Macrogol 15 Hydroxystearate

1 Nonproprietary Names
BP: Macrogol 15 Hydroxystearate
PhEur: Macrogol 15 Hydroxystearate

2 Synonyms
12-Hydroxyoctadecanoic acid polymer with &g-hydro-ω-hydroxy-
poly(oxy-1,2-ethanediyl); 12-hydroxystearic acid polyethylene gly-
col copolymer; macrogoli 15 hydroxystearas; polyethylene glycol-
15-hydroxystearate; polyethylene glycol 660 12-hydroxystearate; 
Solutol HS 15.

3 Chemical Name and CAS Registry Number
2-Hydroxyethyl-12-hydroxyoctadecanoate [70142-34-6]

4 Empirical Formula and Molecular Weight
The PhEur 6.0 describes macrogol 15 hydroxystearate as a mixture 
of mainly monoesters and diesters of 12-hydroxystearic acid and 
macrogols obtained by the ethoxylation of 12-hydroxystearic acid. The 
number of moles of ethylene oxide reacted per mole of 12-
hydroxystearic acid is 15 (nominal value). It contains about 30% 
free macrogols.
C_{20}H_{40}O_4 344.53

5 Structural Formula
See Section 4.

6 Functional Category
Dissolution enhancer; nonionic surfactant; solubilizing agent; 
stabilizing agent.

7 Applications in Pharmaceutical Formulation or 
Technology
Macrogol 15 hydroxystearate is frequently used in preclinical 
testing of drugs, mainly for IV and other parenteral applica-
tions.\(^1\) The solubilizing capacity for some tested drugs (clo-
trimazole, carbamazepine, 17β-estradiol, sulfathiazole, and 
piroxicam) increases almost linearly with increasing concentration 
of solubilizing agent; see Figure 1. This is due to the formation of 
spherical micelles even at high concentrations of macrogol 15 
hydroxystearate. Similarly, tests have revealed that viscosity 
increases with increasing amount of solubilizer, but the amount of 
solubilized drugs does not have any additional influence on the 
kinematic viscosity; see Figure 2. Lipid nanocapsules comprising 
macrogol 15 hydroxystearate and soybean phosphatidylcholine 
containing 3% docetaxel have been successfully prepared by a 
solvent-free inversion process.

Macrogol 15 hydroxystearate has been used in the manufacture 
of aqueous parenteral preparations with vitamin A, D, E and K, and 
a number of other lipophilic pharmaceutical active agents, such as 
propanidid, miconazole, alfadolone, and alfaxalone. It is very 
efficient at solubilizing substances like fat-soluble vitamins and 
active ingredients of hydrophobic nature. It is also an excellent 
solubilizer for parenteral use, at a concentration of 20%, and the 
water solubility of different drugs may be enhanced by a factor of 
10–100, depending on the structure of the drug molecule.

8 Description
Macrogol 15 hydroxystearate is a yellowish-white, almost odorless 
waxy mass or paste at room temperature, which becomes liquid at 
approximately 30°C.

9 Pharmacopeial Specifications
See Table I.

10 Typical Properties
Acidity/alkalinity  pH = 6–7 (10% w/v aqueous solution at 20°C)
Critical micelle concentration  0.005–0.02%
Density  1.03 g/cm\(^3\)
Flash point  272°C
HLB value  14–16
Ignition temperature  360°C
Solidification temperature  25–30°C
Solubility  Soluble in organic solvents such as ethanol (95%), 
propan-2-ol, and very soluble in water to form clear solutions.
The solubility in water decreases with increasing temperature. It is insoluble in liquid paraffin.

**Viscosity (dynamic)** 12 mPa·s (12 cP) for a 30% w/v aqueous solution at 25°C; 73 mPa·s (73 cP) for a 30% w/v aqueous solution at 60°C.

### 11 Stability and Storage Conditions

Macrogol 15 hydroxystearate has a high chemical stability. The prolonged action of heat may induce physical separation into a liquid and a solid phase after cooling, which can be reversed by subsequent homogenization. Macrogol 15 hydroxystearate is stable for at least 24 months if stored in unopened airtight containers at room temperature (maximum 25°C). Aqueous solutions of macrogol 15 hydroxystearate can be heat-sterilized (121°C, 0.21 MPa). The pH may drop slightly during heating, which should be taken into account. Separation into phases may also occur, but agitating the hot solution can reverse this. Aqueous solutions can be stabilized with the standard preservatives used in pharmaceuticals.

Macrogol 15 hydroxystearate should be stored in tightly sealed containers in a dry place.

### 12 Incompatibilities

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### 13 Method of Manufacture

Macrogol 15 hydroxystearate is produced by reacting 15 moles of ethylene oxide with 1 mole of 12-hydroxystearic acid.

### 14 Safety

Macrogol 15 hydroxystearate is used in parenteral pharmaceutical preparations in concentrations up to 50% to solubilize diclofenac, propanidil, and vitamin K1. It has also been used in preclinical formulations in preparing supersaturated injectable formulations of water-insoluble molecules. It is generally regarded as a relatively nontoxic and nonirritant excipient.

Macrogol 15 hydroxystearate is reported not to be mutagenic in bacteria, mammalian cell cultures and mammals.

- \( \text{LD}_{50} \) (dog, IV): >3.10 g/kg\(^{(5)} \)
- \( \text{LD}_{50} \) (mouse, IP): >0.0085 g/kg
- \( \text{LD}_{50} \) (mouse, IV): >3.16 g/kg
- \( \text{LD}_{50} \) (rabbit, IV): 1.0–1.4 g/kg
- \( \text{LD}_{50} \) (rat, oral): >20 g/kg
- \( \text{LD}_{50} \) (rat, IV): 1.0–1.47 g/kg

### 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

### 16 Regulatory Status

Included in the Canadian List of Acceptable Non-medicinal Ingredients.

### 17 Related Substances

Polyethylene glycol.

### 18 Comments

Macrogol 15 hydroxystearate is not restricted solely to parenteral use, but is also suitable for oral applications.

Macrogol 15 hydroxystearate has been investigated as a co-emulsifier in the preparation of parenteral o/w emulsions\(^{(4)}\) and microemulsions.\(^{(11)}\) It has also been investigated as a weak inhibitor of cytochrome P450 3A activity on the metabolism of colchicine and midazolam.\(^{(10)}\)

Oral bioavailability of the highly lipophilic and poorly water-soluble immunosuppressive agent, ciclosporin A, showed twofold higher bioavailability with a macrogol 15 hydroxystearate-based formulation compared to a microsuspension.\(^{(12)}\) It has also been studied along with microcrystalline cellulose to prepare self-emulsifying pellets using an extrusion/spheronization technique to increase the bioavailability of lipophilic drugs.\(^{(13)}\)

Macrogol 15 hydroxystearate has been incorporated as a solubility-increasing additive in rectal suppository dosage form to study the increase in bioavailability of poorly water-soluble drugs.\(^{(14)}\)

Macrogol 15 hydroxystearate has been investigated as a therapeutic agent in the preparation of lipid nanoparticles of an anticancer drug,\(^{(15)}\) and has also been shown to be effective for reversing multidrug resistance, with low toxicity in vivo.\(^{(16)}\)

The PubChem Compound ID (CID) for Solutol HS 15 is 124898.

### 19 Specific References

Magnesium Aluminum Silicate

1 Nonproprietary Names
BP: Aluminium Magnesium Silicate
PhEur: Aluminium Magnesium Silicate
USP-NF: Magnesium Aluminum Silicate

2 Synonyms
Aluminii magnesii silicas; aluminosilicic acid, magnesium salt; aluminium magnesium silicate; Carrisorb; Gelsorb; Magnabrite; magnesium aluminosilicate; magnesium aluminum silicate, colloidal; magnesium aluminum silicate, complex colloidal; Neusilin; Pharmasorb; silicic acid, aluminum magnesium salt; Veegum.

3 Chemical Name and CAS Registry Number
Aluminum magnesium silicate [12511-31-8]
Magnesium aluminum silicate [1327-43-1]

4 Empirical Formula and Molecular Weight
Magnesium aluminum silicate is a polymeric complex of magnesium, aluminum, silicon, oxygen, and water. The average chemical analysis is conventionally expressed as oxides:
- Silicon dioxide 61.1%
- Magnesium oxide 13.7%
- Aluminum oxide 9.3%
- Titanium dioxide 0.1%
- Ferric oxide 0.9%
- Calcium oxide 2.7%
- Sodium oxide 2.9%
- Potassium oxide 0.3%
- Carbon dioxide 1.8%
- Water of combination 7.2%

5 Structural Formula
The complex is composed of a three-lattice layer of octahedral alumina and two tetrahedral silica sheets. The aluminum is substituted to varying degrees by magnesium (with sodium or potassium for balance of electrical charge). Additional elements present in small amounts include iron, lithium, titanium, calcium, and carbon.

6 Functional Category
Adsorbent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology
Magnesium aluminum silicate has been used for many years in the formulation of tablets, ointments, and creams. It is used in oral and topical formulations as a suspending and stabilizing agent either alone or in combination with other suspending agents. The viscosity of aqueous dispersions may be greatly increased by combination with other suspending agents, such as xanthan gum, owing to synergistic effects; see Xanthan Gum. In tablets, magnesium aluminum silicate is used as a binder and disintegrant in conventional or slow-release formulations. See Table I.

Magnesium aluminum silicate may cause bioavailability problems with certain drugs; see Section 12.

8 Description
The USP32–NF27 describes magnesium aluminum silicate as a blend of colloidal montmorillonite and saponite that has been processed to remove grit and nonswellable ore components. Four types of magnesium aluminum silicate are defined: types IA, IB, IC, and IIA. These types differ according to their viscosity and ratio of aluminum and magnesium content; see Table II.

The PhEur 6.3 describes magnesium aluminum silicate (aluminum magnesium silicate) as a mixture of particles with colloidal...