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Super Refined™ Polysorbate 80

Ultra-pure drug delivery

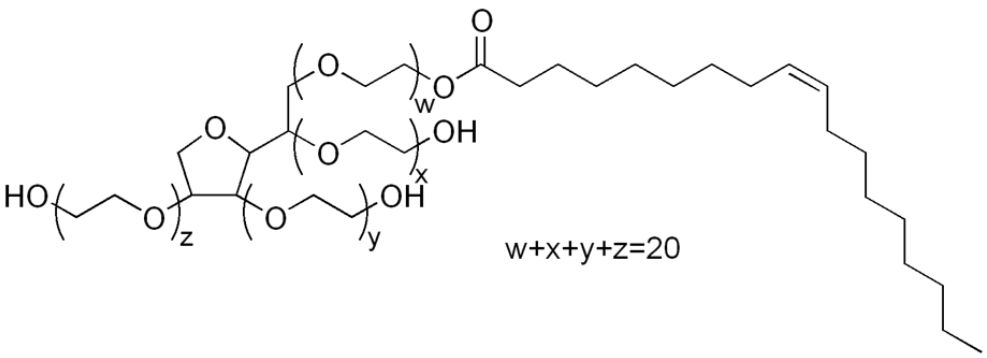
Stable, colourless and pure – Super Refined Polysorbate 80 is recommended when the highest quality Polysorbate 80 is required, especially when formulating with highly sensitive and unstable APIs.

Super Refining removes polar impurities, preventing adverse interactions with Active Pharmaceutical Ingredients (APIs), thereby enhancing the stability of formulations. Removing polar impurities, including primary and secondary oxidation products, also reduces the potential for cellular irritation and due to its very low colour; Super Refined Polysorbate 80 provides an analytical clarity advantage, compared to other grades. The improved taste profile of Super Refined Polysorbate 20 versus its standard compendial counterpart will also enable formulators to design more palatable oral liquid medicines.

Key benefits

- Analytical clarity – essentially colourless - APHA 150 max
- Low peroxide value (PV) - 2.0 meq 02 / Kg max
- Low formaldehyde - 10 ppm max.
- Low residual EO - 1 ppm max
- Low 1,4 dioxane - 5 ppm max
- Low residual Na and K – 5 ppm max
- Low moisture – 0.2% max
- LAL --- 2.0 EU / ml
- Multi-compendial – PhEur, NF, JP
- Decreased cellular irritation
- Non-animal origin
- Strict limit for endotoxin levels in the sorbitol starting material
- Microbial testing performed on each lot of material
- Packaged under nitrogen in metal containers to prevent PV increase
- Improved taste profile allows for easier formulation of oral liquid medicines to enhance palatability

Super Refined Polysorbate 80 is an extremely mild and effective oil-in-water emulsifier and solubiliser with the following general structure:



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Product Features

- HLB 15.0
- Excellent oil-in water emulsifier
- Produces HLB values suitable for either oil in-water or water in-oil systems, when blended with sorbitan esters
- Solubiliser, emulsifier, stabiliser, wetting and dispersing agent
- Plasticiser and tablet lubricant
- Used in Active Pharmaceutical Ingredient(API) production
- Used in parenteral, ophthalmic, oral and topical dosages
- Typical use level: 1-10% as a solubiliser, 0.1-3% as a wetting agent
- Listed in 21 CFR 172.846 for use as a multi-purpose food additive
- Cited in 21 CFR 172.840 for use in vitamin mineral supplements
- Improved taste profile compared to the standard compendial grade

Enhanced oxidative and active stability

One of the industry's greatest challenges in dosage design is formulating a product that maintains the integrity of the API. Impurities present in many excipients can interact with the active and cause instability of the API or interfere with the dosage form or vehicle. Super Refined Polysorbate 80 eliminates the need for concern as Croda's Super Refining process physically removes polar impurities without altering the fundamental structure of the Polysorbate in any way and thereby offers a formulation solution for even the most sensitive of APIs.

Oxidative challenges continue to have a strong presence during drug and formulation development. The use of Super Refined excipients can, greatly, alleviate these concerns due the reduction of oxidative impurities. To demonstrate the oxidative stability of super refining, Super Refined Polysorbate 80 was tested using a Rancimat instrument and the Rancimat method.

To test the material, a stream of air is passed through the sample, which is contained in a sealed and heated reaction vessel. Oxidation of the oil or fat molecules in the sample ultimately results in the formation of aldehydes and ultimately, low molecular weight volatile acids as secondary oxidation products, which are generated after complete destruction of the fatty acids.

These volatile compounds are transported in the stream of air to a second vessel containing distilled water whose conductivity is continuously measured by an electrode. The organic acids cause an increase in conductivity in the water. The time that elapses until these secondary reaction products appear is known as the induction time and essentially, the longer the induction time, the more stable the product is against oxidation. This is essentially the end point of the test.

In this study, Super Refined Polysorbate 80 was tested in comparison to its standard compendial counterpart in order to demonstrate the improvement of oxidative stability that Super Refining provides. The products tested were **Polysorbate 80 NF** and **Super Refined Polysorbate 80**.

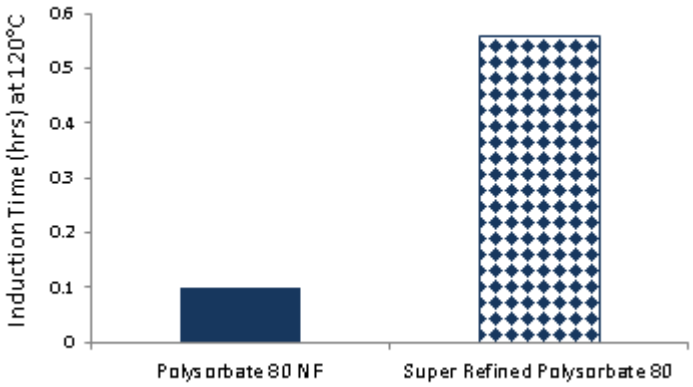

Figure 5: Induction time for Super Refined Polysorbate 80 as compared to its standard compendial counterpart

As can be seen in the above results, the Super Refined grade showed significant increase in induction time thus indicating the excipients' improved stability against oxidation.

Reduced Cellular Irritation

A study was conducted to determine the cellular irritation of Super Refined Polysorbate 80. For the study, kidney (MDCK) cells were cultured under standard conditions using a modified TEP Protocol from Tchao, 1987 (2). Three days prior to experimentation the cells were subcultured into porous cell culture inserts. The Polysorbates were formulated into a simple surfactant system below:

Ingredient	*%w/w*
Sodium Laureth Sulfate	20%
Cocamidopropyl Hydroxysultaine	12%
Polysorbate 80	10%
Germaben II	1%
DI water	q.s.

The simple system or Phosphate Buffer Saline (PBS) was placed in direct contact with the cells for 15 minutes at room temperature. Inserts without cells were used as 100% leakage. After application of the test material, the inserts were washed thoroughly with PBS and sodium fluorescein was added directly to the cell monolayer with PBS placed in the well below. After 30 minutes, the optical density of the well fluid was determined. The experimental optical density was then compared to 100% leakage optical density.

As can be seen in Figure 1, Super Refined Polysorbate 80 displayed a significantly lower irritation potential at all concentrations tested. There was up to a 40% decrease in irritation potential with the Super Refined Polysorbate 80 as compared to standard pharmaceutical grade Polysorbate 80. Based on the data, it can be concluded that Polysorbate purity is critical for minimising cellular irritation

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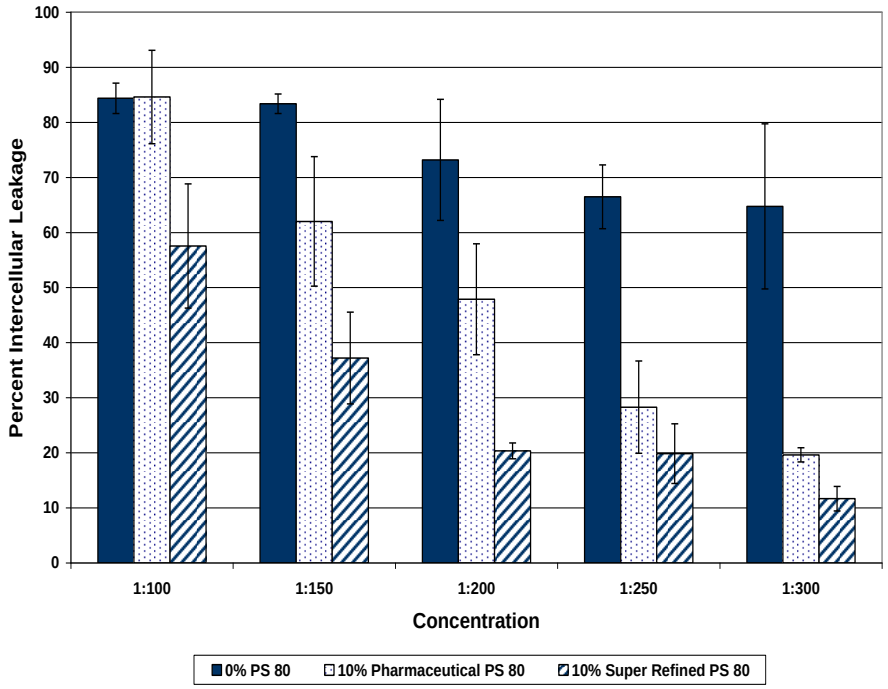

Figure 1: Percent intercellular leakage of Super Refined Polysorbate 80 as compared to standard pharmaceutical grade Polysorbate 80 at various concentration levels

Reduced Formaldehyde Content

A study was conducted to demonstrate the reduction of formaldehyde content due to the Super Refined purification of Polysorbate 80. Formaldehyde content was measured using 2,4-pentanedione (PDO) derivatives and the Polysorbate samples were diluted in water and reacted with PDO reagent containing acidic ammonium acetate as a catalyst. The data showed a significant reduction of formaldehyde content for Super Refined Polysorbate 80 as compared to standard pharmaceutical grade Polysorbate 80.

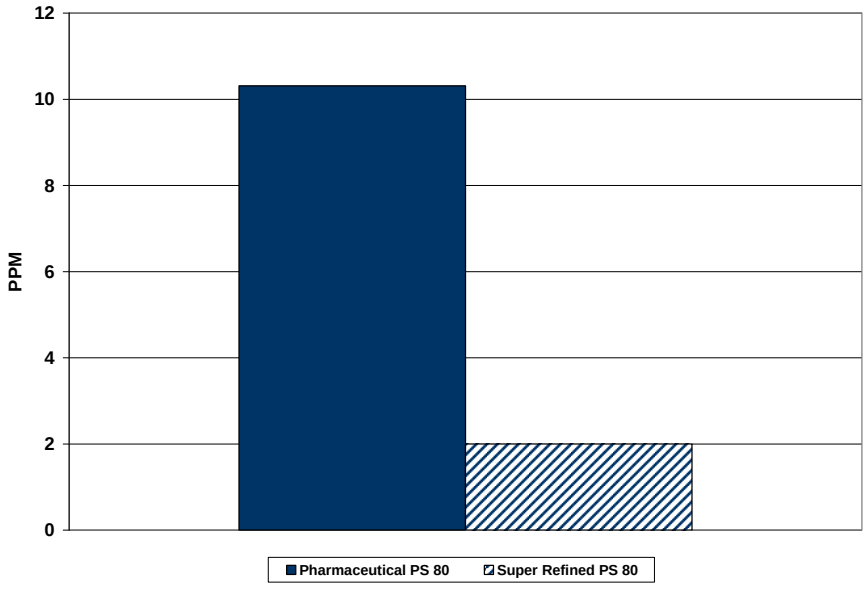

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Figure 2: Formaldehyde content in ppm of Super Refined Polysorbate 80 as compared to standard pharmaceutical grade Polysorbate 80

As can be seen in Figure 2, Super Refined Polysorbate 80 contains significantly less formaldehyde than it's pharmaceutical grade counterpart. The Super Refined Polysorbate 80 contains 81% less formaldehyde as compared to the pharmaceutical grade Polysorbate 80. With this reduction of formaldehyde, the API stability can be enhanced to maximise formulation efficacy.

Consistency in Bulk Chemical Composition

The Super Refining process eliminates or reduces many of the impurities that are normally present in pharmaceutical grade Polysorbates. These impurities include a range of polar and oxidative impurities such as moisture, residual catalyst, peroxides and aldehydes. However, the process does not alter the chemical structure in any way.

To demonstrate this consistency in chemical composition, Super Refined Polysorbate 80 were compared to the pre-Super Refined intermediate (their standard compendial counterparts) using matrix assisted laser desorption/ionization (MALDI) mass spectrometry (MS). MALDI-MS is a simple and fast analytical method that allows scientists to rapidly characterise and analyse complex organic compounds and biomolecules.

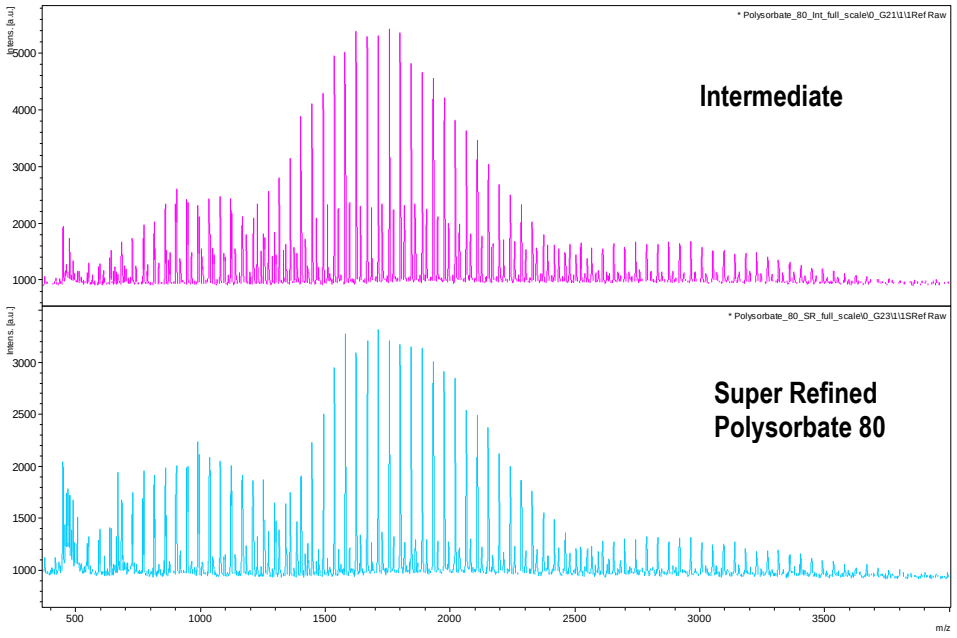

Figure 3: Polysorbate 80 MALDI-MS: Std pharma grade Polysorbate 80 vs. Super Refined Polysorbate 80

As can be seen in Figure 3 above, there are no detectable changes in the chemical composition of Polysorbate 80 upon Super Refining as indicated by MALDI-MS.

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Reduced Taste Impact

To demonstrate that Super Refining can help minimise the taste impact of excipients, a range of excipients were tested by a 3rd party testing company (Sensory Spectrum, Inc.) to quantitatively identify the degree of difference in taste between Super Refined Polysorbate 80 and its standard compendial counterpart. The test panel, which was comprised of extensively trained taste specialists, assigned a Degree of Difference (DOD) score when comparing the Super Refined Polysorbate 80 to the control. The Degree of Difference (DOD) scores ranged from 0-10, with 0 indicating no difference and a 10 indicating an extreme difference. A DOD of 5 or higher marks the point at which consumers will be able to perceive a taste difference while a DOD of 4-5 marks the point at which the consumer might notice a taste difference.

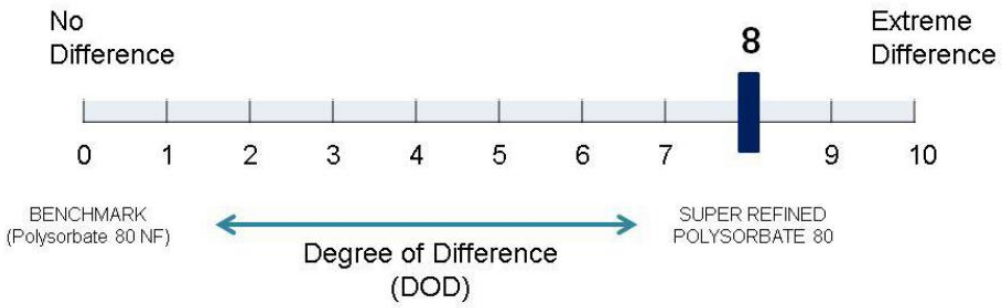

Figure 4: Taste impact and DOD of Super Refined Polysorbate 80 as compared to standard pharmaceutical grade of Polysorbate 80

As seen in Figure 4 above, the DOD for Super Refined Polysorbate 80 versus its standard compendial equivalent was 8. With a DOD of 8, it was concluded that there is a significant consumer-perceivable taste difference between the Super Refined Polysorbate 80 and the control. The qualitative results demonstrated that the Super Refined Polysorbate 80 had a much lower taste impact than the standard compendial grade. Thus, the use of Super Refined Polysorbate 80 will allow formulators greater flexibility when creating more palatable oral liquid dosage forms that can ultimately promote better patient compliance.

References

1. Handbook of Pharmaceutical Excipients, Fourth Edition, 2003; American Pharmaceutical Association and the Royal Press, Royal Pharmaceutical Society of Great Britain.

2. Joseph, L., Taneja, V., Gunderman E., Langley, N., Chromatographically Purified Polysorbate 20, 60, and 80 Reduced Cellular Irritation, American Association of Pharmaceutical Scientists Annual Meeting, Oct 2006.