Croda Pharma

Pharmaceutical excipients for ophthalmic formulations

Developing an ophthalmic drug product requires focus on key factors, such as drug stabilisation, irritation minimisation and meeting low endotoxin level requirements. These factors can impact final formulation success. High purity excipients can maximise the success rate of drug development by offering enhanced API stability, reduced cellular irritation and minimised endotoxin contribution to the final formulation.

Croda's Super Refined process yields highly purified excipients that can maximise drug product value by addressing these key factors.

Drug value:

- Optimised drug performance
- Increased patient compliance
- Decreased formulation development time
- Increased speed to market

Formulation benefits:

- Reduced peroxide values
- Reduced cellular irritation
- Reduced endotoxin levels

Benefits and features:

- LAL testing on each batch
- Low peroxide values
- Low moisture
- Multi-compendial – USP/NF, PhEur, JPE/JP and ChP

Smart science to improve lives™

CRODA

Reduced peroxide values

Super Refining removes potentially hazardous impurities, such as oxidative species (peroxides) and carbonyls, from Croda's high purity range of excipients allowing for increased API stability, a reduction in cellular irritation and improved patient compliance.

To demonstrate improved oxidative stability, the peroxide value of Super Refined PEG 400 was compared to standard compendial grade PEG 400 NF over 4 weeks in accelerated ageing temperatures (50˚C)[1]. It was seen (Figure 1) that the Super Refined excipient, initially and at 4 weeks, continued to exhibit a peroxide value that was >60% lower than the peroxide value of the standard compendial PEG 400 NF. The reduced peroxide value for Super Refined PEG 400 indicates the potential for enhanced protection of the drug active and overall formulation.

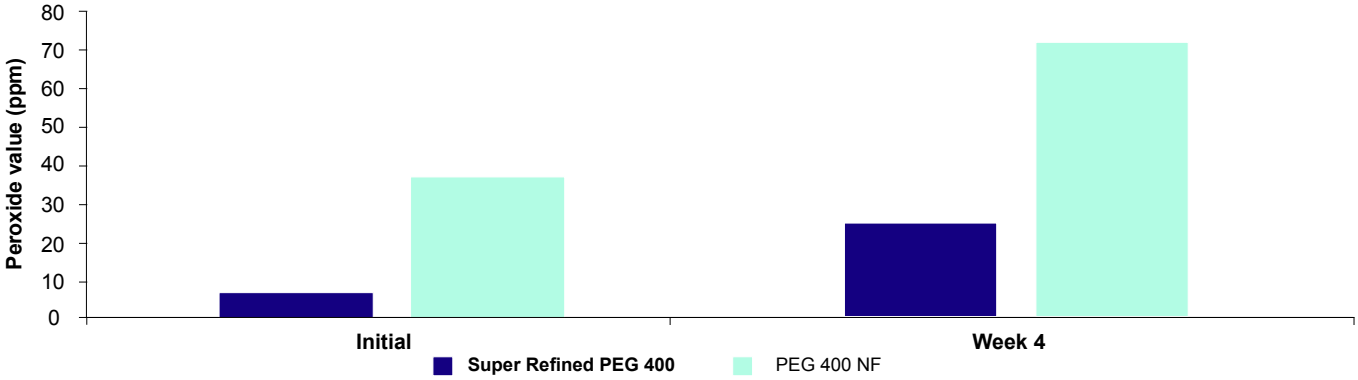

Figure 1: A graph comparing differences in peroxide levels between Super Refined PEG 400 and PEG 400 NF over 4 weeks at 50°C

Reduced cellular irritation

Formaldehyde is a known irritant to the cell membrane with high levels being indicative of greater cellular irritation. The following graph (Figure 2) demonstrates that Super Refined Polysorbate 20 has a significantly lower level of formaldehyde as compared to the standard compendial grade.

In addition, a Trans-Epithelial Permeability (TEP) assay was performed to compare Super Refined Polysorbate 20 against standard compendial grade polysorbate 20. The following graph (Figure 3) demonstrates how the lower impurity profile of Super Refined Polysorbate 20 reduces the potential for cellular irritation[2].

Formaldehyde content in two grades of Polysorbate 20

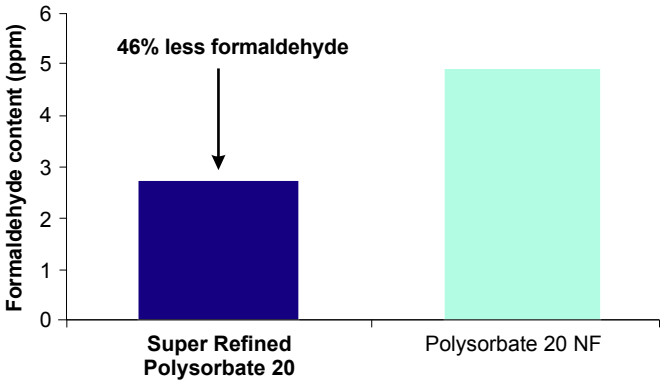

Figure 2: A graph showing differences in formaldehyde levels between Super Refined Polysorbate 20 and Polysorbate 20 NF

TEP assay with three formulations that contain different grades of Polysorbate 20

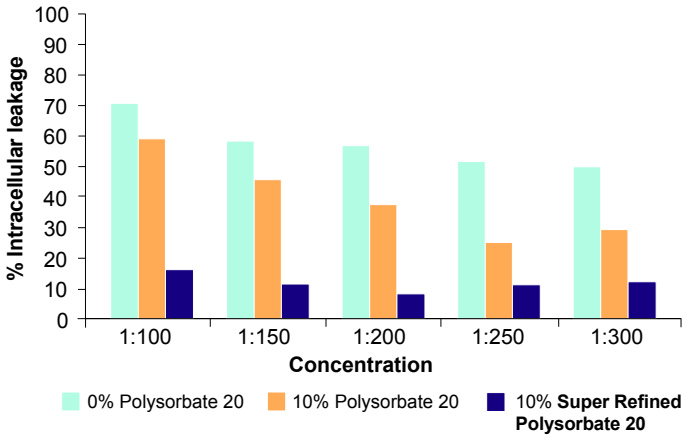

Figure 3: A graph demonstrating the lower percentage of intracellular leakage that Super Refined Polysorbate 20 contributes to various concentrations of a surfactant system as compared to a non-Super Refined polysorbate

Reduced endotoxin levels

With strict guidelines for endotoxin testing on the final drug product, there is a need to formulate with ingredients that have minimal contribution to the total endotoxin level. The Super Refining process yields a reduction in the endotoxin units (EU/ml) of the high purity excipients within this product range as detected by the limulus amoebocyte lysate (LAL) assay using the USP 85 gel clot method.

Figure 4 highlights some examples of the lower endotoxin levels that can be obtained by Super Refining as compared to monograph specification ranges.

Excipient	LAL specification (EU/ml)	LAL typical results (EU/ml)
Super Refined™ Castor Oil	0-0.25	0.12
Super Refined™ PEG 300	0-10	4.0
Super Refined™ PEG 400	0-10	2.0
Super Refined™ Polysorbate 20*	0-10	1.0
Super Refined™ Polysorbate 60	0-2	0.2
Super Refined™ Polysorbate 80	0-1	0.2

*USP 85 kinetic turbidimetric technique

Figure 4: A sample set of Super Refined excipients demonstrating lower endotoxin levels

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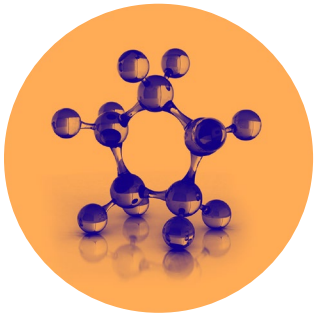
Ophthalmic excipient offerings

The below table includes our ophthalmic excipient offerings, listed in alphabetical order by chemical description.

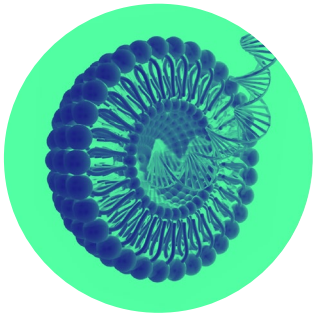
Chemical description	Product name	NF/USP	PhEur	JPE/JP	ChP	FDA IID (Ophthalmic)
Benzyl Alcohol	Super Refined™ Benzyl Alcohol	■	■	■		
Castor Oil	Super Refined™ Castor Oil	■		■	■	■
Diethylene Glycol Monoethyl Ether	Super Refined™ DEGEE	■	■			
Glyceryl Monostearate	Cithrol™ GMS 40 pharma	■	■			■
Lanolin	††	■	■			■
Lanolin Alcohols	Super Hartolan™ pharma	■	■			■
Linseed Oil	Super Refined™ Linseed Oil	†	†			
Peanut Oil	Super Refined™ Peanut Oil	■	■			
Petrolatum	Super Refined™ Petrolatum			■		■
Poloxamer 188	Synperonic™ PE/F 68 pharma	■	■			■
Poloxamer 237	Synperonic™ PE/F 87 pharma	■	■	■		
Poloxamer 407	Synperonic™ PE/F 127	■	■	■		■
Polyethylene Glycol 300	Super Refined™ PEG 300	■	■	■		■
Polyethylene Glycol 400	Super Refined™ PEG 400	■	■	■		■
Polyethylene Glycol 400	Super Refined™ PEG 400 LTG	■	■	■	■	■
Polyoxyl 15 Hydroxystearate	Crodasol™ HS HP	■	■			■
Polyoxyl 35 Castor Oil	Super Refined™ P35 Castor Oil	■	■	■		■
Polyoxyl 40 Hydrogenated Castor Oil	Croduret™ 40 pharma	■	■			■
Polyoxyl 40 Stearate	Myrj™ S40 pharma	■	■		■	■
Polysorbate 20	Super Refined™ Polysorbate 20‡	■	■	■	■	■
Polysorbate 80	Super Refined™ Polysorbate 80‡	■	■	■	■	■
Polysorbate 80 POA	Super Refined™ Polysorbate 80 POA‡	■	■	■	■	
Propylene Glycol	Super Refined™ Propylene Glycol	■		■	■	■

† Super Refined Linseed Oil currently meets all test specifications listed on the USP and PhEur monographs
‡ Used in both ophthalmic formulations applied to eye surface, in addition to biologic formulations injected directly into the eye (intravitreal injection)
†† Please ask your sales representative about our variety of pharmaceutical-grade lanolin products

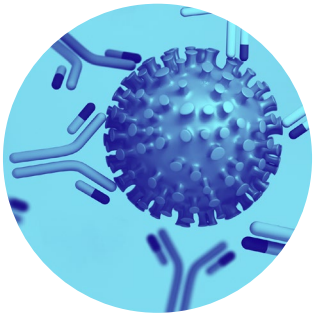


Small Molecule Delivery

Protein Delivery



Nucleic Acid Delivery



Adjuvant Systems

Empowering biologics delivery

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References

[1]Gatchalian N., Joseph L., Westergom C., Langley N. Purity of PEG 400 Affects the Stability of Gelatin Capsules. Poster presented at: AAPS Annual Meeting and Exposition; 2005 Nov 6-10; Nashville, TN.

[2]Joseph L., Taneja V., Gunderman E., Langley N. Chromatographically Purified Polysorbate 20, 60, and 80 Reduce Cellular Irritation. Poster presented at: AAPS Annual Meeting and Exposition; 2006 Oct 29- Nov 2; San Antonio, TX.

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