Technical Information

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Kolliphor™ EL

Macrogolglycerol Ricinoleate Ph. Eur., Polyoxyl 35 Castor Oil USP

(former Tradename Cremphor EL)

Solubiliser and emulsifying agent for the human and veterinary pharmaceutical industries; used in aqueous preparations of hydrophobic API's.

BASF
The Chemical Company

Pharma Ingredients & Services

Regulatory status

Meets currrent Macrogolglycerol Ricinoleate Ph. Eur. and Polyoxyl 35 Castor Oil USP monographs.

Chemical nature

Kolliphor EL is a nonionic solubiliser and emulsifier made by reacting castor oil with ethylene oxide in a molar ratio of 1 : 35.

Composition

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

Description

Kolliphor EL is a pale yellow oily liquid that is clear at temperatures above 26 °C. It has a faint but characteristic odour.

The hydrophilic-lipophilic balance (HLB) lies between 12 and 14.

The critical micelle concentration (CMC) lies at approx. 0.02%.

Solubility

Kolliphor 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, Kolliphor EL becomes less soluble in water at higher temperatures. Thus, aqueous solutions become turbid at a certain temperature.

Kolliphor EL is miscible with all the other Kolliphor 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.

Specification

See separate document: “Standard Specification (not for regulatory purposes)“ available via BASF’s WorldAccount: https://worldaccount.basf.com (registered access).

Stability

Kolliphor EL is stable for at least 2 years if stored in the unopened original containers at room temperature (max. 25 °C).

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

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

Kolliphor EL can be sterilized by heating in an autoclave for 30 minutes at 120 °C. This may give it a deeper shade. To avoid saponification, Kolliphor EL should not be heated together with very acidic or basic substances.

Applications

Kolliphor 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 Kolliphor EL used. It has been found that, as a rule, if Kolliphor EL is present in excess, clear or opalescent liquids are obtained. However, if the proportion of Kolliphor EL is reduced to 5 – 10% of the water-insoluble substance, conditions exist for the formation of an emulsion.

Pharmaceutical preparations

Kolliphor 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 Kolliphor 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
Kolliphor EL	25.0 g
Water	ad 100 ml

The vitamin is mixed with the Kolliphor 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 Kolliphor EL. The concentrations refer to the finished solubilisates.

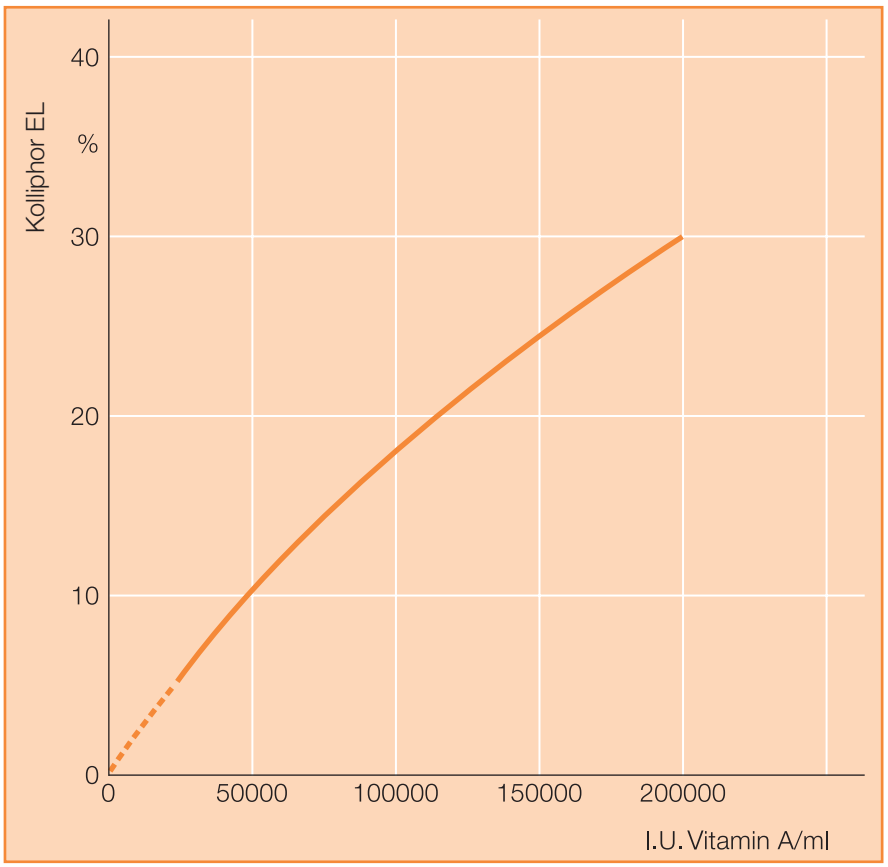

Fig. 1 Vitamin A palmitate

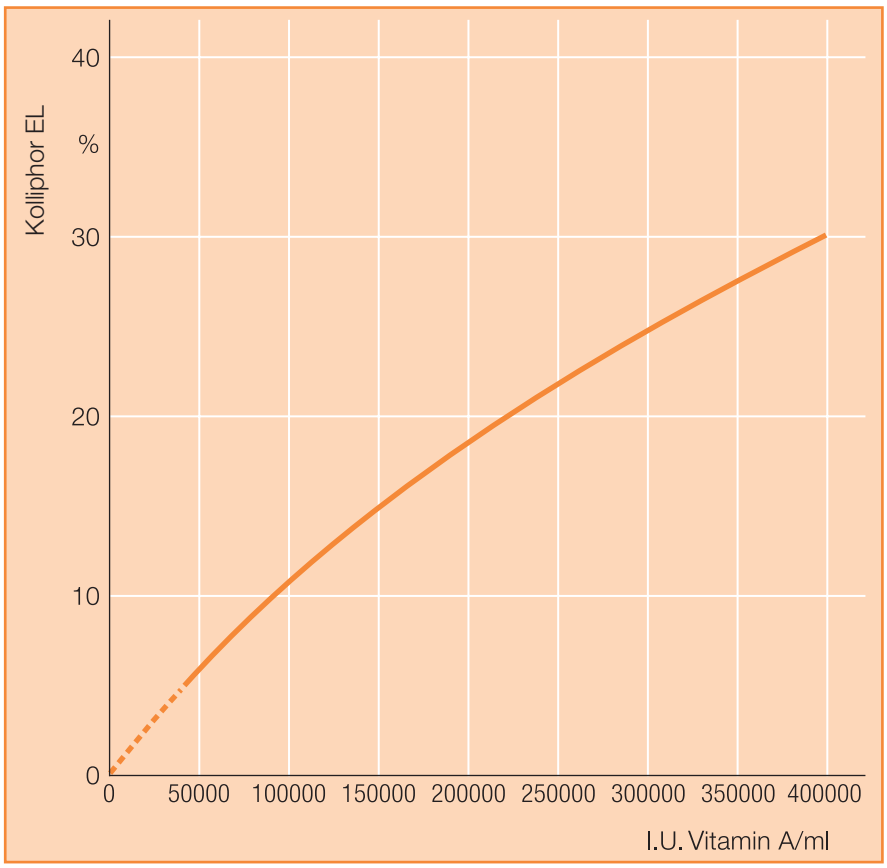

Fig. 2 Vitamin A propionate

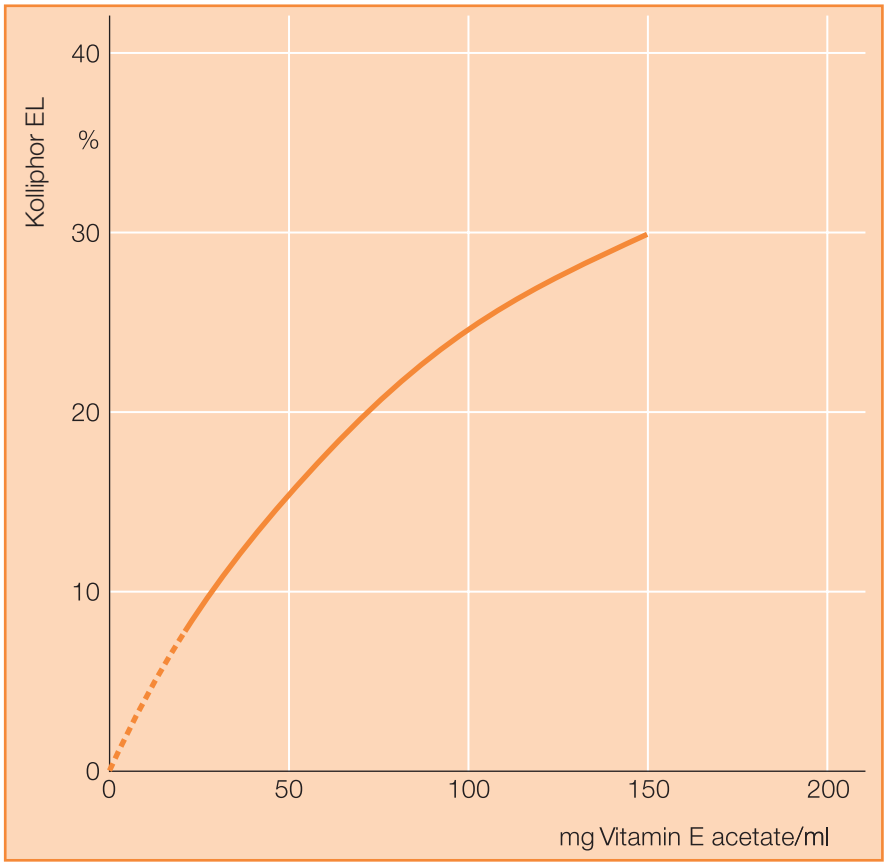

Fig. 3 Vitamin E acetate

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

approx. 200,000 I.U. vitamin D_3/ml or

approx. 10 mg vitamin K_1/ml

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

Vitamin A + vitamin D_3 + 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 D3 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
	Kolliphor 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% = 1 mg/10 ml)

1. Formulation

I.	Vitamin E Acetate	10 mg
	Kolliphor 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 Kolliphor 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, Kolliphor RH 40 which is tasteless. The characteristic taste of Kolliphor EL can usually be masked best with banana aroma.

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

Toxicology

After having signed a secery agreement, reports of the toxicological studies are available on request.

Important note

The fine dispersion of compounds that can be achieved with the aid of Kolliphor EL improves their absorption characteristics and efficacy.

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

Kolliphor EL is subjected to thorough quality controls involving comprehensive chemical and physical tests. The individual production batches are not, however, subjected to biological tests. For this reason, producers of preparations that contain Kolliphor EL must carry out their own tests to check the suitability of the respective material and of the final preparations.

Cattle that have been given certain vaccines or medicaments parenterally and have subsequently been injected with preparations containing Kolliphor EL or similar solubilizers have displayed anaphylactic reactions in isolated cases involving exceptional circumstances. Anaphylactic reactions have occasionally been observed in humans after injections containing Kolliphor EL. For this reason, the health authorities in the Federal Republic of Germany and the UK, for instance, have laid down that the content of polyethoxylated castor oil in injections for parenteral administra-tion to humans must be declared, and that attention must be drawn to the possibility of side effects in the package insert. This is an aspect to which companies producing pharmaceuticals for human use must pay particular attention.

No side effects of this kind have been observed after oral administration of preparations containing Kolliphor EL.

Recommendations for product handling and sampling

For proper product handling and sampling homogenization of the drum content is necessary. The new drums allow the repeated liquefaction of their content at around 60 °C. It is recommended to use electrical drum heaters, heating covers or a heating chamber.

PRD-No.

30554032

Packaging

60 kg and 120 kg removable-head steel drums with a Lupolen® inliner with its own lid.

Storage

Kolliphor EL should be stored in tightly closed containers protected from light. Prolonged storage is not recommended unless the containers are completely full.

Safety Data Sheet

A Safety Data Sheet is available for Kolliphor EL.

Note

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