Emulsifying agent for the pharmaceuticals, cosmetics and feedstuffs industries; used in aqueous preparations of hydrophobic substances, e.g. fat-soluble vitamins and essential oils.
Common names
Polyoxyethyleneglycoltriricinoleat 35 (DAC), Polyoxyl 35 Castor Oil (USP/NF).

Nature
Cremophor EL is a non-ionic solubilizer and emulsifier obtained by causing ethylene oxide to react with castor oil of German Pharmacopoeia (DAB 8) quality in a molar ratio of 35 moles to 1 mole.

Composition
The main component of Cremophor EL is glycerol-polyethylene glycol ricinoleate, which, together with fatty acid esters of polyethylene glycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol.

Properties
Cremophor EL is a pale yellow, oily liquid that is clear at temperatures above 26 °C. It has a slight but characteristic odour and can be completely liquefied by heating to 26 °C. The hydrophilic-lipophilic balance (HLB) lies between 12 and 14.

Specification
<table>
<thead>
<tr>
<th>Property</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Viscosity (Höppler) at 25 °C</td>
<td>700 – 850 mPa·s</td>
</tr>
<tr>
<td>Mass density at 25 °C</td>
<td>1.05 – 1.06 g/ml</td>
</tr>
<tr>
<td>Refractive index at 25 °C</td>
<td>1.465 – 1.475</td>
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<tr>
<td>Saponification value</td>
<td>63 – 72</td>
</tr>
<tr>
<td>Hydroxyl value</td>
<td>65 – 78</td>
</tr>
<tr>
<td>Iodine value</td>
<td>28 – 32</td>
</tr>
<tr>
<td>Acid value</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Water content (K. Fischer)</td>
<td>≤ 3 %</td>
</tr>
<tr>
<td>pH value of 10% aqueous solution</td>
<td>6 – 8</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 0.2 %</td>
</tr>
<tr>
<td>Heavy metals (USP XX method)</td>
<td>≤ 10 ppm</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, the values were determined according to the monograph "Polyoxyäthylenglyceroltriricinoleat 35" of the Deutscher Arzneimittelcodex and to the monograph "Polyoxyl 35 Castor Oil", USP/NF.

Solubility
Cremophor EL forms clear solutions in water. It is also soluble in ethyl alcohol, n-propyl alcohol, isopropyl alcohol, ethyl acetate, chloroform, carbon tetrachloride, trichloroethylene, toulene and xylene.

In contrast to that of anionic emulsifying agents, the solubility in water decreases with rising temperature. Thus, aqueous solutions become turbid at a certain temperature.

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

Stability
Cremophor EL in aqueous solutions is stable towards electrolytes, e.g. acids and salts, provided that their concentration is not too high. Mercury (II) chloride is an exception and forms a precipitate with the product.

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

Cremophor EL can be sterilized by heating in an autoclave for 30 minutes at 120 °C. It may thus acquire a deeper shade. During sterilization, Cremophor EL should not be heated together with substances that are strongly acidic or alkaline and would thus saponify it.

Application
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 degree to which the hydrophobic substance is distributed in the liquid depends largely on its properties and on the amount of Cremophor EL used. A rule of thumb is that, if Cremophor EL is present in excess, clear or opalescent liquids are obtained. However, if the proportion of Cremophor EL is reduced to, say 5 - 10%, expressed in terms of water-insoluble substance, conditions exist for the formation of an emulsion.
In aqueous solution, Cremophor EL emulsifies or solubilizes the fat-soluble vitamins A, D, E and K. In aqueous-alcoholic solutions, it very readily solubilizes essential oils. Other hydrophobic drugs can also be converted into aqueous solutions with Cremophor EL (e.g. Miconazole, Hexedetine, Clotrimazole, Benzocaine).

In order 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 with 1.7 million I.U./g or vitamin A propionate with 2.5 million I.U./g; and the preferred form of vitamin K is vitamin K₁ (phytomenadione).

An important factor is how the water-soluble substance is solubilized. Hence, a typical example, viz. the preparation of an aqueous vitamin A palmitate solution with 150,000 I.U./ml, is described in detail below.

Vitamin A palmitate 1.7 million I.U./g 8.8 g  
Cremophor EL 25.0 g  
Water ad 100 ml

The Cremophor EL is mixed with the vitamin and heated to 60 – 65 °C. The water, also heated to 60 – 65 °C, is intimately incorporated in the mixture by slowly stirring in. Initially, thickening occurs as a result of hydration and reaches a maximum when about half of the water has been added. On addition of the remaining water, the viscosity is reduced again. If the first half of the water is added too rapidly, an opalescent solution may be obtained.

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

Fig. 1 Vitamin A palmitate
Fig. 2  Vitamin A propionate

Fig. 3  Vitamin E acetate
The following amounts of other fat-soluble vitamins can be dissolved in a 6% solution of Cremophor EL:

- ca. 200 000 I.U. vitamin D₃/ml or
- ca. 10 mg vitamin K₁/ml

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

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 reasons of taste, it is recommended that the hydrogenated and thus tasteless form, viz. Cremophor RH 40, be used for oral application in human medicine. The inherent odour of Cremophor EL can best be masked in many cases with banana aroma.

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

**Cosmetics**

In the cosmetics industry, Cremophor EL is used preferentially for solubilizing perfume oils and for emulsifying fatty substances, organic solvents, and additives. Cremophor EL is an outstanding solubilizer for aroma chemicals and ethereal oils in aqueous isopropyl or ethyl alcohol, provided that the alcohol concentration is 30 – 50%. In many cases, extremely small additions of Cremophor EL are adequate under these conditions, so that the inherent odour of the product is completely masked. The solubilizers Cremophor RH 40 and Cremophor RH 60, which are also highly efficient, are completely free from odour and taste.

For the production of completely clear solutions of perfume oil in aqueous alcohol, the perfume oil and the solubilizer should be dissolved together in concentrated alcohol, after which the water is added slowly.

**Animal nutrition and veterinary medicine**

By virtue of its good dispersing action, Cremophor EL enables nutritive and therapeutic substances to be assimilated more completely and thus renders them more effective. This fact is of particular interest for compounded feeds containing oils and fats. A special application of Cremophor EL is the production of cod-liver oil emulsions in veterinary medicine.

**Physiological properties**

Cremophor EL is tolerated extremely well, as tests with single and repeated oral doses and exposure tests on the skin and mucous membranes have shown.

**Acute toxicity**

<table>
<thead>
<tr>
<th>Species</th>
<th>LD₅₀ (7 days follow-up period):</th>
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<tbody>
<tr>
<td>Rat oral</td>
<td>&gt; 6.4 ml/kg</td>
</tr>
<tr>
<td>Rabbit oral</td>
<td>&gt; 10.0 ml/kg</td>
</tr>
<tr>
<td>Cat oral</td>
<td>&gt; 10.0 ml/kg</td>
</tr>
<tr>
<td>Mouse i.v.</td>
<td>2.5 – 4 ml/kg</td>
</tr>
<tr>
<td>Rat percutaneous</td>
<td>&gt; 4.0 ml/kg (maximum applicable dose)</td>
</tr>
</tbody>
</table>

No characteristic toxic symptoms were observed after oral doses or application to the skin, and no pathological changes of the inner organs were discernible with the naked eye during autopsy.

**Acute inhalation toxicity**

Cremophor EL is practically non-volatile. In tests, rats have inhaled air saturated at 20 °C with the volatile components of the product for over eight hours without suffering any irritation of respiratory tract or any injury by absorption.

**Irritation of skin and mucous membranes**

Contact for more than 20 hours between the undiluted product and the highly sensitive skin on the backs and ears of white rabbits caused only slight or insignificant inflammation that disappeared rapidly.

This instillation of 0.05 ml of Cremophor EL in the rabbit’s conjunctival sac only caused slight reddening of the conjunctiva that disappeared within a few hours. The application of a 50% aqueous solution of the product caused slight irritation and lachrymation, both of which disappeared rapidly; 30% aqueous solutions had no irritant effect.
Repeated application of a 50% solution of Cremophor EL in acetone with a brush to the skin of guinea-pigs produced inflammatory reactions at the affected parts but did not cause any sensitization. Intracutaneous injection of 0.05 or 0.1 ml of a 0.1% solution in physiological sodium chloride solution ten times on successive days to a guinea-pig did not cause sensitization.

Subacute toxicity

Repeated oral administration of Cremophor EL in doses of 0.5, 1.0, 2.5 and 5.3 ml/kg daily (5 times a week over four weeks) with the oesophageal sound to beagles did not cause any clinically detectable disorder except for soft faeces in some cases. In clinical-chemical and pathological-histological tests, the experimental animals did not show any pathological changes attributable to Cremophor EL.

Feeding tests

In six-month feeding tests carried out on rats and dogs with Cremophor EL in concentrations of up to 1%, the experimental animals showed no visible symptoms of poisoning, no impairment of feed ingestion or growth, no detectable disorders of the blood and urine, no organic malfunctions, no increase in weight of the organs, and no abnormal organic mutation that could be detected in pathological-histological tests (no-effect level).

Teratological effect

No teratological or embryotoxic effect of Cremophor EL (tested according to the FDA specifications: Guidelines for reproduction studies for safety evaluation of drugs for human use; 1966) after oral application of 10 and 5 ml/kg daily from the 6th to the 15th day post coitum with the oesophageal sound was observed in NMRI mice. Even the addition of 10% and 5% of Cremophor EL to the feed of pregnant Sprague-Dawley rats during the organogenesis period, i.e. day 0 – 20, had no embryotoxic or teratological effect.

Detailed toxicological test reports on Cremophor EL are available on request.

Effect on action of drugs

The fine degree of dispersion resulting from addition of Cremophor EL allows a drug to be absorbed more readily and increases its efficiency.

Cremophor EL promotes the penetration of a number of active substances and exerts either activating or inactivating effects on others, e.g. antibiotics. Therefore, before Cremophor EL preparations are used in practice, it is advisable to subject them to thorough pharmacological tests.

Cremophor EL is subjected to detailed quality control involving comprehensive chemical and physical tests. The individual production batches are not, however, subjected to biological tests. For this reason, all producers of Cremophor EL preparations must carry out their own tests to check the suitability of the material used and the final preparations.

Cattle that have been subjected to parenteral treatment with certain vaccines or medicaments and subsequently injected with preparations containing Cremophor EL or similar solubilizers have displayed anaphylactoid reactions in isolated, exceptional cases. After the application of injections containing Cremophor EL to human beings, anaphylactoid reactions have sometimes been observed. For this reason, the health authorities in the Federal Republic of Germany and the U.K., for instance, have laid down that the content of polyethoxylated castor oil in injections for parenteral application to human beings must be declared, and any possibility of side effects must be pointed out in the package circular. This is an aspect to which companies producing pharmaceuticals for human beings must pay particular attention.

After oral administration of preparations containing Cremophor EL, side effects of this kind have not been observed.

Packaging

Drums of 60 kg and 120 kg capacity.

Product number

00647/1/63

Safety Data Sheet

A Safety Data Sheet is available.

Storage

Cremophor EL should be stored in tightly closed containers and protected from light. Prolonged storage is not advisable unless the containers are completely full.
Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

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