

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 03-106-075

TÍTULO SOLICITADO: "Composición farmacéutica de un inhibidor de lipasa y un éster de ácido graso de sacarosa"

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SOLICITANTE: F. HOFFMANN-LAROCHE AG

APODERADO: ALICIA LLOREDA RICAURTE

TRÁMITE: REMISIÓN DE INFORMACIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, dentro del trámite de la referencia, por medio del presente escrito, procedo a presentar argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario:

I. REMISION DE INFORMACIÓN.

En primer lugar, es importante señalar que la modificación en el capítulo reivindicatorio hecho por el solicitante en su respuesta al requerimiento de información, presentada el 23 de noviembre de 2009, corresponde a un cambio de forma que, como se verá enseguida, pretende evadir de manera superficial los

argumentos expuestos tanto por el examinador técnico, como por el opositor en el escrito oportunamente aportado al trámite de la referencia.

En efecto, el solicitante define en su nueva reivindicación 1 que el ácido del éster de sacarosa que hace parte de las composiciones farmacéuticas reveladas es seleccionado entre sacarosalaurato, sacarosamiristato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato, y enfoca la solicitud a proteger una composición farmacéutica que comprende orlistat, un monoéster de ácido graso de sacarosa seleccionado entre los anteriormente mencionados, y uno o mas excipientes farmacéuticamente aceptables.

Si bien es cierto que de esta forma ha logrado el solicitante superar la objeción relacionada con la reivindicación de un uso y un método de tratamiento, no lo es menos que las reivindicaciones restantes mantienen su improcedencia de patentabilidad en tanto mantienen, en esencia, las mismas características técnicas descritas con anterioridad en el estado de la técnica.

En primer lugar, queremos insistir en que tanto los argumentos dados por el examinador técnico siguen siendo completamente válidos para desacreditar el nivel inventivo de la invención, partiendo del hecho que todas las anterioridades citadas representan una clara guía para cualquier persona medianamente versada en la materia que esté buscando resolver el mismo problema técnico planteado que el solicitante, consistente en buscar la reducción de efectos secundarios asociados al consumo de un inhibidor de lipasa, como por ejemplo el goteo anal de grasa.

Lo anteriormente dicho puede sustentarse en las revelaciones contenidas en los documentos PCT/WO2001/19378 y PCT/WO00/09122, *Preparación De Ésteres De Ácidos Grasos Con Sacarosa Como Emulsionantes Alimentarios Y Evaluación De Sus Propiedades Superficiales Y Emulsionantes*¹ así como en el documento "FAT REPLACERS" Vol. 52, N° 3, publicado en marzo de 1998, los cuales revelan composiciones farmacéuticas que contienen un inhibidor de lipasa, uno (o más) aditivos, espesantes y emulsificantes hidrofílicos y/o coloidales de grado alimenticio y excipientes en donde se pueden utilizar poliésteres de sacarosa

¹ M.G. Megahed. 50(4),1999, 280-282

tales como Ryoto Sugar Esters (nombre comercial para ésteres de ácidos grasos de sacarosa), por ejemplo Ryoto Sugar Ester S-170, que contiene poliésteres de ácido esteárico de sacarosa (pág 3 -líneas 32, 33; pág 4 -líneas 1 a 4); una composición farmacéutica que comprende al menos un inhibidor de lipasa y al menos un éster de ácido graso de polioles, caracterizado en que el éster de ácido graso tiene un punto de fusión cercana a la temperatura del cuerpo y los polioles son seleccionados del grupo que consiste de glicerol, azúcares, derivados de azúcar y mezcla de los mismos; y evidencia de que este tipo esteres de ácidos grasos de sacarosa pertenecen al estado de la técnica y resulta de amplio uso en la industria.

En otras palabras, e independientemente del tipo de componente que se use como tensoactivo, con base en la información expuesta en estas anterioridades, y su combinación con referencias generales disponibles y de fácil acceso, cualquier persona medianamente versada en la formulación de productos farmacéuticos podría optar por el empleo de tales ésteres de sacarosa como agentes tensoactivos en el afán de resolver el citado problema del exceso de grasa en las heces.

Lo anterior es tan cierto, que en la respuesta al requerimiento el solicitante busca diferenciar un monoéster de sacarosa de los poliésteres de sacarosa que menciona la anterioridad WO/2001/19378:

"Por lo tanto, es absolutamente claro que a lo largo del documento D2 NO se menciona la posibilidad de que una molécula de sacarosa sea sustituida por un solo ácido graso, esto es, no se hace alusión a una composición farmacéutica que comprenda un monoéster de ácido graso de sacarosa (...)"

En relación con este punto, si bien es cierto que no hay una correspondencia exacta con los compuestos tensoactivos reivindicados por la solicitud colombiana en cuestión, también lo es que para una persona medianamente versada en la formulación de productos farmacéuticos, la utilidad de un monoéster de sacarosa y/o un poliéster de sacarosa como tensoactivo sería extrapolable, y la decisión de usar uno u otro se resolvería a través de los respectivos ensayos de

preformulación y formulación a los que rutinariamente toda formulación farmacéutica debe someterse.

Prueba de lo anterior, y de la versatilidad con que se podría solucionar el problema técnico planteado a través de otros diversos tipos de agentes tensoactivos, nos la da el mismo solicitante (F. HOFFMANN-LAROCHE AG) a través de otras solicitudes anteriores a esta, en las cuales se plantea el mismo problema técnico a resolver, y se plantea su solución mediante la asociación de Orlistat con un agente tensoactivo (diferente) en proporciones definidas. Las solicitudes en cuestión son el expediente colombiano 00-068-859 titulado "Formulaciones en dispersión que contienen orlistat con eficacia mejorada y disminución de efectos secundarios" y 03-004-385 titulado "Nuevas composiciones farmacéuticas que comprenden un inhibidor de lipasa y un secuestrante de ácidos biliares farmacéuticamente aceptable." En el primer documento el solicitante reivindica una gran variedad de agentes tensoactivos, mientras que en el segundo se inclina por la utilización de ácidos biliares.

Esto no solo evidencia que las anterioridades expuestas en la oposición y por el señor examinador aplican como una clara guía para llevar a cabo el efecto buscado por la solicitud en cuestión, sino que además el mismo solicitante aplica las características inherentes de estos compuestos tensoactivos y la misma estrategia para resolver el mismo problema técnico planteado en sus diferentes solicitudes anteriores, lo cual hace evidente la imposibilidad de otorgar el privilegio de patente que nos ocupa.

También son evidencia de la versatilidad del uso diferentes agentes tensoactivos asociados a orlistat o inhibidores de lipasa la publicación internacional WO 00/13667 publicada el 16 de Marzo de 200 y titulada "LIPSTATIN DERIVATIVE-SOLUBLE FIBER TABLETS"(pagina 3 y capítulo reivindicatorio), la publicación internacional WO 00/09123 publicada el 24 de febrero de 2000 y titulada "PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS AND QUITOSAN" (pagina 1 y capítulo reivindicatorio) y la publicación internacional WO 99/34787 publicada el 15 de julio de 1999 y titulada "FAT BINDING POLYMERS" (paginas 2, 16 y capítulo reivindicatorio).

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- (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).
- (72) Inventors: DE SMIDT, Paschier, Christiaan; Benjamin de Tudela, 25-2B, E-31008 Pamplona (ES). HADVARY, Paul; Neumattenweg 8, CH-4105 Biel-Benken (CH). LENGSELD, Hans; Marschalkenstrasse 35, CH-4054 Basle (CH). SCHMID, Marcel; 2, Rebasse, CH-4153 Reinach (CH). SMALL, David, MacFarland; 87 Harbourside Road, Quincy, MA 02171 (US). STEFFEN, Hans; 36, Fischmarkt, CH-4410 Liestal (CH). TARDIO, Joseph; 14, rue Petite Camargue, F-68300 St. Louis (FR).
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(54) Title: SOLID LIPID FORMULATIONS

(57) Abstract: The present invention refers to a pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols are chosen from the group consisting of sugars, sugar derivatives and mixtures thereof.

Solid lipid formulations

The present invention relates to pharmaceutical compositions comprising at least one lipase inhibitor.

5 Examples of such lipase inhibitors are lipstatin and orlistat. The latter is also known as tetrahydrolipstatin or THL and is derived from a natural product excreted by *Streptomyces toxytricini*. This class of compounds was found to exhibit in vitro as well as in vivo activity against various lipases, such as lingual lipase, pancreatic lipase, gastric lipase, and carboxylester lipase. Its use for the control or prevention of obesity and hyperlipidemia is described, for instance, in US Patent 4,598,089.

10 Orlistat is currently administered at doses of 120 mg per meal and dosing is independent of the body mass of the human subject. Orlistat acts locally in the gastrointestinal (GI) tract and prevents lipase from digesting triglycerides and subsequently inhibits the formation of absorbable lipid degradation products. For this reason, systemic availability of the lipase inhibitors is not required and, instead, local residence in the gastrointestinal tract is preferred.

15 Lipase inhibitor compositions currently administered inhibit around 30% of fat absorption after consumption of a mixed meal; an increase of the lipase inhibitors concentration in the pharmaceutical composition does not increase its clinical efficacy and/or potency while the intensity of local side effects increases.

20 Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. This phenomenon reflects physical separation of some liquid unabsorbed dietary fat from the bulk of solids in the lower large intestine.

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The problem at the root of the present invention is therefore to provide lipase inhibitor compositions which are able to improve the clinical efficacy and/or potency of the inhibitor itself, and to minimize or suppress the above mentioned disadvantages.

- 5 The problem is solved, according to the present invention, by a pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature, i.e. $>37^{\circ}\text{C}$, and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.

- 10 It has surprisingly been found that administering a lipase inhibitor in a composition comprising at least one of the above fatty acid esters clearly improves the efficacy and potency of the lipase inhibitor itself. Furthermore, the inter-subject variability in efficacy and/or potency is reduced, as well as the frequency and intensity of side effects.

- The pharmaceutical compositions according to the present invention have been found to exhibit very favorable effects when applied orally during meal intake in humans.
15 Surprisingly, an increased efficacy and potency compared to the already known compositions was observed. This was unexpected as the compositions according to the invention are solid within the body and should therefore be poorly dispersible among the dietary oil particles in the stomach.

- Furthermore, the compositions according to the present invention reduce
20 unpleasant side effects in the single meal test compared to the already known compositions, despite the greater amount of fat which remains unabsorbed. During the single meal studies with human subjects, it was observed that the stools obtained after intake of compositions according to the present invention show less separation of oil from the main stool mass as compared to the conventional formulations. This was unexpected,
25 as equal or higher amounts of fat were present in the collected stools.

- According to the present invention, the terms "inhibitor of lipases" and "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of
30 microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins, analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterised in that they have been
35 substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also

comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses
5 processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

10 Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that
15 the lipase inhibitor be administered during ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Accordingly, the present invention refers to a composition comprising at least one
20 inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.

The polyols can be chosen, independently from each other, from the group consisting of glycerol, sugars, sugar derivatives and mixtures. This group especially
25 comprises sucrose, glycerol, and sugar alcohols, and most preferably glycerol, i.e. most preferably glyceride esters are used in the compositions according to the present invention.

The term "sugar alcohols" refer to compounds comprising mono-, oligo- and polysaccharides and their reduction products, e.g. mannitol.

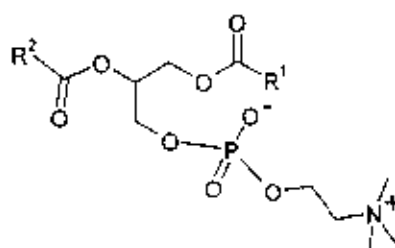
The term "glyceride ester" refers to an ester of glycerol. According to the present
30 invention, an ester may contain one to three, preferably one or three C12 to C20 fatty acid(s) moieties per glycerol moiety or may be a phospholipid, preferably a lecithin or mixtures thereof. For example, the glyceride esters can be chosen from the group consisting of one or more triglycerides, one or more monoglycerides, one or more

phospholipids and mixtures thereof. Preferably, the fatty acid moieties in the fatty acid ester of the polyols have, independently from each other, twelve or more carbon atoms, preferably twelve to twenty carbon atoms. Most preferably, the fatty acid moieties in the fatty acid ester of the polyols have twelve to twenty carbon atoms and are saturated.

- 5 In a preferred embodiment of the present invention suitable triglycerides are trilaurin, trimyristin, tripalmitin and tristearin and mixtures thereof. The most preferred triglycerides are trimyristin and trilaurin.

The monoglycerides can be chosen from the group consisting of monocaprin, monolaurin, monomyristin and monopalmitin and mixtures thereof.

- 10 In a preferred embodiment of the present invention, the phospholipid is preferably a lecithin, e.g. a non-, partially or fully hydrogenated lecithin and mixtures thereof. The term "lecithin" in the context of this invention refers to esters formed of glycerol, two fatty acids, and a phosphorylcholine moiety. A lecithin has the following structure:



- 15 wherein R¹-COO- and R²-COO- are moieties derived from fatty acids as defined above.

The phospholipids, e.g. lecithins, may be chosen from the group consisting of natural lecithin, synthetic lecithin, sojalecithin, egglecithin, synthetic dipalmitoyllecithin, partially or fully hydrogenated lecithin and mixtures thereof.

The fatty acid esters of polyols are known in the art and are commercially available.

- 20 Preferably, the glyceride ester is present in an amount varying between 0.5 and 90 % of the total weight of the composition.

- Advantageously, the pharmaceutical compositions of the present invention further comprise at least one pharmaceutically acceptable excipient. The additional excipient may be useful for enhancing the dispersion and distribution in the stomach. The excipient may be chosen from the group consisting of disintegrants, effervescent and mixtures thereof. Further excipients such as carbohydrates, starch and/or its derivatives, maltodextrines, cellulose, cellulose derivatives, sugars, fillers, antioxidants, anionic and nonionic surfactants such as sodium dodecylsulfate, fatty acid salts, e.g. Na-stearate,
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poly(oxyethylene)alkyl esters, poly(oxyethylene)alkyl ethers and mixtures thereof can also be added. Examples of additional excipients are glucose, lactose, sorbitol, maltodextrin, talcum, magnesium stearate, mannitol, sodium bicarbonate, crospovidone, glycofurol, tartaric acid and mixtures thereof

- 5 The invention is useful with any inhibitor of lipases, but is especially useful for inhibitors of the gastric and pancreatic lipase and, in particular, for the active compound orlistat.

According to the present invention, the lipase inhibitor is present in an amount varying from 1 to 50%, preferably from 5 to 30%, of the total weight of the composition.

- 10 In a preferred embodiment of the present invention the pharmaceutical composition as described above may comprise

- a) 1 to 50% of the total weight of the composition is a lipase inhibitor;
- b) 0.5 to 90% of the total weight of the composition is at least one fatty acid ester of polyols; and optionally

- 15 the composition comprises one or more pharmaceutically acceptable excipient(s).

The compositions according to the present invention can be administered using conventional dosage forms such as hydroxypropylmethylcellulose (HPMC) capsules, hard gelatin capsules, starch capsules, tablets, chewable tablets and capsules, powders, pellets, granules, etc.

- 20 The present invention relates also to a process for preparing pharmaceutical compositions as described above, which process comprises mixing at least one inhibitor of lipases with at least one fatty acid ester of polyols, in the solid or molten state, wherein the fatty acid ester of polyols has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures
25 thereof.

A further aspect of the present invention is to provide a method for controlling or preventing obesity comprising the step of administering to a patient a pharmaceutical composition as described above.

- 30 The invention also relates to the use a composition as defined above for the preparation of a medicament for the prevention and treatment of obesity.

The invention will be now illustrated in details by the following examples.

EXAMPLESExample 1

10 g of melted trimyristin (Dynasan 114, Hüls AG) were mixed with 20 g orlistat
5 during about 30 minutes at a temperature of 57-63°C. 20 g glucose were added to the so
obtained co-melt and mixed until solidification at room temperature. The so obtained
cake was left for an hour at room temperature, ground by means of a dry mixer and
subsequently sieved through meshes of 1.6 mm. The resulting particles were heated at 39°C
for 4.5h under inert atmosphere, cryo-milled with dry ice and subsequently mixed with
10 lactose (lactose : resulting particle = 100 : 15 w/w). The so obtained mixture was finally
pressed into chewable tablets having a diameter of 16 mm, a weight of 1.15 g and
containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose and 1000 mg lactose.

The above chewable tablets were applied to human volunteers during a single meal
test. Human subjects consumed a meal consisting of 130 g hamburger meat, 10 g butter
15 and 100 g French fries (fried in peanut oil) and containing overall about 35 g fat. Stools
were collected from day -1 (a day before eating the single meal) until day 5 after the test
meal. The first and the last stools were employed to assess background fat excretion.
Stools were stored frozen and extracted for total lipid according to Bligh and Dyer (Bligh,
E.G., and Dyer, W.J., *Can. J. Biochem. Physiol.*, 37, (1959), 911). Background excretion of
20 lipids was subtracted to obtain the amount of fat excreted due to the orlistat treatment.
The excreted fat was quantified by gravimetry and expressed as percentage of the fat
content of the test meal.

Example 2

100 g of trimyristin (Dynasan 114, Hüls AG) were melted at 65°C in a suitable high
25 shear mixer vessel. 200 g orlistat were given in the vessel and molten by mixing softly
(mixture = comelt). The molten phase was mixed for 2 minutes. While stirring, 1800 g
maltodextrin DE 21 (ratio comelt : maltodextrin = 1:6 w/w) were added in two portions
and mixed until solidification at room temperature and a flowing granulate was obtained.
The granulate was sieved through meshes of 0.85 mm. Separately, 4950 g sorbitol were
30 sieved through meshes of 0.85 mm and mixed with the co-melted granulate for 3 minutes.
Additionally, the outer phase (375 g talcum and 75 g magnesium stearate) were hand
sieved through meshes of 0.5 mm and mixed with the granulate for 3 minutes. The so
obtained mixture was finally pressed into chewable tablets having a diameter of 20 mm, a
weight of 1.5 g and containing each 40 mg orlistat, 20 mg trimyristin, 360 mg
35 maltodextrin, 960 mg sorbitol, 75 mg talcum and 15 mg magnesium stearate.

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The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 3

1.25 g HPMC (Pharmacoat 603, Shin-Etsu Chemical Co) were dissolved in 39.5 g
5 water at about 75 °C. The solution was cooled to room temperature (25°C) and a
dispersion was obtained by adding thereto 5 g mannitol, 2.5 g sodium bicarbonate and 1 g
Croscopovidone. 0.75 g Kryosomes 1703H (hydrogenated lecithin, Lipoid AG) were
dispersed in 7.5 g water with a homogenizer (Polytron) for 30 seconds and successively
mixed with the above dispersion. The obtained aqueous system was used to make an
10 emulsion by emulsifying, with a Polytron for 1.5 minutes at 65 °C, 4.5 g of a melted oily
mixture obtained by comelting 3.15 g trimyristin (Dynasan 114, Hüls AG) and 6.3 g
orlistat at 65 °C. This emulsion was frozen at -80 °C in a rotating 250 ml round flask in a
dry ice-ethanol mixture and was then lyophilized. The lyophilisate was then milled at room
temperature and 3 g thereof were mixed and sieved through meshes of 0.5 mm. 1.3 g of the
15 mixture was pressed to a chewable tablet having a diameter of 16 mm diameter, a weight of
1.3 g and containing each 60 mg orlistat, 30 mg trimyristin, 15 mg Kryosome, 25 mg
HPMC, 20 mg Croscopovidone, 100 mg mannitol, 50 mg sodium bicarbonate and 1000 mg
lactose.

The above chewable tablets were applied to human volunteers according to the
20 method described in Example 1.

Example 4

30 g orlistat and 15 g trimyristin (Dynasan 114, Hüls AG) were spread through
meshes of 0.9 mm and mixed for 10 minutes. The mixture was again sieved through
meshes of 0.9 mm and mixed for 10 minutes. The so obtained mixture was coarse milled
25 (in portions) for 0.5 minutes in a dry mixer by adding a triple amount of dry ice. This cold
mixture was then cryo-milled with a pin mill to get fine particles. The resulting particles
were dried during 15 minutes under high vacuum and subsequently mixed with 2/3 (w/w)
part of glucose. 15 g of this dry mix was mixed with 100 g lactose for 10 minutes and then
sieved through meshes of 0.5 mm. The so obtained mix-milled granulate was finally
30 pressed into chewable tablets having a diameter of 16 mm, a weight of 1.15 g and
containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose and 1000 mg lactose.

The above chewable tablets were applied to human volunteers according to the
method described in Example 1.

Example 5

- 1.2 g orlistat and 1.8 g glucose were sieved through meshes of 0.9 mm and mixed for 2 minutes. Afterwards 4.0 g Kryosome 1702 (soyalecithin : sucrose = 1:2 w/w; Lipoid AG) were also sieved through meshes of 0.9 mm and mixed with the first mixture for 2 minutes.
- 5 The combined mixture was then cryo-milled with an air-jet mill using dry ice for cooling. The resulting particles were dried for 15 minutes under high vacuum. 3.5 g of the dried particles were mixed with 10 g lactose for 15 minutes. The so obtained powder mixture was finally pressed into chewable tablets having a diameter of 16 mm, a weight of 1.35 g and containing each 60 mg orlistat, 90 mg glucose, 200 mg Kryosome and 1000 mg lactose.
- 10 The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 6

- 4.24 g soyalecithin and 4.24 g orlistat were subsequently dissolved in 31.52 g glycofurol 75 (Roche). Empty hard gelatin capsules were sealed with a 25 % gelatin
- 15 solution in water and were allowed to dry. The sealed hard gelatin capsules were punched and subsequently filled with 565 mg of the orlistat/lecithin/glycofurol-solution. The holes were closed with the above gelatin solution and the closed capsule was allowed to dry for at least 15 minutes. Every capsule contained 60 mg orlistat, 60 mg soyalecithin and 445 mg glycofurol.
- 20 Capsules prepared in this way were applied to human volunteers according to the method described in Example 1.

Example 7

- 10 g of melted trimyristin (Dynasan 114, Hüls AG) were mixed with 20 g orlistat during about 30 minutes at a temperature of 57-63°C. 20 g glucose were added to the so
- 25 obtained co-melt and mixed until solidification at room temperature, ground by means of a dry mixer and subsequently sieved through meshes of 1.6 mm. 48 g of resulted particles were kept at 39°C in a closed vial under inert atmosphere for 4.5h, cryo-milled with dry ice on a pin mill. 15 g of the resulted particles were subsequently mixed with 10 g Kryosome 1702 (Lipoid AG) and 100 g lactose for 30 minutes. The mixture was sieved through
- 30 meshes of 0.5 mm and pressed into chewable tablets, having a diameter of 16 mm, a weight of 1.25 g and containing each 60 mg orlistat, 30 mg trimyristin, 60 mg glucose, 100 mg Kryosome and 1000 mg lactose.

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The above chewable tablets were applied to human volunteers according to the method described in Example 1.

Example 8

- 0.75 g of co-melted and cryo-milled material (orlistat-trimyristin-glucose 2:1:2) from Example 7 and 0.5 g Kryosome 1702 were sieved through meshes of 0.5 mm and mixed for 10 minutes. 3.0 g sodium bicarbonate and 1.5 g tartaric acid were milled at room temperature in a laboratory blade mill, sieved through meshes of 0.5 mm and mixed for 10 minutes. 2.7 g of this effervescent mixture was added to the first mixture and mixed again for 10 minutes. 0.395 g of this mixture were filled into HPMC capsules of size 0, containing 30 mg orlistat, 15 mg trimyristin, 30 mg glucose, 50 mg Kryosome, 180 mg sodium bicarbonate and 90 mg tartaric acid.

The above capsules were applied to human volunteers according to the method described in Example 1.

Example 9

- 20 g orlistat and 10 g trilaurin (Dynasan 112, Hüls AG) were sieved through meshes of 0.5 mm and mixed. This mixture was cryo-milled in a pin mill together with dry ice and subsequently dried under vacuum for 15 minutes. 10 g of this mixture was blended with 15 g glucose. 3g of this blend and 2 g of Kryosomes 1702 (Lipoid AG) were cryo-milled together with dry ice in a laboratory blade-mill and dried overnight in a dessicator under vacuum. 1.25 g of the resulting powder were pressed to a chewable tablet having a diameter of 16 mm, a weight of 1.25 g and containing each 60 mg orlistat, 30 mg trilaurin, 60 mg glucose, 100 mg kryosome and 1000 mg lactose.

The above chewable tablets were applied to human volunteers according to the method described in Example 1.

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Example 10

- 16 g monolaurin (Rylo MG12, Danisco Ingredient AG) and 4 g monocaprin emulsifier TS-PH003 (Danisco Ingredient AG) were comelted at about 70 °C, cooled to room temperature (25°C) and thereby completely solidified. After one day the film was scraped off the wall with a spatula, coarse milled, in portions, in a dry mixer at low temperature by adding dry ice (three times the volume of the to milled material) for about half a minute and then fine cryo-milled in a pin mill and vacuum dried for 15 minutes. 15 g of this mixture and 15 g orlistat were blended. 50 g dry ice were added and the mixture is coarse milled in portions each for half a minute. After vacuum drying the resulting powder

- was sieved through meshes of 0.9mm and fine cryo milled in a pin mill to produce a fine orlistat-monocaprin-monolaurin (50-10-40) powdermix. 2.4 g of a comilled mixture between 2.16 g tartaric acid and 4.56 g sodiumbicarbonate was added to 5.6 g of the above powdermix and 2 g anhydrous lactose, mixed for 5 minutes and sieved through meshes of 0.5 mm and mixed again. 500 mg of the resulting powder were filled in hard gelatin capsules containing 60 mg orlistat, 48 mg monolaurin, 12 mg monocaprin, 100 mg lactose, 190 mg sodium bicarbonate and 90 mg tartaric acid.

The above capsules were applied to human volunteers according to the method described in Example 1.

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Table 1: In vivo results

Example	Orlistat dose (mg)	Excreted fat ⁽¹⁾	n ⁽²⁾	Free oil in stool samples ⁽³⁾
Reference	120 mg (Xenical®)	41.8 ± 11.5	18	9/18
1	60 mg	48.1 ± 3.9	3	1/3
2	40 mg	37.6 ± 17.1	5	0/5
3	60 mg	50.2 ± 13.4	3	1/3
4	60 mg	43.1 ± 15.6	5	0/5
5	60 mg	64.8 ± 14.3	5	0/5
6	60 mg	47.2 ± 12.0	5	n.d.
7	60 mg	82.0 ± 5.5	6	0/6
8	30 mg	40.6 ± 10.6	5	0/5
9	60 mg	60.6 ± 13.3	5	2/5
10	60 mg	54.2 ± 10.9	5	1/5

⁽¹⁾ excreted fat as percentage of fat intake.

⁽²⁾ number of volunteers subjected to the experiments

⁽³⁾ number of stool samples containing free oil/number of volunteers

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As shown in Table 1, the efficacy and/or potency of the compositions according to the present invention is much higher than that of conventional formulations.

- Compositions according to the invention containing just the half or even a quarter of the lipase inhibitor of the known composition are similarly or even much more efficacious
5 and/or potent. For the same lipase inhibition degree, it is now possible to strongly decrease the amount of active compound in the composition, thus minimizing undesired side effects.

- Table 1 shows also the number of stool samples containing free oil for each of the above compositions. Stool samples obtained after intake of compositions according to the
10 present invention show just occasional separation of oil from the main stool mass or no separation at all. The compositions according to the present invention enable therefore to minimize or completely suppress anal leakage of oil which is one of the most undesired side effect of the prior art compositions.

CLAIMS

1. A pharmaceutical composition comprising at least one inhibitor of lipases and at least one fatty acid ester of polyols, characterized in that the fatty acid ester has a melting point above the body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.
2. The pharmaceutical composition according to claim 1, wherein the polyols are chosen, independently from each other, from the group consisting of sucrose, glycerol, and sugar alcohols.
3. The pharmaceutical composition according to claim 1 or 2, wherein the polyol is glycerol.
4. The pharmaceutical composition according to any of claims 1 to 3, wherein the fatty acid ester is a glyceride ester and is chosen from the group consisting of one or more triglycerides, one or more monoglycerides, one or more phospholipids and mixtures thereof.
5. The pharmaceutical composition according to any of claims 1 to 4, wherein the fatty acid moieties in the fatty acid ester of the polyol have, independently from each other, twelve or more carbon atoms and the fatty acid moieties in the fatty acid ester of the polyol are saturated.
6. The pharmaceutical composition according to claim 5, wherein the fatty acid moieties in the fatty acid ester of the polyol have, independently from each other, twelve to twenty carbon atoms.
7. The pharmaceutical composition according to any of claims 4 to 6, wherein the triglycerides are chosen from the group consisting of trilaurin, trimyristin, tripalmitin, tristearin and mixtures thereof.
8. The pharmaceutical composition according to claim 7, wherein the triglyceride is trimyristin or trilaurin or mixtures thereof.
9. The pharmaceutical composition according to any of claims 4 to 6, wherein the monoglycerides are chosen from the group consisting of monocaprin, monolaurin, monomyristin, monopalmitin and mixtures thereof.
10. The pharmaceutical composition according to any of claims 4 to 6, wherein the phospholipid is a lecithin.

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11. The pharmaceutical composition according to claim 10, wherein the phospholipid is a non-, partially or fully hydrogenated lecithin and mixtures thereof.
12. The pharmaceutical composition according to claim 10 or 11, wherein the phospholipids are chosen from the group consisting of natural lecithin, synthetic
5 lecithin, sojalecithin, egglecithin, synthetic dipalmitoyllecithin, partially or fully hydrogenated lecithin and mixtures thereof.
13. The pharmaceutical composition according to any of claims 1 to 12, wherein the fatty acid ester of polyols is present in an amount varying between 0.5 % and 90 % of the total weight of the composition.
- 10 14. The pharmaceutical composition according to any of claims 1 to 13, further comprising at least one pharmaceutically acceptable excipient.
- 15 15. The pharmaceutical composition according to claim 14, wherein the excipient is selected from the group consisting of carbohydrates, starch and/or its derivatives, maltodextrines, cellulose, cellulose derivatives, sugars, fillers, disintegrants, effervescent, antioxidants, anionic surfactants, nonionic surfactants and mixtures
15 thereof.
16. The pharmaceutical composition according to claim 15, wherein the surfactant is selected from the group consisting of sodium dodecylsulfate, fatty acid salts, polyoxyethylene alkyl esters and polyoxyethylene alkyl ethers and mixtures thereof.
- 20 17. The pharmaceutical composition according to any of claims 14 to 16, comprising an excipient selected from the group consisting of glucose, lactose, sorbitol, maltodextrin, talcum, magnesium stearate, mannitol, sodium bicarbonate, Croscopovidone, glycofurol, tartaric acid and mixtures thereof.
- 25 18. The pharmaceutical composition according to any of claims 1 to 17, wherein the inhibitor of lipases is an inhibitor of gastrointestinal lipases.
19. The pharmaceutical composition according to claim 18, wherein the inhibitor of gastrointestinal lipases is orlistat.
20. The pharmaceutical composition according to any of claims 1 to 19, wherein the lipase
30 inhibitor is present in an amount varying from 1 to 50% of the total weight of the composition.
21. The pharmaceutical composition according to claim 20, wherein the lipase inhibitor is present in an amount varying from 5 to 30% of the total weight of the composition.

22. The pharmaceutical composition according to any of claims 1 to 21, wherein
- a) 1 to 50% of the total weight of the composition is at least one lipase inhibitor;
 - b) 0.5 to 90% of the total weight of the composition is at least one fatty acid ester of polyols; and optionally
 - 5 c) the composition comprises one or more pharmaceutically acceptable excipient(s).
23. A process for preparing a pharmaceutical composition according to any one of claim 1 to 22, comprising mixing at least one inhibitor of lipases with at least one fatty acid ester of polyols, wherein the fatty acid ester of polyols has a melting point above the
- 10 body temperature and the polyols are chosen from the group consisting of glycerol, sugars, sugar derivatives and mixtures thereof.
24. Use of a pharmaceutical composition as defined in any one of claim 1 to 22 for controlling or preventing obesity.
25. A method for controlling or preventing obesity comprising the step of administering to
- 15 a patient a pharmaceutical composition as defined in any one of claims 1 to 22.
26. Use of a composition as defined in any of claims 1 to 22 for the preparation of a medicament for the prevention and treatment of obesity.
27. The invention as hereinbefore described.

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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS (57) Abstract Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipase, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and auxiliary excipients.		

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PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS

The present invention relates to pharmaceutical compositions containing an inhibitor of gastrointestinal lipases, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and excipients.

An example of an inhibitor of gastrointestinal lipases is orlistat, previously known as tetrahydrolipstatin or THL. Orlistat reduces the absorption of dietary fat. Its use for the control or prevention of obesity and hyperlipidaemia is described in US patent 4 598 089.

Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. This phenomenon reflects physical separation of some liquid unabsorbed dietary fat from the bulk of unabsorbable solids in the lower large intestine. This physical separation and thus anal leakage of oil can be prevented with the pharmaceutical compositions of the present invention.

In the US patent 5 447 953 it has been demonstrated that by combining a lipase inhibitor with substantial amounts of water-insoluble crude fibers, the inhibiting effect on fat absorption can be increased. This synergistic effect is likely attributable to acceleration of gastrointestinal transit of food by the water-insoluble fiber component. The consequent shortening of the time period available for fat digestion combined with the reducing effect on lipase activity intensifies the inhibitory effect on fat absorption.

Surprisingly, it has now been found that the separation of unabsorbed oil from the feces and thus anal oil leakage can be reduced or prevented, when a lipase inhibitor such as orlistat is administered in combination with low amounts of one or more poorly digestible, poorly

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fermentable, hydrophilic and/or hydrocolloidal food grade thickeners
and/or emulsifiers.

The invention is also concerned with the use of poorly digestible,
poorly fermentable hydrophilic and/or hydrocolloidal food grade
5 thickeners and/or emulsifiers for the combined simultaneous, separate
or chronologically spaced use with lipase inhibitors, e.g. orlistat, in the
treatment of obesity and hyperlipaemia.

The invention is further concerned with the use of the above
thickeners and/or emulsifiers for treating or preventing the syndrome of
10 anal leakage of oil occurring after the administration of a lipase
inhibitor, such as orlistat, or after ingestion of food containing poorly
absorbable or non-absorbable fats or oils or undigestible oily fat
substitutes.

Further examples of lipase inhibitors which can be used in the
15 scope of the present invention are lipstatin, panclicins, hesperidin,
ebelactones, esterastin and their derivatives, and valilactone.

As thickeners there can be cited water soluble natural, synthetic
or semisynthetic polysaccharides, such as methylcellulose, xanthan
gum, psyllium seed, ispaghula husk, plantago ovata seeds, karaya gum
20 and mixtures of such compounds:

Methyl cellulose is the methyl ether of cellulose. It is slowly
soluble in water, giving a viscous, colloid solution.

Xanthan gum is a biosynthetic hydrocolloidal high molecular
weight exopolysaccharide produced by pure culture fermentation of
25 Xanthomonas campestris. It contains D-glucose, D-mannose, and
D-glucuronic acid as the dominant hexose units and is manufactured as
the sodium, potassium, or calcium salt.

Psyllium seed husk, seed coat is a source of soluble fibre. It
comprises cellulose containing walls of endosperm, and mucilage
20 containing epidermis of small dried ripe seeds. A colorless transparent
mucilage forms upon contact with water.

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Ispaghula husk is psyllium hydrophilic mucilloid. It comprises the epidermis and collapsed adjacent layer of Plantago species, e.g. Pl. psyllium. It swells rapidly upon contact with water to form a stiff mucilage.

5 Plantago ovata seeds (seed husk and seed coat) is a source of soluble fibre. It comprises cellulose containing walls of endosperm, and mucilage containing epidermis of small dried ripe seeds. A colorless transparent mucilage forms upon contact with water.

10 Karaya gum is a hydrocolloidal exudate or gum from Sterculia species. It forms a homogenous adhesive gelatinous mass upon contact with water.

Examples of these types of thickeners are contained in OTC products and/or food additives, such as:

15 METHOCEL A4M, a trademark of Dow Chemical Co. for a high viscosity methyl cellulose,

KELTROL TF, a trademark of Merck & Co. Inc., Rahway NJ, for xanthan gum,

MUCILAR, psyllium seed (Psyllii seminis testa), a product of Spirig AG, CH-4622 Egerkingen,

20 METAMUCIL, ispaghula husk (Ispaghulae testae pulvis) a product of Procter & Gamble, CH-1211 Geneve 2,

AGIOCUR, plantago ovata seeds, a product of Madaus AG, D-5000 Köln 91,

25 NORMACOL MITE, a trademark of Norgine Ltd., Great Britain, for karaya gum,

POLY-KARAYA, a trademark of Delalande for karaya gum of Interdelta SA, CH-1701 Fribourg.

30 A further example of a thickener is FIBERCON (polycarbophil), a trademark of Lederle Laboratories Division, American Cyanamid Co., Pearl River NY, for the calcium salt of a synthetic loosely crosslinked hydrophilic resin of the polycarboxylate type.

As emulsifiers which can be utilized in the compositions of the invention, there can be cited saccharose polyesters, such as Ryoto Sugar

Esters, e.g. Ryoto Sugar Ester S-170. Ryoto Sugar Esters are a trade name of Mitsubishi-Kasei Foods Corp., Chuo-Ku, Tokyo 104, for sucrose fatty acid esters. Ryoto Sugar Ester S-170 contains sucrose stearic acid polyesters.

5 Examples of excipients which can be used in the pharmaceutical compositions of the invention are binders, diluents and lubricants, such as AVICEL, polyvinyl pyrrolidone (povidone), talc, stearic acid and sodium stearyl fumarate; sweeteners, such as sorbitol, glucose, saccharose, saccharine-sodium salt and sodium cyclamate; flavour
10 agents, such as passion fruit, citron and limette; flavour enhancers, such as citric acid, monosodium citrate, sodium chloride and chinine sulfate; effervescing agents, such as sodium bicarbonate and tartaric acid; disintegrants, such as sodium starch glycolate; antimicrobial agents, such as p-hydroxybenzoic acid methyl or propyl ester;
15 detergents, such as sodium lauryl sulfate, and colouring agents, such as β -carotene.

 AVICEL essentially comprises microcrystalline cellulose. It is available from FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103, e.g. as AVICEL RC-591 or
20 CL-611, which are mixtures of microcrystalline cellulose (about 92%) and carboxymethylcellulose sodium (about 8%), AVICEL PH 101 or PH 105, which is microcrystalline cellulose with an average particle size of 50 or 20 μ , respectively; AVICEL CE-15 a mixture of microcrystalline cellulose and guar gum.

25 As indicated above, anal leakage of oil, occasionally observed with the therapeutic use of lipase inhibitors such as orlistat, can be reduced or prevented with the pharmaceutical compositions of the invention. This is illustrated by the following in vivo experiments:

 Rats maintained on high fat diet were used as model. Inhibition of
30 fat absorption by diet-admixed orlistat provoked anal leakage of liquid oil. However, the amount of oil leakage could not easily be determined. Due to coprophagia and extensive grooming activity the rats distributed the oil to a large extent over their fur. Moreover, this stressful condition of unsuccessful grooming provoked considerable excitation of the

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animals. The area of greasy fur increased in proportion to the amount of unabsorbed fat and was reduced by dietary admixture of selected examples of the above defined food additives. However, for reasons of animal care for comparative evaluation of the additives a surrogate parameter was used to assess effects on oil leakage. Following a meal containing orlistat, unabsorbed fat is temporarily stored in the caecum of the rat prior to excretion. The fat is partly present as floating liquid oil, partly associated with unabsorbable solids. In validation studies it could be demonstrated that the effect of food additives to bind and sequester unabsorbed liquid oil in the solid phase of the caecum is a reliable surrogate parameter predictive for a corresponding reduction of subsequent oil leakage.

The high fat basal diet used contained by weight 56% lab chow, 12% glucose and 32% olive oil. Food additives were supplemented at three levels, accounting for 12.4, 4.5 and 1.2% of the composite diet by weight. Control diets were supplemented with a corresponding amount of starch. All diets were moistened with water to a similar consistency to facilitate acceptability by the animals. Groups of 6-7 female rats (body weight: 120-140 g) were allocated to each diet. After dietary adaptation for one week, the rats were fasted for 24 hours and on the subsequent experimental day the diets were supplied as single meal (basal diet: 4.25 g, additives or starch: 0.6, 0.2 and 0.05 g). In order to completely block absorption of oil and thus produce a defined amount of unabsorbed fat a high dose of orlistat (45 mg) was dissolved in the olive oil fraction (1.5 ml) of the meal. The animals were sacrificed three hours after supplying the meal. At this point in time the caecum contained the largest fraction of administered dietary oil. To determine the relative amounts of bound and free oil in the caecum, the caecal contents were centrifuged (2000 g, 30 min) and the lipid content of the oil/water and solid phase was quantitated gravimetrically following extraction with solvent.

The food additives tested in the first experimental series were methylcellulose (MC), Ryoto sugar ester S-170 (RS) and xanthan gum (XG). The fat content of the liquid and solid phases in the caecum was expressed as percentage of the amount of oil supplied with the meal. Mean values for experimental groups fed the additives, as compared to

controls (where the thickening or emulsifying additive was replaced by the corresponding weight of starch(ST)), are shown in the following table. For statistical assessment of the effect of the additives, Student's t-test was used: n.s. = $p > 0.05$, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

5 Fat content in caecum in % of the amount of oil supplied:

additive	oil phase	solid phase
MC 0.05 g	24.8 n.s.	16.8 *
ST 0.05 g	25.4	13.4
MC 0.20 g	17.0 **	29.2 ***
ST 0.20 g	24.6	13.2
MC 0.60 g	5.0 ***	32.9 ***
ST 0.60 g	37.9	9.6
RS 0.05 g	18.3 n.s.	13.6 *
ST 0.05 g	23.6	9.0
RS 0.20 g	22.4 n.s.	23.3 ***
ST 0.20 g	24.2	11.0
RS 0.60 g	3.1 ***	37.1 ***
ST 0.60 g	15.8	11.9
XG 0.05 g	12.7 ***	20.3 ***
ST 0.05 g	23.6	9.0
XG 0.20 g	1.1 ***	23.2 ***
ST 0.20 g	24.2	11.0
XG 0.60 g	0.7 ***	18.9 ***
ST 0.60 g	23.6	10.9

As mentioned above 0.6, 0.2 and 0.05 g of food additive provided with the test meal correspond to 12.4, 4.5 and 1.2% by weight in the water-free composite diet.

5 The results shown above clearly demonstrate that in animals administered orlistat in combination with an additive according to the invention, the fraction of unabsorbed fat sequestered in the solid phase of the caecum was significantly increased (and liquid oil reduced) in comparison to control animals supplied with a corresponding amount of starch. Accordingly, the additives are effective in reducing or
10 preventing anal leakage of liquid oil.

Using the same experimental procedure several OTC products containing additives according to the invention as well as water-insoluble crude fiber products were evaluated in a second experimental series. To ensure a relevant comparison of the products their variable
15 content of active additive or fiber was taken into account. Accordingly, the amount of each product added to the diet was chosen in such a way that all the test meals contained the same amount of active additive or fiber (0.2 g, 4.5% by weight). The results of these experiments are given in the following table:

20 Fat content in caecum in % of the amount of oil supplied:

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OTC product	solid phase
AGIOCUR 0.30 g	20 ***
FIBERCON 0.35 g	18 ***
Starch Control 0.20 g	12
NORMACOL MITE 0.32 g	19 **
METAMUCIL 0.41 g	17 **
Starch Control 0.20 g	13
POLY-KARAYA 0.50 g	20 ***
Wheat bran 0.42 g	15 n.s.
Oat bran 1.60 g	11 n.s.
Starch Control 0.20 g	12

As mentioned above, the weight of OTC products indicated in the table correspond to 0.2 g active thickening or emulsifying additive or water-insoluble fiber.

5 The data demonstrate binding and sequestering of caecal oil and thus efficacy in preventing anal leakage of oil for the OTC compounds AGIOCUR, FIBERCON, METAMUCIL, NORMACOL MITE and POLY-KARAYA. Moreover, the results show as well the superiority of
10 additives according to the invention, as exemplified by POLY-KARAYA, over crude water-insoluble fibers, such as oat and wheat bran (no significant effect), which have been proposed in US patent 5 447 953 to improve the inhibitory effect on fat absorption.

15 The compositions of the invention conveniently contain 1 to 300, preferably from 3 to 30 parts by weight of an emulsifier or thickener for 1 part by weight of orlistat or another lipase inhibitor. They conveniently further contain from 1 to 500, preferably from 3 to 200 parts by weight of auxiliary excipients for 1 part by weight of the lipase inhibitor.

20 The compositions of the invention can be in the form of tablets, capsules or liquid formulations, that may be reconstituted from powder,

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granules, pellets, standard or effervescent tablets. They can also be formulated as chewable tablets or lozenges. Furthermore, the compositions can also be incorporated into food preparations, such as wafers, crackers or biscuits.

5 The composition of the invention can also be in the form of a commercial pack containing a lipase inhibitor, such as orlistat, and one or more of the above mentioned thickeners and emulsifiers, with instructions for its use for the simultaneous, separate or chronologically spaced use in the treatment of obesity or hyperlipidaemia.

10 For the treatment or prevention of obesity or hyperlipidaemia, a composition of the invention containing from 50 to 500 mg of orlistat or another lipase inhibitor and from 150 mg to 15 g of an emulsifier or thickener can be administered orally once, twice or three times per day.

15 A preferred composition of the invention is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of karaya gum as the thickener, wherein the dosage is from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat, most preferably wherein the dosage is about 60 mg of orlistat and about 1.5 g of karaya
20 gum or xanthan gum.

 A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprises orally administering from 1 to 3 chewable tablets per fat containing main meal, the dosage of each tablet being from 50 to 150
25 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat. Preferably, this method comprises orally administering orlistat and karaya gum or xanthan gum in a dosage amount of about 100 mg of orlistat and of about 2 g of karaya gum or xanthan gum per fat containing main meal.

30 The following non-limiting examples illustrate pharmaceutical preparations that can be produced in a manner known per se:

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267Example 1

Powder for reconstitution:

	Orlistat	0.12 g
	Xanthan gum	1.20 g
5	Sorbitol	9.91 g
	AVICEL CL 611	1.20 g
	β -Carotene 1% CWS	0.06 g
	Citric acid	0.10 g
	p-Hydroxybenzoic acid methyl ester	0.15 g
10	p-Hydroxybenzoic acid propyl ester	0.03 g
	Flavouring agent (passion fruit)	0.13 g
	AVICEL PH 105	4.00 g
	Monosodium citrate	1.00 g
	Saccharine-sodium salt	<u>0.10 g</u>
15	Total	18.00 g

An oral suspension can be obtained by adding tap-water to the above powder to a volume of about 50 ml.

Example 2

20 Chewable tablets:

	Orlistat	0.060 g
	Karaya gum	1.500 g
	Polyvinyl pyrrolidone	0.750 g
	Sorbitol	0.970 g
25	AVICEL CE-15	1.000 g
	Talc	0.480 g
	Stearic acid (micro-fine powder)	0.240 g
	Total	5.000 g

30 The indicated amounts of orlistat, karaya gum, polyvinyl pyrrolidone, sorbitol and AVICEL CE 15 are mixed and sieved. The talc and stearic acid are sieved and mixed with the above obtained

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mixture. The material is then compressed to chewable tablets with a diameter of 2 cm and a weight of 5 g.

Example 3

5 Pelletized formulation containing an emulsifier:

1. Orlistat pellets:

	Finely milled orlistat	120 mg
	Microcrystalline cellulose	93.6 mg
	Sodium starch glycolate	7.2 mg
10	Sodium lauryl sulfate	7.2 mg
	Povidone	12 mg
	Total	240 mg

For a batch size of 4 kg pellets the following procedure is applied:

15 Sodium lauryl sulfate (120 g) and povidone (200 g) are dissolved in q.s. water. The solution is cooled to 10-15°C → A. Orlistat (2000 g), microcrystalline cellulose (1560 g) and sodium starch glycolate (120 g) are pre-mixed → B.

20 Solution A is given to pre-mix B and kneaded. The resulting material is extruded to spaghettis. This extrudate is spheromized at 700 rpm. The obtained cylinder-shaped wet pellets are dried in a fluidized bed dryer and then sieved. The 0.5-1.25 mm size fractions are collected as orlistat pellets in closed containers.

2. Emulsifier part.

	Ryoto sugar ester S-170	600 mg
25	Microcrystalline cellulose	312 mg
	Sodium starch glycolate	15 mg
	Povidone	15 mg
	Talc	18 mg
	Total	960 mg

30 For a batch size of 16 kg pellets the following procedure is applied:

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Sugar ester (10 kg) is liquefied by heating to 60°C.

Microcrystalline cellulose (5.2 kg), sodium starch glycolate (0.4 kg) and povidone (0.4 kg) are added. The mass is kneaded under cooling to room temperature, then extruded through an extrusion plate with nominal
5 mesh size of 0.7 mm. The fatty extrudate is cut into pieces of 1 mm length and the resulting mass is dusted with talc in a mixer.

Orlistat pellets (2.4 kg) and emulsifier pellets (9.6 kg) are mixed.
The mixture is filled into sachets at a fill weight of 1.2 g, corresponding to 120 mg of orlistat and 600 mg of sugar ester.

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270Claims

1. Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipase, one (or more) additive(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers, and auxiliary excipients.
2. A composition as in claim 1, wherein the additive is a poorly digestible, poorly fermentable, hydrophilic and hydrocolloidal food grade thickener.
3. A composition as in claim 2, wherein the food grade thickener comprises methylcellulose, xanthan gum, psyllium seed, ispaghula husk, plantago ovata seeds, karaya gum or mixtures thereof.
4. A composition as in claim 1, wherein the additive is an emulsifier.
5. A composition as in claim 4, wherein the emulsifier is a saccharose polyester.
6. A composition as in claim 2 or 3 comprising 1 to 300 parts by weight of a thickener per 1 part by weight of an inhibitor of gastrointestinal lipase.
7. A composition as in claim 4 comprising 1 to 300 parts by weight of an emulsifier per 1 part by weight of an inhibitor of gastrointestinal lipase.
8. A composition as in any one of claims 1-7, wherein the inhibitor of gastrointestinal lipase is orlistat.
9. The use of one (or more) compound(s) of the group consisting of poorly digestible, poorly fermentable, hydrophilic and/or hydrocolloidal food grade thickeners and emulsifiers for treating or preventing the syndrome of anal leakage of oil occasionally occurring after the administration of an inhibitor of gastrointestinal lipase, such as

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orlistat, or after ingestion of food containing poorly absorbable or non-absorbable fats or oils or undigestible oily fat substitutes.

10. A composition as in claim 3 or 8, which is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of karaya gum or xanthan gum as the thickener, wherein the dosage is from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat.

11. The chewable tablet as in claim 10, wherein the dosage is about 60 mg of orlistat and about 1.5 g of karaya gum or xanthan gum.

12. A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprising orally administering from 1 to 3 chewable tablets per fat containing main meal, the dosage of each tablet being from 50 to 150 mg of orlistat and from 3 to 30 parts by weight of karaya gum or xanthan gum per 1 part by weight of orlistat.

13. A method of preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of orlistat, comprising orally administering orlistat and karaya gum in a dosage amount of about 100 mg of orlistat and of about 2 g of karaya gum or xanthan gum per fat containing main meal.

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Preparation of sucrose fatty acid esters as food emulsifiers and evaluation of their surface active and emulsification properties

By Mohamed G. Megahed

National Research Centre, Fats and Oils Department, Dokki, Cairo, Egypt.

RESUMEN

Preparación de ésteres de ácidos grasos con sacarosa como emulsionantes alimentarios y evaluación de sus propiedades superficiales y emulsionantes.

Se ha llevado a cabo un método simple para la preparación de ésteres de sacarosa a partir de ácidos grasos y sacarosa de bajo coste. Se han usado ácidos laurico, palmítico y oleico en su preparación, en ausencia de solventes orgánicos. Se obtuvieron rendimientos aceptables del 86.5%, 87.3% y 88.6% para los ésteres del laurico, palmítico y oleico respectivamente.

En los productos se evaluaron sus balances hidrófilo-lipófilo (HLB), sus propiedades de tensión superficial e interfacial así como su estabilidad en emulsiones. Los resultados mostraron que estos ésteres de sacarosa exhiben propiedades similares a las de los compuestos preparados comercialmente.

PALABRAS-CLAVE: Emulsionante alimentario - Ésteres de ácidos grasos con sacarosa - Propiedades emulsionantes - Propiedades superficiales.

SUMMARY

Preparation of sucrose fatty acid esters as food emulsifiers and evaluation of their surface active and emulsification properties.

A simple method for the preparation of sucrose esters, from fatty acids and the least expensive sucrose, has been conducted. Fatty acids namely lauric, palmitic and oleic were used in their preparation in the absence of any organic solvent. Reasonable yields amounting to 86.5%, 87.3% and 88.6% for sucrose esters of laurate, palmitate and oleate were obtained, respectively.

The products were evaluated for their hydrophile-lipophile balance (HLB), surface and interfacial tension properties as well as emulsion stability. The results showed that these sucrose esters exhibit similar properties as those of the commercially prepared compounds.

KEY-WORDS: Emulsification properties - Food emulsifier - Sucrose fatty acid esters - Surface active properties.

1. INTRODUCTION

Emulsifiers are imported in tonnages for their use in foods, household detergents, cosmetic and pharmaceutical products. Different methods of emulsifier preparation were conducted in the presence or absence of solvents. Toxic solvents were usually used for the

preparation of these compounds (Weiss *et al.*, 1971, 1972; Bobalek, 1977; Akoh and Swanson, 1987, 1989), however others excluded solvents in such preparation (Heesen *et al.*, 1976; Rizzi and Taylor, 1978).

It was planned to use a simple method for preparation of emulsifiers from sucrose and different fatty acids (lauric, palmitic and oleic) aiming to develop and improve the method of the preparation of sucrose esters. Therefore, it was objective to modify the method of Heesen *et al.*, (1976) for the preparation of sucrose emulsifiers (solvent-free reaction) by replacing the expensive polyalcohols for the cheaper sucrose which constitutes the hydrophilic portion of the nonionic surfactant. The products were evaluated for the hydrophile-lipophile balance (HLB), surface and interfacial tension properties as well as emulsion stability.

2. MATERIALS AND METHODS

2.1. Materials

Pure sucrose was supplied by Sugar and Integrated Industries Company (Egypt). All fatty acids, solvents and chemicals are high purity grade (BDH, England, and MERCK, Germany).

2.2. Methods

Preparation of sucrose esters (SE)

Sucrose esters having different fatty acid moieties were prepared according to the method of Heesen *et al.*, (1976) replacing polyalcohols with sucrose as a modification of this method. Equimolecular amounts of pure sucrose and fatty acids (lauric, palmitic and oleic) were reacted together in presence of the in situ prepared sodium soap (catalyst) amounting to 20% of the total weight of sucrose. The mixture was heated at 100 °C under nitrogen while the constituents had melted. The temperature was increased to 130 °C under reduced pressure (40 mm Hg) for 16 hours with continuous stirring. The reaction products were dissolved in an equal quantity of warm

butanone and the soap was acidified with 3-5 parts by weight of lactic acid per 100 parts of reaction product. The non-esterified sucrose and excess of lactic acid were then eliminated by two successive extractions with distilled water at 70 °C. The solvent was then removed under reduced pressure to obtain the final sucrose esters.

Analysis of the sucrose esters

1) Purity

The purity of sucrose esters was calculated from the saponification and ester values of the product as follows:

$$\text{Purity \%} = \frac{\text{Ester value}}{\text{Saponification value}} \times 100$$

Ester value is obtained by subtracting acid value of the product from its saponification value.

2) Hydrophile-lipophile balance (HLB)

Hydrophile-lipophile balance of sucrose esters were calculated using the following equation of Griffin (1965):

$$\text{HLB} = 20 \left(1 - \frac{\text{Saponification value}}{\text{Acid value}} \right)$$

3) Surface and interfacial tension

Surface and interfacial tension of sucrose esters were measured according to the methods of Alexander and Hayter (1971) using CSC-DuNouy Interfacial Tensiometer Model 70545 (CSC Scientific Company, Fairfax, VA).

4) Emulsion stability

The ability of sucrose ester emulsifiers to stabilize oil-in-water (O/W) and water-in-oil (W/O) food emulsions were measured according to the method of Akoh (1992), using emulsifiers at 0.5% concentrations and emulsion stability was measured after 0, 2, 4, 8, 12, 24 and 48 hours at room temperature (25 °C) for O/W and at refrigeration temperature (4 °C) for W/O emulsions. Appropriate controls with no emulsifier were used.

All results are the mean of two concordant values; otherwise two other replications were tried to achieve higher accuracy.

3. RESULTS AND DISCUSSION

Purity, surface tension, interfacial tension and hydrophile-lipophile balance (HLB) are recorded in Table I. The purity of the product generally complies with the purity of most of commercial emulsifiers (Heesen *et al.*, 1976; Rizzi and Taylor, 1978). The results also indicated that surface tension of sucrose laurate and palmitate were almost the same value (52.8 and 53.2 dynes/cm², respectively), however, sucrose oleate exhibited lower surface tension (40.2 dynes/cm²). Conversely, interfacial tension of sucrose oleate gave an anomalous value of 21.4 dynes/cm². This result could be attributed to the presence of unsaturated fatty acid moieties (oleic) and the hydrophilic carbohydrate backbone in the carbohydrate polyesters (Akoh, 1992; Akoh and Nwosu, 1992; Cornec *et al.*, 1996). With reference to the HLB values, sucrose laurate and palmitate showed HLB value of 8.2 and 6.8, respectively, however the sucrose oleate showed HLB value of 3.6. The differences in HLB values can be attributed to the difference in fatty acid chain lengths (Ebeler and Walker, 1984). On the other side, HLB value of sucrose oleate is a good indication for its potential use as W/O emulsion, while, on the other hand HLB values of sucrose laurate and palmitate revealed their capacity to stabilize O/W emulsions (Akoh and Nwosu, 1992).

Table I
Purity and surface active properties of the prepared sucrose fatty acid esters

Emulsifier	Purity %	Surface tension (dynes/cm ²)	Interfacial tension (dynes/cm ²)	HLB ^{**}
Sucrose laurate	88.5	52.8	8.2	8.2
Sucrose palmitate	87.3	53.2	6.8	6.8
Sucrose oleate	88.6	40.2	21.4	3.6

* Purity % = (Ester value/Saponification value) x 100

** HLB = 20 [1 - (Saponification value/Acid value)]

Operationally a stable emulsion is one that is very slow to undergo the various processes which result in the separation of oil and water phases. In addition O/W and W/O emulsion stability is illustrated in Figures (1 and 2) showing that sucrose laurate and palmitate have high O/W emulsion stability (30% and 40% emulsion separation, respectively) after 12 hours. While, sucrose oleate on the other hand exhibits low O/W emulsion stability (90% emulsion separation) after the same period. Conversely, W/O emulsion, stabilized by sucrose oleate has more stability (less emulsion separation) after 12 hours, however, sucrose laurate and palmitate give less stability (more emulsion separation). It is known that

HLB value of an emulsifier determines the emulsion type (W/O or O/W) that tend to be formed, whereas low HLB values (ranging from 3 to 6) will promote or stabilize W/O emulsion, while intermediate values (ranging from 8 to 13) can stabilize O/W emulsion (Griffin, 1965; Akoh and Nwosu, 1992; Partal *et al.*, 1997).

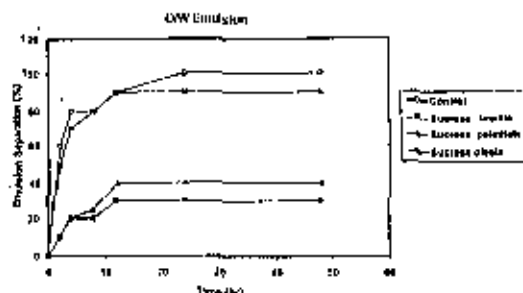


Figure 1

Stability O/W emulsions as a function of time at room temperature (25 °C). A 0.5% emulsifier concentration was used. Control no emulsifier

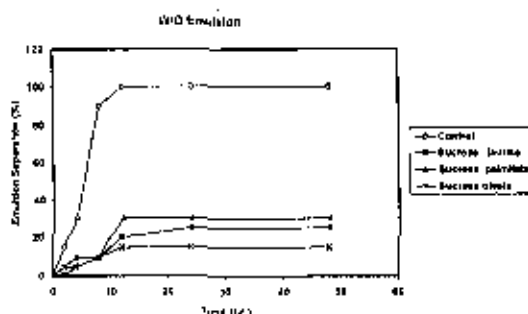


Figure 2

Stability O/W emulsions as a function of time at refrigeration temperature (4 °C). A 0.5% emulsifier concentration was used. Control no emulsifier

Generally, sucrose esters of fatty acids are more safe than those of polyalcohol derivatives since the sucrose esters give no toxic anhydro compounds (Heesen *et al.*, 1976). In addition, the physiological properties of the sucrose esters are unique, since they are nontoxic, odorless and tasteless. When sucrose esters are ingested, they are hydrolyzed to form normal food products (Osipow *et al.*, 1957; Calahorra *et al.*, 1992).

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Fat Replacers

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This Scientific Status

Summary addresses

key characteristics

and functions of fat

replacers.

Awareness of adverse affects of excessive dietary fat intake is virtually universal.

Consequently, health conscious individuals are modifying their dietary habits and eating less fat (Miller and Groziak, 1996). Consumer acceptance of any food product depends upon taste—the most important sensory attribute. Although consumers want foods with minimal to no fat or calories, they also want the foods to taste good. Because several foods formulated with fat replacers do not compare favorably with the flavor of full-fat counterparts, it is difficult for some people to maintain a reduced fat dietary regimen. Food manufacturers continue to search for the elusive "ideal fat replacer" that tastes and functions like conventional fat without the potential adverse health impact. This Scientific Status Summary briefly reviews key characteristics and functions of fat replacers that are commercially available and a few that are under development.

Rationale for Fat Replacers

As a food component, fat contributes key sensory and physiological benefits. Fat contributes to flavor, or the combined perception of mouthfeel, taste, and aroma/odor (Ney, 1988). Fat also contributes to creaminess, appearance, palatability, texture, and lubricity of foods and increases the feeling of satiety during meals. Fat can also carry lipophilic flavor compounds, act as a precursor for flavor development (e.g., by lipolysis or frying), and stabilize flavor (Leland, 1997). From a physiological standpoint, fat is a source of fat-soluble vitamins, essential fatty acids, precursors for prostaglandins, and is a carrier for lipophilic drugs. Fat is the most concentrated source of energy in the diet, providing 9 kcal/g compared to 4 kcal/g for proteins and carbohydrates.

High fat intake is associated with increased risk for obesity and some types of cancer, and saturated fat intake is associated with high blood cholesterol

and coronary heart disease (AHA, 1996; USDHHS, 1988). The 1995 Dietary Guidelines (USDA and USDHHS, 1995) recommend limiting total fat intake to no more than 30% of daily energy intake, with saturated fats no more than 10% and monounsaturated and polyunsaturated fats accounting for at least two thirds of daily energy intake. Consumer surveys indicate that 56% of adult Americans try to reduce fat intake and many show interest in trying foods containing fat replacers (Bruhn et al., 1992). A survey conducted by the Calorie Control Council (CCC, Atlanta, Ga.) found that 88% of adults reported consuming low-fat, reduced-fat or fat-free foods and beverages (CCC, 1996). Although fat intake is declining, probably due to the increased availability of low- and reduced-fat products and lean meats, fat consumption is greater than the recommended levels, and the prevalence of the population classified as overweight is increasing (Frazao, 1996). Foods formulated with fat replacers are an enjoyable alternative to familiar high-fat foods. By choosing these alternative foods, health conscious consumers are able to maintain basic food selection patterns and more easily adhere to a low-fat diet (CCC, 1996).

Fat may be replaced in food products by traditional techniques such as substituting water or air for fat, using lean meats in frozen entrées, skim milk instead of whole milk in frozen desserts, and baking instead of frying for manufacturing or preparing snack foods (CCC, 1992). Fat may also be replaced in foods by reformulating the foods with lipid-, protein-, or carbohydrate-based ingredients, individually or in combination. Fat replacers represent a variety of chemical types with diverse functional and sensory properties and physiological effects. Table 1 lists the general functions of fat replacers in selected applications and food product categories.

Continued on next page

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ditional reading: Akoh, 1995a,b; Artz and Hansen, 1994; CCC, 1996; Gershoff, 1995; Giese, 1996; Gillat and Lee, 1991; Harrigan and Breene, 1989; Hassel, 1993; Haumann, 1986; LaBarge, 1988; Roller and Jones, 1996; Stern and Hermann-Zaidins, 1992; Swanson, 1996; Vanderveen and Glinsmann, 1992.

CASIMIR C. AKOH,
PH.D.

Author Akoh, a Professional Member of IFT, is Associate Professor, Department of Food Science and Technology, The University of Georgia, Athens, Ga.

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Fat Replacers

CONTINUED

Types of Fat Replacers

The terms and definitions used to describe fat replacers vary among authors and are often confusing and misunderstood. Fat replacers chemically resemble fats, proteins, or carbohydrates and are generally categorized into two groups—fat substitutes and fat mimetics.

Fat substitutes are macromolecules that physically and chemically resemble triglycerides (conventional fats and oils) and which can theoretically replace the fat in foods on a one-to-one, gram-for-gram basis. Often referred to as lipid- or fat-based fat replacers, fat substitutes are either chemically synthesized or derived from conventional fats and oils by enzymatic modification. Many fat substitutes are stable at cooking and frying temperatures.

Fat mimetics are substances that imitate organoleptic or physical properties of triglycerides but which cannot replace fat on a one-to-one, gram-for-gram basis. Fat mimetics, often called protein- or carbohydrate-based fat replacers, are common food constituents, e.g., starch and cellulose, but may be chemically or physically modified to mimic the function of fat. The caloric value of fat mimetics ranges from 0–4 kcal/g. Fat mimetics generally adsorb a substantial amount of water. Fat mimetics are not suitable for frying because they bind excessive water and denature or caramelize at high temperatures. Many fat mimetics, however, are suitable for baking and retorting. Fat mimetics are generally less flavorful than the fats that the mimetics are intended to replace; they carry water-soluble flavors but not lipid-soluble flavor compounds. Successful incorporation of lipophilic flavors into foods that are formulated with fat mimetics may, therefore, require emulsifiers.

• **Fat Substitutes.** The composition, developers, and key sources of several synthetic fatty acid-based and lipid-like fat substitutes are listed in Table 2.

Sucrose fatty acid polyesters are mixtures of sucrose esters formed by chemical transesterification or interesterification of sucrose with six to eight fatty acids. Transesterification is the exchange of an acyl group or radicals between an ester and an acid, alcohol, or an amine. Interesterification is the exchange of an acyl group or

Table 1 Selected Applications and Functions of Fat Replacers

Specific Application	Fat Replacer	General Functions*
Baked goods	Lipid based	Emulsify, provide cohesiveness, tenderize, carry flavor, replace shortening, prevent staling, prevent starch retrogradation, condition dough
	Carbohydrate based	Retain moisture, retard staling
	Protein based	Texturize
Frying	Lipid based	Texturize, provide flavor and crispiness, conduct heat
Salad dressing	Lipid based	Emulsify, provide mouthfeel, hold flavorants
	Carbohydrate based	Increase viscosity, provide mouthfeel, texturize
	Protein based	Texturize, provide mouthfeel
Frozen desserts	Lipid based	Emulsify, texturize
	Carbohydrate based	Increase viscosity, texturize, thicken
	Protein based	Texturize, stabilize
Margarine, shortening, spreads, butter	Lipid based	Provide spreadability, emulsify, provide flavor and plasticity
	Carbohydrate based	Provide mouthfeel
	Protein based	Texturize
Confectionery	Lipid based	Emulsify, texturize
	Carbohydrate based	Provide mouthfeel, texturize
	Protein based	Provide mouthfeel, texturize
Processed meat products	Lipid based	Emulsify, texturize, provide mouthfeel
	Carbohydrate based	Increase water holding capacity, texturize, provide mouthfeel
	Protein based	Texturize, provide mouthfeel, water holding
Dairy products	Lipid based	Provide flavor, body, mouthfeel, and texture; stabilize, increase overrun
	Carbohydrate based	Increase viscosity, thicken, aid gelling, stabilize
	Protein based	Stabilize, emulsify
Soups, sauces, gravies	Lipid based	Provide mouthfeel and lubricity
	Carbohydrate based	Thicken, provide mouthfeel, texturize
	Protein based	Texturize
Snack products	Lipid based	Emulsify, provide flavor
	Carbohydrate based	Texturize, aid formulation
	Protein based	Texturize

*Functions are in addition to fat replacement.

radicals between two esters. The sucrose polyester commonly known as olestra (Olean®, The Procter & Gamble Co., Cincinnati, Ohio) is manufactured from saturated and unsaturated fatty acids of chain length C12 and higher, obtained from conventional edible fats and vegetable oils (Akoh, 1994; Akoh

and Swanson, 1990; Rizzi and Taylor, 1978; Shieh et al., 1996).

The first step of the process involves hydrolyzing and methylating fatty acids to form fatty acid methyl esters. The esters are added to sucrose for transesterification or to sucrose octaacetate for ester interchange using catalysts, such as alkali metals or

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their soaps, under anhydrous conditions and high vacuum. As for vegetable oils, the resulting crude olestra product is purified by washing, bleaching, and deodorizing to remove free fatty acids and odors, followed by distillation to remove unreacted fatty acid methyl esters and sucrose esters with low degrees of fatty acid substitution. Olestra is defined by specifications that include the fatty acid composition and degree of esterification (FDA, 1996). The types of fatty acids used in the manufacture of olestra ultimately govern the functionality, physical properties, and potential applications (Akoh and Swanson, 1994).

Olestra is approved (FDA, 1996) for replacing up to 100% of the conventional fat in savory snacks (i.e., snacks that are salty or piquant but not sweet, such as potato chips, cheese puffs, and crackers) and for frying of savory snacks. Olestra (Fig. 1) is not absorbed or metabolized (Grossman et al., 1994; Mattson and Nolen, 1972) and is non-caloric because the large size and number of the nonpolar fatty acid constituents prevent olestra from being hydrolyzed by digestive lipases.

Because olestra passes through the gastrointestinal tract without being digested or absorbed and is lipophilic, olestra has the potential to cause gastrointestinal effects, such as abdominal cramping and stool softening or loosening, and to reduce absorption of fat-soluble vitamins and nutrients, which partition into olestra when ingested at the same time. As a result, the Food and Drug Administration (FDA) requires that foods containing olestra be labeled with the statement: "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added." The label statement is intended to inform consumers about potential gastrointestinal effects and the addition of vitamins to compensate for the effects of olestra on absorption of vitamins A, D, E, and K. The concentration of vitamins A, D, E, and K required for supplementation in olestra-containing foods are 0.34 X RDA for vitamin A/10g

Table 2 Types of Lipid-based Fat Replacers

Generic, Brand Names	Composition	Developers, Sources
Sucrose polyesters, Olestra/Olean [®]	Sucrose polyester of 6-8 fatty acids	The Procter & Gamble Co. (Cincinnati, Ohio), C. Akoh (Univ. Georgia, Athens), B. Swanson (Washington State Univ., Pullman), Unilever (London, England)
Sucrose fatty acid esters	Sucrose with 1-3 fatty acids	Mitsubishi Chemical America, Inc. (N.Y.), Dai-ichi Kogyo Seiyaku Co., (Kyoto, Japan)
Trehalose, raffinose, stachyose polyesters	Carbohydrates, fatty acids	C. Akoh, B. Swanson, Curtice Burns, Inc. (Rochester, N.Y.)
Sorbestrin	Sorbitol, sorbitol anhydrides, fatty acids	Cultor Food Science, Inc. (N.Y.)
Alkyl glycoside polyesters	Alkyl glycosides, fatty acids	C. Akoh, B. Swanson, Curtice Burns, Inc.
Emulsifiers	Mono- and diacylglycerols, sodium stearyl-2-lactylate, lecithin, sorbitan monostearate, propylene glycol mono- and diesters, diacetyl tartaric acid esters	Multiple developers and sources
Medium chain triglycerides	C6-C10 fatty acids	ABITEC (Columbus, Ohio), Stepan Co. (Maywood, N.J.)
Caprenin	C8:0, C10:0, C22:0 fatty acids	The Procter & Gamble Co.
Salatrim /Benefat TM	C2:0-C4:0, C18:0 fatty acids	Nabisco Foods Group (Parsippany, N.J.)/Cultor Food Science, Inc.
Dialkyl dithexadecylmalonate	Fatty alcohol ester of malonic and alkyl malonic acids	Frito-Lay, Inc. (Dallas, Texas)
Esterified propoxylated	Polyether polyol, fatty acids	ARCO Chemical Co. (Wilmington, Del.)/CPC International/Best Foods (Englewood Cliffs, N.J.)
Trialkoxytricarballoylate, trialkoxycitrate, trialkoxyglycerylether	Polycarboxylic acid esterified with fatty alcohols	CPC International

olestra, 0.3 X RDA for vitamin D/10g olestra, 0.94 X RDA for vitamin P/10g olestra, and 1.0 X RDA for vitamin K/10g olestra. Although olestra decreases the absorption of some lipophilic carotenoids, supplementation with vitamin A compensates for olestra's effect on the provitamin A function of carotenoids. Olestra does not significantly affect the absorption of other macronutrients such as carbohydrates, proteins, or water-soluble vitamins and minerals.

A series of 13 studies that were part of the research program to assess the potential for olestra to cause physiological and nutritional effects was published in August 1997 in a Supplement to the *Journal of Nutrition*. Cheskin et al. (1998) reported that ad libitum

consumption during one sitting of potato chips made with olestra was not associated with increased incidence or severity of gastrointestinal symptoms.

In approving olestra, the FDA

concluded that olestra is not toxic, carcinogenic, genotoxic, or teratogenic, all safety issues were addressed, and there is reasonable certainty that no harm will result from the use of olestra in savory snacks (FDA, 1996). The approval of olestra, however, was controversial. The Center for Science in the Public Interest (CSPI, Washington, D.C.), an advocacy and education organization, publicized opposition on the basis of several allegations, including gastrointestinal disturbances, and petitioned the FDA to repeal approval. Despite the controversy and concerns, however, olestra does demonstrate potential to benefit some segments of the population. For example, replacement of conventional fat with olestra can benefit people at high risk of coronary heart disease, obese individuals, and colon cancer patients by helping them to lower total fat intake, lose weight, and possibly lower blood cholesterol levels (Adams et al., 1981; Crouse and Grundy, 1979; Fallat et al., 1976; Clueck et al., 1979, 1983, 1994; Grossman et al., 1994; Grundy et al., 1986; Jandacek et al., 1990; Marsson and Jandacek, 1985). Olestra consumption

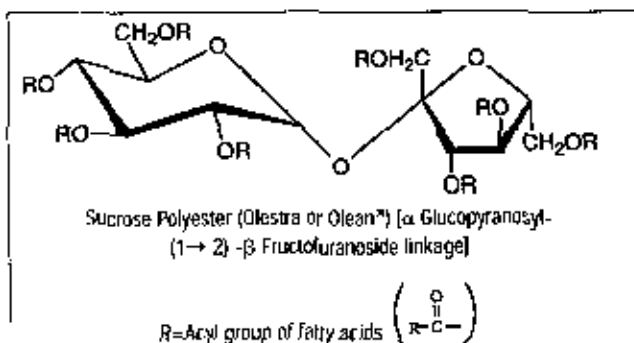


Fig. 1 - Structure of olestra, a lipid-based fat substitute

Fat Replacers

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tion does not appreciably affect the serum concentration of high-density lipoprotein (HDL) cholesterol (FDA, 1996; Grossman et al., 1994; Mellies et al., 1983).

Sucrose fatty acid esters (SFE), a second category of fat substitutes, are mono-, di-, and tri-esters of sucrose with fatty acids, made in a manner similar to sucrose polyester (Osipow et al., 1956). Unlike olestra, with a high degree of fatty acid substitution/esterification, SFEs are easily absorbed and hydrolyzed by digestive lipases and are, thus, caloric. The balance in SFEs of five to seven free hydroxyl groups with one to three fatty acid esters results in hydrophilic and lipophilic properties and, hence, excellent emulsification and surfactant functionality. SFEs are approved (21 CFR 179.859) in the United States for use as emulsifiers and stabilizers in a variety of food categories and as components of coatings to retard ripening and spoilage in several types of fresh fruits. In addition, SFEs are effective lubricants, anticaking agents, thinning agents, and antimicrobials (Harrigan and Breene, 1993; Kabara, 1978; Marshall and Bullerman, 1994).

Other carbohydrate fatty acid esters and polyol fatty acid esters, hold potential for fat replacing systems. Polyol fatty acid esters are prepared by reacting one or more fatty acid esters with a polyol containing at least four hydroxy groups in the presence of a basic catalyst (Unilever NV, 1988). Examples include sorbitol, trehalose, raffinose, and stachyose polyesters (Akoh, 1994). Sorbestrin (Cultor Food Science, Inc., N.Y.), or sorbitol polyester for example, is a mixture of tri-, tetra-, and pentaesters of sorbitol and sorbitol anhydrides with fatty acids. The caloric value of Sorbestrin is 1.5 kcal/g. Sorbestrin is sufficiently heat stable to withstand frying temperatures. Sorbestrin, which is not yet commercially available, is intended for replacement of fat in salad dressings, baked goods, and frying.

Alkyl glycoside polyesters, such as methyl- or octyl glucoside fatty acid polyesters, may be used to replace conventional fat in food formulations (Akoh, 1994). These polyol fatty acid esters are still under development.

Emulsifiers, such as sucrose fatty acid

esters, mono- and diglycerides, sodium stearoyl-2-lactylate, lecithin, and polyglycerol esters, contain both hydrophilic and lipophilic properties that enable the emulsifier to stabilize the interface between fat and water droplets through hydrogen bonding. By acting as surface active molecules, emulsifiers can replace up to 50% of the fat in a formulation (CCC, 1996). They also provide and stabilize aeration, provide lubricity, complex with starch, interact with protein, modify the crystallization characteristics of other fats, promote and stabilize foam, control syneresis, carry flavors, and control rheology. Emulsifiers are most effective in replacing the functionality of fat when used in combination with other ingredients (CCC, 1996). Emulsifiers are useful in margarines, baked goods, frozen desserts, dairy products, spreads and shortenings, processed meats, whipped toppings, cake frostings and fillings, and confections.

Structured lipids (SL, Fig. 2) are triglycerides containing short chain fatty acids (SCFA) and/or medium chain fatty acids (MCFA), and long chain fatty acids (LCFA). SL are prepared by chemical and enzymatic synthesis or random transesterification (Akoh, 1995a; Heird et al., 1986; Kennedy, 1991). SL are developed for specific purposes, such as reducing the amount of fat available for metabolism and, potentially, caloric value (Akoh, 1995a).

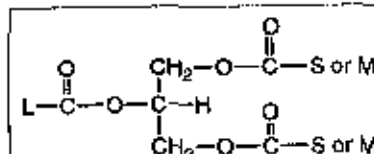
Medium chain triglycerides (MCTs) contain predominantly saturated fatty acids of chain length C8:0 (caprylic) to C10:0 (capric) with traces of C6:0 and C12:0 fatty acids. MCTs are manufactured from vegetable oils, such as coconut and palm kernel oils, by hydrolysis followed by fractionation of the resulting fatty acids to concentrate C8 and C10 fatty acids, and reesterification with glycerol to form triglycerides (Babayan, 1987; Bach et al., 1996; Megremis, 1991). The chemical structure of MCTs results in functional properties that are different from conventional fats and oils. MCTs, which contain saturated fatty acids, are stable at high temperatures and do not readily undergo oxidation (Babayan and Rosenau, 1991). MCTs are also stable at temperatures as low as 0°C and remain clear and nonviscous. MCTs are more soluble in water than long chain triglycerides (LCT). MCTs, which provide 8.3 kcal/g, are commercially available on the basis of GRAS self determination. They are used to replace liquid vegetable oils in low- and reduced-calorie foods; to carry flavors, colors, and vitamins; and

to provide gloss and prevent sticking on confectionery products.

MCTs have been used clinically since the 1950s in enteral and parenteral diets for individuals with lipid absorption, digestion, or transport disorders. MCTs are metabolized differently from LCTs (LaBerge, 1988). MCTs are absorbed intact into the intestine as free fatty acids, without the need for enzymes or bile salts as is required for LCT metabolism. MCTs bind to serum albumin and are transported to the liver via the portal system rather than the lymphatic system. In the liver, MCTs are oxidized to ketone bodies. Although MCTs are not a source of essential fatty acids, they are a source of readily absorbed, rapidly utilizable energy (Megremis, 1991). MCTs are less likely than LCTs to be stored in adipose tissue. For these reasons, fitness enthusiasts, body builders, and runners, in particular, may use MCTs as an energy source.

Caprocarylobehenic triacylglyceride, commonly known as caprenin (The Procter & Gamble Co.), is manufactured from glycerol by esterification with caprylic (C8:0), capric (C10:0), and behenic (C22:0) fatty acids. Because behenic acid is only partially absorbed and capric and caprylic acids are more readily metabolized than other longer chain fatty acids, caprenin provides only 5 kcal/g. Caprenin's functional properties are similar to those of cocoa butter. As a result, caprenin is suitable for use in soft candy and confectionery coatings. The Procter & Gamble Co. filed a GRAS affirmation petition for use of caprenin as a confectionery fat in soft candy and confectionery coatings (CCC, 1996). Caprenin, in combination with polydextrose, was commercially available briefly in reduced-calorie and reduced-fat chocolate bars.

Salatrim (short and long acyl triglyceride molecule) is the generic name for a family of structured triglycerides comprised of a mixture containing at least one short chain fatty acid (primarily C2:0, C3:0, or C4:0 fatty acids) and at least one long chain fatty acid (predominantly C18:0, stearic acid) randomly attached to



General Structure of Structured Lipids

S, M, or L is for short-chain, medium-chain, or long-chain fatty acid, respectively. The position of S, M, or L is interchangeable.

Fig. 2 - General structure of structured triglycerides

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the glycerol backbone. Because short chain fatty acids have a lower caloric value than long chain fatty acids and because stearic acid is incompletely absorbed, the caloric value of Salatrim is only 55% or 5/9 the value of conventional fats (Smith et al., 1994). Developed by Nabisco Foods Group (Parsippany, N.J.), Salatrim is licensed to Caltor Food Science, which established the brand name Benefat™ for manufacture and marketing. FDA accepted for filing in 1994 a GRAS affirmation petition submitted by Nabisco Foods Group.

Salatrim compositions with differing amounts of SCFA and LCFA provide select functional and physical properties, e.g., a range of melting points, hardness, and appearance. Salatrim was designed for a variety of applications, including chocolate-flavored coatings, deposited chips, caramels and toffees, fillings and inclusions for confectionery and baked goods, peanut spreads, savory dressings, dips and sauces, and dairy products such as sour cream, frozen dairy desserts, and cheese (Kosmark, 1996). Salatrim, however, is not suitable for frying. The first Salatrim product, Benefat 1, was developed primarily to replace cocoa butter in confectionery applications.

Dialkyl dihexadecylmalonate (DDM) is a fatty alcohol dicarboxylic acid ester of malonic acid and alkylmalonic acid, synthesized by reacting a malonyl dihalide with a fatty alcohol. Alkyl halide, in a basic solvent, may be used to increase the molecular weight of DDM (Artz and Hansen, 1994). Frito-Lay, Inc. (Dallas, Texas) patented DDM for use in replacing oil in food formulations or in frying (Fulcher, 1986). DDM is noncaloric because it is not digested or absorbed. It is not yet commercially available.

Esterified propoxylated glycerols (EPGs) comprise a family of derivatives of propylene oxide, synthesized by reacting glycerol with propylene oxide to form a polyether polyol that is subsequently esterified with fatty acids. EPGs differ from conventional triglycerides in the positioning of an oxypropylene group between the glycerol backbone and the fatty acids. Patented by ARCO Chemical (Wilmington, Del.) in the United States (White and Pollard, 1989) and in Europe (Cooper, 1990), EPGs are being developed by ARCO Chemical Co. and CPC International/Best Foods (Englewood Cliffs, N.J.) as a replacement for fats and oils in a variety of products including frozen desserts, salad dressings, baked goods, and spreads and for cook-

ing and frying. EPGs can be tailored to produce specific functional properties (Harrigan and Breene, 1993) and are expected to be low in caloric value due to their lipase resistance. EPGs are not yet commercially available.

Trialkoxytricarballoylate (TATCA), trialkoxycitrate (TAC), and trialkoxyglyceryl ether (TGE) are polycarboxylic acids with two to four carboxylic acid groups esterified with saturated or unsaturated alcohols having straight or branched chains of 8–30 carbon atoms (Hamm, 1985). Because the ester units of the substances are reversed from the corresponding ester present in triglycerides, these compounds are not susceptible to complete hydrolysis by lipases (Hauermann, 1986). The synthesis and functional properties of the polycarboxylic acid esters and ethers are described by Hamm (1984). A U.S. patent (Hamm, 1985) for the polycarboxylic acid esters and ethers was assigned to CPC International. TATCA, TAC, and TGE are not yet commercially available.

Protein-based Fat Mimetics. Several fat replacers are derived from a variety of protein sources, including egg, milk, whey, soy, gelatin, and wheat gluten. Some of these protein based fat mimetics are microparticulated (sheared under heat) to form microscopic coagulated round deformable particles that mimic the mouthfeel and texture of fat. Some fat mimetics are processed to modify other aspects of ingredient functionality, such as water binding and emulsification properties. Although the substances are generally not sufficiently heat stable to withstand frying, they are suitable for use as ingredients in foods that may undergo cooking, reorting, and ultra high temperature processing. Protein based fat mimetics are generally used in dairy products, salad dressings, frozen desserts, and margarines.

One of these mimetics, *Simplese*®, is manufactured from whey protein concentrate by a patented microparticulation process. Developed by the NutraSweet Kelco Co. (a unit of Monsanto Co., San Diego, Calif.), Simplese was affirmed as GRAS (21 CFR 184.1498) in 1990 for use in frozen dessert products and in 1994 for use in yogurt, cheese spreads, frozen desserts, cream cheese, and sour cream. Simplese is suitable for use in additional products that do not require frying, such as baked goods, dips, frostings, salad dressing, mayonnaise, margarine, sauces, and soups. The caloric value of Simplese, on a dry basis, is 4

kcal/g. Formulation with hydrated gel forms, however, enables caloric reduction; for example, a 25% gel provides 1 kcal/g. Simplese provides fat-like creaminess in high-moisture applications, but like other proteins it tends to mask flavor. Simplese retains the biological value of the protein used and, hence, any antigenic/allergenic properties of the protein (Gershoff, 1995).

• Carbohydrate-based Fat Mimetics.

Carbohydrates have been used in some foods for several years to partially or totally replace fat. Digestible carbohydrates such as modified starches and dextrins provide 4 kcal/g, while nondigestible complex carbohydrates provide few calories. Many carbohydrates serve as thickeners or gelling agents in foods. Gums, starches, pectin, cellulose, and other carbohydrate ingredients provide some of the functions of fat in foods by binding water. They also provide texture, mouth feel, and opacity (Giese, 1996). Corn syrups, syrup solids, and high-fructose corn syrups are used as fat replacers in many fat-free and reduced-fat cookies to control water activity (a_w). Polyols such as sorbitol and maltitol as well as fructooligosaccharides may also be used to control a_w . Fat-free salad dressings contain xanthan gum and carrageenan as stabilizers. Carbohydrate-based fat mimetics are not suitable for frying but can be used as fat barriers for frying and for baking.

Gums are high molecular weight negatively-charged carbohydrates used as thickeners to increase viscosity at concentrations of 0.1–0.5%, and as stabilizers and gelling agents. Gums that are used in fat replacing systems with other gums, fat replacers, or bulking agents include guar, xanthan, locust bean gum, carrageenan, gum arabic, and pectins. Gums are used in salad dressings, icings and glazes, desserts and ice cream, ground beef, baked goods, dairy products, and soups and sauces.

Starches of varying sources, types, and functional properties are used in fat replacing systems to provide sensory properties of oil, e.g., slippery mouthfeel. Starch sources include common corn and high amylose corn, waxy maize, wheat, potato, tapioca, rice, and waxy rice. Although native starch can sometimes be used to replace fat, starch modified (21 CFR 172.892) by acid or enzymatic hydrolysis, oxidation, dextrinization, crosslinking, or mono-substitution is more commonly used to achieve desired functional and sensory properties. Available in pregelatinized or instant forms, starches generally perform well in high moisture

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Fat Replacers

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foods, such as margarine spreads, salad dressings and sauces, baked goods, frostings and fillings, and in meat emulsions like sausages, but generally do not perform well in low moisture foods, such as cookies or crackers.

Several forms of cellulose are used, frequently in combination with other hydrocolloids, such as gums and pectins, to replace fat. Cellulose-based fat replacers that are plant in origin are obtained by mechanical grinding (e.g., powdered cellulose), chemical depolymerization and wet mechanical disintegration (e.g., microcrystalline cellulose/cellulose gel) and chemical derivatization (e.g., sodium carboxymethyl cellulose/cellulose gum, methyl cellulose/modified vegetable gum and hydroxypropyl methylcellulose/carbohydrate gum).

Microcrystalline cellulose, considered GRAS, is noncaloric. Microcrystalline cellulose mimics fat in aqueous systems; contributes body, consistency, and mouthfeel; stabilizes emulsions and foams; controls syneresis; and adds viscosity, gloss, and opacity to foods. Applications include salad dressings, frozen desserts, sauces, and dairy products. Powdered cellulose, also GRAS, can retain three to ten times its weight—a useful property for reduced fat sauces. Powdered cellulose is also effective in reducing the fat in fried batter coatings and fried cake donuts and in increasing the volume of baked goods, because it can stabilize air bubbles and minimize after-baking shrinkage (CCC, 1996). Methyl cellulose (MC)/modified vegetable gum, which is GRAS (21 CFR 182.1480), and hydroxypropyl methyl cellulose (HPMC)/carbohydrate gum, an approved food additive (21 CFR 172.874), are surface active and can hydrate in water, form films in solution, and gel upon heating as a result of methoxy and hydroxypropyl constituents. MC and HPMC impart creaminess, lubricity, air entrapment, and moisture retention in baked goods, frozen desserts, dry mix sauces, and pourable and spoonable sauces and dressings (CCC, 1996).

Maltodextrins are GRAS (21 CFR 184.1444), nonsweet, nutritive (4 kcal/g on a dry basis) mixtures of saccharide

polymers of varying chain lengths. They are produced by partial hydrolysis of starch obtained from corn or potato starch. Maltodextrins obtained from oat, rice, wheat, or tapioca starch are available on the basis of GRAS self determination. The average molecular weight and degree of hydrolysis of maltodextrins varies up to a dextrose equivalence (DE) of 20. Dextrose equivalence is a measure of the reducing sugar content, expressed as glucose. Molecular weight and DE determine maltodextrin functional properties, such as viscosity/bodying ability and browning ability. Maltodextrins are used to build solids and viscosity, bind/control water, and contribute smooth mouthfeel in fat replacing systems for table spreads, margarine, imitation sour cream, salad dressings, baked goods, frostings, fillings, sauces, processed meat and frozen desserts.

Polydextrose is a randomly-bonded polymer of glucose, sorbitol, and citric or phosphoric acid. Polydextrose is available in liquid or powdered and acidic or neutralized forms. Polydextrose is only partially metabolizable, providing 1 kcal/g. Approved (21 CFR 172.841) as a bulking agent, formulation aid, humectant, and texturizer, polydextrose is used in several food categories, including baked goods and baking mixes, chewing gum, confections and frostings, salad dressings, frozen dairy desserts and mixes, gelatins, puddings and fillings, hard and soft candy, peanut spreads, fruit spreads, sweet sauces, toppings, and syrups. Polydextrose can contribute a slight smoothness in high-moisture formulations and a fat sparing effect. Because of the potential for a laxative effect, the labeling of food products containing more than 15 g polydextrose/single serving must state: "Sensitive individuals may experience a laxative effect from excessive consumption of this product."

Oatrim is made by partial enzymatic hydrolysis of the starch-containing portion of the hull or bran obtained from whole oat and/or corn flour. Oatrim contains 5% β -glucan and can be added to foods as a dry powder (4 kcal/g) or as a gel (1 kcal/g) hydrated with three parts water. The mouthfeel of oatrim mimics that of regular triglycerides. Oatrim is thermally stable and can withstand retort and high-temperature short-time processing conditions, but is not suitable for frying (CCC, 1996). Oatrim may be used in dairy products, confectionery, frozen desserts, cereals, baked goods, and meat

products. Oatrim was developed by the U.S. Dept. of Agriculture's (USDA) National Center for Agricultural Utilization Research (Peoria, Ill.) and patented by USDA. Oatrim is licensed to Conagra (Omaha, Neb.), Quaker Oats (Chicago, Ill.), and Rhone-Poulenc (Cranbury, N.J.).

Z-Trim (Z represents zero calorie), developed by the USDA for blending with Oatrim, is an indigestible insoluble fiber made from the high-cellulose portion of the hulls of oats, soybeans, peas, rice, or bran from corn or wheat. The hulls or bran are processed into broken cellular fragments and purified, then dried and milled into a powder. The powder may be rehydrated for use as a gel. Z-trim is expected to contribute fiber and provide moistness, density, and smoothness to a variety of foods, including cheeses, baked goods, and meat patties. In gel form, Z-trim is suitable for frying hamburgers, for example, but is not suitable for deep fat frying. Commercial availability is expected to follow completion of commercial process development, patenting, and licensing.

Conclusion

At present there is no single ideal fat replacer that can recreate all the functional and sensory attributes of fat. As a result, a systems approach using several ingredients individually or in combination is frequently used to achieve the characteristics of fat (CCC, 1996). Further development in fat replacement is needed, particularly with respect to the effect of water on food formulations containing fat replacers. Much emphasis is being placed on heat-stable fat substitutes to maintain the taste and texture of fried foods. A desirable future outcome will include successful development of fat replacers that do not interfere with nutrient or drug utilization and that are safe, inexpensive, noncaloric, and suitable for frying as well as cooking. Genetic engineering will likely play a role in future fat replacement.

The final message to health conscious consumers may be that there is no "magic bullet" to achieving dietary goals. A prudent approach, however, is combining proper nutrition, dietary variety, with a healthy lifestyle, regular exercise, and a reduction of total dietary fat aided by choosing foods formulated with fat replacers.

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INSTITUTE OF FOOD TECHNOLOGISTS

The Society for Food Science and Technology

221 N. LaSalle St., Ste. 300, Chicago, IL 60601-1291 USA

Tel. 312-782-8424 • Fax: 312-782-8348

E-mail: info@ift.org • URL: http://www.ift.org

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CONSULTA DE NUEVAS CREACIONES

Jueves 8 de Julio de 2010

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Ver Actuaciones

Consulta Actos Administrativos

Cerrar Ventana

Datos de PATENTES DE INVENCION

Expediente	0 68859	Fecha de solicitud	de 2000-09-12 16:42:01
Sector	QUIMICA FARMACEUTICA	Clasificación	A61K 9/10 AC; A61K 31/365 AC; A61K 31/19 AC; Ipc
Certificado	28901	Tipo concesión	TOTAL
Vigencia desde	12/09/2000	Hasta	19/09/2020
Iupac	-Nombre Iupac ORLISTAT -Nombre Comun ORLISTAT, TENSOACTIVOS, DISPERSANTE (COMPOSICION) -Indicación INHIBIDORES DE LIPASA, TRATAMIENTO OBESIDAD		
Título	COMPOSICION FARMACEUTICA DE ORLISTAT QUE CONTIENE TENSOACTIVOS Y DISPERSANTES		
Dueño(s)	F. HOFFMANN - LA ROCHE A.G.		
Inventor(es)	PASSCHIER CHRISTIAAN DE SMIDT PAUL HADVARY HANS LENGSELD THOMAS RADES HANS STEFFEN JOSEPH TARDIO		
Prioridad	EP 99118180.1 13/09/1999 AC		
Gaceta	Numero	Fecha	NP
	518	30/07/2002	587
Estado	CONCESION 2007-03-23 18:41:36		
	Etapas del Trámite		

Resumen

- 1.- Una composición farmacéutica que comprende, por lo menos, un inhibidor de lipasa, por lo menos un tensioactivo y por lo menos un dispersante.
- 25.- Un procedimiento para la preparación de una composición farmacéutica de conformidad con cualquiera de las reivindicaciones 1 a 24, que comprende mezclar por lo menos, un inhibidor de lipasas con por lo menos un tensioactivo y por lo menos un dispersante.

REGISTRO INICIAL

Expediente	0 68859 Secu even.0	Fecha de solicitud	de 2000-09-12 16:42:01
Solicitante(s)	F. HOFFMANN - LA ROCHE A.G.		
Apoderado	JOSE ANTONIO LLOREDA		
Inventor(es)	PASSCHIER CHRISTIAAN DE SMIDT PAUL HADVARY		

08/07/2010

Nuevas Creaciones-SIC

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283
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HANS LENGSELD
THOMAS RADES
HANS STEFFEN
JOSEPH TARDIO

Actos
Administrativos
OFICIO 1230 de 12/02/2003
OFICIO 10298 de 02/11/2005
OFICIO 3100 de 15/03/2006
OFICIO 7377 de 12/07/2006
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RESOLUCION 11505 de 18/04/2008
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CONSULTA DE NUEVAS CREACIONES

Jueves 8 de Julio de 2010

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Datos de PCT-PATENTE DE INVENCION CAPITULOS I Y II

Expediente 3 4385 Fecha de 2003-01-23
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Sector QUIMICA Clasificación A61K 31/16 ; A61P 3/6 ;
FARMACEUTICA lpc

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lupac
-Nombre lupac TETRAHIDROLIPSTATINA
-Nombre Comun ORLISTAT, ALMIDON, CELULOSA, DEXTRANO, SEQUESTRANTE DE ACIDOS
BILIARES, COLESTIRAMINA, COLESTIPOL, C
-Indicación COLESTIMIDA, SEVELAMER; INHIBIDOR DE LIPASA, PREVENCIÓN DE LA
OBESIDAD Y DE HIPERLIPIDEMIA

Título NUEVA COMPOSICION FARMACEUTICA

Solicitante(s) F. HOFFMANN - LA ROCHE AG

Inventor(es) PIERRE BARBIER
PAUL HADVARY
HANS LENGSELD

Prioridad EP 00116393.0 28/07/2000 AC

Gaceta
Numero Fecha NP
543 01/06/2004 45

Estado REQUERIMIENTO 45 2009-06-18 11:40:08
Etapas del Trámite

Resumen
1.- Una composición farmacéutica, que comprende un inhibidor de lipasa y un secuestrante farmacéuticamente aceptable de ácidos biliares.
2.- Una composición farmacéutica, según la reivindicación 1, que comprende uno o más excipientes farmacéuticamente aceptables.
3.- Una composición farmacéutica, según las reivindicaciones 1 ó 2, en donde, el inhibidor de lipasa, es orlistat
4.- La composición según una cualquiera de las reivindicaciones 1 a 3, en donde, el secuestrante farmacéuticamente aceptable de ácidos biliares, se selecciona de entre el grupo consistente en colestiramina, colestipol, colesetam, colestimida, sevelamer, derivados de la celulosa y del dextrano, almidón y derivados del almidón, y sales farmacéuticamente aceptables de éstos.

5.- La composición según una cualquiera de las reivindicaciones 1 a 4, en donde, el secuestrante de ácidos biliares, es un derivado de la celulosa o del dextrano.

6.- La composición según una cualquiera de las reivindicaciones 1 a 5, en donde, el derivado de celulosa o de dextrano, se selecciona de entre el grupo consistente en DEAE-celulosa, guanidinoetilcelulosa, y DEAE-sefadex.

7.- La composición según una cualquiera de las reivindicaciones 1 a 4, en donde, el almidón o derivado del almidón, se selecciona de entre el grupo consistente en β - ó γ -ciclodextrina, almidón retrogradado y/o degradado, almidón degradado, almidón hidrofóbico, amilosa, almidón-dietilaminoetiléter y almidón-3-hidroxietiléter.

8.- La composición según la reivindicación 7, en donde, el derivado del almidón, se selecciona de entre β - ó γ -ciclodextrina.

9.- La composición según la reivindicación 1 a 4, en donde, el secuestrante de ácidos biliares, se selecciona de entre el grupo consistente en colestiramina, colestipol, colesevelam, colestimida, sevelamer, celulosa, DEAE-celulosa, guanidinoetilcelulosa, y DEAE-sefadex, almidón, β - ó γ -ciclodextrina.

10.- La composición según la reivindicación 9, en donde, el secuestrante de ácidos biliares, se selecciona de entre el grupo consistente en colestiramina, colestipol, colestimida, colesevelam, sevelamer, DEAE-celulosa, y β - ó γ -ciclodextrina.

REGISTRO INICIAL

Expediente 3 4385 Secu even.0 Fecha de 2003-01-23
solicitud 00:00:00

Solicitante(s) F. HOFFMANN - LA ROCHE AG

Apoderado JOSE ANTONIO LLOREDA

Inventor(es) PIERRE BARBIER
PAUL HADVARY
HANS LENGSELD

Actos OFICIO 8194 de 02/10/2003

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/14, 9/16, 9/20, 9/32, 9/34, 9/36	A1	(11) International Publication Number: WO 00/13667 (43) International Publication Date: 16 March 2000 (16.03.00)
(21) International Application Number: PCT/US99/20744 (22) International Filing Date: 8 September 1999 (08.09.99) (30) Priority Data: 60/099,399 8 September 1998 (08.09.98) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DAGGY, Bruce, P. [US/US]; 7 Rutledge Road, Pine Brook, NJ 07058 (US). MANDEL, Kenneth, G. [US/US]; 9 Doric Avenue, Parsippany, NJ 07054 (US). (74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	(81) Designated States: AE, AL, AU, AZ, BA, BR, BG, CA, CN, CR, CZ, DM, EE, GE, GH, GM, HR, HU, ID, IL, IN, JS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PT, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, 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. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: LIPSTATIN DERIVATIVE-SOLUBLE FIBER TABLETS (57) Abstract The present invention relates to a novel pharmaceutical composition and process for preparing swallowable rapidly disintegrating methylcellulose and lipstatin derivatives together in combination with a suitable diluent and excipients.		

DETAILED DESCRIPTION OF THE INVENTION

The need for a safe clinically effective anti-obesity compound appears to have been found in the lipase inhibitors, of which orlistat is one of several. The mode of action of the lipase inhibitors is by to block fat absorption by inhibiting gastric and pancreatic lipase enzymes which break down fat molecules to smaller absorbable fatty acids and glycerol derivatives. When taken with a well-balanced, slightly hypocaloric diet, these inhibitors will inhibit absorption of approximately 30% of ingested fat.

The weight loss obtained with clinically effective doses of orlistat are approximately the same as those obtained with CNS-acting appetite suppressant drugs, such as fenfluramine, dexfenfluramine and sibutramine (5-10% of bodyweight in 1 year). While these drugs have potential CNS, and other, toxicities these are not an issue with the lipase inhibitors as they are not absorbed from the gastrointestinal tract. However, these inhibitors do have their own side-effect issues which are gastrointestinal tract in nature. These effects can range from mild diarrhea to faecal incontinence, as well as nausea, vomiting, flatulence, abdominal pain, liquid stools, and oily stools.

While patients may find some of these side effects tolerable, others, particularly faecal incontinence and steatorrhea, are not.

The present invention, therefore provides for a swallowable solid dosage form of a combination product which contains a bulking soluble fiber, preferably methylcellulose, which is convenient to take and transport, is preferably sugar free, and a lipstatin derivative, preferably orlistat. This tablet will be easily administered to the consumer who will not need to carry and ingest a powder diluted with water along with the orlistat tablet, but preferably will have the combined tablet in one dosage form. This becomes an ideal formulation to assist in patient compliance, and to help control the undesired side effects of the lipstatin inhibitors.

Therefore, one aspect of the present invention is a pharmaceutical composition comprising:

- (a) at least one water soluble, non-fermentable cellulose derivative;
- (b) at least one lipase inhibitor in an amount effective for treating adiposity; and
- (c) at least one excipient which is selected from an edible calcium salt; or mixtures thereof.

The lipase inhibitor is selected from: (i) a lipstatin in pure form; (ii) a biomass comprising a lipase inhibitor, the biomass being obtained by a process of

What is Claimed Is:

1. A pharmaceutical composition for a tablet comprising:
(a) at least one water soluble, non-fermentable cellulose derivative;
5 (b) at least one lipase inhibitor in an amount effective for treating adiposity; and
(c) at least one excipient which is selected from an edible calcium salt; or mixtures thereof.
- 10 2. The composition according to Claim 1 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose having a viscosity of > 1000 centipoise.
- 15 3. The composition according to Claim 2 wherein the edible calcium salt is dibasic calcium phosphate dihydrate, calcium phosphate anhydrous, or tribasic calcium phosphate; or mixtures thereof.
- 20 4. The composition according to Claim 3 wherein the edible calcium salt is dibasic calcium phosphate dihydrate salt.
- 25 5. The composition according to Claim 2 which further comprises a binding agent which is PVP, hydroxypropylcellulose, hydroxypropyl methylcellulose, acacia, gelatin, tragacanth, pregelatinized starch, or starch.
6. The composition according to Claim 2 which further comprises a disintegrating agent which is sodium starch glycolate, sodium carboxymethylcellulose, Ac-di-sol®,
25 carboxymethylcellulose, veegum, alginates, agar, guar, tragacanth, locust bean, karaya, pectin, or crospovidone.
7. The composition according to Claim 2 which further comprises a wetting
30 agent, and/or a lubricating agent.
8. The composition according to Claim 2 wherein the methylcellulose has a viscosity of >3000 centipoises.

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9. The composition according to Claim 2 wherein the methylcellulose is present in an amount of about 450 to about 550mg.
10. The composition according to any of Claims 1 to 9 wherein the lipase inhibitor is orlistat.
11. The composition according to any one of Claims 1 to 9 compressed into a tablet.
12. *A method for the dual treatment of adiposity and the faecal incontinence and steatorrhea associated therewith which method comprises administering to a mammal in need thereof a compressed tablet comprising:*
(a) at least one water soluble, non-fermentable cellulose derivative;
(b) at least one lipase inhibitor in an amount effective for treating adiposity; and
(c) at least one excipient which is selected from an edible calcium salt; or mixtures thereof.
13. A pharmaceutical composition for a tablet comprising:
(a) at least one water soluble, non-fermentable cellulose derivative;
(b) at least one lipase inhibitor in an amount effective for treating adiposity; and
(c) at least one swellable diluent or filler, selected from microcrystalline cellulose, corn starch, or Starch 1500.
14. The composition according to Claim 13 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose having a viscosity of > 2000 centipoise.
15. The composition according to Claim 14 which further comprises a disintegrating agent.
16. The composition according to Claim 15 which further comprises a wetting agent, and/or a lubricating agent.
17. The composition according to Claim 16 which further comprises a binding agent.

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18. The composition according to Claim 14 wherein the diluent is *microcrystalline cellulose* and is present in a ratio of methylcellulose to microcrystalline cellulose from about 2:1 to about 14:1.
- 5 19. The composition according to Claim 14 wherein the diluent is corn starch and is present in a ratio of methylcellulose to cornstarch of from about 7.5 to about 15:1.
- 10 20. A method for the dual treatment of adiposity and the faecal incontinence and steatorrhea associated therewith which method comprises administering to a mammal in need thereof a compressed tablet comprising:
- (a) at least one water soluble, non-fermentable cellulose derivative;
- (b) at least one lipase inhibitor in an amount effective for treating adiposity; and
- 15 (c) at least one swellable diluent or filler, selected from microcrystalline cellulose, corn starch, or Starch 1500.
21. A process for preparing a tablet formulation which process comprises:
- a) blending together to form an intragranular mixture high viscosity
- 20 methylcellulose of > 3000cps; a diluent selected from microcrystalline cellulose, corn starch, or Starch 1500, or a mixture thereof, a lipase inhibitor, a lubricating agent and optionally a disintegrant; and
- b) adding to the mixture of step (a), a PVP aqueous solution, or alternatively spraying the mixture of step (a) with a PVP aqueous solution; and preparing
- 25 granulates; and
- c) blending together an extragranular mixture of a wetting agent; a lubricating agent; a diluent; and a disintegrant, or a mixture thereof; and
- d) compacting the granulates of step (b) with the extragranular mixture of
- 30 step (c).
22. The process according to Claim 21 wherein the admixture of the lipase inhibitor is added in step c) rather than step a).
23. A process for the manufacture of a pharmaceutical tablet, which process
- 35 comprises mixing

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- a) granulates comprising high viscosity methylcellulose of > 3000cps; at least one edible calcium salt, or mixtures thereof; a lipase inhibitor, and optionally together with an intra-granular disintegrant, and/or wetting agent, and/or colouring agent; with
- b) adding to the mixture of step (a), a PVP aqueous solution, or alternatively
- 5 spraying the mixture of step (a) with a PVP aqueous solution; and preparing granulates; and
- c) blending together an extragranular mixture of a wetting agent; a lubricating agent; a diluent; and a disintegrant, or a mixture thereof; and
- d) compacting the granulates of step (b) with the extragranular mixture of
- 10 step (c).

24. The process according to Claim 21 wherein the admixture of the lipase inhibitor is added in step c) rather than step a).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant: F. HOFFMANN-LA ROCHE AG (CH/CH); Grenzacherstrasse 124, CH-4070 Basle (CH).			
(72) Inventors: BAILLY, Jacques; 8, rue des Pierres, F-68170 Rixheim (FR). PLEURY, Andre; Kirschweg 25, CH-4145 Gempen (CH). HADVARY, Paul; Neumattenweg 8, CH-4105 Biel-Benken (CH). LENGSELD, Hans; Marschalkenstrasse 35, CH-4054 Basle (CH). STEFFEN, Hans; Fischmarkt 36, CH-4410 Liestal (CH).			
(74) Agent: POPPE, Regina; 124 Grenzacherstrasse, CH-4070 Basle (CH).			
(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS AND CHITOSAN			
(57) Abstract Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary excipients.			

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PHARMACEUTICAL COMPOSITIONS CONTAINING LIPASE INHIBITORS AND CHITOSAN

The present invention relates to pharmaceutical compositions containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary
5 excipients.

An example of an inhibitor of gastrointestinal lipases is orlistat, previously known as tetrahydrolipstatin or THL. It reduces the absorption of dietary fat. Its use for the control or prevention of obesity and hyperlipaemia, is described in US patent 4 598 089. Orlistat is the N-formyl-L-leucine ester with (3S,4S)-3-hexyl-4-
10 [(2S)-2-hydroxytridecyl]-2-oxetanone.

Anal leakage of oil (oily spotting) is an adverse effect which is occasionally observed in patients treated with lipase inhibitors. It results from physical separation of some liquid unabsorbed dietary fat from the bulk of the fecal mass in the lower large intestine. This effect can be prevented with the pharmaceutical
15 compositions of the present invention.

In the US patent 5 447 953 it has been demonstrated that by combining a lipase inhibitor with substantial amounts of water insoluble crude fibers, the inhibiting effect on fat absorption can be increased.

Surprisingly, it has now been found that by combining the lipase inhibitor
20 with low amounts of chitosan or a derivative or a salt thereof, the phenomenon of anal leakage of oil can be strongly reduced.

The invention is also concerned with the use of chitosan or a derivative or a salt thereof for the combined simultaneous, separate or chronologically spaced use with an inhibitor of gastrointestinal lipases, such as orlistat, in the treatment of
25 obesity and hyperlipaemia and their comorbidities, such as type II diabetes mellitus.

Artificial non-absorbed fats, mostly sucrose polyester, are used in the food industry for the production of low fat foods, such as low fat potatoe chips, low fat

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294Claims

1. Orally administrable pharmaceutical composition containing an inhibitor of gastrointestinal lipases, one (or more) additional compound(s) of the group consisting of chitosan, its derivatives and salts thereof, and auxiliary excipients.

5 2. A composition as in claim 1 comprising from 500 mg to 20 g, preferably from 2 g to 10 g of the additional compound(s) and from 10 mg to 500 mg of an inhibitor of gastrointestinal lipases.

3. A composition as in claim 1 or 2 wherein the inhibitor of gastrointestinal lipases is orlistat.

10 4. A composition as in claim 1, 2 or 3 wherein the additional compound is chitosan.

5. The use of chitosan, its derivatives or its salts for treating or preventing the syndrome of anal leakage of oil occasionally occurring after the oral administration of an inhibitor of gastrointestinal lipases, such as orlistat, or after ingestion of food
15 containing poorly absorbable or non-absorbable fats or oils or of undigestible oily fat substitutes.

6. A composition as in claim 3 or 4 which is a chewable tablet for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 120 mg of orlistat and from 0.5 to 5 g of chitosan.
20

7. The chewable tablet as in claim 6, wherein the dosage is about 60 mg of orlistat and about 2.5 g of chitosan.

8. A composition as in claim 3 or 4 which is a wafer for the treatment of obesity, consisting essentially of orlistat as the active ingredient and of chitosan as the additional compound, wherein the dosage is from 10 to 200 mg of orlistat and
25 from 1 to 10 g of chitosan.

9. The wafer as in claim 8, wherein the dosage is about 120 mg of orlistat and about 5 g of chitosan.

10. A method of preventing the syndrome of anal leakage of oil occasionally
30 occurring after the oral administration of orlistat, comprising orally administering

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(21) International Application Number: PCT/US99/00028 (22) International Filing Date: 4 January 1999 (04.01.99) (30) Priority Data: 09/004,963 9 January 1998 (09.01.98) US 09/166,453 5 October 1998 (05.10.98) US (71) Applicant: GELTEX PHARMACEUTICALS, INC. (US/US); 9 Fourth Avenue, Waltham, MA 02451 (US). (72) Inventors: MANDEVILLE, W., Harry, III.; 7 Pillings Pond Road, Lynnfield, MA 01940 (US); WHITESIDES, George, M.; 124 Grasmere Street, Newton, MA 02458 (US); HOLMES-PARLEY, Stephen, Randall; 20 Norfolk Road, Arlington, MA 02476 (US). (74) Agents: ELMORE, Carolyn, S. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).	(83) 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, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), DAPI patent (BR), BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: FAT-BINDING POLYMERS		
(57) Abstract The present invention relates to a method for treating obesity, a method for reducing the absorption of dietary fat, and a method for treating hypertriglyceridemia in a patient and to particular polymers for use in the methods or in a manufacture of a medicament. The methods comprise the step of orally administering to a mammal, such as a human, a therapeutically effective amount of one or more fat-binding polymers. The administration of the fat-binding polymer of the invention facilitates the removal of fat from the body prior to digestion, with minimal side effects and low toxicity. In a preferred embodiment, the one or more fat-binding polymers are administered in combination with one or more lipase inhibitors, for example, lipstatin and tetrahydrolipstatin.		

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SUMMARY OF THE INVENTION

The present invention relates to a method for treating obesity, a method for reducing the absorption of dietary fat, and a method for treating hypertriglyceridemia in a patient and to particular polymers for use in the methods or in a manufacture of a medicament. The methods comprise the step of orally administering to a mammal, such as a human, a therapeutically effective amount of a fat-binding polymer. The administration of a fat-binding polymer of the invention facilitates the excretion of fat from the body without digestion, with minimal side effects and low toxicity. In a preferred embodiment, the fat-binding polymers are administered in combination with a therapeutically effective amount of a lipase inhibitor, such as the pancreatic lipase inhibitors described in U.S. Patent No. 4,598,089 to Hadvary *et al.* The combination administration can reduce undesirable side effects often encountered when lipase inhibitors, in particular, the pancreatic lipase inhibitors lipstatin and tetrahydrolipstatin are administered alone. For example, a serious side effect resulting from the administration of a lipase inhibitor is steatorrhea, or fatty stools.

The fat-binding polymers of the invention comprise at least one fat-binding region. A fat-binding region can include a region having a positive charge, a region which is hydrophobic or a region having a positive charge and which is hydrophobic.

In one embodiment, the fat-binding polymer is an aliphatic polymer selected from the group consisting of polyalkylacrylates, polyacrylamides, polyalkylmethacrylates, polymethacrylamides, poly-N-alkylacrylamides, poly-N-alkylmethacrylamides, substituted derivatives thereof and copolymers thereof. For example, the substituted derivatives of the polymers can be characterized by one or more substituents, such as substituted or unsubstituted, saturated or unsaturated alkyl, and substituted or unsubstituted aryl groups. Suitable substituents to employ on the alkyl or aryl groups include, but are not limited to, cationic or neutral groups, such as alkoxy, aryl, aryloxy, aralkyl, halogen, amine, and ammonium groups. For example, the polymer can be poly(dimethylamino propylacrylamide), poly(trimethylammonium ethylacrylate), poly(trimethylammonium ethyl methacrylate), poly(trimethylammonium propyl acrylamide), poly(dodecyl

lipase inhibitor which is covalently bound to a polymer as described in U.S.S.N. 09/005,379 filed on January 9, 1998, and U.S.S.N. 09/166,510 filed on October 5, 1998, the entire contents of which are incorporated herein by reference.

As used herein, the terms "therapeutically effective amount" and
5 "therapeutic amount" are synonymous. The terms refer to an amount which is sufficient to treat obesity, reduce the absorption of fat, facilitate the removal of fat prior to digestion or treat hypertriglyceridemia. The dosage of fat-binding polymer administered to the patient will vary depending among other things on the weight of the patient and the general health of the patient. The dosage can be determined with
10 regard to established medical practice. The amount of fat-binding polymer administered can be in the range of from about 0.01 mg/kg of body weight/day to about 1g/kg of body weight/day. The amount of lipase inhibitor which can be administered in combination with the fat-binding polymers of the invention can be determined with regard to accepted medical
15 practice.

As disclosed above, in a preferred embodiment, the fat-binding polymer is administered in combination with a lipase inhibitor, as described herein. The term "in combination" in this context includes both simultaneous or sequential
administration (either type of compound first) of the fat-binding polymer and lipase
20 inhibitor. The fat-binding polymer and lipase inhibitor, when used in combination, can be employed together in the same dosage form or in separate dosage forms taken at the same time or within a time period, wherein both the fat-binding polymer and lipase inhibitor are present in a therapeutically effective amount.

The fat-binding polymers of the invention can be formulated using
25 conventional inert pharmaceutical adjuvant materials into dosage forms which are suitable for oral administration. The oral dosage forms include tablets, capsules, suspension, solutions, and the like. The identity of the inert adjuvant materials which are used in formulating the fat-binding polymers of the invention will be immediately apparent to persons skilled in the art. These adjuvant materials, either
30 inorganic or organic in nature, include, for example, gelatin, albumin, lactose, starch, magnesium stearate, preservatives (stabilizers), melting agents, emulsifying agents, salts, and buffers.

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CLAIMS

What is claimed is:

1. A method for treating obesity in a *mammal*, comprising the step of orally administering to the mammal an effective amount of one or more fat-binding
5 polymers in combination with one or more lipase inhibitors.
2. The method of Claim 1 wherein the fat-binding polymer is selected from the group consisting of polyalkylacrylates, polyacrylamides, polyalkylmethacrylates, polymethacrylamides, poly-N-alkylacrylamides, poly-N-alkylmethacrylamides, substituted derivatives thereof and
10 copolymers thereof.
3. The method of Claim 2 wherein the fat-binding polymer is poly(dimethylamino propylacrylamide), poly(trimethylammonium ethylacrylate), poly(trimethylammoniummethyl methacrylate), poly(trimethylammoniumpropyl acrylamide), poly(dodecyl acrylate),
15 poly(octadecyl acrylate), poly(octadecyl methacrylate) or copolymers thereof.
4. The method of Claim 2 wherein the polymer is crosslinked by a multifunctional co-monomer.
5. The method of Claim 4 wherein the multifunctional co-monomer is selected
20 from the group consisting of diacrylates, triacrylates, tetraacrylates, dimethacrylates, diacrylamides, dimethacrylamides, diallylacrylamides and polyvinylarenes.
6. The method of Claim 5 wherein the multifunctional comonomer is selected from the group consisting of ethylene glycol diacrylate, propylene glycol diacrylate, butylene glycol diacrylate, ethylene glycol dimethacrylate,
25 butylene glycol dimethacrylate, methylene bis(methacrylamide), ethylene

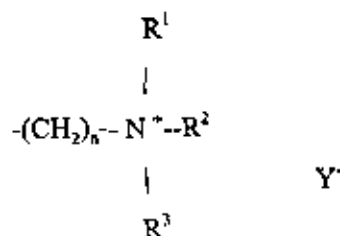
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bis(acrylamide), ethylene bis(methacrylamide), ethylidene bis(acrylamide), ethylidene bis(methacrylamide), bisphenol A dimethacrylate, bisphenol A diacrylate, pentaerythritol tetraacrylate, trimethylolpropane triacrylate and divinylbenzene.

- 5 7. The method of Claim 4 wherein the amount of crosslinking agent is between about 0.5 and about 25 weight percent based on the combined weight of crosslinking agent and monomers.
8. The method of Claim 1 wherein the lipase inhibitor is selected from
10 lipstatin, tetrahydrolipstatin or a combination thereof.
9. The method of Claim 1 wherein the fat-binding polymer is a synthetic amine polymer.
10. The method of Claim 9 wherein the amine polymer is selected from the group consisting of poly(allylamine), poly(ethyleneimine),
15 poly(vinylamine), poly(diallylamine), and poly(diallylmethylamine).
11. The method of Claim 10 wherein the amine polymer is crosslinked by means of a multifunctional crosslinking agent, said agent being present in an amount from about 0.5%-25% weight, based upon the combined weight of monomer and crosslinking agent.
- 20 12. The method of Claim 9 wherein the amine polymer further comprises one or more hydrophobic regions bound to a portion of the amine nitrogens.
13. The method of Claim 12 wherein the hydrophobic regions are bound to between about 1 and about 60 percent of the amine nitrogens.
14. The method of Claim 13 wherein the hydrophobic regions are bound to
25 between about 1 and about 30 percent of the amine nitrogens.

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15. The method of Claim 12 wherein the hydrophobic region is a substituted or unsubstituted, normal, branched or cyclic alkyl group having at least four carbons.
16. The method of Claim 15 wherein the hydrophobic region is an alkyl group of between about four and thirty carbons.
17. The method of Claim 16 wherein the hydrophobic region is an alkyl group of about 6 carbons.
18. The method of Claim 16 wherein the hydrophobic region is an alkyl group of about 8 carbons.
19. The method of Claim 16 wherein the hydrophobic region is an alkyl group of about 10 carbons.
20. The method of Claim 16 wherein the hydrophobic region is an alkyl group of about 12 carbons.
21. The method of Claim 16 wherein the hydrophobic region is an alkyl group of about 18 carbons.
22. The method of Claim 9 wherein the amine polymer further comprises one or more positively charged regions bound to a portion of the amine nitrogens.
23. The method of Claim 22 wherein the positively charge region comprises a quaternary amine-containing moiety having the following formula:



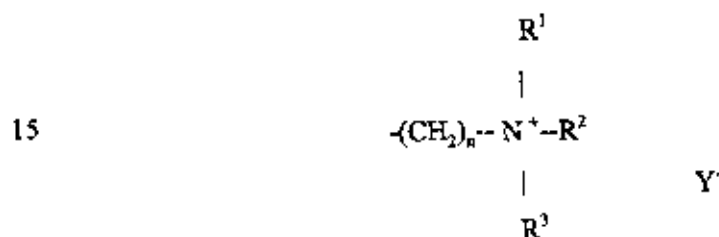
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R^1 , R^2 and R^3 represent hydrogen or an alkyl group, wherein each R, independently, is a normal or branched, substituted or unsubstituted, normal, branched or cyclic alkyl group having a carbon atom chain length of between about one to about twenty-four carbon atoms;

n is an integer having a value of three or more; and

Y is a negatively-charged counterion.

24. The method of Claim 9 wherein the amine polymer further comprises one or more hydrophobic regions comprising an alkyl group of between about four and about twenty-four carbons, and one or more positively charged regions comprising a quaternary amine-containing moiety having the following formula:

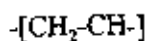


- 20 R^1 , R^2 and R^3 represent an alkyl group, wherein each R, independently, is a normal or branched, substituted or unsubstituted, normal, branched or cyclic alkyl group having a carbon atom chain length of between about one to about twenty-four carbon atoms;

n is an integer having a value of three or more; and

- 25 Y is a negatively-charged counterion.

25. The method of Claim 1 wherein the fat-binding polymer comprises a monomer of the formula

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wherein R is a hydrophobic region.

26. The method of Claim 25 wherein the hydrophobic region comprises a substituted or unsubstituted, normal, branched or cyclic alkyl group having at least about four carbons.
- 10 27. The method of Claim 25 wherein the hydrophobic region comprises an alkyl group of between about four and thirty carbons.
28. The method of Claim 25 wherein the hydrophobic region comprises an alkyl group of about 6 carbons.
29. The method of Claim 1 wherein the fat-binding polymer is substituted with a
15 lipase inhibitor.
30. A method for reducing the absorption of dietary fat in a mammal, comprising the step of orally administering to the mammal a therapeutic amount of one or more fat-binding polymers in combination with one or more lipase inhibitors.
- 20 31. A method for treating steatorrhea resulting from the administration of a lipase inhibitor in a mammal, comprising the step of orally administering to the mammal a therapeutic amount of one or more fat-binding polymers.

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32. A method for treating steatorrhea, comprising the step of orally administering to the mammal a therapeutic amount of one or more fat-binding polymers.
- 5 33. A method for treating hypertriglyceridemia in a mammal, comprising the step of orally administering to the mammal an effective amount of one or more fat-binding polymers in combination with one or more lipase inhibitors.
- 10 34. A method for treating obesity in a mammal, comprising the step of orally administering to the mammal an effective amount of one or more fat-binding polymers.

Tabla 1

ESCORE DE CALIDAD METODOLÓGICA PARA ARTÍCULOS DE TERAPIA

Ítem 1. Diseño del estudio	Puntaje asignado
Ensayo clínico multicéntrico	12
Ensayo clínico aleatorio con ciego doble*	9
Ensayo clínico (sin ciego o simple, sin aleatorización)**	6
Cohorte concurrente	4
Casos y controles y estudios de cohorte histórica	3
Corte transversal	3
Serie de casos	1
Ítem 2. Población estudiada x factor de justificación	Puntaje asignado
≥ 201	6 ó 12
151-200	5 ó 10
101-150	4 ó 8
61-100	3 ó 6
≤ 30	1 ó 2
Ítem 3. Metodología empleada	Puntaje asignado
Objetivo	
- Se plantean objetivos claros y concretos	3
- Se plantean objetivos vagos	2
- No se plantean objetivos	1
Diseño	
- Se menciona y justifica el diseño empleado	3
- Se menciona el diseño empleado	2
- No se menciona ni justifica el diseño empleado	1
Criterios de selección de la muestra	
- Se describen criterios de inclusión y de exclusión	3
- Se describen criterios de inclusión o de exclusión	2
- No se describen criterios de selección	1
Tamaño de la muestra	
- Justifica la muestra empleada	3
- No justifica la muestra empleada	1
Escore final	Puntaje total
Ítem 1 + (Ítem 2 x factor justificación) + Ítem 3	6 a 36

* Incluye ensayos clínicos con aleatorización restringida (conglomerados) y quasi-experimentales.

** Incluye estudios experimentales (antes y después).

mera valoración a menudo es suficiente con la lectura del resumen, evaluando si la información que contiene sobre el diseño del estudio permite suponer que es metodológicamente adecuado y si, en el supuesto de que la conclusión del estudio sea válida, tiene relevancia clínica y es aplicable a la situación concreta que se desea resolver. Esto permitirá descartar un número muy significativo de estudios, hecho que no significa que nos quedaremos con los resultados y conclusiones de aquellos artículos que nos parecieron interesantes. Por el contrario, estos serán los artículos que analizaremos con mayor detención.

A continuación aportaremos al lector una guía para lectura crítica de artículos de terapia (Tabla 2) y un escore de calidad metodológica (Tabla 1), generados por nuestro grupo de trabajo. El escore contiene 3 ítems; el primero relacionado con el tipo de diseño del estudio, el segundo con el tamaño de la población estudiada ajustado por la justificación o no de este tamaño de muestra, y el tercero relacionado con la metodología empleada en el estudio en cuestión (objetivos, justificación del diseño, criterios de selección de la muestra y justificación de ésta). De esta forma se genera una escala que es la sumatoria de los ítems 1, 2 y 3, cuyo puntaje total

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30x

Tabla 2
GUÍA PARA LA LECTURA CRÍTICA DE UN ARTÍCULO SOBRE TERAPIA

A. ¿Son válidos los resultados del estudio?

Preguntas de "eliminación": si el artículo no responde adecuadamente las siguientes tres preguntas, no es aconsejable continuar con la lectura crítica.

Guía	Comentarios
1. ¿Se orienta el artículo a una pregunta claramente definida? - Si - No - No se puede decir	Pistas Una pregunta debe definirse en términos de: - La población en estudio - La intervención realizada - Los resultados considerados
2. ¿Fue aleatoria la asignación de los pacientes al tratamiento? - Si - No - No se puede decir	- ¿Se mantuvo oculta la secuencia de la aleatorización?
3. ¿Fueron adecuadamente considerados hasta el final del estudio, todos los pacientes que entraron a él? - Si - No - No se puede decir	Pistas - ¿El seguimiento fue completo? - ¿Los pacientes fueron analizados en los grupos a los que fueron aleatorizados? (análisis con intención de tratamiento)

Preguntas de detalle

Guía	Comentarios
1. ¿Estuvieron los pacientes, el personal de salud y el personal involucrado en el estudio enmascarados ("ciegos") respecto del tratamiento? - Si - No - No se puede decir	Pistas - Los pacientes - El personal de salud que aplica las terapias - El personal del estudio que realiza las mediciones
2. Los grupos en estudio, ¿eran similares al inicio del estudio? - Si - No - No se puede decir	Pista - Verificar otros factores que pudieran tener efecto sobre el resultado: edad, sexo, etc.
3. Aparte de la intervención en estudio ¿los grupos fueron tratados en forma similar? - Si - No - No se puede decir	

B. ¿Cuáles fueron los resultados?

Guía	Comentarios
1. ¿Cuál fue la magnitud del efecto del tratamiento?	- ¿Qué resultados se midieron? - ¿Qué estimadores se utilizaron?
2. ¿Cuán precisa fue la estimación del efecto del tratamiento?	- ¿Cuáles son sus intervalos de confianza?

C. ¿Me ayudarán estos resultados en el cuidado de mis pacientes?

Guía	Comentarios
1. ¿Los resultados pueden ser aplicados en el cuidado de mis pacientes? - No - Si - No se puede decir	Pista - Los pacientes incluidos en el estudio son lo suficientemente parecidos a mis pacientes?
2. ¿Se consideraron todos los resultados de importancia clínica? - Si - No - No se puede decir	Pista - ¿En caso negativo, en qué afecta esto en la decisión a tomar?
3. ¿Los beneficios a obtener justifican los riesgos y los costos del tratamiento? - Si - No	Pista - Es improbable que pueda deducirse del estudio, pero ¿qué piensa usted al respecto?

puede fluctuar entre 6 y 36 puntos, asignando 6 puntos al estudio de menor calidad metodológica y 36 puntos al de mejor calidad metodológica.² Por su parte la guía para lectura consta de 3 "preguntas de eliminación" relacionadas con la validez del estudio, y cuyo objetivo es realizar el primer tamizaje del artículo (si lo que buscamos es calidad metodológica evidentemente), pues si éste no permite responder adecuadamente estas preguntas, no es aconsejable continuar con la lectura crítica. Luego, la guía contiene elementos que permiten objetivar la calidad de los resultados y si éstos pueden o no ser aplicados en el cuidado de nuestros pacientes. Está compuesta por 2 columnas, a la izquierda la guía propiamente tal, y a la derecha una serie de "pistas" o acotaciones que ayudan a responder en forma más apropiada la guía.

En las próximas líneas podrán aplicar estos instrumentos en forma práctica a 1 artículo de terapia publicado en una prestigiosa revista científica quirúrgica.

EjemPlo 1

Drenaje percutáneo comparado con cirugía para el tratamiento de los quistes hidatídicos hepáticos. Khuroo MS, Wani NA, Javid G et al: N Engl J Med 1997; 337: 881-87.6

A. ¿Son válidos los resultados del estudio?

Preguntas de eliminación

1. ¿Se orienta el artículo a una pregunta claramente definida? **No se puede decir**, pues si bien es cierto que se define la población en estudio (sujetos mayores de 14 años con quistes no complicados) y la intervención (drenaje percutáneo vs cirugía), no se considera una variable resultado concreta que permita comparar ambas cohortes.

2. ¿Fue aleatoria la asignación de los pacientes al tratamiento? **Si**, sin embargo, se ha de considerar lo siguiente: La asignación de los pacientes a las 2 formas de terapia fue aleatoria, sin embargo, no se precisa tipo de aleatorización empleada como tampoco si la secuencia de ésta se mantuvo oculta. Tampoco, se realizó cálculo del tamaño de la muestra (sólo se comparan 2 cohortes de 25 pacientes).

3. ¿Fueron adecuadamente considerados hasta el final del estudio todos los pacientes que entraron a él? **No se puede decir**. A pesar que los pacientes fueron efectivamente analizados en los grupos en los que fueron aleatorizados y que el seguimiento fue similar en ambos grupos (media de 17 meses),

en ambos grupos hay pacientes que sólo fueron seguidos por 9 meses.

A estas alturas de la lectura podríamos decidir si seguir o no adelante con la lectura crítica, pues en 2 de las preguntas de eliminación, en el artículo no hay elementos para su apropiada respuesta. Sin embargo, seguiremos el análisis a modo de ejercicio. Para ello pasaremos a la siguiente fase del análisis crítico del artículo.

Preguntas de detalle

1. ¿Estuvieron los pacientes, el personal de salud y el personal involucrado en el estudio enmascarado o "ciegos" respecto del tratamiento? **No**. Ni los pacientes ni el personal de salud que aplicaba las terapias estuvieron enmascarados a las terapias en estudio. El personal que realizaba las mediciones, pudo estar enmascarado, sin embargo, no se precisa en el artículo quienes midieron y cómo; por ende, a lo sumo, pudiera haber un enmascaramiento o ciego simple.

2. Los grupos en estudio, ¿eran similares al inicio del estudio? **Si**. En la Tabla 1, se aprecia que los cohortes eran similares en las variables edad, género, duración de la enfermedad, cuadro clínico, diámetro promedio de los quistes, localización de las lesiones y títulos de inmunoglobulinas. Sin embargo, hay factores que pueden influir en los resultados finales del estudio que merecen ser considerados y no fueron tomados en cuenta en este estudio, como el tipo de quistes (¿será igual tratar quistes univesiculares que multivesiculares?) y la especie de echinococcus (se sabe que existen diferentes serotipos de echinococcus, cuyas características genéticas pudieran ser responsables de algunas características de la enfermedad, por ejemplo, la agresividad de ésta).

3. Aparte de la intervención en estudio ¿los grupos fueron tratados en forma similar? **Si**. No hay evidencias que permitan pensar que hubo diferencias en el resto de la terapia en ambos grupos. Aparentemente (a pesar que no queda claramente explicitado), ambas cohortes sólo tuvieron como diferencia terapéutica la intervención en estudio.

B. ¿Cuáles fueron los resultados?

1. ¿Cuál fue la magnitud del efecto del tratamiento? En este estudio se midieron las variables estancia hospitalaria, diámetro del quiste después del tratamiento, desaparición del quiste, títulos de inmunoglobulinas y morbilidad; y, para ello, se consideraron como indicadores los intervalos de confianza de 95% (IC 95%) y los Odds ratios (razones

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de probabilidad) como medidas de fuerza de la asociación.

2. ¿Cuán precisa fue la estimación del efecto del tratamiento? Sólo 2 variables exhiben diferencias significativas (estancia hospitalaria y morbilidad). Estancia hospitalaria tiene un IC de 95% de 5,8, 11,2 y la variable morbilidad tiene un IC de 95% de 2,7, 36,0. Sin embargo, en esta última variable que pudiese ser la de mayor impacto clínico, existen reparos sobre el tipo de complicaciones consideradas, en especial "la fiebre". Si ésta se eliminara como complicación (de hecho cuesta pensar que un signo sea una complicación), no habría diferencias entre ambas cohortes, y entonces la diferencia terapéutica estaría dada sólo por la estancia hospitalaria que evidentemente debe ser más corta si se compara un procedimiento (por definición semi-ambulatorio) con una cirugía que muchas veces puede ser compleja. Lo interesante de este punto radica en que si volvemos al cálculo del tamaño de la muestra y jugamos un poco con los números obtendríamos los siguientes escenarios:

2.1. Si la variable resultado fuese estancia hospitalaria, con la diferencia observada, un IC 95% y poder de 80%, el tamaño de muestra necesario para conducir esta investigación sería tan solo de 7 sujetos en cada cohorte.

2.2. Por otro lado, si la variable resultado fuese morbilidad, con la diferencia observada, un IC 95% y poder de 80%, el tamaño de muestra necesario sería de 21 sujetos en cada cohorte.

2.3 Sin embargo, si reconsiderásemos como complicación "la fiebre" y "la hipotensión" quedaríamos con proporciones de morbilidad de 4/25 (para el grupo de drenaje) vs 5/25 (para el grupo de cirugía), escenario en el cual con un IC 95% y poder de 80%, la muestra necesaria para realizar el estudio sería de 1497 sujetos en cada cohorte.

C. ¿Me ayudarán estos resultados en el cuidado de mis pacientes?

1. ¿Los resultados pueden ser aplicados en el cuidado de mis pacientes? **No se puede decir.** Esto dependerá del tipo de pacientes a los que tenemos acceso en el centro donde nosotros atendemos. A modo de ejemplo, responderemos en relación con nuestra realidad. Por una parte, pudieran existir diferencias en el serotipo de *echinococcus*, que se sabe puede ser muy diferente en distintos lugares, hecho que influye directamente en el resultado de la terapia en términos de recidivas; el diámetro de las lesiones que tratan en el estudio en cuestión, es menor a lo que habitualmente vemos en nuestra realidad (mediana de 15

cm); la evolutividad de las lesiones es diferente, pues en nuestro centro, el 32% de los pacientes tiene alguna complicación evolutiva al momento de su ingreso (absceso hepático de origen hidatídico,⁷ colangiolitiasis,⁸ etc.).

2. ¿Se consideraron todos los resultados de importancia clínica? **No.** El tiempo de seguimiento de las cohortes es muy corto (debiera ser superior a 4 años). Se desconoce que ocurrió con la germinal y las vesículas hijas, pues éstas se dejaron *in situ*. Tampoco, se precisa como se midió el efecto terapéutico, por ejemplo sobre los escólices (¿cuál era la viabilidad de éstos?).

3. ¿Los beneficios a obtener justifican los riesgos y los costos del tratamiento? **No.** A nuestro modo de ver los potenciales beneficios no justifican los riesgos y costos. Ambos puntos pueden ser materia de discusión y no se deducen del estudio, pero la administración del Albendazol tiene un costo elevado, hay riesgos de toxicidad implícitos,⁹ y su utilidad como escolicida es aún controversial.¹⁰

Por otra parte, al aplicar el escora de calidad metodológica UFR0, podemos constatar una sumatoria de 16 puntos (6 a 36 puntos). Si consideramos que el punto de corte establecido para "calidad metodológica apropiada" es 18 puntos, tenemos en este artículo un estudio de calidad metodológica baja.

En resumen, se trata de un ensayo clínico aleatorio de baja calidad metodológica, con nivel de evidencia y recomendación de lectura de Sacket de 2b y B respectivamente.

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ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMI
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-106075-00017-0000

Fecha: 2010-10-01 16:28:53 Dep. 2020 DIR.NUEVASOR
Trá. 11 PATENI CIVI Eje: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 5

Re: P1.-F.HOFFMANN-LA ROCHE AG.-Solicitud de Patente de invención en Fase Nacional PCT para "COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UN INHIBIDOR DE LIPASA Y UN ÉSTER DE ÁCIDO GRASO DE SACAROSA".-Clase A61K 31/365.-Expediente número 03-106.075.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 9 de Julio de 2010.

2. Con el fin de responder a las objeciones de nivel inventivo expuestas por el señor Examinador en su Concepto Técnico No. 1512, atentamente me permito presentar los siguientes argumentos técnicos por medio de los cuales no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de dicha invención.

3. ANÁLISIS DEL NIVEL INVENTIVO DE LA SOLICITUD

El señor Examinador ha objetado el nivel inventivo de la solicitud en cuestión basándose en las enseñanzas de los siguientes documentos:

(D1) → WO 00/09122

(D2) → WO 01/19378

En este sentido, el señor Examinador argumenta básicamente que la principal diferencia entre la solicitud de patente en cuestión y D2 es que dicha anterioridad no enseña composiciones farmacéuticas que emplean un monoéster seleccionado entre sacarosalaurato, sacarosamilristato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato.

Sin embargo, de acuerdo con el señor Examinador el documento D1 divulga composiciones que comprenden un Inhibidor de lipasas y un emulsificante (tal como

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un éster de ácido graso de sacarosa), las cuales se caracterizan porque mejoran la absorción del principio activo y disminuyen el goteo anal de aceite.

Con base en lo anterior, el señor examinador concluye que el experto en la materia habría optado por la sugerencia explícita de D1 de utilizar ésteres de ácido graso de sacarosa para mejorar la efectividad de la composición y evitar los efectos secundarios asociados a la administración del principio activo como el goteo anal en las composiciones reveladas por D2, para llegar a la materia presentada en la presente invención.

Visto lo anterior y con el ánimo de demostrar que la solicitud en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas del arte previo, atentamente me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

(a) En primer lugar me permito señalar que en la solicitud de patente en cuestión se revela una composición farmacéutica que comprende: i) orlistat, ii) un monoéster de ácido graso de sacarosa seleccionado entre sacarosalaurato, sacarosaministato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato, y, iii) uno o más excipientes farmacéuticamente aceptables. Dicha novedosa composición se caracteriza porque permite superar satisfactoriamente el problema técnico existente en el estado de la técnica relacionado con el hecho de que la actividad del orlistat como inhibidor de lipasas es dependiente del tipo de comida ingerida.

En relación con lo anterior, me permito dirigir la atención de ese Despacho a las enseñanzas contenidas en la página 3 de la presente solicitud, en donde se establece la existencia de un problema técnico relacionado con la administración de inhibidores de lipasa, toda vez que *"la eficacia de los inhibidores de lipasas puede depender fuertemente de la clase de alimento ingerido, encontrándose una mayor eficacia en las comidas compuestas por papas fritas, salchichas y hamburguesas, mientras que se observa una menor eficiencia para el queso y otros productos lácteos"*.

Ahora bien, tal como puede verificarse en los apartes de la descripción de la solicitud en estudio que a continuación se mencionan, el problema técnico relacionado con el hecho de que la actividad del orlistat como inhibidor de lipasas sea dependiente del tipo de comida ingerida ha sido solucionado mediante el empleo de un monoéster de ácido graso de sacarosa:

- Ejemplo 1 (páginas 15 y 16 de la descripción), en donde se establece que la combinación de orlistat (cuyo nombre comercial es Xenical) con L-1695 (sacarosalaurato), P-1670 (sacarosapalmitato), S-1670 (sacarosaestearato) ó

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O-1570 (sacarosaoileato) permite lograr una eficiente inhibición de la actividad de las lipasas gastrointestinales independientemente del tipo de comida ingerida. En contraste con lo anterior, se muestra que la actividad inhibitoria lograda al administrar únicamente orlistat es menor y depende del tipo de comida ingerida.

- Ejemplo 11, (páginas 20 a 22 de la descripción), en donde se evalúa in vitro la dependencia de la comida para una inhibición de lipasas con grasas accesibles y resistentes, encontrando que la dependencia de la comida in vitro de las formulaciones basadas en monoésteres de sacarosa es alrededor de 6 veces menor comparado con orlistat (Xenical).
- Ejemplo 13, (página 23 de la descripción), en donde se concluye que, *"la dependencia de la comida de orlistat se puede minimizar sustancialmente mediante las formulaciones basadas en el monoéster de ácido graso de sacarosa"*.

De acuerdo con lo anterior, es posible verificar que la composición de la presente solicitud presenta una nueva y mejorada propiedad como lo es la menor dependencia de la comida en el tratamiento de la obesidad, lo cual se logra empleando monoésteres de ácido graso de sacarosa, toda vez que la combinación de éstos con el inhibidor de lipasas gastrointestinales permite reducir la dependencia de los resultados logrados con el tipo de comida ingerida.

(b) Por su parte, el documento D1 divulga composiciones farmacéuticas que comprenden un inhibidor de lipasa gastrointestinal, uno o más aditivos escogidos del grupo conformado por espesantes y emulsificantes hidrofílicos, no digeribles y no fermentables, y excipientes auxiliares.

De acuerdo con los autores de D1, las composiciones farmacéuticas previamente mencionadas permiten reducir o prevenir el goteo anal de aceite que se produce como consecuencia de la separación de aceite no absorbido de las heces luego de haber consumido inhibidores de lipasas.

Los espesantes señalados en D1 como posibles componentes de las composiciones farmacéuticas allí reveladas son polisacáridos naturales, sintéticos o semisintéticos solubles en agua, tales como metil celulosa, goma xantán, semillas de psyllium, cáscara de ispágula, semillas de plantago ovata, goma de karaya y mezclas de los mismos.

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Los emulsificantes señalados en D1 como posibles componentes de las composiciones farmacéuticas allí reveladas son los poliésteres de sacarosa, tales como los ésteres de azúcar de Ryoto.

(c) De otro lado, el documento D2 básicamente divulga composiciones farmacéuticas que comprenden al menos un inhibidor de lipasas y al menos un éster de ácido graso de polioles, en donde éste último se caracteriza porque el éster de ácido graso tiene un punto de fusión mayor a la temperatura corporal y los polioles son escogidos entre el grupo conformado por azúcares, derivados de azúcares y mezclas de los mismos.

De acuerdo con los autores de tal anterioridad, las composiciones previamente mencionadas permiten mejorar la eficacia clínica y la potencia de los inhibidores de lipasa, minimizando o suprimiendo los efectos secundarios tales como el goteo anal de aceite.

Los polioles que hacen parte de las composiciones de D2 son escogidos preferiblemente entre sacarosa y ésteres de glicerol, en donde la porción éster puede comprender entre 1 y 3 fragmentos de ácido graso C_{12} a C_{20} por porción de glicerol, y en donde dicho éster de glicerol puede escogerse entre uno o más triglicéridos, uno o más monoglicéridos, uno o más fosfolípidos, y mezclas de los mismos (páginas 3 y 4 de la descripción del documento D2).

Con base en lo anterior, atentamente me permito manifestar ante ese Despacho que las composiciones farmacéuticas reveladas en la solicitud de patente en cuestión presentan un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1, D2 ó la combinación de los mismos, toda vez que:

- i. Los documentos D1 y D2 no enseñan y tampoco sugieren de manera alguna una combinación que comprenda orlistat con un monoéster de sacarosa seleccionado entre sacarosalaurato, sacarosaministato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato.

De acuerdo con el señor Examinador en el documento D1 se hace la sugerencia explícita de utilizar ésteres de ácido graso de sacarosa en conjunto con inhibidores de lipasas gastrointestinales, mientras que en el documento D2 se sugiere el empleo de ésteres de ácidos grasos de polioles.

A éste respecto, inicialmente me permito señalar que las enseñanzas del documento D1 de ninguna manera pueden afectar el nivel inventivo de la presente solicitud de patente debido a que en dicha anterioridad únicamente

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se hace referencia a los ésteres de ácido graso de sacarosa como agentes emulsificantes de la composición allí divulgada, estableciendo explícitamente que: *"como emulsificantes que pueden utilizarse en las composiciones de la invención, pueden citarse políesteres de sacarosa..."* (página 3 de la descripción de D1); por consiguiente, es claro que no existe en dicho documento alguna indicación técnica que gulara a la persona medianamente versada en la materia a emplear específicamente un monoéster de ácido graso de sacarosa en conjunto con un agente inhibidor de flpasas gastrointestinales, como parte de una composición farmacéutica.

En relación con lo anterior, considero relevante mencionar que para una persona medianamente versada en la materia es claro que las propiedades fisicoquímicas de diferentes ésteres de ácidos grasos de sacarosa pueden *variar considerablemente entre sí, lo que por ende representa drásticas diferencias* en sus posibles aplicaciones. Así, por ejemplo, un éster de ácido graso de sacarosa puede emplearse en emulsiones de agua en aceite si su valor HLB (balance lipofílico-hidrofílico) es menor a 9, mientras que un éster de ácido graso de sacarosa debe emplearse en emulsiones de aceite en agua si su valor HLB es mayor a 9.

Ahora bien, de conformidad con lo anteriormente expuesto y haciendo referencia explícita a las enseñanzas de D1, me permito señalar que en dicha anterioridad se menciona el compuesto "Ryoto sugar ester S-170" como el políéster de sacarosa que puede emplearse como agente emulsificante dentro de las composiciones farmacéuticas allí divulgadas, el cual se caracteriza porque tiene un valor HLB = 1. Contrario a esto, los monoésteres de sacarosa que se emplean en la solicitud de patente en cuestión se caracterizan por presentar los siguientes valores HLB:

sacarosalaurato L-1965 → HLB = 16
sacarosapalmitato P-1670 → HLB = 16
sacarosaestearato S-1670 → HLB = 16 y,
sacarosaoleato O-1570 → HLB = 15

Lo anterior permite verificar que es claro y evidente que los políesteres y los monoésteres son completamente diferentes, y por lo tanto son utilizados para propósitos completamente diferentes; y en consecuencia no es evidente su intercambio.

Teniendo en cuenta lo anterior, si una persona versada en la materia se basara en las enseñanzas del documento D1 y pretendiera reemplazar el Ryoto sugar ester S-170, le resultaría lógico emplear un emulsificante con

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propiedades similares (esto es, adecuado para realizar emulsiones agua en aceite), tales como los poliésteres de sacarosa comercialmente disponibles (ésteres S-270 o S-370), pero nunca hubiera podido derivar de dichas enseñanzas el empleo de monoésteres de ácidos grasos de sacarosa en combinación con agentes inhibidores de lipasas gastrointestinales.

Por su parte, el documento D2 divulga el empleo de ésteres de ácidos grasos de polioles, los cuales deben ser escogidos entre azúcares, derivados de azúcares y mezclas de los mismos, y según lo establecido en la página 3 (líneas 25 y 26) de dicha anterioridad, el poliol empleado puede escogerse entre sacarosa y glicerol, preferiblemente ésteres de glicerol, los cuales pueden contener entre 1 y 3 porciones de ácido graso por cada molécula de glicerol. Debido a lo anterior, es claro que el documento D2 menciona la posibilidad de emplear compuestos monoglicéridos como parte de composiciones farmacéuticas que potencialicen y/o mejoren la eficacia de los agentes inhibidores de lipasas gastrointestinales.

Visto lo anterior, me permito señalar que los documentos D1, D2 ó la combinación de los mismos no enseñan y tampoco sugieren el empleo de un monoéster de sacarosa.

Finalmente, de la manera más atenta me permito resaltar ante ese Despacho que al parecer el análisis realizado por el señor Examinador no se ha enfocado de ninguna manera en el momento en que el solicitante de la invención en cuestión se planteó sus objetivos técnicos, es decir, el señor Examinador realmente no está teniendo en cuenta la imperiosa necesidad que existe de que el examen de patentabilidad que lleve a cabo lo realice haciendo el esfuerzo intelectual de colocarse en la situación afrontada por el técnico con conocimientos medios en la materia antes de que el solicitante de la presente invención diera a conocer sus sorprendentes y ventajosos hallazgos técnicos.

- ii. Ahora bien, adicionalmente a lo anterior considero de gran importancia reiterar ante ese Despacho que ninguno de los documentos D1 y D2 se encuentra dirigido a solucionar el problema técnico relacionado con la dependencia que existe entre el tipo de comida ingerida y la actividad del orlistat como agente inhibidor de lipasas gastrointestinales, hecho que indiscutiblemente debe ser tenido en cuenta como parte del análisis del nivel inventivo realizado por el señor Examinador.

De manera específica me permito resaltar que en las líneas 15 a 17 y 25 a 29 de la página 1 del documento D1 se menciona que las composiciones

divulgadas en dicha anterioridad permiten prevenir la separación física entre las heces y el aceite no absorbido como consecuencia de la inhibición de las lipasas gastrointestinales, y por lo tanto eliminan o disminuyen el goteo anal de aceite en los pacientes que consumen agentes activos como Orlistat.

Por su parte, en las líneas 1 a 3 de la página 2 del documento D2 se menciona claramente que el problema abordado en dicha anterioridad es aquel relacionado con la necesidad de obtener una composición inhibidora de lipasas gastrointestinales capaz de mejorar la eficacia y/o la potencia del agente inhibidor de lipasas (por ejemplo orlistat), pero minimizando o suprimiendo el goteo anal de aceite que se observa ocasionalmente en pacientes tratados con inhibidores de lipasas.

En consecuencia, es claro que la persona medianamente versada en la materia que esté interesada en obtener una composición farmacéutica que permita eliminar la dependencia que existe entre el tipo de comida ingerida y la actividad del orlistat como agente inhibidor de lipasas gastrointestinales, no habría considerado las enseñanzas de documentos del arte previo que, como en el caso de D1 y D2, no se encuentran dirigidos a solucionar el mismo problema técnico, toda vez que dicha persona medianamente versada en la materia no se vería incitada a tener en cuenta tales documentos y mucho menos encontraría la solución propuesta en la presente invención. En otras palabras, me permito señalar que la persona medianamente versada en la materia no podría encontrar en los documentos D1 y D2 alguna indicación técnica que le sugiera la solución a un problema técnico que no se plantea en tales documentos.

Visto lo anterior, me permito manifestar ante ese Despacho que la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1, D2 o la combinación de los mismos, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 18 de la Decisión 486 de 2000.

4. CONCESIÓN DE LA PATENTE EN OTROS PAÍSES Y REGIONES

Finalmente, de la manera más atenta me permito resaltar ante ese Despacho que la solicitud de patente en cuestión ya ha sido aceptada por las Oficinas de Propiedad Industrial de la Unión Europea (EP 1399152 B1) y Perú (Patente 4862 - concedida el 23 de Enero de 2008).

Ante todo, es preciso señalar que con la información mencionada anteriormente de ninguna manera pretendo desconocer la Independencia de la que goza la

Superintendencia de Industria y Comercio al momento de analizar los méritos de patentabilidad de una solicitud, de acuerdo con las disposiciones del Convenio de París para la protección de la propiedad industrial.

Sin embargo, si considero de gran importancia resaltar el hecho de que la materia técnica revelada en la solicitud de patente en cuestión ha sido catalogada como novedosa, inventiva e industrialmente aplicable por los Examinadores de las Oficinas de Propiedad Intelectual de los países y regiones previamente mencionados, entre los que se cuenta Perú, esto es, un país que hace parte de la Comunidad Andina de Naciones y que por lo tanto comparte con Colombia la misma legislación en materia de patentes, hecho que evidentemente representa un claro indicio de que la materia técnica revelada en la solicitud de patente negada por ese Despacho cumple a cabalidad con los requisitos de patentabilidad establecidos en la Decisión 486 de 2000.

5 CONCLUSIÓN

De conformidad con lo mencionado en el presente memorial, es claro que las novedosas composiciones farmacéuticas reveladas en la presente invención permiten solucionar el problema técnico relacionado con la dependencia que existe entre el tipo de comida ingerida y la actividad del orlistat como agente inhibidor de lipasas gastrointestinales, lo cual corresponde a un importante aporte al estado de la técnica anterior. En este sentido, también es claro que tales composiciones presentan un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1, D2 o la combinación de los mismos, toda vez que dichas anterioridades no se encuentran dirigidas a solucionar el mismo problema técnico y tampoco le enseñan o le sugieren a la persona medianamente versada en la materia que una composición que comprende orlistat y un monoéster de ácido graso de sacarosa seleccionado entre sacarosalaurato, sacarosamiristato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato permita eliminar la dependencia del agente activo con el tipo de comida ingerida por el paciente bajo tratamiento.

Por lo tanto, teniendo en cuenta los argumentos técnicos presentados para demostrar el inequívoco carácter inventivo de la invención en cuestión, resulta completamente claro que se han superado las objeciones expuestas por el señor Examinador en su Concepto Técnico, y por lo tanto, dicha invención es merecedora del privilegio de patente solicitado.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

Radicación No. 03 106 075

Clasificación Internacional (IPC): A61K 31/437

Concepto Técnico No. 4068

Patente de Invención



Patente de Modelo de Utilidad



Vía Nacional



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

EP 01113793.2

Fecha de Presentación Interna.

06/06/2001

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados

Descripción:

Folios 39 a 74 como se radicó inicialmente.

Reivindicaciones:

Folios 75 a 80 como se radicó inicialmente
Folios 176 a 180 como se modificó en fase nacional.
Folios 197 a 200 como se modificó en fase nacional.
Folios 226 a 228 como se modificó en fase nacional.

Dibujos:

Folios 98 a 102 como se radicó inicialmente

Oposiciones:

Folios 116 a 159; opositor: TECNOQUIMICAS S.A.

Rta. del Solicitante:

Folios: 162 a 174 frente a la oposición
Folios: 187 a 195 frente a Concepto Técnico 989
Folios: 223 a 225 frente a Concepto Técnico 2607

Objeto de la invención

El Título de la solicitud es "COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UN INHIBIDOR DE LIPASA Y UN ÉSTER DE ÁCIDO GRASO DE SACAROSA", f.1.

El objeto de la presente solicitud de patente de invención consiste en:

Reivindicaciones 1- 20: Composiciones que contienen Orlistat.

El problema planteado en esta solicitud es la necesidad de una composición de inhibidor de lipasas cuya efectividad no dependa de la clase de alimento ingerido y tenga menos efectos secundarios (folio 39).

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Para solucionar este problema técnico la solicitud en estudio proporciona una composición que contiene Orlistat.

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De la solicitud de Patente

Descripción (artículo 28 D. 486)

La descripción cumple con los requisitos de claridad de acuerdo con el artículo 28 de la D. 486.

Reivindicaciones (artículo 30 D. 486)

Posterior a las modificaciones realizadas por el solicitante, se encuentra que el capítulo reivindicatorio define, es claro y conciso y además está lo suficientemente sustentado por la descripción. Por lo anterior, las reivindicaciones sí cumplen con el art. 30 de la Decisión 486.

Excepción a la patentabilidad (artículo 20 D. 486 literal a)-d))

Una vez realizadas las modificaciones al capítulo reivindicatorio, según los requerimientos realizados en el art. 45, ya no existen reivindicaciones exceptuadas de patentabilidad, y por lo tanto el objeto de la solicitud no se encuentra dentro del alcance de las excepciones.

Por lo anterior, las reivindicaciones cumplen con el artículo 20 de la D. 486.

Análisis de la Oposición (artículo 43 D. 486)

Después de la lectura de los argumentos presentados por el señor José Luis Reyes, así como de la respuesta por parte del solicitante se concluye lo siguiente:

Las oposiciones presentadas por el Dr. Reyes se fundamentan en que los inhibidores de lipasa como orlistat son conocidos desde 1985, así como sus formulaciones son conocidas desde antes de la fecha de prioridad de la presente solicitud y que los ésteres de ácido graso de sacarosa son conocidos en el estado de la técnica. De otra parte argumenta que las composiciones que se reivindican son anticipadas por el documento WO 00/09122 que revelan composiciones de orlistat, emulsificantes como ésteres de ácidos grasos de sacarosa y otros excipientes, también cita el documento WO 01/19378 que enseña composiciones de inhibidor de lipasa y un éster de ácido graso de poliol (azúcares). Finalmente dice que el procedimiento reivindicado es indeterminado y que hay reivindicaciones de uso y de método de tratamiento.

El solicitante argumenta en su respuesta a las oposiciones que primero se hicieron modificaciones al capítulo reivindicatorio y segundo el opositor no ha sido capaz de identificar el problema técnico a resolver y que ha cometido grandes errores de apreciación y que hay incongruencias en el planteamiento de falta de novedad. A continuación explica que hay diferencias entre las composiciones plateadas en WO 00/09122 ya que ésta solo se relaciona con un éster de ácido graso, mientras la presente solicitud revela mezcla de éstos; en cuando al documento WO 01/19378 dice que éste no revela ningún ejemplo específico que caiga bajo las reivindicaciones de la presente solicitud. Finalmente dice que el capítulo

reivindicatorio presentado (folios 176-180) supera las objeciones del opositor, debido a que no contiene reivindicaciones de uso.

Teniendo en cuenta lo anterior, si bien en el Oficio 8524 de 13.07.07 se tuvieron en cuenta los documentos citados por la oposición para la evaluación del nivel inventivo, vale la pena aclarar que como respuesta a dicho Oficio, el solicitante presenta un nuevo capítulo reivindicatorio (folios 197-200), en donde se restringió dentro del contenido de la composición a monoéster de sacarosa de ácido graso, (ya que los documentos citados por la oposición describen composiciones de orlistat en donde se utilizan poliésteres de sacarosa de ácido graso), haciendo que dichos documentos ya no sean relevantes para objetar el nivel inventivo de la presente solicitud; además en su respuesta el solicitante explica las ventajas de la utilización del monoéster de sacarosa dentro de composiciones que contienen orlistat (ver ejemplos 1, 11 y 13), en donde se demuestra que la utilización del monoéster de sacarosa soluciona el problema de efectividad del orlistat que presentaban las composiciones conocidas en el estado de la técnica.

En conclusión, el nuevo capítulo reivindicatorio presentado ya no se ve afectado por los documentos WO 00/9122 y WO 01/19378 adjuntados con las oposiciones presentadas y, por lo tanto dichos documentos no son relevantes para el estudio del nivel inventivo de la presente solicitud.

Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica es: 06.06.2001

Consultadas las bases de datos con que cuenta la oficina y las otras fuentes utilizadas para determinar el estado de la técnica y habiéndose subsanado las objeciones realizadas en el anterior concepto técnico 1512, no se encontró documento alguno que afecte el objeto de la solicitud.

Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D. 486)

Se reivindica una composición farmacéutica que comprende orlistat, un éster de ácido graso de sacarosa en donde el éster de ácido graso de sacarosa es un monoéster, y opcionalmente uno o más excipientes farmacéuticamente aceptables, en donde dicho monoéster es seleccionado entre sacarosalaurato, sacarosamiristato, sacarosapalmitato, sacarosaestearato, sacarosaraquidonato y sacarosabehanato." (f. 226)

No se encontró dentro del estado de la técnica, documento alguno que evidenciara la existencia de la invención para el momento de la presentación prioritaria.

Por tal razón las reivindicaciones 1 a 20 folios 226 a 228 son novedosas según lo estipulado en el artículo 16 de la Decisión 486.

Nivel Inventivo (artículo 18 D486)

Las reivindicaciones estudiadas corresponden del numeral 1 a 20 contenidas los folios 226 a 228.

Aunque los documentos citados en los anteriores requerimientos intentan resolver el problema técnico planteado inicialmente en la solicitud, se aceptan los argumentos del solicitante por cuanto la nueva composición se encuentra fuera del alcance citado en el documento D1 y D2. Debido a que la descripción demuestra el efecto de la composición reclamada y a que no existía evidencia para un técnico medio versado en la materia de que las formulaciones de Orlistat con monoésteres de ácidos grasos de sacarosa lograran minimizar sustancialmente la dependencia de la comida del Orlistat.

Por consiguiente se concluye que la presente solicitud tiene nivel inventivo de acuerdo a lo estipulado en el art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

Aplicación industrial (*artículo 19 D 486*)

Las reivindicaciones estudiadas corresponden de la número 1 a la 20 contenidas en los folios 226 a 228.

La presente invención si tiene Aplicación Industrial ya que su objeto puede ser aplicado en la industria de farmacéuticos

Conclusión

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Conceder** las reivindicaciones: 1 a 20 (folios: 226 a 228) con el título **"Composiciones farmacéuticas que comprenden Orlistat como un inhibidor de lipasa y un monoéster de ácido graso de sacarosa"**.

Bogotá, D.C.,

CONCEPTO TÉCNICO
No. 4068

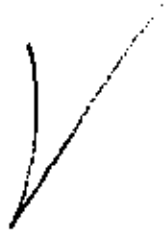
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Código No. 202092

AVISO DE NOTIFICACION
CORREO CERTIFICADO
Industria y Comercio
SUPERINTENDENCIA

325

Radicación :	3-106075- -20-0	Fecha: 2011-02-24 09:48:11
Trámite :	11 PATENTE I Y II	
Evento :	379 FASE NACIONAL II	
Actuación :	432 COMUNICACION ACTO ADM	
Destinatario :	JOSE LUIS REYES VILLAMIZAR Folios 1	

Señor (a) (es)
JOSE LUIS REYES VILLAMIZAR
CARRERA 17 NO 88 - 23 OF 205
BOGOTA D.C.



Referencia RESOLUCION : 9570
Fecha : 23/02/2011
Expediente : 3-106075
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 379 FASE NACIONAL INCLUIDO CAPITULO II
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

Comendidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Tercero (3), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:00 a.m. a 4:30 p.m. jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción trámites y servicios - de carácter general transversal - consulta actos administrativos y providencias.

En caso de que se haya notificado, haga caso omiso de este aviso.

Secretaria General
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Al contestar favor indique el número de radicación consignado en el sticker

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Call Center 6513240 . Línea 018000-910165
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AVISO DE NOTIFICACION
CORREO CERTIFICADO

326

Industria y Comercio
SUPERINTENDENCIA

Radicación :	3-106075- -19-0	Fecha: 2011-02-24 09:48:11
Trámite :	11 PATENTEIYII	
Evento :	379 FASE NACIONALII	
Actuación :	432 COMUNICACTOADM	
Destinatario :	ALICIA LLOREDA RICAURTE Folios 1	

Señor (a) (es)
ALICIA LLOREDA RICAURTE
CALLE 72 NO.5-83 PISO 5
BOGOTA D.C.

Referencia RESOLUCION : 9570
Fecha : 23/02/2011
Expediente : 3-106075
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 379 FASE NACIONAL INCLUIDO CAPITULO II
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En caso de que se haya notificado, haga caso omiso de este aviso.

Secretaría General
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Al contestar favor indique el número de radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 pisos 3, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26- 55 Int. 2 Tel 5880070
Call Center 6513240, Línea 018000-910185
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia

Señor (a)
Director (a) de la División de Nuevas Creaciones
Superintendencia de Industria y Comercio
E. S. D.

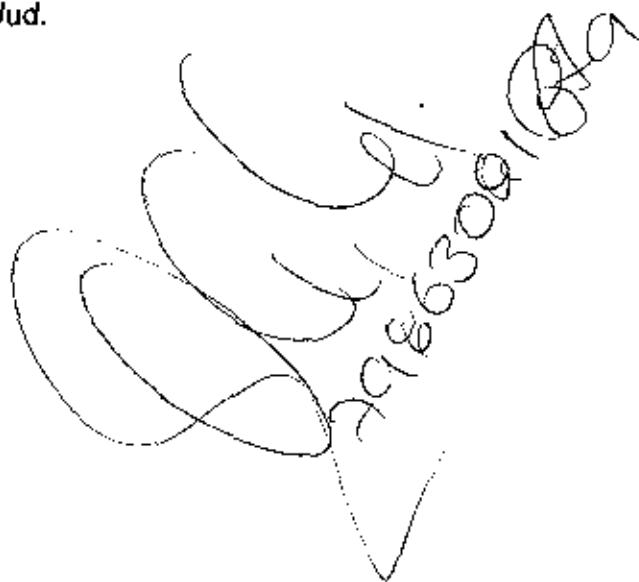
Ref.: Resolución : 9570
Fecha : 23/02/2011
Expediente No. : 03-106075

Yo JOSE LUIS REYES VILLAMIZAR, *identificado como aparece al pie de mi firma*, autorizo al señor BLADIMIR GOMEZ identificado con C.C. No.79.863.081 de Bogotá, *para que en mi nombre se notifique de la resolución enunciada en la referencia.*

Atentamente,



JOSE LUIS REYES VILLAMIZAR
C.C. No. 79.152.473 de Usaquén
T.P. No. 44655 del C.S. de la Jud.



REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No.
Por la cual se otorga una patente de invención

CERTIFICADO No.

Rad. PCT/ 03-106075

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las conferidas en el numeral 38 del artículo 3° del Decreto 1687 de 2010, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el día 02 de diciembre de 2003 con el N° 03106075-00000000, la doctora Alicia Lloreda Ricaurte, en su calidad de apoderada de F. Hoffmann - La Roche AG, presentó la solicitud de patente de invención titulada "COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UN INHIBIDOR DE LIPASA Y UN ÉSTER DE ÁCIDO GRASO DE SACAROSA", correspondiente a la solicitud internacional PCT/EP 02/05889 de fecha 29 de mayo de 2002, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que el extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial N° 554 del 29 de julio de 2005, habiéndose presentado oposición por parte de la sociedad Tecnoquímicas S.A., representada legalmente por su apoderado doctor José Luis Reyes Villamizar, oposición que una vez fue estudiada por el Despacho, no desvirtuó la patentabilidad del objeto en estudio como se analizará mas adelante.

TERCERO: Que realizado el examen de fondo mediante Oficio N° 8757 y notificado por fijación en lista el 09 de julio de 2010 se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 229 a 233 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión, para la concesión de la patente.

CUARTO: Que el solicitante mediante escrito radicado bajo el número 03-106075-00017-0000 del 01 de octubre de 2010 respondió oportunamente el requerimiento formulado, y presentó las aclaraciones correspondientes en relación con las observaciones carácter técnico efectuadas en el examen de fondo.

Análisis de la oposición presentada por la sociedad Tecnoquímicas S.A.

La oposición presentada por el doctor José Luis Reyes Villamizar se fundamenta en el hecho de que los inhibidores de lipasa como orlistat, son conocidos desde el año 1985, al igual que sus formulaciones son conocidas desde antes de la fecha de prioridad de la



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presente solicitud, lo mismo ocurre con los ésteres de ácido graso de sacarosa, que también son conocidos en el estado de la técnica.

Argumenta el opositor que las composiciones que se reivindican son anticipadas por el documento WO 00/09122, que revela composiciones de orlistat, emulsificantes como ésteres de ácidos grasos de sacarosa y otros excipientes, también cita como referencia el documento WO 01/19378, que enseña composiciones de inhibidor de lipasa y un éster de ácido graso de poliol (azúcares). Finalmente dice que el procedimiento reivindicado es indeterminado y que hay reivindicaciones de uso y de método de tratamiento.

Por su parte, el solicitante argumenta en su respuesta que se hicieron modificaciones al capítulo reivindicatorio, que el opositor no ha identificado el problema técnico a resolver y que se presentan errores de apreciación e incongruencias en el planteamiento de falta de novedad de la solicitud. Explica que hay diferencias entre las composiciones planteadas en la anterioridad WO 00/09122, por cuanto ésta solo se relaciona con un éster de ácido graso, mientras que la presente solicitud revela mezcla de éstos.

En cuando al documento WO 01/19378, señala que éste no revela ningún ejemplo específico descrito en el capítulo reivindicatorio de la presente solicitud. Finalmente dice que el capítulo reivindicatorio presentado (Fls. 176 a 180) supera las objeciones del opositor, debido a que no contiene reivindicaciones de uso.

Teniendo en cuenta lo anterior, si bien en el Oficio 8524 del 13 de julio de 2007 se tuvieron en cuenta los documentos citados por la oposición para la evaluación del nivel inventivo, vale la pena aclarar que como respuesta a dicho Oficio, el solicitante presenta un nuevo capítulo reivindicatorio, en donde se restringe dentro del contenido de la composición a monoéster de sacarosa de ácido graso, (teniendo en cuenta que los documentos citados por la oposición describen composiciones de orlistat en donde se utilizan poliésteres de sacarosa de ácido graso), haciendo que dichos documentos ya no sean relevantes para objetar el nivel inventivo de la presente solicitud; además en su respuesta el solicitante explica las ventajas de la utilización del monoéster de sacarosa dentro de composiciones que contienen orlistat (Ejemplos 1, 11 y 13), en donde se demuestra que la utilización del monoéster de sacarosa, soluciona el problema de efectividad del orlistat que presentaban las composiciones conocidas en el estado de la técnica.

En conclusión, el nuevo capítulo reivindicatorio presentado ya no se ve afectado por los documentos WO 00/9122 y WO 01/19378 adjuntados con la oposición presentada y, por lo tanto dichos documentos no son relevantes para el estudio del nivel inventivo de la presente solicitud. 

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QUINTO: Que en virtud de lo dispuesto en el artículo 14 de la Decisión 486 expedida por la Comisión de la Comunidad Andina "[l]os países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

SEXTO: Que en el presente caso las reivindicaciones 1 a 20 contenidas en los folios 226 a 228 cumplen los requisitos indicados en el considerando anterior y, en consecuencia, este Despacho encuentra procedente conceder para las mismas la patente solicitada.

SEPTIMO: Que de acuerdo con el objeto concedido se modifica el título de la invención, el cual quedará de la siguiente manera: "COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN ORLISTAT COMO UN INHIBIDOR DE LIPASA Y UN MONOÉSTER DE ÁCIDO GRASO DE SACAROSA".

RESUELVE:

ARTICULO PRIMERO: Otorgar patente de invención a la solicitud que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), para la creación titulada:

" COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN ORLISTAT COMO UN INHIBIDOR DE LIPASA Y UN MONOÉSTER DE ÁCIDO GRASO DE SACAROSA "

Clasificación IPC: A 61 K 31/437.

Reivindicaciones: 1 a 20 **Folios:** 226 a 228.

Titular: F. HOFFMANN – LA ROCHE AG.

Domicilio: Basilea, Suiza.

Inventores: Karsten Maeder, Rainer Eugen Martin, Susanne Raab, Lukas Christoph Scheibler, Thomas Schindler y Marco Schroeder.

Prioridad N°: EPO 01113793.2 **Fecha:** 06 de junio de 2001.

Solicitud Internacional N°: PCT/EP 02/05889 **Fecha:** 29 de mayo de 2002.

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No.
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CERTIFICADO No.

Rad. PCT/ 03-106075

Vigente desde: 29 de mayo de 2002 **Hasta:** 29 de mayo de 2022

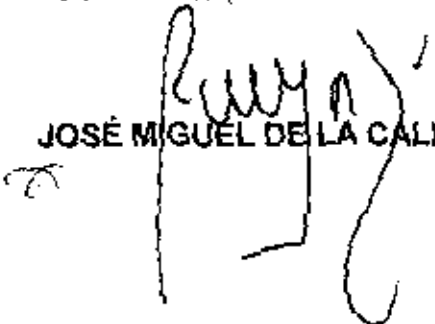
ARTICULO SEGUNDO: El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y en las demás disposiciones legales vigentes sobre propiedad industrial, precisando que para mantener vigente la patente se deberá cancelar la tasa anual de mantenimiento, conforme lo dispone el artículo 80 de la referida norma comunitaria.

ARTICULO TERCERO: Entregar al titular copia auténtica de esta resolución y el certificado de patente, previas las anotaciones en los libros de registro.

ARTICULO CUARTO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, en su calidad de apoderada de F. Hoffmann - La Roche AG, y al doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A., sociedad opositora, o a quienes hagan sus veces, entregándoles copia de la misma, advirtiéndoles que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio, del cual podrán hacer uso al momento de la notificación personal o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JOSÉ MIGUEL DE LA CALLE RESTREPO

Doctora
ALICIA LLOREDA RICAURTE
Calle 72 N° 5 - 83, Piso 5.
Bogotá D.C.

Doctor
JOSÉ LUIS REYES VILLAMIZAR
Carrera 17 N° 88 - 23, Of. 205.
Bogotá D.C.

202021

Página 4 de 4

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Sede CAN: Av. Carrera 50 No. 27-56, Int. 2.
Consultadores: 5870000 y 5880234
Fax: 5870284. Línea 0180000-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

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SUPERINTENDENCIA DE INDUSTRIA
EL SECRETARIO GE

Certifico que la Resolución 9570 de fecha 2
fue notificado mediante listado número 34
fiado el 11/03/2011 y desahado el 23/03/2011

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bladimir Gomez

Comparendo
Identificación
y T.P. No.
Con el
Rectificación
Contratación
La
Por
Domicilio
En
Fecha

[Handwritten signature]

08 MAR 2011

anexo Poder

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

~~Notificador~~