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Super Refined™ Polysorbate 20

High Purity Polysorbate 20

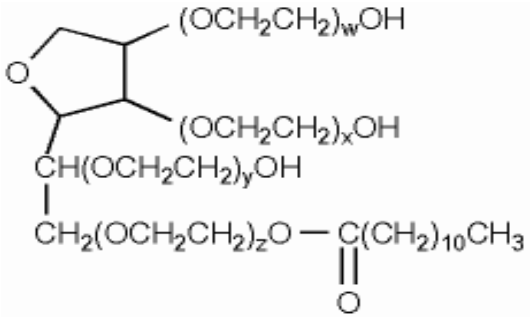
Super Refined Polysorbate 20 offers the complete solution when formulating a wide range of pharmaceutical products. Super Refining is Croda's proprietary process that removes polar impurities, such as peroxides, aldehydes and ketones. Removal of these polar impurities eliminates their adverse interaction with Active Pharmaceutical Ingredients (APIs), thereby enhancing the stability of the drug and/or vehicle itself.

Super Refined Polysorbate 20 is recommended when the highest quality polysorbate 20 is required, especially when formulating with highly sensitive and unstable APIs. Due to its very low colour, it provides an analytical clarity advantage compared to other grades of polysorbate 20. 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
- Peroxide value (PV) – 2.0 meq 0_2 /kg max
- Formaldehyde – 10 ppm max.
- Residual EO – 1 ppm max
- 1,4 dioxane – 5 ppm max
- Residual Na and K – 5 ppm max
- Moisture – 0.2% max
- Multi-compendial – PhEur, NF, JPE
- Decreased cellular irritation
- Non-animal origin
- Strict limit for endotoxin levels in the sorbitol starting material
- Microbial testing performed on each lot of material
- Improved taste profile allows for easier formulation of oral liquid medicines to enhance palatability

Super Refined Polysorbate 20 is an extremely mild and effective oil-in-water emulsifier and solubiliser with the following general structure:



w + x + y + z = 20

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Product Features

- HLB 16.7
- 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
- Used in Active Pharmaceutical Ingredient (API) production
- GRAS listed
- FDA Inactive Ingredients Guide (Auricular, IM-SC, Intramuscular, Intravenous, IV, Nasal, Ophthalmic, Oral, Subcutaneous, Topical and Vaginal preparations)
- Listed in 21 CFR 178.3400 for use as an emulsifier for food additives
- Listed in 21 CFR 310.527 for use as an ingredient for OTC drug hair products
- Packaged under nitrogen in metal containers to prevent PV increase
- Improved taste profile compared to the standard compendial grade

Reduced Cellular Irritation

A study was conducted to determine the cellular irritation of Super Refined Polysorbate 20. 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 20	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 20 displayed a significantly lower irritation potential at all concentrations tested. There was up to a 73% decrease in irritation potential with the Super Refined Polysorbate 20 as compared to standard pharmaceutical grade polysorbate 20. Based on the data, it can be concluded that polysorbate purity is critical for minimising cellular irritation.

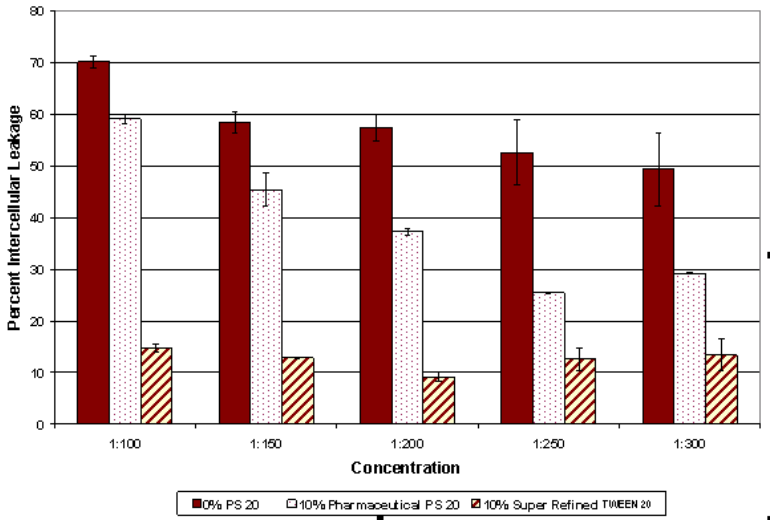

Figure 1. Percent intercellular leakage of Super Refined Polysorbate 20 as compared to standard pharmaceutical grade polysorbate 20 at various concentration levels

Reduced Formaldehyde Content

A study was conducted to demonstrate the reduction of formaldehyde content due to the Super Refined purification of polysorbate 20. 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 20 as compared to standard pharmaceutical grade polysorbate 20.

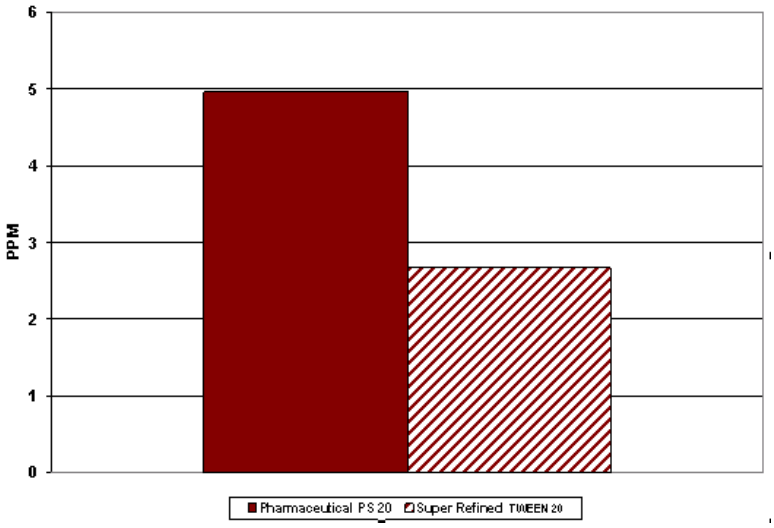

Figure 2. Formaldehyde content in ppm of Super Refined Polysorbate 20 as compared to standard pharmaceutical grade polysorbate 20

As can be seen in Figure 2, Super Refined Polysorbate 20 contains significantly less formaldehyde than its pharmaceutical grade counterpart. The Super Refined Polysorbate 20 contains 46% less formaldehyde as compared to the pharmaceutical grade polysorbate 20. With this reduction in formaldehyde the API stability can be enhanced to maximise formulation efficacy.

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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 20 was compared to the pre-Super Refined intermediate (its standard compendial counterparts) using matrix assisted laser desorption/ionisation (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.

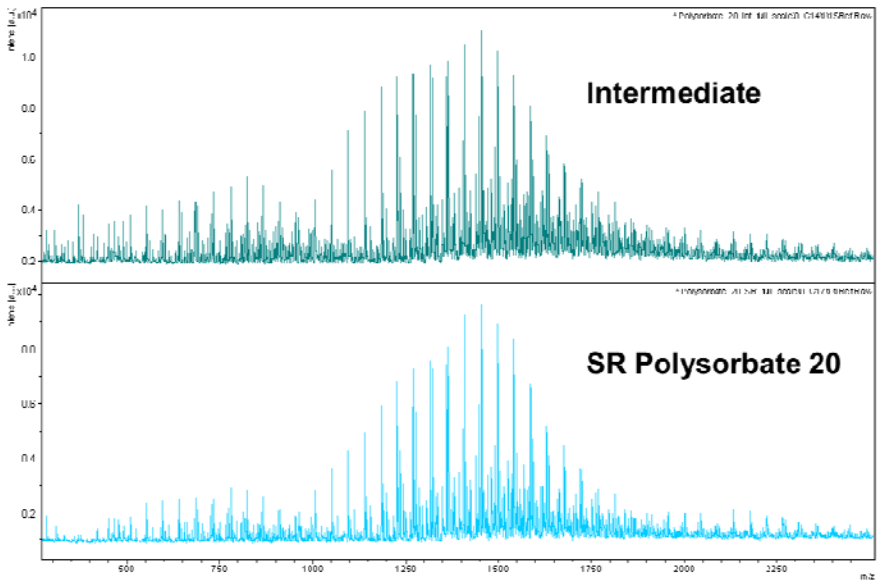

Figure 3: Polysorbate 20 MALDI-MS. Std pharma grade polysorbate vs. Super Refined Polysorbate 20

As can be seen in Figure 3 above, there are no detectable changes in the chemical composition of polysorbate 20 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 20 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 20 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 of Super Refined Polysorbate 20 as compared to standard pharmaceutical grade of Polysorbate 20

As seen in Figure 4 above, the DOD for Super Refined Polysorbate 20 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 20 and the control. In addition, the qualitative results demonstrated that the Super Refined Polysorbate 20 had a much lower taste impact than the standard compendial grade. Thus the use of Super Refined Polysorbate 20 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.