7. The preparation according to claim 1, wherein the biodegradable carrier is albumin and the active ingredient is interferon.

8. The preparation according to claim 1, wherein the biodegradable carrier is polyglutamic acid and the active ingredient is indomethacin.

9. The preparation according to claim 1, wherein the biodegradable carrier is selected from the group consisting of proteins and polysaccharides.

10. The preparation according to claim 1, wherein the biodegradable carrier is selected from the group consisting of collagen, gelatin, albumin and a mixture thereof.

11. The preparation according to claim 1, wherein the viscous solvent for injection is selected from the group consisting of vegetable oils, polyethylene glycol, propylene glycol, silicone oil, and medium-chain fatty acid triglycerides.

12. The preparation according to claim 1, wherein the viscous solvent for injection is selected from the group consisting of peanut oil, cotton seed oil, sesame oil, castor oil, olive oil, corn oil, and iodinated poppy seed oil fatty acid ethyl esters.

13. The preparation according to claim 1, wherein the viscous solvent is sesame oil.

14. The preparation according to claim 1, wherein the active ingredient is incorporated into the biodegradable carrier in the following state:

- (i) the active ingredient is chemically bonded to the carrier matrix,
- (ii) the active ingredient is bound to the carrier matrix by intermolecular action, or
- (iii) the active ingredient is physically embraced within the carrier matrix.

15. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of mitomycin, bleomycin, adriamycin, tespamin, indomethacin, 4-carbamoyl-5-hydroxyimidazole or a salt or hydrate thereof, prostaglandins, prostacyclins, tissue plasminogen activator, bio-hormones, interferons, interleukins, tumor necrosis factor, and other cytokines.

16. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting of tissue plasminogen activator, prostaglandins, prostacyclins, bio-hormones, interferons, interleukins, tumor necrosis factor, and other cytokines.

17. The preparation according to claim 1, wherein the active ingredient is selected from the group consisting



US005756450A

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United States Patent [19]

Hahn et al.

[11] Patent Number: 5,756,450

[45] Date of Patent: May 26, 1998

[54] WATER SOLUBLE MONOESTERS AS
SOLUBILISERS FOR
PHARMACOLOGICALLY ACTIVE
COMPOUNDS AND PHARMACEUTICAL
EXCIPIENTS AND NOVEL CYCLOSPORIN
GALENIC FORMS

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[21] Appl. No.: 335,523

[22] Filed: Nov. 7, 1994

Related U.S. Application Data

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abandoned, which is a continuation of Ser. No. 478,187,
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Ser. No. 243,577, Sep. 13, 1988, abandoned.

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C07K 5/00; C07K 7/00

[52] U.S. Cl. 514/9; 530/317

[58] Field of Search 514/9; 530/317

[56] References Cited

U.S. PATENT DOCUMENTS

4,388,307	6/1983	Cavvack	424/177
4,798,823	1/1989	Witzel	514/11
4,943,560	7/1990	Wigness et al.	514/11

FOREIGN PATENT DOCUMENTS

60-7160285	4/1985	Japan	
61-280435	of 1986	Japan	A61K 37/02
19312987	2/1989	Japan	
1134878	11/1968	United Kingdom	A61K 3/00
1601613	11/1981	United Kingdom	A61K 9/08
2126588	3/1984	United Kingdom	C07G 7/00

OTHER PUBLICATIONS

Chemical Abstracts No. 107: 46298J.
Chemical Abstracts No. 95: 225610 K.
Takeda et al. *Chem. Abstr.* vol. 107 No. 6., 1986 Abstr. No.
46298J.
Anon. *Chem. Abstr.* vol. 95. 1981. p. 375. Abstr. No.
225610K.
Chemical Abstracts, vol. 75. 1981. CH: 225610K.
Takeda et al. *Chemical Abstract.* vol. 107(1). 1986 CH:
46298J.

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[57] ABSTRACT

A combination of a pharmacologically active compound and
a water soluble monoester of a saturated or unsaturated
(C₆₋₁₈) fatty acid and a polyol, especially a saccharide,
particularly as a solid solution of the active compound in the
monoester.

The solid solution is especially suitable for substantially
water insoluble active compounds, particularly such
polypeptides, e.g. cyclosporins and is in all desirable weight
ratios miscible with water.

The invention also, in particular, provides pharmaceutical
compositions comprising a cyclosporin as active ingredient
together with a fatty acid saccharide monoester.

2 Claims, 2 Drawing Sheets

27

28

-continued

Time (min.)	% of weight of Ciclosporin dissolved	standard deviation mean value (n = 3)
5	3	2.2
10	14	3.5
15	29	6.8
30	65	7.0
60	98	0.6
120	98	0.6
180	98	0.6

C) Preparation of a liquid micellar solution and its use
For human application the solid solution is preferably transformed into a liquid (aqueous) micellar solution, of which generally a dose is used corresponding to an amount of 40 to 2000 mg of Ciclosporin for oral or intravenous application. For the oral application the higher dosage and for intravenous application the lower dosage within the range are taken.

EXAMPLE 10

16 mg of Ciclosporin are solubilised in 1 ml of an isotonic aqueous solution of 10% of weight of saccharose monolaurate L-1695. The solution is used for the treatment of Psoriasis by intralesional injection. Repeated injection is effective in the treatment of Psoriasis.

EXAMPLE 11

1000 mg of saccharose monolaurate L-1695 and 160 mg of Ciclosporin are dissolved in a liquid mixture of 16 ml of 1,2-propylene glycol and 91 ml of distilled water, sterilised by filtration and filled in an ampoule for injection. The dosage of 1.5 mg of Ciclosporin pro ml of solubilisate solution corresponds to the average dosage range and a dilution to a ratio of 1:33 of the normal Ciclosporin infusion concentrate of 50 mg/ml.

EXAMPLE 12

With p-hydroxy benzoic acid methyl ester as a substantially water insoluble excipient, Proquazone (Blarison®) and Progesterone as substantially water insoluble pharmaceutically active compounds, clear solubilisate solutions are prepared with saccharose monolaurate L-1695. In an aqueous solution of solubilisate (10% by weight) 8 mg of p-hydroxybenzoic acid methyl ester, 3 mg of Proquazone and 3 mg of Progesterone can be solubilised per ml. The solubilisate solutions are stable over a long period of time at room temperature. A solid solution is obtained by removing the water by freeze drying.

D) Preparation of compositions comprising a component (a), (b) and (c) as heretofore set forth.

EXAMPLES

INGREDIENT	RELATIVE AMOUNT (mg)
13. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) 1,2-propylene glycol	100.0
TOTAL	462.5
14. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) Glycerol	100.0
TOTAL	462.5

INGREDIENT	RELATIVE AMOUNT (mg)
15. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) PEG 200	100.0
TOTAL	462.5
16. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) PEG 400	100.0
TOTAL	462.5
17. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	350.0
c) 1,2-propylene glycol	100.0
d) Eudragit E	30.0
TOTAL	510.0
18. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	350.0
c) 1,2-propylene glycol	100.0
d) Medrol K100	110.0
TOTAL	610.0
19. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	350.0
c) 1,2-propylene glycol	100.0
d) Ansoil 200	15.0
TOTAL	515.0
20. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	350.0
c) PEG 400	200.0
d) Eudragit L	2.5
TOTAL	682.5
21. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) Gelucir (e.g. Gelucir 42/12, 44/14 or 35/10)	100.0
TOTAL	462.5
22. a) Ciclosporin (e.g. Ciclosporin)	30.0
b) Saccharose monolaurate L-1695	312.5
c) Gelucir	100.0
d) Klucoel LF	30.0
TOTAL	512.5

The composition of example 13 is prepared by dissolving components (a) and (b) with stirring and warming over an oil bath at 100° C. in component (c). The compositions of examples 14 to 22 are prepared analogously. In the case of examples 17 and 20 component (d) is dissolved in the initially obtained mixture of components (a) to (c). In the case of examples 18, 19 and 22 component (d) is suspended in (a) to (c).

The obtained compositions are filled, with warming, into hard gelatin capsules, size 1 (examples 13 to 15 and 21), or size 0 (examples 17 to 19 and 22), to give an encapsulated end-product with each capsule containing 50 mg ciclosporin (e.g. Ciclosporin) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 capsules daily.

EXAMPLES

INGREDIENT	RELATIVE AMOUNT (mg)
23. a) Ciclosporin (e.g. Ciclosporin)	100.0
b) Saccharose monolaurate L-1695	300.0

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-continued

INGREDIENT		RELATIVE AMOUNT (mg)
e)	Phadon XL	330.0
d)	Avicel PH 102	150.0
a)	Sodium-laurylsulfate	25.0
TOTAL		925.0
24. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b ¹⁾	Saccharose monolaurate	330.0
L-1695		
b ²⁾	Saccharose monolaurate	30.0
c)	Cholepovidone	230.0
d)	Ethanol	150.0
e)	Magnesium-stearate	30.0
TOTAL		980.0
25. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b)	Saccharose monolaurate	160.0
L-1695		
c)	Phadon XL 10	200.0
d ¹⁾	Pharmacoate 603	25.0
d ²⁾	Avicel PH 101	75.0
e)	Magnesium-stearate	20.0
TOTAL		605.0

The above compositions 23 to 25 each suitably additionally comprise 25 mg (f) tartaric acid and/or 50 mg (g) dioctyl succinate, preferably both, giving an end weight: for composition 23 of 1.000 mg; for composition 24 of 1.055 mg; and for composition 25 of 6180 mg.

Compositions 23 to 25 are prepared as follows: Components (a) and (b) are dissolved in absolute ethanol and the ethanol evaporated exhaustively at 50° C. under reduced pressure. Components (c) to (e) are thoroughly admixed [with addition of (f) and (g) when used] employing conventional mixing techniques. The solid solution comprising [(a)+(b)] is milled to a fine powder and mixed uniformly into [(c)-(g)] and the resultant uniform mass pressed into tablets each containing 100. 50 or 25 mg (a) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 tablets daily.

EXAMPLES

INGREDIENT		RELATIVE AMOUNT (mg)
26. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b)	Saccharose monolaurate	312.5
L-1695		
c)	Paraffinum subliquidum	397.5
TOTAL		760.0
27. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b)	Saccharose monolaurate	312.5
L-1695		
c)	Elison oil DC 200	397.5
TOTAL		760.0

Components (a) and (b) are dissolved in absolute ethanol and the ethanol evaporated exhaustively at 50° C. under reduced pressure. The obtained solid solution is milled to a fine powder and suspended uniformly in component (c). The obtained liquid suspension is filled into hard gelatin capsules, size 0 to give an encapsulated end-product with each capsule containing 50 mg cyclosporin (e.g. Cyclosporin) and suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune diseases, e.g. on administration of from 1 to 5 capsules daily.

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EXAMPLES

INGREDIENT		RELATIVE AMOUNT (mg)
5 28. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b)	Saccharose monolaurate	312.5
L-1695		
c)	Paraffinum subliquidum	372.5
d)	Paraffinum durum	25.0
TOTAL		760.0
10 29. a)	Cyclosporin (e.g. Cyclosporin)	30.0
b)	Saccharose monolaurate	312.5
L-1695		
c)	Paraffinum subliquidum	397.5
d)	Aurooil	10.0
TOTAL		770.0

Compositions 28 and 29 are prepared analogously to 26 and 27 above. In the case of composition 28 (c) and (d) are first combined by melting and intimately stirring together. The solid solution comprising [(a)+(b)] is then suspended in [(c)+(d)]. In the case of composition 29, (d) is suspended, together with [(a)+(b)] in (c).

Equivalent compositions to those of examples 1 to 29 above may be prepared by substituting any other cyclosporin, e.g. [Nva]¹-Cyclosporin, for Cyclosporin as component (a), or substituting any other fatty acid saccharide monoester, e.g. as hereinbefore set forth, for example raffinose monolaurate, for saccharose monolaurate as component (b) in each case in the same or equivalent amount or relative proportion.

Utility of compositions in accordance with the invention may be shown in animal or clinical trials, for example performed as follows:

BIOAVAILABILITY STUDY FOR
COMPOSITIONS IN ACCORDANCE WITH THE
INVENTION IN THE DOG

a) Test compositions

COMPOSITION I	as per example	13
COMPOSITION II	as per example	26

b) Test method

Groups of 8 beagle dogs (male, ca. 11-13 kg) are used. Animals receive no food within 18 hours of administration of test composition but are allowed free access to water until administration. Test compositions are administered by gavage, followed by 20 ml NaCl 0.9% solution. The animals are allowed free access to food and water three hours after administration of test composition.

2 ml blood samples (or 5 ml for the blank) are taken from the vena saphena and collected in 5 ml plastic tubes containing EDTA at -15 min. (blank), 30 min., and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post administration. Blood samples are stored at -18° C. pending assay.

Blood samples are analysed by RIA. Areas under the blood drug concentration versus time curves are calculated by the trapezoidal rule. Analysis of variance is performed with respect to AUC (area under curve), Cmax (maximum concentration) and Tmax (time of maximum).

c) Results

Calculated average AUC (in mg hr/ml⁻¹) and Cmax (in mg/ml⁻¹) values from typical trial runs are shown in the

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United States Patent [19]

Terada et al.

[11] **Patent Number:** **4,734,284**

[43] **Date of Patent:** **Mar. 29, 1988**

[54] **ETOPOSIDE PREPARATIONS**

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[21] **Appl. No.:** 823,362

[22] **Filed:** Jan. 28, 1986

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.⁴** A61K 9/48

[52] **U.S. Cl.** 424/433; 424/436

[58] **Field of Search** 424/433, 436

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,609,640 9/1986 Morishita et al. 514/12
4,609,644 9/1986 Nemes 514/27

FOREIGN PATENT DOCUMENTS

0161915 11/1985 European Pat. Off. .
1421144 1/1976 United Kingdom .

2155789 10/1985 United Kingdom .

OTHER PUBLICATIONS

Rote Liste, 85 046 B (1981).
Falkson et al., "A Clinical Trial of the Oral Form of 4'-Demethyl-Epipodophyllotoxin-D Ethylidene Glucoside (NSC 141540) VP 16-213," *Cancer*, vol. 35, pp. 1141-1144 (1975).
Nissen et al., "Phase I Clinical Trial of an Oral Solution of VP-16-213," *Cancer Treatment Reports*, vol. 60, pp. 943-945 (1976).

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Attorney, Agent, or Firm—Banner, Birch, McKie and Beckett

[57] **ABSTRACT**

This invention relates to etoposide solution preparations, which exhibit excellent absorbability in vivo, comprising a container and, enclosed therein, an etoposide solution composition containing etoposide and a water-soluble cellulose derivative or polyvinylpyrrolidone.

12 Claims, No Drawings

TABLE 1

Sample No.	Additive	Amount added to 1 part of etoposide
1	Hydroxypropylcellulose (3-4 cps)	0.005
2	"	0.01
3	"	0.05
4	"	0.2
5	(Hydroxypropyl) (methyl)cellulose (6 cps)	0.05
6	Methylcellulose (400 cps)	0.05
7	Polyvinylpyrrolidone (M.W. 40,000)	0.05
8	"	0.20

2. Testing method:

Dissolution tester: that described in Pharmacopeia of Japan, 10th Ed.

Testing liquid: Distilled water (250 ml) at 37° C.

Agitation: Paddle stirrer at 50 r.p.m.

Thirty minutes after the addition of 5 ml of the sample solution into the testing liquid, a portion of the latter was filtered through a membrane filter, then diluted 10-fold with distilled water, and the absorbance at 282 nm was determined. Also, the time of first appearance of crystals was visually observed.

3. Results: The results of test were as shown in Table 2.

TABLE 2

Sample No.	Absorbance* (282 nm)	Time elapsed before Crystallization
1	1.192	No crystallization*
2	1.120	"
3	1.109	"
4	1.274	"
5	1.154	"
6	1.135	"
7	1.135	12 min. (slight crystallization)
8	0.935	No crystallization
Control 1	0.147	1 min.

*Observation after 30 minutes from the beginning of test.

As is apparent from Table 2, after 30 minutes from the beginning of test, the solution composition of this invention showed a high absorbance and substantially no precipitation of crystals, whereas the control sample showed a very low absorbance and a large amount of crystalline precipitated.

(2) Test for drug concentration in blood

1. Sample: Each 1,300 mg of the sample solutions No. 2 and No. 3 and the control sample used in the crystallization experiment was filled in a soft gelatin capsule.

2. Testing method: Each sample capsule was perorally administered to a male beagle and the change with time in etoposide content of the blood was determined over a period of 150 minutes. From the curve of etoposide content of the blood, the total concentration of etoposide over a period of 150 minutes was determined and the ratio of total etoposide concentration to that determined for the control was calculated by assuming the latter to be 100.

3. Results: The results obtained were as shown in Table 3.

TABLE 3

Sample No.	Ratio
2	200
3	223
Control	100

As is apparent from Table 3, the solution preparation of this invention showed more than twice as much absorption of etoposide compared with the control preparation. The preparation of this invention, therefore, exhibits advantages of reduced crystallization of etoposide in water and improved absorbability of etoposide. A further advantage is the increased and sustained concentration of etoposide in blood of the living body. A still further advantage is the reduction of solvent volume to about one third of that in the case of conventional solution preparation, such a volume reduction being the prerequisite for the production of capsules.

The invention is illustrated in detail hereunder with reference to Examples, in which "parts" are parts by weight.

EXAMPLE 1

Into a mixed solvent of 108 parts of polyethylene glycol 400 and 10 parts of glycerol, was dissolved 10 parts of etoposide followed by 2 parts of polyvinylpyrrolidone to obtain a filling solution. Capsules each containing 50 mg of etoposide were prepared by filling 650 mg of the filling solution in No. 0 hard gelatin capsule shells by means of a capsule filling apparatus provided with a liquid filling unit.

EXAMPLE 2

A filling solution was prepared by dissolving 100 parts of etoposide in 1,100 parts of polyethylene glycol 300 and adding to the resulting solution 1 part of hydroxypropylcellulose. Soft capsules each containing 100 mg of etoposide were prepared by filling 1,300 mg of the filling solution in soft gelatin capsule shells by means of a rotary die process machine and drying the filled capsules.

EXAMPLE 3

A filling solution was prepared by dissolving 100 parts of etoposide in a mixture of 1,100 parts of polyethylene glycol 400 and 30 parts of glycerol and adding to the resulting solution 5 parts of (hydroxypropyl)(methyl)cellulose. Soft capsules each containing 100 mg of etoposide were obtained by filling 1,235 mg of the filling solution in each gelatin capsule by the plate process and drying the filled capsules.

EXAMPLE 4

A solution for oral administration of the following composition was prepared:

	Parts
Etoposide	100
Polyethylene glycol 400	1,770
Polyvinylpyrrolidone K30	20
Citric acid	5
Glycerol	100
Orange flavor	5

The uniform solution (2.5 g) was filled in a glass vial to obtain a solution medicine.

EXAMPLE 5

Into a mixture of 1,100 parts of polyethylene glycol 300 and 30 parts of glycerol, was dissolved 100 parts of etoposide followed by 5 parts of methylcellulose to prepare a filling solution for soft gelatin capsules. In a

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP96/02431 (22) International Filing Date: 4 June 1996 (04.06.96) (30) Priority Data: 468,493 6 June 1995 (06.06.95) US 616,233 7 May 1996 (07.05.96) US (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH). (72) Inventors: BAILEY, Carole, Anne; 31 Highmount Avenue, Warren, NJ 07059 (US). FERDINANDO, Josephine, Christine; 16 Lytham Close, Monkton Park, Chippenham, Wiltshire SN15 3XW (GB). SHAH, Navnit; 203 Beverly Hill Road, Clifton, NJ 07012 (US). (74) Agent: GROSSNER, Lutz; Grenzacherstrasse 124, CH-4070 Basle (CH).	(81) Designated States: AU, BG, BR, CA, CN, CZ, HU, IL, IS, JP, KR, LK, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A PROTEINASE INHIBITOR AND A MONOGLYCERIDE (57) Abstract Compositions which increase the bioavailability of proteinase inhibitors are disclosed. The compositions include a pharmaceutically acceptable carrier comprising monoglycerides of medium chain-fatty acids.		

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TABLE A

Material	A 23	A 24	A 25
Proteinase Inhibitor	200	200	200
dl- α -tocopherol	5	5	5
CAPMUL MCM	795	765	400
PEG 400			275
Polyoxyl(40) castor oil			100
Polyvinylpyrrolidone		30	20
Total	1000	1000	1000

5 The Examples below describe work conducted using N-tert.-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginy]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (referred to hereinbelow as "Compound A") and its pharmaceutically acceptable salts as an
10 example of a proteinase inhibitor. Those of ordinary skill in the art also will appreciate how the invention and examples relate to those proteinase inhibitors described hereinabove and other proteinase inhibitors in general.

Example 1

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 The various formulations tested below and the others which are contemplated by the present invention were made in the following manner. As an example, Formulation A-63, discussed below, was made as follows:

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 Compound A was sieved to remove large material.

 769.0 mg of CAPMUL MCM and 1.0 mg of dl- α -tocopherol, all as liquids, were placed in a suitable vessel and were heated to
25 55-60°C with continuous stirring. 30.0 mg of polyvinylpyrrolidone K30 (PVP K30; average molecular weight of