Critical Excipients in Topical and Parenteral Dermatological Formulations: Novel Analytical Approaches and Risk Mitigation

Michael Herbig, Dirk Evers
RaDes GmbH
Schnackenburgallee 114
22525 Hamburg, Germany

Background & Introduction

- Excipients play a crucial role in efficacy, safety and quality of medicinal products. In topical dermatological formulations, often complex excipients of natural or semi-synthetic origin with broad specifications are used (1). In parenteral drug delivery, non-ionic surfactants are key components of biopharmaceutical formulations that are playing an increasingly important role in dermatological indications such as psoriasis and atopic eczema.
- Petrolatum or "white soft paraffin" is a commonly used excipient in topical and ophthalmic formulations. It consists of two solid hydrocarbon waxes and a liquid hydrocarbon fraction and can be described as an oleogel [2]. Pharmacopeial specifications are broad [3] and have little relevance to critical performance and process parameters in semi-solid formulations.
- Polysorbates are widely used as non-ionic surfactants in biopharmaceutical antibody formulations. They are complex mixtures of partial esters of fatty acids with sorbitol or isosorbide with approximately 20 moles of ethylene oxide per mole of sorbitol/isosorbide. In injectables, polysorbate degradation has become a focus of attention as chemical or enzymatic degradation can lead to the appearance of sub-visible and visible particles.
- The fatty acid ether lauromacrogol 400, also known as polidocanol, can be used as an emulsifying excipient, but also as an active ingredient for local anesthetics (topical) or for vein sclerotherapy (injectable).

Methods

- Rheometry was performed on a MCR 102 rheometer from Anton Paar, Germany, with a CP25-1 system at 25°C. A low-stress sample application method was used; tempering time was 300 s. Amplitude sweeps were performed in oscillation mode with 0.01 to 100% deformation and a constant angular of frequency of 10 rad/s.
- Polysorbate analysis was performed with a UPLC system (ACQUITY UPLC H-Class PLUS, Waters). Eluents were aqueous 10 mmol/L ammonium acetate and acetonitrile containing 0.1% formic acid at a flowrate of 0.5 mL/min. A gradient from 5 v% to 85 v% organic phase was used. Peaks were detected with a single quadrupole mass spectrometer (QDa, Waters, mass range 30–1250 m/z). For details see [4].

Results

a) Impact of Petrolatum Variability on Topical Formulations

By means of oscillatory rheology, 14 different Pharm. Eur. compliant petrolatum variants from three different suppliers (blue) and four batches of one variant (red) were investigated. The complex modulus (G*), a measure for the rigidity of the material, showed a variability of factor four between the least and most rigid variant. For the flow point (τ_F), a measure for the structural strength of petrolatum, even a variability of almost factor ten was observed (Fig. I).
This high variability renders different variants differently well suitable for different purposes of application. Often, they are not mutually interchangeable without affecting the properties of the resulting product. Rheological analysis can support a rational selection of petrolatum variants suitable for their respective purpose.

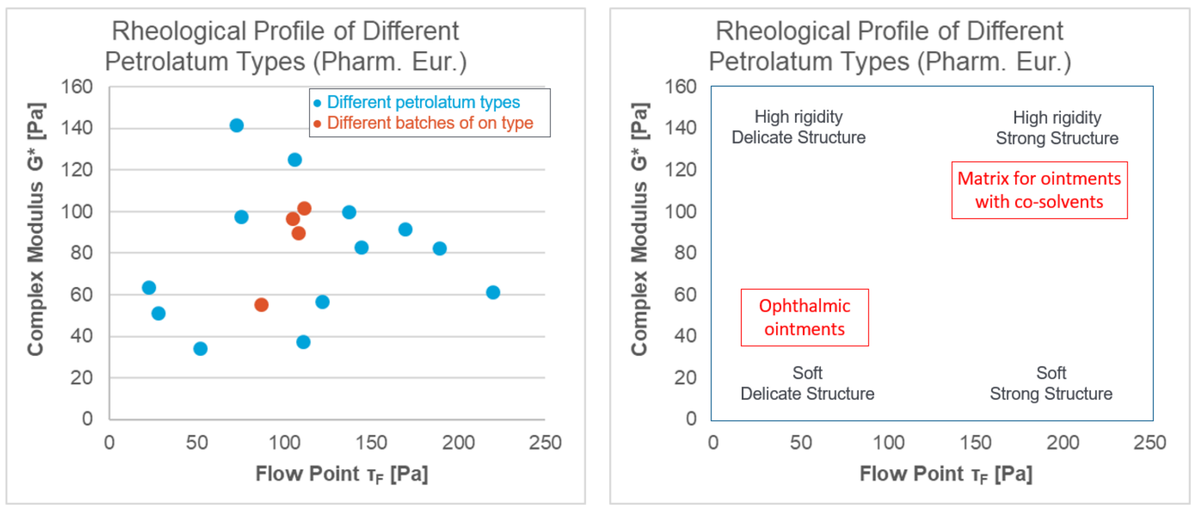

Figure I. Rheological profiling of different petrolatum variants

b) Analysis of Polysorbate 20 in Biopharmaceutical Formulations

In the USP, polysorbate 20 is still referred to as 'polyoxyethylene 20 sorbitan monolaurate'. However, Evers et al. identified 676 subspecies of the excipient (4) with only a few percent of polyoxyethylene 20 sorbitan monolaurate (Fig. II).

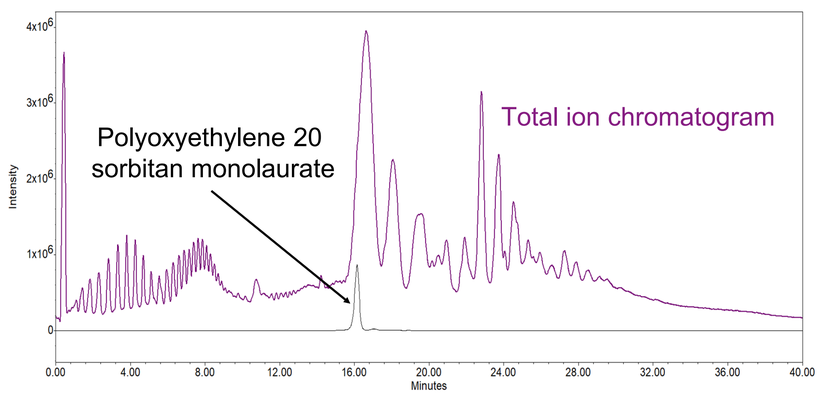

Figure II. Total ion scan of polysorbate 20 (violet) and the polyoxyethylene 20 sorbitan monolaurate peak (black)

From the multitude of identified polysorbate subspecies, marker compounds for different species such as sorbitan and isosorbide mono-, di-, and tri-esters, as well as polyoxyethylene esters and non-esterified compounds can be quantified. Differences in polysorbates from different manufacturers and batch-to-batch variability exist (Fig. III) which can be quantified via the respective marker.

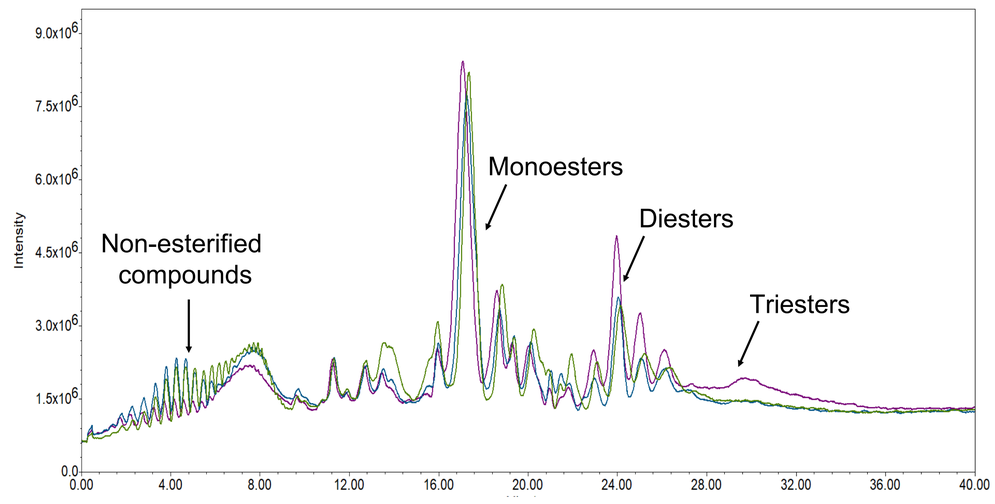

Figure III. Overlay of total ion scans of three different polysorbate 20 batches

In addition, distinct degradation patterns can be obtained for hydrolytic, oxidative and enzymatic degradation, so that even enzyme-specific degradation can be detected. Corresponding methods are also available for polysorbate 80.

c) Batch to Batch Variability of Lauromacrogol 400

According to the European Pharmacopeia monograph for the drug substance, the number of moles of ethylene oxide reacted per mole of lauryl alcohol is 9. As shown in Figure IV, the number of ethylene oxide moles per mole lauryl alcohol with the highest incidence may also be 10 (supplier 1, blue) or 12 (supplier 2, green). The differences can affect the performance of the compounds both as excipient (emulsifier) and as active.

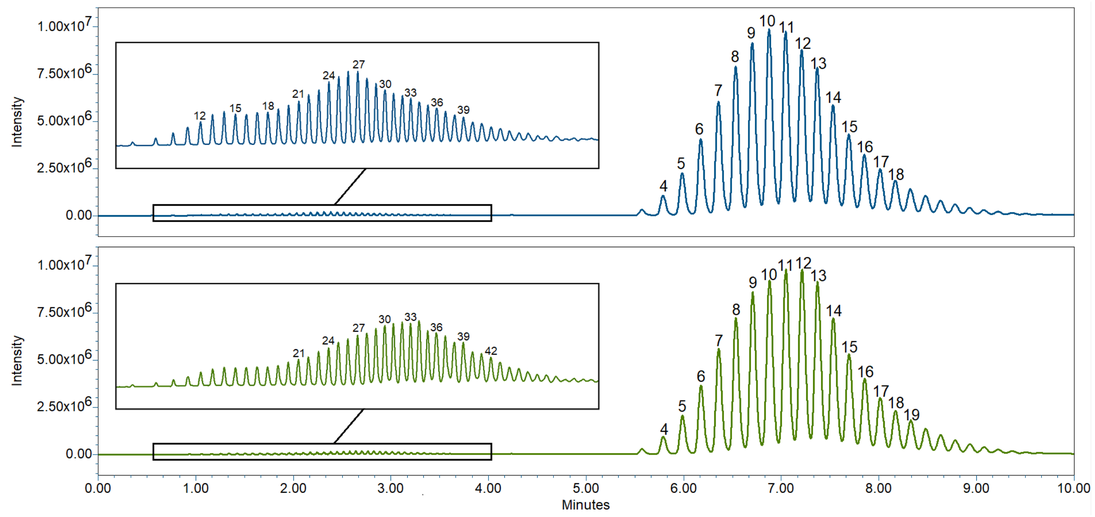

Figure IV. Chromatograms of lauromacrogol 400 of two different suppliers. Numbers indicate the number of polyoxyethylene (POE) units. Insert represents free POE

Conclusions

- Oscillatory rheology provides important insight into the physical properties of complex topical drug delivery excipients such as petrolatum. UHPLC-MS analysis allows identification and quantification of subspecies of highly complex surfactant-type excipients used in parenteral delivery.
- Identifying and understanding the differences in complex excipients from supplier to supplier, batch to batch, or fresh to aged materials enables risk mitigation and product optimization.

References

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(2) Van Heugten AJP, Vromans H. Drug Development and Industrial Pharmacy 43:4 (2017) 595-599
(3) European Pharmacopeia 10.5. 07/2009: 1799: Paraffin, white soft
(4) Evers D-H, et al. Development and validation of a selective marker-based quantification of polysorbate 20 in biopharmaceutical formulations using UPLC QDa detection, Journal of Chromatography B 1157 (2020) 122287