

## #27963 Cremophor™ EL

## CAS 61791-12-6

### Composition

The main component of Cremophor EL is glycerol polyethylene glycol ricinoleate. Together with fatty acid esters of polyethylene glycol, this forms the hydrophobic part of the product. The smaller hydrophilic part consists of free polyethylene glycols and ethoxylated glycerol.

### Applications

Cremophor EL is recommended as a solubilizer and emulsifier in many different branches of industry. It is particularly suitable for the production of liquid preparations.

The form in which a hydrophobic substance is distributed in a liquid depends largely on its properties and on the amount of Cremophor EL used. It has been found that, as a rule, if Cremophor EL is present in excess, clear or opalescent liquids are obtained. However, if the proportion of Cremophor® EL is reduced to 5–10% of the water-insoluble substance, conditions exist for the formation of an emulsion.

### Solubility

Cremophor EL forms clear solutions in water. It is also soluble in many organic solvents, e.g. ethyl alcohol, n-propyl alcohol, isopropyl alcohol, ethyl acetate, chloroform, carbon tetrachloride, trichloroethylene, toluene and xylene.

In contrast to anionic emulsifying agents, Cremophor EL becomes less soluble in water at higher temperatures. Thus, aqueous solutions become turbid at a certain temperature.

Cremophor EL is miscible with all the other Cremophor grades and, on heating, also with fatty acids, fatty alcohols and certain animal and vegetable oils. It is thus miscible with oleic and stearic acids, dodecyl and octa-decyl alcohols, castor oil, and a number of lipid-soluble substances.

Saponification value	65–70
Acid value	≤ 2.0%
Hydroxyl value	65–78
Iodine value	25–35
Water	≤ 2.8%
pH (10% in water)	6–8
Ethylene oxide	≤ 1 ppm
1,4-Dioxane	≤ 10 ppm
Clarity (10% in water)	Conforms
Colour (10% in water)	Max. BY <sub>6</sub>
Density (25°C)	1.05–1.06 g/ml
Viscosity (25°C)	700–800 mPa · s
Sulfated ash (USP-NF)	≤ 0.2%
Ash (Ph. Eur.)	≤ 0.2%
Heavy metals	≤ 10 ppm
Residual solvents (Ph.Eur. 5.4):	Only the Class II solvents, ethylene glycol, and 1,4-dioxane, and Class III solvents are likely to be present. Residual ethylene glycol is below the Option 1 limit of 620 ppm. Residual 1,4-dioxane is below the Option 1 limit of 380 ppm and is separately specified. Residual Class III solvents are below 0.5%.
Microbiological status (Ph.Eur. 5.1.4, Cat. 2 + 3 a)	Conforms

**Pharmaceutical preparations**

Cremophor® EL emulsifies or solubilizes the fat-soluble vitamins A, D, E and K in aqueous solutions for oral and topical administration. In aqueous-alcoholic solutions, it very readily solubilizes essential oils. Aqueous solutions of hydrophobic drugs (e.g. Miconazole, Hexedetine, Clotrimazole, Benzocaine) can also be prepared with Cremophor EL.

To ensure that the fat-soluble vitamins yield clear aqueous solutions, they must first be intimately mixed with the solubilizer. The preferred forms of vitamin A for this purpose are Vitamin A Palmitate 1,700,000 I.U./g or Vitamin A Propionate 2,500,000 I.U./g; the preferred form of vitamin K is the K1 form (phytomenadione).

As the method used to solubilise a substance plays an important role, a typical example, the preparation of an aqueous vitamin A palmitate solution is described in detail below.

Vitamin A Palmitate 1,700,000 I. U./g	8.8 g
Cremophor EL	25.0 g
Water	ad 100 ml

The vitamin is mixed with the Cremophor EL, heated to 60–65°C and incorporated into the water also heated to 60–65°C. Initially, thickening occurs as a result of hydration, which reaches a maximum when about half of the water has been added. On addition of the remaining water, the viscosity decreases again. If the first half of the water is added too rapidly, a turbid solution may be obtained.

The following three diagrams show that clear aqueous solutions with very high concentrations of vitamin A palmitate, vitamin A propionate or vitamin E acetate can be obtained with the aid of Cremophor EL. The concentrations refer to the finished solubilisates.

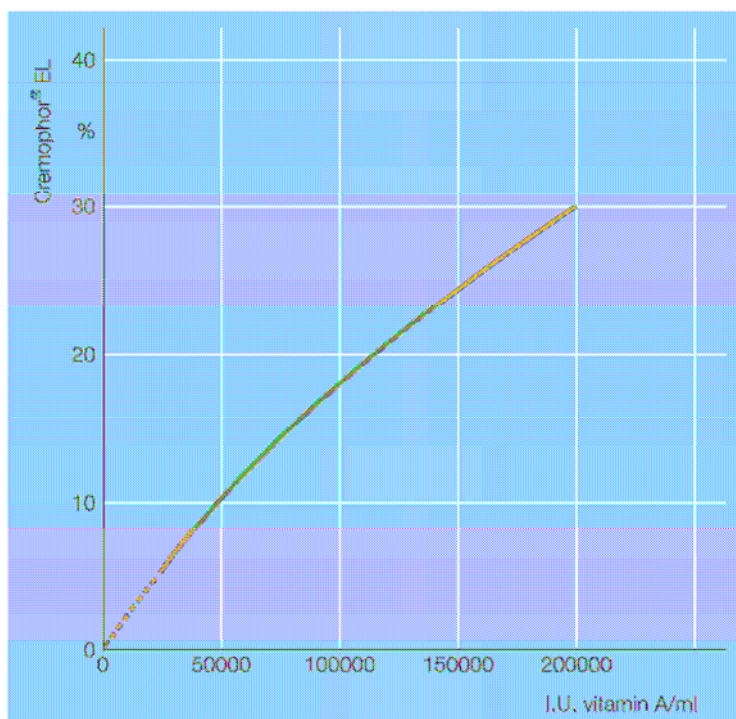


Fig. 1 Vitamin A palmitate

The following amounts of other fat-soluble vitamins can be dissolved in a 6% solution of Cremophor EL:

approx. 200,000 I.U. vitamin D<sub>2</sub>/ml or

approx. 10 mg vitamin K<sub>1</sub>/ml

As a rule, less Cremophor EL is required for mixtures of different vitamins.

**Vitamin A + vitamin D<sub>3</sub> + vitamin concentrate, water-miscible  
(120,000 I. U. + 60,000 I. U. + 40 mg/l)**

1. Formulations

I. Vitamin A Palmitate 1,700,000 I. U./g	7.10 g	–
Vitamin A Propionate 2,500,000 I. U./g	–	4.80 g
Vitamin D <sub>3</sub> 40,000,000 I. U./g	0.15 g	0.15 g
Vitamin E Acetate	4.20 g	4.20 g
Butylhydroxytoluene	0.06 g	0.06 g
Cremophor EL	30.0 g	30.0 g
II. Glycerin	6.50 g	6.50 g
Preservative	q. s.	q. s.
Water	ad 100 ml	ad 100 ml

2. Procedure

Heat Mixtures I and II to about 65°C and slowly incorporate Mixture II into Mixture I with stirring.

3. Properties of the solution

Clear yellow viscous liquid that is miscible with water.

Clarity: Formulation No. 1: 28 FTU

Formulation No. 2: 32 FTU

**Vitamin E solution with ethanol (0.01 % = 1mg/10 ml)**

1. Formulation

I. Vitamin E Acetate	10 mg
Cremophor EL	4.0–5.0 g
II. Water	57.0 g
Ethanol	38.0 g

2. Procedure

Heat Mixture I to about 60°C and slowly incorporate the warm solvent mixture II with stirring.

3. Properties of the solution

Clear colourless liquid of low viscosity.

The processing temperature and, in some cases, the amount of Cremophor EL required can be reduced by adding small amounts of polyethylene glycol (Lutrol® E 400), propylene glycol or glycerol. The stability of many solubilisates may be affected by light.

For oral dosage forms in human medicine, it is recommended to use the hydrogenated form, Cremophor RH 40 which is tasteless. The characteristic taste of Cremophor EL can usually be masked best with banana aroma.

A solution of one part of azulene in about four parts of Cremophor EL is freely miscible with water. In addition, Cremophor EL has proved to be a useful additive in the production of glycerol suppositories.

Manufacturing process

- synthetic
- semi-synthetic following fermentation
- purification of natural products
- Others

GMO

- GMO free (produced without genetic engineering)
- GMO-DNA free (not containing GMO-DNA)
- See attached statement*