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.
**Generic name**
Polyoxyl 40 Hydrogenated Castor Oil (USP/NF).
Macroglol-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**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solidification point</td>
<td>20 - 28 °C</td>
</tr>
<tr>
<td>Saponification value</td>
<td>50 – 60</td>
</tr>
<tr>
<td>Hydroxyl value</td>
<td>60 – 75</td>
</tr>
<tr>
<td>Acid value</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Iodine value</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Water content, K. Fischer</td>
<td>≤ 2 %</td>
</tr>
<tr>
<td>pH value of 10% aqueous solution</td>
<td>6 – 7</td>
</tr>
<tr>
<td>Colour strength of 10% aqueous solution (Ph. Eur.)</td>
<td>Yellow 6 max.</td>
</tr>
<tr>
<td>Viscosity, Hœppler, at 25 °C, 30% aqueous solution</td>
<td>20 – 40 mPa·s</td>
</tr>
<tr>
<td>Ash</td>
<td>≤ 0.25%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 10 ppm</td>
</tr>
</tbody>
</table>

Unless stated otherwise, the analytical methods have been taken from the monograph “Macroglol-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.
Application

Solubilization

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 150 000 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
Likewise, the following vitamin quantities can be solubilized by a 6% Cremophor RH 40 solution.

- 8 – 9 mg/ml Vitamin D\textsubscript{2} (400 000 I. U.), or
- 5 mg/ml Vitamin D\textsubscript{3} (125 000 I. U.), or
- 10 mg/ml Vitamin K\textsubscript{1}

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

A small addition of polyethylene glycol (Lutrol\textsuperscript{®} 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
- Hexeditine
- Levomepromazine
- Thiopental
- Benzocaine
- Clotrimazole
- Diazepam
- Miconazole
- Gramicidin
- Eucalyptol
- Azulene
- Oil of anise
- Oil of sage

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:

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD 50 (g/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>oral</td>
<td>&gt; 16.0</td>
</tr>
<tr>
<td>Mouse</td>
<td>intraperitoneal</td>
<td>&gt; 6.4</td>
</tr>
<tr>
<td>Mouse</td>
<td>intravenous</td>
<td>&gt; 12.0</td>
</tr>
</tbody>
</table>

#### 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.
Inhalation toxicity
Air saturated at 20 °C with any volatile components that may have been given off by the product was inhaled by rats for eight hours without any injury. It should also be noted that the use of Cremophor RH 40 in surface active inhalants for aerosol application to the mucous membranes of the human respiratory tract does not cause any irritation.

Compatibility with the skin and mucous membranes
Swab tests have demonstrated that Cremophor RH 40 is compatible with human skin.

The compatibility with the mucous membranes was investigated by applying a 30% aqueous solution of Cremophor RH 40 to the eyes of rabbits. This solution did not cause any inflammation.

Sensitization
Cremophor RH 40 solutions of 20% and 50% concentration in acetone were brushed ten times onto the skin of guinea pigs. They did not cause any sensitization of the skin. Likewise, no indications of a sensitizing effect on the skin of guinea pigs were observed in the Magnusson and Kligman maximization test (J. invest. Derm., 52, 268 – 276 [1969]).

Teratogenicity
This was investigated by the FDA guidelines for reproduction studies for safety evaluation of drugs for human use (Food and Drug Administration, Washington, January 1966). Cremophor RH 40 was administered orally ten times in doses of 5 000 and 10 000 mg/kg of body weight to pregnant NMRI mice from the sixth to the fifteenth day post coitum. No teratogenic or embryotoxic effects were detected.

Likewise, 5% and 10% of Cremophor RH 40 added on days zero to twenty post coitum to the feed of pregnant Sprague-Dawley rats did not exert any embryotoxic or teratogenic effects.

General
In common with other surfactants, Cremophor RH 40 may alter the rate of absorption of active substances. For this reason, it is advisable to subject preparations containing Cremophor RH 40 to pharmacological and clinical tests before they are released for general use. Attention is also drawn to local legislation concerning the handling of foodstuffs, food wrappings, cosmetics etc.

As there have been isolated reports of an anaphylactic reaction in animals and humans to the parenteral use of pharmaceutical products containing Cremophor EL (see technical leaflet Cremophor EL, BASF), similar reactions cannot be precluded for products containing Cremophor RH 40.

No such reactions have been observed after oral administration.

Storage
The drums in which Cremophor RH 40 is stored should be kept tightly closed.

The method of production employed for Cremophor RH 40 ensures that it is practically sterile. If the containers are repeatedly opened, microorganisms may grow in the product, particularly if the equipment used is not sterile.

Packaging
Drums of 40 kg capacity.

Product No.
67 363/1/36

Safety Data Sheet
A Safety Data Sheet is available.

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.

BASF Aktiengesellschaft
Unternehmensbereich Feinchemie
67056 Ludwigshafen, Germany