Application of rheology and particle characterization in formulation development

Dr. Melanie Köllmer
RaDes GmbH
Anton Paar Webinar
10.02.2022

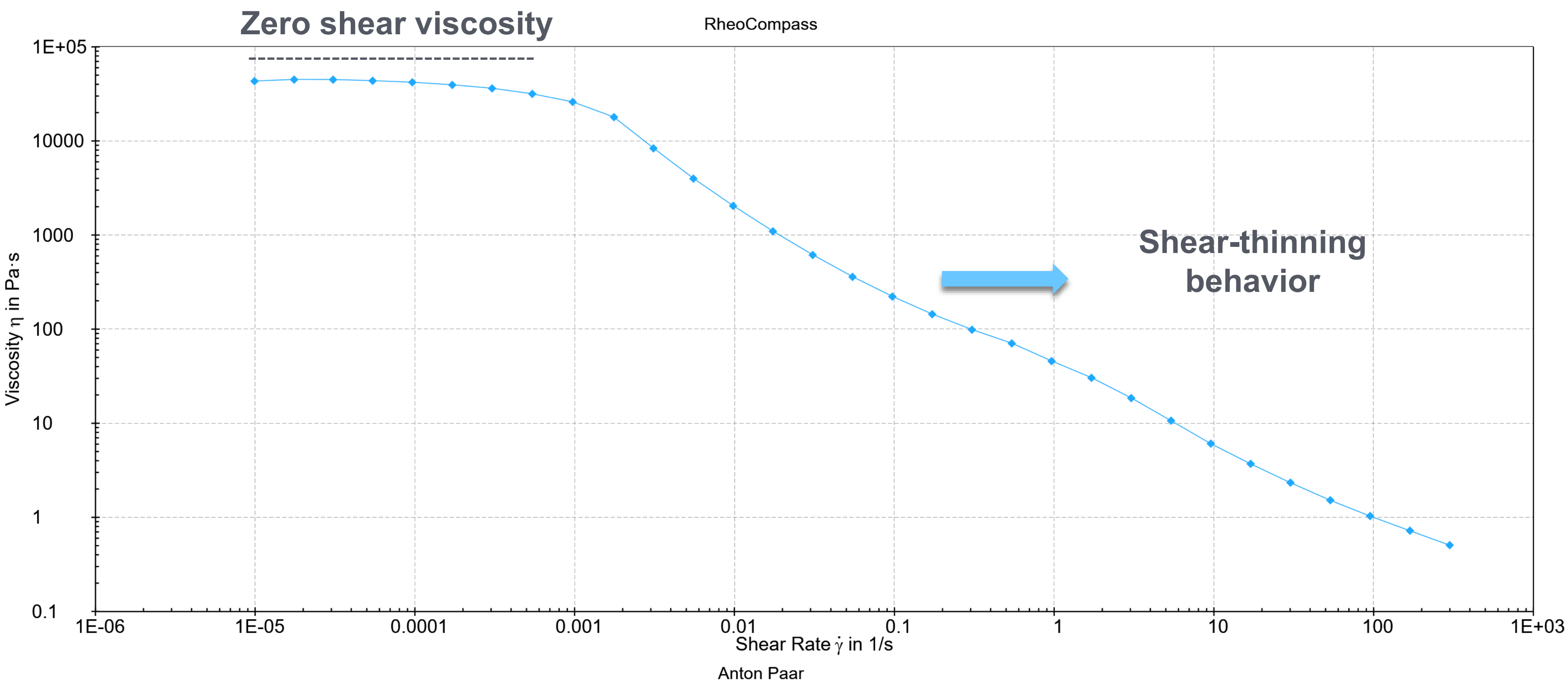
RaDes
RATIONAL DESIGN
OF FORMULATIONS

Rheological characterization of emulsions

What rheological properties are relevant for creams / lotions?

- High viscosity at rest for stability (Stokes equation)
- Shear-thinning behavior (pourable)

$$v_p = \frac{2}{9}\frac{r^2 g\ (\rho_p - \rho_f)}{\eta}$$



Rheological characterization of emulsions

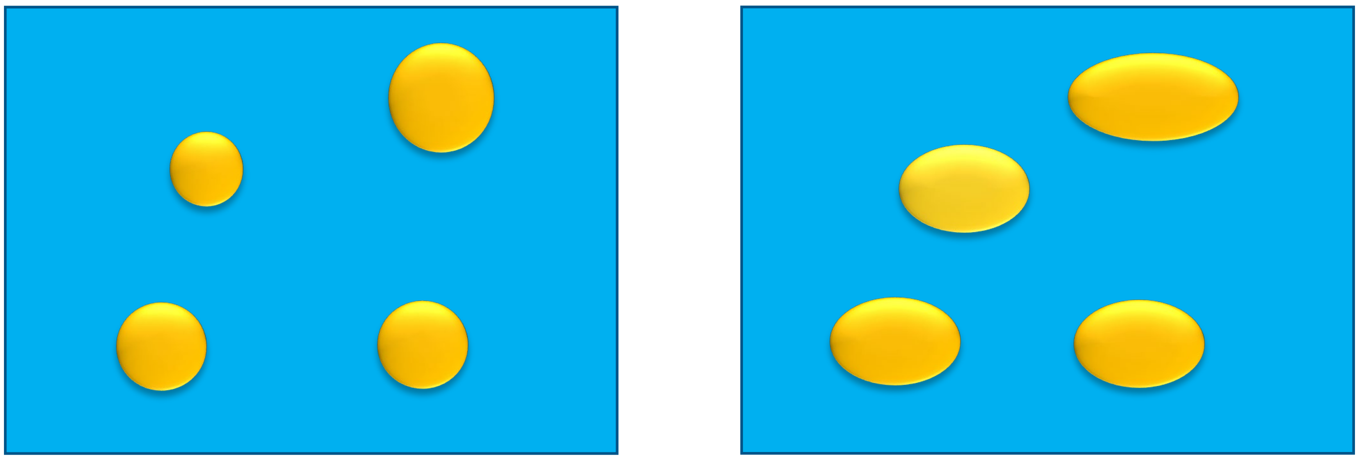
What information can be obtained from a flow curve?

Process	Shear rates (1/s)	Practical example
Sedimentation of particles	< 0.001	Emulsions, suspensions
Pipe flow	$10 – 10^4$	Emulsions, crude oils
Mixing, stirring	$10 – 10^4$	Emulsions, polymer blends
Spraying	$1000 - 10^4$	Nose spray aerosols
Rubbing	$1000 - 10^5$	Skin creams, lotions, ointments

Thomas G. Mezger. The rheology handbook, third edition 2020

Rheological characterization of emulsions

Emulsion droplets



at rest

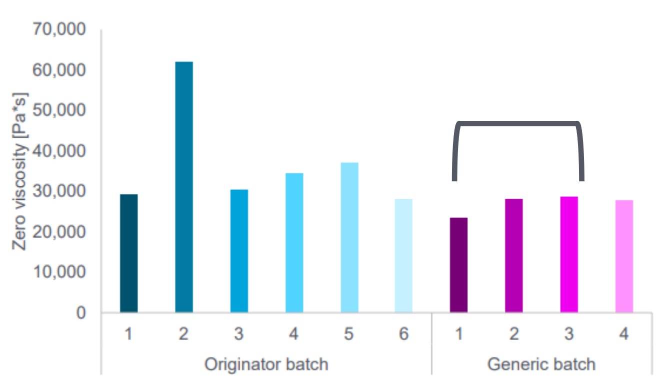
under shear stress

Rheological characterization of emulsions

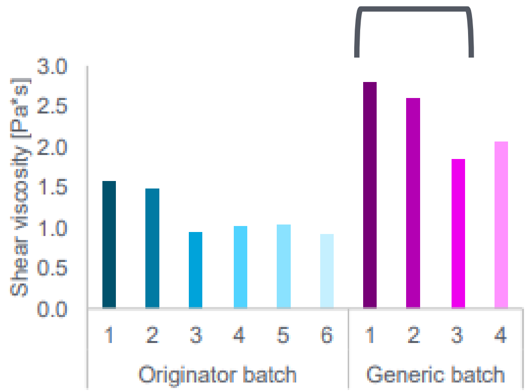
Example 1: Importance of a viscosity curve

- Historically, mainly shear viscosities in the mid-shear region have been determined in quality control. However, also the zero-shear viscosity is relevant for the characterization of semi-solid formulations.
- Viscosity curves covering a wide shear rate range provide comprehensive information of the rheological behavior of a formulation (viscosity ranking of the formulation can change).

Zero-shear viscosity



100 1/s



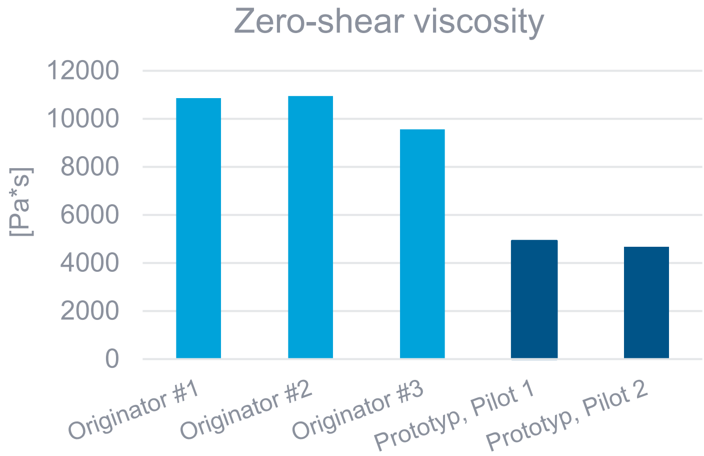
Melanie Köllmer, Application of rheology and particle characterization in formulation development, Anton Paar Webinar

Differences in shear viscosities in the non-plateau region of the viscosity curve and implications for rheological method development and release testing of semisolid products. Poster presentation at Skin Forum 2019.

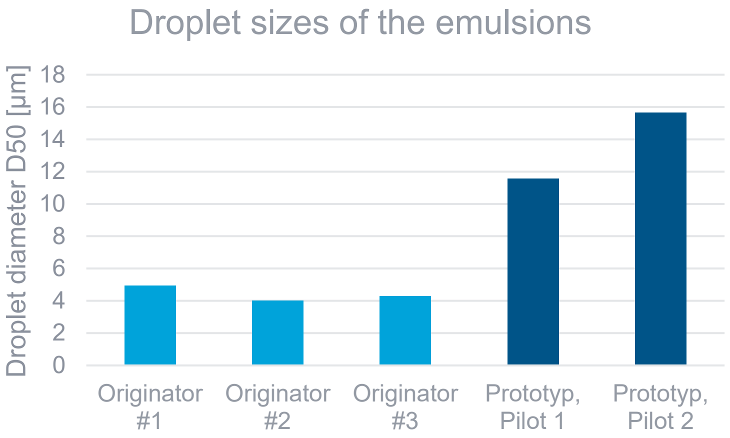
Rheological and particle characterization of emulsions

Example 2: Generic drug development of an emulsion

- Assessment of pilot batches:
  - In the past, matching viscosities at a certain shear rate were required. Today, a comprehensive rheological profile is needed (EMA „Draft guideline on quality and equivalence of topical products”).
  - Zero-shear viscosity is relevant for physical stability and release of the API
  - Droplet sizes of pilot batches were also different (inverse relationship to zero-shear viscosity)



The samples were analyzed with the rheometer MCR 102 from Anton Paar GmbH.

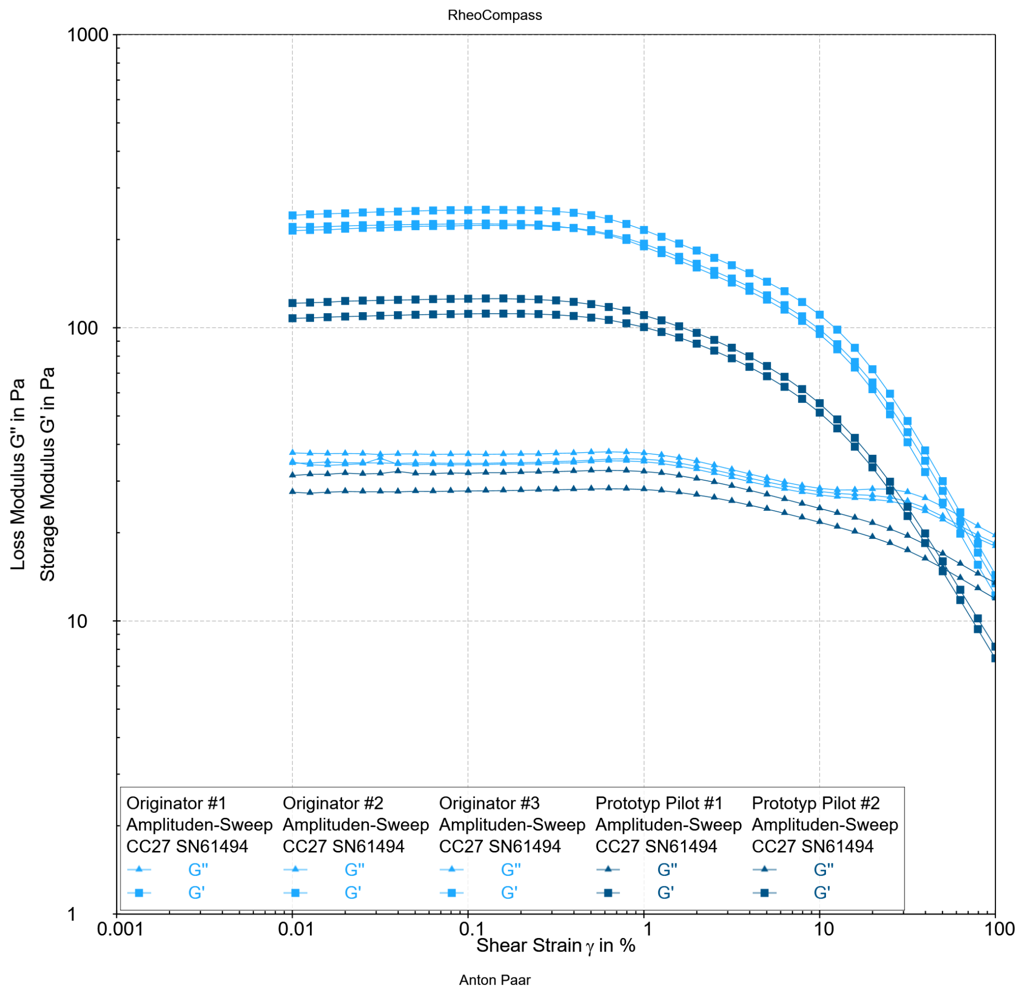


Particle size distribution was evaluated with laser diffraction using a PSA 1190 from Anton Paar.

Amplitude sweep: originator versus prototype

Example 2: Generic drug development of an emulsion

…viscoelastic properties were also different



Calculation of the shear deformation γ :

$$\gamma = \frac{displacement\ s}{plate\ gap\ h} = 10\ \mu m / 1000\ \mu m = 0.01 = 1\%$$

Amplitude sweep: originator versus prototype

Example 2: Generic drug development of an emulsion

What information can be obtained from oscillatory rheology?

Formulation	Storage modulus G' [Pa]	Loss modulus G'' [Pa]	Phase angle delta [°]
Originator #1	214,9	34,6	8,9
Originator #2	242,2	37,4	8,5
Originator #2	213,8	34,4	8,9
Prototype 1	121,6	31,4	14,4
Prototype 2	107,9	27,6	14,1

- Higher storage moduli and lower phase angles of originator => more „solid-like“, more „inner structure“
- Viscous fraction (excipient composition) seems to be similar
- Emulsion contains consistency agents (fatty alcohols)

Rheological characterization of emulsions

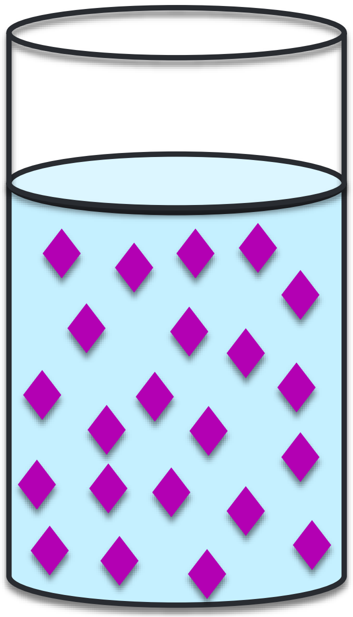
Example 2: Generic drug development of an emulsion

Interpretation / Diagnosis:

- Generic prototypes from the pilot process show larger droplets and a ‚weaker' inner structure.
- It seems that the difference in the quality is not caused by the „material / excipients" but due to the formation of inner structures with different strengths.
- It is likely that an optimization of the manufacturing process (stronger / longer homogenization) will lead to more similar products.
- Possibly, also the cooling step (formation of gel structures with the consistency agents) plays a role.

Rheological requirements of dispersions

Bulk before filling



High viscosity to prevent sedimentation

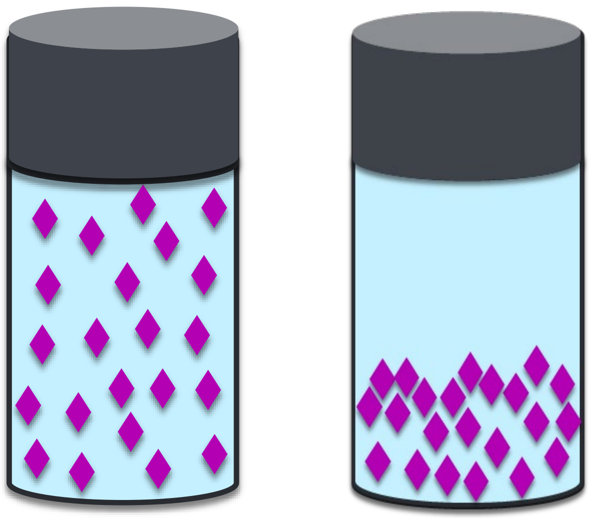
Stokes equation:

$$v_p = \frac{2}{9}\frac{r^2 g\ (\rho_p - \rho_f)}{\eta}$$

Filling

Shear-thinning to warrant filling process

Bulk after filling



$= \eta_{Start}$ $\ll \eta_{Start}$

Fast recovery of the original viscosity to prevent de-mixing

Oscillation / Rotation / Oscillation: ORO-Test

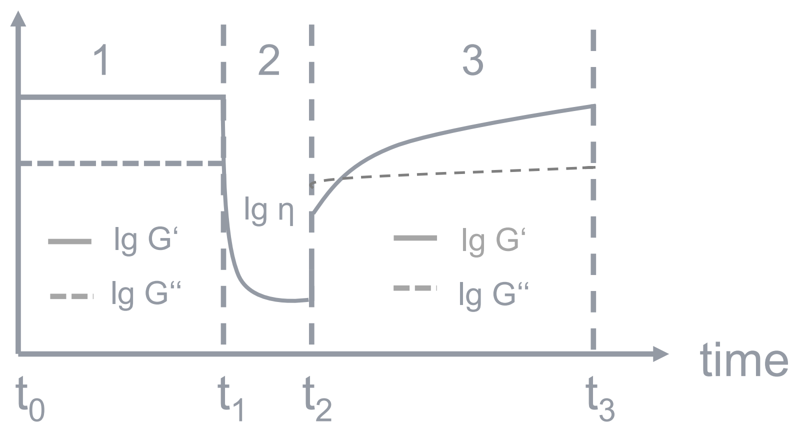
How long does it take to rebuild or recover the original structure after shear stress (f.i. after filling or spraying)?

ORO-Test:

(1) Simulation of the resting behaviour: **O**scillation at low deformation values within the linear viscoelastic region (LVE)

(2) Simulation of the structure decomposition of the sample during high shear stress; **R**otation at a high shear rate

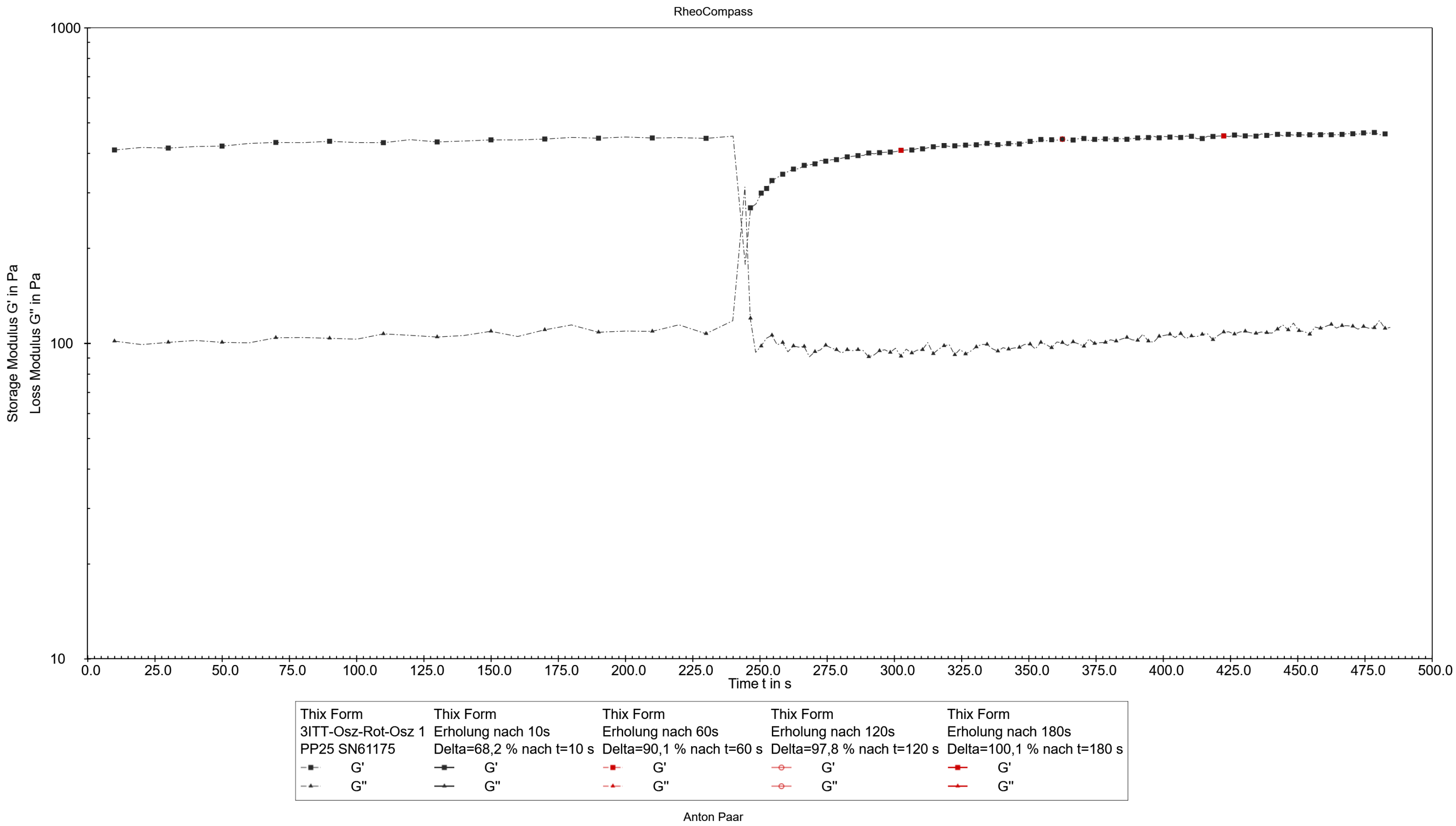
(3) Simulation of the structure recovery at rest; **O**scillation at low deformation values (like segment 1)



Time-dependent structure recovery after shear stress and thixotropic behaviour.

Example: ORO-Test of a thixotropic sample

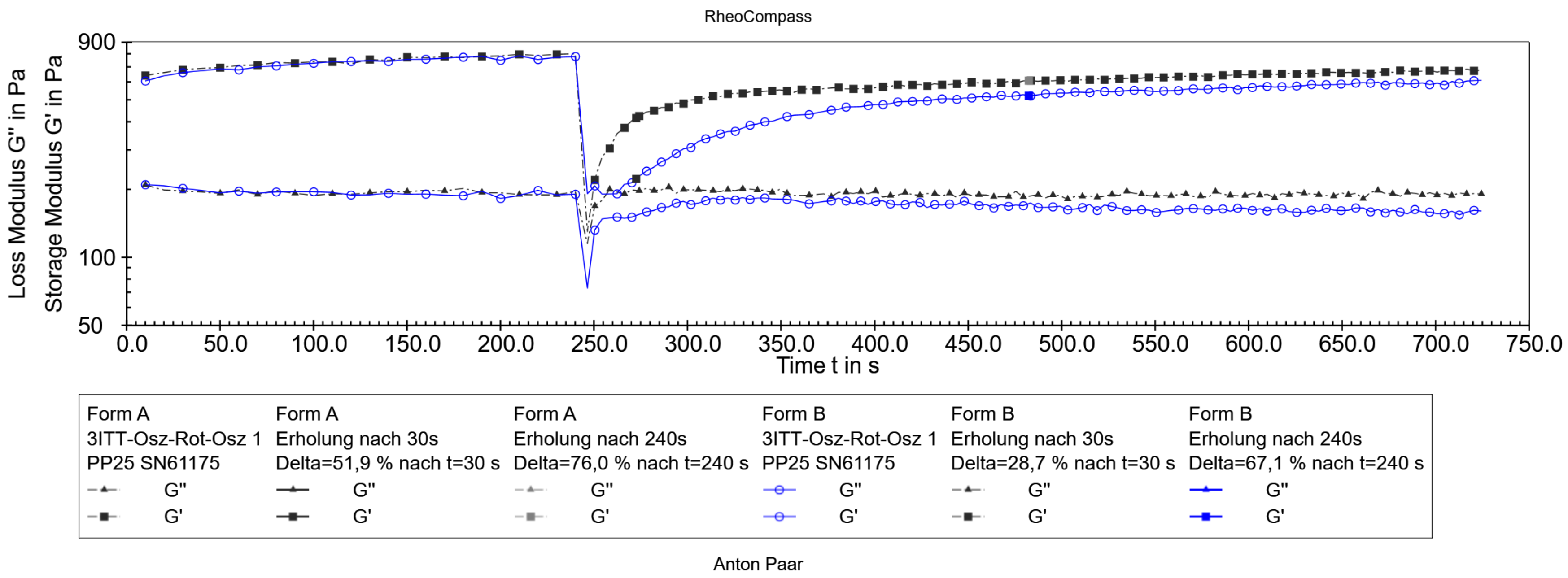
G‘, G“ (t)



Fast regeneration of the formulation after application of shear stress.
After 10 s ca. 70 %, after 1 min ca. 90 % & after 2 min ca. 98 % of the original viscoelastic structure reached.

Example: ORO-Test

G‘, G“ (t)

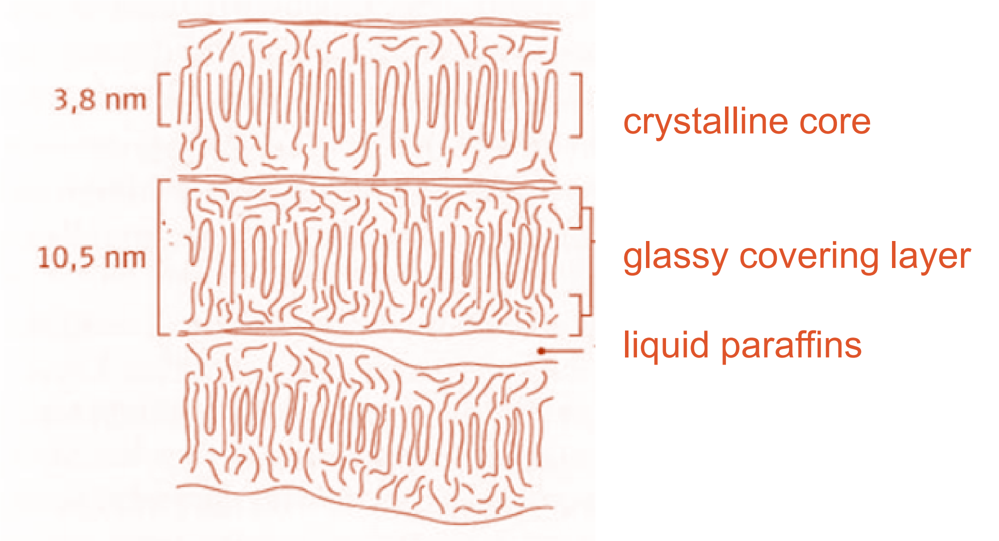


- Formulation A with faster structure regeneration than formulation B

Rheological “profiling” of different petrolatum variants

- Petrolatum is a mix of liquid (highly branched i-paraffins) and solid, purified, bleached and saturated paraffin hydrocarbons (less branched n-paraffins).
- Plastic gel with layered structure
- Dripping point and consistency have a wide specification in the pharmacopoeia

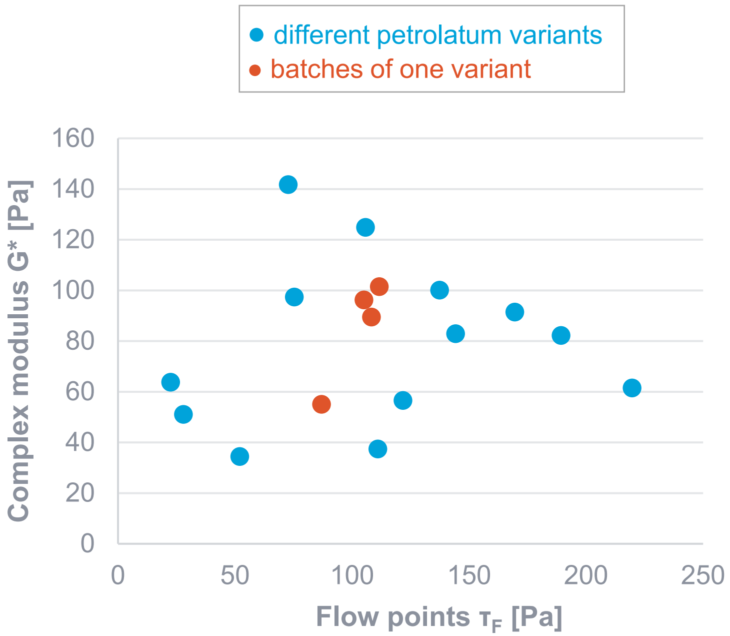
Model of the colloidal composition of petrolatum

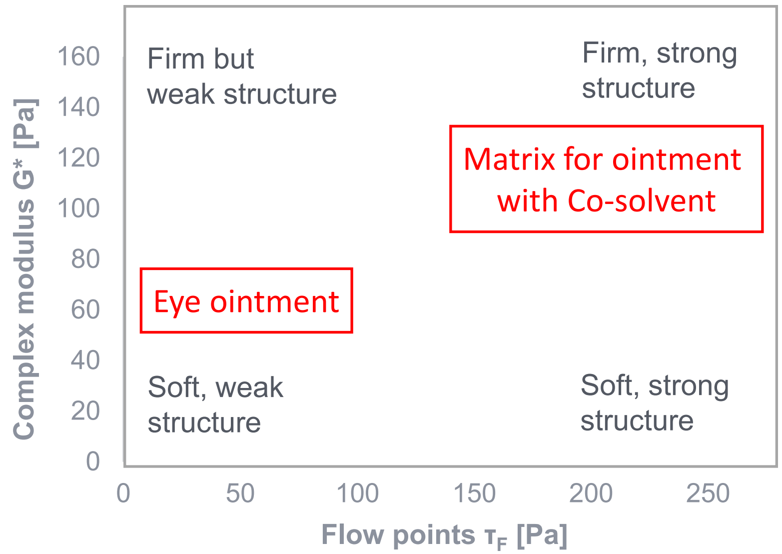


How do petrolatum variants differ with regards to rheological properties?

Rheological "profiling" of different petrolatum variants with amplitude sweeps

- All tested petrolatum variants in Pharm. Eur. quality





- Significant differences in the rheological properties with relevance for the intended use, the formulation and process.
- Rheological „profiling" can help to assess changes of petrolatum variants in a formulation.

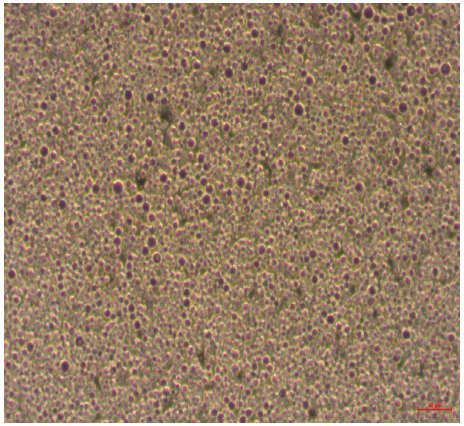
Summary

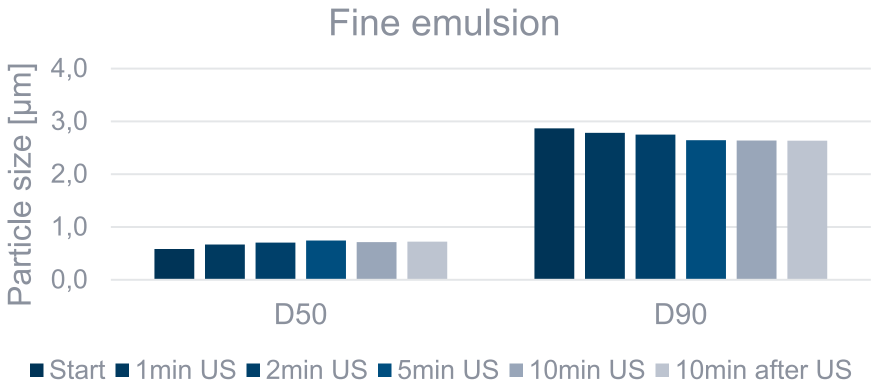
Rotational & oscillatory rheology as well as particle size characterization are relevant in the formulation development and helpful for:

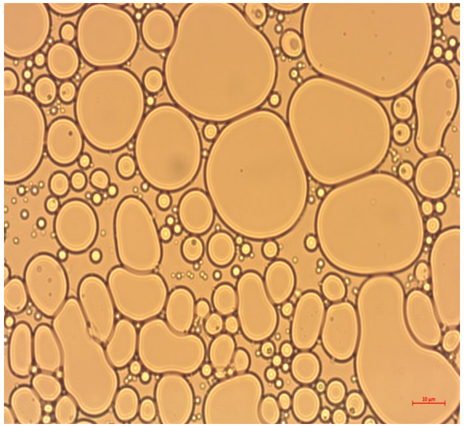
- Viscosity ranking of development formulations
- Development of generics
- Troubleshooting of products from the portfolio
- Process optimization of the manufacturing process / preparation of the scale up
- Assessment of the influence of different excipient batches on a formulation
- Quality control

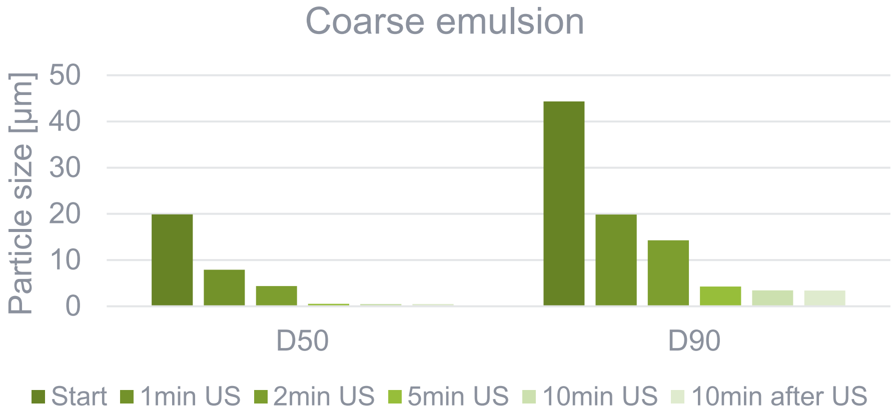
Particle size characterization of emulsions

- Impact of ultrasound in particle size characterization of emulsions with **polymeric thickener**









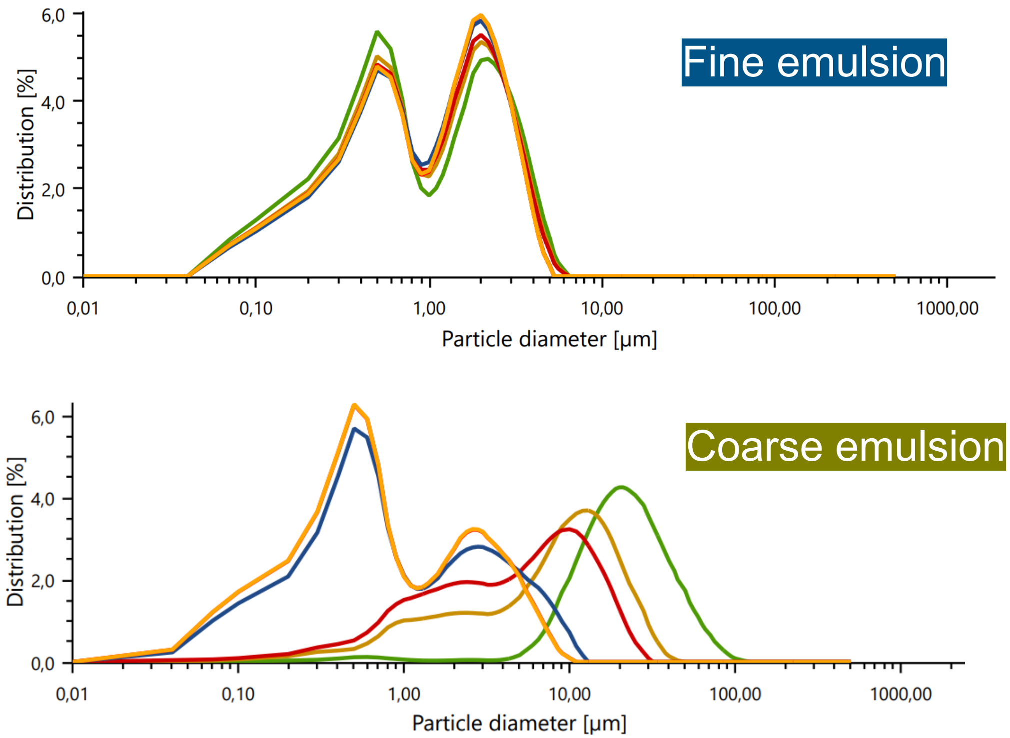
Particle size distribution was evaluated with laser diffraction using a PSA 1090 from Anton Paar. The Mie model was used for analysis.

Particle size characterization of emulsions

- Impact of ultrasound in particle size characterization of emulsions with **polymeric thickener**

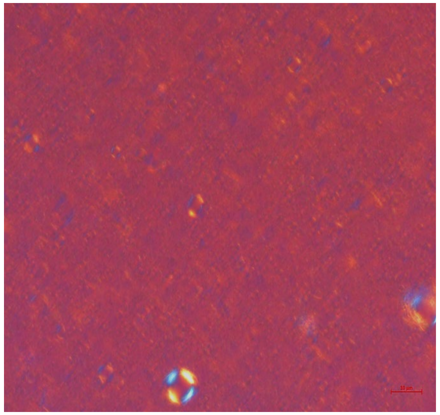
- **Volume distribution:**

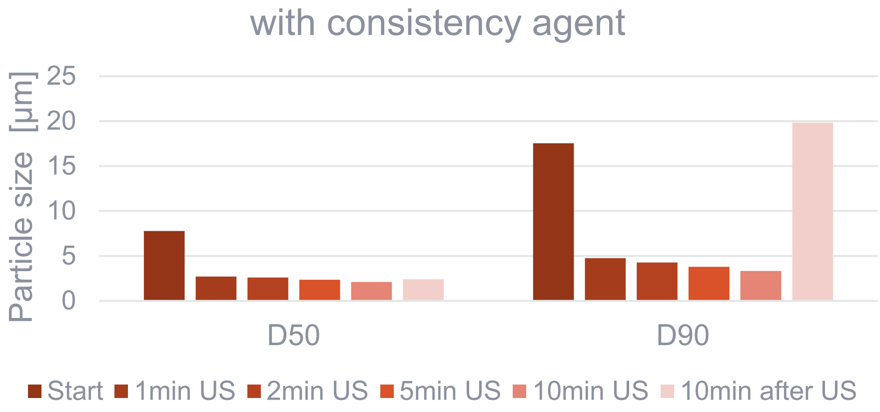
Start
1 min US
2 min US
5 min US
10 min US
10 min after US

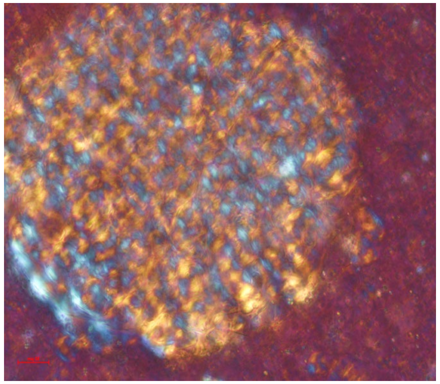


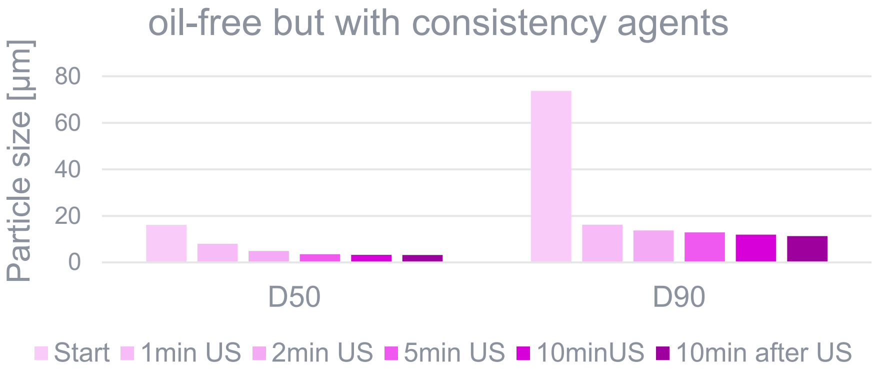
Particle size characterization of emulsions

- Impact of ultrasound in particle size characterization of emulsions with **consistency agents**





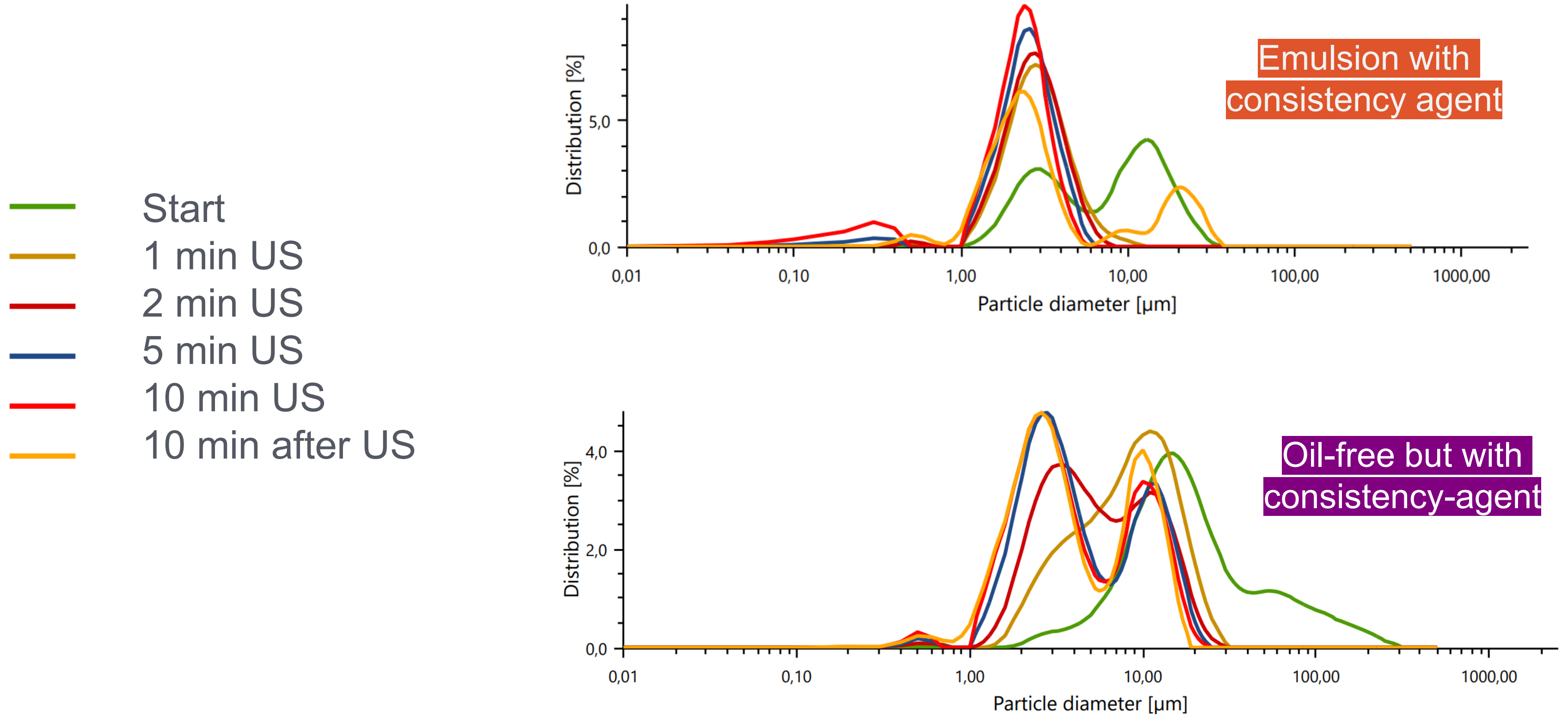




Particle size distribution was evaluated with laser diffraction using a PSA 1090 from Anton Paar. The Fraunhofer model was used for analysis.

Particle size characterization of emulsions

- Impact of ultrasound in particle size characterization of emulsions with **consistency agents**
- **Volume distribution:**



Particle size characterization of emulsions

- Knowledge of the formulation composition is important for method development of particle size distribution (PSD) measurements.
- **Emulsions with small and uniformly dispersed oil droplets** show only marginal variations between different measurements => Low impact of ultrasound
- **Emulsions with larger droplets** showed a decrease in droplet diameter with increasing ultrasound duration indicating a ‚shredding' of droplets.
- **Formulations stabilized with consistency agents that form liquid-crystalline structures** are also more susceptible to changes during sample preparation. Decreasing droplet sizes after 1 min of ultrasound treatment and only marginal decrease after subsequent ultrasound treatments. Breaking up of liquid-crystalline structures seems to be reasonable.
- Assessment of the ‚true' particle (oil droplet) size appears to be more complex in consistency agent-containing formulations than for polymer-containing formulations.
- Choosing a suitable sample preparation method is as important as choosing the appropriate analysis model (Mie / Fraunhofer).

Thank you!

Melanie Köllmer, PhD
T: +49 40 50729541
melanie.koellmer@rades-development.com

RaDes GmbH
Schnackenburgallee 114
22525 Hamburg, Germany
www.rades-development.com