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Control Strategies for Particles Arising from HCP-mediated Degradation of Polysorbate: A Regulatory Perspective

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Presentation Overview

- Overview
  - Particles, polysorbate, HCP
- Regulatory Expectations
  - Investigation and studies
- Control strategy
  - Particles
  - Polysorbate
  - HCP

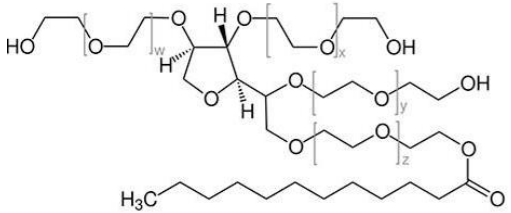
Particle Formation

- USP <787-790> and <1178> provide guidance on particles in injectables
- Particles can be classed as;
  - Extrinsic
  - Intrinsic
  - Inherent
- The concerns regarding particles include;
  - Potential risk to patient safety
  - Potentially immunogenic
  - Potential impact to product quality
  - Potential impact to processes (filters)

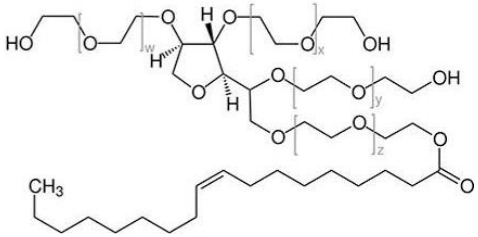
Polysorbate Overview

- Polysorbate is a common surfactant used to protect biopharmaceuticals against interfacial stresses experienced during manufacture, transport, and storage
- Function to prevent protein aggregation
- Sorbitan group with polymerized ethylene oxide groups and partial esters of fatty acids

Polysorbate 20



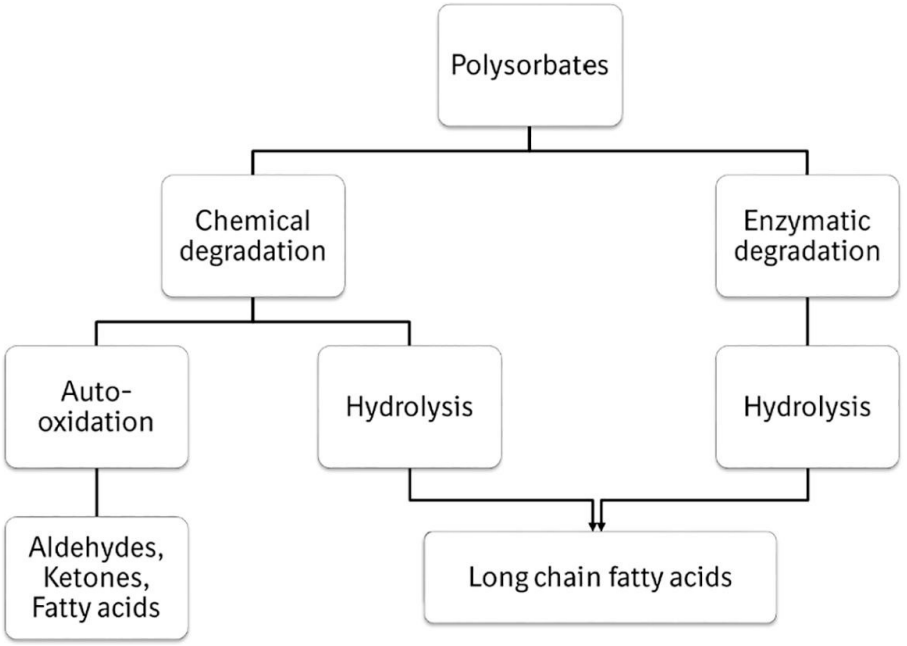
Polysorbate 80



Taken from Dwivedi et al., Int. J. Pharm, 2018

Degradation Mechanisms

- Polysorbate can degrade through oxidative or hydrolytic mechanisms
  - Oxidation is typical due to the presence of oxygen and the product contact material
  - Hydrolysis can be either chemical or enzymatic
- The degradation products are indicative of the mechanism of degradation



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HCPs

- ‘Hitch-hiker proteins’ co-elute by binding to the product
  - Binding has been localized to the CDR in the Fab region
  - Binding has been characterized as weak
  - Binding is mAb-dependent

- Examples of HCP known to co-elute with mAbs include;
  - Triacylgycerol lipase
  - Phospholipase B-like 2 (PLBL2)
  - Lipoprotein lipase
  - Lysomonal phospholipase A2
  - Carboxyl ester hydrolase

HCPs and polysorbate degradation

- Typical narrative for uncovering particles arising from HCP-mediated degradation of polysorbate
  - Out-of-specification or out-of-trend result is observed at 12-18 months for drug product on stability under long-term storage conditions of 2-8°C
    - Particles – Visible (VP) or subvisible (SVP)
    - Clarity - turbidity
  - Polysorbate levels are observed to have decreased over the same period

Regulatory Expectations

- Demonstrate that the manufacturing process is capable of consistently producing product with the desired qualities and with very low levels of impurities

- Investigations and studies are expected to be provided when polysorbate degradation and/or particle formation have been observed

- Results of the investigations and studies are used to inform the manufacturing process changes and control strategies

Investigation – Particle Composition

- Composition of the particles can be indicative of the root cause of the particle formation
  - SVP and VP containing FA esters, aldehydes, and ketones are likely due to oxidation
  - SVP and VP composed primarily of FFA and free of protein are likely due to enzymatic degradation of polysorbate
  - SVP and VP composed of proteinaceous components likely result from factors other than HCP-mediated degradation of polysorbate

Investigation – Root Cause

- Source of degradation – Enzymatic
  - Protein dilution studies
    - HCP assay – no change in result with sample dilution
    - Polysorbate degradation assay – decrease in result with sample dilution
  - Lipase inhibitor studies
- Quantification and Identification of lipolytic HCPs
  - Quantify level of the contaminating HCP
    - Low levels (<LOQ of the assay) v. high levels (~100 ppm)
  - Identification of the lipolytic HCP
    - Sensitive identification methods

Investigation – Questions

- Was the increase in particles the result of a process change?
  - Change in cell line
  - Removal of HIC chromatography step
  - New supplier of polysorbate

- Was the increase in particles the result of a test method change?
  - Previous methods not sensitive to SVP particles
  - Previously not monitoring polysorbate levels

Additional Assessments

- Toxicological Assessment
  - FFA from particles
  - Immunogenicity of the contaminating HCP

- Establish the minimum effective level for polysorbate to ensure CQAs of the product are maintained at release and over the shelf life of the drug product

Control Strategy

- The aim of the control strategy should be to minimize the contaminating HCP and to decrease particle formation in response to degradation of polysorbate

- Polysorbate should be defined as a critical excipient if changes in polysorbate levels are observed over the shelf life and result in an increase in the formation of particles

- A control strategy is required when particles arise from HCP-mediated degradation of polysorbate

Control Strategy

- Control of Raw Materials
  - Testing of polysorbate to ensure quality
  - Selection of polysorbate starting material
    - Customized polysorbates with higher contents of shorter chain FA
      - Shorter chain FA are more soluble and are less likely to form particles
      - Potential to change prevent degradation of polysorbate

Control Strategy

- Control during manufacturing process
  - Lipase-free cell line
  - Addition of a HIC chromatography step
  - In-process control for HCP / identified HCP-lipase
  - In-process control to ensure correct amount of polysorbate is added
    - Based on manufacturing process development and formulation development studies that identify the level of polysorbate required to ensure product quality

Control Strategy

- Controlling particles and polysorbate for release and stability of the drug product
  - Controlling VP and SVP particles should be included in the stability protocol and as part of the long-term, accelerated, and stressed stability studies
  - Polysorbate content should be controlled as part of the stability protocol with an appropriate specification

- Use of an in-line filter prior to administration to remove particles

Health Canada

- We welcome regulatory questions via pre-CTA meetings or pre-NDS meetings in-person or via teleconference
- Contact Office of Regulatory Affairs

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