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For the pharmaceuticals industry

Cremophor RH 40 is a solubilizer for fat-soluble vitamins, essential oils and other hydrophobic pharmaceuticals. Particular features are that it has very little odour and in aqueous solutions is almost tasteless.

The use of Cremophor RH 40 grades in cosmetic preparations is the subject of a separate leaflet.

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Macrogol-Glycerolhydroxystearat (DAB).
Polyoxyethylenglyceroltrihydroxystearat (DAC).

Chemical nature

Cremophor RH 40 is a nonionic solubilizer and emulsifying agent obtained by reacting 45 moles of ethylene oxide with 1 mole of hydrogenated castor oil.

The main constituent of Cremophor RH 40 is glycerol polyethylene glycol oxystearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate.

Properties

Cremophor RH 40 is a white to yellowish thin paste at 20 °C. The HLB value lies between 14 and 16.

Particular features are that it has very little odour and in aqueous solutions is almost tasteless.

Specification

Solidification point	20 – 28 °C
Saponification value	50 – 60
Hydroxyl value	60 – 75
Acid value	≤ 1
Iodine value	≤ 1
Water content, K. Fischer	≤ 2 %
pH value of 10 % aqueous solution	6 – 7
Colour strength of 10 % aqueous solution (Ph. Eur.)	Yellow 6 max.
Viscosity, Hoeppler, at 25 °C, 30 % aqueous solution	20 – 40 mPa · s
Ash	≤ 0.25 %
Heavy metals	≤ 10 ppm

Unless stated otherwise, the analytical methods have been taken from the monograph "Macrogol-Glycerolhydroxystearat" in DAB. The product fulfills the requirements of this monograph and those of USP/NF monograph "Polyoxyl 40 Hydrogenated Castor Oil".

Solubility

Cremophor RH 40 forms clear solutions in water, ethanol, 2-propanol, n-propanol, ethyl acetate, chloroform, carbon tetrachloride, toluene and xylene.

Solutions become cloudy as the temperature increases.

Cremophor RH 40 can be mixed with all other Cremophors. At elevated temperatures it forms clear mixtures with fatty acids and fatty alcohols.

Stability

Pure Cremophor RH 40 is chemically very stable. Prolonged exposure to heat can cause physical separation into a liquid and a solid phase on cooling but the product can be restored to its original form by homogenization.

Cremophor RH 40 is stable in aqueous alcohol and purely aqueous solutions. However, it must be noted that strong bases or acids should not be added, as otherwise the ester components may be saponified.

Aqueous Cremophor RH 40 solutions can be sterilized by heating to 120 °C. Allowance must be made for the fact that this can cause a slight decrease in the pH value. The phases may also separate during sterilization, but this can be remedied by agitating the solution while it is still hot.

The preservatives normally used in the pharmaceuticals industry may be added to the aqueous solutions. The requisite concentrations should be determined in tests.

Cremophor RH 40 is largely insensitive to water hardness.

Aqueous solutions of vitamins A, D, E and K for oral and topical administration can be prepared with the aid of Cremophor RH 40. The fact that the solubilizer has very little taste and odour is an asset for such applications.

In order to ensure that clear, aqueous solutions are obtained, the fat-soluble vitamins must first be intimately mixed with the solubilizer. Best results with vitamin A are obtained if it is in the form of vitamin A palmitate 1.7 million I.U./g, or vitamin A propionate 2.5 million I.U./g; or, in the case of vitamin K, if it is in the form of vitamin K 1 (phytomenadione).

As the method of preparing the solubilize is very important, the production of a 150000 I.U./ml aqueous vitamin A palmitate solution is described in detail as a typical example:

Vitamin A palmitate 1.7 million I.U./g	8.8 g
Cremophor RH 40	25.0 g
Water	ad 100 ml

The vitamin is mixed with Cremophor RH 40 and heated to 60 – 65 °C. The water, also heated to 60 – 65 °C, is added very slowly with thorough stirring into this mixture. As a result of hydration, the solution thickens, with the viscosity attaining a maximum after about half of the water has been added. Further addition of water then decreases the viscosity again. If the first half of the water is added too quickly, the solution can become opalescent. Alternatively, the warm mixture of the vitamin and Cremophor RH 40 can be slowly stirred into the water, which results in a lower increase in intermediate viscosity.

The following three diagrams demonstrate the use of Cremophor RH 40 for producing clear, highly concentrated, aqueous solutions of vitamin A palmitate, vitamin A propionate and vitamin E acetate.

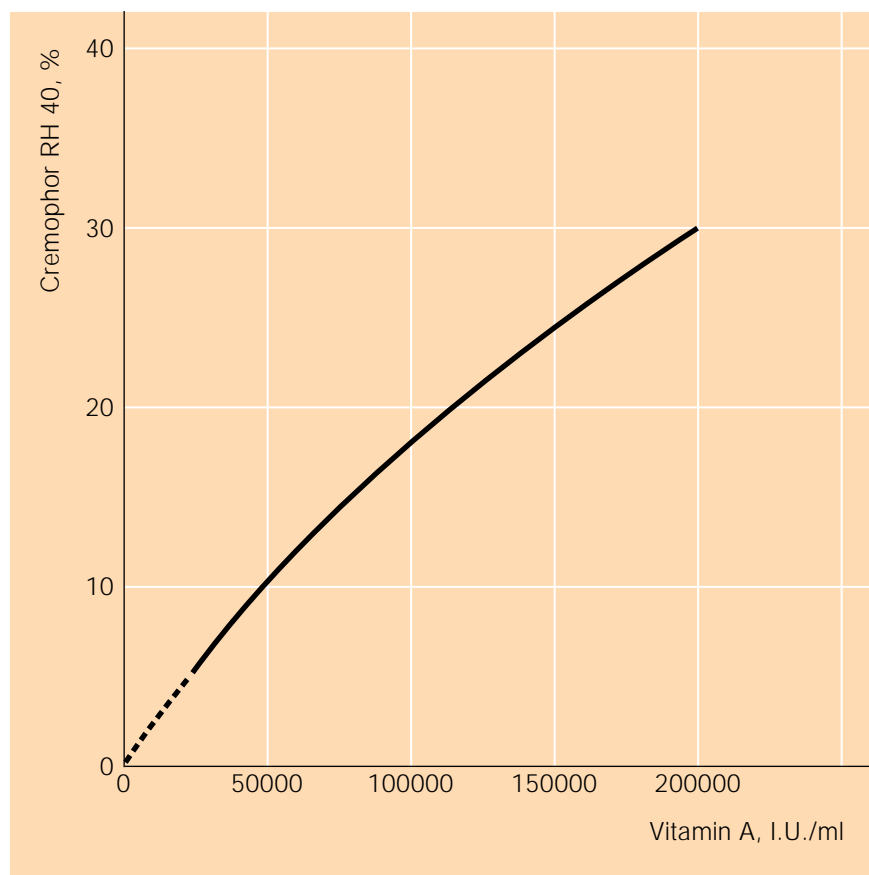


Fig. 1 Solubilization of vitamin A palmitate 1.7 million I.U./g

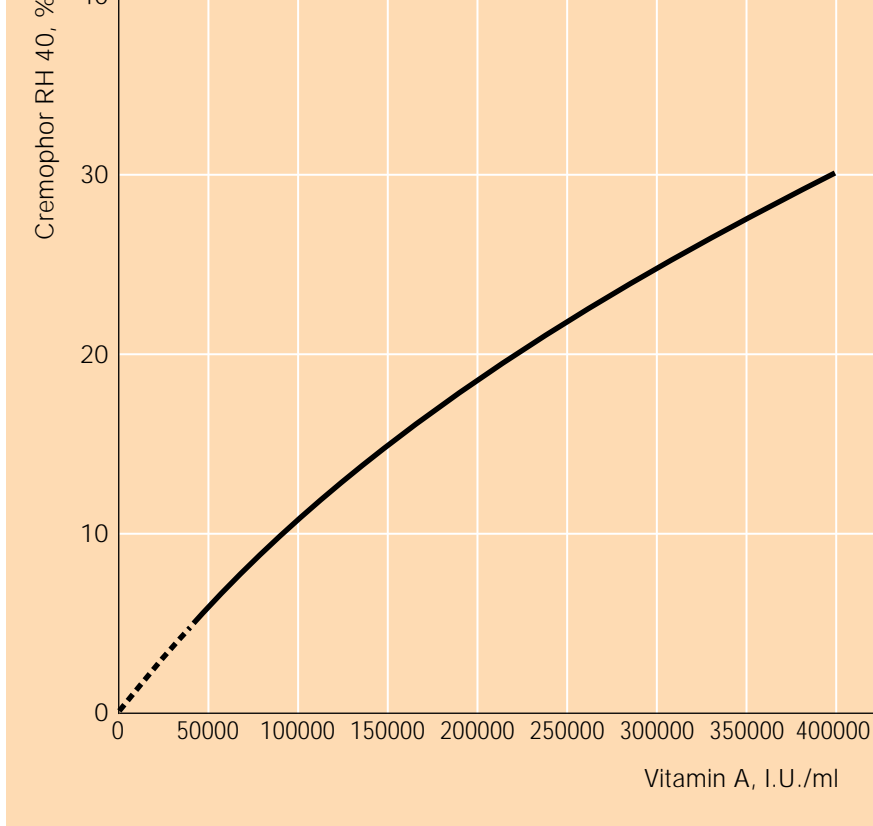


Fig. 2 Solubilization of vitamin A propionate 2.5 million I. U./g

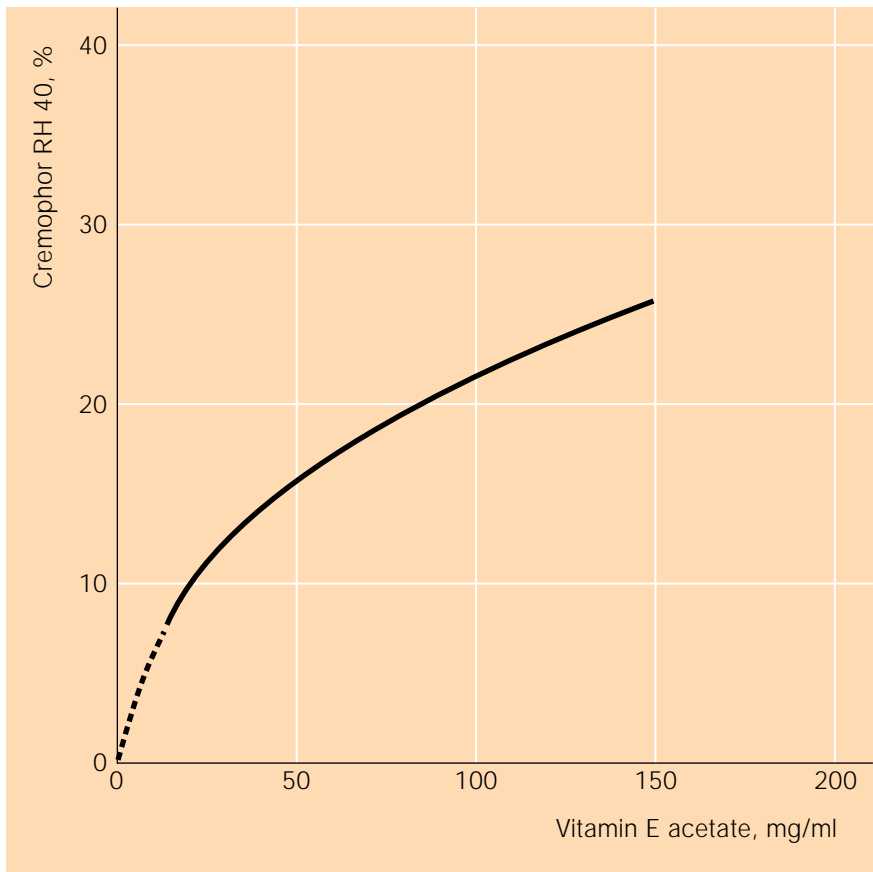


Fig. 3 Solubilization of vitamin E acetate

8 – 9 mg/ml Vitamin D₂ (400 000 I. U.), or
 5 mg/ml Vitamin D₃ (125 000 I. U.), or
 10 mg/ml Vitamin K₁

Less Cremophor RH 40 is usually required for mixtures of vitamins.

A small addition of polyethylene glycol (Lutrol® E 400), 1,2-propylene glycol or glycerol allows the preparation temperature and sometimes also the concentration of Cremophor RH 40 to be reduced. Typical formulations are contained in the brochure "Vitamin formulations – Solutions and tablets". The stability of most solubilized vitamins is affected by light.

Miscellaneous
 solubilizer applications

Clear, aqueous solutions of hydrophobic substances other than vitamins can be obtained with Cremophor RH 40. Examples are essential oils and certain drugs for oral and topical application. A feature of the solutions thus obtained is their good stability. The following substances serve as examples:

Hexachlorocyclohexane	Miconazole
Hexeditine	Gramicidin
Levomepromazine	Eucalyptol
Thiopental	Azulene
Benzocaine	Oil of anise
Clotrimazole	Oil of sage
Diazepam	

Cremophor RH 40 shows little tendency to foaming, which is particularly important for solutions in aqueous ethanol. Further foam suppression can be obtained by the addition of a small quantity of Polypropylene Glycol 2000.

Use as emulsifier

Cremophor RH 40 is also very suitable as an emulsifying agent. It will emulsify a wide range of hydrophobic substances, e.g. fatty acids, fatty alcohols and drugs.

Toxicity

Acute toxicity

The following values for the average lethal dose (LD 50) with a seven-day follow-up period were determined for Cremophor RH 40:

Species	Route	LD 50
		g/kg body weight
Rat	oral	> 16.0
Mouse	intraperitoneal	> 6.4
Mouse	intravenous	> 12.0

Subacute toxicity

For four weeks, rats were given feed containing Cremophor RH 40 in proportions of 3.2% and 6.4%. None of the animals displayed any symptoms whatever of poisoning.

Similarly, beagles tolerated Cremophor RH 40 in concentrations of 1%, 3% and 9% in their feed for four weeks without any clinically detectable symptoms.

The tolerance of Cremophor RH 40 was checked by intravenous administration in rats over a period of four weeks. It was found that, of the three dosages tested, the lowest, 300 mg/kg body weight/day was tolerated locally, while the next, 900 mg/kg body weight/day was tolerated generally.

Chronic toxicity

In feeding tests that lasted for six months, Cremophor RH 40 was tolerated in concentrations of up to 5% by dogs and in concentrations of up to 10% by rats.

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