

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

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Abogado
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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	Trámite	011
	Evento	378
	Actuación	519
	Oficio	E - 20100
	Folios	018

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐	Cap. I	☒
Vía PCT (fase nacional)	☒	Cap. II	☐

No. Solicitud Internacional PCT/GB2009/050293
Fecha de Presentación Internacional 26 de marzo de 2009

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de a Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 37 a 60	28 de Octubre de 2010
Reivindicaciones:	Folios 61 a 64	28 de Octubre de 2010
Prioridad:	US 61/040,732	28 de marzo de 2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque:
Esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486).
Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Composiciones farmacéuticas que comprenden una sal hidrógeno sulfato del ácido 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3H-benzoimidazol-5-acido carboxílico y un vehículo matriz". (cambiado en el folio 96)

El problema planteado en esta solicitud consiste en la necesidad de suministrar composiciones farmacéuticas que contengan la sal de sulfato de hidrógeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3H-benzoimidazol-5-acido carboxílico (2-hidroxi-etoxi)-amida, con propiedades mejoradas.

Para resolver este problema técnico la solicitud en estudio proporciona una
Primer Artículo 45- Expediente 10-134209

composición que comprende sal de sulfato de hidrógeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5-acido carboxílico dispersado en una matriz portadora.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 9/48, A61K 9/14, A61K 31/4184, C07D 235/06

4. Excepción a la Patentabilidad (Art 20 D 486 literales (a) – (d))

El objeto de las reivindicaciones 17 no es patentable de acuerdo con el artículo citado.

5. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque el compuesto del estudio es sal de sulfato de hidrógeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5-acido carboxílico (2-hidroxi-etoxi)-amida, por lo cual se sugiere al Solicitante cambiar el título por: "Composiciones farmacéuticas que comprenden una sal hidrógeno sulfato del ácido 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5-acido carboxílico (2-hidroxi-etoxi)-amida y un vehículo matriz".

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara porque contiene dos partes caracterizantes, por lo que se sugiere al solicitante separarlas en reivindicaciones separadas.

Las reivindicaciones 1, 2 y 3 no son claras ni concisas cuando:

Hace uso de la expresión "consiste esencialmente en uno o más portadores[...]", "consiste esencialmente en uno o ambos portadores[...]" puesto que no define adecuadamente la materia que se desea proteger ni limita su alcance, se sugiere al solicitante definir la materia de forma precisa e inequívoca".

Utiliza los términos "glicéridos poliglicolizados", "grasas duras" puesto que incluyen a todos los compuestos que cumplen las características mencionadas, lo cual va más allá de lo soportado en el capítulo descriptivo. Se sugiere al solicitante restringir su solicitud a aquellos "glicéridos poliglicolizados" y "grasas duras" que fueron adecuadamente soportadas en el capítulo descriptivo.

Las reivindicaciones 4 y 5 hacen referencia al Lauril Macrogol 32, que es una Marca Registrada y por tanto no definen al producto porque su composición puede cambiar con el paso del tiempo aunque conserve el mismo nombre. Se sugiere aclarar cuáles son las características del producto en cuestión.

Las reivindicaciones 10 y 11 no son claras porque no definen adecuadamente la materia que se desea proteger. Se le recuerda al solicitante que una composición se define inequívocamente cuando se define en razón de sus componentes y proporciones, teniendo en cuenta que no se define otro tipo de características en las

reivindicaciones mencionadas, se sugiere al solicitante eliminarlas del pliego reivindicatorio.

6. Determinación del Estado de la Técnica

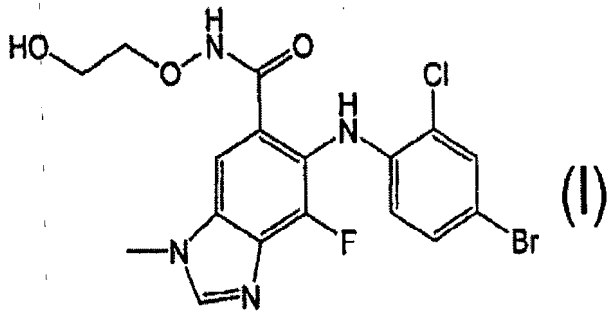
El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: 28 de marzo de 2008

Y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	WO2007076245	Novel Hydrogen Sulfate Salt	05 de julio de 2007
D2	Handbook of Pharmaceutical Excipients, Fifth Edition, Edited by Raymond C Rowe, Paul J Sheskey and Siân C Owen	Monographs Aliphatic Polyesters, Polyethylene Glycol, Páginas 24-27; 545-550	2006

D1
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2007076245A2&KC=A2&FT=D&ND=&date=20070705&DB=&locale=en_EP

La presente invención se refiere al compuesto 1



sal de sulfato de hidrógeno y solvatos, formas cristalinas y formas amorfas de los mismos, y a procedimientos para su preparación.

D2 (folios 119-131)
Handbook of Pharmaceutical Excipients, Fifth Edition, Edited by Raymond C Rowe, Paul J Sheskey and Siân C Owen, 2006. Monographs Aliphatic Polyesters, Polyethylene Glycol, Páginas 24-27;454-456 y 545-550,

Divulga los usos, propiedades y características de seguridad de los excipientes farmacéuticos

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art 18 D486)

La reivindicación 1 consiste en una composición farmacéutica que comprende una sal de sulfato de hidrogeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3H-

benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida, y una matriz portadora, donde la matriz portadora consiste esencialmente en uno o más portadores farmacéuticamente aceptables seleccionados de los siguientes grupos:

- (a) succinato de d-alfa-tocoferil polietileno glicol 1000/
- (b) gliceridos poliglicolizados;
- (c) polietileno glicoles (PEG);
- (d) grasas duras.

y donde la sal de sulfato de hidrogeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida, es dispersada dentro de la matriz portadora

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
una composición farmacéutica que comprende	Una composición farmacéutica_
sal de sulfato de hidrogeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3 <i>H</i> -benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida	de oxcarbazepina sal de sulfato de hidrogeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3 <i>H</i> -benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida
Una matriz portadora	Disperso en excipientes farmacéuticamente aceptables
D2	
el polietilenglicol (párrafo 545), poliglicosidos son utilizados para mejorar la estabilidad de los principios activos (páginas 24 y 25), y el uso de triglicéridos como excipientes de preparaciones farmacéuticas, el cual puede producir efectos positivos sobre la estabilidad (páginas 453-456)	

El documento D1 se considera el estado de la técnica más cercano a la invención definida en la reivindicación 1 porque divulga, composiciones de una sal de sulfato de hidrogeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida (párrafo 20), las composiciones son útiles para administración oral entre las que se encuentran tabletas, capsulas blandas emulsiones o polvos dispersables (párrafo 44), dicho compuesto se encuentra disperso en excipientes farmacéuticamente aceptables (ejemplo 3)

La diferencia entre la actual invención y la composición de D1 consiste en que la actual invención especifica los vehículos farmacéuticamente aceptables (o agente dispersante), (A) d-alfa-tocoferil polietilenglicol 1000 succinato, (B) glicéridos poliglicosilados, C) polietilenglicoles (PEGs), (D) las grasas sólidas.

El efecto que logra la diferencia es que la sal de sulfato de hidrógeno de 6-(4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3*H*-benzoimidazol-5- ácido carboxílico (2-hidroxi-etoxi)-amida, es estable dentro de estos portadores durante el procesamiento y almacenamiento de productos farmacéuticos.

Por lo tanto, el Problema técnico objetivo a resolver consiste en: “como proporcionar composiciones farmacéuticas estables de la sal de sulfato de hidrógeno de 6 - (4-bromo-2-cloro-fenilamino)-7-fluoro-3-metil-3H-benzoimidazol -5-ácido carboxílico (2-hidroxi-etoxi)-amida

Sin embargo, D2 divulga que el uso de excipientes tales como el polietilenglicol (folios 119-124, páginas 545-550), poliglicósidos son utilizados para mejorar la estabilidad de los principios activos (folios 125-128, páginas 24 y 27), y el uso de triglicéridos como excipientes de preparaciones farmacéuticas, el cual produce efectos positivos sobre la estabilidad (folios 129-131, páginas 453-456)

En consecuencia, la persona normalmente versada en la materia una vez planteado el problema de la presente solicitud, incluiría excipientes tales como el polietilenglicol y poliglicosidos divulgados en D2, en la composición conocida en D1 para llegar así al objeto de la presente solicitud, por lo cual se considera obvia.

Las reivindicaciones dependientes 2-17 no incluyen características que hagan nueva o inventiva la reivindicación uno por lo cual no se considera inventiva.

Conclusión:
La reivindicación 1 cumple el requisito de novedad (Art. 16), y pero no con el requisito de nivel inventivo (Art. 18).

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2007076245	1-17	Nivel Inventivo
D2	Handbook of Pharmaceutical Excipients,	1-17	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 06 NOV. 2012

Elaborado por: Harvey Jaramillo Vergara 
Revisado Por: Jacqueline Alfonso Rozo.

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols
JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000
PhEur: Macrogola
USPNF: Polyethylene glycol

2 Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

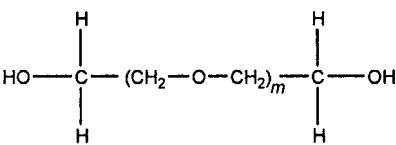
4 Empirical Formula and Molecular Weight

HOCH₂(CH₂OCH₂)_mCH₂OH where *m* represents the average number of oxyethylene groups.
Alternatively, the general formula H(OCH₂CH₂)_nOH may be used to represent polyethylene glycol, where *n* is a number *m* in the previous formula + 1.
See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	<i>m</i>	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.⁽¹⁾
Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; see Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.⁽²⁾ Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.
Mixtures of polyethylene glycols can be used as suppository bases,⁽³⁾ for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.
Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.
Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.
In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.
In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.⁽⁴⁾ However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5%

w/w. When used for thermoplastic granulations,⁽⁵⁻⁷⁾ a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.⁽⁸⁾ Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.⁽⁹⁾ The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin;^(10,11) it has been used in inhalation preparations to improve aerosolization;⁽¹²⁾ polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine;⁽¹³⁾ it has been used in self-assembled polymeric nanoparticles as a drug carrier;⁽¹⁴⁾ and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.⁽¹⁵⁾

8 Description

The USP NF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG >1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density:

1.11–1.14 g/cm³ at 25°C for liquid PEGs;
1.15–1.21 g/cm³ at 25°C for solid PEGs.

Flash point:

182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point:

<–65°C PEG 200 sets to a glass;
–15 to –8°C for PEG 300;
4–8°C for PEG 400;
15–25°C for PEG 600.

Melting point:

37–40°C for PEG 1000;
44–48°C for PEG 1500;
40–48°C for PEG 1540;
45–50°C for PEG 2000;
48–54°C for PEG 3000;
50–58°C for PEG 4000;
55–63°C for PEG 6000;
60–63°C for PEG 8000;
60–63°C for PEG 20000.

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. See Figures 1, 2 and 3.

Particle size distribution: see Figures 4 and 5.

Refractive index:

n_D^{25} = 1.459 for PEG 200;
 n_D^{25} = 1.463 for PEG 300;
 n_D^{25} = 1.465 for PEG 400;
 n_D^{25} = 1.467 for PEG 600.

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%),

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	–
Characters	–	+	–
Acidity or alkalinity	–	+	–
Appearance of solution	–	+	+
Density	–	See Table IV	–
Freezing point	See Table III	See Table IV	–
Viscosity	–	See Table IV	See Table V
Average molecular weight	See Table III	–	See Table V
pH (5% w/v solution)	See Table III	–	4.5–7.5
Hydroxyl value	–	See Table IV	–
Reducing substances	–	+	–
Residue on ignition	See Table III	–	≤0.1%
Sulfated ash	–	≤0.2%	–
Limit of ethylene glycol and diethylene glycol	≤0.25%	≤0.4%	≤0.25%
Ethylene oxide	–	≤1 ppm	≤10 µg/g
1,4-Dioxane	–	≤10 ppm	≤10 µg/g
Heavy metals	–	≤20 ppm	≤5 µg/g
Organic volatile impurities	–	–	+
Water	≤1.0%	≤2.0%	–
Formaldehyde	–	≤15 ppm	–

Table III: Specifications from JP 2001.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	≤0.1%
1500	—	37–41	4.0–7.0	≤0.1%
4000	2 600–3 800	53–57	4.0–7.5	≤0.25%
6000	7 300–9 300	56–61	4.5–7.5	≤0.25%
20000	15 000–25 000	56–64	4.5–7.5	≤0.25%

and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic): see Tables IV, V, and VI.

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.⁽¹⁶⁾ Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Table IV: Specifications from PhEur 2005.

Type of PEG	Density (g/cm ³)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm ² /s (cSt)]
300	1.120	—	340–394	80–105	71–94
400	1.120	—	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	≥57	—	2 700–3 500	2 500–3 200
35000	1.080	≥57	—	11 000–14 000	10 000–13 000

12 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13 Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.^(17–19)

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.⁽²⁰⁾

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.⁽²¹⁾ Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

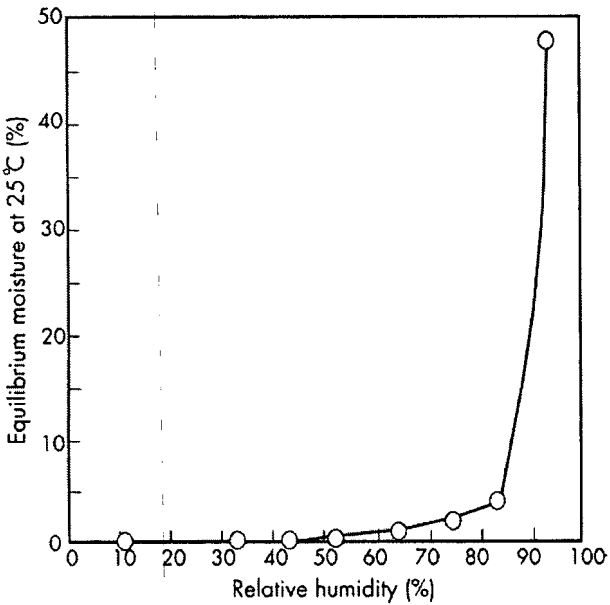


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192-8209) at 25°C.

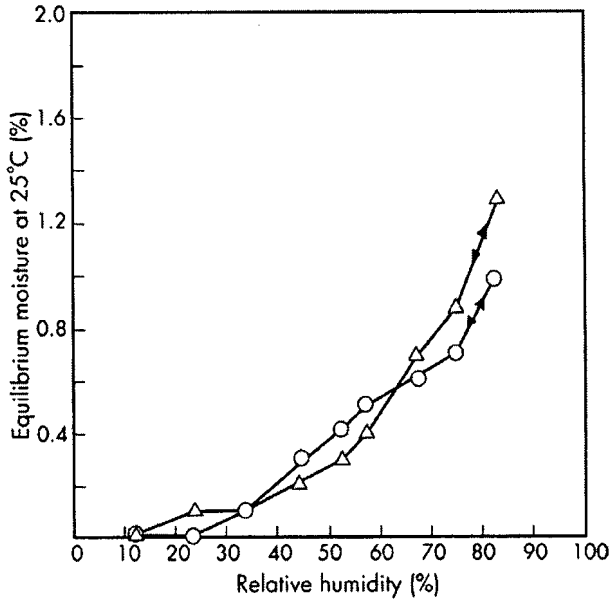


Figure 3: Equilibrium moisture content of PEG 6000 at 25°C.
○: PEG 6000 powder (Union Carbide Corp., Lot no. B-507)
△: PEG E-6000 (BASF, Lot no. WPNA-124B)

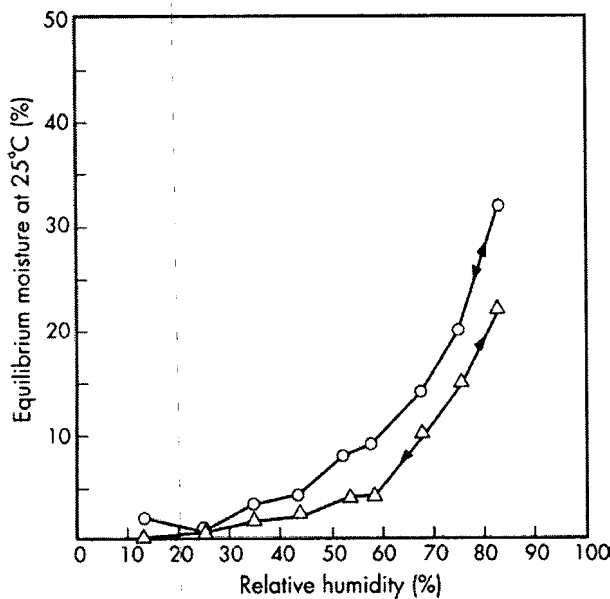


Figure 2: Equilibrium moisture content of PEG 4000 at 25°C.
○: PEG 4000 powder (Union Carbide Corp, Lot no. B-251)
△: PEG E-4000 (BASF, Lot no. WPYA-575B)

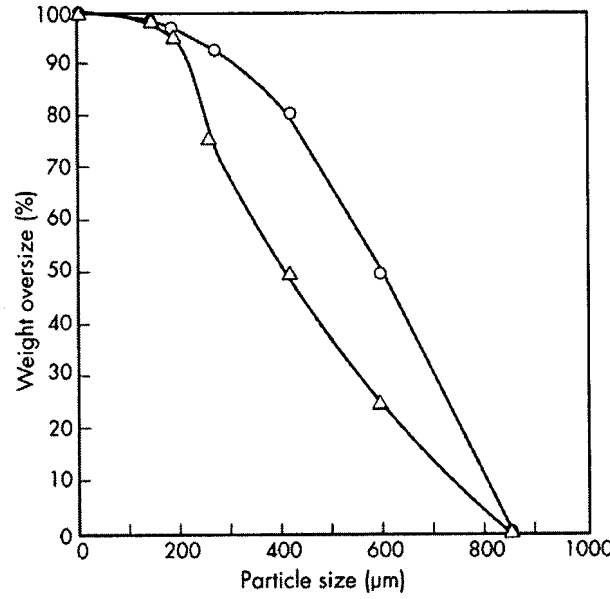


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.
○: PEG 4000 flakes
△: PEG 6000 flakes

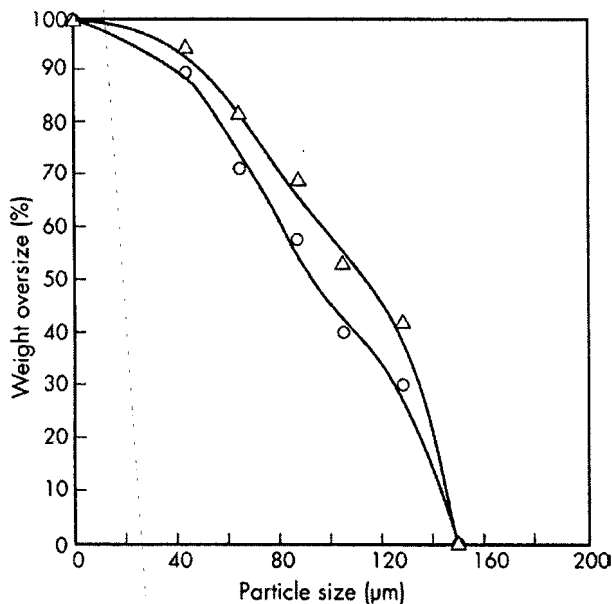


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.
○: PEG 4000 powder
△: PEG 6000 powder

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.⁽²²⁾

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.⁽²³⁾

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data, see Table VII.⁽²⁴⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9°C ± 0.3°C from the USPNF 23.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm ² /s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

Table VI: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm ² /s (cSt)]	
	25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6 900	—

Table VII: Animal toxicity data (LD₅₀) for various grades of polyethylene glycol.⁽²⁴⁾

PEG grade	LD ₅₀ (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	—	7.5	—	34	19.9	—	—	—	28.0
PEG 300	19.6	—	—	—	17.3	—	—	—	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	—
PEG 600	—	—	—	47	—	—	—	—	38.1
PEG 1000	—	20	—	—	—	—	15.6	—	32
PEG 1500	28.9	—	—	—	28.9	8	17.7	—	44.2
PEG 4000	50.9	—	16	—	76	—	11.6	—	50
PEG 6000	50	—	—	—	—	—	6.8	—	—

17 Related Substances

Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

18 Comments

A specification for polyethylene glycol is contained in the Food Chemicals Codex (FCC).

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22 Date of Revision

29 August 2005.

Aliphatic Polyesters

1 Nonproprietary Names

See Table I.

2 Synonyms

See Table I.

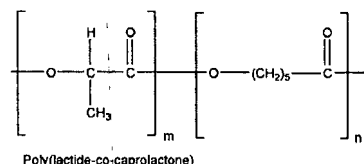
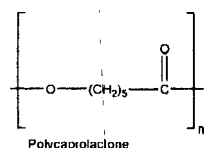
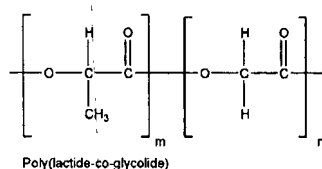
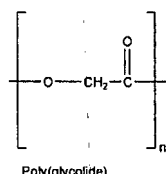
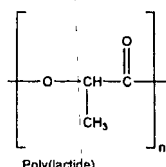
3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

Aliphatic polyesters are synthetic homopolymers or copolymers of lactic acid, glycolic acid, and ϵ -hydroxycaproic acid. Typically, the molecular weights of homopolymers and copolymers range from 2000 to >100 000.

5 Structural Formula



6 Functional Category

Bioabsorbable; biocompatible; biodegradable material.

7 Applications in Pharmaceutical Formulation or Technology

Aliphatic polyesters are a group of synthesized, nontoxic, biodegradable polymers. In an aqueous environment, they undergo hydrolytic degradation, through cleavage of the ester linkages, into nontoxic hydroxycarboxylic acids. Aliphatic polyesters are eventually metabolized to carbon dioxide and water, via the citric acid cycle. Owing to their reputation as safe materials and their biodegradability, aliphatic polyesters are primarily used as biocompatible and biodegradable polymers for formulation of many types of implantable and injectable drug-delivery systems for both human and veterinary use. Examples of implantable drug delivery systems include rods, cylinders, tubing, films,⁽¹⁾ fibers,⁽²⁾ pellets, and beads.⁽³⁾ Examples of injectable drug-delivery systems include microcapsules,⁽⁴⁾ microspheres,⁽⁵⁾ nanoparticles, and liquid injectable controlled-release systems. The rate of biodegradation and drug-release characteristics from these systems formulated with the aliphatic polyesters can be controlled by changing the physicochemical properties of the polymers, such as crystallinity, hydrophobicity, monomer stereochemistry, copolymer ratio, and polymer molecular weight.

8 Description

Aliphatic polyesters are a group of synthesized homopolymers or copolymers. They are nontoxic and can easily be fabricated into a variety of novel devices, such as rods, screws, nails, and cylinders. The polymers are commercially available in varying molecular weights as both homopolymers and copolymers. Molecular weights of polyesters range from 2000 to greater than 100 000.

Co-monomer ratios of lactic acid and glycolic acid for poly(DL-lactide-co-glycolide) range from 85:15 to 50:50. Table I shows the chemical and trade names of different commercially available aliphatic polyesters.

9 Pharmacopeial Specifications

10 Typical Properties

For typical physical and mechanical properties of the aliphatic polyesters, see Table II.

Polymer composition and crystallinity play important roles in the solubility of these aliphatic polyesters. The crystalline homopolymers of glycolic acid are soluble only in strong solvents, such as hexafluoroisopropanol. The crystalline homopolymers of lactic acid also do not have good solubility in most organic solvents. However, amorphous polymers of DL-lactic acid and copolymers of lactic acid and glycolic acid with a low glycolic acid content are soluble in many organic solvents (Table II). Aliphatic polyesters are slightly soluble or insoluble in water, methanol, ethylene glycol, heptane, and hexane.

Table I: Chemical names and CAS registry numbers of the aliphatic polyesters.

Generic name	Composition (%)		Synonyms	Trade name	Manufacturer	CAS name	CAS number
	Lactide	Glycolide					
Poly(DL-lactide)	100	0	0	D-PLA	Purasorb PD	PURAC	(3Rcis)-3,6-Dimethyl-1,4-dioxane-2,5-dione homopolymer [25038-75-9]
Poly(L-lactide)	100	0	0	L-PLA	Lactel L-PLA Medisorb 100 L Purasorb PL Resomer L 206, 207, 209, 210, 214	BPI Alkermes PURAC BI	Propanoic acid, 2-hydroxy-, homopolymer [26161-42-2]
Poly(DL-lactide)	100	0	0	DL-PLA	Lactel DL-PLA Medisorb 100 DL Purasorb PDL Resomer R 202, 202H, 203, 206, 207, 208	BPI Alkermes PURAC BI	Propanoic acid, 2-hydroxy-, homopolymer [34346-01-5]
Poly(glycolide)	0	100	0	PGA	Lactel PGA Medisorb 100 PGA Purasorb PG Resomer G-205	BPI Alkermes PURAC BI	Acetic acid, hydroxy-, homopolymer [34346-01-5]
Poly(L-lactide-co-glycolide)	75	25	0	L-PLGA (75 : 25)	Purasorb PLG	PURAC	1,4-Dioxane-2,5-dione, polymer with (3S)-3,6-dimethyl-1,4-dioxane-2,5-dione [30846-39-0]
Poly(L-lactide-co-glycolide)	50	50	0	L-PLGA (50 : 50)	Purasorb PLG	PURAC	1,4-Dioxane-2,5-dione, polymer with (3S)-3,6-dimethyl-1,4-dioxane-2,5-dione [30846-39-0]
Poly(DL-lactide-co-glycolide)	85	15	0	Polyglactin:DL-PLGA (85:15)	Lactel 8515 DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid [26780-50-7]
Poly(DL-lactide-co-glycolide)	75	25	0	Polyglactin:DL-PLGA (75 : 25)	Medisorb 8515 DL Resomer RG 858 Lactel 7525 DL-PLGA	Alkermes BI BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid [26780-50-7]
Poly(DL-lactide-co-glycolide)	65	35	0	Polyglactin:DL-PLGA (65 : 35)	Purasorb PDIG Resomer RG 752, 755, 756 Lactel 6535 DL-PLGA	PURAC BI BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid [26780-50-7]
Poly(DL-lactide-co-glycolide)	50	50	0	Polyglactin:DL-PLGA (50 : 50)	Lactel 5050 DL-PLGA	BPI	Propanoic acid, 2-hydroxypolymer with hydroxyacetic acid [26780-50-7]
Poly-ε-caprolactone	0	0	100	PCL	Medisorb 5050 DL Purasorb PDIG Resomer RG 502, 502H, 503, 503H, 504, 504H, 505, 506	Alkermes PURAC BI	2-Oxepanone, homopolymer [24980-41-4]
Poly(DL-lactide-co-caprolactone)	75	0	25	DL-PLCL (75 : 25)	Lactel PCL Lactel 7525 DL-PLCL	BPI BPI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 2-oxepanone [70524-20-8]
Poly(DL-lactide-co-caprolactone)	25	0	75	DL-PLCL (25 : 75)	Lactel 2575 DL-PLCL	BPI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 2-oxepanone [70524-20-8]

Alkermes, Alkermes Inc.; BI, Boehringer Ingelheim; BPI, Birmingham Polymers Inc.; PURAC, PURAC America.

Table II: Typical physical and mechanical properties of the aliphatic polyesters.^(a)

	50/50 DL-PLG	65/35 DL-PLG	75/25 DL-PLG	85/15 DL-PLG	DL-PLA	L-PLA	PGA	PCL
Molecular weight	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	> 100 000	> 100 000	80–150 000
Inherent viscosity (mPa s)	0.5–0.8 ^(b)	0.5–0.8 ^(b)	0.5–0.8 ^(c)	0.5–0.8 ^(c)	0.5–0.8 ^(c)	0.9–1.2 ^(c)	1.1–1.4 ^(b)	0.7–1.3 ^(c)
Melting point (°C)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	173–178	225–230	58–63
Glass transition (°C)	45–50	45–50	50–55	50–55	55–60	60–65	35–40	–65 to –60
Color	White to light gold	White to light gold	White to light gold	White to light gold	White	White	Light tan	White
Solubility ^(d)	MeCl ₂ , THF, EtOAc, C ₃ H ₆ O, CHCl ₃	MeCl ₂ , THF, EtOAc, C ₃ H ₆ O, CHCl ₃	MeCl ₂ , THF, EtOAc, C ₃ H ₆ O, CHCl ₃	MeCl ₂ , THF, EtOAc, C ₃ H ₆ O, CHCl ₃	MeCl ₂ , THF, EtOAc, C ₃ H ₆ O, CHCl ₃	MeCl ₂ , CHCl ₃	HFIP, HFASH	MeCl ₂ , CHCl ₃ , C ₃ H ₆ O
Specific gravity	1.34	1.30	1.30	1.27	1.25	1.24	1.53	1.11
Tensile strength (psi)	6000–8000	6000–8000	6000–8000	6000–8000	4000–6000	8000–12 000	10 000+	3000–5000
Elongation (%)	3–10	3–10	3–10	3–10	3–10	5–10	15–20	300–500
Modulus (psi)	2–4 × 10 ⁵	2–4 × 10 ⁵	2–4 × 10 ⁵	2–4 × 10 ⁵	2–4 × 10 ⁵	4–6 × 10 ⁵	1 × 10 ⁶	3–5 × 10 ⁴

Note. DL-PLG: D,L-poly(lactico-glycolic acid); DL-PLA: D,L-poly(lactic acid); L-PLA: L-poly(lactic acid); PGA: polyglycolic acid; PCL: poly-ε-caprolactone.
^(a) Specifications obtained from Birmingham Polymers, Inc.
^(b) [HFIP] hexafluoroisopropanol.
^(c) [CHCl₃] chloroform.
^(d) Partial listing only. MeCl₂, methylene chloride; THF, tetrahydrofuran; EtOAc, ethyl acetate; HFIP, hexafluoroisopropanol; HFASH, hexafluoroacetone sesquihydrate; C₃H₆O, acetone.

11 Stability and Storage Conditions

The aliphatic polyesters are easily susceptible to hydrolysis in the presence of moisture. Hence, they should be properly stored, preferably refrigerated at below 0°C. It is necessary to allow the polymers to reach room temperature before opening the container. After the original package has been opened, it is recommended to re-purge the package with high-purity dry nitrogen prior to resealing.

12 Incompatibilities

13 Method of Manufacture

Generally, aliphatic polyesters can be synthesized via polycondensation of hydroxycarboxylic acids and catalytic ring-opening polymerization of lactones. Ring-opening polymerization is preferred because polyesters with high molecular weights can be produced. Moreover, the dehydration of hydroxycarboxylic acids to form lactones does not have to be carried to a high degree of completion. Lactones can easily be purified owing to the differences of their physical and chemical properties from those of the corresponding hydroxycarboxylic acid.

14 Safety

Poly(lactide), poly(glycolide), poly(lactide-co-glycolide), and polycaprolactone are used in parenteral pharmaceutical formulations and are regarded as biodegradable, biocompatible, and bioabsorbable materials. Their biodegradation products are nontoxic, noncarcinogenic, and nonteratogenic. In general, these polyesters exhibit very little hazard.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Contact with eyes, skin, and clothing, and breathing the dust of the polymers should be avoided. Aliphatic polyesters produce acid materials such as hydroxyacetic and/or lactic acid in the presence of moisture; thus, contact with materials that will react with acids, especially in moist conditions, should be avoided.

16 Regulatory Status

GRAS listed. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Lactic acid.

18 Comments

Due to their ability to form complexes with heavy metal ions, aliphatic polyesters are added to skin-protective ointments.⁽⁶⁾

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21 Authors

RK Chang, AJ Shukla, Y Sun.

22 Date of Revision

26 August 2005.

Medium-chain Triglycerides

1 Nonproprietary Names

BP: Medium-chain triglycerides

PhEur: Triglycerida saturata media

USPNF: Medium-chain triglycerides

2 Synonyms

Bergabest; caprylic/capric triglyceride; *Captex 300*; *Captex 355*; *Crodamol GTC/C*; glyceryl tricaprylate/caprate; *Labrafac CC*; MCT oil; *Miglyol 810*; *Miglyol 812*; *Myritol*; *Neobee M5*; *Nesatol*; oleum neutrale; oleum vegetable tenue; thin vegetable oil; *Waglinol 3/9280*.

3 Chemical Name and CAS Registry Number

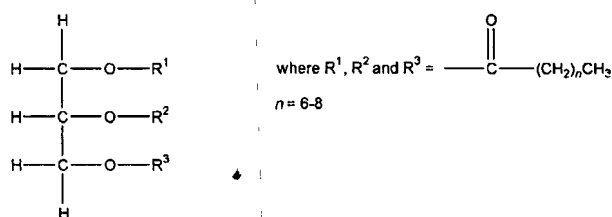
Medium-chain triglycerides [73398-61-5]

4 Empirical Formula and Molecular Weight

≈500 (average)

The PhEur 2005 describes medium-chain triglycerides as the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and of capric acid. They contain not less than 95% of saturated fatty acids.

5 Structural Formula



See also Section 4.

6 Functional Category

Emulsifying agent; solvent; suspending agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Medium-chain triglycerides have been used in a variety of pharmaceutical formulations including oral, parenteral, and topical preparations.

In oral formulations, medium-chain triglycerides are used as the base for the preparation of oral emulsions, microemulsions, self-emulsifying systems, solutions, or suspensions of drugs that are unstable or insoluble in aqueous media, e.g. calciferol. Medium-chain triglycerides have also been investigated as intestinal-absorption enhancers^(1,2) and have additionally been

used as a filler in capsules and sugar-coated tablets, and as a lubricant or antiadhesion agent in tablets.

In parenteral formulations, medium-chain triglycerides have similarly been used in the production of emulsions, solutions, or suspensions intended for intravenous administration.⁽³⁻⁹⁾ Medium-chain triglycerides have been particularly investigated for their use in total parenteral nutrition (TPN) regimens in combination with long-chain triglycerides.⁽⁴⁾

In cosmetics and topical pharmaceutical preparations, medium-chain triglycerides are used as a component of ointments, creams, and liquid emulsions.⁽⁵⁾ In rectal formulations, medium-chain triglycerides have been used in the preparation of suppositories containing labile materials.

Therapeutically, medium-chain triglycerides have been used as nutritional agents.⁽¹⁰⁾ Diets containing medium-chain triglycerides are used in conditions associated with the malabsorption of fat, such as cystic fibrosis, since medium-chain triglycerides are more readily digested than long-chain triglycerides. Medium-chain triglycerides provide 35 kJ (8.3 kcal) of energy per gram.

Although similar to long-chain triglycerides, medium-chain triglycerides have a number of advantages in pharmaceutical formulations, which include better spreading properties on the skin; no impedance of skin respiration; good penetration properties; good emollient and cosmetic properties; no visible film on the skin surface; good compatibility; good solvent properties; and good stability against oxidation.

8 Description

A colorless to slightly yellowish oily liquid that is practically odorless and tasteless. It solidifies at about 0°C. The oil is free from catalytic residues or the products of cracking.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acid value:

- ≤0.1 for *Crodamol GTC/C*;
- ≤0.1 for *Miglyol 810*;
- ≤0.1 for *Miglyol 812*;
- ≤0.05 for *Neobee M5*.

Cloud point:

- ≤5°C for *Crodamol GTC/C*;
- ≈10°C for *Miglyol 810*;
- ≈10°C for *Miglyol 812*.

Color:

- ≤60 (Hazen color index) for *Crodamol GTC/C*;
- ≤90 (Hazen color index) for *Miglyol 810*;
- ≤60 (Hazen color index) for *Miglyol 812*;
- ≤100 (Hazen color index) for *Neobee M5*.

Density:

- 0.94–0.96 g/cm³ for *Crodamol GTC/C* at 20°C;
- 0.94–0.95 g/cm³ for *Miglyol 810* at 20°C;
- 0.94–0.95 g/cm³ for *Miglyol 812* at 20°C;
- 0.94 g/cm³ for *Neobee M5* at 20°C.

Table I: Pharmacopeial specifications for medium-chain triglycerides.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Appearance	+	+
Alkaline impurities	+	+
Relative density	0.93–0.96	0.93–0.96
Refractive index	1.440–1.452	1.440–1.452
Viscosity	25–33 mPa s	25–33 mPa s
Acid value	≤0.2	≤0.2
Hydroxyl value	≤10	≤10
Iodine value	≤1.0	≤1.0
Peroxide value	≤1.0	≤1.0
Saponification value	310–360	310–360
Unsaponifiable matter	≤0.5%	≤0.5%
Composition of fatty acids		
Caproic acid	≤2.0%	≤2.0%
Caprylic acid	50.0–80.0%	50.0–80.0%
Capric acid	20.0–50.0%	20.0–50.0%
Lauric acid	≤3.0%	≤3.0%
Myristic acid	≤1.0%	≤1.0%
Heavy metals ^(a)	≤10 ppm	≤10 ppm
Water	≤0.2%	≤0.2%
Total ash	≤0.1%	≤0.1%
Chromium	≤0.05 ppm	≤0.05 ppm
Copper ^(a)	≤0.1 ppm	≤0.1 ppm
Lead ^(a)	≤0.1 ppm	≤0.1 ppm
Nickel ^(a)	≤0.2 ppm	≤0.1 ppm
Tin ^(a)	≤0.1 ppm	≤0.1 ppm

^(a)For medium-chain triglycerides intended for use in parenteral nutrition, the test for heavy metals is replaced by the tests for chromium, copper, lead, nickel, and tin.

Freezing point: −5°C for *Neobee M5*

Hydroxyl value: ≤8 for *Neobee M5*

Iodine number:

- ≤1.0 for *Crodamol GTC/C*;
- ≤0.5 for *Miglyol 810*;
- ≤0.5 for *Miglyol 812*;
- ≤0.5 for *Neobee M5*.

Moisture content:

- ≤0.15% w/w for *Crodamol GTC/C*;
- ≤0.10% w/w for *Miglyol 810*;
- ≤0.10% w/w for *Miglyol 812*;
- ≤0.15% w/w for *Neobee M5*.

Peroxide value:

- ≤1.0 for *Miglyol 810*;
- ≤1.0 for *Miglyol 812*;
- ≤0.5 for *Neobee M5*.

Refractive index:

- 1.4485–1.4500 for *Crodamol GTC/C* at 20°C;
- 1.4485–1.4505 for *Miglyol 810* at 20°C;
- 1.4490–1.4510 for *Miglyol 812* at 20°C;
- 1.4480–1.4510 for *Neobee M5* at 20°C.

Saponification value:

- 325–345 for *Crodamol GTC/C*;
- 335–355 for *Miglyol 810*;
- 325–345 for *Miglyol 812*;
- 335–360 for *Neobee M5*.

Solubility: soluble in all proportions at 20°C in acetone, benzene, 2-butanone, carbon tetrachloride, chloroform, dichloromethane, ethanol, ethanol (95%), ether, ethyl acetate, petroleum ether, special petroleum spirit (boiling range 80–110°C), propan-2-ol, toluene, and xylene. Mis-

cible with long-chain hydrocarbons and triglycerides; practically insoluble in water.

Surface tension:

- 32.2 mN/m for *Crodamol GTC/C* at 25°C;
- 31.0 mN/m for *Miglyol 810* at 20°C;
- 31.1 mN/m for *Miglyol 812* at 20°C;
- 32.3 mN/m for *Neobee M5* at 25°C.

Viscosity (dynamic):

- 27–30 mPa s (27–30 cP) for *Miglyol 810* at 20°C;
- 28–32 mPa s (28–32 cP) for *Miglyol 812* at 20°C;
- 23 mPa s (23 cP) for *Neobee M5* at 25°C.

11 Stability and Storage Conditions

Medium-chain triglycerides are stable over the wide range of storage temperatures that can be experienced in tropical and temperate climates. Ideally, however, they should be stored at temperatures not exceeding 25°C and not exposed to temperatures above 40°C for long periods.

In the preparation of microemulsions and self-emulsifying systems, emulsions, or aqueous suspensions of medium-chain triglycerides, care should be taken to avoid microbiological contamination of the preparation, since lipase-producing microorganisms, which become active in the presence of moisture, can cause hydrolysis of the triglycerides. Hydrolysis of the triglycerides is revealed by the characteristic unpleasant odor of free medium-chain fatty acids.

Medium-chain triglycerides may be sterilized by maintaining at 170°C for 1 hour.

At low temperatures, samples of medium-chain triglycerides may become viscous or solidify. Samples should therefore be well melted and mixed before use, although overheating should be avoided.

Medium-chain triglycerides should be stored protected from light in a well-filled and well-closed container. When stored dry, in sealed containers, medium-chain triglycerides remain stable for many years.

12 Incompatibilities

Preparations containing medium-chain triglycerides should not come into contact with polystyrene containers or packaging components since the plastic rapidly becomes brittle upon contact. Low-density polyethylene should also not be used as a packaging material as the medium-chain triglycerides readily penetrate the plastic, especially at high temperatures, forming an oily film on the outside. High-density polyethylene is a suitable packaging material. Closures based on phenol resins should be tested before use for compatibility with medium-chain triglycerides. Polyvinyl chloride packaging should also be tested for compatibility since medium-chain triglycerides can dissolve some plasticisers, such as phthalates, out of the plastic.

Materials recommended as safe for packaging medium-chain triglycerides are low-density polyethylene, polypropylene, glass, and metal.

13 Method of Manufacture

Medium-chain triglycerides are obtained from the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. Hydrolysis of the fixed oil followed by distillation yields the required fatty acids, which are then re-esterified to produce the medium-chain triglycerides.

Although the PhEur 2005 specifies that medium-chain fatty acids are obtained from coconut oil, medium-chain triglycerides are also to be found in substantial amounts in the kernel

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oils of certain other types of palm-tree, e.g., palm kernel oil and babassu oil. Some animal products, such as milk-fat, also contain small amounts (up to 4%) of the medium-chain fatty acid esters.

14 Safety

Medium-chain triglycerides are used in a variety of pharmaceutical formulations including oral, parenteral, and topical products and are generally regarded as essentially nontoxic and nonirritant materials.

In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed; for example, when they were patch-tested on more than 100 individuals, no irritation was produced on either healthy or eczematous skin. Medium-chain triglycerides are not irritating to the eyes.

Similarly, chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglycerides following inhalation or intraperitoneal, oral, and parenteral administration.

In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein.

In patients consuming diets based on medium-chain triglycerides, adverse effects reported include abdominal pain and diarrhea.

LD₅₀ (mouse, IV): 3.7 g/kg
 LD₅₀ (mouse, oral): 29.6 g/kg
 LD₅₀ (rat, oral): 33.3 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (topical preparations). Included in nonparenteral and parenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Suppository bases, hard fat; vegetable oil, hydrogenated.

18 Comments

19 Specific References

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20 General References

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22 Date of Revision

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