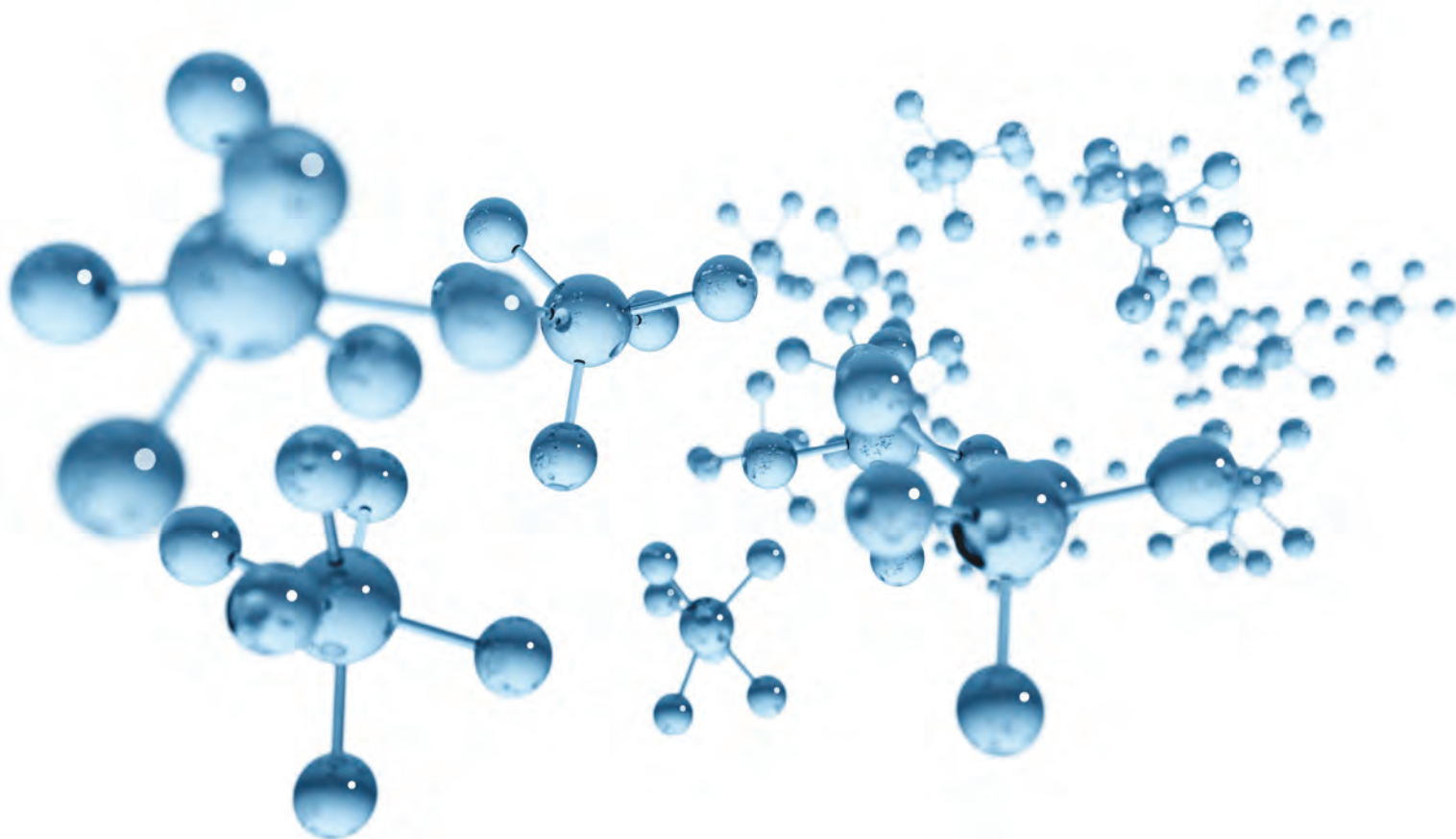


The Power of Excipient Purity in API Stability



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.

Visit www.crodahealthcare.com
for more information

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

Innovation you can build on™

CRODA

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 40°C. 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 40°C.

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.

	Progesterone	Docetaxel	Propofol	Etoposide	Ketoconazole	Cyclosporine	Haloperidol	Diltiazem HCl	Ritonavir	Fulvestrant
Polysorbate 80	API Unstable	API Unstable	API Stable	API Stable	API Stable	API Stable	API Unstable	API Unstable	API Unstable	API Unstable
Propylene Glycol	API Stable	API Stable	API Stable	API Stable	API Stable	API Stable	API Unstable	API Stable	API Unstable	API Stable
PEG 400	API Stable	API Stable	API Stable	API Stable	API Stable	API Stable	API Unstable	API Unstable	API Unstable	API Unstable
Sesame Oil	API Stable	API Stable	API Stable	Not Tested	Not Tested	API Stable	API Unstable	Not Tested	Not Tested	Not Tested
Soybean Oil	API Stable	API Stable	API Stable	Not Tested	Not Tested	API Stable	API Unstable	Not Tested	Not Tested	Not Tested

■ API Unstable ■ API Stable ■ Not Tested

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 40°C. 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.

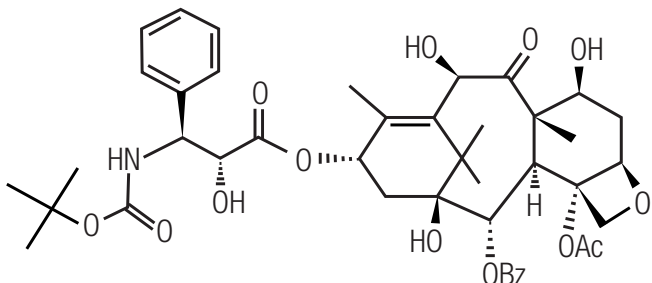


Figure 1: Structure of docetaxel

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 40°C. 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.

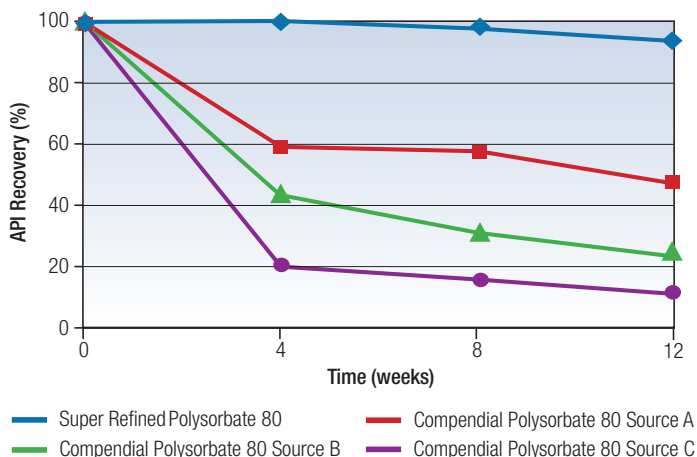


Figure 2: % docetaxel recovery in polysorbate 80 at 40°C

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 40°C. 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.

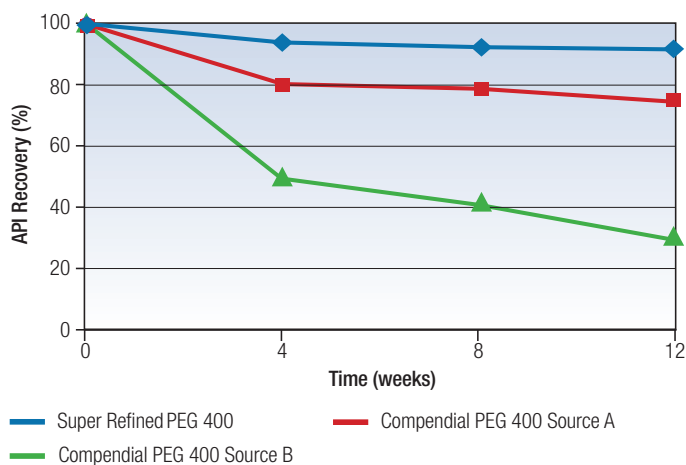


Figure 3: % docetaxel recovery in PEG 400 at 40°C

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 40°C. 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.

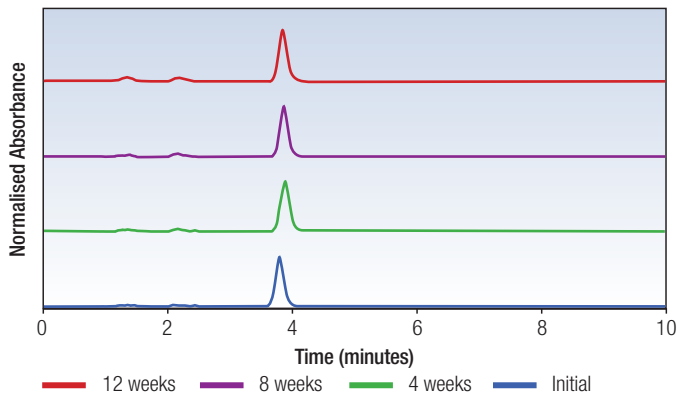


Figure 4a: Chromatogram of docetaxel in Super Refined Polysorbate 80 at 40°C

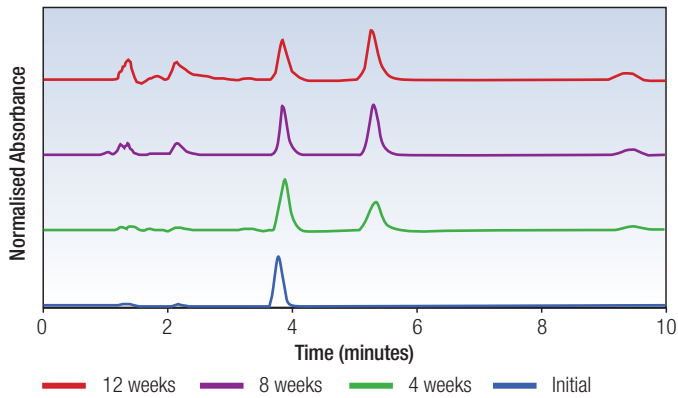


Figure 4b: Chromatogram of docetaxel in standard compendial grade polysorbate 80 at 40°C

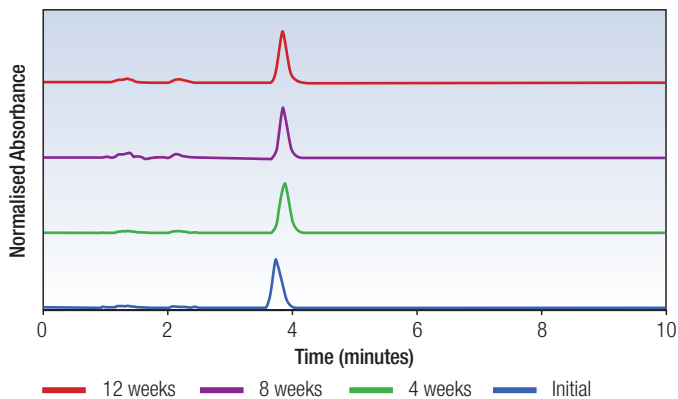


Figure 5a: Chromatogram of docetaxel in Super Refined PEG 400 at 40°C

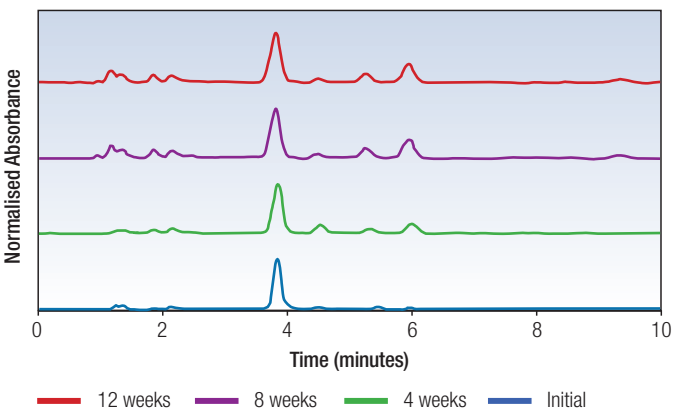


Figure 5b: Chromatogram of docetaxel in standard compendial grade PEG 400 at 40°C

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.

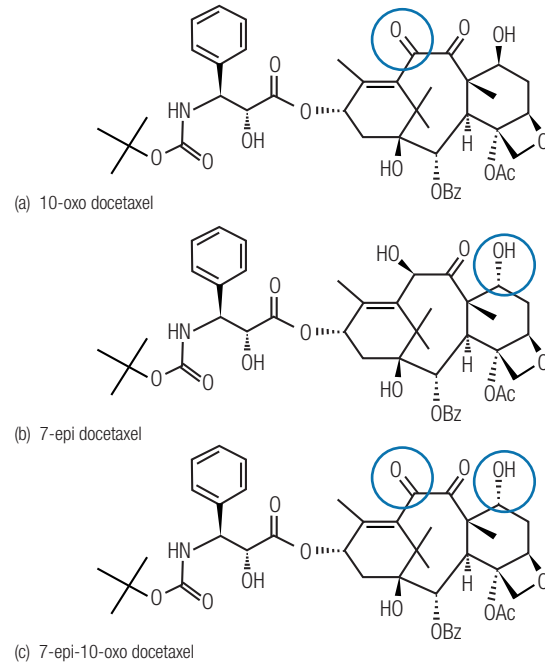


Figure 6: Docetaxel degradation products

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.

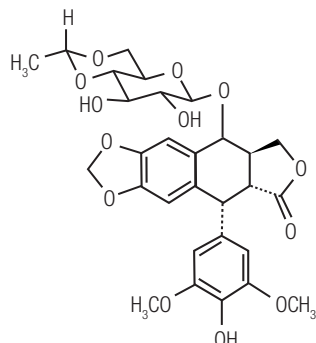


Figure 7: Structure of etoposide

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 40°C 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.

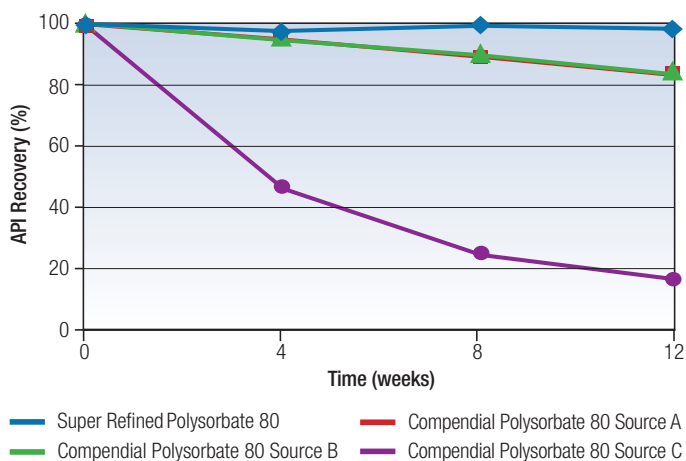


Figure 8: % etoposide recovery in polysorbate 80 at 40°C

The results for etoposide recovery at 40°C 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.

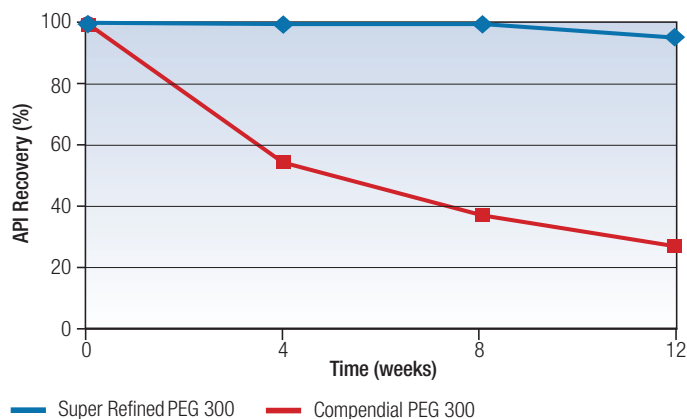


Figure 9: % etoposide recovery in PEG 300 at 40°C

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 40°C. This demonstrates good stability of the API in the Super Refined excipients.

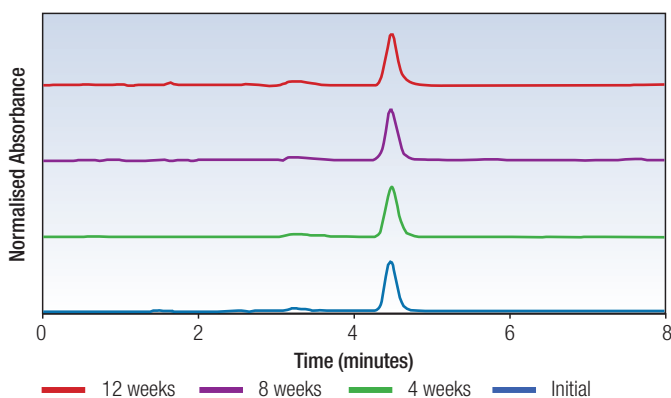


Figure 10a: Chromatogram of etoposide in Super Refined Polysorbate 80 at 40°C

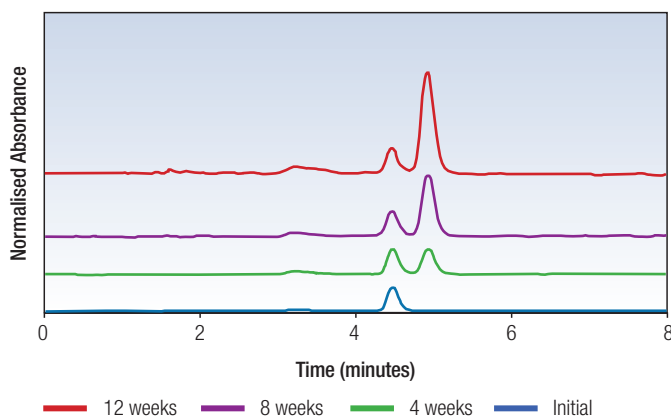


Figure 10b: Chromatogram of etoposide in standard compendial grade polysorbate 80 at 40°C

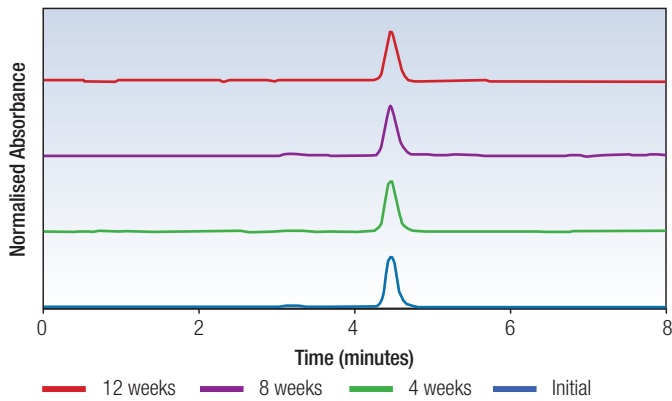


Figure 11a: Chromatogram of etoposide in Super Refined PEG 300 at 40°C

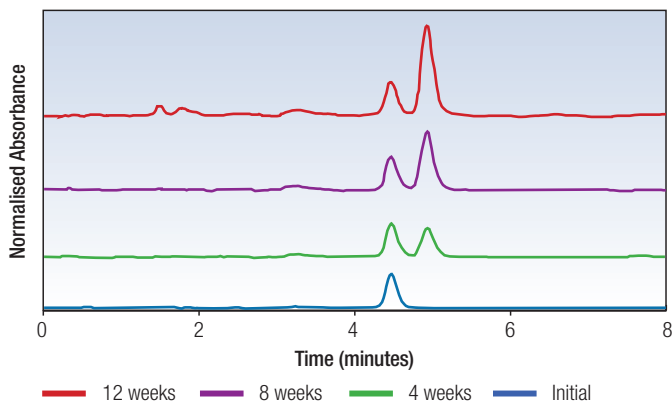


Figure 11b: Chromatogram of etoposide in standard compendial grade PEG 300 at 40°C

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.

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.

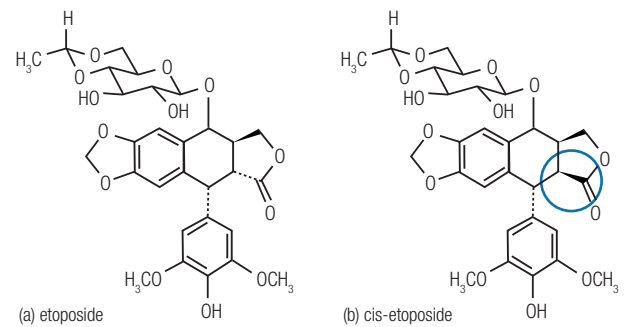


Figure 12: Etoposide and its epimerised degradation product

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

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

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

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