

Technical Information

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Kolliphor™ P Grades

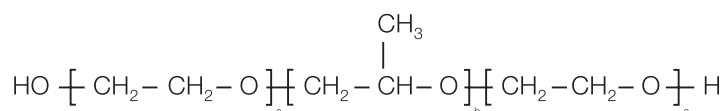
(former Tradename Lutrol F Grades)

Poloxamers Ph. Eur., Poloxamer USP/NF

Poloxamers for Pharmaceutical Use

Chemical nature

The Lutrol L and F-block copolymers are synthetic copolymers of ethylene oxide and propylene oxide represented by the following chemical structure:



Wherein a and b blocks have the following values:

Kolliphor	Poloxamer	a	b
P 188	188	80	27
P 237	237	64	37
P 338	338	141	44
P 407	407	101	56

CAS-No.

9003-11-6

Description

The Kolliphor P grades are white, coarse-grained powders with a waxy consistency. They contain an appropriate quantity of the antioxidant BHT.

PRD-Nos.

30554048	Kolliphor P 188
30555084	Kolliphor P 237
30555125	Kolliphor P 338
30555080	Kolliphor P 407

Specifications

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

US Drug Master File

BASF maintains a Drug Master File for Poloxamers at the FDA and is familiar with supplying information to the FDA to assist customers in obtaining FDA authorizations.

Further Typical Properties

Kolliphor	P 188	P 237	P 338	P 407
Physical Form	Solid, prill	Solid, prill	Solid, prill	Solid, prill
Cloud point, 10%, °C	>100	>100	>100	>100
APHA Color	100 max.	100 max.	80 max.	120 max.
BHT, ppm	50 – 125	50 – 125	50 – 125	50 – 125
D,l-alpha tocopherol, ppm	–	–	–	–
Specific gravity	1.06	1.04	1.06	1.05
Viscosity, cps	1000	700	2800	3100
Pour/melt point	52 °C	49 °C	57 °C	56 °C
Cloud point (1% aqueous)	>100 °C	>100 °C	>100 °C	>100 °C
Surface tension (0.1% aqueous at 25 °C) dynes/cm	50	44	41	41
HLB*-value	>24	>24	>24	18 – 23
Solubility in water at 25 °C	>10%	>10%	>10%	>10%

* HLB = hydrophilic-lipophilic balance

The poloxamers are not only readily soluble in water but also in polar and non-polar organic solvents.

The average particle size of the prilled Kolliphor P grades is around 1000 µm. Apart from the prilled products some microprilled poloxamers were developed for specific formulation needs. The microprilled products Kolliphor P 188 micro (microprilled Poloxamer 188) and Kolliphor P 407 micro (microprilled poloxamer 407) were microprilled to an average particle size of approximately 50 µm. Both products contain BHT.

For further information on the microprilled Kolliphor grades please refer to the individual Technical Information sheets.

Product Properties and fields of application

When dispersed in the liquid at low concentrations, Poloxamers exist individually as monomolecular micelles. When the concentration of the poloxamers in the system increases, this results in the formation of multimolecular aggregates. Polypropylene oxide (PPO) usually forms central hydrophobic cores wherein methyl groups interact via Van der Waals forces with the substance undergoing solubilization. However, water solubility is believed to be due to the polyethylene oxide (PEO) block by hydrogen bonding interactions of ether oxygen with water molecules. Due to these interactions, poloxamers are readily soluble in polar and non-polar organic solvents which allows a wide range of dosage forms to be formulated with these Excipients.

Kolliphor P 188 and Kolliphor P 237

Kolliphor P 188 and Kolliphor P 237 are used as wetting agents, as emulsifiers and solubilizers. Kolliphor P 188 and Kolliphor P 237 are suitable to prepare solid dispersions and to improve the solubility, absorption and bioavailability of low-solubility actives in solid oral dosage forms. The corresponding dosage forms are usually processed by melting or granulation. In addition, Kolliphor P 188 can also act as a co-emulsifier in creams and emulsions.

Aqueous solutions of Kolliphor P 188 have Newtonian flow properties that change to non-Newtonian behavior at higher concentrations. Aqueous solutions containing more than 20% Kolliphor P 188 are thermoreversible, i.e. the minimum viscosity is between 15 and 60 °C and the maximum viscosity between 75 and 80 °C (see Fig. 1).

Repeated heating and cooling does not affect this property.

The gelling properties of individual poloxamers depend on their molecular weight. Those with higher molecular weights show a pronounced gelling effect at lower concentrations. Thus Kolliphor P 338 and Kolliphor P 407 are the preferred poloxamers for gels. At lower concentrations, the poloxamers can be used to modulate the viscosity of liquid formulations.

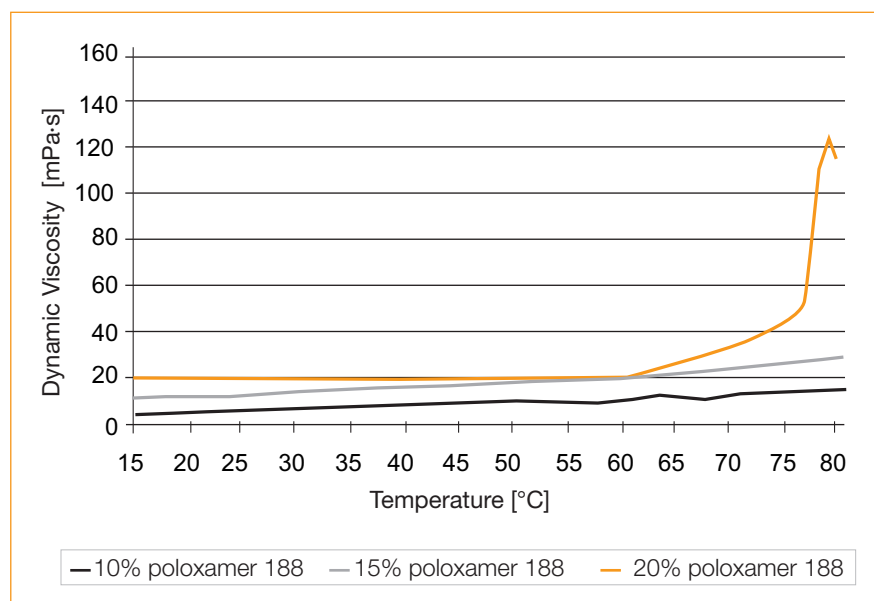


Fig. 1: Dynamic viscosity of aqueous solutions of Kolliphor P 188 as a function of temperature using a HAAKE Rheostress 6000 (RS) with a plate/plate configuration PP60Ti with 1,0mm distance and an amplitude of 0.010rad and a frequency of 1000/s

Kolliphor P 338 and Kolliphor P 407

Kolliphor P 338 and Kolliphor P 407 are used primarily as thickening agents and gel formers, but also as co-emulsifiers and consistency enhancers in creams and liquid emulsions. Kolliphor P 407 is also used as a solubilizer for certain active substances such as nifedipine, naproxen and fenticonazole as well as for essential oils in pharmaceutical formulations.

Moreover, Kolliphor P 407 is suitable for the formulation of active substances that show reduced solubility as well as chemical stability as a result of neutralization of gel formulations. Owing to its ability to affect viscosity, Kolliphor P 338 and Kolliphor P 407 are suitable as stabilizers for topically administered suspensions. Kolliphor P 407 is also used in toothpastes, gargles and mouthwashes.

In solid oral dosage forms the microprilled products Kolliphor P 188 micro and Kolliphor P 487 micro are successfully formulated because the very coarse prilled products are not very suitable as content uniformity of the solid oral dosage form will be influenced.

It is advised not to use the Kolliphor P grades outside the scope of recommended use. BASF especially advises customers to test Kolliphor P grade batches for applicability in biotechnological processes. Any application outside the recommended use is at customer's own risk and responsibility.

Thermoreversible gelation

Kolliphor P 338 and Kolliphor P 407 show the characteristic property of thermo-reversible gelation. The reversible thermal behavior of these two poloxamers in case of dilute as well as concentrated solutions was studied extensively. Generally, this type of behavior is observed in aqueous solutions of concentration range 16 – 30% w/w. They are liquid when refrigerated (4 – 5 °C) or heated to temperatures exceeding 70 °C but turn into gel form when at room temperature. They exhibit maximum viscosity in the range of 30 – 60 °C.

The gels thus formed are reversible again on cooling or heating.

Preparation of gels

Gels may generally be prepared by two methods:

1. "Cold process"

Kolliphor P 338 or Kolliphor P 407 are completely dissolved in water at room temperature or water pre-cooled to approx. 5 °C. Active substances that are insoluble in water are dissolved in ethanol, isopropanol or propylene glycol and mixed with the aqueous phase containing the poloxamer at 5 °C to form a homogeneous mass.

2. "Hot process"

Kolliphor P 407 is dissolved in water at approx. 70 °C. Active substances that are insoluble in water are dissolved in ethanol, isopropanol or propylene glycol at 70 °C and mixed with the warm aqueous phase to form a homogeneous mass. The gel forms when the solution cools to room temperature.

Both methods of preparation will generally yield gels with comparable properties.

Adding Kolliphor P 338 or Kolliphor P 407 to the hot aqueous phase to fast the formation of lumps may happen. These will only dissolve after standing for several hours. Any loss of solvent must be replaced, otherwise a thixotropic effect may be observed.

The "cold process" for the preparation of gels, particularly if active substances sensitive to heat are formulated is highly recommended. In order to prevent the gel to entrap air bubbles, a vacuum should be applied to the formulation before it starts to gel.

Gels using identical concentrations of Kolliphor P 407 but being prepared by either of the two methods described above did not reveal differences in their viscosity (see figure 2).

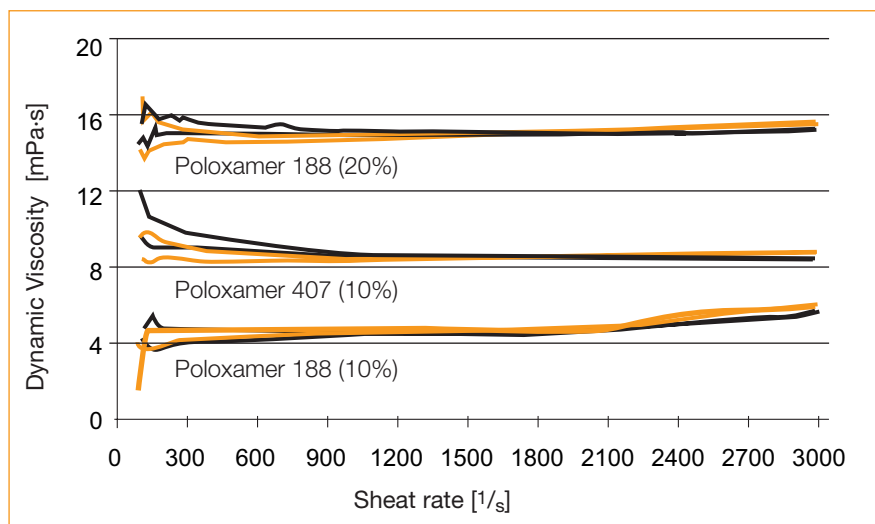


Fig. 2: Viscosity of aqueous Kolliphor P 407 prepared either by the hot (orange curve) or cold (black curve) process. Viscosity determination using a HAAKE Rotovisco 1 rotational viscometer with a double gap concentric cylinder measuring geometry DG43 with a cup.

The following figure shows the influence of increasing concentrations of Kolliphor P 407 on sol-gel transition temperature and on the gel strength. The determination is performed using an oscillating plate/plate configuration to avoid detrimental effects of higher shear rates on the gel strength.

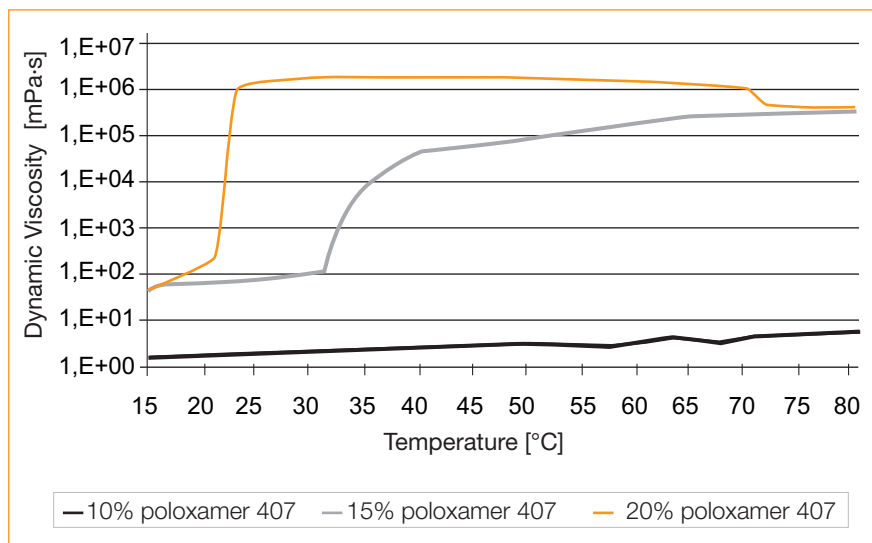


Fig. 3: Complex dynamic viscosity of aqueous Kolliphor P 407-gels as a function of temperature. Viscosity determination was performed using a HAAKE Rheostress 6000 with a plate/plate configuration PP60Ti with an amplitude of 0.010 and a frequency of 1000/s

Figure 4 shows the influence of the shear rate on the viscosity of a gel formulated with 20% Kolliphor P 407. The dynamic viscosity was determined using a HAAKE Rotovisco 1 (RV) with a double gap concentric cylinder measuring geometry DG43 with a cup. For the complex dynamic viscosity a HAAKE Rheostress 6000 (RS) with a plate/plate configuration PP60Ti with 1.0 mm distance and an amplitude of 0.010 rad and a frequency of 1000/s was applied

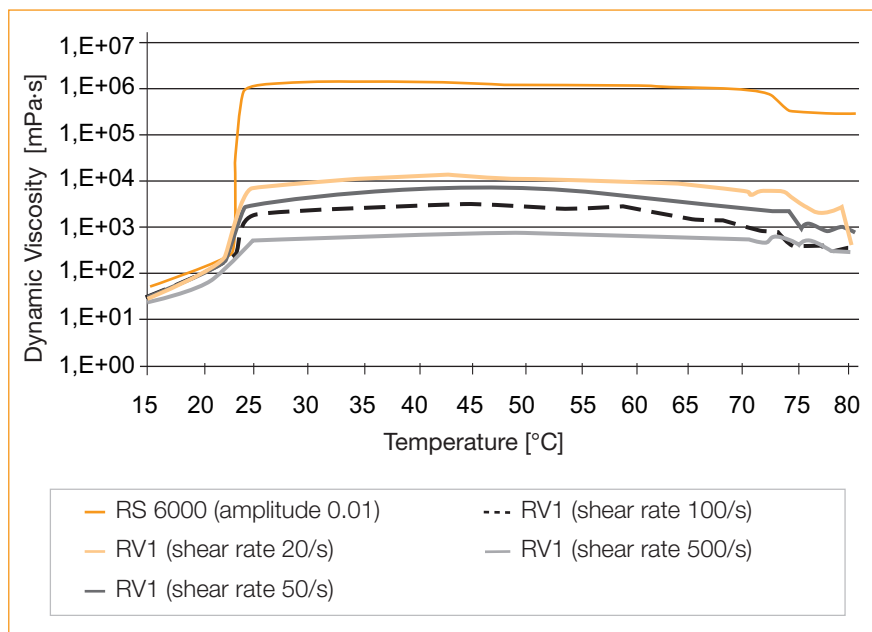


Fig. 4: Influence of the shear rate on the gel strength of a 20% Kolliphor P 407-gel

The dynamic viscosity of Kolliphor P 338 and Kolliphor P 407 gels may be affected by the addition of electrolytes, moisturizers, alcohols and surfactants. Figure 5 demonstrate the influence of sodium chloride and potassium chloride in a 20% Kolliphor P 407-gel. The addition of electrolytes at concentrations of around 1% increases the viscosity with little or no impact on the sol-gel transition temperature. Higher concentrations demonstrate a reduced gelling temperature with increased dynamic viscosity readings. In contrast to this, ethanol increases the gel formation temperature. The use of anionic surfactants may inhibit gel formation, even at Kolliphor P 487 micro concentrations exceeding 20%. This is true, for example, for sodium lauryl sulphate at concentrations above 2%. Low pH values affect both the sol-gel transition temperature and the viscosity.

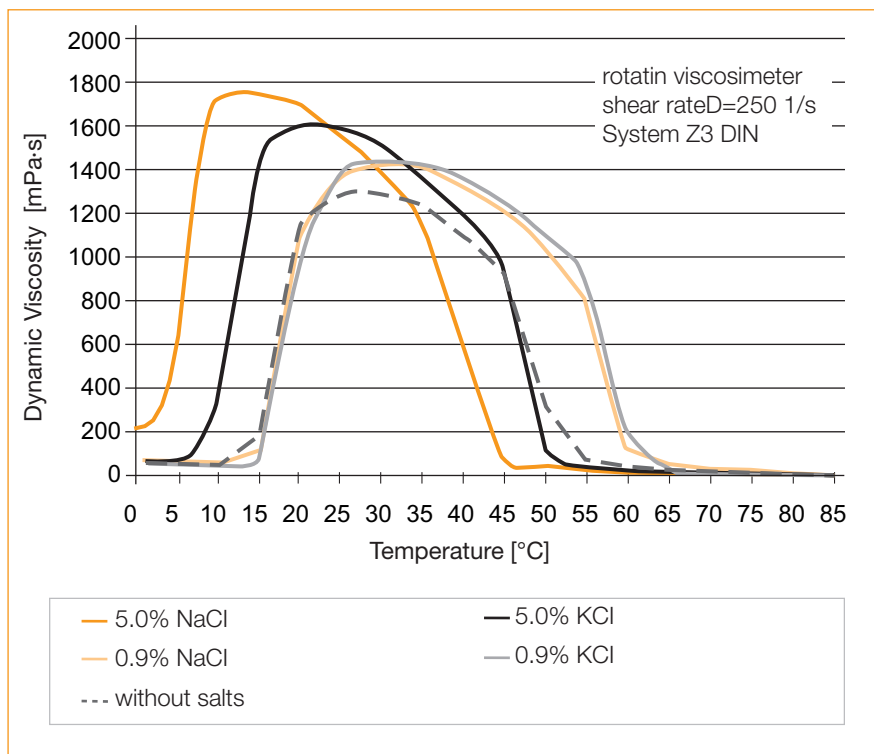


Fig. 5: Pour point of 25% aqueous Kolliphor P 407 gels at different NaCl – or KCl – levels (temp. 25 °C)

Examples for Gel Formulations

Typically applied gels formulated with Kolliphor P 338 and Kolliphor P 407 feel tacky to a certain extent. This tackiness can be minimized when the gels are formulated with 1% to 2% of either propylene carbonate or isopropyl myristate.

Kolliphor P 407 gel

Active substance	x g
Ethanol	18.0 g
Propylene carbonate	1.0 g
Kolliphor P 407	23.0 g
Purified water	58.0 g

Description: clear, stable, colorless gel.

Kolliphor P 338 gel

Active substance	x g
Isopropanol	10.0 g
Kolliphor IPM	2.0 g
Kolliphor P 338	20.0 g
Purified water	68.0 g

Description: clear, stable, colorless gel.

Kolliphor gel

Active substance	x g
Propylene glycol	20.0 g
Kolliphor P 407	22.0 g
Kolliphor P 338	5.0 g
NaCl	1.0 g
Water	51.0 g

Description: clear, stable, colorless gel

Article numbers & Packaging

Kolliphor	P 188	P 237	P 338	P 407
Bulk containers	57-gallon fiber drum			
Net weight, kg	102		80	90
Article number	50252131		50254773	50254757
Mid size containers	13 ½-gallon fiber drum			
Net weight, kg	25	25	18	25
Article number	50253396	50254772	50254774	50254789
Samples				
Net weight, kg	0.5	0.5	0.5	0.5
Article number	51633115	50102804	50118158	51632903

Stability and storage

The retest period for the Kolliphor P Grades is two years when stored in properly sealed containers at temperatures below 25 °C.

Handling and Disposal

Please refer to the individual Material Safety Data Sheet (MSDS) for instructions on safe and proper handling and disposal.

Kollisolv P 124

For proper product handling and sampling homogenization of the drum content is necessary (thoroughly mixing at room temperature).

Note

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