Enhancing Parenteral Performance Through Purity

Super Refined™ Excipients

The formulation of actives for parenteral delivery demands the highest quality standards and attention to detail. The selection of an excipient is critical to drug stability, formulation integrity and, ultimately, patient safety. Proper excipient selection is especially challenging when working with highly sensitive, high value actives.

Croda's Super Refined excipients offer various benefits to provide additional value for the final drug product.

Formulation Benefits:

- Minimised API degradation
- Reduced impurities for improved drug compatibility
- Reduced oxidation potential for increased drug stability
- Minimised potential for allergic reaction

Drug Product Value:

- Optimised drug efficacy
- Increased shelf life
- Decreased formulation development time
- Decreased time to market

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

- **Improved API Stability**
- **Increased Oxidative Stability**
- **Reduced Impurity Profile**
- **Reduced Cellular Irritation**
- **Reduced Total Nitrogen Content**
- **Low Peroxide Values**
- **Low Moisture**
- **Multi-compendial – NF, PhEur, JPE**

Innovation you can build on™

CRODA

Minimised API Degradation

The parenteral route of administration is selectively chosen for multiple reasons during formulation development. As this route allows medications to be directly absorbed into the body quickly and more predictably, minimising any Active Pharmaceutical Ingredient (API) degradation is vital to the drug product's integrity and overall efficacy.

Super Refining is a proprietary process that removes impurities such as peroxides and formaldehyde. These are major oxidation products that, along with other impurities, can react with an API to create degradation products affecting its stability in pharmaceutical formulations.

To demonstrate the purity benefits of a Super Refined excipient on drug stability, a chemotherapy API (docetaxel) was dissolved in Super Refined Polysorbate 80 and Super Refined PEG 400. The solutions were compared to docetaxel dissolved in several sources of standard compendial grade polysorbate 80 and PEG 400. The samples were aged for 12 weeks at 40ºC and analysed by HPLC at various time points.

After 12 weeks of accelerated ageing, the Super Refined Polysorbate 80 (Figure 1) and Super Refined PEG 400 (Figure 2) had a >90% drug recovery while the standard compendial sources of polysorbate and PEG demonstrated significant loss of docetaxel.

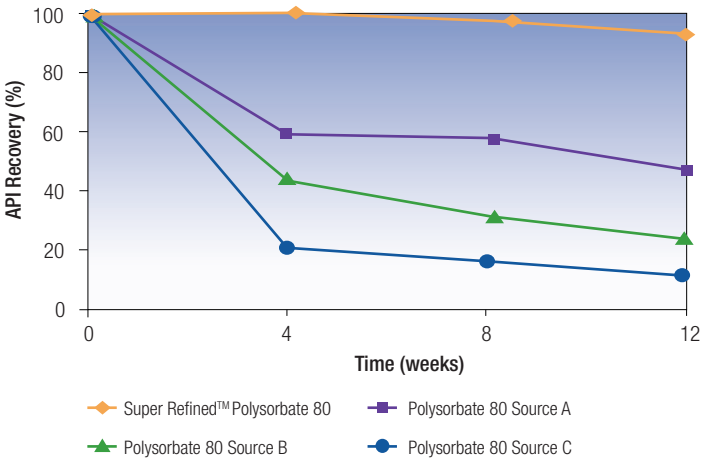

Figure 1: A graph comparing % docetaxel recovery in Polysorbate 80 at 40°C during a 12 week study

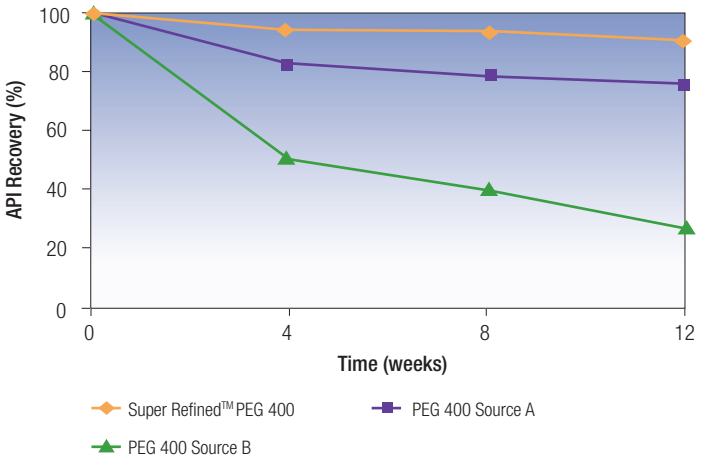

Figure 2: A graph comparing % docetaxel recovery in PEG 400 at 40°C during a 12 week study

In addition, the chromatographs indicated an increasing presence of degradation products during the 12 week study when the active was incorporated in all three sources of standard grades of polysorbate 80. An example of the HPLC of one of the polysorbate sources can be seen below (Figure 4). In contrast, there was an absence of degradation products with the docetaxel incorporated into Super Refined Polysorbate 80 (Figure 3).

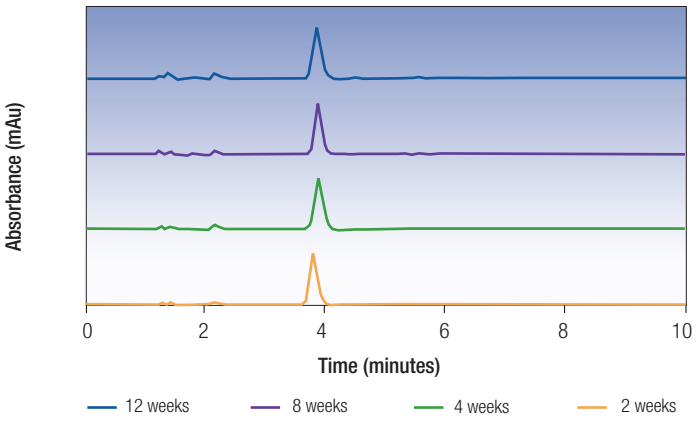

Figure 3: An HPLC chromatograph of docetaxel in Super Refined Polysorbate 80 at 40˚C

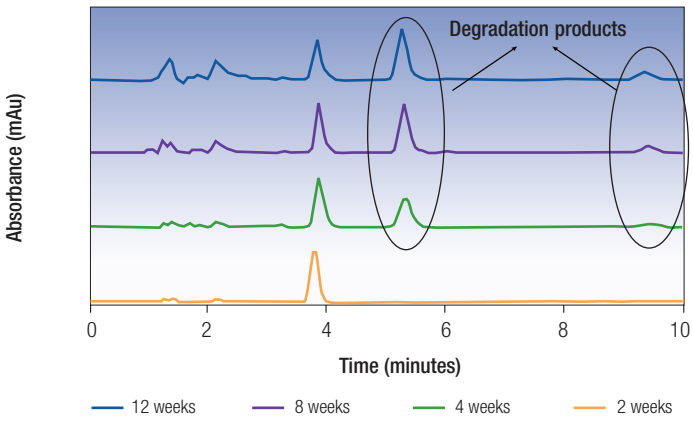

Figure 4: An HPLC chromatograph of docetaxel in standard compendial polysorbate 80 at 40˚C

Reduced Oxidation Potential – Peroxide Value and Iodine Value

Oxidation is a known chemical process that results in a parenteral drug's degradation. It will cause excipient/API incompatibility and lead to drug instability. A common way to measure oxidative stability is through the measurement of peroxide and iodine values which can provide an early indication of final drug stability to the parenteral formulator.

Peroxide value is used for identifying the onset of primary 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.

Another indicator of primary oxidation is iodine value. Iodine value is an indicator of oxidation across double bonds in the alkyl chains. In the determination of oxidative stability, the higher the iodine value, the greater the double bond character, which corresponds to less primary oxidation.

To demonstrate superior oxidative stability, five lots of Super Refined Castor Oil were compared against five lots of standard compendial grade castor oil over a period of 8 weeks at 50ºC [1]. Both peroxide and iodine value were analysed according to the USP test method.

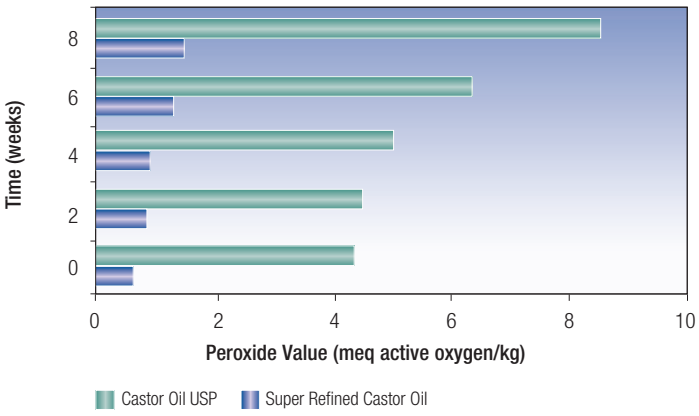

Figure 5: A graph showing differences in peroxide value between Super Refined Castor Oil and castor oil USP during an 8 week study at 50ºC

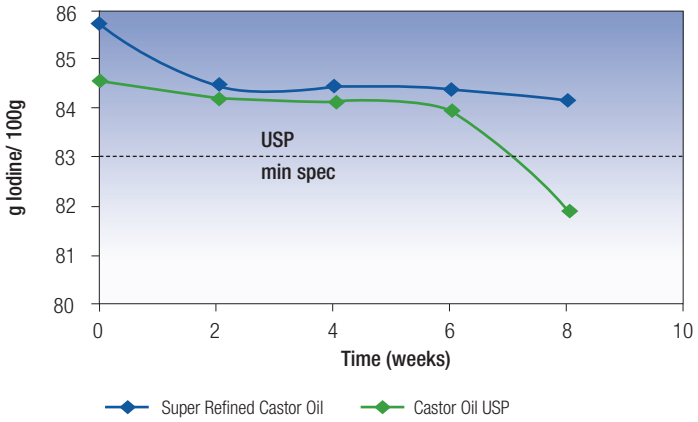

Figure 6: A graph showing differences in iodine value between Super Refined Castor Oil and castor oil USP during an 8 week study at 50ºC

It was noted that the Super Refined Castor Oil maintained a low peroxide (<2ppm) for the duration of the study while the standard grade exhibited a significantly higher initial peroxide value with an 83% increase after 8 weeks (Figure 5). In addition, the Super Refined Castor Oil maintained a higher iodine value throughout the duration of the study, indicating better oxidative stability. The Super Refined grade was able to keep the excipient within the monograph specification while the compendial grade castor oil fell below the USP spec at the 8 week time point (Figure 6).

Reduced Oxidation Potential – 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 Cottonseed and Super Refined Oleic Acid were compared to their standard compendial grade counterparts to demonstrate enhanced oxidative stability[2].

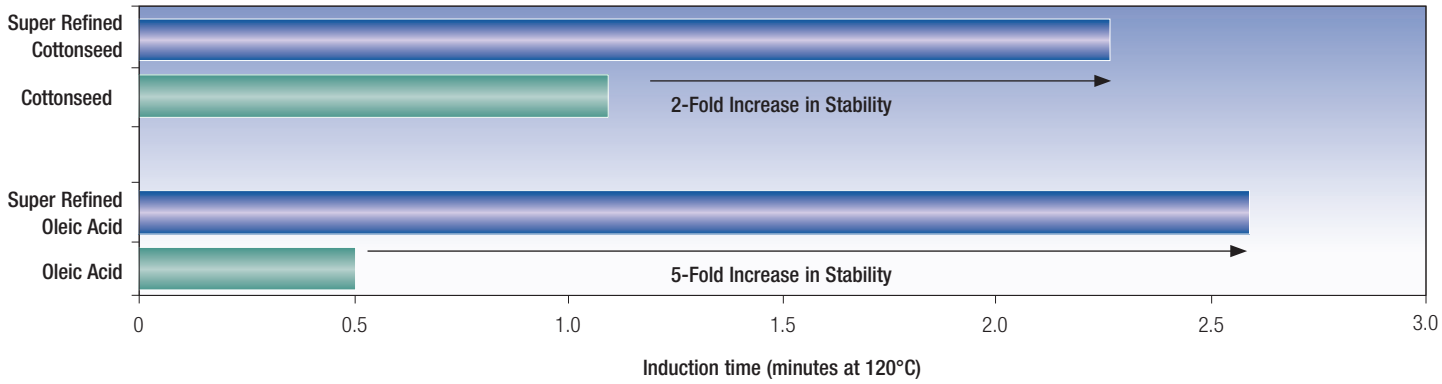

Figure 7: A graph showing the detection of secondary oxidation products of Super Refined Cottonseed and Super Refined Oleic Acid vs. their standard pharmaceutical grade counterparts as determined by induction time

It can be seen in Figure 7 that the oxidative stability for Super Refined Cottonseed is twice that of the standard grade cottonseed oil while the oxidative stability for Super Refined Oleic Acid is five times that of the standard grade oleic acid. The increase in stability seen from the Super Refined grade excipients indicates the high potential for enhanced protection of the drug active from secondary oxidation.

Reduced Impurities – Formaldehyde Levels

The presence of formaldehyde in excipients has been linked to the degradation of many drug products as the impurity can react with the API to form chemical additions with primary and/or secondary amine groups. These adducts can cause drug instability that can lead to reduced drug potency and reduced product performance. In addition, formaldehyde is a known irritant to the cell membrane with high levels being indicative of greater cellular irritation at the site of injection.

To demonstrate the reduced formaldehyde levels in Super Refined excipients, both Super Refined Polysorbate 20 and 80 were compared to standard compendial polysorbate 20 and 80, respectively[3]. The polysorbate samples were diluted in water and reacted with 2,4-Pentanedione (PDO) reagent containing acidic ammonium acetate as a catalyst. The reaction was carried out in a 50ºC oven for 30 minutes with a 15 minute cool-down. Formaldehyde content was detected using HPLC.

As can be seen below (Figure 8), Super Refined Polysorbate 20 contained approximately 46% less formaldehyde as compared to standard compendial grade polysorbate 20. In addition, the Super Refined Polysorbate 80 showed even greater % reduction as compared to its compendial counterpart with 81% less formaldehyde (Figure 9).

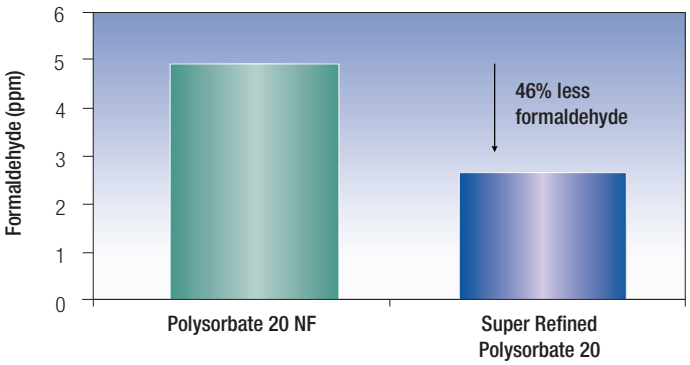

Figure 8: A graph showing the difference in formaldehyde content between Super Refined Polysorbate 20 and standard pharmaceutical grade polysorbate 20

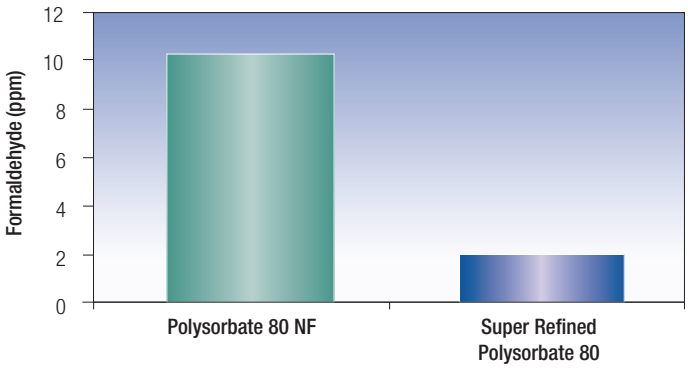

Figure 9: A graph showing the difference in formaldehyde content between Super Refined Polysorbate 80 and standard pharmaceutical grade polysorbate 80

Reduced Impurities - Volatiles

The Super Refining process yields an excipient with superior purity with regards to a number of criteria, including the removal of potentially undesirable volatile impurities that can impact the stability of certain APIs.

By combining the use of gas chromatography (GC) and mass spectrometry (MS), it is possible to identify and compare the relative levels of such impurities in our Super Refined products. To demonstrate this, Super Refined Soybean was analysed with GC/MS and compared to standard compendial soybean oil JP. As can be seen in Figure 10, the chromatograph for the standard grade excipient showed the detection of a number of impurities; two aldehydes (pentanal and hexanal) and three lower chain fatty acids (acetic, formic and hexanoic acid). These impurities can significantly impact the integrity and stability of the drug active and final drug product. In contrast, the detection of impurities were very low for Super Refined Soybean which demonstrated a reduction of impurities by 96-100% as compared to its standard compendial counterpart.

This complements other data we have for other known impurities such as formaldehyde and peroxide levels that are reduced by our Super Refining process.

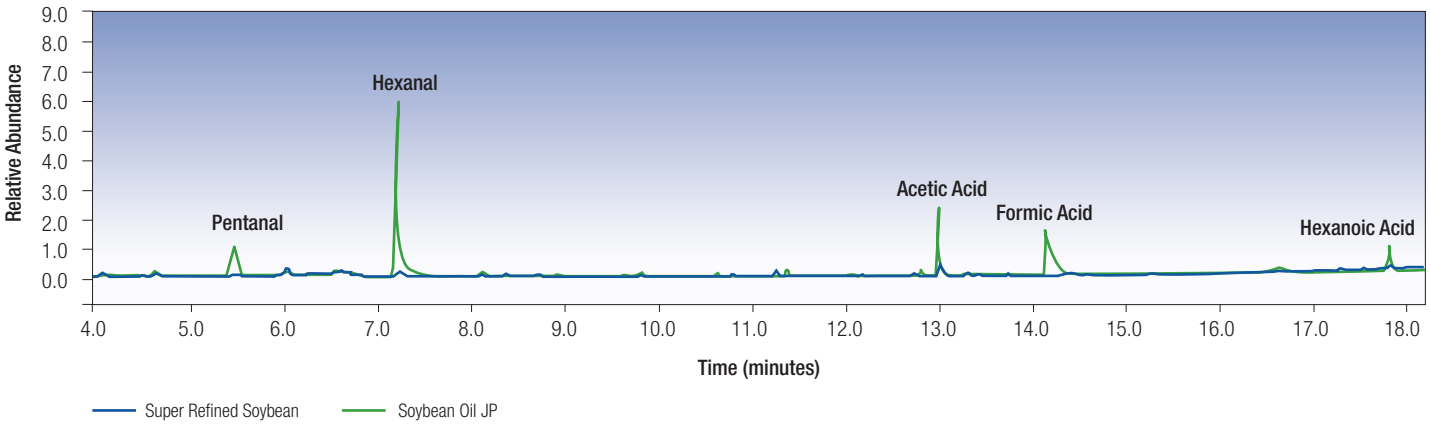

Figure 10: A chromatograph comparing the identification of Super Refined Soybean and standard compendial grade soybean oil JP through GC/MS

Minimised Allergic Reaction Potential

Total nitrogen content is a value associated with the levels of protein residue within an excipient. This residual protein can ultimately be an indicator for the potential of a mild allergenic reaction or one as severe as anaphylaxis.

To demonstrate the link between the purity of lipid excipients and the total nitrogen content, a study was conducted on a selection of parenteral excipients to test for total nitrogen. The Super Refined grades were compared against the standard compendial grades. As the NP grades of the Super Refined Oils do not contain any antioxidants, these grades were used in this study to ensure no interference from the antioxidant on the results of this study.

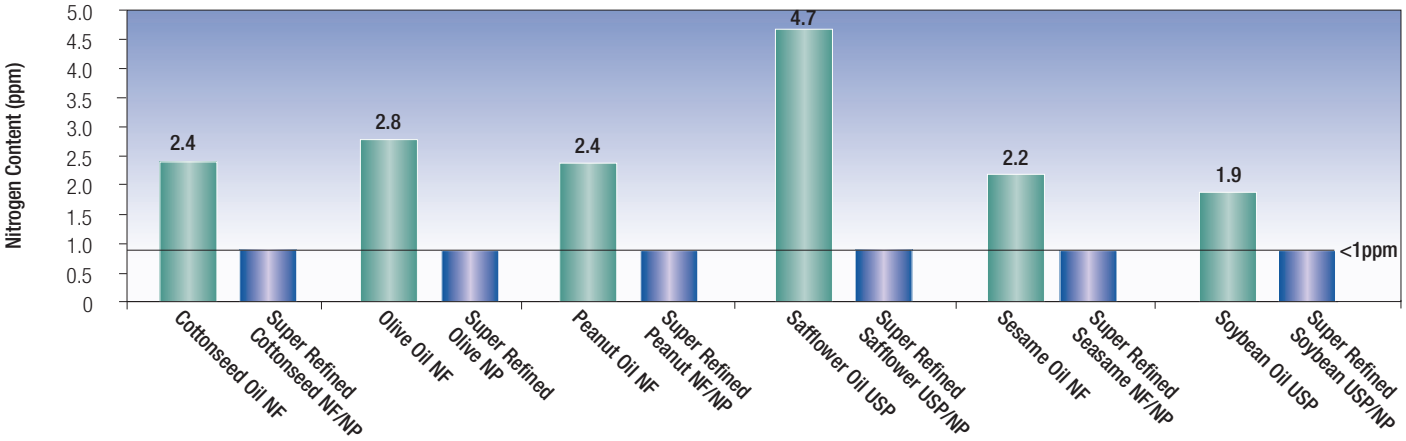

Figure 11: A graph showing the comparison of nitrogen content in Super Refined excipients vs. their compendial counterparts

It can be seen above (Figure 11) that the Super Refined grades of each oil showed a noticeable reduction in total nitrogen content; all were detected at less than 1.00 ppm. This indicated the possibility that the purity offered by Super Refining can help minimise the allergy potential of commonly used parenteral excipients.

Super Refined offering (listed in alphabetical order by chemical description)

*FDA IIG listing for parenteral dosage forms only

Chemical Description	Product Name	NF/USP	PhEur	JPE/JP	FDA IIG* (Parenteral)
Castor Oil	Super Refined Castor Oil	■		■	■
Corn Oil	Super Refined Corn	■	■		■
Cottonseed Oil	Super Refined Cottonseed	■			■
Oleic Acid	Super Refined Oleic Acid	■	■	■	■
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	■	■	■	■
Polysorbate 80	Super Refined Polysorbate 80 A				■
Propylene Glycol	Super Refined Propylene Glycol	■		■	■
Sesame Oil	Super Refined Sesame	■	■	■	■
Soybean Oil	Super Refined Soybean	■	■	■	■

References

[1] Rizzo G, Valerio J, Ellis S, Rumbelow S. The Effects of Chromatographic Purification Upon the Oxidative Stability of Lipophilic Excipients. Poster presented at: AAPS Annual Meeting and Exposition; 2011 Oct 24-26; Washington, DC.

[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] 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.

www.crodahealthcare.com

Europe, Middle East & Africa: hc-europe@croda.com
North America: marketing-usa@croda.com
Latin America: marketingla@croda.com
Asia Pacific: hc-asia@croda.com

06/17 HTCMS044v1 EN