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Industria y Comercio
SUPERINTENDENCIA

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE OPOSICION 2000-12

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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**SOLICITUD
PUBLICADA**

Número del expediente: 02-079-431

Solicitante: Astrazeneca AB

Apoderado: José Antonio Lloreda

Título de la nueva creación o denominación del signo:

**"NUEVO SISTEMA AUTO EMULSIFICANTE PARA LIBERACIÓN DE
MEDICAMENTO."**

Gaceta: 531 de 29/08/03, Página 401 Número de Publicación 11

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OPOSICION PRESENTADA POR:

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FUNDAMENTOS DE LA OPOSICION:

Causa: Incumplimiento de los requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los Arts. 14 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 15 (productos y procedimientos que no se consideran invención), 16 (una invención se considera nueva cuando no es obvia ni se deriva de manera evidente del estado de la técnica), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) y 20 (improcedencia de patentabilidad)

Justificación: La composición pretendida como sus partes carecen de novedad y nivel inventivo al se tiene en cuenta lo revelado por documentos todos anteriores a la fecha de prioridad de la solicitud tales como la US 5.993.858 de 1999-11-30, en donde se encuentra ya revelado el sistema autoemulsificante pretendido, su principio técnico y sus características particulares. De la misma forma el sistema de liberación propuesto ya se encontraba revelado con anterioridad a la fecha de prioridad de la presente solicitud, como se manifiesta en la PCT/WO97/25084.

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Comprobante de pago No. 03 85 924 (Oposición) Fecha 25 Noviembre
03 85 925 (Prórroga) Fecha 28 Noviembre

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Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☒ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 02-079-431

TÍTULO SOLICITADO: "Nuevo sistema autoemulsificante para liberación de medicamento"

PUBLICACIÓN: Gaceta 531 de 29-08-2003 – No. de publicación 1533

SOLICITANTE: ASTRA ZENECA AB

APODERADO: JOSÉ ANTONIO LLOREDA

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44855 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIOS LEGRAND S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 02-079-431, por no cumplir con lo dispuesto por los artículos 14, 15, 18 y 20 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIOS LEGRAND S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, composiciones farmacéuticas y métodos de entrega de medicamentos carentes de novedad y nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

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III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud pretende, en esencia, obtener exclusiva sobre una composición farmacéutica apropiada para administración oral, en forma de pre-concentrado para emulsión, la cual comprende

- i) una o más NSAIDs liberadoras de Óxido Nítrico;
- ii) uno o más tensioactivos;
- iii) opcionalmente un aceite o grasa semisólida;

La composición forma *in situ* una emulsión *aceite en agua* luego del contacto con medios acuosos como lo son los fluidos gastrointestinales, y comprende adicionalmente uno o más alcoholes de cadena corta, y unidades recubiertas con revestimiento entérico, individuales, de un inhibidor de la bomba de protones ácido-sensible, ó de una sal alcalina farmacéuticamente aceptable de éste, preferiblemente omeprazol, una sal alcalina de omeprazol, o una sal de magnesio de (S)-omeprazol o una sal alcalina de (S)- omeprazol.

Según lo anterior, la composición pretendida se caracteriza por:

1. Proporcionarse en forma de pre-concentrado para emulsión. (Para administración directa o para inclusión en cápsulas blandas o duras de gelatina, pastillas masticables o ampollitas, entre otras formas preferidas de entrega)
2. Emplear un sistema autoemulsificante -*Self Emulsifying Drug Delivery System* o SEDDS- para liberación de medicamento, basado en uno o más tensioactivos, opcionalmente en un aceite o grasa semisólida, y en uno o más alcoholes de cadena corta.
3. Comprender como principios activos un NSAID liberador de Óxido Nítrico - NO- y un compuesto inhibidor de la bomba de protones, particularmente Omeprazol o Esomeprazol y sus sales, según las proporciones y cantidades descritas en las reivindicaciones.

De igual manera cabe anotar cuáles son los problemas técnicos cuya solución pretende el solicitante:

1. Mejorar la pobre solubilidad en agua de los NSAID liberadores de Óxido Nítrico y su consecuente baja biodisponibilidad luego de la administración oral;

2. Evitar el efecto adverso de los NSAID liberadores de NO sobre el TGI, administrando simultánea o secuencialmente un PPI seleccionado.

3.1. CARENCIA DE NOVEDAD Y NIVEL INVENTIVO DE LA FORMULACIÓN PRETENDIDA

Con las anteriores consideraciones en mente, me permito llamar la atención del despacho hacia la materia revelada en los siguientes documentos, todos ellos anteriores a la fecha de prioridad de la solicitud en curso (2000-03-08), cuyas enseñanzas permiten a una persona medianamente versada en la materia, combinando de manera obvia tales documentos, anticipar y derivar el objeto reivindicado.

1. En cuanto al sistema autoemulsificante *-Self Emulsifying Drug Delivery System* o SEDDS -: Patente US 5.993.858 de 1999-11-30 – "Method and Formulation for Increasing the Bioavailability of Poorly Water-Soluble Drugs" (Port Systems LLC)

Este documento proporciona como solución para mejorar la solubilidad y biodisponibilidad de fármacos en general, una formulación de excipientes en forma de sistema autoemulsificante, basada en una emulsión que contiene un aceite u otro lípido, un tensioactivo y un tensioactivo hidrofílico que es un alcohol – sin especificar su longitud de cadena-.

Una simple lectura del documento anexo permite concluir que el sistema autoemulsificante ahora pretendido, tanto en su principio técnico como en sus características particulares había sido revelado con anterioridad, pero sin limitar su uso a formulaciones de NSAIDs.

De igual manera, cabe anotar que ambos sistemas, además de compartir su efecto autoemulsificante, comparten su presentación en emulsión y la presencia de los mismos grupos de excipientes – UNO O MÁS TENSIOACTIVOS, UN ACEITE Y UN ALCOHOL. Es así como la única diferencia entre la formulación pretendida y la revelada con anterioridad es que la primera limita el grupo de principios activos cuya solubilidad pretende mejorar a los NSAIDs liberadores de NO, al paso que la segunda revela la composición autoemulsificante de excipientes sin limitar su empleo a una sola categoría farmacéutica.

Conocida la posibilidad de emplear una formulación de excipientes en forma de sistema autoemulsificante para mejorar la biodisponibilidad de fármacos poco

solubles, resulta obvia la posibilidad de aplicar tal principio técnico a un grupo de fármacos que según la literatura especializada y el propio solicitante, presenta conocidos problemas de solubilidad.

En conclusión, el documento reseñado permitiría a una persona medianamente versada en la materia derivar efectivamente el objeto pretendido, combinando sus enseñanzas con aquellas que dan cuenta de la pobre solubilidad de los NSAIDs liberadores de NO, en particular con las referencias patentarias citadas por el mismo solicitante. Así las cosas, el sistema de liberación pretendido habla sido revelado antes de la fecha de prioridad de la solicitud, y carece por ello de novedad. Sin perjuicio de lo anterior, si se toma la muy discutible tesis de la novedad textual, resulta lógico afirmar que el mismo sistema carece de nivel inventivo, pues resulta obvia su aplicación – o yuxtaposición – en presencia de NSAIDs.

2. En cuanto al empleo de pre-concentrados en formulaciones para emulsión para mejorar la biodisponibilidad de principios activos en particular: Publicación PCT/WO99/44584 de 1999-09-10 – “Emulsion Preconcentrates Containing Cyclosporin or a Macrolide” (Novartis AG)

Para delimitar las enseñanzas del punto precedente, llamo la atención a la materia revelada en el documento citado, consistente en un pre-concentrado para emulsión o microemulsión, que comprende específicamente un principio activo de difícil solubilidad transportado en un agente apropiado, un segundo componente seleccionado de una amplia gama de excipientes, incluyendo alcoholes, aceites y ácidos grasos, y uno o más tensioactivos.

No hacen falta mayores análisis para concluir que el documento reseñado anticipa el empleo de pre-concentrados para emulsión para lograr formulaciones biodisponibles sobre principios poco solubles, para este caso las ciclosporinas, en presencia de los mismos grupos de excipientes y transportadores empleados en la solicitud colombiana en curso.

3. En cuanto a la formación de sistemas autoemulsificantes en medio acuoso: Patente US 5.980.939 de 1999-11-09 – “Cyclosporin-containing pharmaceutical composition” (Chong Kun Dang C rp.)

Este documento revela una composición farmacéutica que contiene ciclosporina, un aceite, y uno o más tensioactivos, la cual presenta la propiedad de lograr la

disolución de dicha formulación en medio acuoso, en particular en fluidos gastrointestinales artificiales para formar un autoemulsificante.

Simplemente cabe anotar aquí que el efecto logrado por obra de esta formulación es el mismo pretendido en la solicitud que nos ocupa, en tanto una y otra pueden ejercer su acción en medio acuoso -en particular en los fluidos gastrointestinales-, y actúan de esa forma gracias a la presencia de excipientes adecuados para la formación de sistemas autoemulsificantes, en especial de aceites y tensioactivos.

También se llama la atención al hecho de que la composición revelada, al igual que en la solicitud colombiana 02-079-431, es apta para su formulación en preparaciones orales líquidas o sólidas, en especial en cápsulas blandas o duras. Lo anterior, para significar que la forma de administrar esta clase de formulaciones también pertenece, al igual que todas las características revisadas hasta el momento, a las revelaciones del arte anterior.

4. En cuanto a la existencia de formulaciones para administración oral que comprenden NSAIDs y PPIs, en donde los PPIs están entéricamente recubiertos: Publicación PCT/WO97/25064 de 1997-07-17- "Oral Pharmaceutical Dosage Forms Comprising a Proton Pump Inhibitor and a NSAID" (Astra Aktiebolag)

Hasta este punto se ha demostrado de qué manera el sistema de liberación propuesto, tanto en su principio técnico, como en sus componentes y efecto, había sido revelado con anterioridad a la fecha de prioridad de la presente solicitud. Aunque este hecho impediría de suyo la concesión de la solicitud por carencia de novedad, cabe revisar ahora de qué manera el arte anterior también revela las demás características de la pretendida invención, referidas ahora a la administración simultánea o secuencial de NSAIDs y PPIs. n. l.

En particular, llamo la atención a la materia revelada en la Publicación PCT/WO97/25064, la cual revela una forma farmacéutica de dosificación oral preferida en forma de tabletas o cápsulas, que comprende un PPI sensible al ácido y uno o más NSAIDs, estando el primer componente y la formulación entéricamente recubiertos, y cuya utilidad es el tratamiento de los efectos gastrointestinales adversos ocasionados por tratamientos con NSAIDs.

Cabe recordar en este punto que la formulación pretendida comprende como primer principio activo un NSAID según las características que ya hemos

mencionado, y como segundo componente un inhibidor de la bomba de protones, particularmente Omeprazol o Esomeprazol y sus sales.

De nuevo salta a la vista que el objeto pretendido, ahora en relación con los principios activos presentes en él, y con su efecto y utilidad, habían sido revelados por el mismo solicitante tres (3) años antes de la fecha de prioridad de la presente solicitud.

Cabe preguntarse entonces si la inclusión de esta formulación en un sistema autoemulsificante involucra alguna clase de Nivel Inventivo, teniendo en cuenta no sólo esta revelación sino aquellas que hemos explicado en el presente escrito. Desde luego, la respuesta es negativa. En primer lugar, nótese cómo la formulación revelada en el documento PCT/WO97/25064 supone la inclusión de cualquier NSAID, sin limitar su alcance a aquellos liberadores de NO. Así, la escogencia de una clase determinada, de una especie, carece por completo de nivel inventivo pues el arte anterior revelaba la posibilidad de emplear cualquier compuesto de esta familia sin limitaciones de ninguna índole.

De igual manera, esta publicación anticipa la posibilidad de formular composiciones farmacéuticas para administración oral, simultánea o secuencial de las mismas dos familias que se emplean en la solicitud que nos ocupa, esto es, de NSAIDs y PPIs, con el propósito de lograr el mismo efecto que ahora se presenta como novedoso.

Si a lo anterior se suma el hecho de que los PPIs preferidos son, al igual que en la solicitud en curso, las sustancias Omeprazol y S-Omeprazol, sus sales o enantiómeros, en especial la sal magnésica de S-Omeprazol, entre otras de la misma categoría, y que el PPI está entéricamente recubierto, al igual que ocurre en la presente solicitud – en particular en la reivindicación 6 y sus dependencias-, sólo cabe concluir que la formulación pretendida, en las características que hemos reseñado en este punto, había sido revelada por completo en el arte anterior.

5. En cuanto a la existencia de formulaciones combinadas de NSAIDs y PPIs para el tratamiento del dolor y desórdenes gastrointestinales – Patente US 5.417.980 de 1995-05-23– “Pharmaceutical Compositions and Methods for Treating the Symptoms of OverIndulgence” (Mc Neil-PPC, Inc.)

Como referencia final me permito llamar la atención hacia este documento, que revela el empleo combinado de cantidades efectivas de NSAIDs e inhibidores de las bombas de protones –PPIs-, en una misma composición farmacéutica, para el

tratamiento simultáneo del dolor y la indigestión ocasionadas por el exceso en la ingestión de comida y bebida. La primera reivindicación de esta patente revela la composición mencionada, indicando como PPI preferido el principio activo Omeprazol y permitiendo la selección del segundo componente de una amplia gama de NSAIDs.

3.2. EL "KIT" DE LAS REIVINDICACIONES 38 A 40 ES UN MÉTODO TERAPÉUTICO

De manera breve cabe anotar que un KIT, según el Diccionario de la Real Academia Española¹, es "Un conjunto de productos y utensilios suficientes para conseguir un determinado fin, que se comercializan como una unidad. Un *kit de maquillaje*."

Aquí resulta claro que el pretendido *kit* no constaría de inofensivas piezas de maquillaje sino de composiciones farmacéuticas de uso extendido y conocidas *per se*, la primera basada en un NSAID en formulación autoemulsificante, y la otra consistente, simplemente, en un PPI, en particular en Omeprazol entéricamente recubierto.

Basta llamar la atención al hecho de que el solicitante pretende ahora proteger individualmente cada una de las partes que deberían conformar un único concepto inventivo, con el agravante de que el empleo individual, combinado o secuencial de dichos componentes, como parte de un tratamiento, pertenece a la órbita de la prescripción médica y constituye, simplemente, un método de tratamiento consistente en tomar un analgésico y luego inhibidor de la bomba de protones.

La pretensión de vender "como una unidad" los componentes de una invención por separado no puede ser objeto de patente –pues equivaldría en este caso y según la definición de kit a proteger un método comercial–, ni mucho menos cuando se está en presencia de una eventual restricción para el empleo de Omeprazol recubierto o de formulaciones de NSAIDs por vía de formulaciones autoemulsificantes.

¹ Vigésima Segunda Edición, 2001. Página 1336.

3.3. LAS REIVINDICACIONES 41 y 42 REVELAN UN MÉTODO TERAPÉUTICO

Como el Despacho sabe que los métodos terapéuticos están expresamente excluidos de patentabilidad bajo el Régimen Andino, simplemente dejo enunciada esta afirmación que puede corroborarse en el propio expediente.

CONCLUSIÓN

Ha quedado suficientemente demostrado que tanto el conjunto pretendido como sus partes componentes hablan sido revelados en el arte anterior, y que por ello aquel y estas carecen de novedad. También se ha explicado de qué manera una persona versada en la materia, conociendo las dificultades de disolución y los efectos adversos de los dos grupos de principios activos que se incluyen en la formulación y en el *kit*, y las soluciones de formulación y mecanismos de entrega proporcionadas por el arte anterior, necesariamente llegaría a combinar tales enseñanzas para derivar de manera evidente el objeto reivindicado, tanto en sus partes como en su conjunto.

Por todo lo expuesto reitero la petición de declarar fundada la presente oposición, de negar en consecuencia el privilegio solicitado, y de ordenar el archivo del expediente respectivo.

IV. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de aquellas que puedan presentarse al vencimiento de la prórroga solicitada y de aquellas que el Despacho considere oficiosamente, las siguientes:

- o Apartes de la Patente US 5.993.858 de 1999-11-30
- o Apartes de la Publicación PCT/WO99/44584
- o Apartes de la Patente US 5.980.939
- o Apartes de la Publicación PCT/WO97/25064

o Apartes de la Patente US 5.417.980

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Poder para actuar.
2. Certificado de existencia y representación legal de LEGRAND S.A.
3. Constancia de pago de las tasas de tramitación de oposición y de la prórroga de que trata el artículo 42, inciso 2º de la Decisión 486.
4. Copia para correr traslado al solicitante.
5. Los mencionados en el acápite de pruebas

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Laboratorios Legrand S.A. las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 21 # 68 B - 50 de Bogotá.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P. 44655 de C.S.J.



US005993858A

United States Patent [19]

[11] Patent Number: 5,993,858

Crison et al.

[45] Date of Patent: Nov. 30, 1999

[54] METHOD AND FORMULATION FOR INCREASING THE BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS

[75] Inventors: John R. Crison; Gordon L. Amidon, both of Ann Arbor, Mich.

[73] Assignee: Fort Systems L.L.C., Ann Arbor, Mich.

[21] Appl. No.: 08/867,161

[22] Filed: Jun. 13, 1997

Related U.S. Application Data

[60] Provisional application No. 60/019,797, Jun. 14, 1996.

[51] Int. Cl.⁶ A61K 9/10

[52] U.S. CL. 424/490; 424/455; 424/498; 514/937

[58] Field of Search 424/489, 490, 424/455, 497, 498; 514/937, 938

[56] References Cited

U.S. PATENT DOCUMENTS

4,540,612 9/1985 Motoyama et al. 427/213.31

OTHER PUBLICATIONS

Farah, N., Laforet, J.P., Denis, J., Self Micro Emulsifying Drug Delivery Systems (SMEDDS) For Improving Dissolution of Drugs: In Vitro, In Vivo Evaluations, 1994 AAPS Annual Meeting—San Diego 1994, Gattefosse Patented Technology.

Bird et al., (1960) in *Transport Phenomena*, John Wiley & Sons, New York, Chapters 16 and 21.

Farah et al. (1993) Self-microemulsifying drug delivery systems for improving in-vitro dissolution of drugs. AAPS Annual Meeting, Orlando, Florida.

Grundy et al., (1994) Sensitive high-performance liquid chromatographic assay for nifedipine in human plasma ... *J. Chrom. B. Biomedical Applications*, 654:146.

Hernell et al., (1990) Physical-chemical behavior of dietary and biliary lipids during intestinal digestion ... *Biochemistry*, 29:2041-2056.

Remington's Pharmaceutical Sciences (1975) Hoover, J.E. editor, 15th ed., Mack Publishing Co., Easton, PA, pp. 334-339.

Ritschel (1980) Gastrointestinal absorption of peptides using microemulsions as delivery systems. *Geneosse*, No. 83, pp. 7-21.

Sarciaux et al., (1995) Using microemulsion formulations for oral drug delivery of therapeutic peptides. *Int'l. Journal of Pharmaceutics*, 120:127-136.

Staggers et al., (1990) Physical-chemical behavior of dietary and biliary lipids during intestinal digestion and absorption ... *Biochemistry*, 29:2028-2040.

Primary Examiner—Thurman K. Page

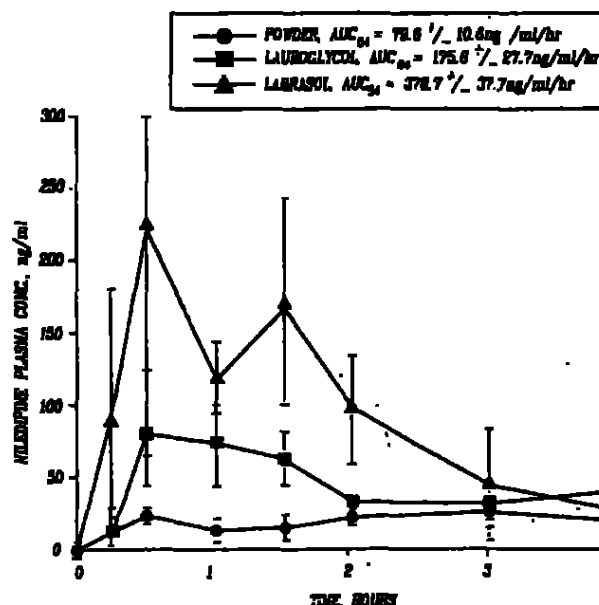
Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—Kohn & Associates

[57] ABSTRACT

A self-microemulsifying excipient formulation for increasing the bioavailability of a drug which includes an emulsion including an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant. A method for making a drug delivery system for increasing the bioavailability of a drug by emulsifying at least one drug with a self-microemulsifying excipient comprising an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant and drugs formulated thereby.

12 Claims, 4 Drawing Sheets



solution were then added and vortexed for three seconds. Next, 5 ml of MTBE-isooctane (75:25 v/v) was added and vortexed for one minute, then centrifuged at 3000 rpm (1800 g) for five minutes. The upper layer was transferred to a glass tube, evaporated to dryness at room temperature, and reconstituted with 250 ml of mobile phase [Grundy et al., 1994].

HPLC Conditions

Column: Supelco, C-8, 4.6x250 mm, 5 mm
 Detection: 350 nm
 Flow rate: 1.0 ml/min
 Injection: 100 µl
 Run time: 20 minutes
 Mobile phase: 50:50 methanol/water, pH adjusted to 4.0 with acetic acid and TEA to 1% and 0.03% final concentration, respectively.

Stock Solutions

nifedipine: 1 mg/ml in methanol
 griseofulvin: 1 mg/ml in methanol

Standard Curve

nifedipine: 200, 100, 50, 25, 12.5 ng/ml
 griseofulvin: 50 ng/ml

RESULTS AND DISCUSSION

Formulations

At room temperature, the lipid formulations appeared to be physically stable semi-solids. When added to either Simulated Gastric Fluid, without Enzymes, USP or Simulated Intestinal Fluid without Enzymes, USP at 37° C., the formulations formed stable microemulsions up to dilutions of seven to one, aqueous to oil.

Dog Studies

FIG. 1 shows the mean plasma concentration-time profiles for the three treatments in dogs. The AUC₀₋₄ (mean±standard error of the mean for these curves are 79.8±10.8, 175.8±27.7 and 378.7±37.7 ng/ml/hr for the bulk powder, formulation containing LAUROGLYCOL (Gattefosse Corporation, Westwood, N.J.) and the formulation containing LABRASOL (Gattefosse Corporation, Westwood, N.J.), respectively. Based on these AUC's, the lipid formulation containing a high HLB co-surfactant was five times greater than that of the powder and two times greater than that of the lipid formulation containing a co-surfactant with the low HLB. Assuming drug absorption immediately follows gastric emptying, the plasma concentrations in FIG. 1 were corrected for gastric emptying by eliminating zero concentrations at early time points as shown in FIG. 2. The AUC₀₋₄ for the curves in FIG. 2 are 76.2±9.8, 174.7±28.5 and 348.7±20.4 ng/ml/hr for the bulk powder, formulation containing LAUROGLYCOL and the formulation containing LABRASOL, respectively. While this correction did not change the comparison between the three formulations, it eliminated some of the variability and double peaking.

CONCLUSIONS

The results of these experiments showed that semi-solid lipid filled hard gelatin capsules can be an effective method of improving the oral bioavailability of water insoluble drugs. A clear trend was shown in the improvement of the

bioavailability of nifedipine in dogs using a co-surfactant with a high HLB (HLB=14) value over that of a co-surfactant with a low HLB (HLB=4) value even though both formulations appeared to solubilize the drug equally.

Throughout this application, various publications are referenced by citation and number. Full citations for the publications are listed below, the disclosure of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of the description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, that the invention may be practiced otherwise than as specifically described.

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- What is claimed is:
1. A self-microemulsifying excipient formulation for increasing the bioavailability of a drug which comprises: an emulsion including an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant, said hydrophilic co-surfactant having a hydrophilic-lipophilic balance (HLB) greater than 8.
 2. A method for making a drug delivery system for increasing the bioavailability of a drug by emulsifying at least one drug with a self-emulsifying excipient comprising an oil or other lipid material, a surfactant, a hydrophilic co-surfactant, and a solvent which includes triacetin.
 3. A self-microemulsifying excipient formulation as set forth in claim 1, wherein said hydrophilic co-surfactant has a hydrophilic-lipophilic balance (HLB) between approximately 10 and 14.
 4. A self-microemulsifying excipient formulation as set forth in claim 1, wherein said hydrophilic co-surfactant is an alcohol.
 5. A self-microemulsifying excipient formulation as set forth in claim 1 further including a solvent.
 6. A self-microemulsifying excipient formulation for increasing the bioavailability of a drug which comprises:

an emulsion including an oil or other lipid material, a surfactant, a hydrophilic co-surfactant, and a solvent including triacetin.

7. A self-microemulsifying excipient formulation as set forth in claim 1, wherein said oil is a lipid.

8. A method for making a drug delivery system for increasing the bioavailability of a drug by emulsifying at least one drug with a self-microemulsifying excipient comprising an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant, wherein the hydrophilic co-surfactant has a hydrophilic-lipophilic balance (HLB) greater than 8.

9. A pharmaceutical ingredient coated with formulation according to claim 1.

10. A method as set forth in claim 8, wherein the hydrophilic co-surfactant has a hydrophilic-lipophilic balance (HLB) between approximately 10 and 14.

11. A method as set forth in claim 8, wherein the hydrophilic co-surfactant is an alcohol.

12. A method as set forth in claim 8 further including the step of solubilizing the drug, surfactant, and co-surfactant in a solvent.

* * * * *

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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 9/107, 38/13, 31/435, 9/48	A1	(11) International Publication Number: WO 99/44584 (43) International Publication Date: 10 September 1999 (10.09.99)
(21) International Application Number: PCT/EP99/01415 (22) International Filing Date: 4 March 1999 (04.03.99) (30) Priority Data: 9804742.6 6 March 1998 (06.03.98) GB 9805104.8 10 March 1998 (10.03.98) GB 9805199.8 11 March 1998 (11.03.98) GB (71) Applicant (for all designated States except AT US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1235 Vienna (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): AMBÜHL, Michael [CH/CH]; Bahnhofstrasse 93a, CH-4313 Möhlin (CH). LÜCKEL, Barbara [DE/DE]; Pestalozzistrasse 22, D-79540 Lörrach (DE). RICHTER, Friedrich [DE/DE]; Am Böhlig 12, D-67157 Wachenheim (DE). HÄBERLIN, Barbara [CH/CH]; Haselrain 77, CH-4125 Riehen (CH). MEINZER, Armin [DE/DE]; Fliederweg 2, D-79426 Buggingen (DE).	(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Dept., CH-4002 Basel (CH). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: EMULSION PRECONCENTRATES CONTAINING CYCLOSPORIN OR A MACROLIDE (57) Abstract This invention provides an emulsion, e.g. microemulsion, pre-concentrate comprising a difficultly soluble active agent and a carrier medium. The active agent may e.g. be a cyclosporin or a macrolide.		

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III**CLAIMS**

1. A composition in form of an emulsion or microemulsion pre-concentrate for oral administration comprising
- 1) a cyclosporine or macrolide, and a carrier medium comprising
- 2) a second component selected from the group consisting of
- (i) triethyl citrate or acetyl triethyl citrate,
 - (ii) polyethylene glycol glyceryl C₆-C₁₀ fatty acid ester,
 - (iii) glyceryl di C₆-C₁₆ fatty acid ester,
 - (iv) glyceryl mono C₆-C₁₄ fatty acid ester,
 - (v) a mixture of mono-, diglycerides of C₆-C₁₆ fatty acids,
 - (vi) propylene glycol mono C₆-C₁₂ fatty acid ester,
 - (vii) fatty acids and alcohols,
 - (viii) N-methyl pyrrolidone,
 - (ix) glycerol triacetate,
 - (x) benzyl alcohol, and
 - (xi) alkylene polyol ether or ester,
- 3) a lipophilic component, and
- 4) a surfactant,
- with the proviso that when component 2)
- (a) consists of triethyl citrate, said composition is free or substantially free of ethanol, and/or
 - (b) consists of a mixture of mono-, diglycerides of C₆-C₁₀ fatty acids, said composition is free or substantially free of a C₆-C₁₂ fatty acid triglyceride.
2. A composition according to claim 1 comprising the cyclosporine or macrolide in an amount of 1 to 15% by weight of the composition.
3. A composition according to claim 1 or 2 comprising the second component in an amount of 5 to 50 %, the lipophilic component in an amount of 5 to 85 %, and the surfactant in an amount of 5 to 80 % by weight of the carrier medium.

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4. A composition according to any preceding claim, the relative proportion of the cyclosporine or macrolide, the second component, the lipophilic component and the surfactant in said composition being such that upon dilution with water to a ratio of 1 part by weight of said composition to 1 to 10 parts by weight of water, an oil-in-water microemulsion having particles of a mean size of less than 200 nm, is spontaneously formed.
5. A composition according to any preceding claim wherein the cyclosporine is Cyclosporin A.
6. A composition according to any preceding claim wherein the second component is triethyl citrate.
7. A composition according to any preceding claim wherein the second component is N-methylpyrrolidone.
8. A composition according to any preceding claim wherein the lipophilic component is selected from the group consisting of (i) medium chain fatty acid triglycerides, (ii) mixed mono-, di-, tri-glycerides, and (iii) transesterified ethoxylated vegetable oils.
9. A composition according to any preceding claim wherein the surfactant is selected from the group consisting of (i) reaction products of natural or hydrogenated vegetable oil and ethylene oxide, and (ii) polyoxyethylene sorbitan fatty acid esters.
10. A composition according to any preceding claim wherein the ratio of the cyclosporine or macrolide: second component : lipophilic component : surfactant is 1 : 0.1 to 10 : 1 to 10 : 1 to 10 on the basis of weight.
11. A composition according to any preceding claim wherein a hydrophilic cosurfactant is additionally present.

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12. A composition according to claim 11 wherein the hydrophilic cosurfactant is polyoxyethylene polyoxypropylene block copolymer.

5 13. A composition according to claim 11 or 12 wherein the second component and the hydrophilic cosurfactant are combined in the ratio of 1 : 0.1 to 5 on the basis of weight.

14. A composition of any preceding claim in unit dosage form.

10 15. A method of reducing the variability of bioavailability levels of a cyclosporin or macrolide for patients during cyclosporin or macrolide therapy, said method comprising orally administering an oral pharmaceutical composition according to any preceding claim.

15 16. A method of orally administering a pharmaceutical composition, said method comprising orally administering to a patient in need of cyclosporin or macrolide therapy a composition according to any preceding claim.

20 17. The use of a composition according to any preceding claim in the manufacture of a medicament for the treatment and prevention of an autoimmune or inflammatory condition or for the treatment and prevention of transplant rejection or for the treatment of multi-drug resistance.

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United States Patent [19]
Kim et al.

[11] Patent Number: 5,980,939
[45] Date of Patent: *Nov. 9, 1999

[54] CYCLOSPORIN-CONTAINING
PHARMACEUTICAL COMPOSITION

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[*] Notice: This patent issued on a continued pro-
secution application filed under 37 CFR
1.53(d), and is subject to the twenty year
patent term provisions of 35 U.S.C.
154(a)(2).

[21] Appl. No.: 08/801,117

[22] Filed: Feb. 14, 1997

[30] Foreign Application Priority Data

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A61K 47/24; A61K 47/34

[52] U.S. Cl. 424/435; 514/937; 514/962;
514/975; 424/452

[58] Field of Search 424/409, 452,
424/455, 456, 400, 439; 514/937, 962,
975

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Attorney, Agent, or Firm—Obion, Spivak, McClelland,
Maier & Neustadt, P.C.

[57] ABSTRACT

The present invention relates to a pharmaceutical composi-
tion containing cyclosporin. More specifically, the present
invention relates to a pharmaceutical composition contain-
ing cyclosporin, an oil component, a hydrophilic cosurfac-
tant consisting of propylene carbonate or a mixture of
propylene carbonate and polyoxyethylene-
polyoxypropylene block copolymer, and a surfactant. The
composition of the present invention is characterized in that
it can be dissolved in an external phase such as water,
artificial gastric juice and intestinal juice, etc. to form a
self-emulsion with mild stirring and therefore, by appropri-
ately adjusting the constitutional ratio of each component
the diameter of particles in the inner phase of the emulsion
thus formed can be readily controlled to 100 nm or below.
The composition of the present invention can be formulated
into the oral preparations such as soft capsules, hard cap-
sules sealed with gelatin hending at the conjugated portion,
oral liquid preparations, etc. When the composition of the
present invention using propylene carbonate or its mixture
with polyoxyethylene-polyoxypropylene block copolymer
in a liquid state at room temperature is formulated into the
soft capsule, it provides some advantages that it can inhibit
the change in the capsule appearance and the precipitation of
active ingredient due to the change in the solvent content,
reduces the manufacturing cost to provide an economical
effect and is substantially less toxic, in comparison to the
soft capsule using ethanol, transcutol, propylene glycol,
glycofurol, dimethylisobutide, etc., in the prior art.

17 Claims, 4 Drawing Sheets

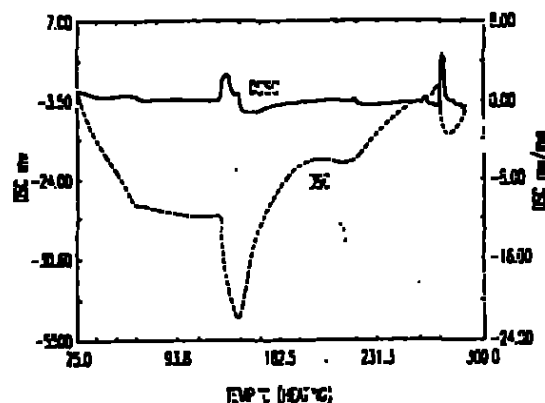


TABLE 8

Bioavailability of the test preparation of the present invention and the comparative preparation					
Parameters	Comparative preparation (A)		Test preparation (B)		P
	Mean	S.E.*	Mean	S.E.	
AUC _{0-12 hr} (ng · h/ml)	5379.2	194.1	5370.3	176.2	0.99
C _{max} (ng/ml)	1243.4	35.2	1268.9	28.6	0.97
T _{max} (hr.)	1.6	0.1	1.6	0.1	1.0

(Notes)

*S.E.: standard error

**P(B/A): Ratio of average of the test preparation to the average of the comparative preparation

As can be shown from Table 8 and FIG. 4, the cyclosporin-containing pharmaceutical composition using propylene carbonate and poloxamer 124 as the hydrophilic surfactant according to the present invention shows a substantially equivalent absorption pattern of cyclosporin in comparison to the commercial preparation according to the prior art. In addition, in the test preparation the error level for blood concentration parameters is reduced in comparison to the comparative preparation. Therefore, it can be assumed that in comparison to the comparative preparation the test preparation can form a better microemulsion in gastro-intestinal tract and is more uniformly absorbed.

From the results of experiments as mentioned above, it is apparent that the cyclosporin-containing pharmaceutical composition according to the present invention can ensure the reliable therapeutic pharmacological effect on at least the same level to the prior preparation and solve the above-mentioned numerous problems involved in the prior preparations.

What is claimed is:

1. A cyclosporin-containing pharmaceutical composition, comprising:

- (1) cyclosporin;
- (2) propylene carbonate;
- (3) Poloxamer 124;
- (4) (i) a medium chain triglyceride, or (ii) a mixture of a mono- and a di-glyceride, or a mixture of (i) and (ii); and
- (5) an additional pharmaceutically acceptable surfactant other than (2) or (3), wherein the composition is in the form of a micro emulsion pre-concentrate suitable for oral administration, the Poloxamer 124 is a liquid at room temperature, and the composition contains (1), the total amount of (2) and (3), (5), and (4), in a weight ratio of 1:0.5-5:1-7:0.5-5.

2. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein (1) is cyclosporin A.

3. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein the composition contains (2) and (3) in a weight ratio of 1:0.1-5.

4. The cyclosporin-containing pharmaceutical composition according to claim 3, wherein the composition contains (2) and (3) in a weight ratio of 1:0.1-1.

5. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein the medium chain triglyceride is a triglyceride of a C₈-C₁₀ fatty acid.

6. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein the mono- and di-glyceride is a mixture of glycerol mono- and di- esters of a fatty acid.

7. The cyclosporin-containing pharmaceutical composition according to claim 1, (4) is a mixture of medium chain triglyceride and mono- and di- glyceride in a weight ratio of 1:0.1-1.

8. The cyclosporin-containing pharmaceutical composition according to claim 7, wherein (4) is a mixture of medium chain triglyceride and mono- and di- glyceride in a weight ratio of 1:0.1-0.5.

9. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein (5) is selected from the group consisting of polyoxyethylene glycolated natural vegetable oils, polyoxyethylene glycolated hydrogenated vegetable oils, polyethylene glyco mono- and di- fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene alkyl esters, transesterification products of natural vegetable oil triglyceride and polyalkylene polyol, and mixtures thereof,

10. The cyclosporin-containing pharmaceutical composition according to claim 9, wherein (5) is selected from the group consisting of polyoxyethylene glycolated natural or hydrogenated vegetable oils, polyoxyethylene glycolated hydrogenated vegetable oils, and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol.

11. The cyclosporin-containing pharmaceutical composition according to claim 10, wherein (5) is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oils and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol, in a weight ratio of 1:0.1-1.

12. The cyclosporin-containing pharmaceutical composition according to claim 11, wherein (5) is a mixture of polyoxyethylene glycolated natural or hydrogenated vegetable oil and transesterification products of natural vegetable oil triglyceride and polyalkylene polyol, in a weight ratio of 1:0.1-0.5.

13. The cyclosporin-containing pharmaceutical composition according to claim 1, wherein the composition contains (1), the total amount of (2) and (3), (5) and (4), in a weight ratio of 1:1-3:3-7:1-3.

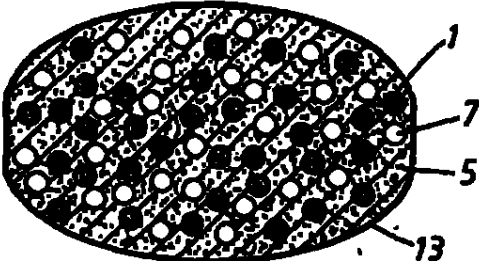
14. The cyclosporin-containing pharmaceutical composition according to claim 1, further comprising one or more pharmaceutically acceptable additives selected from the group consisting of antioxidants, preservatives, and stabilizers.

15. The cyclosporin-containing pharmaceutical composition according to claim 1, which is in the form of an orally administrable preparation.

16. The cyclosporin-containing pharmaceutical composition according to claim 15, wherein the orally administrable preparation is a soft capsule, a hard capsule sealed with a gelatin beading at the conjugated portion, or an oral liquid preparation.

17. A method of orally administering cyclosporin, comprising administering to a subject the composition of claim 1.

* * * * *

(51) International Patent Classification: A61K 45/06, 31/44, 31/19, 31/54, 9/26, 9/54	A1	(11) International Publication Number: WO 97/25064 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01735 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600070-8 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DÉPUI, Helena [FR/SE]; Wrangelsgatan 7B, S-416 62 Göteborg (SE). LUNDBERG, Per, Johan [SE/SE]; Torngatan 6, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	(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, 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, TJ, TM, TR, TT, UA, UG, US, 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: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND A NSAID (57) Abstract An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more NSAIDs in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer. The fixed formulation is in the form of an enteric coating layered tablet, a capsule or a multiple unit tableted dosage form. The multiple unit dosage forms are most preferred. The new fixed formulation is especially useful in the treatment of gastrointestinal side-effects associated with NSAID treatment. 		

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with at least one Non Steroidal Antiinflammatory Drug (NSAID) and optionally pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components, and wherein at least the proton pump inhibitor is protected by an enteric coating layer.
2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.
3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.
4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
5. A dosage form according to claim 1, wherein the dosage form comprises a proton pump inhibitor and one NSAID.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is unprotonated, an alkaline salt thereof, one of its single enantiomers or an alkaline salt thereof.
7. A dosage form according to claim 6, wherein the proton pump inhibitor is S-oxapiprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is

14 -isopropazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

- 25 9. A dosage form according to claim 1, wherein the proton pump inhibitor is pantoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.
10. A dosage form according to one of claims 5 - 9, wherein the NSAID is ibuprofen, diclofenac, piroxicam or naproxen, or a pharmaceutical acceptable salt thereof.
11. A dosage form according to one of claims 6 - 9, wherein the NSAID is diclofenac, or piroxicam, or pharmaceutically acceptable salt thereof.
12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-50 mg and the amount of NSAID(s) is in the range of 10-250 mg.
13. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of NSAID(s) is in the range of 10-250 mg.
14. A tableted dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising a proton pump inhibitor and the other layer, comprising one or more NSAIDs.
- 15 20 15. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the proton pump inhibitor in the form of individually enteric coating layered pellets compressed together with NSAID comprising granules into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the NSAID comprising granules and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the individually enteric coating layered pellets.

16. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopoeia.

17. A tableted dosage form according to claim 15, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

18. A tableted dosage form according to claim 15, wherein the enteric coating of the individual pellets comprises a phorbol ester enteric coating layer material.

19. A tableted dosage form according to claim 19, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.

20. A tableted dosage form according to claim 15, wherein the tablet is divisible.

21. A tableted dosage form according to claim 20, wherein the tablet is dispersible in an aqueous suspension comprising NSAID(s) and enteric coating layered pellets of a proton pump inhibitor.

22. A tableted dosage form according to claim 2, wherein the tablet consists of two separate layers, one layer comprising the proton pump inhibitor in the form of enteric coating layered pellets compressed with tablet excipients into a layer, and the other layer given an extended release of the incorporated NSAID(s).

23. A tableted dosage form according to claim 22, wherein the layer comprising the NSAID(s) is a gelling matrix giving extended release.

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24. A tablet dosage form according to claim 1, wherein the tablet is an enteric coating layered tablet comprising a mixture of the proton pump inhibitor and the NSAID comprising granules, optionally comprising a water soluble or in water rapidly disintegrating separating layer in between the tablet core and the enteric coating layer.

25. A tablet dosage form according to claim 2, wherein the tablet comprising enteric coating layered pellets of the proton pump inhibitor compressed into a tablet, which tablet is covered by a separate layer comprising the NSAID(s).

26. A tablet dosage form according to claim 25, wherein the tablet is covered by a pigmented tablet film-coating layer.

27. A tablet dosage form according to claim 2, wherein the tablet consists of two types of enteric coating layered pellets, one type comprises the proton pump inhibitor, and the other type comprises NSAID(s), together compresses with tablet excipients into a tablet.

28. A tablet dosage form according to claim 2, wherein the tablet consists of enteric coating layered pellets comprising the proton pump inhibitor, and pellets comprising the NSAID(s) coating layered with an extended release film, and enteric coating layered pellets are compressed with tablet excipients into a tablet.

29. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a capsule, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and that the pellets are filled into a capsule together with prepared NSAID granules or enteric coating layered NSAID pellets, or NSAID pellets coating layered with an extended release film, optionally the mixture of pellets or granules are mixed with pharmaceutically acceptable excipients, and filled in a capsule.

30. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a multiple unit tablet dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with prepared NSAID granules and optionally pharmaceutically acceptable tablet excipients whereafter the dry mixture is compressed into a multiple unit tablet without giving any significant change of the acid permeance of the enteric coating layer.

31. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAIDs in a multiple unit tablet dosage form, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets and the NSAID(s) is prepared in the form of coating layered pellets wherein the coating layer is an extended release layer or an enteric coating layer and the prepared pellets are mixed with tablet excipients and compressed into a tablet.

32. A process for the manufacture of a fixed dosage form comprising a proton pump inhibitor and one or more NSAID(s) in an enteric coating layered tablet characterized in that the proton pump inhibitor is admixed with the NSAID(s) and pharmaceutically acceptable excipients whereafter the mixture is compressed into a tablet, and the tablet is covered with an enteric coating layer and optionally covered with a separating layer before the enteric coating layer is applied.

33. A method for the treatment of gastrointestinal side-effects associated with NSAID treatment in mammals and man by administering to a host in need thereof a therapeutically effective dose of a multiple unit tablet dosage form according to any of claims 1 to 32.

34. A method according to claim 33, wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

35. Use of a dosage form according to any of claims 1 to 28 for the manufacture of a medicament for treatment or prevention of gastro-intestinal side-effects associated with NSAID(s) treatment disorders.

36. Use according to claim 35 wherein the disorder is an upper gastrointestinal disorder associated with NSAID treatment.

1
INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE 96/01735

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 45/06, A61K 31/44, A61K 31/19, A61K 31/54, A61K 9/26, A61K 9/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, US FULLTEXT, WPI, WPIL, CLAIMS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0426479 A1 (MCNEIL-PPC, INC.), 8 May 1991 (08.05.91) --	1-36
A	STN International, File CAPLUS, CAPLUS accession no. 1992:187668, Scheiman, James M. "Pathogenesis of gastroduodenal injury due to nonsteroidal antiinflammatory drugs", Semin. Arthritis Rheum: (1992), 21(4), 201-10 --	1-36
A	EP 0247983 A2 (AKTIEBOLAGET HXSLE), 2 December 1987 (02.12.87), page 4, line 25 - page 5, line 2; page 8, line 22 - line 32 --	12-36

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

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United States Patent [19]
Goldman et al.

US005417980A
[11] Patent Number: 5,417,980
[45] Date of Patent: May 23, 1995

[34] PHARMACEUTICAL COMPOSITIONS AND
METHODS FOR TREATING THE
SYMPTOMS OF OVERINDULGENCE

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[21] Appl. No.: 268,865
[22] Filed: Jun. 29, 1994

Related U.S. Application Data

- [60] Continuation of Ser. No. 46,534, Apr. 13, 1993, abandoned, which is a division of Ser. No. 876,824, Apr. 29, 1992, Pat. No. 5,204,118, which is a continuation of Ser. No. 430,837, Nov. 2, 1989, abandoned.
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[52] U.S. Cl. 424/464; 424/441;
514/810; 514/811; 514/926; 514/927
[58] Field of Search 424/464, 441; 514/810,
514/811, 926, 927

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Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—Bernard F. Plantz

[57] ABSTRACT

This invention relates to a pharmaceutical composition for treating the symptoms of overindulgence comprising an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug and a gastric acid inhibiting effective amount of an H₁ or H₂ blocker, proton pump inhibitor or a combination thereof and methods of treating the symptoms of overindulgence comprising administering such pharmaceutical compositions.

7 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS AND METHODS FOR TREATING THE SYMPTOMS OF OVERINDULGENCE

This is a continuation of application Ser. No. 08/046,534, filed Apr. 13, 1993, now abandoned, which is division of application Ser. No. 07/876,824, filed Apr. 29, 1992, now U.S. Pat. No. 5,204,118, which is a continuation of application Ser. No. 07/30,837, filed Nov. 2, 1989, now abandoned. All of these applications are hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition.

BACKGROUND OF THE INVENTION

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAID(S)") and acetaminophen (hereinafter referred to as "APAP") are known to be effective analgesics for the treatment of mild to moderate pain. Histamine receptor blockers (referred to generically herein as H₁ or H₂ blockers) are effective inhibitors of gastric acid production. Proton pump inhibitors have been recently introduced as effective gastric acid inhibitors.

The symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis. These latter symptoms collectively are sometimes referred to as acid indigestion or sour stomach. Indigestion has been variously described and will be defined herein as encompassing one or more of the following symptoms: abdominal pain and/or pressure, heartburn, a sense of abdominal fullness or bloating, excessive belching or flatulence and a vague feeling that digestion has not proceeded naturally (See Friedman, L. S., and K. J. Iselbacher, "Indigestion", *Harrison's Principles of Internal Medicine*, 11th Edition, McGraw Hill Book Company, N.Y., p 171-173, 1986).

The pathophysiology of indigestion is generally believed to be related to increased intraluminal acidity. The effects of alcohol and/or food on the gastrointestinal tract are influenced by a number of factors, including the mental state of the patient, the amount and type of food concurrently ingested, the individual subject's tolerance for alcohol and the presence or absence of disease. Gastric secretions stimulated by alcohol are rich in acid and normal in pepsin content. Stimulation of the nasal mucosa by alcohol also leads to increased gastric secretion. Histamine has also been shown to be released in response to the alcohol-gastrin inter-relationship. (See Glass, G. B. J., B. L. Slomiansky and A. Slomiansky, "Biochemical and Pathological Derangements of the Gastrointestinal Tract following Acute and Chronic Ingestion of Ethanol", *Biochemistry and Pharmacology of Ethanol*, Vol 1, Plenum Press, N.Y., p 551-586, 1979.)

Alcohol in concentrations of about 10% in the stomach results in an acid rich secretion. Alcoholic drinks of 40% concentration and over are quite irritating to the

gastric mucosa and cause congestive hyperemia and inflammation of the gastric mucosa and can produce erosive gastritis (See Ritchie, J. M., "The Aliphatic Alcohols", *The Pharmacological Basis of Therapeutics*, 7th Edition, MacMillan Publishing Co, N.Y., p 372-386, 1985). The irritation produced by alcohol stimulates sensitized visceral afferent nerves which accompany the abdominal sympathetic pathway and is responsible for the symptom of abdominal discomfort which accompanies overindulgence. Inflammation also generally lowers the threshold for pain from visceral distention or exaggerated muscular contraction (See Lorber, S. H., and V. P. Dimoso, Jr., "Diseases of the Gastrointestinal Tract", *The Biology of Alcoholism*, Vol 3, Clinical Pathology, Plenum Press, N.Y., p 339-357, 1974).

Heartburn or pyrosis is frequently associated with overindulgence and is the result of reflux of acidic gastric content into the lower esophagus after a large meal or excessive alcohol intake. Heartburn is described as a sensation of warmth or burning located subinternally or high in the epigastrium with occasional radiation into the neck and occasionally to the arms.

Treatment of the gastric mucosal irritation and heartburn associated with overindulgence due to alcohol has traditionally been directed toward reducing gastric acidity with various oral antacids. Recent introduction of H₂ receptor blocking agents has added another dimension to the treatment regimen and has only lately been considered as a routine therapy for gastric mucosal irritation due to a variety of causes. Histamine is known to stimulate the release of gastric acid. Evidence is available that blocking the histamine gastric response is possible with agents which selectively block the H₁ receptor. Similarly, combinations of H₁ and H₂ receptor blocking agents have been shown to have a synergistic effect on protecting the gastric mucosa. An appropriate treatment of heartburn or pyrosis could encompass a composition containing an H₁ receptor blocking agent, an H₂ receptor blocking agent or a combination of the two depending upon the desired result or severity of the condition.

Headache due to excessive food or alcohol ingestion is a much more obscure subject. While the etiology of the common headache due to overindulgence may be related to the essential oils, metabolic by-products of ethyl alcohol metabolism or osmotic changes induced by the anhydrous nature of the alcohol itself, specific details of the mechanism are difficult to determine. Should etiologies and mechanisms of headache production be more precisely known, therapy can be more specifically oriented. Meanwhile, treatment has been directed at avoidance and symptomatic therapy with analgesic compositions, e.g. aspirin or APAP (See Adams, R. D. and J. B. Martin, "Headache", *Harrison's Principles of Internal Medicine*, 11th Edition, McGraw Hill Book Company, N.Y., p 26-33, 1986).

The treatment of the symptoms of overindulgence often requires the co-administration of an analgesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn. For example, effervescent products comprising aspirin or APAP combined with an antacid such as sodium or calcium carbonates have been commercially available as treatments for the symptoms of overindulgence.

The concept of combining an agent to reduce or inhibit the production of gastric acid with an analgesic in a single composition has, however, heretofore been

overlooked as a method of treating overindulgence. Such a combination would be a significant advance and meet a long felt need for treating the symptoms of overindulgence, permitting a single composition to more effectively treat all the symptoms concurrently.

SUMMARY OF THE INVENTION

The foregoing object of fulfilling a long felt need for pharmaceutical compositions which can relieve the symptoms of overindulgence defined herein as headache and acid indigestion has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention, as embodied and fully described herein, the invention comprises pharmaceutical compositions and methods for treating the symptoms of overindulgence comprising an analgesic effective amount of an NSAID or APAP and a gastric acid inhibiting effective amount of an H₁ or H₂ blocker, or a proton pump inhibitor or a combination thereof.

In preferred embodiments the NSAID is selected from the group consisting of propionic acid derivatives including ibuprofen, fenoprofen, naproxen and ketoprofen; fenamic acid derivatives, including meclofenamate and mefenamic acid; oxicams, including piroxicam; indole acetic acids, including indomethacin, sulindac, tolmetin; and pharmaceutically acceptable salts thereof. The preferred H₁ or H₂ or proton pump inhibitors are selected from the group consisting of the H₂ receptor blocking drugs cimetidine, ranitidine and famotidine; the proton pump inhibitor drug omeprazole; and the H₁ receptor blocking drugs, from the group ethanolamines including diphenhydramine, dimenhydrinate, carbinoxamine, from the group ethylenediamines, including tripeleminamine, pyrilemine, from the group alkylamines, including chlorpheniramine, from the group piperazines, including hydroxyzine, cyclizine, meclizine, from the group phenothiazines, including promethazine. In more preferred embodiments the APAP or ibuprofen are used in combination with cimetidine.

As embodied and broadly described herein, the invention further comprises a method for treating the symptoms of overindulgence comprising administering a combination pharmaceutical composition to a patient comprising an analgesic effective amount of APAP or an NSAID and a gastric acid inhibiting effective amount of an H₁ or H₂ blocker, or a proton pump inhibitor or a combination thereof as is described above.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating the symptoms of overindulgence an analgesic effective amount of APAP or an NSAID is combined with a gastric acid inhibiting effective amount of an H₁ or H₂ blocker or a proton pump inhibitor or a combination thereof.

The treatment of overindulgence with the combinations of the invention which combine gastric acid inhibiting amounts of H₁ or H₂ blocker or a proton pump inhibitor or a combination thereof with such NSAIDs is directed to the symptomatic relief of the complaints of acid indigestion and headache. This requires the use of

an agent which would treat the headache, abdominal discomfort and reduce the intraluminal gastric acidity. Since no single agent has been found to be capable of treating the multiple symptoms of overindulgence, a composition such as is described in this invention is recommended.

APAP, a well-known clinically proven analgesic and antipyretic, produces analgesia by elevating the pain threshold. APAP is indicated as an analgesic for both acute and chronic pain conditions, including arthritic and rheumatic conditions involving musculoskeletal pain, headache, dysmenorrhea, myalgias and neuralgias. APAP is an extremely safe analgesic, rarely producing side-effects and is especially well tolerated by aspirin-sensitive patients. (Seegers, A. J. M., L. P. Jager, and J. Van Noordwijk, "Effects of Phenacetin Paracetamol and Caffeine on the Erosive Activity of Acetylsalicylic Acid in the Rat Stomach: Dose-Response Relationships, Time Course of Erosion Development and Effects of Acid Secretion", *J. Pharmacol.* 31:840-848, 1979), have shown that APAP decreases the gastric erosive activity of a strongly ulcerogenic NSAID. (Stern, A. I., D. L. Hogan, L. H. Kahn, and J. I. Isenberg, "Protective Effect of Acetaminophen Against Aspirin- and Ethanol-Induced Damage to the Human Gastric Mucosa", *Gastroenterology*, 86:728-733, 1984), have additionally shown that a single dose of APAP prevents a significant amount of gastric mucosal damage caused by both aspirin and alcohol. Further, APAP is particularly well suited as an analgesic in patients with hemostatic disturbances as well as in patients with upper gastrointestinal disorders including ulcers, gastritis and hiatus hernia.

Aspirin and other NSAIDs are commonly used for the treatment of pain and inflammation of a variety of etiologies. The mechanism of action of this class of drugs is by inhibition of the enzyme of prostaglandin synthetase, both centrally and peripherally. The peripheral prostaglandin synthetase inhibiting activity of aspirin and other NSAIDs is responsible for the anti-inflammatory and analgesic activity as well as for many of the varied side-effects of these drugs. Aspirin is specifically excluded from this invention since aspirin, by itself, causes severe inflammation of the gastric mucosa. In the presence of alcohol, this effect of aspirin is enhanced. Similarly, prolongation of bleeding time induced by aspirin, is enhanced in the presence of alcohol (See Daykin, D., P. Janson and L. McMahon, "Ethanol Potentiation of Aspirin-Induced Prolongation of the Bleeding Time", *New England Journal of Medicine*, 306:852-854, 1982). For these reasons aspirin is not a rational choice either alone or in combination with other compositions for treating acid indigestion in general and as it relates to overindulgence. While other NSAIDs can by themselves lead to increased stomach upset, this effect is not as severe as with aspirin, and they are thus useful in treating the symptoms of overindulgence in accordance with the combination composition of the invention.

The presence of gastrin, acetylcholine and histamine in the stomach interacting with the histamine receptor on the parietal cell results in the increased secretion of hydrochloric acid. The activity of gastrin and acetylcholine are believed to be influenced by histamine. Inhibition of the histamine receptor prevents the attachment of histamine to the parietal cell and subsequently inhibits acid secretion. Omeprazole, a proton pump inhibitor,

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irreversibly inhibits the enzyme responsible for acid production.

The histamine receptors are differentiated by the class of inhibitor so that while the acid secreting histamine receptor is called an H₂ receptor with the inhibitors of this site being called the H₂ receptor blocker, the histamine H₁ receptor site blockers comprise another class of antihistamine drugs. The combination of H₁ and H₂ blockers can synergistically protect the gastrointestinal mucosa from the effects of chemically induced damage such as occurs in alcohol and food related overindulgence.

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts either acetaminophen from 500 to 1000 mg per dose or one of several NSAIDs from the group of: propionic acid derivatives including ibuprofen (the term ibuprofen is meant to include administration of both the racemic mixture of R- and S-enantiomers and the substantially pure S-enantiomer which is the analgesic active form of ibuprofen) from 200 to 400 mg per dose; naproxen from 200 to 500 mg per dose; fenoprofen from 200 to 600 mg per dose; ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose; piroxicam from 10 to 20 mg per dose; indomethacin from 25 to 200 mg per dose; sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose; in combination with the H₂ receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the proton pump inhibitor drugs including omeprazole from 60 to 500 mg per dose; and/or an H₁ receptor blocking drug from the group ethanalamines including diphenhydramine 25 to 200 mg per dose; dimenhydrinate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose; from the group ethylenediamines including tripelemamine from 25 to 300 mg per dose; pyrrolamine from 25 to 100 mg per dose; from the group alkylamines including chlorpheniramine from 2 to 24 mg per dose, from the group piperazines including hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose; and from the group phenothiazines including promethazine from 12.5 to 50 mg per dose.

The dosage ranges described above are preferred adult doses and may vary depending upon the age and weight of the patient as would be known by those skilled in the pharmaceutical arts. Further, if a combination of, for example an H₁ and H₂ blocker is used, the dosage for each may be reduced.

To establish the efficacy of the composition of this invention in humans, patients suffering from the symptoms of overindulgence which will include any of the constellation of signs of indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis and headache can be administered acetaminophen or a non-steroidal anti-inflammatory drug with and without histamine receptor blockers (H₁ and/or H₂ blocking agents). To determine efficacy, patients are asked to subjectively estimate onset of relief, duration of relief and time to maximum relief. Appropriate statistical methods are used to show that on the average, acetaminophen or non-steroidal anti-inflammatory agents with H₁ histamine and/or H₂ histamine receptor blocking drugs are more efficacious.

Since appropriate animal models for the evaluation of overindulgence are not available, studies will not be conducted involving laboratory animals.

Other ingredients both active and inactive can be added to the combination pharmaceutical compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. Further, antidiarrheal, antifatulent, antispasmodic and/or anticholinergic compositions may be added to the compositions of the invention to reduce and relieve gastrointestinal distress, which may be associated with acid indigestion. Examples of antidiarrheals include loperamide, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof. An example of an antifatulent is simethicone. Examples of antispasmodics include phenobarbital, dicyclomine HCl, belladonna alkaloids, and atropine.

EXAMPLES

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. Example 1-10 disclose various formulations for preparing tablets or caplets in accordance with the invention. Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by *Remington's Pharmaceutical Science*, Mack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985). The disclosure of this reference is hereby incorporated herein by reference.

Example 1

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 2

A tablet consisting of:
500 mg of acetaminophen;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 3

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 4

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 5

A tablet consisting of:
200 mg of ibuprofen;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 6

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 7

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 8

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 9

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 10

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 11

A tablet consisting of:
500 mg of acetaminophen;
60 mg of omeprazole; and
other auxiliary agents and coloring agents.

Example 12

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole; and
other auxiliary agents and coloring agents.

Example 13

A tablet consisting of:
500 mg acetaminophen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Example 14

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension or chewable tablet form employing the dosage actives provided above or other dosage amounts in accordance with the present invention. A liquid suspension of ibuprofen to which cimetidine, diphenhydramine, ranitidine or combinations thereof in the amounts provided above can be added to the ibuprofen suspension disclosed in co-pending U.S. patent application Ser. No. 372,734, the entire disclosure of this Patent Application is hereby incorporated herein by reference.

Method of Treating Patients for the Symptoms of Overindulgence

A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-10.

The scope of the present invention is not limited by the description, examples and suggested uses herein and modifications can be made without departing from the spirit of the invention. For example, the pharmaceutical compositions of the invention may be provided in a sustained release formulation for prolonged and/or nighttime treatment of the symptoms of overindulgence. Application of the compositions and methods of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the presently claimed invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A pharmaceutical composition for treating the symptoms of overindulgence due to the excessive or inappropriate intake of food and/or alcoholic beverages comprising in an oral tablet or caplet dosage form a therapeutically effective amount of an analgesic and a gastric acid inhibiting effective amount of a proton pump inhibitor wherein the therapeutically effective amount of the analgesic is selected from the group consisting of acetaminophen from 500 to 1000 mg per dose, ibuprofen from 200 to 400 mg per dose, naproxen from 200 to 500 mg per dose, fenopirofen from 200 to 600 mg per dose, ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose, piroxicam from 10 to 20 mg per dose, indomethacin from 25 to 200 mg per dose, salindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose and their pharmaceutically acceptable salts; in combination with an effective amount of the proton pump inhibitor omeprazole of from 60 to 500 mg per dose.
2. A pharmaceutical composition in accordance with claim 1 comprising a combination of ibuprofen and omeprazole.
3. A pharmaceutical composition in accordance with claim 1 comprising acetaminophen and omeprazole.
4. A pharmaceutical composition in accordance with claim 1 comprising a racemic mixture of R- and S-ibuprofen, substantially pure S-ibuprofen or naproxen and omeprazole.
5. A pharmaceutical composition in accordance with claim 1 wherein additionally there is present a therapeutically effective amount of an H₁ or H₂ receptor blocker selected from the group consisting of cimetidine from 150 to 800 mg per dose, ranitidine from 50 to 300 mg per dose, famotidine from 5 to 40 mg per dose, diphenhydramine 25 to 200 mg per dose, dimenhydrinate from 50 to 400 mg per dose, carbinosamine from 4 to 8 mg per dose, tripeleannamine from 25 to 300 mg per dose, pyrillamine from 25 to 100 mg per dose, chlorpheniramine from 2 to 24 mg per dose, hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose and promethazine from 12.5 to 50 mg per dose.
6. A pharmaceutical composition in accordance with claim 1 comprising naproxen and omeprazole.
7. A pharmaceutical composition in accordance with claim 1 wherein the pharmaceutical is in chewable dosage form.

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B/1129

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO.
E. S. D.

Ref. PODER ESPECIAL - PRESENTACIÓN DE OPOSICIÓN

EXPEDIENTE: 02-079-431
TÍTULO SOLICITADO: "Nuevo sistema autoemulsificante para liberación de medicamento"
SOLICITANTE: AstraZeneca AB
APODERADO: JOSÉ ANTONIO LLOREDA

DIANA LUCÍA GUARÍN LONDOÑO, mayor de edad e identificada como aparece al pie de la firma, actuando en nombre y representación legal de **LABORATORIOS LEGRAND S.A.**, sociedad comercial, organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Bogotá, según consta en el certificado de existencia y representación legal que se anexa, debidamente facultada para actuar, por medio del presente escrito confiero poder especial, amplio y suficiente al Dr. **JOSÉ LUIS REYES VILLAMIZAR**, mayor de edad y vecino de Bogotá, identificado como aparece al pie de su firma, abogado portador de la T.P. 44655 del C. S. de la J., para que en nombre de la sociedad que represento presente oposición contra la solicitud de patente de invención indicada en la referencia.

En ejercicio de su encargo, mi apoderado queda ampliamente facultado para realizar todas las gestiones inherentes y necesarias para la oportuna atención de los intereses de la empresa que represento, y queda investido de las facultades mencionadas en el artículo 70 del C.P.C., en especial para recibir, desistir, conciliar, transigir, sustituir, reasumir, presentar recursos, así como para realizar todas las demás actuaciones administrativas y judiciales relacionadas con el trámite en cuestión.

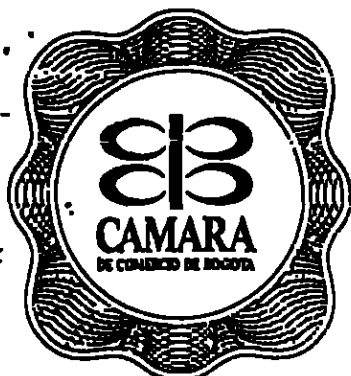
Señor Superintendente,


DIANA LUCÍA GUARÍN LONDOÑO
C.C. 41.747.129 de Bogotá

Acepto,



JOSÉ LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C.S.J.



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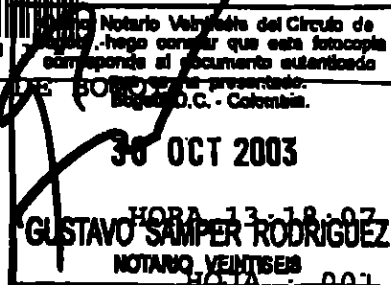
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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

28 DE ENERO DE 2003

02N07012817302EXY0529



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : LABORATORIOS LEGRAND S A

N.I.T. : 08605316022

DOMICILIO : BOGOTA D.C.

MATRICULA NO. 00263786

CERTIFICA :

CERTIFICA :

CONSTITUCION: E.P. NO. 1733 NOTARIA 10 DE BOGOTA DEL 29 DE MAYO - DE 1.986 INSCRITA EL 3 DE JUNIO DE 1.986 BAJO EL NO. 191306 DEL - LIBRO IX, SE CONSTITUYO LA SOCIEDAD COMERCIAL DENOMINADA: "LABORATORIOS LEGRAND S.A."

CERTIFICA :

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
86	14-I- 1.988	10 BOGOTA	17-II-1.988 NO. 228.974
420	11-II-1.988	10 BOGOTA	17-II-1.988 NO. 228.974
2.293	5-VII-1.988	10 BOGOTA	6- X-1.988 NO. 247.430
1.586	28-V -1.993	10 STFE BTA	8-VII-1.993 NO. 411.794

CERTIFICA :

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 29 DE MAYO DE 2085 .

CERTIFICA :

OBJETO SOCIAL: FABRICAR, IMPORTAR, EXPORTAR, COMPRAR, VENDER, DISTRIBUIR Y REPRESENTAR PREPARACIONES FARMACEUTICAS, MEDICAS, QUIMICAS, PLASTICAS, BIOLOGICAS, INSECTICIDAS, HERBICIDAS, PRODUCTOS - VETERINARIOS, PRODUCTOS DE CONTENIDO ALIMENTICIO, COSMETICOS, DROGAS MEDICINALES, ANTIBIOTICOS, UNGUENTOS, LINIMENTOS, SUEROS, VACUNAS, DULCES Y PRODUCTOS AZUCARADOS, PRODUCTO MATERNO-INFANTILES APARATOS DE CIRUGIA, PRODUCTOS MEDICOS Y EQUIPOS PARA HOSPITALES Y LA INVESTIGACION DE TODO LO CONEXO CON LO ANTERIORMENTE EXPUESTO. PODRA IGUALMENTE COMPRAR, VENDER, DISTRIBUIR, REPRESENTAR, IMPORTAR Y EXPORTAR TODAS LAS MAQUINARIAS Y EQUIPOS DESTINADOS A LA PREPARACION EN CUALQUIERA DE SUS FASES DE LOS PRODUCTOS ANTES ENUMERADOS Y REPRESENTAR FIRMAS NACIONALES O EXTRANJERAS DENTRO DE ESTE CAMPO. EN DESARROLLO DE SU OBJETO SOCIAL LA SOCIEDAD PODRA HACER TODA CLASE DE OPERACIONES CIVILES Y COMERCIALES SOBRE BIENES MUEBLES O INMUEBLES Y CONSTITUIR TODO TIPO DE GRAVAMENES SOBRE ELLOS; CELEBRAR TODA CLASE DE CONTRATOS CON PERSONAS JURIDICAS O NATURALES; EFECTUAR OPERACIONES DE CAMBIO, MUTUO, PRESTAMOS, REDESCUENTOS, CUENTA CORRIENTE, RECIBIR Y DAR GARANTIAS PERSONALES O REALES, INCLUIDAS LAS HIPOTECAS, GIRAR ENDOSAR Y DESCONTAR TODA CLASE DE TITULOS VALORES, ADQUIRIR Y NE-



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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

28 DE ENERO DE 2003

HORA 13:18:07

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HOJA : 002

00745676 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE
PRESIDENTE

IDENTIFICACION

MONTEJO FRANCO EDUARDO

C.C.00017010368

QUE POR ACTA NO. 0000061 DE JUNTA DIRECTIVA DEL 29 DE AGOSTO DE 2001 , INSCRITA EL 29 DE MAYO DE 2002 BAJO EL NUMERO 00829141 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE
PRIMER SUPLENTE DEL PRESIDENTE

IDENTIFICACION

QUIJANO BARRIGA JUAN PABLO

C.C.00079589041

QUE POR ACTA NO. 0000054 DE JUNTA DIRECTIVA DEL 16 DE MARZO DE 1999 , INSCRITA EL 23 DE MARZO DE 1999 BAJO EL NUMERO 00672970 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE
SEGUNDO SUPLENTE DEL PRESIDENTE

IDENTIFICACION

GUARIN LONDONO DIANA LUCIA

C.C.00041747129

CERTIFICA :

FACULTADES DEL REPRESENTANTE LEGAL: A) EJECUTAR LOS ACUERDOS Y RESOLUCIONES DE LA ASAMBLEA GENERAL Y LA JUNTA DIRECTIVA. B) EJECUTAR Y CELEBRAR TODOS LOS ACTOS Y CONTRATOS NECESARIOS PARA EL CUMPLIMIENTO DEL OBJETO SOCIAL DE LA EMPRESA, CON LA LIMITACION ESTABLECIDA EN EL LITERAL F) DEL ARTICULO 25. C) CONSTITUIR APODERADOS ESPECIALES, BIEN SEA JUDICIALES O EXTRAJUDICIALES. D) DAR Y RECIBIR DINERO EN CALIDAD DE MUTUO CON O SIN INTERESES CON LAS LIMITACIONES SEÑALADAS EN EL LITERAL F) DEL ARTICULO 25. E) CELEBRAR TODA CLASE DE CONTRATOS Y OPERACIONES CON ENTIDADES BANCARIAS O CREDITICIAS, CON LA LIMITACION ESTABLECIDA EN EL LITERAL F) DEL ARTICULO 25. F) HACER TODA CLASE DE NEGOCIACIONES CON TITULO VALORES, TALES COMO OTORGAR, ADQUIRIR, NEGOCIAR, AVALAR, PROTESTAR Y COBRAR, ETC. CON LA LIMITACION ESTABLECIDA EN EL LITERAL F) DEL ARTICULO 25. G) CUIDAR DE LA RECAUDACIONES E INVERSION DE LOS FONDOS DE LA EMPRESA. H) PRESENTAR A LA JUNTA DIRECTIVA A SUS SESIONES ORDINARIAS LOS BALANCES DE PRUEBA QUE DEBA ELABORAR RUTINARIAMENTE Y MANTENERLA INFORMADA DE LOS NEGOCIOS SOCIALES. I) VELAR PORQUE TODOS LOS EMPLEADOS DE LA SOCIEDAD CUMPLAN Estrictamente SUS DEBERES Y AVISAR A LA JUNTA DIRECTIVA SOBRE LAS FALTAS GRAVES QUE OCURRAN EN ESE PARTICULAR. J) CREAR LOS EMPLEOS QUE JUZGUE NECESARIOS PARA EL FUNCIONAMIENTO DE LA SOCIEDAD Y SEÑALAR A LOS EMPLEADOS SUS FUNCIONES Y ATRIBUCIONES. K) NOMBRAR Y REMOVER A TODOS LOS EMPLEADOS DE LA SOCIEDAD, SALVO EL CASO DE EMPLEADOS DIRECTIVOS QUE A SU VEZ SEAN SOCIOS DE LA SOCIEDAD CASO EN EL CUAL REQUERIRA APROBACION DE LA JUNTA DIRECTIVA. L) ENAJENAR, ADQUIRIR O GRAVAR BIENES MUEBLES O INMUEBLES PARA EL CUMPLIMIENTO DEL OBJETO SOCIAL, CON LA LIMITACION ESTABLECIDA EN EL LITERAL F) DEL ARTICULO 25. M) DAR Y RECIBIR BIENES MUEBLES E INMUEBLES EN CALIDAD DE ARRENDAMIENTO. N) OBTENER CREDITOS Y SUSCRIBIR LAS GA-



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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

28 DE ENERO DE 2003

HORA 13:18:08

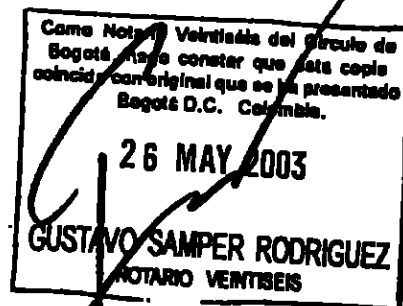
02N07012817302EXY0529

HOJA : 003

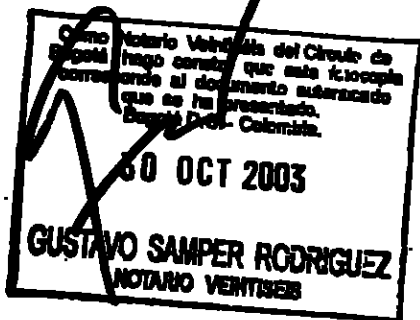
EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : \$ 2,300.00

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.



EN BLANCO
NOTARIA VEINTISEIS



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SUPERINDUSTRIA Y COMERCIO
Radicación : 020/9461 00000003 Folios: 3/
Fecha (HH): 2003-11-25 16:41:11
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 85,925
FECHA : NOVIEMBRE 25 DE 2003

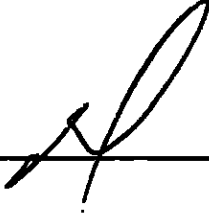
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JUAN PABLO REYES	CONSIGNACION	BANCO POPULAR	050-00110-6	5053506	25/11/2003	32,000.00
JUAN PABLO REYES	CONSIGNACION	BANCO POPULAR	050-00110-6	16388384	25/11/2003	54,000.00
JUAN PABLO REYES	CONSIGNACION	BANCO POPULAR	050-00110-6	16388385	25/11/2003	272,000.00
JUAN PABLO REYES	CONSIGNACION	BANCO POPULAR	050-00110-6	16388386	25/11/2003	544,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	60,000.00
	TOTAL :	\$ 60,000.00

SON: SESENTA MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____