Expanding the toolbox of surfactants available for biologics formulations with Kolliphor® HS 15 and Kolliphor® ELP

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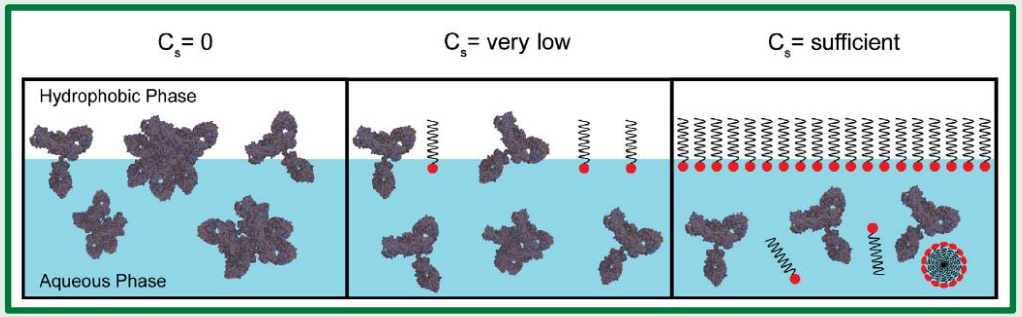
INTRODUCTION

Biologics comprise a diverse array of therapeutic modalities that include antibodies, proteins, and vaccines. While their biological activity is highly dependent on their structural conformation, their structural integrity can be easily damaged due to common stresses that can lead to reduced biological efficacy. Therefore, biologics formulations require excipients to stabilize the active pharmaceutical ingredients (APIs) to ensure safe and efficacious drugs can be delivered to patients. Surfactants are a key excipient used in biologics formulations that stabilize protein conformations by reducing interfacial and hydrophobic interactions that can damage protein conformations and lead to aggregation. The current toolbox of surfactants used in biologics formulations is limited to polysorbate 80, polysorbate 20, and poloxamer 188, with polysorbate 80 being the most commonly used surfactant. However, it is well established that polysorbates suffer from degradation issues that can cause safety concerns and damage to APIs. Additionally, every biologic has a unique and complex chemical makeup, which necessitates the development of custom-made formulations. Therefore, there is an unmet need within the biopharmaceutical industry for additional surfactants that can be used to stabilize biologics formulations for parenteral administration. Here we present two surfactants, Kolliphor® HS 15 and Kolliphor® ELP, that can stabilize proteins against commonly experienced stresses and have a prior history of use in FDA approved parenteral formulations.

Proteins can aggregate and destabilize when exposed to hydrophobic environments such as air-water interfaces and hydrophobic patches on nearby proteins. In biologics formulations, protein aggregation can lead to reduced biological activity and safety concerns for patients.



Surfactants stabilize proteins in formulations by:

- Interactions at interfacial regions
- Interactions between hydrophobic surfaces on proteins

1 *Reference: Khan et al., European Journal of Pharmaceutics and Biopharmaceutics 97 (2015) 60–67.*

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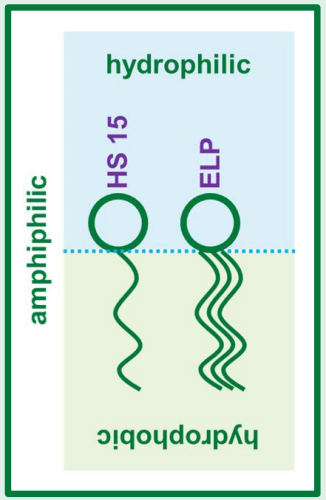
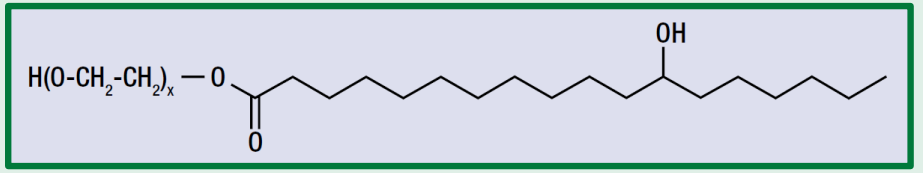
Kolliphor® HS 15 and Kolliphor® ELP

Nonionic surfactants for use in parenteral biologics formulations

Biologics drug products experience many environmental stresses from the time of manufacturing, to transport, and final delivery to patients. When proteins are exposed to various mechanical and chemical stresses, their structural and chemical integrity can be damaged, leading to aggregation and denaturation. For the drug product, such damage leads to a loss of therapeutic activity and can lead to safety issues. Therefore, excipients including surfactants are added to biologics formulations to stabilize the proteins against structural and chemical damage. The amphiphilic nature of surfactants reduce unwanted interactions between proteins and other protein, air interfaces, and the surfaces of containers used to hold the drug products.



Kolliphor® HS 15

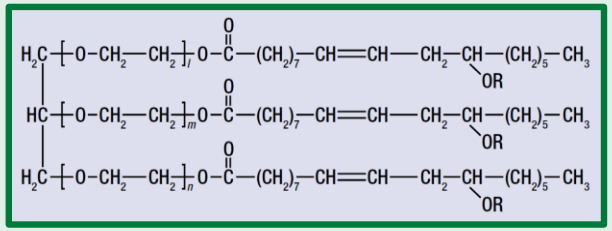


- Water soluble, amphiphilic, and nonionic surfactant
- Critical micelle concentration of 0.02%
- Hydrophilic lipophilic balance of 15

Product	Functionality	Monograph title	Chemical category	FDA IID listing
Kolliphor® HS 15	Nonionic solubilizer and emulsifier (surfactant; HLB = 15)	Macrogol 15 Hydroxystearate (Ph. Eur.) Polyoxyl 15 Hydroxystearate (USP/NF)	Polyethoxylated 12-hydroxystearic acid	Yes[1]
Kolliphor® ELP	Nonionic solubilizer and emulsifier (surfactant; HLB = 12–14)	Macrogolglycerol ricinoleate (Ph. Eur.) Polyoxyl-35-castor oil (USP/NF)	Polyethoxylated castor oil	Yes

[1]Kolliphor® HS 15 is used in a recently FDA-approved parenteral drug. For over ten years Kolliphor® HS 15 has been used in injectable drug formulations in both Canada and Europe.

Kolliphor® ELP



- Water soluble, amphiphilic, and nonionic surfactant
- Critical micelle concentration of 0.02%
- Hydrophilic lipophilic balance of 12-14

Reference: Reintjes, T. Solubility Enhancement with BASF Pharma Polymers: Solubilizer Compendium (2011).

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Kolliphor® HS 15 and Kolliphor® ELP in biologics formulations

Enhance the stability of proteins against environmental stresses

Mechanical Stress: Visible Aggregates

Model Protein BSA

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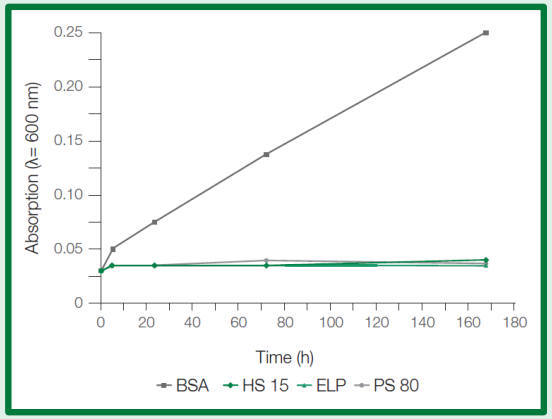
Mechanical Stress
stir a 40 mg/mL solution for 168 h at 40ºC

↓

Monitor Protein Stability
measure aggregation



Mechanical Stress: Sub-Visible Aggregates

Model Protein BSA

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Mechanical Stress
stir a 40 mg/mL solution for 168 h at 40ºC

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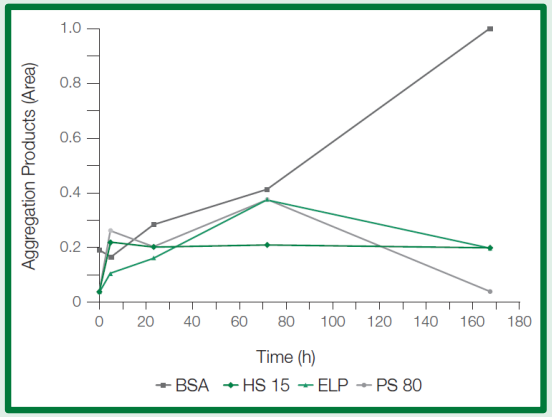
Monitor Protein Stability
measure aggregation



Chemical Stress: Autooxidation

Model Enzyme α-Amylase

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Chemical Stress
incubate for 60 days at RT with surfactants

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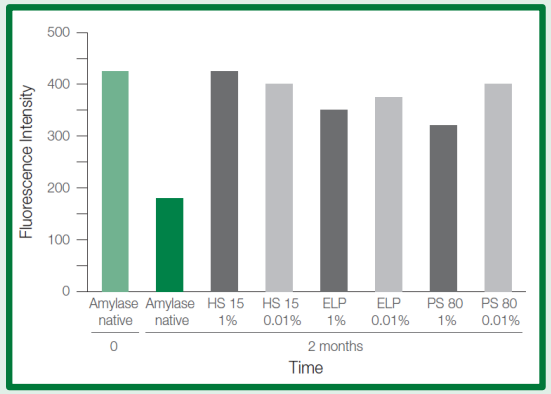
Measure Enzyme Activity
quantitative enzyme assay



DISCUSSION

Polysorbate 80 is the most commonly used surfactant in biologics formulations for stabilizing proteins against common stresses. Thus, we evaluated the performance of Kolliphor® HS 15, Kolliphor® ELP, and polysorbate 80 in protein formulations by monitoring mechanical and chemical stresses. We evaluated the stabilizing effects of the three surfactants in the presence of mechanical stress. When BSA solutions were stressed by vigorously stirring solutions at elevated temperatures, all three surfactants were able to significantly reduce the formation of visible protein aggregates with aggregate formation remaining consistently low for the duration of the 168 h study. Similar results were observed when viewing the formation of sub-visible aggregates with all three surfactants demonstrating comparable performance. Additionally, excipients used in protein formulations can contain impurities that cause oxidative damage to proteins, thereby reducing their biological activity. Accordingly, we assessed the activity of a model enzyme after 60 days of incubation in the absence and presence of surfactants. In the absence of surfactants, we observed a more than 50% reduction in enzyme activity, however α-amylase maintained its enzymatic activity in the presence of all three surfactants. Therefore, Kolliphor® HS 15, Kolliphor® ELP, and polysorbate 80 demonstrate similar performance, where they do not contribute to oxidative damage and can stabilize protein formulations against mechanical stress.

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Kolliphor® HS 15 and Kolliphor® ELP

Production adheres to the highest quality and regulatory standards

Made In

Kolliphor® HS 15 and Kolliphor® ELP for parenteral applications are produced in Ludwigshafen, Germany by qualified and experienced personnel in line with the highest quality standards.

Customer Support

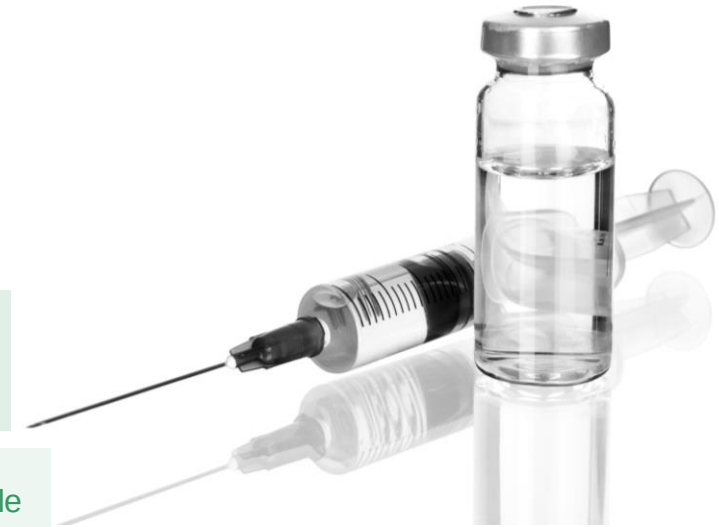
We support our customers with our technical expertise, access to industry-leading tools and analytics, and a deep and profound understanding of our excipients, which allows us to enable our customers to tackle their formulation challenges rapidly and efficiently.

Parenteral Formulations

Kolliphor® HS 15 and Kolliphor® ELP have previously been used for the parenteral delivery of challenging APIs and are listed in the FDA IID.

Sterilization

Kolliphor® HS 15 and Kolliphor® ELP are proven to maintain their stability after sterile filtration, autoclave sterilization and heat stress cycling.



The quality and regulatory benchmarks BASF applies to its excipients for parenteral use is comprised of:

- ✓ Manufacturing according to IPEC-PQG GMP
- ✓ Compendial compliance covering current and proposed major global pharmacopoeia standards
- ✓ Elemental impurity limits according to ICH Q3D, stability studies according to ICH conditions
- ✓ Endotoxin and microbial testing
- ✓ Regulatory documentation, registration and submission support
- ✓ Non-clinical safety data

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