Technical Information

Kolliphor® HS 15

Macrogol 15 Hydroxystearate (Ph. Eur.)

Polyoxyl 15 Hydrostearate (USP/NF)

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1. Introduction

Kolliphor® HS 15 is a nonionic solubilizer and emulsifying agent obtained by reacting 15 moles of ethylene oxide with 1 mole of 12-hydroxy stearic acid.

Description

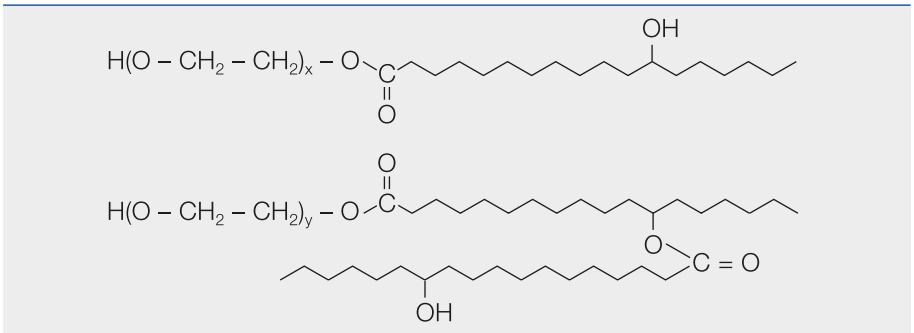
Kolliphor® HS 15 is a yellowish white paste at room temperature that becomes liquid at approx. 30 °C.

The hydrophilic-lipophilic balance lies between 14 and 16.

2. Technical properties

Structural formula

The main components of the lipophilic part have the following chemical structures:



A small part of the 12-hydroxy group can be etherified with polyethylene glycol.

CAS number

70142-34-6

Composition

Kolliphor® HS 15 consists of polyglycol mono- and di-esters of 12-hydroxystearic acid (= lipophilic part) and of about 30% of free polyethylene glycol (= hydrophilic part). The free polyethylene glycol can be determined by HPLC.

Critical micelle concentration

The critical micelle concentration (CMC) lies between 0.005 and 0.02%.
Micelles are typically in the range of 10-15 nm in diameter (dynamic light scattering) and slightly larger (up to 25 nm) when loaded with API. There is a sharp increase in micelle size at temperatures greater than 60.

Solubility

Kolliphor® HS 15 is soluble in water, ethanol and 2-propanol to form clear solutions. Its solubility in water decreases with increasing temperature. It is insoluble in liquid paraffin.

3. Example application

Kolliphor® HS 15 is a non-ionic, potent surfactant.

Kolliphor® HS 15 is now listed in the FDA IID and used in FDA approved parenteral and ophthalmic drugs.

Note: prior to sampling, filing or processing Kolliphor® HS 15 should be melted and lightly homogenized to ensure a representative sample. A recommended temperature is 50 – 65°C.

In order to test the effect of external stress on Kolliphor® HS 15, product was tested for applied stress for key applications. As noted, heating and mixing is beyond what is considered normal stability conditions, therefore this was tested independently and provided as technical data (not intended for regulatory or quality purposes). The product was subjected to 20 heat-cool cycles; each cycle started by heating the product to 65 °C and holding for 24 hours, the product was subsequently cooled to 4 °C and held for 24 hours prior to repeating the cycle. Key stability indicating parameters were tested.

As the product is also routinely sterilized for parenteral applications, key stability indicating parameters were evaluated pre and post sterilization via a 0.20 µm sterile filter (cellulose acetate) and one standard autoclave cycle (20 mins, 121 °C). The results of all three stress tests are compared in Table 1.

Table 1. Stress Test of Kolliphor® HS 15 as original sample, after filter and autoclave sterilization and after a 20 cycle heat stress test.

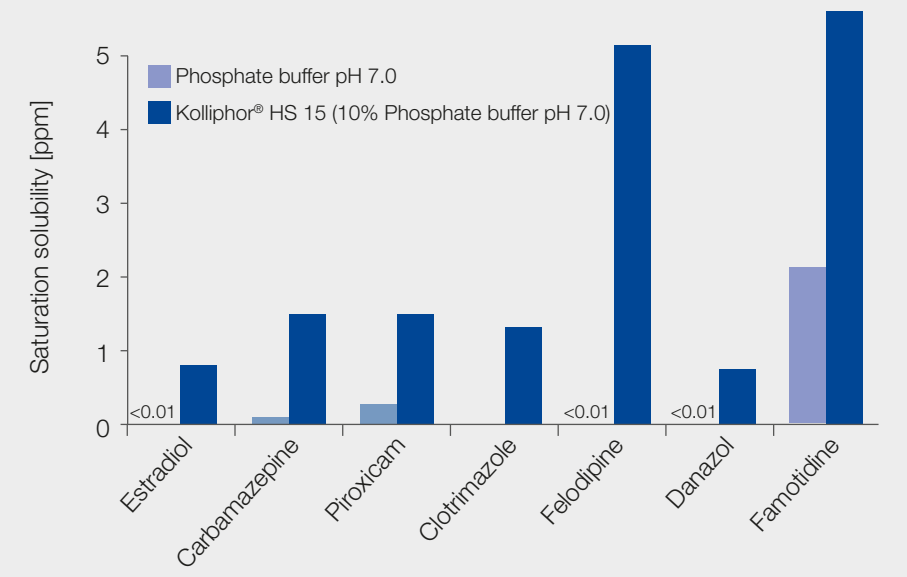
Kolliphor® HS 15 - 20%

		Blank	Filter	Autoclave	Stress Test
pH Value 20% (aq.)		6.64	6.62	6.29	5.6
Viscosity [mPas], 25 °C@1000 1/s		5.45	5.61	5.28	5.8
Aldehyde [mg/kg]	Formaldehyde	<1	<1	2	3
	Acetaldehyde	4	4	3	4
	Propionald.	<1	<1	<1	1
Peroxide Value [meq/kg]		<2	<2	<2	1
Hydoxyl Value [mg KOH/kg]		27	23	23	33
Iodine Value [g I2/100g]		0.3	0.4	0.3	0.2
Acid Value [mg KOH/g]		0.1	0.1	0.1	0.2

Gamma sterilization is not recommended for Kolliphor® HS 15.

Kolliphor® HS 15 is a potent, non-ionic solubilizer specifically designed for poorly water-soluble drugs in parenteral applications. Specifically, this solubilizer has been shown to increase the solubility several orders of magnitude of numerous poorly water-soluble drugs with relevant parenteral applications (see Figure 1.)

Figure 1. Several orders of magnitude increase in solubility shown for 10% buffered solutions of Kolliphor® HS 15.



Kolliphor® HS 15 was specifically designed to provide a low immunogenicity during parenteral administration. This is demonstrated by testing haemolytic activity, an assay designed to measure haemolysis (destruction of red blood cells, 100% considered poor). In this assay, Kolliphor® HS 15 at low concentrations shows no haemolysis, and at 10% exhibited slightly less, yet comparable results to a standard Polysorbate 80 (common parenteral solubilizer).

Next, histamine release is measured in a separate series of experiments, where post-injection, the serum histamine level (beagle dogs) is compared for Kolliphor® HS 15 vs. Polysorbate 80 at 0, 15 and 60 minutes. Specifically, the histamine release at 15 minutes post-injection is several orders of magnitude lower indicating an extremely low immunogenicity – this effect remains and returns to near baseline values after 60 minutes while lingering effects are noted for Polysorbate 80. All comparative data is shown in Table 2.

	Haemolytic activity [% Haemolysis]			Serum histamine level (beagle dogs) [nM]		
	0.1%	1%	10%	0 min	15 min	60 min
Kolliphor® HS 15	0	0	8.7	5	220	8
Polysorbate 80	0	0	11.1	3	>50000	247

4. Safety data sheet

Safety data sheets are available on request and are sent with every consignment.

5. Retest date and storage conditions

Please refer to Quality & Regulatory Product Information (QRPI).

6. Stability

Please refer to Quality & Regulatory Product Information (QRPI).

7. Toxicological data

The toxicological abstract is available on request.

8. PRD and Article numbers

PRD-No.*	Product name	Article numbers	Packaging	
30554050	Kolliphor® HS 15	50259817	0.5 kg	Plastic bottle
		50581346	50 kg	Steel drums

* BASF's commercial product number.

9. Publications

http://pharmaceutical.basf.com/en.html

10. Literature

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(6) D. B. Smith et al. Br. J. Cancer 57, 623 (1988)

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