Maximise the Performance of Your Active Pharmaceutical Ingredients

Discover the Benefits of Super Refined™ Excipients

Innovation you can build on™

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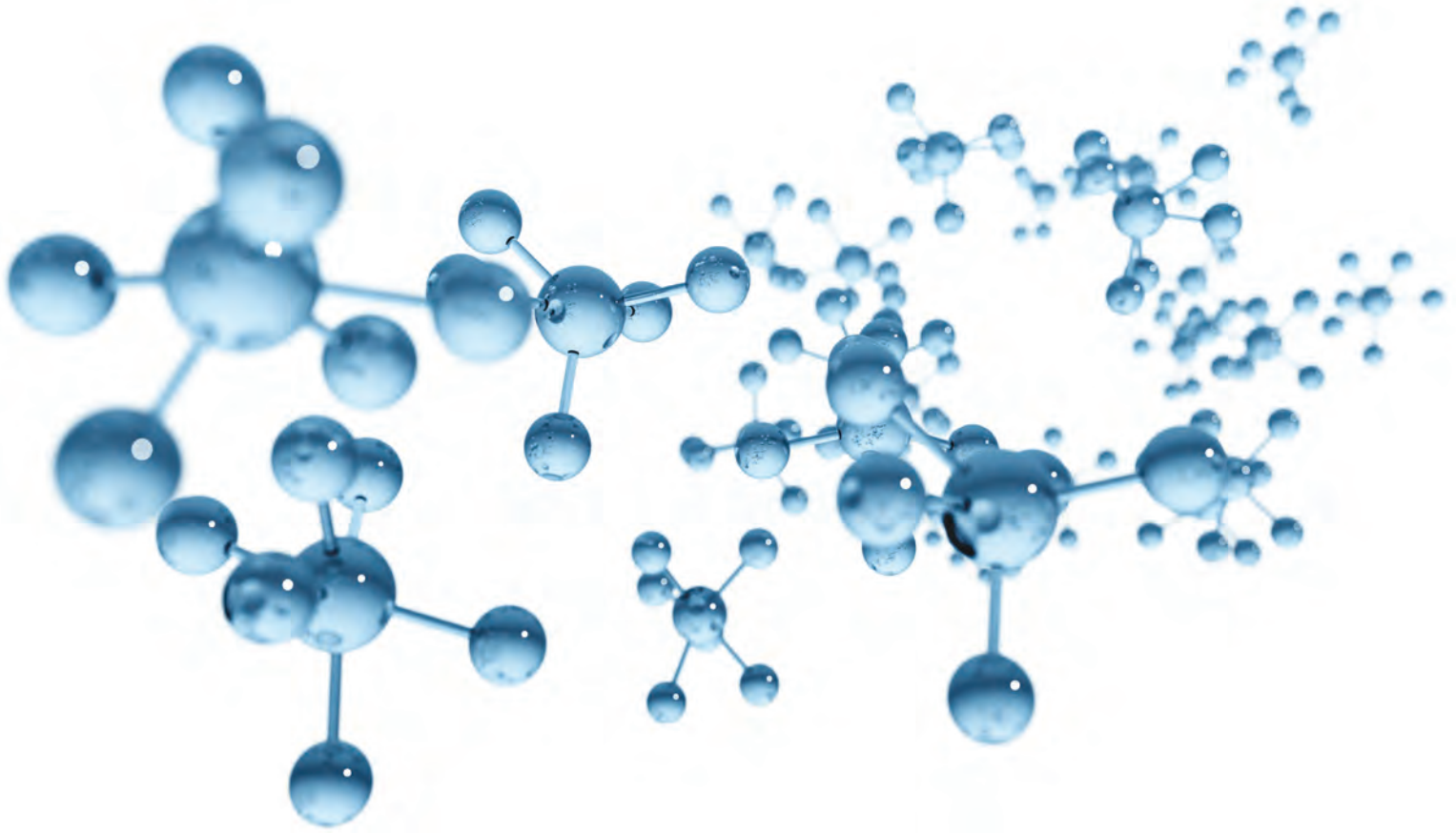
The Power of Excipient Purity in API Stability



Active Pharmaceutical Ingredient (API) stability is one of the most important factors in pharmaceutical formulation development. Degradation and instability are common problems that can lead to extended development timescales, additional regulatory hurdles and reduced product shelf life. API degradation can have a significant impact on product efficacy, with breakdown products causing potential safety and toxicity issues.

The choice of pharmaceutical excipients can play a critical role in enhancing formulation stability. At Croda, our highly purified ingredients are designed to reduce the risk of product degradation, improving the chances of successful formulation development.

Our exclusive range of **Super Refined**™ excipients has been specially developed to optimise API stability and improve the performance of pharmaceutical formulations. Super Refined materials demonstrate clear benefits, adding real value to the drug development process.

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Benefits of Super Refined Excipients

- Enhanced API and formulation stability
- Fewer formulation degradation products
- Minimised analytical complexity
- Simplified formulations
- Reduced resource, time and development costs
- Improved chance of formulation success
- Multi-compendial - NF, PhEur, JPE

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What are Super Refined excipients?

Croda's Super Refined products are a range of highly purified pharmaceutical excipients in which impurities commonly found in standard compendial grade excipients have been removed. Super Refined excipients are manufactured using a proprietary process to reduce the level of impurities such as peroxides, aldehydes, moisture and catalyst residues, which are known to have an adverse effect on formulation stability.

The Super Refined excipients comprise a wide range of polysorbates, polyethylene glycols and oils, making them suitable for parenteral, oral and topical applications.

Super Refined excipients are highly purified to remove impurities found in standard compendial grades

Initial API stability screening study

A study was carried out using 10 widely used APIs to assess their stability in standard compendial grade excipients. The APIs were selected to represent a range of different chemistry types and therapeutic areas. The excipients chosen to investigate the problem are some of the most commonly utilised in pharmaceutical formulations and include those found in the formulations of the API products.

Experimental details

Each API was dissolved in a standard compendial grade excipient at a concentration of 1 or 10 mg/g, depending on the API solubility. The API/excipient solutions were prepared in glass vials with plastic caps with a small air headspace above each sample. After an initial measurement of API concentration by high performance liquid chromatography (HPLC), samples were stored at temperatures of 4, 25 and 40ºC. At timepoints of 4, 8 and 12 weeks, samples were removed and the API concentration determined. The API recovery rate was calculated as a percentage of the initial concentration. An API was considered "unstable" if the percentage recovery was less than 90% after incubation for 12 weeks at 40ºC.

Results

The stability screening results (Table 1) show API degradation in a variety of excipients. Most of the APIs showed instability in at least two excipients, with two APIs (haloperidol decanoate and ritonavir) being unstable in all excipients tested. In polysorbate 80, a widely used excipient, 70% of APIs demonstrated instability.

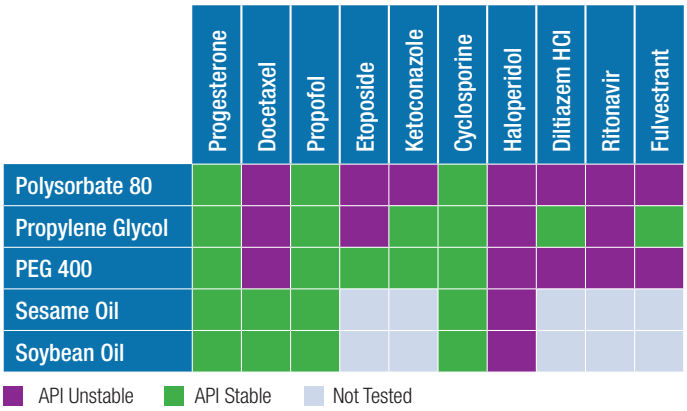


Table 1: API stability in standard compendial grade excipients

Conclusion

API instability is a common problem and can have a significant impact on formulation development.

70% of APIs were unstable in at least one standard compendial grade excipient

Further API stability studies

For selected APIs shown to be unstable in standard grade compendial excipients, further studies were carried out to investigate the effect of excipient purity and source on API stability. APIs were dissolved in either Super Refined excipients or standard compendial grade excipients from different sources.

In each case, degradation studies were carried out at 4, 25 and 40ºC. API recovery rates were determined by HPLC as described in the screening study. In addition, the chromatograms were analysed to determine the presence of any additional peaks arising during the stability study, indicating the formation of API degradation products. In selected cases, identification of these degradation products was carried out by liquid chromatography – mass spectrometry (LC-MS) with reference to known standards.

Case Study: Docetaxel Stability in Polysorbate 80 and PEG 400

Docetaxel (Figure 1) is a chemotherapy drug, used in the treatment of various forms of cancer. It is a member of the taxane class of drugs, a semi-synthetic analogue of paclitaxel and structurally similar to cabazitaxel. The taxanes represent a challenge to formulators as they have very low solubility in water, and docetaxel is often formulated with polysorbate 80 to overcome this insolubility.

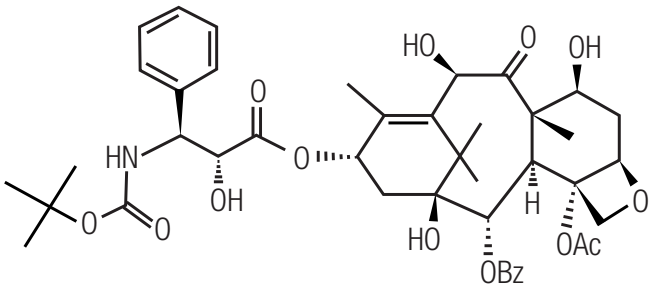


Figure 1: Structure of docetaxel

The screening study showed that docetaxel is unstable in standard compendial grade polysorbate 80. Polysorbate 80 is an excipient that is present at significant concentration in the commercial originator and generic versions of the drug. Docetaxel is also unstable in standard compendial grade PEG 400, another excipient commonly used in many dosage forms. This study examines the stability of docetaxel in Super Refined Polysorbate 80 and Super Refined PEG 400 in comparison with standard compendial grade equivalents from different sources.

API recovery

The data presented in Figure 2 shows docetaxel recovery in polysorbate 80 over a 12-week period at 40ºC. In Super Refined Polysorbate 80, the recovery rate after 12 weeks was greater than 90%. In contrast, the recovery of docetaxel in polysorbate 80 from three other sources dropped to between 20% and 60% after 4 weeks and between 10% and 50% after 12 weeks.
This demonstrates that the stability of docetaxel in Super Refined Polysorbate 80 is substantially higher than in the corresponding standard compendial grades.

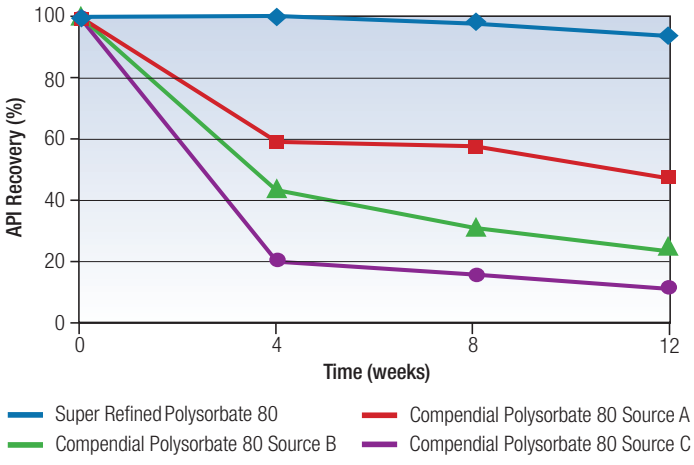


Figure 2: % docetaxel recovery in polysorbate 80 at 40ºC

The findings are similar for the stability of docetaxel in PEG 400 (Figure 3). The recovery rate of docetaxel in Super Refined PEG 400 was greater than 90% after 12 weeks at 40ºC. At the same time point, API recovery in the two standard compendial grade PEG 400 samples were 75% and 30% respectively. The stability of docetaxel in Super Refined PEG 400 is substantially higher than in standard compendial grade excipients.

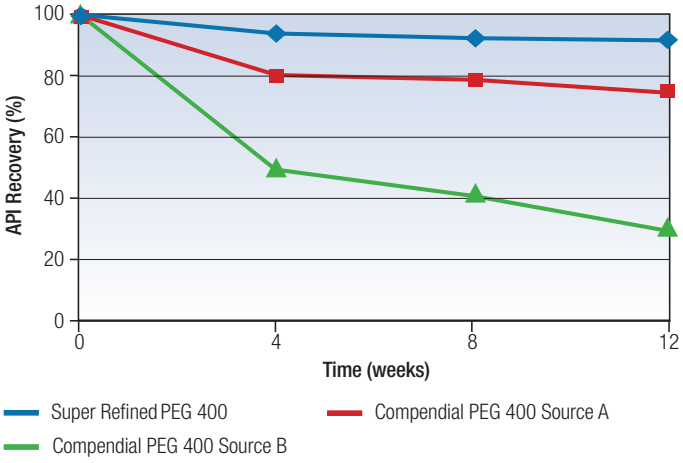


Figure 3: % docetaxel recovery in PEG 400 at 40ºC

Docetaxel is more stable in **Super Refined** excipients than in standard compendial grade products

API degradation – epimerisation and oxidation

Analysis of docetaxel samples in Super Refined and standard compendial grade excipients was carried out by HPLC (Figures 4 and 5) at each time point. In both Super Refined Polysorbate 80 and Super Refined PEG 400 docetaxel appears as a single peak at a retention time of 3.8 minutes, even after 12 weeks at 40ºC. This demonstrates excellent stability of the API in the Super Refined excipients.

In standard compendial grade polysorbate 80, two additional peaks are observed at retention times of 5.3 and 9.4 minutes. In standard compendial grade PEG 400, additional peaks are observed at 4.3, 5.3, 5.9 and 9.4 minutes. The intensity of each of these peaks increases during the study, indicating progressive formation of several API degradation products in the standard compendial grade excipients.

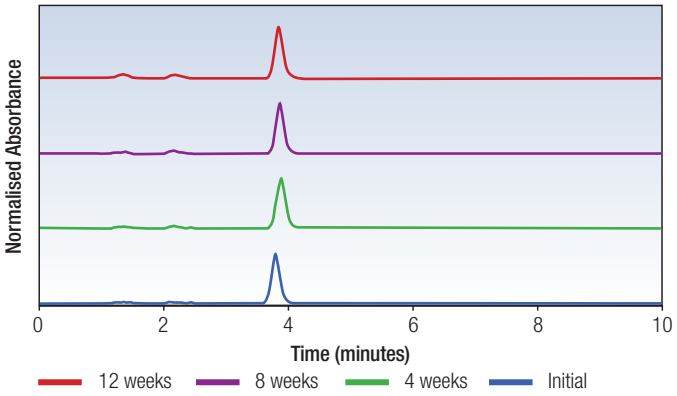


Figure 4a: Chromatogram of docetaxel in Super Refined Polysorbate 80 at 40ºC

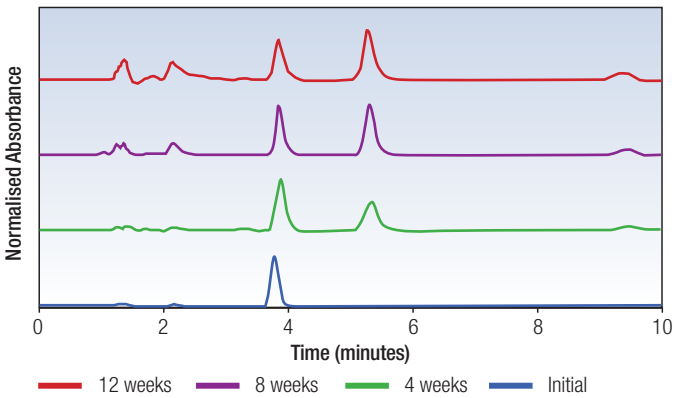


Figure 4b: Chromatogram of docetaxel in standard compendial grade polysorbate 80 at 40ºC

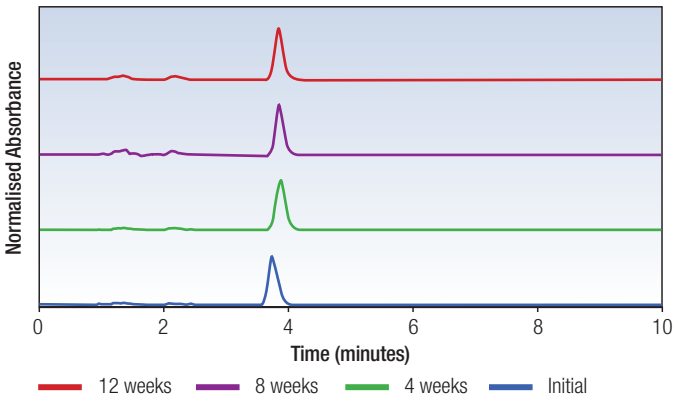


Figure 5a: Chromatogram of docetaxel in Super Refined PEG 400 at 40ºC

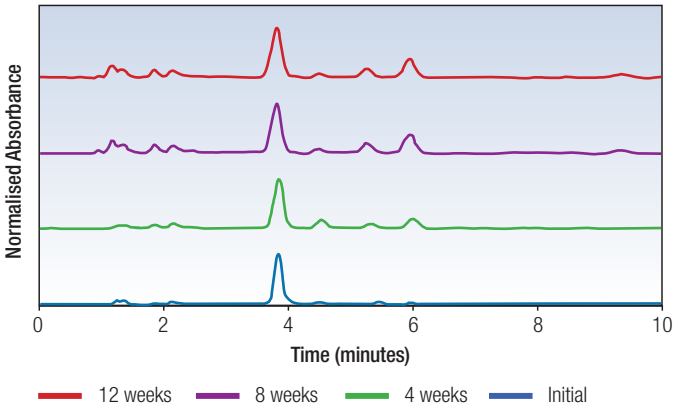
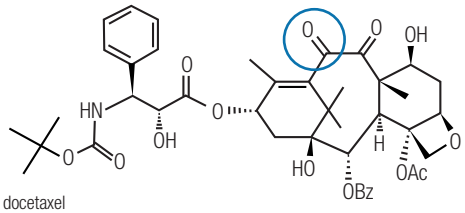
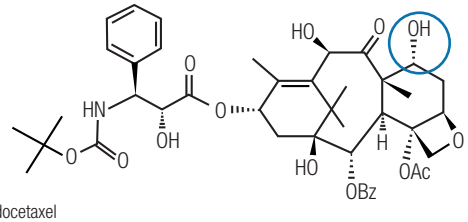


Figure 5b: Chromatogram of docetaxel in standard compendial grade PEG 400 at 40ºC

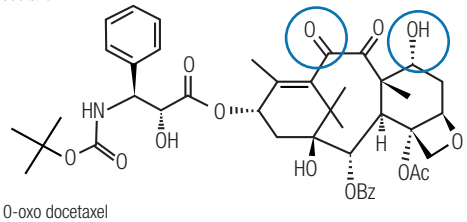
The docetaxel degradation products have been identified by LC-MS using reference standards. The peaks at 4.3, 5.3 and 5.9 minutes were confirmed as 10-oxo docetaxel (Figure 6a), an oxidation product, 7-epi docetaxel (Figure 6b), an epimer of docetaxel and 7-epi-10-oxo docetaxel (Figure 6c), an epimer of the oxidation product. All of these degradation products were detected in standard compendial grade PEG 400. The epimer 7-epi docetaxel was also detected in standard compendial grade polysorbate 80. None of these degradation peaks were seen in Super Refined PEG 400 or Super Refined Polysorbate 80.



(a) 10-oxo docetaxel



(b) 7-epi docetaxel



(c) 7-epi-10-oxo docetaxel

Figure 6: Docetaxel degradation products

Key Findings

- Docetaxel stability is enhanced in Super Refined excipients in comparison with standard compendial grade products
- Multiple API degradation products are formed in standard compendial grade products that are not seen in Super Refined excipients

Case Study: Etoposide Stability in Polysorbate 80 and PEG 300

Etoposide (Figure 7) is a chemotherapy drug used in the treatment of ovarian cancer and leukaemia. It is sparingly soluble in water and structurally similar to another chemotherapy drug, teniposide. Etoposide is formulated as an intravenous infusion with polysorbate 80 and PEG 300.

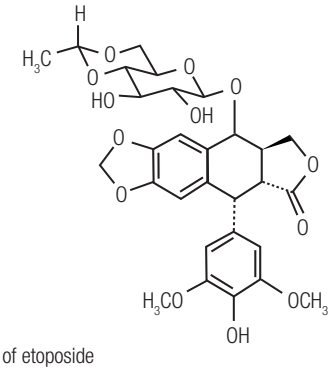


Figure 7: Structure of etoposide

This study investigates the stability of etoposide in Super Refined and standard compendial grade polysorbate 80 and PEG 300 to determine the effect of excipient purity on API degradation.

API recovery

The results for etoposide recovery at 40ºC in polysorbate 80 are shown in Figure 8. In Super Refined Polysorbate 80 the recovery rate was nearly 100% after 12 weeks. In contrast, the recovery rate in standard compendial excipients varied between 17% and 85%. This demonstrates the enhanced stability of the API in Super Refined Polysorbate 80 in comparison with standard compendial grade alternatives.

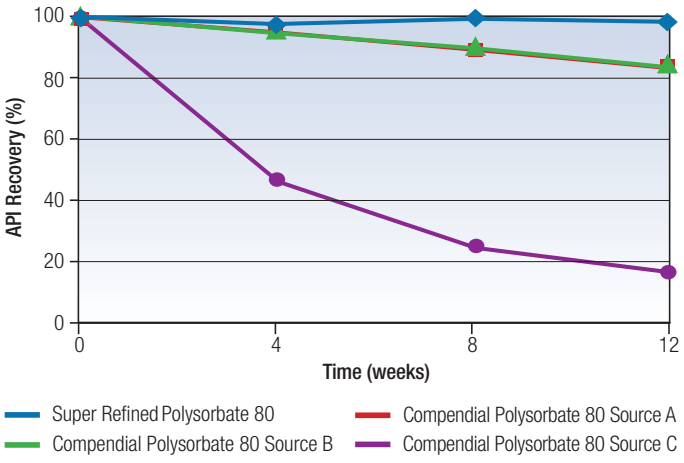


Figure 8: % etoposide recovery in polysorbate 80 at 40ºC

The results for etoposide recovery at 40ºC in PEG 300 are shown in Figure 9. In Super Refined PEG 300 the recovery rate was over 90% after 12 weeks. In contrast, the recovery rate in standard compendial grade PEG 300 was less than 30%. This demonstrates that the stability of etoposide in Super Refined PEG 300 is substantially higher than in the corresponding compendial grade excipient.

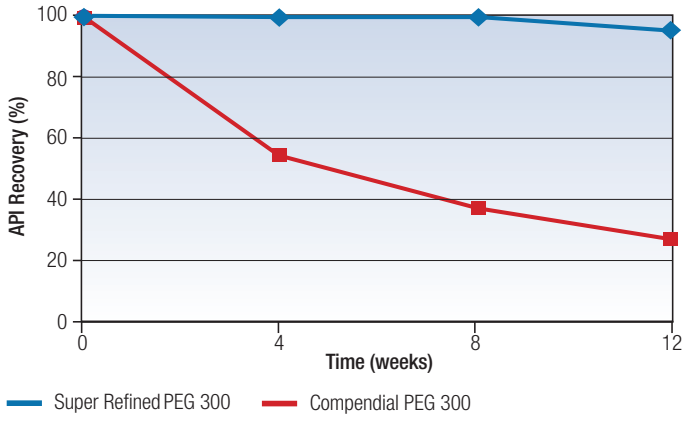


Figure 9: % etoposide recovery in PEG 300 at 40ºC

API degradation - epimerisation

Analysis of etoposide samples in Super Refined and standard compendial grade excipients was carried out by HPLC (Figures 10 and 11) at each time point. In both Super Refined Polysorbate 80 and Super Refined PEG 300 etoposide appears as a single peak at a retention time of 4.4 minutes, even after 12 weeks at 40ºC. This demonstrates good stability of the API in the Super Refined excipients.

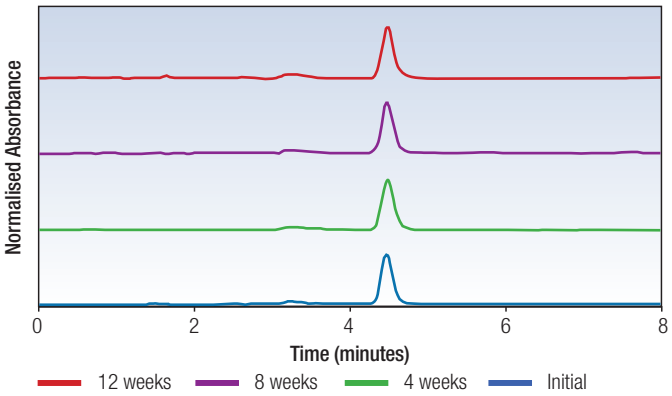


Figure 10a: Chromatogram of etoposide in Super Refined Polysorbate 80 at 40ºC

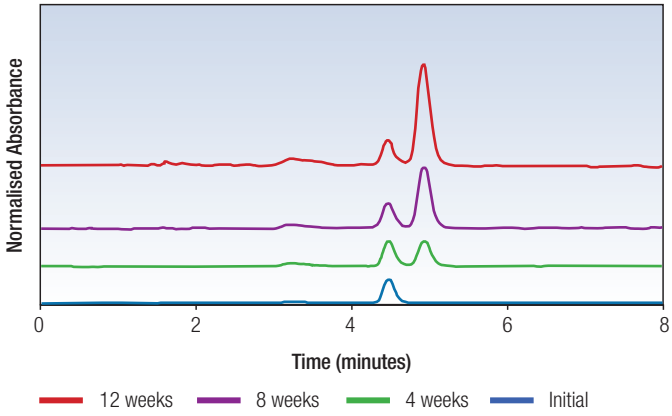


Figure 10b: Chromatogram of etoposide in standard compendial grade polysorbate 80 at 40ºC

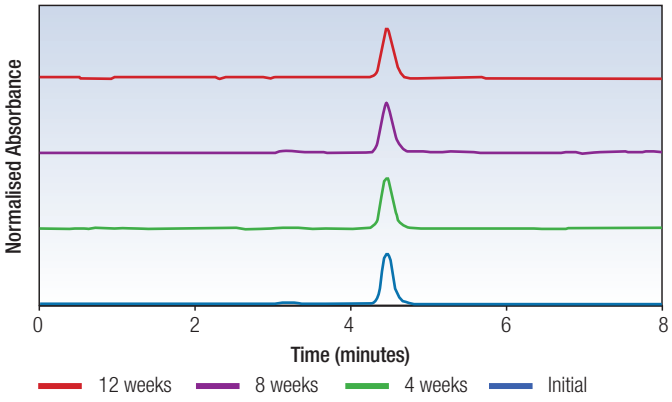


Figure 11a: Chromatogram of etoposide in Super Refined PEG 300 at 40ºC

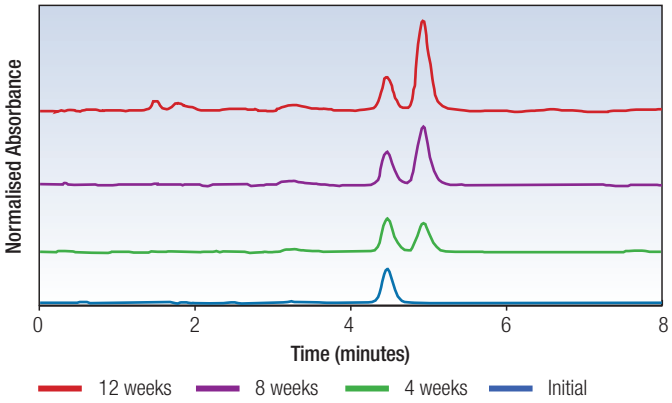


Figure 11b: Chromatogram of etoposide in standard compendial grade PEG 300 at 40ºC

In both standard compendial grade polysorbate 80 and PEG 300 an additional peak is observed at a retention time of 4.9 minutes. The intensity of this peak increases during the study, indicating progressive formation of an API degradation product in the standard compendial grade excipients.

No degradation products are seen in **Super Refined** excipients

The etoposide degradation product has been identified as cis-etoposide by LC-MS using a reference standard. Cis-etoposide is a known degradation product of etoposide formed by API epimerisation (Figure 12). No degradation products are observed in Super Refined excipients.

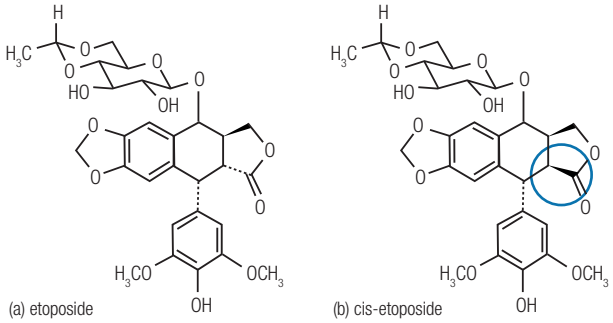


Figure 12: Etoposide and its epimerised degradation product

Key Findings

- Etoposide stability is enhanced in Super Refined excipients in comparison with standard compendial grade products
- API degradation occurs in standard compendial grade excipients. In contrast, no degradation products are seen in Super Refined excipients

Stability of APIs in Super Refined™ PEG

Polyethylene glycols (PEGs) are excipients that are widely used in oral, parenteral and topical delivery dosage forms. Low molecular weight PEGs, such as PEG 300 and PEG 400 in particular, are used as solvents in concentrated formulations that are then diluted prior to injection via infusion.

As PEGs can be used at relatively high concentration in the formulation, it is important that they do not cause the Active Pharmaceutical Ingredient (API) to degrade.

A screening study on the stability of APIs in standard compendial excipients has revealed that 5 out of 10 APIs are unstable in PEG 400.

Croda's range of **Super Refined™** excipients has been specially developed to optimise API stability and improve performance of pharmaceutical formulations. Super Refined materials demonstrate clear benefits, adding real value to the drug development process.

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The following case studies demonstrate the effect of excipient purity on the stability of two APIs, fulvestrant and diltiazem hydrochloride.

Case Study: Fulvestrant Stability in PEG 400

Fulvestrant (Figure 1) is a selective oestrogen receptor degrader, used to treat hormone receptor positive metastatic breast cancer in post-menopausal women. It is a steroid with an alkyl-sulfinyl moiety, delivered via intramuscular injection in a formulation that contains castor oil.

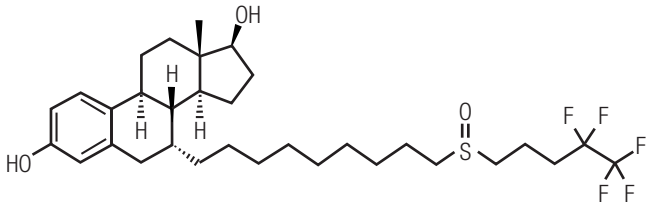

Figure 1: Structure of fulvestrant

API recovery

The results for fulvestrant at 40°C in PEG 400 are shown in Figure 2. In standard compendial grade PEG 400 the API recovery rate after 12 weeks was 34%. In contrast, the recovery rate in Super Refined PEG 400 was considerably higher at 74%. This demonstrates that the stability of fulvestrant in Super Refined PEG 400 is substantially higher than in the corresponding standard compendial grade.

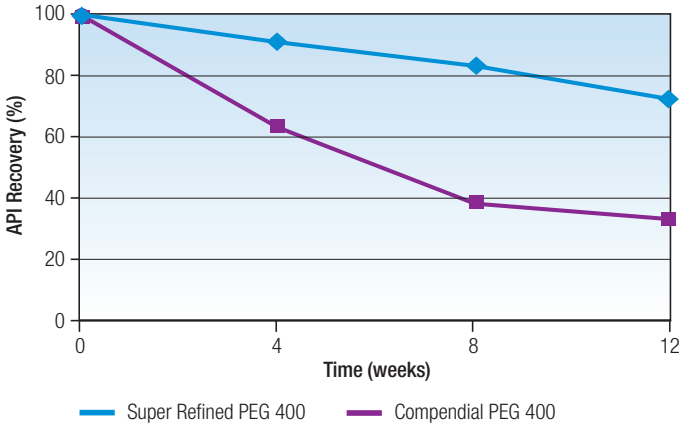

Figure 2: % fulvestrant recovery in PEG 400 after 12 weeks at 40°C

Excipient choice can make all the difference in formulation development

API degradation

In both Super Refined and standard compendial grade excipients the reduction in recovery is accompanied by the presence of an additional peak in the chromatogram (Figure 3). Fulvestrant elutes at a retention time of 5.1 minutes. An additional peak also elutes at a retention time of 6.9 minutes. Even though this peak is appearing in both grades of PEG 400, the height is considerably lower in the Super Refined PEG 400. This demonstrates the substantially increased stability of the API in Super Refined PEG 400.

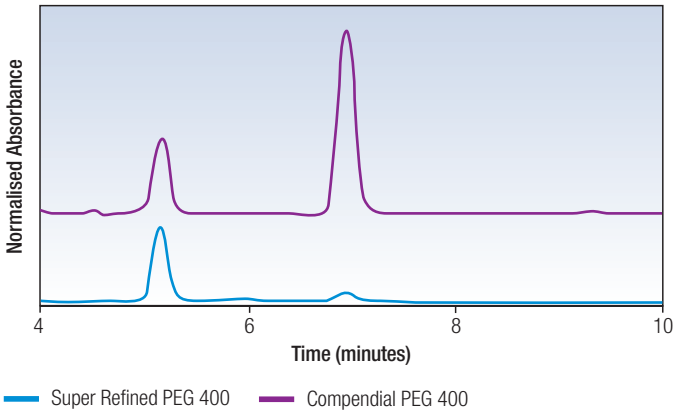

Figure 3: Chromatogram of fulvestrant in PEG 400 after 12 weeks at 40°C

Key Findings

- The stability of fulvestrant is substantially enhanced in Super Refined PEG 400 in comparison with that in standard compendial grade PEG 400
- Formulation in Super Refined PEG 400 results in substantially less degradation than is seen in a standard compendial grade product

Case Study: Diltiazem Hydrochloride Stability in PEG 400

Diltiazem hydrochloride (Figure 4) is a calcium channel blocker, used in the treatment of angina and hypertension. It is a non-dihydropyridine class of calcium channel blocker based on benzothiazepine. It is usually administered orally as a tablet or capsule. It has also been administered via injection and topical cream.

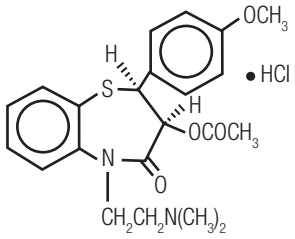

Figure 4: Structure of diltiazem hydrochloride

API recovery

The results for diltiazem hydrochloride recovery at 40°C after 16 weeks are shown in Figure 5. In standard compendial PEG 400 the recovery rate was 57%. In contrast, the recovery rate in Super Refined PEG 400 was 94%. This shows the considerably improved stability of the API in Super Refined PEG 400.

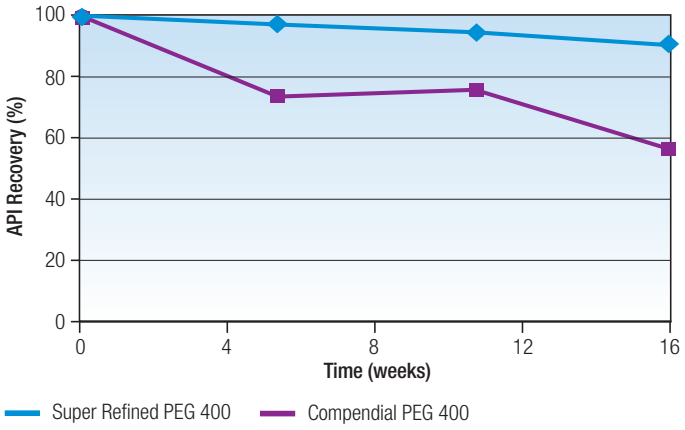

Figure 5: % recovery of diltiazem hydrochloride after 16 weeks at 40°C

API degradation

Diltiazem hydrochloride elutes with a retention time of 3.8 minutes as shown in Figure 6. Initially this peak appears symmetrical, but over the course of the stability study the peak develops a shoulder in standard compendial PEG 400. The presence of this shoulder suggests degradation of the API, resulting in the formation of a degradation product that elutes at a time similar to diltiazem hydrochloride. The shoulder is not observed in Super Refined PEG 400. This shows the substantially increased stability of the API in the Super Refined grade.

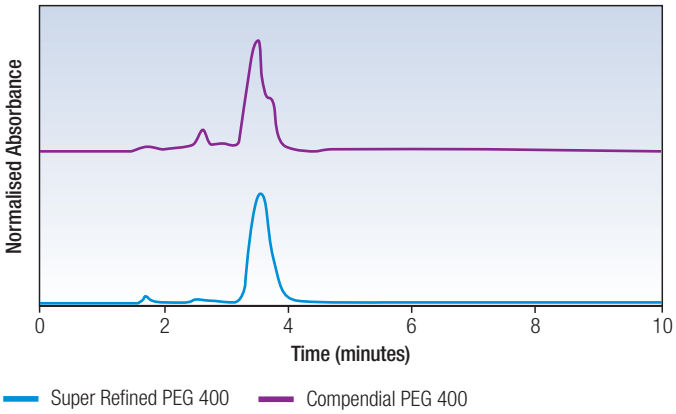

Figure 6: Chromatogram of diltiazem hydrochloride in PEG 400 after 16 weeks at 40°C

Key Findings

- The stability of diltiazem hydrochloride is enhanced in Super Refined PEG 400 in comparison with that in standard compendial grade PEG 400
- Formulation in Super Refined PEG 400 results in substantially less degradation than is seen in a standard compendial grade product

Stability of APIs in Super Refined™ Oils

Excipient choice can make all the difference in successful formulation development. The selection of pharmaceutical excipients in a drug formulation can have a significant impact on development timescales, Active Pharmaceutical Ingredient (API) integrity and product stability. These in turn negatively impact upon the time to market, storage conditions, shelf life, efficacy and product safety.

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The following case studies with ritonavir and haloperidol decanoate demonstrate the importance of excipient selection in formulation development.

Case Study: Ritonavir Stability in Oleic Acid

Ritonavir (Figure 1) is a water-insoluble drug for the treatment of HIV/AIDS. It is used either alone or in combination with lopinavir in a range of tablet, liquid and capsule formats. The soft gel capsule product is formulated with oleic acid. Ritonavir has been shown to be unstable in a range of standard compendial excipients.

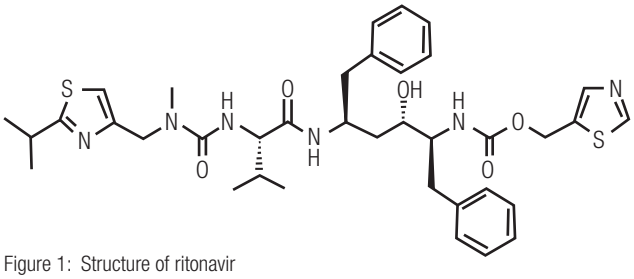

Figure 1: Structure of ritonavir

This case study investigates the stability of ritonavir in Super Refined and standard compendial grade oleic acid to determine the effect of excipient purity on API degradation.

API recovery

The results for ritonavir recovery at 40ºC in oleic acid are shown in Figure 2. In standard compendial grade oleic acid the API recovery rate after 12 weeks was 24%. In contrast, the recovery rate in Super Refined Oleic Acid was more than double that at 55%. This demonstrates that the stability of ritonavir in Super Refined Oleic Acid is substantially higher than in the corresponding standard compendial grade excipient.

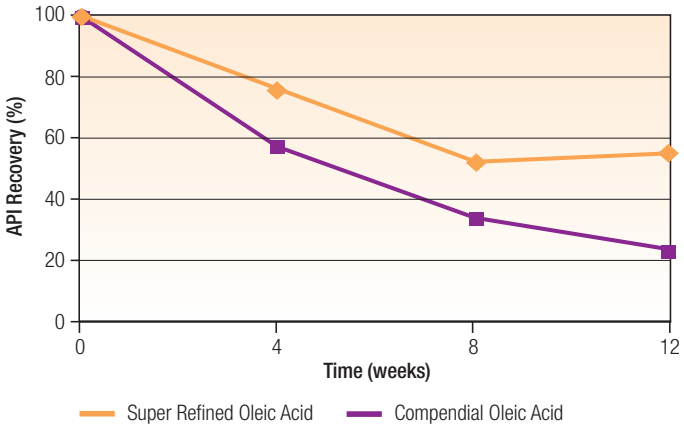

Figure 2: % ritonavir recovery in oleic acid at 40ºC

Excipient choice can make all the difference in formulation development

API degradation

Ritonavir appears in the chromatogram as a single peak at a retention time of 4.8 minutes (Figure 3). In standard compendial grade oleic acid, numerous additional peaks are observed, indicating extensive API degradation. In Super Refined Oleic Acid, fewer, smaller peaks are seen, confirming the increased stability of ritonavir in comparison with that in the standard compendial grade excipient.

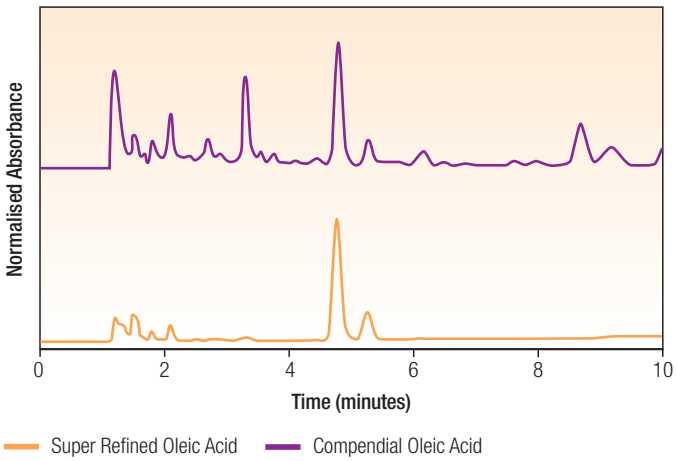

Figure 3: Chromatogram of ritonavir in oleic acid after 12 weeks at 40°C

Key Findings

- The stability of ritonavir is enhanced in Super Refined Oleic Acid in comparison with that in standard compendial grade oleic acid
- Formulation in Super Refined Oleic Acid results in fewer degradation products than are seen in a standard compendial grade product

Case Study: Haloperidol Decanoate Stability in Sesame Oil

Haloperidol decanoate (Figure 4) is an antipsychotic drug used in the treatment of schizophrenia. It is administered by intramuscular injection as an extended release formulation in sesame oil.

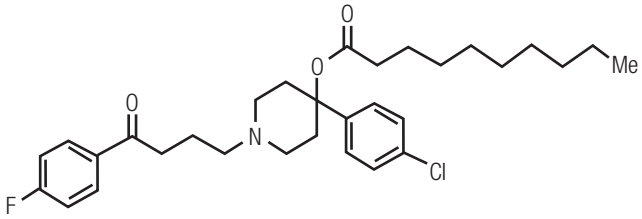

Figure 4: Structure of haloperidol decanoate

API recovery

This case study investigates the stability of haloperidol decanoate in Super Refined Sesame Oil and standard compendial grade equivalents to determine the effect of excipient purity on API degradation. In Super Refined Sesame Oil more than 93% haloperidol decanoate recovery was obtained after incubation at 40ºC for 12 weeks. In contrast, the recovery rate in standard compendial excipients varied between 68% and 79%, showing enhanced stability of the API in Super Refined Sesame Oil in comparison with standard compendial grade alternatives.

API stability is enhanced in **Super Refined** excipients in comparison with standard compendial grade products

API degradation

Haloperidol decanoate appears in the chromatogram as a single peak at a retention time of 3.2 minutes (Figure 5). In standard compendial grade sesame oil several additional peaks are observed, indicating formation of API degradation products. In Super Refined Sesame Oil, fewer, smaller peaks are seen, confirming the increased stability of haloperidol decanoate in comparison with that in the standard compendial grade excipient.

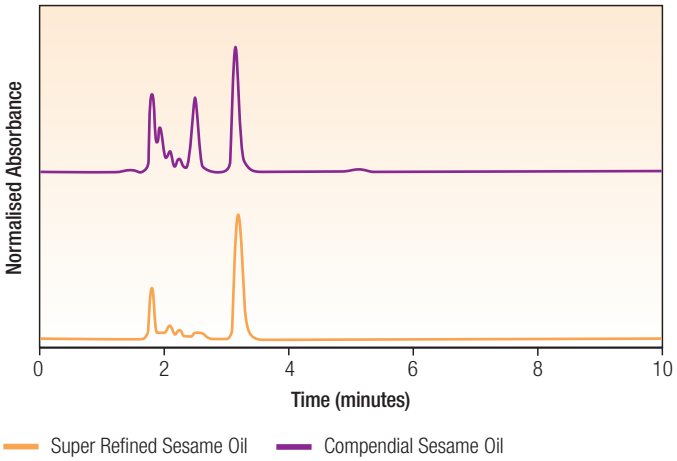

Figure 5: Chromatogram of haloperidol decanoate in sesame oil after 12 weeks at 40ºC

Key Findings

- The stability of haloperidol decanoate is enhanced in Super Refined Sesame Oil in comparison with that in standard compendial grade sesame oil
- Formulation in Super Refined Sesame Oil results in fewer degradation products than are seen in standard compendial grade products

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