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Señor Director

División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Industria y Turismo

E. S. D.

Re.: Expediente **No. 10 053419**

Solicitud de Patente de invención para: **"COMPOSICIONES OFTALMICAS QUE COMPRENDEN DERIVADOS DE PROSTAGLANDINA"**

Solicitante: **SUN PHARMA ADVANCED RESEARCH COMPANY LIMITED**

RESPUESTA AL EXAMEN DE FONDO

Yo, **Margarita Castellanos Abondano**, identificada como aparece al pie de mi firma, atentamente me permito presentar respuesta al oficio **No.19983** notificado por fijación en lista del 6 de noviembre de 2012, en los siguientes términos:

De la solicitud de patente

Su Despacho concluye que el pliego reivindicatorio de la presente solicitud de patente no cumple con las disposiciones del artículo 30 de la Decisión 486. El Examinador señala lo siguiente:

- "De acuerdo con lo revelado en el capítulo reivindicatorio, en la reivindicación 1 no se especifica el derivado de prostaglandina así como el vehículo farmacéuticamente aceptable que hagan diferente la composición de las ya conocidas".

Con el fin de atender las observaciones formuladas a este respecto, y de acuerdo con el artículo 34 de la Decisión 486, se presenta un nuevo capítulo reivindicatorio conformado por 6 reivindicaciones como sustituto del anteriormente presentado. De tal manera que, las objeciones formuladas a este respecto se deben tener por superadas de la siguiente manera:

- Se ha redactado nuevamente el pliego reivindicatorio, de conformidad con las sugerencias del Señor Examinador y se ha limitado de forma significativa el alcance dela reivindicación 1 especificando el derivado de prostaglandina y las proporciones en que se encuentra el mismo en la composición. Por lo tanto, la objeción formulada a este respecto se debe tener por superada.

- Adicionalmente, se pone de presente que la materia de invención incluida en la reivindicación 1 modificada se encuentra debidamente sustentada en el pliego descriptivo tal como fue originalmente presentado (ver reivindicación 6 original y página 5, líneas 34-37 de la publicación internacional; página 6, líneas 28-34 de la publicación internacional; página 7, líneas 26-28 de la publicación internacional).

Así entonces, teniendo en cuenta las modificaciones efectuadas al capítulo reivindicatorio, consideramos que las objeciones que por claridad hizo su Despacho quedan superadas ya que el nuevo capítulo reivindicatorio se encuentra redactado en los términos sugeridos por su Despacho y el mismo es ahora claro, conciso y la materia reivindicada se encuentra debidamente soportada en la descripción.

Nivel inventivo

Su Despacho concluye que los documentos WO2006050836 (D1) y US5849792 (D2) afectan el nivel inventivo de la presente solicitud de patente. En particular, el Examinador señala lo siguiente:

- "La diferencia entre la invención definida en la reivindicación 1 y la composición del documento D1 consiste en que no está especifico el ácido graso con el cual está el polioxietileno".

- "La diferencia entre la invención definida en la reivindicación 1 y la composición del documento D2 consiste en que no se menciona específicamente el ácido graso con el cual está el PEG 15".

- "El efecto que confiere la diferencia es que reduce la adsorción de los derivados de prostaglandina en el envase durante el almacenamiento en contenedores".

- "Sin embargo, la utilización de estabilizantes tipo polietilenglicol o derivados polioxietilados para mejorar la estabilidad de los fármacos con los cuales se encuentran en una formulación dada, ya está divulgada en el documento D2 que se refiere a composiciones de prostaglandinas estables al almacenamiento (Resumen) y que emplean aceite de ricino polietoxilado clasificado como aceite de ricino PEG15 (Col 2, líneas 11-23); tener en cuenta que es sabido por la persona del oficio normalmente versada en la materia que el ácido 12-hidroxiesteárico polietoxilado es el mismo polietilenglicol 15-hidroxiestearato y que es ampliamente utilizado como estabilizante en formulaciones liquidas, por ejemplo, para administración vía parenteral o para preparaciones oftálmicas".

- "En consecuencia, era obvio para la persona del oficio normalmente versada en la materia referirse a las enseñanzas divulgadas en el documento D2 con el fin de mejorar la estabilidad de prostaglandinas en composiciones farmacéuticas oftálmicas descritas en el documento D1 para llegar así al objeto de la reivindicación 1".

- "En ausencia de un efecto inesperado mostrado por las composiciones reivindicadas en relación con las formulaciones del arte anterior, la solución al problema técnico parece ser obvia a la luz de los documentos D1 y D2".

En cuanto a las objeciones del examinador deseamos poner de presente lo siguiente:

De acuerdo con el artículo 18 de la Decisión 486:

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

De conformidad con los anteriores artículos, se exponen a continuación las razones por las cuales la presente invención posee nivel inventivo frente a las enseñanzas de los documentos D1 y D2:

El problema planteado en la presente solicitud consiste en la necesidad de proporcionar composiciones oftálmicas que comprenden derivados de prostaglandina que, durante el almacenamiento no presenten pérdidas del fármaco. Este problema es el que precisamente soluciona la presente invención toda vez que las composiciones de la presente solicitud presentan los efectos deseados.

Ninguno de los documentos D1 y D2 citados por su Despacho enseña o sugiere el uso del "poli etilenglicol hidroxi estereato". Asimismo, el surfactante divulgado en D1 y D2 es químicamente diferente del surfactante polietilen glicol hidroxiestereato. En efecto, el surfactante de la composición acá reivindicada es un derivado del poli etilenglicol del ácido 12-hidroxiestearico.

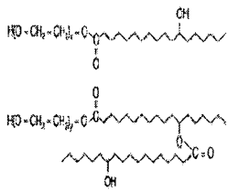
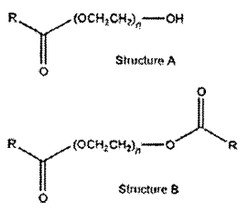
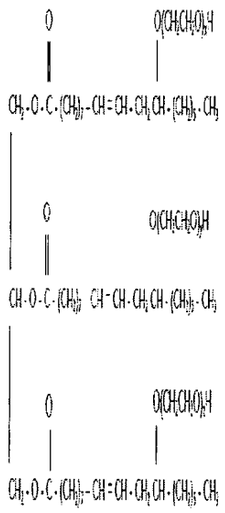
Los documentos D1 y D2 divulgan derivados del polioxietileno aceite de ricino como surfactantes, el cual corresponde a un derivado polioxietileno del aceite de ricino en lugar de un derivado polioxietileno del ácido 12-hidroxiestearico tal como se reivindica en la presente solicitud.

Adicionalmente, D1 también divulga el polioxilestereato el cual es un derivado poli etoxilado del ácido esteárico en lugar de un derivado polioxietileno del ácido 12- hidroxi esteárico.

A continuación se presentan las diferencias entre el polietilenglycol 15 hidroxiestereato y el polioxilestereato y derivados polioxietileno aceite de ricino:

[USP 34 NF Monograph: Polyethyleneglycol 15 Hydroxystearate (seeAnnexure I); USP 34 NF Monografía de polioxilestereato (Ver anexo II) y USP 34 NF Monografía derivado polioxietileno aceite de ricino (Ver anexo III).

Diferencia	**Presente invención**: Anexo I Polietilenglycol 15 hidroxiestereato (Solutol HS 15)	**Anexo II** Polioxilestereato (e.g. Polioxil 40 estereato,Polioxil 8 estereato, Polioxil 100 estereato)	**AnexoIII**Derivado Polioxietileno aceite de ricino (polioxil 35 aceite de ricino)
Composición	Consiste de poliglicol mono y di ester de ácido 12-hidroxiestearico (parte lipofilica) y aproximadamente 30% de propilenglycol libre (parte hidrofilica)	**Polioxil 40estereato** es una mezcla de mono-esteres y di-esteres del ácido estearico con dioles de polioxietilenos mezclados, la longitud promedio del polímero es equivalente a 40 unidades oxietileno	**Polioxil 35 aceite de ricino (Cremofor EL),** los constituyentes hidrofobicos comprenden aproximadamente 83% de la mezcla total, el componente principal es , the relatively hydrophobic constituents comprise about 83% of the total mixture, the main component being polietilenglicolricinoleato de glycerol
Formula estructural	Poietilen glicol 15 hidroxiestereato • Poliollibre HO(CH2CH2O)n H • Monoester ROHCOO(CH2CH2O)	**Polioxil 40 Estearato:** • poliollibre HO(CH2CH2O)n H • monoester RCOO(CH2CH2O)n H	Derivado Polioxietilen aceite de ricino

	n H • Diester (CH2CH2O)n OCROH • Grupo 12 hidroxieterificado de ácido hidroxiestearico con PEG ROCOO(CH2CH2O)n H ROHCO 	• diester RCOO(CH2CH2O)n OCR  La estructura A aplica al monoestereato; en donde el valor promedio de n es 6 para polioxil 6 estereato, 8 para polioxil 8 estereato, etc. La estructura B aplica para un distereato, en donde el valor promedio de n es 12 para polioxil 12 distereato, 32 para polioxil 32 distereato, etc. En ambas estructuras, R representa el grupo alquilo del acido graso parental. Con el ácido esteárico R esCH3(CH2)16.	
HLB	• 14 a 16	Polioxil 40 estereato: 16.9	Polioxil 35 aceite de ricino (Cremofor EL): 12-14
Método de manufactura	-Obtenido por medio de la etoxilación de ácido 12-hidroxiestearico. -Macrogol 15 hidroxiestereato es producido reaccionado 15 moles de oxido de etileno con 1 mol de ácido 12-hidroxiestearico	.Producido por polietoxilación del ácido estearico -Los polioxietilenestereatos son preparados por la reacción directa de ácidos grasos, particularmente ácido esteárico, con óxido de etileno	-Los derivados de polioxietileno aceite de ricino son preparados reaccionando cantidades variables de oxido de etileno con ya sea aceite de ricino o aceite de ricino hidrogenado bajo condiciones controladas.. -Polioxil aceite de ricino es producido reaccionando 1 mol de aceite de ricino con 35-40 moles de oxido de etileno.

Los anexos I y II se diferencian de forma significativa entre el surfactante poli etilenglicol hidroxi estearato y el surfactante poli oxil estereato divulgado en D1. Los anexos I y III claramente diferencian el surfactante polietilen glicol hidroxi estereato y el surfactante derivado de polioxietileno aceite de ricino divulgado en D1 y D2. A este respecto, vale la pena resaltar que el Examinador ha cometido un error al considerar ambos estabilizantes como el mismo (i.e. polietilen glicol hidroxiestearato y aceite de ricino polietoxilado).

Adicionalmente, se pone de presente que con la presente invención se encontró de forma sorprendente que la cantidad de surfactante reivindicada (entre 0.001% y 3.0% p/v) con una pequeña cantidad de aceite cuando son incluidos en una composición farmacéutica, reduce la adsorción del derivado de prostaglandina en los contenedores de polietileno (ver páginas 16-17 de la solicitud internacional).

De modo que, es claro el salto tecnológico de las composiciones reivindicadas frente a composiciones similares conocidas en el estado de la técnica y por consiguiente, se debe tener por superada la objeción formulada por nivel inventivo toda vez que tal como lo señala el Manual para el examen de solicitudes de patentes de invención en las oficinas de propiedad industrial de los países de la comunidad andina,en su inciso 10.8.1.a:

"un compuesto químico o composición química tiene nivel inventivo cuando:

- *El compuesto tiene una estructura inesperada (caso poco frecuente); o,*
- ***Presenta un efecto inesperado, (es el caso más frecuente sobre todo se el compuesto es similar a otros del estado de la técnica). El efecto inesperado puede ser completamente diferente de los descritos para los compuestos similares conocidos, o bien ser igual pero con una mejora en los resultados"***

Así entonces, teniendo en cuenta que las enseñanzas de la anterioridades D1 y D2 citadas por su Despacho no llevan a un técnico versado en la materia a

obtener la composición acá reivindicada toda vez que no enseñan ni sugieren como un todo las características técnicas esenciales de las mismas y que las composiciones reivindicadas presentan un efecto mejorado e inesperado en comparación con composiciones similares del estado de la técnica, es claro que a partir de dichos documentos no era posible para un técnico medio obtener de manera obvia y/o evidente la presente invención.

Dado que la presente solicitud cumple con las disposiciones de los artículos 30 y 18 de la Decisión 486, respetuosamente solicito a ese Despacho que se proceda con la concesión de la presente solicitud.

Anexos

Nuevo capítulo reivindicatorio conformado por 6 reivindicaciones.

Señor Director,

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REIVINDICACIONES

1. Una composición farmacéutica adecuada para uso oftálmico que comprende uno o más derivados de prostaglandina o sales seleccionadas del grupo que consiste de bimatoprost, travoprost, latanoprost y unoprostona, un poli etilenglicol hidroxi estearato en una cantidad entre 0.001% a 3.0% p/v y un vehículo farmacéuticamente aceptable, comprendiendo excipientes seleccionados del grupo que consiste de preservantes, agentes osmóticos, agentes amortiguadores, agentes ajustadores de pH y potenciadores de la viscosidad.

2. Una composición farmacéutica como se reivindica en la reivindicación 1 en donde el poli etilenglicol hidroxi estearato contiene poliglicol éster del ácido 12-hidroxiestearico como el componente hidrofóbico y polietilenglicol como el componente hidrofílico.

3. Una composición farmacéutica como se reivindica en la reivindicación 1 en donde la composición farmacéutica además comprende uno o más aceites.

4. Una composición farmacéutica como se reivindica en la reivindicación 3 en donde el aceite es aceite de ricino.

5. Una composición farmacéutica como se reivindica en la reivindicación 3 en donde la relación de aceite a poli etilenglicol hidroxi estearato es menos de 1.0.

6. Una composición farmacéutica como se reivindica en la reivindicación 1 en donde el vehículo farmacéuticamente aceptable está libre de compuestos de amonio cuaternario.

Annexure-I

Macrogol 15 Hydroxystearate

1 Nonproprietary Names

BP: Macrogol 15 hydroxystearate
PhEur: Macrogoli 15 hydroxystearas

2 Synonyms

12-Hydroxyoctadecanoic acid polymer with α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl); polyethylene glycol 660 12-hydroxystearate; *Solutol HS 15*.

3 Chemical Name and CAS Registry Number

Polyethylene glycol-15-hydroxystearate [70142-34-6]

4 Empirical Formula and Molecular Weight

The PhEur 2005 describes macrogol 15 hydroxystearate as a mixture of mainly monoesters and diesters of 12-hydroxystearic acid and macrogols obtained by the ethoxylation of 12-hydroxystearic acid. The number of moles of ethylene oxide reacted per mole of 12-hydroxystearic acid is 15 (nominal value). It contains about 30% free macrogols.

5 Structural Formula

See Section 4.

6 Functional Category

Dissolution enhancer; nonionic surfactant; solubilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Macrogol 15 hydroxystearate is frequently used in preclinical testing of drugs, mainly for IV and other parenteral applications.[1–4] The solubilizing capacity for some tested drugs (clotrimazole, carbamazepine, 17β-estradiol, sulfathiazole, and piroxicam) increases almost linearly with increasing concentration of solubilizing agent; *see* Figure 1. This is due to the formation of spherical micelles even at high concentrations of macrogol 15 hydroxystearate. Similarly, tests have revealed that viscosity increases with increasing amount of solubilizer, but the amount of solubilized drugs does not have any additional influence on the kinematic viscosity; *see* Figure 2. Lipid nanocapsules comprising macrogol 15 hydroxystearate and soybean phosphatidylcholine containing 3% docetaxel have been successfully prepared by a solvent-free inversion process.

8 Description

Macrogol 15 hydroxystearate is a yellowish-white waxy mass at room temperature, which becomes liquid at approximately 30°C.

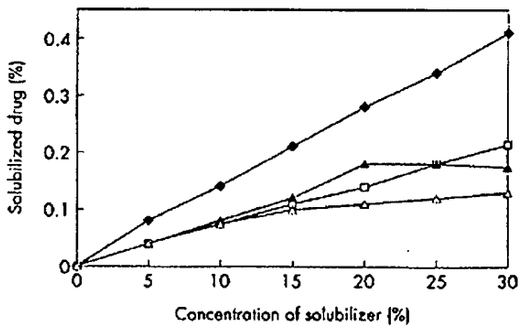

Figure 1: Solubilizing capacity of macrogol 15 hydroxystearate (*Solutol HS 15*, BASF Plc).
◆: *Solutol HS 15* with clotrimazole
□: *Solutol HS 15* with 17β-estradiol
▲: Polysorbate 80 with clotrimazole
△: Polysorbate 80 with 17β-estradiol

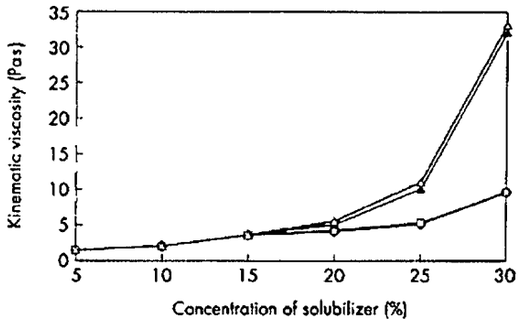

Figure 2: Kinematic viscosity of macrogol 15 hydroxystearate (*Solutol HS 15*, BASF Plc).
◆: *Solutol HS 15*
□: *Solutol HS 15* with clotrimazole
▲: Polysorbate 80
△: Polysorbate 80 with clotrimazole

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 6–7 (10% w/v aqueous solution at 20°C)
Critical micelle concentration: 0.005–0.02%
Density: 1.03 g/cm^3
Flash point: 272°C
HLB value: 14–16
Ignition temperature: 360°C

Table I: Pharmacopeial specifications for macrogol 15 hydroxystearate.

Test	PhEur 2005
Identification	+
Characters	+
Solution appearance	+
Acid value	≤1.0
Hydroxyl value	90–110
Iodine value	≤2.0
Peroxide value	≤5.0
Saponification value	53–63
Free macrogols	27.0–39.0%
Ethylene oxide	≤1 ppm
Dioxane	≤50 ppm
Nickel	≤1 ppm
Water	≤1%
Total ash	≤0.3%

Solidification temperature: 25–30°C

Solubility: soluble in ethanol, propan-2-ol, and water to form clear solutions. The solubility in water decreases with increasing temperature. It is insoluble in liquid paraffin.

Viscosity (dynamic): 12 mPa s (12 cP) for a 30% w/v aqueous solution at 25°C; 73 mPa s (73 cP) for a 30% w/v aqueous solution at 60°C.

11 Stability and Storage Conditions

Macrogol 15 hydroxystearate has a high chemical stability. The prolonged action of heat may induce physical separation into a liquid and a solid phase after cooling, which can be reversed by subsequent homogenization. Macrogol 15 hydroxystearate is stable for at least 24 months if stored in unopened airtight containers at room temperature (maximum 25°C). Aqueous solutions of macrogol 15 hydroxystearate can be heat-sterilized (121°C, 2.1 bar). The pH may drop slightly during heating, which should be taken into account. Separation into phases may also occur, but agitating the hot solution can reverse this. Aqueous solutions can be stabilized with the standard preservatives used in pharmaceuticals.

12 Incompatibilities

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13 Method of Manufacture

Macrogol 15 hydroxystearate is produced by reacting 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid.

14 Safety

Macrogol 15 hydroxystearate is used in parenteral pharmaceutical preparations in concentrations up to 50% to solubilize diclofenac, propanidid, and vitamin K1. It has also been used in preclinical formulations in preparing supersaturated injectable formulations of water-insoluble molecules. It is generally regarded as a relatively nontoxic and nonirritant excipient.

Macrogol 15 hydroxystearate is reported to not be mutagenic in bacteria, mammalian cell cultures and mammals.

LD_{50} (rat, oral): >20 g/kg[5]

15 Handling Precautions

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

16 Regulatory Status

—

17 Related Substances

Polyethylene glycol.

18 Comments

Macrogol 15 hydroxystearate is not restricted solely to parenteral use, but is also suitable for oral applications.

19 Specific References

1 von Corswant C, Thoren P, Engström S. Triglyceride-based microemulsion for intravenous administration of sparingly soluble substances. *J Pharm Sci* 1998; 87: 200–208.

2 Buszello K, Harnisch S, Müller RH, Müller BW. The influence of alkali fatty acids on the properties and the stability of parenteral O/W emulsions modified with Solutol HS 15. *Eur J Pharm Biopharm* 2000; 49: 143–149.

3 Bittner B, Mountfield RJ. Formulations and related activities for the oral administration of poorly water-soluble compounds in early discovery animal studies. *Pharm Ind* 2002; 64: 800.

4 Strickley R. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004; 21: 201–230.

5 BASF. Solutol HS 15. http://www.pharma-solutions.basf.com/(50jqle450ewrum55koxl2kmy)/products.aspx?GrpID=60 (accessed 18 May 2005).

20 General References

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Frömming K-H, Kraus C, Mehnert W. Physico-chemical properties of the mixed micellar system of Solutol HS 15 and sodium deoxycholate. *Acta Pharm Technol* 1990; 36: 214–220.

Lorenz W, Schmal A, Schult H, *et al.* Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: analysis of various components in Cremophor EL and development of a compound with reduced toxicity. *Agents Actions* 1982; 12: 64–80.

Smith DB, Ewen C, Mackintosh J, *et al.* A phase I and pharmacokinetic study of amphethinile. *Br J Cancer* 1988; 57: 623–627.

Woodburn K, Sykes E, Kessel D. Interactions of Solutol HS 15 and Cremophor EL with plasma lipoproteins. *Int J Biochem Cell Biol* 1995; 27: 693–699.

21 Authors

J-P Mittwollen, T Schmeller.

22 Date of Revision

25 May 2005.

Annexure- II

Polyoxyethylene Stearates

1 Nonproprietary Names

The polyoxyethylene stearates are a series of polyethoxylated derivatives of stearic acid. Of the large number of different materials commercially available, one type is listed in the USPNF 23.

JP: Polyoxyl 40 stearate
USPNF: Polyoxyl 40 stearate
See also Sections 2, 3, 4, and 5.

2 Synonyms

Ethoxylated fatty acid esters; macrogol stearates; *Marlosol*; PEG fatty acid esters; PEG stearates; polyethylene glycol stearates; poly(oxy-1,2-ethanediyl) α-hydro-ω-hydroxyoctadecanoate; polyoxyethylene glycol stearates.

Polyoxyethylene stearates are nonionic surfactants produced by polyethoxylation of stearic acid. Two systems of nomenclature are used for these materials. The number '8' in the names 'poloxyl 8 stearate' or 'polyoxyethylene 8 stearate' refers to the approximate polymer length in oxyethylene units. The same material may also be designated 'polyoxyethylene glycol 400 stearate' or 'macrogol stearate 400' in which case, the number '400' refers to the average molecular weight of the polymer chain.

For synonyms applicable to specific polyoxyethylene stearates, *see* Table I.

3 Chemical Name and CAS Registry Number

Polyethylene glycol stearate [9004-99-3]
Polyethylene glycol distearate [9005-08-7]

4 Empirical Formula and Molecular Weight

See Table II.

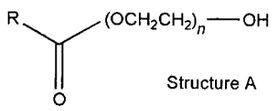
Table I: Synonyms of selected polyoxyethylene stearates and distearates.

Name	Synonym
Polyoxyl 2 stearate	*Hodag DGS; Lipo DGS;* PEG-2 stearate.
Polyoxyl 4 stearate	*Acconon 200-MS; Hodag 20-S;* PEG-4 stearate; polyethylene glycol 200 monostearate; polyoxyethylene (4) monostearate; *Protamate 200-DPS.*
Polyoxyl 6 stearate	*Cerasynt 616; Kessco PEG 300 Monostearate; Lipal 300S; Lipo PEG 3-S;* PEG-6 stearate; polyethylene glycol 300 monostearate; polyoxyethylene (6) monostearate; *Polystate C; Protamate 300-DPS.*
Polyoxyl 8 stearate	*Acconon 400-MS; Cerasynt 660; Cithrol 4MS; Crodet S8; Emerest 2640; Grocor 400; Hodag 40-S; Kessco PEG-400 Monostearate; Lipo-PEG 4-S;* macrogol stearate 400; *Myrj 45;* PEG-8 stearate; *Pegosperse 400 MS;* polyethylene glycol 400 monostearate; polyoxyethylene (8) monostearate; *Protamate 400-DPS; Ritapeg 400 MS.*
Polyoxyl 12 stearate	*Hodag 60-S; Kessco PEG 600 Monostearate; Lipo-PEG 6-S;* PEG-12 stearate; *Pegosperse 600 MS;* polyethylene glycol 600 monostearate; polyoxyethylene (12) monostearate; *Protamate 600-DPS.*
Polyoxyl 20 stearate	*Cerasynt 840; Hodag 100-S; Kessco PEG 1000 Monostearate; Lipo-PEG 10-S; Myrj 49; Pegosperse 1000 MS;* PEG-20 stearate; polyethylene glycol 1000 monostearate; polyoxyethylene (20) monostearate; *Protamate 1000-DPS.*
Polyoxyl 30 stearate	*Myrj 51;* PEG-30 stearate; polyoxyethylene (30) stearate.
Polyoxyl 40 stearate	*Crodet S40;* E431; *Emerest 2672; Hodag POE (40) MS; Lipal 395; Lipo-PEG 39-S;* macrogol stearate 2000; *Myrj 52;* PEG-40 stearate; polyoxyethylene glycol 2000 monostearate; polyoxyethylene (40) monostearate; *Protamate 2000-DPS; Ritox 52.*
Polyoxyl 50 stearate	*Atlas G-2153; Crodet S50; Lipal 505; Myrj 53;* PEG-50 stearate; polyoxyethylene (50) monostearate.
Polyoxyl 100 stearate	*Lipo-PEG 100-S; Myrj 59;* PEG-100 stearate; polyethylene glycol 4400 monostearate; polyoxyethylene (100) monostearate; *Protamate 4400-DPS; Ritox 53.*
Polyoxyl 150 stearate	*Hodag 600-S;* PEG-150 stearate; *Ritox 59.*
Polyoxyl 4 distearate	*Hodag 22-S;* PEG-4 distearate.
Polyoxyl 8 distearate	*Hodag 42-S; Kessco PEG 400 DS;* PEG-8 distearate; polyethylene glycol 400 distearate; *Protamate 400-DS.*
Polyoxyl 12 distearate	*Hodag 62-S; Kessco PEG 600 Distearate;* PEG-12 distearate; polyethylene (12) distearate; polyethylene glycol 600 distearate; *Protamate 600-DS.*
Polyoxyl 32 distearate	*Hodag 154-S; Kessco PEG 1540 Distearate;* PEG-32 distearate; polyethylene glycol 1540 distearate; polyoxyethylene (32) distearate.
Polyoxyl 150 distearate	*Hodag 602-S; Kessco PEG 6000 DS; Lipo-PEG 6000-DS;* PEG-150 distearate; polyethylene glycol 6000 distearate; polyoxyethylene (150) distearate; *Protamate 6000-DS.*

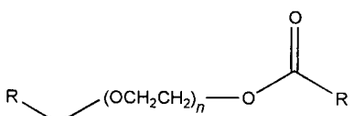
Table II: Empirical formulas and molecular weights of selected polyoxyethylene stearates.

Name	Empirical formula	Molecular weight
Polyoxyl 6 stearate	$C_{30}H_{60}O_8$	548.80
Polyoxyl 8 stearate	$C_{34}H_{68}O_{10}$	636.91
Polyoxyl 12 stearate	$C_{42}H_{84}O_{14}$	813.12
Polyoxyl 20 stearate	$C_{58}H_{116}O_{22}$	1165.55
Polyoxyl 40 stearate	$C_{98}H_{196}O_{42}$	2046.61
Polyoxyl 50 stearate	$C_{118}H_{236}O_{52}$	2487.15
Polyoxyl 100 stearate	$C_{218}H_{436}O_{102}$	4689.80

5 Structural Formula



Structure A



Structure B

Structure A applies to the monostearate; where the average value of n is 6 for polyoxyl 6 stearate, 8 for polyoxyl 8 stearate, and so on.

Structure B applies to the distearate; where the average value of n is 12 for polyoxyl 12 distearate, 32 for polyoxyl 32 distearate, and so on.

In both structures, R represents the alkyl group of the parent fatty acid. With stearic acid, R is $CH_3(CH_2)_{16}$. However, it should be noted that stearic acid usually contains other fatty acids, primarily palmitic acid, and consequently a polyoxyethylene stearate may also contain varying amounts of other fatty acid derivatives such as palmitates.

6 Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene stearates are generally used as emulsifiers in oil-in-water-type creams and lotions. Their hydrophilicity or lipophilicity depends on the number of ethylene oxide units present: the larger the number, the greater the hydrophilic properties. Polyoxyl 40 stearate has been used as an emulsifying agent in intravenous infusions.[1]

Polyoxyethylene stearates are particularly useful as emulsifying agents when astringent salts or other strong electrolytes are present. They can also be blended with other surfactants to obtain any hydrophilic–lipophilic balance for lotions or ointment formulations. *See* Table III.

Table III: Uses of polyoxyethylene stearates.

Use	Concentration (%)
Auxiliary emulsifier for o/w intravenous fat emulsion	0.5–5
Emulsifier for o/w creams or lotions	0.5–10
Ophthalmic ointment	7
Suppository component	1–10
Tablet lubricant	1–2

8 Description

See Table IV.

Table IV: Description of various polyoxyethylene stearates.

Name	Description
Polyoxyl 6 stearate	Soft solid
Polyoxyl 8 stearate	Waxy cream
Polyoxyl 12 stearate	Pasty solid
Polyoxyl 20 stearate	Waxy solid
Polyoxyl 40 stearate	Waxy solid, with a faint, bland, fat-like odor, off-white to light tan in color
Polyoxyl 50 stearate	Solid, with a bland, fat-like odor or odorless
Polyoxyl 100 stearate	Solid
Polyoxyl 12 distearate	Paste
Polyoxyl 32 distearate	Solid
Polyoxyl 150 distearate	Solid

9 Pharmacopeial Specifications

See Table V.

Table V: Pharmacopeial specifications for polyoxyethylene stearates.

Test	JP 2001	USPNF 23
	Polyoxyl 40 stearate	Polyoxyl 40 stearate
Identification	+	+
Clarity and color of solution	+	–
Congealing range	39–44°C	37–47°C
Congealing point of the fatty acid	≥53°C	–
Residue on ignition	≤0.10%	–
Water	–	≤3.0%
Arsenic	≤3 ppm	–
Heavy metals	≤10 ppm	≤0.001%
Acid value	≤1	≤2
Hydroxyl value	–	25–40
Saponification value	25–35	25–35
Free polyethylene glycols	–	17–27%
Organic volatile impurities	–	+

10 Typical Properties

Flash point: >149°C for poloxyl 8 stearate (*Myrj 45*).
Solubility: *see* Table VI. *See also* Table VII.

Table VI: Solubility of polyoxyethylene stearates.

Name	Solvent		
	Ethanol (95%)	Mineral oil	Water
Polyoxyl 6 stearate	S	S	DH
Polyoxyl 8 stearate	S	I	D
Polyoxyl 12 stearate	S	I	S
Polyoxyl 20 stearate	S	I	S
Polyoxyl 40 stearate	S	I	S
Polyoxyl 50 stearate	S	I	S
Polyoxyl 100 stearate	S	I	S
Polyoxyl 12 distearate	S	–	DH
Polyoxyl 32 distearate	S	–	S
Polyoxyl 150 distearate	I	–	S

D = dispersible; I = insoluble; S = soluble; DH = dispersible (with heat).

11 Stability and Storage Conditions

Polyoxyethylene stearates are generally stable in the presence of electrolytes and weak acids or bases. Strong acids and bases can cause gradual hydrolysis and saponification.

The bulk material should be stored in a well-closed container, in a dry place, at room temperature.

12 Incompatibilities

Polyoxyethylene stearates are unstable in hot alkaline solutions owing to hydrolysis, and will also saponify with strong acids or bases. Discoloration or precipitation can occur with salicylates, phenolic substances, iodine salts, and salts of bismuth, silver, and tannins.[2–4] Complex formation with preservatives may also occur.[5] The antimicrobial activity of some materials such as bacitracin, chloramphenicol, phenoxymethylpenicillin, sodium penicillin, and tetracycline may be reduced in the presence of polyoxyethylene stearate concentrations greater than 5% w/w.[6,7]

13 Method of Manufacture

Polyoxyethylene stearates are prepared by the direct reaction of fatty acids, particularly stearic acid, with ethylene oxide.

14 Safety

Although polyoxyethylene stearates are primarily used as emulsifying agents in topical pharmaceutical formulations, certain materials, particularly polyoxyl 40 stearate, have also been used in intravenous injections and oral preparations.[1,4]

Polyoxyethylene stearates have been tested extensively for toxicity in animals[8–13] and are widely used in pharmaceutical formulations and cosmetics. They are generally regarded as essentially nontoxic and nonirritant materials.

Polyoxyl 8 stearate:
LD_{50} (hamster, oral): 27 g/kg
LD_{50} (rat, oral): 64 g/kg
Polyoxyl 20 stearate:
LD_{50} (mouse, IP): 0.2 g/kg
LD_{50} (mouse, IV): 0.87 g/kg

15 Handling Precautions

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

Polyoxyethylene stearates that contain greater than 100 ppm of free ethylene oxide may present an explosion hazard when stored in a closed container. This is due to the release of ethylene oxide into the container headspace, where it can accumulate and so exceed the explosion limit.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental solutions; IV injections; ophthalmic preparations; oral capsules and tablets; otic suspensions; topical creams, emulsions, lotions, ointments, and solutions; and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyethylene glycol; stearic acid.

18 Comments

—

Table VII: Typical properties of polyoxyethylene stearates.

Name	Acid value	Free ethylene oxide	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Saponification value	Water content (%)
Polyoxyl 6 stearate	≤5.0	≤100 ppm	9.7	–	≤0.5	28–32	95–110	–
Polyoxyl 8 stearate	≤2.0	≤100 ppm	11.1	87–105	≤1.0	28–33	82–95	≤3.0
Polyoxyl 12 stearate	≤8.5	≤100 ppm	13.6	55–75	≤1.0	≈ 37	62–78	≤1.0
Polyoxyl 20 stearate	≤1.0	≤100 ppm	14	50–62	≤1.0	≈ 28	46–56	≤1.0
Polyoxyl 30 stearate	≤2.0	–	16	35–50	–	–	30–45	≤3.0
Polyoxyl 40 stearate	≤1.0	–	16.9	27–40	–	≈ 38	25–35	≤3.0
Polyoxyl 50 stearate	≤2.0	–	17.9	23–35	–	≈ 42	20–28	≤3.0
Polyoxyl 100 stearate	≤1.0	≤100 ppm	18.8	15–30	–	≈ 46	9–20	≤3.0
Polyoxyl 8 distearate	≤10.0	–	–	≤15	≤0.5	≈ 36	115–124	–
Polyoxyl 12 distearate	≤10.0	≤100 ppm	10.6	≤20	≤1.0	≈ 39	93–102	≤1.0
Polyoxyl 32 distearate	≤10.0	≤100 ppm	14.8	≤20	≤0.25	≈ 45	50–62	≤1.0
Polyoxyl 150 distearate	7–9	≤100 ppm	18.4	≤15	≤0.1	53–57	14–20	≤1.0

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SC Owen.

22 Date of Revision

31 August 2005.

Annexure - III

Polyoxyethylene Castor Oil Derivatives

1 Nonproprietary Names

BP: Polyoxyl castor oil
Hydrogenated polyoxyl castor oil

PhEur: Macrogolglyceroli ricinoleas
Macrogolglyceroli hydroxystearas

USPNF: Polyoxyl 35 castor oil
Polyoxyl 40 hydrogenated castor oil

Polyoxyethylene castor oil derivatives are a series of materials obtained by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil. Several different types of material are commercially available, the best-known being the *Cremophor* series (BASF Corp.). Of these, two castor oil derivatives are listed in the PhEur 2005 and USPNF 23. *See also* Sections 2, 3 and 4.

2 Synonyms

Synonyms applicable to polyoxyethylene castor oil derivatives are shown below. *See* Table I for information on specific materials.

Acconon; *Arlatone*; *Cremophor*; *Etocas*; *Eumulgin*; *Jeechem*; *Lipocol*; *Mapeg*; *Marlowet*; *Nikkol*; *Protachem*; *Simulsol*.

3 Chemical Name and CAS Registry Number

Polyethoxylated castor oil [61791-12-6]

4 Empirical Formula and Molecular Weight

Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components. Members within each range have different degrees of ethoxylation (moles)/PEG units as indicated by their numerical sufffix (*n*). The chemical structures of the polyethoxylated hydrogenated castor oils are analogous to polyethoxylated castor oils with the exception that the double bond in the fatty chain has been saturated by hydrogenation.

The PhEur 2005 states that polyoxyl castor oil contains mainly ricinoleyl glycerol ethoxylated with 30–50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate, and of the corresponding free glycols. The PhEur 2005 also states that polyoxyl hydrogenated castor oil contains mainly trihydroxystearyl glycerol ethoxylated with 7–60 molecules of ethylene oxide (nominal value).

In polyoxyl 35 castor oil (*Cremophor EL*), the relatively hydrophobic constituents comprise about 83% of the total mixture, the main component being glycerol polyethylene glycol ricinoleate. Other hydrophobic constituents include fatty acid esters of polyethylene glycol along with some unchanged castor oil. The hydrophilic part (17%) consists of polyethylene glycols and glycerol ethoxylates. *Cremophor ELP*, a 'purified' grade of *Cremophor EL* is also a polyoxyl 35 castor oil; it has a lower content of water, potassium, and free fatty acids and hence is claimed to have improved stability.

In polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*), approximately 75% of the components of the mixture are hydrophobic. These comprise mainly fatty acid esters of

Table I: Synonyms of selected polyoxyethylene castor oil derivatives.

Name	Synonym
Polyoxyl 5 castor oil	*Acconon CA-5*; castor oil POE-5; *Etocas 5*; *Hetoxide C-5*; *Jeechem CA-5*; PEG-5 castor oil; polyoxyethylene 5 castor oil.
Polyoxyl 9 castor oil	*Acconon CA-9*; castor oil POE-9; *Jeechem CA-9*; PEG-9 castor oil; polyoxyethylene 9 castor oil; *Protachem CA-9*.
Polyoxyl 15 castor oil	*Acconon CA-15*; castor oil POE-15; *Jeechem CA-15*; PEG-15 castor oil; polyoxyethylene 15 castor oil; *Protachem CA-15*.
Polyoxyl 35 castor oil	Castor oil POE-35; *Cremophor EL*; *Cremophor ELP*; *Etocas 35*; glycerol polyethyleneglycol ricinoleate; PEG-35 castor oil; polyethoxylated castor oil; polyoxyethylene 35 castor oil.
Polyoxyl 40 castor oil	Castor oil POE-40; *Cirrasol G-1284*; *Croduret 40*; *Etocas 40*; *Eumulgin RO*; *Hetoxide C40*; *Jeechem CA-40*; *Marlowet R40*; *Nikkol CO 40TX*; *Nonionic GR-40*; PEG-40 castor oil; polyoxyethylene 40 castor oil; *Protachem CA-40*.
Polyoxyl 40 hydrogenated castor oil	*Cremophor RH 40*; *Croduret 40*; *Eumulgin HRE 40*; glycerol polyethyleneglycol oxystearate; *Hetoxide HC40*; hydrogenated castor oil POE-40; *Jeechem CAH-40*; PEG-40 hydrogenated castor oil; polyethoxylated hydrogenated castor oil; polyoxyethylene 40 hydrogenated castor oil; *Lipocol HCO-40*; *Lipocol LAV HCO 40*; *Nikkol HCO 40 Pharma*; *Nonionic GRH-40*; *Protachem CAH-40*.
Polyoxyl 60 castor oil	Castor oil POE-60; *Jeechem CA-60*; *Nikkol CO 60TX*; PEG-60 castor oil; polyoxyethylene 60 castor oil.
Polyoxyl 60 hydrogenated castor oil	*Croduret 60*; *Eumulgin HRE 60*; *Hetoxide HC60*; hydrogenated castor oil POE-60; *Jeechem CAH-60*; PEG-60 hydrogenated castor oil; polyoxyethylene 60 hydrogenated castor oil; *Lipocol HCO-60*; *Nikkol HCO 60 Pharma*; *Protachem CAH-60*.
Polyoxyl 100 castor oil	Hydrogenated castor oil POE-100; *Jeechem CA-100*; PEG-100 hydrogenated castor oil; polyoxyethylene 100 hydrogenated castor oil.
Polyoxyl 100 hydrogenated castor oil	*Cirrasol G-1300*; *Jeechem CA-100*; *Nikkol HCO 100*; polyoxyethylene 100 hydrogenated castor oil.
Polyoxyl 200 castor oil	*Hetoxide C200*; *Jeechem CA-200*; polyoxyethylene 200 castor oil; PEG-200 castor oil; castor oil POE-200.
Polyoxyl 200 hydrogenated castor oil	Hydrogenated castor oil POE-200; *Jeechem CAH-200*; PEG-200 hydrogenated castor oil; polyoxyethylene 200 hydrogenated castor oil.

glycerol polyethylene glycol and fatty acid esters of polyethylene glycol. The hydrophilic portion consists of polyethylene glycols and glycerol ethoxylates.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene castor oil derivatives are nonionic surfactants used in oral, topical, and parenteral pharmaceutical formulations.

Polyoxyl 35 castor oil is mainly used as an emulsifing and solubilizing agent, and is particularly suitable for the production of aqueous liquid preparations containing volatile oils, fat-soluble vitamins, and other hydrophobic substances.[1,2] *Cremophor EL* emulsifies or solubilizes the fat-soluble vitamins A, D, E, and K in aqueous solutions for oral and topical administration. In 1 mL of a 25% v/v aqueous polyoxyl 35 castor oil (*Cremophor EL*) solution it is possible to incorporate approximately 10 mg of vitamin A palmitate; approximately 10 mg of vitamin D; approximately 120 mg of vitamin E acetate; or approximately 120 mg of vitamin K_1.

In aqueous alcoholic solutions, it very readily solubilizes essential oils. Aqueous solutions of hydrophobic drugs (e.g. miconazole, hexetidine, clotrimazole, benzocaine) can also be prepared with *Cremophor EL*. *Cremophor EL* has also been used as a solubilizing agent for drugs like cyclosporin A,[3] paclitaxel,[4] and cisplatin.[5] *Cremophor ELP* is manufactured by purifying *Cremophor EL* and is therefore suitable for parenteral applications, e.g. *Taxol* preparations. In oral formulations, the taste of polyoxyl 35 castor oil (*Cremophor EL*) can be masked by a banana flavor.

Polyoxyl 35 castor oil (*Cremophor EL*) has also been used as a solvent in proprietary injections of diazepam, propanidid, and alfaxalone with alfadolone acetate; *see* Section 14. A self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability, and the enhancement of halofantrine,[6] and simvastatin,[7] has been prepared using *Cremophor EL*. *Cremophor EL* has also been used as a buffering agent for aqueous tropicamide eyedrops.[8] It has also been used in an aqueous mixture together with caprylic/capric glyceride for mucosal vaccination, providing a potential alternative to parenteral vaccination.[9] It has also been used to enhance the permeability of peptides across monolayers of Caco-2 cells by inhibiting the apically polarized efflux system, enhancing intestinal absorption of some drugs.[10] *Cremophor* has been used as a vehicle for boron neutron-capture therapy in mice; which is a form of radiation therapy used in the treatment of glioblastoma multiforme.[11] Polyoxyl 35 castor oil is also used in the production of glycerin suppositories.

In veterinary practice, polyoxyl 35 castor oil can be used to emulsify cod liver oil, and oils and fats incorporated into animal feeding stuffs.

In cosmetics, polyoxyl 35 castor oil is mainly used as a solubilizing agent for perfume bases and volatile oils in vehicles containing 30–50% v/v alcohol (ethanol or propan-2-ol). In hand lotions, it can be used to replace castor oil.

Polyoxyl 40 hydrogenated castor oil may be used in preference to polyoxyl 35 castor oil in oral formulations since it is almost tasteless. In aqueous alcoholic or completely aqueous solutions, polyoxyl 40 hydrogenated castor oil can be used to solubilize vitamins, essential oils, and certain drugs. Using 1 mL of a 25% v/v aqueous solution of polyoxyl 40 hydrogenated castor oil, it is possible to solubilize approximately 88 mg of vitamin A palmitate, or approximately 160 mg of vitamin A propionate. Other materials that can be solubilized are alfadolone, alfaxalone, hexachlorophene, hexetidine, levomepromazine, miconazole, propanidid, and thiopental.

In aerosol vehicles that include water, the addition of polyoxyl 40 hydrogenated castor oil improves the solubility of the propellant in the aqueous phase. This enhancement applies both to dichlorodifluoromethane and to propane/butane mixtures.

Foam formation in aqueous ethanol solutions containing polyoxyl 40 hydrogenated castor oil can be suppressed by the addition of small amounts of polypropylene glycol 2000.

Polyoxyl 40 hydrogenated castor oil is also used as an emulsifier of fatty acids and alcohols.

Polyoxyethylene castor oil derivatives have been used experimentally as a surfactant for the controlled release matrix pellet formulation containing nanocrystalline ketoprofen,[12] and for the transdermal delivery of vinpocetin.[13]

Hydrogenated castor oil (HCO) derivatives containing more than 20 oxyethylene units were found to prolong the plasma circulation times of menatetrenone incorporated in lipid emulsions.[14] Polyoxl 60 hydrogenated castor oil has been reported to provide a self-microemulsifying system with enhanced oral absorption,[15] and a drastic reduction in plasma clearance of lipid emulsions.[16] It has been used in the formulation of liposomes,[17] and it has been suggested that more than 60% aids in the targeting of liposomes to the liver.[18] Also, polyoxyl 60 hydrogenated castor oil micellar solutions of cyclosporin A delivered the drug via the GI tract to the lymphatics with an extremely high selectivity.[19,20]

Cremophor RH 40 and *RH 60* have been used as additives to enhance the drug release from suppository formulations.[21,22]

8 Description

Polyoxyl 35 castor oil occurs as a pale yellow, viscous liquid that is clear at temperatures above 26°C. It has a slight but characteristic odor and can be completely liquefied by heating to 26°C.

Polyoxyl 40 hydrogenated castor oil occurs as a white to yellowish, semisolid paste at 20°C that liquefies at 30°C. It has a very faint characteristic odor and is almost tasteless in aqueous solution.

Polyoxyl 60 hydrogenated castor oil occurs as a white paste at room temperature. It has little taste or odor in aqueous solution.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

See Tables III, IV, and V.

11 Stability and Storage Conditions

Polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) forms stable solutions in many organic solvents such as

Table II: Pharmacopeial specifications for polyoxyethylene castor oil derivatives.

Test	PhEur 2005		USPNF 23	
	Polyoxyl castor oil	**Polyoxyl hydrogenated castor oil**	**Polyoxyl 35 castor oil**	**Polyoxyl 40 hydrogenated castor oil**
Identification	+	+	+	+
Characters	+	+	–	–
Appearance of solution	+	+	–	–
Alkalinity	+	+	–	–
Relative density	≈1.05	–	–	–
Specific gravity	–	–	1.05–1.06	–
Congealing temperature	–	–	–	16–26°C
Viscosity at 25°C	500–800 mPa s	–	650–850 cP s	–
Water	≤3.0%	≤3.0%	≤3.0%	≤3.0%
Total ash	≤0.3%	≤0.3%	–	–
Residue on ignition	–	–	≤0.3%	≤0.3%
Heavy metals	≤10 ppm	≤10 ppm	≤0.001%	≤0.001%
Acid value	≤2.0	≤2.0	≤2.0	≤2.0
Hydroxyl value	+	+	65–80	60–80
Dioxan	≤10 ppm	≤10 ppm	–	–
Free ethylene oxide	≤1 ppm	≤1 ppm	–	–
Organic volatile impurities	–	–	+	+

chloroform, ethanol, and propan-2-ol; it also forms clear, stable, aqueous solutions. Polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is miscible with other polyoxyethylene castor oil derivatives and on heating with fatty acids, fatty alcohols, and some animal and vegetable oils. Solutions of polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) in aqueous alcohols are also stable.

On heating of an aqueous solution, the solubility of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is reduced and the solution becomes turbid. Aqueous solutions of polyoxyl hydrogenated castor oil (*Cremophor RH* grades) heated for prolonged periods may separate into solid and liquid phases on cooling. However, the product can be restored to its original form by homogenization.

Aqueous solutions of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) are stable in the presence of low concentrations of electrolytes such as acids or salts, with the exception of mercuric chloride; *see* Section 12.

Aqueous solutions of polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) can be sterilized by autoclaving for 20 minutes at 121°C. In this process, a product may acquire a deeper color but this has no significance for product stability. Aqueous solutions of polyoxyl hydrogenated castor oil (*Cremophor RH*) can similarly be sterilized by autoclaving at 121°C, but this may cause a slight decrease in the pH value.

Although the method of manufacture used for polyoxyethylene castor oil derivatives ensures that they are near-sterile, microbial contamination can occur on storage.

Polyoxyethylene castor oil derivatives should be stored in a well-filled, airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

In strongly acidic or alkaline solutions, the ester components of polyoxyethylene hydrogenated castor oil are liable to saponify.

In aqueous solution, polyoxyl 35 castor oil (*Cremophor EL* and *Cremophor ELP*) is stable toward most electrolytes in the concentrations normally employed. However, it is incompatible with mercuric chloride since precipitation occurs.

Some organic substances may cause precipitation at certain concentrations, especially compounds containing phenolic hydroxyl groups, e.g. phenol, resorcinol, and tannins.

Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) and polyoxyl 60 hydrogenated castor oil are largely unaffected by the salts that cause hardness in water. *Cremophor RH 40* was found to prolong the dissolution time of digoxin tablets.[23]

13 Method of Manufacture

Polyoxyethylene castor oil derivatives are prepared by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil under controlled conditions.

Polyoxyl 35 castor oil is produced in this way by reacting 1 mole of castor oil with 35–40 moles of ethylene oxide.

Polyoxyl 40 hydrogenated castor oil is produced by reacting 1 mole of hydrogenated castor oil with 40–45 moles of ethylene oxide. Polyoxyl 60 hydrogenated castor oil is similarly produced by reacting 1 mole of hydrogenated castor oil with 60 moles of ethylene oxide.

14 Safety

Polyoxyethylene castor oil derivatives are used in a variety of oral, topical, and parenteral pharmaceutical formulations.

Acute and chronic toxicity tests in animals have shown polyoxyethylene castor oil derivatives to be essentially nontoxic and nonirritant materials; *see* Table VI.[24,25] However, there are reports of cardiovascular changes and nephrotoxicity in various species of animals.[26] Several serious anaphylactic reactions,[27–38] cardiotoxicity,[39–41] nephrotoxicity,[42,43] neurotoxicity,[44] and pulmonary toxicty[45] have also been observed in humans and animals following parenteral administration of formulations containing polyoxyethylene castor oil derivatives. The precise mechanism of the reaction is not known.

Table III: Typical physical properties of selected commercially available polyoxyethylene castor oil derivatives.

Name	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Water content (%)	Melting point (°C)	Solidification point (°C)	Cloud point for a 1% aqueous solution (°C)
Polyoxyl 35 castor oil (*Cremophor EL*)	≤2.0	12–14	65–78	25–35	65–70	2.80	19–20	–	72.5
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	≤2.0	12–14	65–78	25–35	65–70	≤0.5	–	–	–
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	≤1.0	14–16	60–80	≤1	50–60	≤2.0	≈30	20–28	95.6
Polyoxyl 60 hydrogenated castor oil	≤1.0	15–17	50–70	≤1	40–50	≤2	≈40	–	–
Etocas 29	–	11.7	–	–	–	–	–	–	–
Etocas 35	–	12.7	–	–	–	–	–	–	–
Etocas 40	–	13	–	–	–	–	–	–	–
Croduret 7 Special	–	4.9	–	–	–	–	–	–	–
Croduret 40	–	13	–	–	–	–	–	–	–
Croduret 50 Special	–	14.1	–	–	–	–	–	–	–
Croduret 60	–	14.7	–	–	–	–	–	–	–
Eumulgin HRE 40	≤1.0	–	60–75	≤2	50–60	≤1.0	–	–	76–82
Eumulgin HRE 60	≤1.0	–	50–67	–	40–50	≤1	–	<22	80–86
Arlatone G Pharma	–	10.8	–	–	–	–	≈7	–	–
Cirrasol G-1284	–	13.1	–	–	–	–	–	–	–
Hetoxide C5	–	4	–	–	–	–	–	–	–
Hetoxide C-16	–	8.6	–	–	–	–	–	–	–
Hetoxide C-25	–	10.8	–	–	–	–	–	–	–
Hetoxide HC-16	–	8.6	–	–	–	–	–	–	–
Hetoxide HC-40	–	13.1	–	–	–	–	–	–	–
Hetoxide HC-60	–	14.8	–	–	–	–	–	–	–
Jeechem CA-5	≤1.5	–	128–140	63–73	138–153	≤1.0	–	–	–
Jeechem CA-15	≤1.0	–	–	–	95–100	≤1.0	–	–	–
Jeechem CA-25	–	–	75–85	–	77–85	≤1.0	–	–	–
Jeechem CA-40	≤2.0	–	77–89	24–30	57–64	≤3.0	–	–	–
Jeechem CA-60	≤2.0	–	42–55	–	28–38	≤12.0	–	–	–
Jeechem CA-100	≤2.0	–	–	–	27–37	≤1.0	–	–	–
Jeechem CA-200	≤2.0	–	20–34	–	14–20	≤1.0	125	–	–
Jeechem CAH-25	≤2.0	–	73–84	≤1.0	77–87	≤2.0	–	–	–
Jeechem CAH-40	≤3.0	–	59–68	≤2.0	50–65	≤1.0	–	–	–
Jeechem CAH-60	≤1.5	–	39–49	–	41–51	≤1.0	–	–	–
Jeechem CAH-200	≤2.0	–	20–33	–	14–22	≤1.0	125	–	–
Lipocol HCO-40	≤3.0	–	–	≤2.0	60–67	–	–	–	–
Lipocol LAV HCO-40	≤1.0	–	60–80	≤2.0	45–69	≤3.0	–	–	–
Lipocol HCO-60	≤1.0	–	50–70	≤1.0	40–50	≤21.0	–	–	–
Nikkol CO-3	–	3	–	–	–	–	–	–	–
Nikkol CO-10	–	6.5	–	–	–	–	–	–	–
Nikkol HCO-50	–	13.5	–	–	–	–	–	–	–
Nikkol HCO-80	–	15	–	–	–	–	–	–	–
Nikkol HCO-100	–	16.5	–	–	–	–	–	–	–

Table IV: Typical physical properties of selected commercially available polyoxyethylene castor oil derivatives.

Name	Density (g/cm^3)	pH	Refractive index at 20°C	Surface tension of 0.1% w/v aqueous solution (mN/m)	Viscosity at 25°C (mPa s)	Critical micelle concentration (%)
Polyoxyl 35 castor oil (*Cremophor EL*)	1.05–1.06	6–8	1.471	40.9	650–800	≈0.009
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	1.05–1.06	5–7	—	—	600–750	≈0.009
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	—	6–7	1.453–1.457	43.0	20–40[a]	0.039
Polyoxyl 60 hydrogenated castor oil	—	6–7	—	—	—	—
Eumulgin HRE 40	1.0220–1.0260 at 70°C	6–7	—	—	—	—
Eumulgin HRE 60	1.0340–1.0380 at 70°C	6–7	—	—	—	—
Arlacel 989	—	—	—	—	1200	—
Arlatone G Pharma	≈1.0	—	—	—	≈1400	—
Cirrasol G-1284	≈1.10	7–9	—	—	1500	—
Jeechem CA-5	1.0	6–8	—	—	—	—
Jeechem CA-9	1.02	5.5–7.5	—	—	—	—
Jeechem CA-15	1.021	6.0–7.5	—	—	—	—
Jeechem CA-25	1.04	6.0–7.5	—	—	—	—
Jeechem CA-30	1.01	6.5–7.5	—	—	—	—
Jeechem CA-40	1.1	5.0–8.0	—	—	—	—
Jeechem CA-60	1.068	5.0–7.0	—	—	—	—
Jeechem CA-100	—	5.5–7.0	—	—	—	—
Jeechem CA-200	1.08	5.0–7.0	—	—	—	—
Jeechem CAH-16	1.02	6.0–7.5	1.4665–1.4685	—	—	—
Jeechem CAH-25	1.03	5.0–7.5	—	—	—	—
Jeechem CAH-40	1.1	5.5–7.5	—	—	—	—
Jeechem CAH-60	—	3.5–6.1	—	—	—	—
Jeechem CAH-100	1.1	3.5–6.1	—	—	—	—
Jeechem CAH-200	1.1	—	—	—	—	—
Lipocol HCO-40	1.0	—	—	—	—	—
Lipocol HCO-60	1.05	—	—	—	—	—

[a] 30% w/v aqueous solution.

Table V: Solubility of selected commercially available polyoxyethylene castor oil derivatives.

Name	Solubility							
	Castor oil	Chloroform	Ethanol	Fatty acids	Fatty alcohols	Olive oil	Mineral oil	Water
Polyoxyl 35 castor oil (*Cremophor EL*)	S	S	S	S	S	S	–	S
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	S	S	S	S	S	S	–	S
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	S	S	S	S	S	S	–	S
Polyoxyl 60 hydrogenated castor oil	S	–	S[a]	S	S	S	–	S
Etocas 5	S	–	S	–	S	–	I	I
Etocas 29	S	–	S	–	S	–	I	S
Etocas 35	S	–	S	–	S	–	I	S
Etocas 40	S	–	S	–	PS	–	I	S
Croduret 7 Special	S	–	PS	–	S	–	I	I
Croduret 40	D	–	S	–	D	–	I	S
Croduret 50 Special	D	–	S	–	I	–	I	S
Croduret 60	D	–	S	–	D	–	I	S
Arlacel 989	–	–	S	–	–	–	–	I
Arlatone G Pharma	–	–	S	–	–	–	I	S
Cirrasol G-1284	–	–	–	–	–	–	I	D
Jeechem CA-5	–	–	–	–	–	–	–	D
Jeechem CA-9	–	–	–	–	–	–	–	D
Jeechem CA-15	–	–	–	–	–	–	–	PS
Jeechem CA-25	–	–	–	–	–	–	–	S
Jeechem CA-30	–	–	–	–	–	–	–	S
Jeechem CA-40	–	–	–	–	–	–	–	S
Jeechem CA-60	–	–	–	–	–	–	–	PS
Jeechem CA-200	–	–	–	–	–	–	–	S
Jeechem CAH-16	–	–	–	–	–	–	–	D
Jeechem CAH-25	–	–	–	–	–	–	–	D
Jeechem CAH-40	–	–	–	–	–	–	–	S
Jeechem CAH-60	–	–	–	–	–	–	–	S
Jeechem CAH-100	–	–	–	–	–	–	–	S
Jeechem CAH-200	–	–	–	–	–	–	–	S
Lipocol LAV HCO-40	–	–	–	–	–	–	–	S
Lipocol HCO-40	–	–	–	–	–	–	–	S
Lipocol HCO-60	–	–	–	–	–	–	–	S

S = soluble, PS = partially soluble, I = insoluble, D = dispersible.

[a] Need to add 0.5–1.0% water to maintain a clear solution.

Table VI: LD_{50} values of selected polyoxyethylene castor oil derivatives.[24,25]

Name	Animal and route	LD_{50} (g/kg body-weight)
Polyoxyl 35 castor oil (*Cremophor EL*)	Cat (oral)	>10
	Dog (IV)	0.64
	Mouse (IV)	2.5
	Rabbit (oral)	>10
	Rat (oral)	>6.4
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	Mouse (IP)	>12.5
	Mouse (IV)	>12.0
	Rat (oral)	>16.0
Polyoxyl 60 hydrogenated castor oil	Mouse (IP)	>12.5
	Rat (oral)	>16.0

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections and ophthalmic solutions). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene stearates.

18 Comments

Note that the trade name *Cremophor* (BASF Corp.) is also used for other polyoxyethylene derivatives, e.g., the *Cremophor A* series are polyoxyethylene alkyl ethers of cetostearyl alcohol.

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22 Date of Revision

30 August 2005.

Annexure - IV

Etocas and Croduret

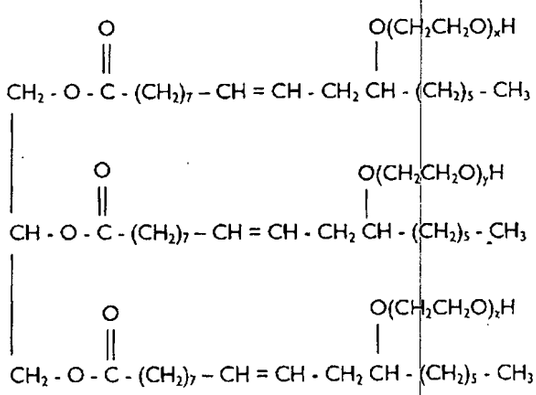
Castor oil derivatives for agrochemicals

Etocas and Croduret are vegetable-derived nonionic surfactants which find widespread use in agrochemicals as general emulsifiers and solubilisers. They are of particular value as biodegradable, sustainable alternatives to nonyl phenol ethoxylates.

Etocas and Croduret are ethoxylated castor oil and ethoxylated hydrogenated castor oil respectively. Members within each range have different degrees of ethoxylation (moles) as indicated by their numerical suffix. Standard products are Etocas 5, 10, 29, 35, 40 and Croduret 7, 40 and 50. Members having different levels of ethoxylation from the standard range may also be made available subject to minimum batch quantities.

As primary refiners of castor oil, Croda is in the unique position of ensuring uniformity of the feedstock and hence performance consistency of the derived ethoxylate.

The principle chemical structure of the Etocas series of products is shown below, where (x + y + z) is the total molar addition of ethylene oxide per molecule of castor oil.



The chemical structure of the Crodurets is analogous to that of Etocas with the exception that the double bond has been saturated by hydrogenation.

Etocas products with 5 to 54 moles of ethylene oxide are covered for use in pesticide formulations applied to growing crops and to raw agricultural commodities after harvest as specified in CFR : Title 40, section 180.1001 (2), subsection C (EPA exempt list). They are similarly permitted for use as inert ingredients in pesticide formulations applied to animals (subsection E).

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Table 1 gives data on the solubility/miscibility of the Etocas series at 10% w/w in a range of common solvents and oils at 25°C.

Etocas	Water	Mineral oil	Kerosene	Rapeseed oil	Methyl oleate
5	◐	●	●	○	○
10	◐	●	●	○	◐
29	○	●	●	○	●
35	○	●	●	○	●
40	○	●	●	●	●

Key
○ – Soluble ◐ – Partially soluble/dispersible ● – Insoluble

Table 1 Solubility/miscibility

Table 2 indicates the quality of emulsions produced at 25°C when water (90 parts by weight) is added under normal stirring conditions to the solvent or oil (10 parts by weight) containing 10% w/w Etocas (ie surfactant concentration in the test system is 1% w/w).

Etocas	Mineral oil	Kerosene	Rapeseed oil	Methyl oleate
5	F	F	G	P
10	P	P	G	G
29	P	P	G	G
35	P	P	P	G
40	P	P	P	G

Key
G – Good emulsion F – Fair P – Poor

Table 2 Emulsification

The emulsion characteristics judged were
1. Ease of dispersion of the surfactant/solvent mixture in water at 25°C
2. The particle size of the resulting emulsion

The Croduret series

Table 3 gives data on the solubility/miscibility of the Croduret series at 10% w/w in a range of common solvents and oils at 25°C.

Croduret	Water	Mineral oil	Kerosene	Rapeseed oil	Methyl oleate
7	◐	●	●	○	○
40	○	●	●	◐	◐
50	○	●	●	◐	◐

Key
○ – Soluble ◐ – Partially soluble/dispersible ● – Insoluble

Table 3 Solubility/miscibility

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Table 4 indicates the quality of emulsions produced at 25°C when water (90 parts by weight) is added under normal stirring conditions to the solvent or oil (10 parts by weight) containing 10% w/w Croduret (ie surfactant concentration in the test system is 1% w/w).

Croduret	Mineral oil	Kerosene	Rapeseed oil	Methyl oleate
7	P	P	G	G
40	P	P	P	P
50	P	P	P	P

Key
G – Good emulsion F – Fair P – Poor

Table 4 Emulsification

The emulsion characteristics judged were
1. Ease of dispersion of the surfactant/solvent mixture in water at 25°C
2. The particle size of the resulting emulsion

Applications
Castor oil ethoxylates are commonly formulated with the calcium salt of a linear or branched chain dodecyl benzene sulphonate as balanced pair surfactants for emulsifiable concentrate formulations. In particular, the more hydrophilic members such as Etocas 40 and Etocas 35, are utilised to improve stability against coalescence following dilution of the emulsifiable concentrate in water.

Castor oil ethoxylates are also relevant as biodegradable alternatives to nonyl phenol ethoxylates. In terms of HLB, Etocas 40 represents a suitable alternative emulsifier to ethoxy (9) nonyl phenol (NPE9). Similarly Etocas 35 is a suitable alternative emulsifier to ethoxy (7) nonyl phenol (NPE7).

Used in isolation, Etocas 29 in particular, is an effective emulsifier for aromatic solvents such as naphtha and xylene. Etocas 29 also finds application in the preparation of aqueous microemulsions of pyrethroid and organophosphorous insecticides. Specific details are available on request.

Lower molar ethoxylates of castor oil are used as dispersing agents for oil based systems. Used in conjunction with members of the Crillet range of surfactants, lower molar ethoxylates of castor oil are useful for the emulsification of various vegetable oils including rapeseed oil and sesame oil. Specific details are available on request. Croduret 7 is particularly useful for the production of liquid water in oil emulsions.

Specifications
Copies of individual product specifications are available on request.

Health and safety
Etocas and Croduret are established raw materials and are generally considered to present no special hazards. However, as with other nonionic surface active agents of this type, they may be irritating to the eyes as supplied. Therefore, contact with the eyes should be avoided. In case of contact, flush the eyes with plenty of water and seek medical advice.

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