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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 04-118276-00002-0000
Fec: 2006-05-30 17:31:11 Dep. 2020 NUECREACIONES
Tia. 11 PATENTEYH
Eve: 370 FABENACIONALII
Act 538 PETICION Folios: 2

Trámite : 011
Evento : 379
Actuación: 538

Referencia : Expediente No. 04.118.276
Asunto : Solicitud de patente para **COMPOSICIONES FARMACEUTICAS DE DERIVADOS DE FOSFOLIPIDO.**
Solicitante : **PERL, RUDOLF**
Fecha de Solicitud : 24 de noviembre de 2004
Publicada en : La Gaceta No. 562 Del 31 de marzo de 2006

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 presentada de acuerdo con el Capítulo II del PCT y 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 por valor de \$ 194.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 35582 de 28 de diciembre de 2005.

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, 30 MAYO 2006
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO 14504 841 001 8
FCC/ASG/ID-000007/WPC14504

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 36,092
FECHA : MAYO 15 DE 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 04-118278- -00002-0000
Fec: 2008-05-30 17:31:11 Dep. 2020 NUECREACIONES
Tia. 11 PATENTEIYN
Evr: 370 FASENACIONALII
Adi 538 PETICION Folios: 2

***** CONSIGNACION *****

SITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54982575	15/05/2006	47,972,500.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-11 EXAMEN DE PATENTIBILID	194,000.00
	TOTAL :	194,000.00

SON: CIENTO NOVENTA Y CUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cob 14504-841-001-6



DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 04- 118276

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

– PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 582,

DE FECHA 31 DE MARZO DE 2006, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 05 DE JULIO DE 2006.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

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

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N° 00007352

REFERENCIA	Radicación	04 118276
	Trámite	002
	Evento	001
	Actuación	430
	Folios	014

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 04 118276, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 53-61
- . Ejemplos: folios 61-72
- . Capítulo reivindicatorio estudiado: folios 73-75
- . No se reivindica prioridad

Objeto de la invención

Según las reivindicaciones 1 a 9 de la presente solicitud, se refiere a formulaciones farmacéuticas orales que contienen derivados de fosfolípido y al menos un excipiente no reactivo que no son higroscópicas porque son libres de lactosa o al menos no contienen más del 1% de la misma.

Clasificación internacional de patentes A 61 K 31/685

Claridad de la solicitud

El art. 30 de la decisión 486 contempla 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”*

Los términos “derivados de fosfolípido” y “excipiente no reactivo” de la reivindicación 1 son muy amplios y pueden incluir derivados de fosfolípidos y excipientes que no se encuentran revelados en la descripción.

La reivindicación 1 está caracterizando una composición por lo que no contiene (no más del 1% de lactosa), lo cual no delimita de manera correcta la materia que se desea proteger. Se le recuerda al solicitante que una composición debe caracterizar por sus componentes específicos y las proporciones de los mismos para que se pueda diferenciar de manera clara de las del estado de la técnica.

Favor hacer las aclaraciones y correcciones del caso

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 - 26.04.02-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9937289	"Composiciones farmacéuticas sólidas que contienen miltefosina para administración oral en el tratamiento de leishmaniasis"	29.07.99
2	US 4837023	"Composiciones que contienen hexadecilfosfocolina y alquilgliceroles y sus usos"	06.06.89
3	US 4687766	"Preparación farmacéutica para tratamiento terapéutico de enfermedades reumáticas"	18.08.87
4	US 4684632	"Formulación con 1,2-diacilglicero-3-fosfocolinas para el tratamiento de desórdenes gastrointestinales"	04.08.87

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 artículo 16 de la decisión 486 establece que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9937289, en sus ejemplos 7,9 y 10 revela composiciones de miltefosina libres de lactosa que contienen:

- Miltefosina (derivado de fosfolípido)
- Celulosa microcristalina
- Estearato de magnesio
- Fosfato dicálcico

La patente US 4837023 revela composiciones libres de lactosa que comprenden:

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- Miltefosina (derivado de fosfolípido)
- Celulosa

La patente US 4687766 publica formulaciones libres de lactosa que contienen derivados de fosfolípidos en combinación con excipientes no reactivos (ver ejemplos 1,2 y 7)

La patente US 4684632 enseña formulaciones libres de lactosa que comprenden derivados de fosfolípidos y excipientes no reactivos (ver ejemplos 11, 13, 15, 17, 19-25)

La composición de la presente solicitud comprende:

- Derivado de fosfolípido
- Excipiente
- Libre de lactosa

Comparando elemento por elemento, las composiciones de la presente solicitud son iguales a las de los documentos citados y pueden afectar la novedad de la presente solicitud.

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9937289	1-9	Novedad
2	US 4837023	1-9	Novedad
3	US 4687766	1-9	Novedad
4	US 4686632	1-9	Novedad

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


Álex Carmona Cepedez de Vergel
Jefe de la División de Nuevas Creaciones

15 JUN. 2007

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

CONCEPTO TÉCNICO Número 0849	EXAMINADOR TÉCNICO Código 202024
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(51) International Patent Classification 6 : A61K 9/20, 9/48, 31/685	A1	(11) International Publication Number: WO 99/37289 (43) International Publication Date: 29 July 1999 (29.07.99)
(21) International Application Number: PCT/EP98/00345 (22) International Filing Date: 22 January 1998 (22.01.98) (71) Applicant (for all designated States except US): ASTA MED-ICA AG [DE/DE]; An der Fikardie 10, D-01277 Dresden (DE). (72) Inventors; and (73) Inventors/Applicants (for US only): ENGEL, Jürgen [DE/DE]; Erlenweg 3, D-63755 Alzenau (DE). SAR-LIKIOTIS, Werner [DE/DE]; Im Eichwäldchen 20, D-60488 Frankfurt (DE). KLENNER, Thomas [DE/DE]; Im Karmengleiser 4, D-55218 Ingelheim (DE). HILGARD, Peter [DE/DE]; Beethovenstrasse 40, D-60325 Frankfurt (DE). SAUERBIER, Dieter [DE/DE]; Raube Horst 18, D-33824 Werther (DE). MILSMANN, Eckhard [DE/DE]; Alkenstrasse 23, D-33649 Bielefeld (DE).		(51) Designated States: AL, AM, AT, AU, AZ, BE, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, 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, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: SOLID PHARMACEUTICAL COMPOSITIONS CONTAINING MILTEPOSIINE FOR ORAL ADMINISTRATION IN THE TREATMENT OF LEISHMANIASIS (57) Abstract The present invention relates to new solid pharmaceutical compositions containing hexadecylphosphocholine (milteposine) for oral administration in the treatment of leishmaniasis, a process for the manufacture of said pharmaceutical composition, a dosage scheme for oral administration of said pharmaceutical composition in the treatment of leishmaniasis, and finally a combination comprising said solid pharmaceutical composition, an antiemeticum, and/or an antidiarrhoeal.		

Each capsule as obtained has a total weight of 446 mg and contains 200 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.095 : 0.65 (parts by weight).

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Example 6: Hard gelatine capsule (content: 250 mg miltefosine)

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250 g hexadecylphosphocholine, 80 g lactose, 50 g microcrystalline cellulose, 5 g talc, 5 g highly dispersed silicon dioxide and 15 g magnesium stearate were blended according to the process as described in Example 1. The thus obtained filling mixture is filled in portions of 405 mg into gelatin hard capsules of 97 mg weight in a known way by using a suitable capsules machine.

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Each capsule as obtained has a total weight of 502 mg and contains 250 mg hexadecylphosphocholine. The ratio between hexadecylphosphocholine : flowability-controlling agent : fillers in the filling mixture is 1 : 0.1 : 0.52 (parts by weight).

Example 7: Tablets (content: 250 mg of hexadecylphosphocholine)

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50 g of hexadecylphosphocholine, 24.25 g of microcrystalline cellulose and 22.00 g of anhydrous dicalcium phosphate are sieved and blended. 3.75 g of magnesium stearate are sieved and added to the blend. Then the mixture is blended again. The resulting blend is compressed into tablets each weighing 500 mg. One tablet contains 250 mg hexadecylphosphocholine.

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The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.07 : 0.925 (parts by weight).

Example 8: Tablets (content: 30 mg of hexadecylphosphocholine)

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23 g of hexadecylphosphocholine, 23 g of microcrystalline cellulose, 52 g of spray-dried lactose are sieved and blended. 1 g of colloidal silicon dioxide and 1 g of magnesium stearate are added. The mixture is then blended again.

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The resulting blend is compressed into tablets each weighing 130.5 mg. One tablet contains 30 mg hexadecylphosphocholine.

The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.087 : 0.31 (parts by weight).

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Example 9: Effervescent tablets and blend (content of hexadecylphosphocholine: 250 mg)

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1700 g of granular sodium bicarbonate are given in an oven and heated at 100 °C for 60 min. After cooling to room temperature the converted bicarbonate is mixed with 160 g of granular monobasic calcium phosphate, 1030 g of granular anhydrous citric acid, 100 g of talcum and 50 g of magnesium stearate. To the resulting mixture are added 300 g of hexadecylphosphocholine and blended for 10 minutes.

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The resulting effervescent blend is compressed into tablets each weighing 278 mg. One effervescent tablet contains 250 mg of hexadecylphosphocholine.

The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.50 : 0.53 (parts by weight).

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Alternatively, the effervescent blend can be filled in an amount of 278 mg into sachets thus obtaining an effervescent blend.

5 Example 10: Effervescent tablets and blend (content: 50 mg of hexadecylphosphocholine)

- 1 600 g of granular sodium bicarbonate are given in an oven and heated at 100 °C for 80 min. After cooling to room temperature the converted bicarbonate is mixed
10 with 150 g of granular monobasic calcium phosphate, 900 g of granular anhydrous citric acid, 80 g of talcum and 30 g of magnesium stearate. To the resulting mixture are added 200 g of hexadecylphosphocholine und blended for 10 minutes.
The resulting mixture is compressed into tablets each weighing 740 mg. One effervescent tablet contains 50 mg of hexadecylphosphocholine.
15 The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the tablet is 1 : 0.55 : 0.75 (parts by weight).

Alternatively, the effervescent blend can be filled in an amount of 740 mg into
20 sachets thus obtaining an effervescent blend.

Example 11: Drinkable blend (Sachets) (content: 50 mg of hexadecylphosphocholine)

- 25 5 g of hexadecylphosphocholine, 308 g of lactose, 280 g of microcrystalline cellulose, 5 g of saccharin and 2 g of colloidal silicon dioxide are blended. The blend is filled into sachets. One sachet weighs 6 g and contains 50 mg of hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant
30 : fillers in the blend is 1 : 0.4 : 117.5 (parts by weight).

Example 12: Drinkable blend (Sachets) (content: 100 mg of hexadecylphosphocholine)

- 35 10 g of hexadecylphosphocholine, 200 g of lactose, 250 g of microcrystalline cellulose, 7 g of saccharin and 3 g of colloidal silicon dioxide are blended. The blend is filled into sachets. One sachet weighs 4.7 g and contains 100 mg of hexadecylphosphocholine.
40 The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the blend is 1 : 0.3 : 45 (parts by weight).

45 Example 13: Drinkable blend (Sachets) (content: 200 mg of hexadecylphosphocholine)

- 20 g of hexadecylphosphocholine, 306 g of lactose, 403 g of microcrystalline cellulose, 5 g of saccharin and 6 g of colloidal silicon dioxide are blended. The blend
50 is filled into sachets. One sachet weighs 7.4 g and contains 200 mg of hexadecylphosphocholine.
The ratio between hexadecylphosphocholine : flowability-controlling agent/surfactant : fillers in the blend is 1 : 0.3 : 35.5 (parts by weight).

United States Patent [19]**Ehl**[11] **Patent Number:** 4,837,023[45] **Date of Patent:** Jun. 6, 1989

[54] **COMPOSITIONS CONTAINING
HEXADECYLOPHOSPHOCHOLINE AND
ALKYLGLYCEROLS AND USES THEREOF**

[75] **Inventor:** Hans-Jörg Ehl, Bovenden, Fed. Rep.
of Germany

[73] **Assignee:** Max-Planck-Gesellschaft Zur
Förderung der Wissenschaften,
Göttingen, Fed. Rep. of Germany

[21] **Appl. No.:** 97,960

[22] **PCT Filed:** Dec. 4, 1986

[86] **PCT No.:** PCT/EP86/00705

§ 371 Date: Oct. 2, 1987

§ 102(e) Date: Oct. 2, 1987

[87] **PCT Pub. No.:** WO87/03480

PCT Pub. Date: Jun. 18, 1987

[30] **Foreign Application Priority Data**

Dec. 4, 1985 [DE] Fed. Rep. of Germany 3542893

Feb. 28, 1986 [DE] Fed. Rep. of Germany 3606631

[51] **Int. Cl.⁴** A61K 9/10; A61K 31/685;
C07F 9/09

[52] **U.S. Cl.** 424/439; 514/77;
424/400

[58] **Field of Search** 514/77; 424/439

[56] **References Cited**

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and related derivatives against *leishmania donovani*.
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Primary Examiner—William R. Dixon, Jr.

Assistant Examiner—David M. Brunaman

Attorney, Agent, or Firm—Fells & Lynch

[57] **ABSTRACT**

Cytotoxically-effective medicaments containing hex-
adecylphosphocholine as active material.

13 Claims, No Drawings

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EXAMPLE 1

Preparation of hexadecylphosphocholine.H₂O

(a) Hexadecylphosphoethanolamine (phosphorylation, ring closure and ring opening)

Hexadecanol (1 mole, 243 g.) and triethylamine (1.8 mole, 180 g.) are dissolved in 1.5 l. THF (tetrahydrofuran) and added dropwise to a vigorously stirred solution of phosphorus oxychloride (1.2 mole, 184 g.) in 120 ml. THF in such a manner that the temperature in the reaction vessel (three-necked, 5 l., with dropping funnel, thermometer and stirrer) does not exceed 10° C. For the acceleration of the procedure, the reaction vessel is cooled with an ice-salt mixture. Immediately after the dropping in, the reaction is terminated (detection via TLC in ether: Rf values of 0.8 for the starting product, of 0.0 for the reaction product after hydrolysis with water).

One removes the ice bath and drops into the reaction mixture, with vigorous stirring, a solution of ethanolamine (1.5 mole, 92 g.) and triethylamine (1.8 mole, 180 g.) in 1 l. dioxan in such a manner that the temperature in the reaction vessel increases to 65° to 70° C. The ring formation is then concluded (detection by TLC in ether: Rf value of 0.2). One filters off from precipitated triethylamine hydrochloride while still warm and mixes the filtrate at 40° to 50° C. with 1.5 l. 2N formic acid. After 15 minutes, the ring opening is concluded (detection of TLC in ether: Rf value 0.0; TLC in chloroform/methanol/acetic acid, water 100:60:20:5 in vol.: Rf value 0.8). One cools to -20° C., filters off the precipitate which consists substantially of pure hexadecylphosphoethanolamine. In the case of slight impurities, a chromatographic purification is carried out (see Example 2). Microanalysis (M.W. 365.50):

calc. (%):	C 59.15	H 11.03	N 1.83	P 8.48
found (%):	59.01	10.95	1.79	8.31

(b) (Methylation of 1)

The crystals obtained according to Example 1 are, without further purification, taken up in 1.2 l. 2-propanol and 0.4 l. dichloromethane. One mixes the suspension of the crystals, with vigorous stirring, with potassium carbonate (4 mole, 560 g.) in 1 l. of water. The two-phase reaction mixture is mixed dropwise and while stirring with dimethyl sulphate (4 mole, 500 g.) in such a manner that the temperature does not exceed 40° C. The reaction is ended 60 minutes after the dropping in (detection by TLC in chloroform/methanol/25% ammonia 59:50:5 in vol.: Rf value 0.3). After phase separation at 20° C., the upper phase contains the product. One removes the solvent on a rotary evaporator under vacuum and chromatographs the viscous residue on silica gel (Merck Art. 7733, silica gel 60, grain size 0.2 to 0.5 mm.).

Chromatograph

Silica gel, 2 kg., are mixed with chloroform/methanol/25% ammonia (200/15/1 in vol.) and filled into a chromatography column. One dissolves the viscous oil in 800 ml. of above solvent mixture and applies the crude product to the column (insoluble components are previously filtered off). One elutes with elution agents of increasing polarity until the impurities are washed out. The product is finally eluted with chloroform/methanol/25% ammonia (50/50/5 in vol.). The combined

eluates are rotary evaporated and the residual water removed with toluene. The residue is taken up in 600 ml. dichloromethane and mixed with 4 l. of acetone. The crystals which separate out at -20° C. are washed with cold acetone, then with pentane and dried in a vacuum. The yield of pure hexadecylphosphocholine amounts of 250 g. (about 70% referred to hexadecylglycerol).

	Microanalysis (M.W. 407.58)			
	C	H	N	P
calc. (%):	59.27	11.37	3.29	7.28
found (%):	59.98	11.31	3.31	7.11

Examples for pharmaceutical compositions

Example for a solution:

25 g. 1-n-propoxy-2,3-propanediol, 12.5 g. 1-n-hexyloxy-2,3-propanediol, 12.5 g. 1-n-nonyloxy-2,3-propanediol, 44 g. water and 1 g. phenoxyethanol are mixed and 5 g. hexadecylphosphocholine dissolved in this mixture. The solution is freed from visible particles by filtration over a suitable filter.

1 g. of solution contains 50 mg. hexadecylphosphocholine.

Example for a salve:

5 g. of substance hexadecylphosphocholine are suspended in 35 g. very viscous paraffin, 30 g. emulsifying cetyl stearyl alcohol and 30 g. white vaseline are added thereto and melted. This melt is stirred until cold. A homogeneous active material distribution is achieved by working up of the cooled melt by means of a suitable homogenisation apparatus (for example a three-roll mill).

1 g. of the hydrophilic salt contains 50 mg. hexadecylphosphocholine.

Example for an emulsion:

11.83 g. 1-n-propyloxy-2,3-propanediol, 5.91 g. 1-n-hexyloxy-2,3-propanediol, 5.91 g. 1-n-nonyloxy-2,3-propanediol, 20.35 g. water and 1.0 g. phenoxyethanol are mixed and 5 g. hexadecylphosphocholine dissolved in this mixture. On a waterbath, 30 g. white vaseline, 15 g. cetyl alcohol and 5 g. sorbitan monopalmitate are melted, heated to 70° C. and the active material solution, also heated to 70° C., emulsified in the fat phase with the help of a high-speed dispersion apparatus. Subsequently, the cream is cooled to 30° C. while stirring.

1 g. of water-in-oil cream contains 50 mg. hexadecylphosphocholine.

Example for capsules:

1.25 kg. hexadecylphosphocholine are dissolved in 5 kg. chloroform and 1.25 kg. Aerosil suspended in this solution. Subsequently, the solvent is stripped off in a vacuum. The dry mass is passed through a 1 mm. sieve and again dried in a vacuum at 30° C. in order to remove last residues of solvent. This granulate is filled in known manner on a suitable capsuling machine into hard gelatine capsules of the size 00 in an amount of 500 mg.

One capsule contains 250 mg. hexadecylphosphocholine.

Example for a lyophilisate:

In 3 liters of water for injection purposes are dissolved, with nitrogen gassing, 500 g. mannitol, 50 g. hexadecylphosphocholine are dispersed with the help

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United States Patent [19]
Wendel et al.

[11] **Patent Number:** 4,687,766
[45] **Date of Patent:** Aug. 18, 1987

[54] **PHARMACEUTICAL PREPARATION FOR
THE THERAPEUTIC TREATMENT OF
RHEUMATIC DISEASES**

[75] **Inventors:** Armin Wendel, Cologne; Sigurd
Leyck, Pulheim; Helmut Weitzel,
Pulheim-Sinnerdorf; Jorg Hager,
Cologne; Manfred Durr,
Pulheim-Dansweiler; Miklos
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[73] **Assignee:** A. Nathmann & Co., GmbH,
Cologne, Fed. Rep. of Germany

[21] **Appl. No.:** 685,152

[22] **Filed:** Dec. 21, 1984

[51] **Int. Cl.⁴** A61K 31/635; A61K 31/54

[52] **U.S. Cl.** 514/78; 514/222;
514/825

[58] **Field of Search** 514/78, 222, 825

[56] **References Cited**

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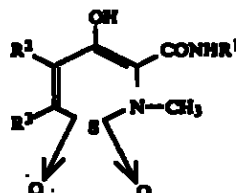
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[57] **ABSTRACT**

Pharmaceutical preparation containing phospholipids
for the therapeutic treatment of rheumatic diseases
which contain in addition to the antiphlogistically act-
ing oxican derivatives of the general formula



special 1,2-diacyl-glycero-3-phosphocholines wherein
75-86% by weight of the acyl radicals are unsaturated
fatty acid radicals, and the preparation thereof.

16 Claims, No Drawings

triglycerides and their mixtures, such as cocoa butter, and conventional suppository masses, for example based on triglycerides, such as for example Witepsol suppository masses (H. P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete* [Encyclopedia of auxiliary substances for the pharmaceutical, cosmetic and related fields], 1971, Vol. 9 p. 548-50 and 632-634); fatty alcohols; solid hydrocarbons, such as vaseline or solid paraffin; saturated fatty acids, such as lauric acid, myristic acid, palmitic acid, stearic acid; emulsifiers, such as ethoxylated triglycerides, polyethoxylated vegetable oils; fatty acid sugar esters; silicones, gelatine, methylcellulose; hydroxypropoxycellulose; hydroxypropylcellulose; polyethylene glycols; polyvinylpyrrolidone; polyvinylalcohol, polyacrylic acid and their salts.

Ethanol is added to the masses in an amount such that a concentrated product but one that is flowable at room temperature or slightly elevated temperatures, is obtained, i.e. that the product at such a temperature has just the lowered or not lowered viscosity for transportation and that this product may be filled in known filling installations with an auxiliary installation for liquid filling and with a heatable filler nozzle, similar to the methods described in DE-OS No. 30 22 136.

The special 1,2-diacyl-glycero-3-phosphocholines may be processed together with the oxicams by the process wherein they are worked for example into the viscous 1,2-diacyl-glycero-3-phosphocholine masses prior to the filling, or added after the filling of the 1,2-diacyl-glycero-3-phosphocholines in a powder or tablet form. To produce tablets and powder mixtures the special 1,2-diacyl-glycero-3-phosphocholines are converted into a solid form. Because of the viscosity of the substances, this is extremely difficult. However, by the addition of 2-10% by weight of calcium chloride, solid preparations are obtained.

To produce solid preparations, the special 1,2-diacyl-glycero-3-phosphocholines are dissolved or emulsified with the addition of the usual auxiliary substances in water or an organic solvent, for example alcohols, such as methanol, ethanol or isopropanol, in hydrocarbons, such as hexane, chlorinated hydrocarbons or their mixtures, the calcium chloride added, the mixture agitated with slight heating and subsequently the solvent drawn off. A dry powder is obtained.

Calcium chloride is added in amounts of 1-20%, in particular 2-10%, with respect to the weight of 1,2-diacyl-glycero-3-phosphocholine.

Preferred solvents for the 1,2-diacyl-glycero-3-phosphocholines are alcohols, in particular ethanol. Wash liquids are water or alcohols, such as methanol or ethanol. Conventional methods, such as vacuum roll drying, spray drying, freeze drying, are suitable for drying. The dried, comminuted 1,2-diacyl-glycero-3-phosphocholine-calcium chloride mixtures may also be comminuted or granulated by the usual processes. To stabilize the products, advantageously 0.1-2% by weight with respect to the 1,2-diacyl-glycero-3-phosphocholine used of a stabilizer or stabilizer mixture, such as tocopherol acetate and/or ascorbic acid palmitate, is added.

The production of the solid, oral forms of the drug, consisting of oxicams and the special 1,2-diacyl-glycero-3-phosphocholines may also be effected by the following processes:

Powder mixtures:

The oxicams and a 1,2-diacyl-glycero-3-phosphocholine-calcium chloride mixture comminuted to the

proper grain size, are mixed together with the addition of conventional galenic auxiliary substances and pressed into tablets or filled into capsules.

Spray deposition:

The solution or dispersion of the oxicam in organic solvents or water are mixed together with a solution or emulsion of the 1,2-diacyl-glycero-3-phosphocholine in organic solvents or water and the solution of calcium chloride in water or organic solvents, optionally with further conventional galenic auxiliary substances, and spray dried. The spray dried product obtained may be pressed with the addition of further galenic auxiliary substances into tablets or filled into capsules.

Coated products:

The solution or emulsion of the special 1,2-diacyl-glycero-3-phosphocholines in organic solvents or water are mixed with a solution of the calcium chloride in organic solvents or water and applied in a fluid bed to the oxicam previously comminuted to the grain sized desired. The powdered, free flowing product is either pressed into tablets with the addition of galenic auxiliary materials or filled into capsules. The ratio of the oxicam to the 1,2-diacyl-glycero-3-phosphocholine-calcium chloride may vary as a function of the therapeutic requirements within molar ratios of 1:0.5 to 1:20. Advantageously, depending on the dosage of the oxicam, 50-250 mg of the 1,2-diacyl-glycero-3-phosphocholine-calcium chloride mixture are added.

The specific 1,2-diacyl-glycero-3-phosphocholines used in the following examples comprise in the two positions acyl radicals of the aforesaid mixtures.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that these examples are intended only to be illustrative without serving as a limitation on the scope of the present invention.

EXAMPLE 1

a. Oxicam powder mixture

Piroxicam: 100 g
Tabletose (special aluminumhydroxysilicate): 800 g
Avicel (microcrystalline cellulose): 60 g
Aerosil (pyrogenic silica): 20 g
Sodium carboxymethyl starch: 10 g
Magnesium stearate: 10 g

The substances are mixed homogeneously.

b. Filler mass

Special 1,2-diacyl-glycero-3-phosphocholine: 9 kg
Polyethylene glycol 400: 1 kg
Ethanol: 0.3 kg

are mixed homogeneously in a kneader at 60° C.

c. Of the filler mass described under b. in a hard gelatine capsule machine with the addition for liquid filling 160 mg of the mixture are measured out per hard gelatine capsule of size 2. Subsequently, in the same hard gelatine capsule filling machine with the aid of a filler station for powder, 100 mg of the powder mixture described under a. are added and the capsule sealed.

The capsules contain 50 to 250 mg 1,2-diacyl-glycero-3-phosphocholine and 10-20 mg nonsteroidal antiinflammatory agents.

EXAMPLE 2

a. Oxicam powder mixture

Piroxicam: 100 g
Tabletose (special aluminumhydroxysilicate): 800 g
Avicel (microcrystalline cellulose): 60 g
Aerosil (pyrogenic silica): 20 g

Sodium carboxymethyl starch: 10 g

Magnesium stearate: 10 g

The substances are mixed homogeneously and pressed into 100 mg tablets with a diameter of 5 mm.

b. Filler mass

Special 1,2-diacyl-glycero-3-phosphocholine: 76.5 kg

Witepsol suppository mass: 14.3 kg

Soybean oil: 9.2 kg

Ethanol: 3.0 kg

are mixed homogeneously in a kneader at 60° C.

c. In a hard gelatine capsule machine with a filler station for liquid 270 mg of the filler mass described under b. are filled into a hard gelatine capsule of size 2. Subsequently, in the same machine with the aid of a filler station for tablets a pressed tablet of the composition described under a. is inserted into the capsule and the capsule sealed.

EXAMPLE 3

Piroxicam: 100.0 g

Special 1,2-diacyl-glycero-3-phosphocholine: 76.5 g

Witepsol suppository mass: 14.3 g

Soybean oil: 9.2 g

Ethanol: 3.0 g

are mixed in a storage vessel and heated with agitation to approx. 40° C. The solution is filled in a capsule filling installation of the Zanussi AZ 20L type by the metering device, which is heated to 80° C., into capsules at a rate of 12,000 capsules per hour. The mixture immediately solidifies in the capsule. The capsule may be sealed and taken from the installation.

EXAMPLE 4

Piroxicam capsules:

Piroxicam: 10.0 mg

Silica: 3.7 mg

Special 1,2-diacyl-glycero-3-phosphocholine: 50.0 mg

Calcium chloride: 1.3 mg

250 g special 1,2-diacyl-glycero-3-phosphocholine are dissolved in 400 ml chloroform and mixed with a solution of 6.875 g calcium chloride, anhydrous, in 70 ml methanol. This solution is sprayed in a fluid bed onto a powder mixture of 50 g piroxicam, ground to less than 50 μ m and 18.5 g silica. The granules obtained are screened to over 0.5 mm and filled into hard gelatine capsules with 10 mg piroxicam.

EXAMPLE 5

Isoxicam capsules:

Isoxicam: 100.0 mg

Silica: 3.1 mg

Special 1,2-diacyl-glycero-3-phosphocholine: 100.0 mg

Calcium chloride: 6.9 mg

Preparation as in Example 4.

EXAMPLE 6

Tenoxicam capsules:

Tenoxicam: 10.0 mg

Silica: 3.5 mg

Special 1,2-diacyl-glycero-3-phosphocholine: 50.0 mg

Calcium chloride: 1.5 mg

Preparation as in Example 4.

EXAMPLE 7

Piroxicam tablets:

Piroxicam: 10.0 mg

Special 1,2-diacyl-glycero-3-phosphocholine: 50.0 mg

Silica: 10.0 mg

Calcium chloride: 4.0 mg

Sodium carboxymethyl starch: 10.0 mg

Microcrystalline cellulose: 26.0 mg

Magnesium stearate: 10.0 mg

- 5 500 g special 1,2-diacyl-glycero-3-phosphocholine are dissolved in 1000 ml chloroform, mixed with 40 g calcium chloride, anhydrous, in 500 ml methanol and sprayed in a fluid bed onto a powder mixture containing
10 100 g piroxicam ground to less than 50 μ m, and 10 g silica. The product obtained is mixed with 90 g silica, 100 g sodium carboxymethyl starch, 260 g microcrystalline cellulose and 100 g magnesium stearate in a conventional powder mixer and pressed into tablets with 10 mg
15 piroxicam.

EXAMPLE 8

Piroxicam capsules:

20 Piroxicam: 20 mg

Special 1,2-diacyl-glycero-3-phosphocholine: 100 mg

Silica: 40 mg

Microcrystalline cellulose: 40 mg

- 25 500 g special 1,2-diacyl-glycero-3-phosphocholine, comminuted, are ground cold with the addition of 150 g silica. The powder obtained is mixed after reaching room temperature with 50 g silica and 200 g calcium hydrogen phosphate and filled into capsules at 20 mg piroxicam.

- 30 The pharmaceutical preparations prepared according to the examples are used for the treatment of rheumatic diseases and exhibit substantially lesser side effects compared with active oxycam ingredients administered in identical doses with respect to inflammations of the gastrointestinal tract and damage to the liver.

RESEARCH REPORT ON THE
EFFECTIVENESS OF THE COMBINATION OF
THE INVENTION

1. Acute test

Male rats with a weight of approximately 160 g were used in the experiments. The experimental animals receive a diet of soft rolls for 3 days, which is discontinued one day before the onset of the experiments. Tap water remains available ad libitum.

- The control and treated groups consist of 10 animals each. The substances are administered p. o. in a volume of 5 ml/kg body weight. Three and a half hours after the administration of the substance the stomachs are removed and examined for ulcers. Evaluation is performed macroscopically with the aid of index numbers.
55 The ulcer frequently is determined additionally. Reference: K. Takagi, S. Okabe: Jap. J. Pharmacol., Vol. 18, 1968, 9-18.

2. Subacute test

- 60 Male rats, fed in a normal manner, with a weight of approx. 160 g are used in the experiment. The control and treated groups consist of 10 animals each.

- The animals receive the test substance on three successive days, p. o., in a volume of 5 ml/kg body weight. Three and a half hours after the last application of the substance the stomachs are removed and examined and evaluated as in the acute test.

United States Patent [19]

Schulz et al.

[11] Patent Number: 4,684,632

[45] Date of Patent: Aug. 4, 1987

[54] FORMULATION WITH SPECIAL,
1,2-DIACYLGLYCERO-3-PHOSPHOCHO-
LINES FOR THE TREATMENT OF
GASTROINTESTINAL DISORDERS

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[52] U.S. Cl. 514/78; 514/925;

514/926; 514/927; 514/928

[58] Field of Search 514/78, 925, 926, 927,
514/928

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Mathis

[57] ABSTRACT

Pharmaceutical formulations for the treatment of gas-
trointestinal disorders, which contain as the active com-
ponent an effective gastrointestinal disorder alleviating
amount of a 1,2-diacylglycero-3-phosphocholine in
which 75-86% by weight of the acyl radicals are unsat-
urated fatty acid radicals having a chain length of 16, 18
or 20 carbon atoms. The mixtures of fatty acid radicals
in the acyl groups in the 1- and 2-positions preferably
have different compositions. The formulations can also
contain other active compounds, in particular those
which display injurious gastrointestinal side effects.

17 Claims, No Drawings

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The composition described under (a) is filled into hard gelatin capsules in a hard gelatin capsule machine having a filling point for liquid filling material at 60° C. Capsule size 0 elongated, dose 658 mg.

EXAMPLE 5

Drink ampoules
1,2-diacylglycerol-3-phosphocholine 97.8 g
Combination Syrup 160.0 g
Mocha essence 2.0 ml
Marsala essence 3.2 ml
Purified water to 2000.0 ml

The 1,2-diacylglycerol-3-phosphocholine is dispersed, with stirring, in 1.4 l of water and then homogenized using a slit homogenizer. After addition of an aqueous solution of the combination syrup and the flavorings, the mixture is made up to 2 l with water and sterilized by filtration. The solution is then filled, under aseptic conditions, into injection vials (5 ml).

EXAMPLE 6

98 g of 1,2-diacylglycerol-3-phosphocholine are dissolved, with warming, in ethanol, and mixed with a solution of 2 g of calcium chloride (anhydrous) in 50 ml of methanol. The solvents are removed in vacuo, and the resulting product is reduced, with the addition of 1% Aerosil 200, to a particle size <100 μ . The resulting powder is filled into capsules.

The mixture, with the addition of suitable auxiliaries, can also be compressed to form tablets.

EXAMPLE 7

90 g of 1,2-diacylglycerol-3-phosphocholine are dissolved in 200 ml of chloroform, mixed with a solution of 10 g of anhydrous CaCl_2 in 200 ml of methanol, and the mixture is dried using a Buchi type 190 spray dryer.

The resulting product, with the addition of 1% Aerosil 200, is reduced to a particle size <100 μ , and can then be filled into capsules or compressed to form tablets.

EXAMPLE 8

94 g of a mixture of 80% by weight of 1,2-diacylglycerol-3-phosphocholine and 20% by weight of 1,2-diacylglycerol-3-phosphoethanolamine are dissolved in ethanol and mixed with a solution of 6 g of CaCl_2 (anhydrous) in 120 ml of ethanol. The solvent is removed in vacuo and the resulting product is processed in analogy to Example 6.

EXAMPLE 9

90 g of 1,2-diacylglycerol-3-phosphocholine are emulsified in 500 ml of distilled water, mixed with a solution of 10 g of anhydrous CaCl_2 in 50 ml of distilled water and processed in analogy to Example 6.

EXAMPLE 10

Aqueous dispersion.
1,2-diacylglycerol-3-phosphocholine/ CaCl_2 56.0 kg
Cream aroma 0.8 kg
Mocha chocolate essence 5.6 kg
Vanillin 0.4 kg
Dextrose 37.0 kg
Saccharin sodium 0.16 kg

are homogeneously mixed in a powder mixer.

To prepare the aqueous dispersion ready for drinking, immediately before use 12.5 g of powder mixture are

added to 100 ml of water and the mixture is briefly shaken.

EXAMPLE 11

5 ASA tablets:
ASA-acetylsalicylic acid 300 mg
1,2-diacylglycerol-3-phosphocholine/ CaCl_2 100 mg
Aerosil 200 20 mg
Na carboxymethylcellulose 20 mg
10 Hydrogenated castor oil 10 mg
Microcrystalline cellulose 150 mg
The ingredients listed are mixed, compressed and provided in a customary manner with known tablet coating agents, for example cellulose acetate phthalate or hydroxypropylmethylcellulose phthalate.

EXAMPLE 12

ASA capsules:
ASA-acetylsalicylic acid, milled 100 300 mg
20 1,2-diacylglycerol-3-phosphocholine/ CaCl_2 100 mg
Vehicle 15 mg
A solution consisting of 90 g of 1,2-diacylglycerol-3-phosphocholine/ CaCl_2 , 200 ml of chloroform and 10 g of anhydrous CaCl_2 with 200 ml of methanol is sprayed onto ASA, milled <100 μ , in a fluidized bed. The resulting free-flowing powder is filled into hard gelatin capsules containing 300 mg of ASA per capsule.

Example 13

30 Phenylbutazone tablets:
Phenylbutazone 200 mg
1,2-diacylglycerol-3-phosphocholine/ CaCl_2 100 mg
Aerosil 200 30 mg
Na carboxymethylcellulose 20 mg
35 Hydrogenated castor oil 10 mg
Microcrystalline cellulose 140 mg
200 g of phenylbutazone are dissolved in 500 ml of chloroform, 93.5 of the phospholipid are stirred in, and 6.5 g of CaCl_2 , dissolved in 100 ml of methanol, are added. The resulting mixture is spray-dried, mixed with the remaining components, comminuted, compressed to form tablets each containing 200 mg of phenylbutazone, and coated in analogy to Example 11.

EXAMPLE 14

Indomethacin capsules:
Indomethacin 50 mg
1,2-diacylglycerol-3-phosphocholine/ CaCl_2 100 mg
Vehicle 5 mg
50 A solution consisting of 90 g of 1,2-diacylglycerol-3-phosphocholine in 500 ml of isopropanol and 10 g of CaCl_2 in 100 ml of methanol is sprayed onto the milled indomethacin in a fluidized bed. The resulting powder is treated as described in Example 6.

EXAMPLE 15

Ibuprofen tablets:
Ibuprofen 200 mg
1,2-diacylglycerol-3-phosphocholine/ CaCl_2 100 mg
Aerosil 200 30 mg
Microcrystalline cellulose 150 mg
Sodium carboxymethylstarch 20 mg
Magnesium stearate 10 mg
Preparation in analogy to Example 6.

EXAMPLE 16

Ibuprofen capsules:
Ibuprofen 200 mg

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1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100 mg
Vehicle 10 mg
Preparation in analogy to Example 12.

EXAMPLE 17

Sulindac tablets:
Sulindac 100 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100 mg
Aerocel 200 20 mg
Microcrystalline cellulose 100 mg
Sodium carboxymethylcellulose 20 mg
Magnesium stearate 10 mg
Preparation in analogy to Example 11.

EXAMPLE 18

Naproxen capsules:
Naproxen 250 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100 mg
Adsorbent 15 mg
Preparation in analogy to Example 12.

EXAMPLE 19

Diclofenac sodium tablets:
Diclofenac sodium 50 mg
1,2-Diacylglycerol-3-phosphocholine 100 mg
Aerocel 200 15 mg
Microcrystalline cellulose 75 mg
Magnesium stearate 10 mg
Sodium carboxymethylcellulose 5 mg
Preparation in analogy to Example 11.

EXAMPLE 20

Tablets containing diclofenac:
Diclofenac sodium 1000 g
Avicel PH 102 1460 g
Aerocel 200 20 g
Magnesium stearate 25 g
Sodium carboxymethylstarch 25 g
The mixture is compressed to form biconvex tablets each containing 150 mg of diclofenac sodium, and these are then coated with a coating composition consisting of

1,2-Diacylglycerol-3-phosphocholine 15.0%
HPMC cps 7.5%
Colloidal SiO₂ 1.5%
Ethanol 38.0%
Methylene chloride 38.0% in amounts of about 100 mg per tablet.

EXAMPLE 21

Capsules containing diclofenac:
(a) Diclofenac sodium 1000 g
Avicel PH 102 460 g
Aerocel 200 10 g
Magnesium stearate 15 g
Sodium carboxymethylstarch 15 g
(b) Filling composition:
1,2-Diacylglycerol-3-phosphocholine 9 kg
Polyethylene glycol 400 1 kg
Ethanol 0.3 kg
The mixture is mixed homogeneously in a kneader at 60° C.
(c) Using the filling composition described under (b) in a hard gelatin capsule machine with accessory for filling liquids, 350 mg of the mixture are metered into each hard gelatin capsule of size 0. Then, using the same hard gelatin capsule filling equipment and a filling point for powders, 150 mg of the powder mix-

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ture described under (a) are metered into each capsule, and the capsule is closed.

The capsules contain 50 to 1500 mg of 1,2-diacylglycerol-3-phosphocholine and 10-250 mg of non-steroidal antiinflammatory agents, the ratio of anti-inflammatory agents to 1,2-diacylglycerol-3-phosphocholine advantageously being 1:0.1 to 1:10.

EXAMPLE 22

10 Capsules containing diclofenac:
(a) Diclofenac sodium 1000 g
Avicel PH 102 460 g
Aerocel 200 10 g
Magnesium stearate 15 g
15 Sodium carboxymethylstarch 15 g
The substances are mixed homogeneously and compressed to form 150 mg tablets having a diameter of 6.5 mm.
(b) Filling composition
20 1,2-Diacylglycerol-3-phosphocholine 76.5 kg
Whitepol 14.3 kg
Soya oil 9.2 kg
Ethanol 3.0 kg are homogeneously mixed in a kneader at 60° C.
25 (c) 500 mg of the filling composition described under (b) are filled into a hard gelatin capsule of size 0 in a hard gelatin capsule machine having a filling point for liquids. Then, using the same machine and a filling point for tablets, a tablet of the composition described under (a) is introduced into the capsule, and the capsule is closed.

EXAMPLE 23

Prednisolone tablets:
35 Prednisolone 5 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100 mg
Microcrystalline cellulose 60 mg
Aerocel 200 10 mg
Sodium carboxymethylstarch 15 mg
Magnesium stearate 10 mg
Preparation in analogy to Example 13.

EXAMPLE 24

Dexamethasone tablets
45 (9-Fluoro-16 α -methylprednisolone)
Dexamethasone 0.5 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 50.0 mg
Microcrystalline cellulose 30.0 mg
Aerocel 200 5.0 mg
30 Sodium carboxymethylstarch 4.5 mg
Magnesium stearate 10 mg
Preparation in analogy to Example 13.

EXAMPLE 25

35 Methotrexate tablets
Methotrexate 2.5 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100.0 mg
Microcrystalline cellulose 50.0 mg
Aerocel 15.0 mg
60 Magnesium stearate 7.5 mg
Preparation in analogy to Example 13.

EXAMPLE 26

p-Aminosalicylic acid tablets:
Sodium p-aminosalicylate.2H₂O 400.0 mg
1,2-Diacylglycerol-3-phosphocholine/CaCl₂ 100.0 mg
STA-RX 1500 (special corn starch) 45.0 mg

EXAMEN TÉCNICO DE FONDO			
N° Radicación	104-118776	Fecha de presentación	24.11.2004
N° Prioridad	- 0 -	Fecha de Prioridad	0 - - -
Palabras clave			
Diferencia			
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9148			

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ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Relv. afectadas
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D1 4832023		
D3 4657766		
D3 4656657		

LITERATURA NO PATENTES		
Documento	Relevancia	Relv. afectadas

Observaciones

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