Optimising Oral Drug Performance Through Purity

Super Refined™ Excipients

Oral drug development of both new and existing chemical entities often face numerous challenges including poor solubility, formulation instability and ineffective drug delivery. Regardless of the challenge, the ultimate goal is to create successful drug products with shortened development timelines. The selection of the right oral excipient during early phase development is critical to achieve this goal.

Croda's Super Refined proprietary process creates highly purified excipients that deliver benefits when formulating an oral drug product. These formulation benefits can then be translated into increased final drug value.

Formulation Benefits:

- Increased drug stability
- Improved gelatine capsule stability
- Reduced taste, odour & colour impact
- Expanded options for SEDDS & SMEDDS

Drug Value:

- Enhanced drug performance and stability
- Improved shelf life
- Increased patient compliance
- Improved bioavailability
- Decreased formulation development time
- Decreased time to market

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

Innovation you can build on™

Benefits & Features:

- Improved API Stability
- Increased Gelatine Capsule Stability
- Improved Taste Impact
- Reduced Colour Impurities
- Creation of SEDDS & SMEDDS
- Low Peroxide Values
- Low Moisture
- Multi-compendial – NF, PhEur, JPE

CRODA

Increased Drug Stability

Stabilisation of an Active Pharmaceutical Ingredient (API) is crucial to successful drug develoment. As API degradation can be initiated and accelerated by impurities that can be introduced by excipients in the formulation, carefully selecting the right oral excipient can be essential to formulation success.

To demonstrate enhanced API stability, the degradation of the oral antipsychotic drug perphenazine in Super Refined Propylene Glycol was compared with that in standard compendial propylene glycol over a 6 week period at 50°C[1].

Using Liquid Chromatography-Mass Spectrometry (LC-MS), it can be seen (Figure 1) that the perphenazine in Super Refined Propylene Glycol exhibited only a 96% drug recovery while the same API in propylene glycol USP exhibited only a 72% recovery. The study clearly demonstrates that Super Refined Propylene Glycol improves drug stability of the API over USP grade propylene glycol.

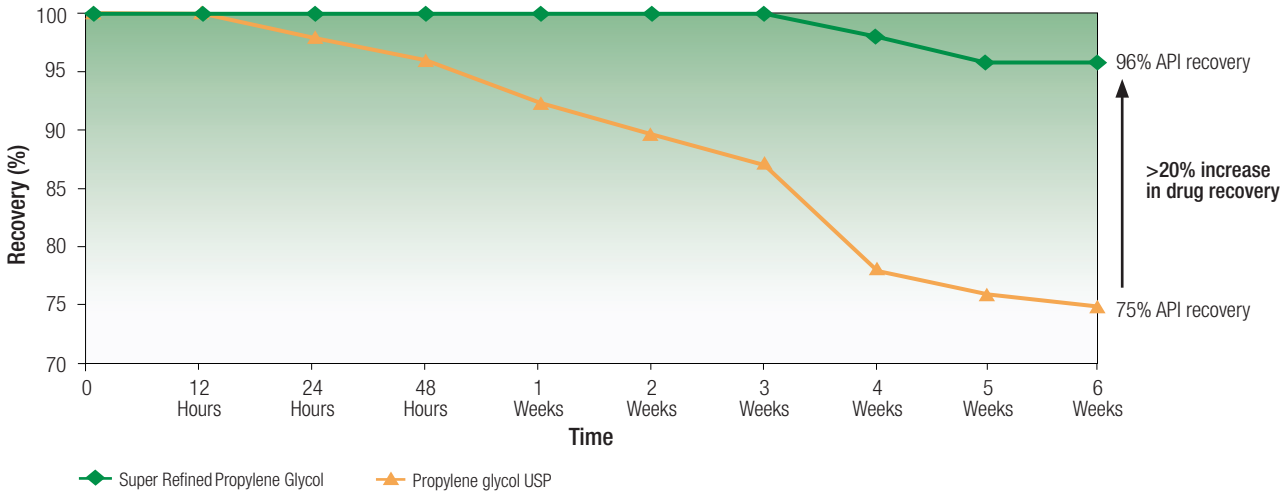

Figure 1: Comparison of perphenazine recovery in Super Refined Propylene Glycol as compared to propylene glycol USP over a 6 week period at 50°C.

Improved Gelatine Capsule Stability

Over time, the impurities found in commonly used solvents and fillers in gelatine capsules can preferentially absorb moisture from the gelatine shell. This moisture absorption can cause the gelatine to crosslink which, ultimately, cause the capsule to harden. The hardening of the capsule can result in either cracking or longer disintegration times leading to unacceptable drug efficacy.

To demonstrate that the lower impurity profile of Super Refined PEG 400 reduces crosslinking and decreases hardening of gelatine capsules, solutions were made containing 1 part gelatine (1% w/v in water) and 2 parts PEG 400[2]. Compendial grade PEG 400 NF gelatine solutions were compared to gelatine solutions made with Super Refined PEG 400. The solutions were centrifuged at 3,500 rpm and 10,000 rpm for 10 minutes with the level of precipitation used as an indicator of crosslinking.

Super Refined PEG 400 - lots A & B

PEG 400 NF - lots A & B

Figure 2: Comparison of gelatine dissolved in Super Refined PEG 400 vs. standard compendial grade, centrifuged at 3,500 rpm

Super Refined PEG 400 NF

PEG 400 NF

Figure 3: Comparison of gelatine dissolved in Super Refined PEG 400 vs. standard compendial grade, centrifuged at 10,000 rpm

It can be seen in Figure 2 and 3 that the Super Refined PEG 400 keeps the gelatine in suspension while the impurities in the standard grade PEG 400 NF cause the gelatine to crosslink forming a precipitate which is clearly observed upon centrifugation.

Reduced Taste Impact

The impact of an excipient on the taste of an oral drug can significantly affect patient compliance and repeat purchase. To demonstrate that Super Refining can help minimise the taste impact of excipients, a 3rd party testing company (Sensory Spectrum, Inc.) was contracted to quantitatively identify the degree of difference in taste between Super Refined Polysorbate 80 and its standard compendial counterpart[3]. A taste panel of extensively trained taste specialists assigned a Degree of Difference comparing 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 indicates that consumers will be able to distinctly perceive a difference in taste.

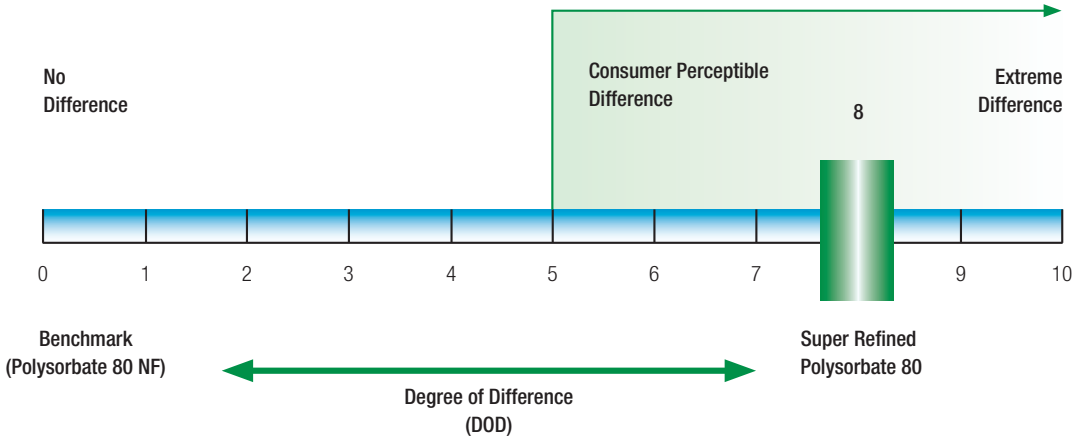

Figure 4: Taste impact and DOD of Super Refined Polysorbate 80 as compared to standard pharmaceutical grade of polysorbate 80

As seen in Figure 4, the DOD for Super Refined Polysorbate 80 versus its standard compendial equivalent was an 8. With a DOD of 8, it is clear 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 to promote better patient compliance.

Reduced Colour Impact & Impurities

The Super Refining process yields a highly purified excipient with a reduction in both colour and overall impurity levels. The purification of oral excipients yields improved drug appearance as well as improved stability of the excipient; the API and drug formulation results in enhanced product performance.

In Figure 5, the colour impact of the Super Refined process can be clearly seen. In addition, the Super Refining process yields significant reductions in multiple impurities including aldehydes, ketones, lower chain fatty acids and hydrocarbons. (Figure 6)

Beeswax intermediate | Super Refined Beeswax

Figure 5: Beeswax before and after the Super Refining process

Detected Impurities	Impurity Reduction Through Super Refining (%)
Hydrocarbons (such as Undecane, Dodecane, Pentadecane, Tetradecane, etc.)	82-100%
Aldehydes (such as 3-Methylbutanal, Octanal, Dodecanal, etc.)	90-100%
Lower Chain Fatty Acids (such Acetic acid, Butanoic acid, Pentanoic acid, Hexanoic acid, etc)	82-100%
Lower Chain Alcohols (such as Ethanol, 2-Heptanol, Nonanol, etc.)	77-100%

Figure 6: Detected impurities by GC-MS that were reduced during the Super Refining process of beeswax

Expanded Options for SEDDS & SMEDDS

Self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery system (SMEDDS) are lipid-based formulations that aim to deliver hydrophobic drugs that typically are associated with poor water solubility and low bioavailability. In order to design and streamline the development of SEDDS and SMEDDS, ternary phase diagrams were developed to determine optimum blends between surfactant to co-system (surfactant or solvent) and surfactant to oil in the purified excipient combinations selected (Figure 7)[4].

Pure surfactant and certain surfactant to co-system ratios when diluted in distilled water [fasted (1:50) and fed (1:250)] exhibited similar particle sizes with an approximate z average less than 50 d.nm. As the Super Refined Polysorbate 20 or 80 concentration decreased and the Etocas™ 35 or Super Refined PEG 300 or 400 concentration increased, the particle size distribution was observed to be multimodal.

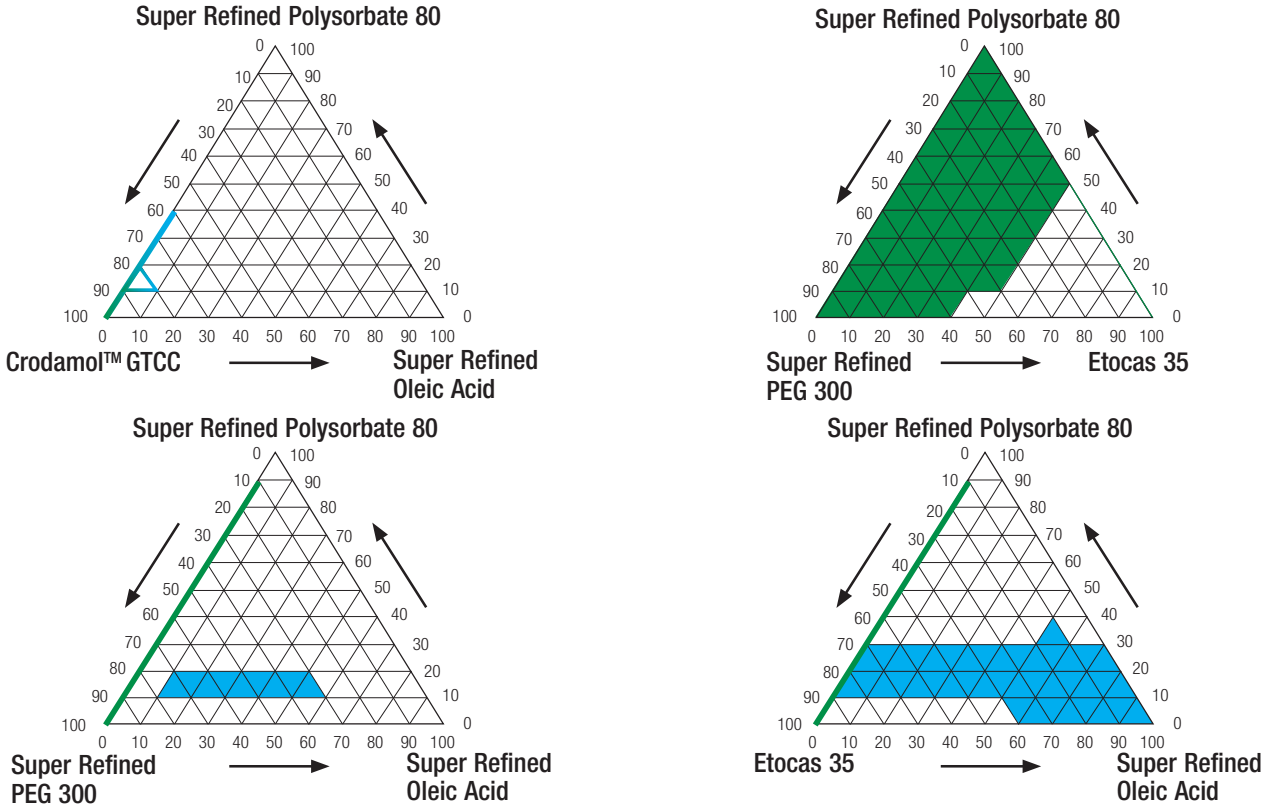

Figure 7: Phase diagrams of diluted, purified surfactants (Super Refined Polysorbate 20 or 80) co-surfactant (Etocas 35*), co-solvents (Super Refined PEG 300 and 400) and oils (Super Refined Oleic Acid or Crodamol™ GTCC*) in distilled water. [**Green = SMEDDS (particle size of <50 nm)**; **Light Blue = SEDDS (particle size of 100-300 nm)**]

Through the development of these phase diagrams, it was determined that purified surfactants, co-surfactants, co-solvents and oils enable the formation of a wide range of colloidal phases including micelles, microemulsions (oil-in-water; water-in oil, bicontinuous) and liquid crystals (lamellar and hexagonal). This work can, in turn, be used to design custom-made, purified, lipid-based formulations.

Recommended high purity components for SEDDS and SMEDDS development:

Carrier Oils	Primary Surfactant	Co-Solvents
Super Refined Castor Oil	Super Refined Polysorbate 20	Super Refined PEG 300
Super Refined Corn Oil	Super Refined Polysorbate 60	Super Refined PEG 400
Super Refined Cottonseed Oil	Super Refined Polysorbate 80	Super Refined PEG 600
Super Refined Oleic Acid		Super Refined Propylene Glycol
Super Refined Olive Oil		
Super Refined Peanut Oil		
Super Refined Sesame Oil		
Super Refined Soybean		

**Etocas 35 (co-surfactant) and Crodamol GTCC (carrier oil) are exclusive trademarked excipients of Croda*

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

*FDA IIG listing for oral dosage forms only

Chemical Description	Product Name	NF/USP	PhEur	JPE/JP	FDA IIG* (Oral)
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	■	■		■
Petrolatum	Crolatum V			■	■
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 Proplyene Glycol	■		■	■
Sesame Oil	Super Refined Sesame	■	■	■	■
Soybean Oil	Super Refined Soybean	■	■	■	■
White Wax (Beeswax)	Super Refined Beeswax	■	■	■	■

References

[1] Rizzo G.J., Ellis S., Rumbelow S. The Purity of Propylene Glycol: The Impact of API Stability and Prention of N-Oxidation by Chromatographic Purification. Poster T3114 presented at: AAPS Annual Meeting and Exposition; 2012 Oct 14-18; Chicago, IL.

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

[3]Kaziska A., Grant C. Taste Testing of Oral Dose Excipients – Comparing Chromatographically Purified and Standard Products. Poster T2259 presented at: AAPS Annual Meeting and Exposition; 2015 Oct 25-29; Orlando, FL.

[4]Hall N., Humphrey J., Radwick A., Rumbelow S. Designing Self-Emulsifying Lipid-Based Formulations for Drug Delivery with Purified Excipients. Poster 28W0300 presented at: AAPS Annual Meeting and Exposition; 2016 Nov 13-17; Denver, CO.

www.crodahealthcare.com

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

08/17 HTCMS012 EN