Enhancing Skin Science Through Purity

Super Refined™ Excipients

As topical formulations for pharmaceuticals become increasingly popular, there becomes growing need to address the challenges that can affect drug delivery: API instability, poor API solubilisation and skin irritation that minimises patient compliance.

Super Refined Excipients can address formulation concerns and, ultimately, maximise the value of your topical drug product. Croda's high purity range optimises troubled formulations by:

- Improving stability of both drug and formulation
- Reducing oxidation potential
- Decreasing cellular irritation to improve patient compliance
- Maximising drug targeting on the skin surface

Visit **www.crodahealthcare.com** for more information

- **Improved API Stability**
- **Improved Formulation Stability**
- **Increased Oxidative Stability**
- **Reduced Cellular Irritation**
- **Maximised Drug Targeting**
- **Reduced Impurity Profile**
- **Reduced Triglyceride Polymerisation**
- **Low Peroxide Values**
- **Low Moisture**
- **Multi-compendial – NF, PhEur, JPE**

Innovation you can build on™

CRODA

API Stability

Super Refining removes impurities, yielding a superior excipient with a significantly reduced impurity profile. This minimises interactions between the excipient and the drug active, greatly enhancing the stability of the API.

To demonstrate enhanced API stability, Lidocaine was incorporated into SUPER REFINED CRODAMOL OO (oleyl oleate) and compared with standard compendial oleyl oleate. Using HPLC analysis to determine the recovered % of the drug active, comparisons were made at multiple time points throughout the study. It can be clearly seen that Lidocaine maintains its integrity and stability at 98% drug recovery over the 19 day period at 60˚C in SUPER REFINED CRODAMOL OO while the drug recovery percentage decreases to 81% in standard compendial grade oleyl oleate.

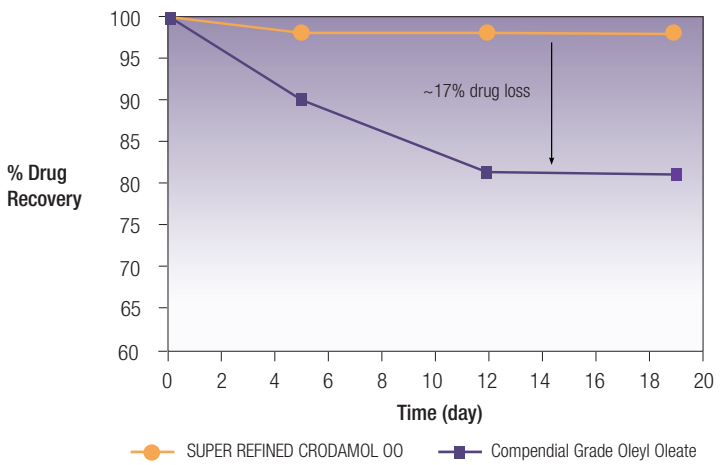


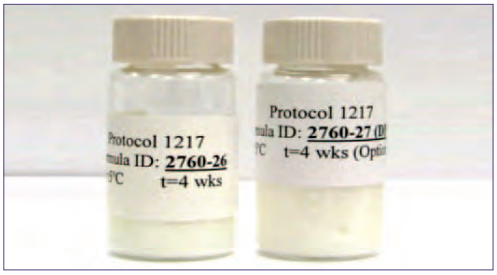
Figure 1: A graph comparing lidocaine stability in Super Refined Crodamol OO and compendial grade oleyl oleate after 19 days at 60˚C.

Formulation Stability

Optimising the stability of the final formulation can be as important as optimising the stability of the drug active. Both are connected and can directly impact drug development success or failure. To demonstrate the formulation stability benefits of the Super Refined range, SUPER REFINED ARLASOLVE DMI was compared to standard grade dimethyl isosorbide (DMI) in a topical emulsion formulation model containing Benzocaine[1]. In addition, SUPER REFINED ARLASOLVE DMI and SUPER REFINED OLEIC ACID were compared to standard grade dimethyl isosorbide and pharmaceutical grade oleic acid in a spray (solution) formulation model containing Benzocaine[1]. The formulations were placed on accelerated stability for 4 weeks.

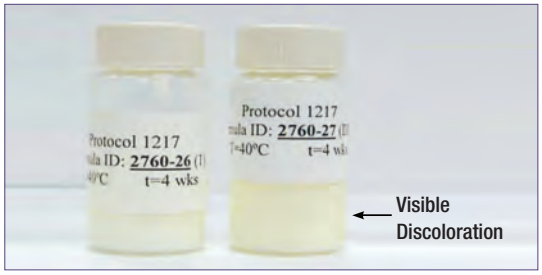
Emulsion Stability: After 4 weeks at 40˚C, an increase in colour was noted in the emulsion containing the standard grade of dimethyl isosorbide. In addition, phase separation was noted at 4 weeks at 50˚C in the same standard grade DMI formulation.

Initial, Time = 0



SUPER REFINED DMI Standard DMI

40˚C, 4 Weeks



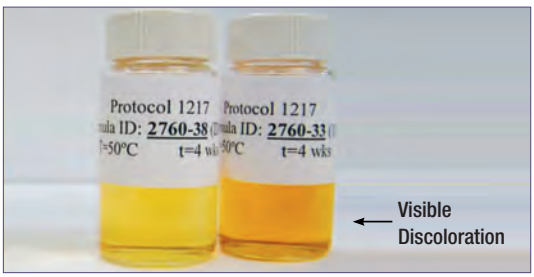
SUPER REFINED DMI Standard DMI

Solution Stability: After 4 weeks at 40˚C and 50˚C, an increase in colour was noted in the solution containing the standand grade of dimethyl isosorbide as compared to the Super Refined grade.

Initial, Time = 0

SUPER REFINED DMI Standard DMI

50˚C, 4 Weeks



SUPER REFINED DMI Standard DMI

It was seen that both the emulsions and solutions containing the Super Refined excipients demonstrated enhanced stability and maintained the topical delivery characertistics of Benzocaine relative to the corresponding standard grade containing formulations.

Oxidative Stability – Peroxide Value

Peroxide value (POV) is used for identifying the onset of oxidative change in lipids, during which the oxygen molecule reacts with the lipid molecule forming a peroxide group. This value gives a measure of the extent to which a sample has undergone primary oxidation.

To demonstrate oxidative stability, the peroxide value of SUPER REFINED CRODAMOL OO (oleyl oleate) was compared to standard compendial grade oleyl oleate over a 40 day study in accelerated ageing temperatures (60˚C). It was noted that the Super Refined excipient maintained a low peroxide value while the standard compendial grade exhibited an approximate 70-fold increase in peroxide value.

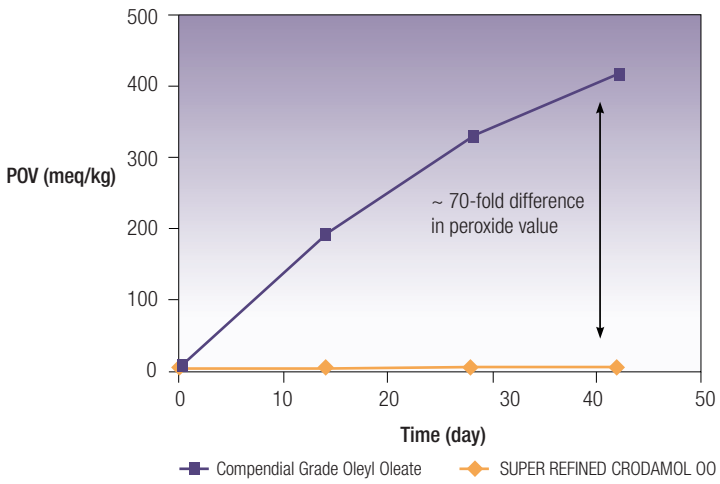


Figure 2: A graph comparing peroxide value of Super Refined Crodamol OO and compendial grade oleyl oleate.

Oxidative Stability – Rancimat

As oxidation is a chain reaction, there is a period where the onset is slower before it reaches a point where the rate of oxidation increases rapidly. This inflection point is called the induction time and indicates the detection of secondary oxidation products. The longer this induction time, the more oxidatively stable the excipient is. Using the Rancimat technique for measuring induction time, SUPER REFINED POLYSORBATE 80 was compared to standard compendial grade polysorbate 80 to demonstrate enhanced oxidative stability[2].

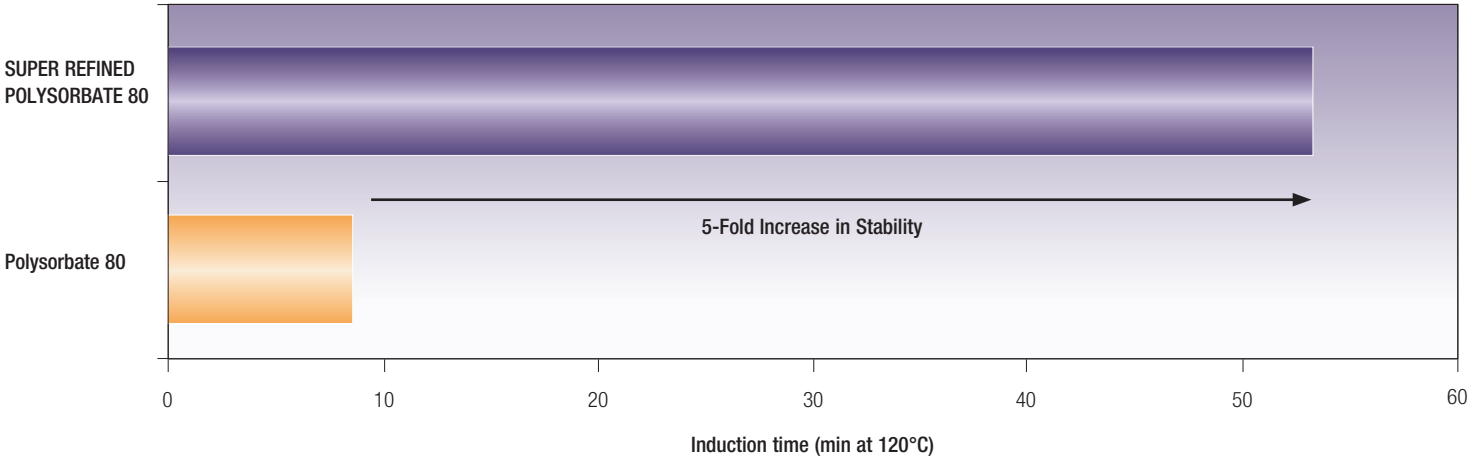


Figure 3: A graph showing the detection of secondary oxidation products of SUPER REFINED POLYSORBATE 80 vs. standard pharmaceutical grade polysorbate 80 as determined by induction time.

It can be seen that the oxidative stability for SUPER REFINED POLYSORBATE 80 is five times that of the standard grade polysorbate 80 indicating the potential for enhanced protection of the drug active and overall formulation.

Reduction of Cellular Irritation - TEP Assay

The human cell membrane is susceptible to oxidation stresses, particularly peroxides and carbonyls, which cause cellular disruption and ultimately irritation. Super Refining removes these stresses from Croda's high purity excipients.

Formaldehyde is a known irritant to the cell membrane with high levels being indicative of greater cellular irritation. The following graph (Figure 4) demonstrates that SUPER REFINED POLYSORBATE 80 has a lower level of formaldehyde as compared with the standard compendial grade.

By Super Refining polysorbate 80, it has been possible to dramatically reduce the formaldehyde levels within the excipient. Using SUPER REFINED POLYSORBATE 80 in a formulation reduces the potential for cellular disruption and skin irritation.

A Trans-Epithelial Assay (TEP) is an in vitro analysis that mimics the effect ingredients have on the skin's surface. The following graph (Figure 5) demonstrates how the lower impurity profile of SUPER REFINED POLYSORBATE 80 reduces the potential for cellular irritation[3].

Formaldehyde Content in Two Grades of Polysorbate 80

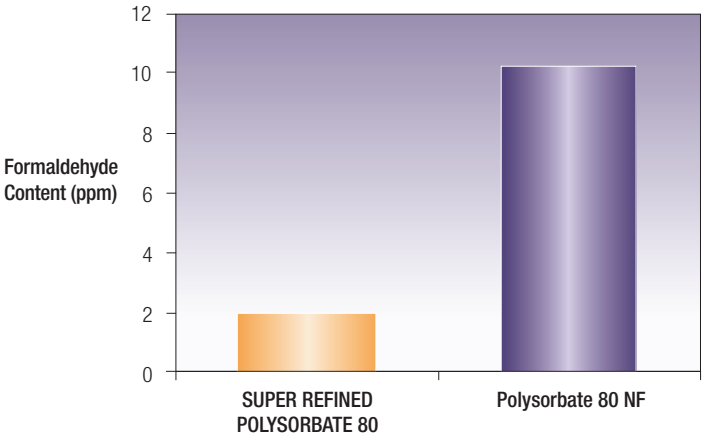


Figure 4: A graph showing differences in formaldehyde levels between SUPER REFINED POLYSORBATE 80 and Polysorbate 80 NF.

TEP Assay With 3 Formulations That Contain Different Grades of Polysorbate 80

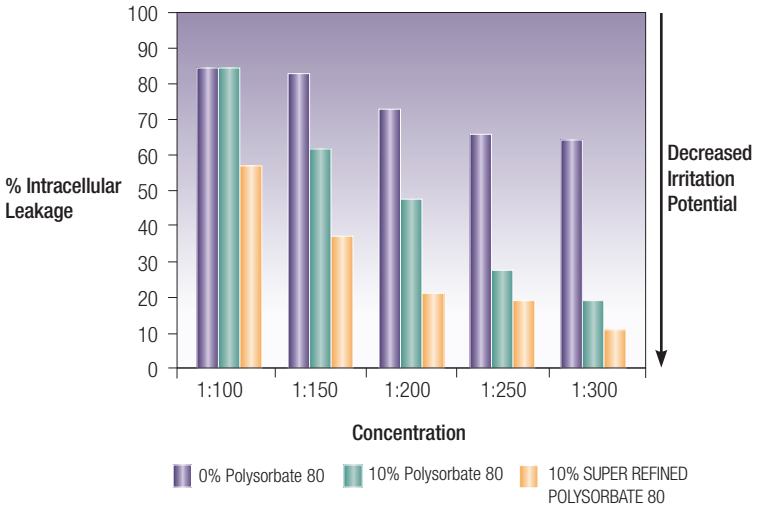


Figure 5: A graph demonstrating the lower percentage of intracellular leakage that SUPER REFINED POLYSORBATE 80 contributes to various concentrations of a surfactant system as compared to a non-Super Refined polysorbate

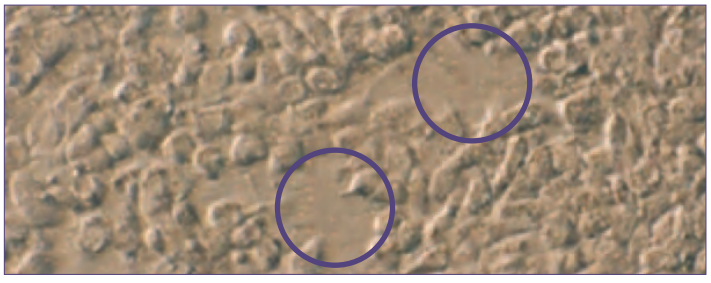
SUPER REFINED POLYSORBATE 80 displays a significant decrease in irritation potential at all concentrations. Purity of the ingredient is crucial to maintain cellular homeostasis and minimise application site irritation regardless of whether the dosage form is parenteral, topical, nasal or ophthalmic.

As with Super Refined Polysorbate above, SUPER REFINED OLEIC ACID'S lower impurity profile also allows for reduced celluar irritation. As oleic acid aids in drug targeting in the skin by means of skin lipid disruption, it can cause irritation at the site of application. A cell's phospholipid bilayer is prone to oxidative stresses that can damage cellular integrity. In addition, oxidative stresses result in free radical peroxides forming on the skin's surface which can affect the skin barrier and cause irritation.

The following images show the effect of SUPER REFINED OLEIC ACID (vs. standard compendial grade oleic acid) on confluent cell monolayers composed of Marin Darby Canine Kidney (MDCK) cells[4]. This comparison was demonstrated using a Trans-Epithelial Assay (TEP), an in vitro analysis that mimics the effect excipients have on the skin's surface.

SUPER REFINED OLEIC ACID cell monolayer

Oleic Acid NF cell monolayer



It can be seen that the compendial grade oleic acid cell monolayer shows areas of cell disruption, a leading indicator for irritation. In contrast, the SUPER REFINED OLEIC ACID cell monolayer shows zero cellular disruption, demonstrating the excipient's ability to mitigate cellular irritation.

Topical Drug Delivery and Targeting - Franz Cell Diffusion Analysis

Topical pharmaceutical formulations are intended to deliver therapeutically effective concentrations of drug in skin layers which is their targeted site. SUPER REFINED ARLASOLVE DMI is designed for this purpose: to boost the penetration of the topical API through the stratum corneum into the epidermis to allow for more targeted skin delivery. SUPER REFINED ARLASOLVE DMI increases the polarity of the upper skin layers to increase the reception of hydrophilic actives within the formulation.

To demonstrate the targeting of this excipient, a Franz cell diffusion analysis was used to determine the delivery of samples with and without SUPER REFINED ARLASOLVE DMI. The results below show that SUPER REFINED ARLASOLVE DMI improves the delivery of the active to the epidermis to maximise targeting of the drug as well as its effectiveness.

The addition of 10% SUPER REFINED ARLASOLVE DMI increases the delivery of the active ingredient to the epidermis by 15% while minimising the amount of active remaining ineffective on the Stratum Corneum. This is achieved without increasing transdermal delivery, ensuring that the active is targeted to where it is needed most.

SUPER REFINED ARLASOLVE DMI improves delivery to the epidermis

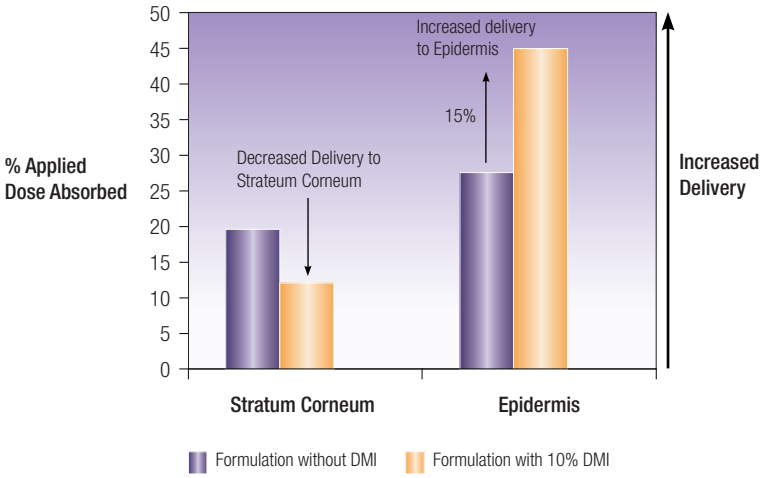


Figure 6: A graph demonstrating the delivery potential of SUPER REFINED ARLASOLVE DMI into the epidermis

SUPER REFINED offering (listed in alphabetical order by chemical description)

*FDA IIG listing for Topical dosage forms only

Chemical Description	Product Name	NF/USP	PhEur	JPE/JP	FDA IIG* (Topical)
Beeswax (white wax)	SUPER REFINED BEESWAX	■	■	■	■
Castor Oil	SUPER REFINED CASTOR OIL	■		■	■
Corn Oil	SUPER REFINED CORN	■	■		
Cottonseed Oil	SUPER REFINED COTTONSEED	■			
Dimethyl Isosorbide	SUPER REFINED ARLASOLVE DMI				■
Hexyl Laurate	SUPER REFINED CRODAMOL HL			■	
Isopropyl Myristate	SUPER REFINED CRODAMOL IPM	■	■	■	■
Isopropyl Palmitate	SUPER REFINED CRODAMOL IPP			■	■
Lauryl Lactate	SUPER REFINED CRODAMOL LL				
Oleic Acid	SUPER REFINED OLEIC ACID	■	■	■	■
Oleth-2	SUPER REFINED BRIJ O2				■
Oleyl Alcohol	SUPER REFINED NOVOL	■			■
Oleyl Oleate	SUPER REFINED CRODAMOL OO	■		■	■
Olive Oil	SUPER REFINED OLIVE				■
Peanut Oil	SUPER REFINED PEANUT	■	■		■
Polyethylene Glycol 300	SUPER REFINED PEG 300	■	■	■	■
Polyethylene Glycol 400	SUPER REFINED PEG 400	■	■	■	■
Polyethylene Glycol 600	SUPER REFINED PEG 600	■	■	■	■
Polysorbate 20	SUPER REFINED POLYSORBATE 20	■	■	■	■
Polysorbate 60	SUPER REFINED POLYSORBATE 60	■	■	■	■
Polysorbate 80	SUPER REFINED POLYSORBATE 80	■	■	■	■
Propylene Glycol	SUPER REFINED PROPLYENE GLYCOL	■		■	■
Safflower Oil	SUPER REFINED SAFFLOWER	■			
Sesame Oil	SUPER REFINED SESAME	■	■	■	
Soybean Oil	SUPER REFINED SOYBEAN	■	■	■	■
Stearyl Octanoate (and) Cetyl Octanoate	SUPER REFINED CRODAMOL SCO				

References

[1] Winckle G, Ginger J, Jhutti P, Zhang H, Crawford B, Lowe L, Langley N. Chromatographically Purified Excipients: Stability Enhancement and Topical Delivery of Benzocaine. Poster presented at: AAPS Annual Meeting and Exposition; 2008 Nov 16-20; Atlanta, GA.

[2] Kasizka A. Oxidative Stability of Pharmaceutical Excipients by a Rancimat Method. Poster presented at: AAPS Annual Meeting and Exposition; 2015 Oct 25-29; Orlando, FL.

[3] Rizzo G, Chen K. (2010, September). The Importance of Chromatographically Purified Excipients [PDF file]. Retrieved from IPTonline The Pharmaceutical Technology Journal. http://www.iptonline.com/synopsis.asp?cat=7&article=680

[4] Joseph L, Langley N, Loberger L. Topical Lipid Oxidation and Cellular Irritation. Pharmaceutical Formulation & Quality. June/July 2004. Print.

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