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 2002 and USPNF 20.
See also Sections 2–4.

2 Synonyms

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

Arlatone; *Cremothon*; *Mapeg*; *Marlowet*; *Simulsol.*

Table I: Synonyms of selected polyoxyethylene castor oil derivatives.

Name	Synonym
Polyoxyl 5 castor oil	*Acconon CA-5*; PEG-5 castor oil; polyoxyethylene 5 castor oil.
Polyoxyl 9 castor oil	*Acconon CA-9*; castor oil POE-9; PEG-9 castor oil; polyoxyethylene 9 castor oil; *Protachem CA-9.*
Polyoxyl 15 castor oil	*Acconon CA-15*; castor oil POE-15; PEG-15 castor oil; polyoxyethylene 15 castor oil; *Protachem CA-15.*
Polyoxyl 35 castor oil	*Cremophor EL; Cremophor ELP; Etocas 35*; glycerol polyethyleneglycol ricinoleate; polyethoxylated castor oil; polyoxyethylene 35 castor oil.
Polyoxyl 40 castor oil	Castor oil POE-40; *Croduret 40; Eumulgin RO; Nonionic GR-40*; PEG-40 castor oil; polyoxyethylene 40 castor oil; *Protachem CA-40.*
Polyoxyl 40 hydrogenated castor oil	*Cremophor RH 40; Eumulgin HRE 40*; glycerol polyethyleneglycol oxystearate; hydrogenated castor oil POE-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; Nonionic GRH-40; Protachem CAH-40.*
Polyoxyl 60 hydrogenated castor oil	*Eumulgin HRE 60;* hydrogenated castor oil POE-60; PEG-60 hydrogenated castor oil; polyoxyethylene 60 hydrogenated castor oil; *Lipocol HCO-60; Nikkol HCO 60; Protachem CAH-60.*

3 Chemical Name and CAS Registry Number

Polyethoxylated castor oil [61791-12-6]

4 Empirical Formula Molecular Weight

Polyoxyethylene castor oil derivatives are complex mixtures of various hydrophobic and hydrophilic components.

The PhEur 2002 states that polyoxyl castor oil contains mainly ricinoleyl glycerol ethoxylated with 30–50 molecules of ethylene oxide (nominal value). The PhEur 2002 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 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. They are also used in cosmetics and animal feeds.

Polyoxyl 35 castor oil (*Cremophor EL*) 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] 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.

To solubilize fat-soluble vitamins, the active ingredient or ingredients should first be dissolved in polyoxyl 35 castor oil (*Cremophor EL*). Water should then be added very slowly with vigorous stirring. As the water is added, the viscosity increases, reaching a maximum at a water content of approximately 40%

v/v. Solubilization can be facilitated by heating to approximately 60°C for a short time and in some cases by adding polyethylene glycol and/or propylene glycol. 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. Polyoxyl 35 castor oil (*Cremophor EL*) is also used in the production of glycerin suppositories.

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

In cosmetics, polyoxyl 35 castor oil (*Cremophor EL*) 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 (*Cremophor RH 40*) may be used in preference to polyoxyl 35 castor oil (*Cremophor EL*) in oral formulations since it is almost tasteless. In aqueous alcoholic or completely aqueous solutions, polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) 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 (*Cremophor RH 40*), 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 (*Cremophor RH 40*) 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 (*Cremophor RH 40*) can be suppressed by the addition of small amounts of polypropylene glycol 2000.

Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) is also used as an emulsifier of fatty acids and alcohols.

8 Description

Polyoxyl 35 castor oil (*Cremophor EL*) 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 (*Cremophor RH 40*) occurs as a white, semisolid paste that liquefies at 30°C. It has a very faint characteristic odor and a slight taste in aqueous solution.

Polyoxyl 60 hydrogenated castor oil (*Cremophor RH 60*) 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 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.

Table II: Pharmacopeial specifications for polyoxyethylene castor oil derivatives.

Test	PhEur 2002	PhEur 2002	USPNF 20	USPNF 20
	Polyoxyl castor oil	Polyoxyl hydrogenated castor oil	Polyoxyl 35 castor oil	Polyoxyl 40 hydrogenated castor oil
Identification	+	+	+	+
Characters	+	+	—	—
Appearance of solution	+	+	—	—
Alkalinity	+	+	—	—
Specific gravity	≈1.05	—	1.05–1.06	—
Congealing temperature	—	—	—	16–26°C
Viscosity at 25°C	500–800 mPa s	—	650–850 mPa s	—
Water	≤3.0%	≤3.0%	≤3.0%	≤3.0%
Residue on ignition	≤0.3%	≤0.3%	≤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
Iodine value	25–35	≤5	25–35	≤2.0
Saponification value	+	+	60–75	45–69
Dioxan	≤10 ppm	≤10 ppm	—	—
Free ethylene oxide	≤1 ppm	≤1 ppm	—	—
Organic volatile impurities	—	—	+	+

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	28–32	65–70	≤3%	19–20	—	72.5
Poloxyl 35 castor oil, purified (*Cremophor ELP*)	≤2.0	12–14	65–78	28–32	65–70	≤0.5%	—	—	—
Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*)	≤1.0	14–16	60–80	≤1	50–60	≤2%	≈30	21–23	95.6
Polyoxyl 60 hydrogenated castor oil	≤1.0	15–17	50–70	≤1	40–50	≤2%	≈40	—	—

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	—	—	—	—

[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	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

S = Soluble.

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

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 (*Cre-*) 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 (*Cremophor RH*) 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.

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 (*Cremophor EL*) is produced in this way by reacting 1 mole of castor oil with 35–40 moles of ethylene oxide.

Polyoxyl 40 hydrogenated castor oil (*Cremophor RH 40*) 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.[3,4] However, several serious anaphylactic reactions have been observed in humans and animals following parenteral administration of formulations containing polyoxyethylene castor oil derivatives.[5–16] The precise mechanism of the reaction is not known.

Table VI: LD_{50} values of selected polyoxyethylene castor oil derivatives.[3,4]

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.

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.

19 Specific References

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20 General References

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