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Survey of Galenic Stability of Dispersed Systems via the Optical Centrifuge

Version: 1.1 **Date:** 11.02.2015

Abstract:

The physical (galenic) stability of cosmetic and technical emulsion- and dispersion-products is a parameter that has the same importance for evaluation of shelf-life of products as the microbiological stability.

During the development of new products the physical stability usually is surveyed by storage-tests at various temperature-conditions with visual documentation of separation-phenomena. Criteria of shelf-life then are derived from these observations.

By using the novel optical centrifuge (LUMiSizer, Company LUM, Berlin) BCL has a versatile instrument for significant acceleration of getting information on separation-effects. With this method the emulsion-product is centrifuged in special cells, while transmission-profiles repeatedly are recorded. A dense array of photocells operating in the near-infrared region is used for recording the profiles. At this wavelength not the colour of the product, but its particularity is measured. Phase-separations thus become evident even if they are not visible by eye. If separation is recorded, separation-speed is calculated from the profiles.

The system allows the application of gravity-forces up to 2300 g by exact adjustment of rotation-speed. By varying the g-forces can be found whether the separation will occur also at normal storage conditions (1 g).

If the product additionally is thermally treated, further and more complex properties of the product-stability can be measured. So, our experience shows that it is sufficient to expose the product to only two thermal changes (40°C / 5°C), in order to detect instabilities due to this thermal effect by the centrifuge-technique.

Another important issue is the upscaling of products from laboratory- to production-sizes. Dispersing properties of laboratory equipment and production-machinery often are not comparable, thus causing different particle-sizes being generated in both processes. By comparing laboratory-samples with batches from small size production machines the optical centrifuge allows an easy measurement of the influence of particle-sizes onto the physical stability of an emulsion or dispersion.

Due to special procedures with the optical centrifuge also particle-sizes directly can be measured and compared with the optical centrifuge.

So, the developer of an emulsion or dispersion is able to differ between stable and unstable formulations within very a short time. Under classical procedures this often would last several months.

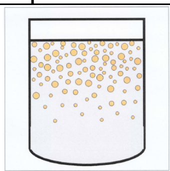
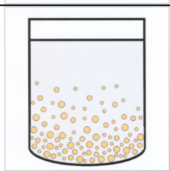
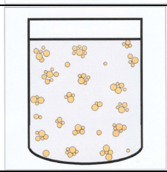
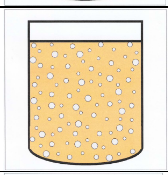
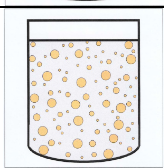
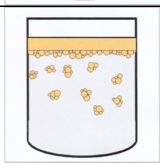
The influence of chemical effects, however, cannot be measured with the centrifuge-technique. So, if the stable formulation is found, a classical storage-test with measurement of physical parameters like pH, viscosity, colour, a.s.o. is recommended.

1) Stability of emulsions and dispersions

Emulsions and dispersions are liquid or viscous products, consisting of two or more phases. In an outer solvent-phase insoluble compounds are dispersed as very small particles. An important factor for the stability of such dispersions (solids in liquids) or emulsions (liquids in liquids) is the size of the particles dispersed. In case of solid particles the size usually is adjusted by milling-processes, while liquids are dispersed using dispersing-machines. For stabilising the particles in the outer liquid phase either chemicals with an emulsifying property are used or structure-forming substances are added, that are hindering the particles from sedimentation or creaming.

In principle emulsions and dispersions are meta-stable systems that are stabilised for a certain time against dissociation by special additives and the way of preparation. Thus, with respect to evaluating a shelf-life of such products it is necessary to know the time that a product remains without significant changes in its emulsion-structure.

When the stability is measured, processes are used that may discover possible instabilities. Usually this is done in storage-tests at varying temperatures and with measurement of physical parameters. Several phenomena can express galenic instabilities:

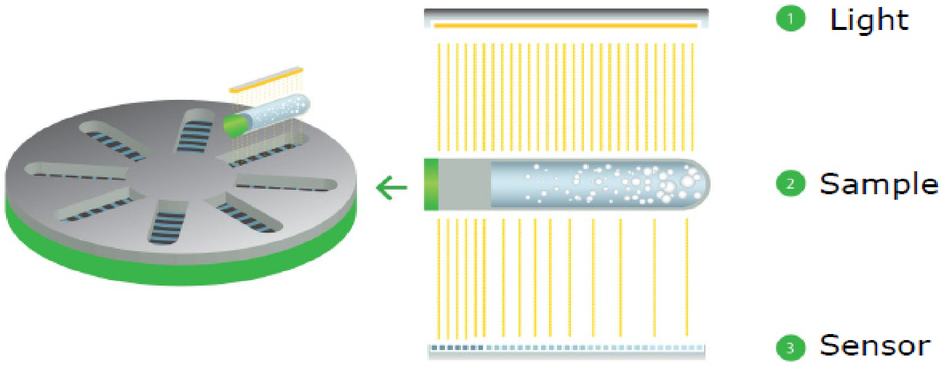
Phenomenon:	Schematic representation	Description
Creaming		Emulsified particles are drifting toward the surface; a clear solvent-phase is formed at the bottom of the vessel.
Sedimentation		Dispersed particles are sinking towards the bottom of the vessel. A clear phase is residing in the upper part of the product.
Flocculation		Emulsified particles stick together forming huger aggregates that become visible as flakes.
Phase inversion		An oil-in-water emulsions changes into a water-in-oil emulsion or *vice versa*.
Ostwald-Ripening		Small particles by diffusion loose substance that is gathered by big particles. Thus particle-sizes are growing
Coalescence		Particles are melting together, finally forming pure phases.

The phenomena described above can be observed with physical methods. Especially optical inspection allows the measurement of formation of sediments or clear phases. Particle-sizes can be measured with microscopes. Also centrifuges are used in order to accelerate the dissociation-processes by enlarged gravitational force.

2) The measuring-principle of the optical centrifuge

The optical centrifuge (LUMiSizer, company LUM, Berlin) is a sensitive device gaining data on separation-properties of dispersed systems out of transmission-profiles recorded at high precision.

The following draft shows this principle schematically:

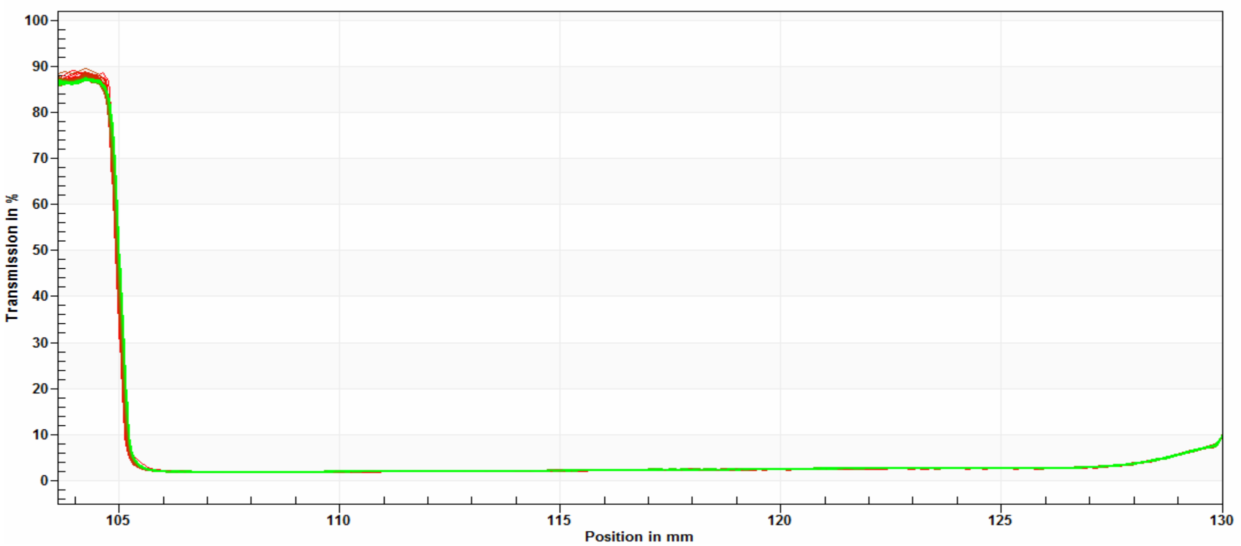


(Picture with friendly permission of LUM GmbH Berlin)

The product to be surveyed is filled into special cells that are placed into the rotor of the centrifuge. After thermal equilibration the centrifuge starts and adjusts the rotation speed exactly to the value demanded. The cells are passing an array of photodiodes and microscopic photocells at the opposite side. Thus, transmission profiles are recorded at a wavelength in the near infrared spectrum. This wavelength is independent of the colour of the medium and observes the particle-property instead. During one run a lot of such profiles is recorded and stored in a PC.

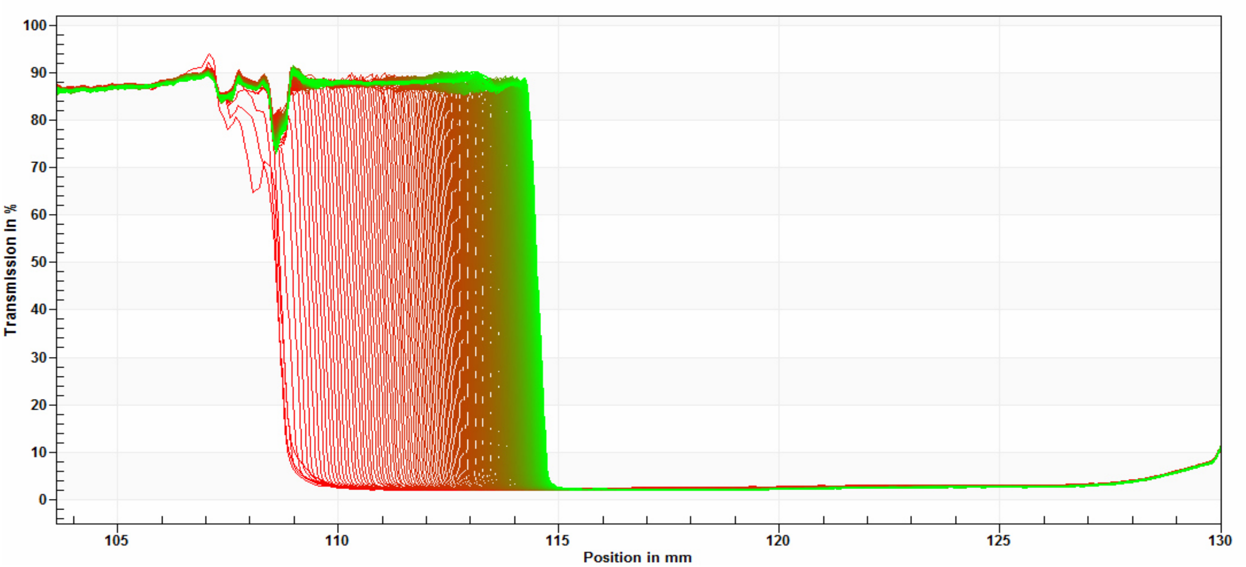
The software then superposes the profiles, starting with red colour for the older and green for the younger ones. The graphical representation shows the cell: The values of the x-scale contain the distance from the centre of the rotor (in mm), the y-scale shows the transmission: At a turbid point this value is near to 0, at a clear point and above the meniscus near to 90% (the rest is loss by scattering and reflections at the cell).

Thus, a product that is physically stable during the centrifugation shows the following image of transmission-profiles:

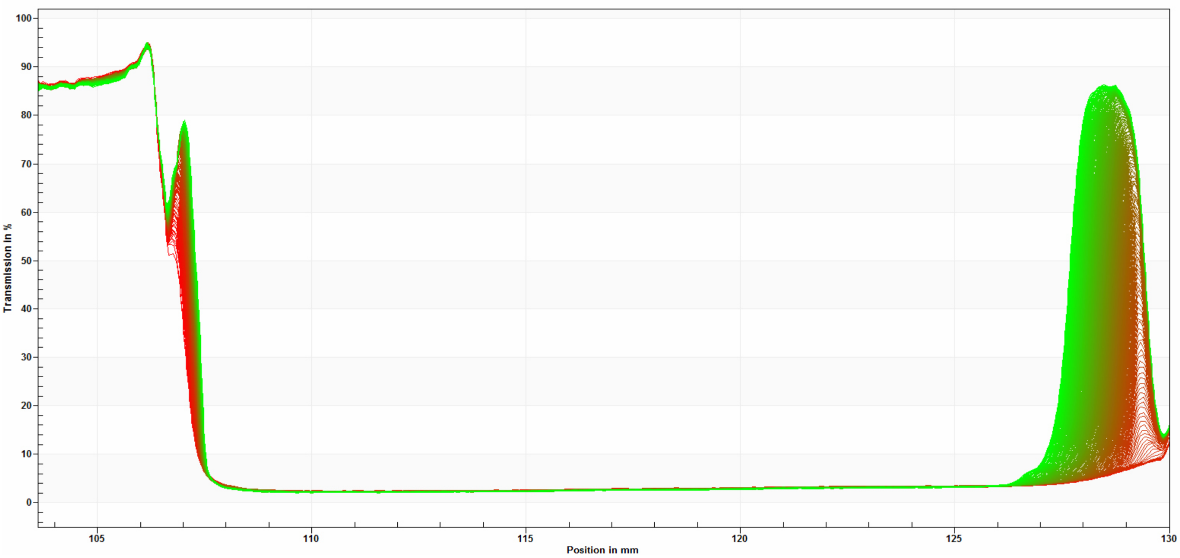


All profiles are directly superposed. No dissociation-phenomenon is visible with this product.

If a product develops dissociation, images of the following type are gained:



The first profile (lowest, red) shows that initially a turbid product (emulsion) is in the cell. During the run more and more profiles are recorded that show – in this case at the top of the sample – a clarification: A lightweight (oil-) phase is separated from the further turbid emulsion. This describes a sedimentation-process. If, however, a clear phase is formed at the bottom of the cell, a creaming-process is measured:

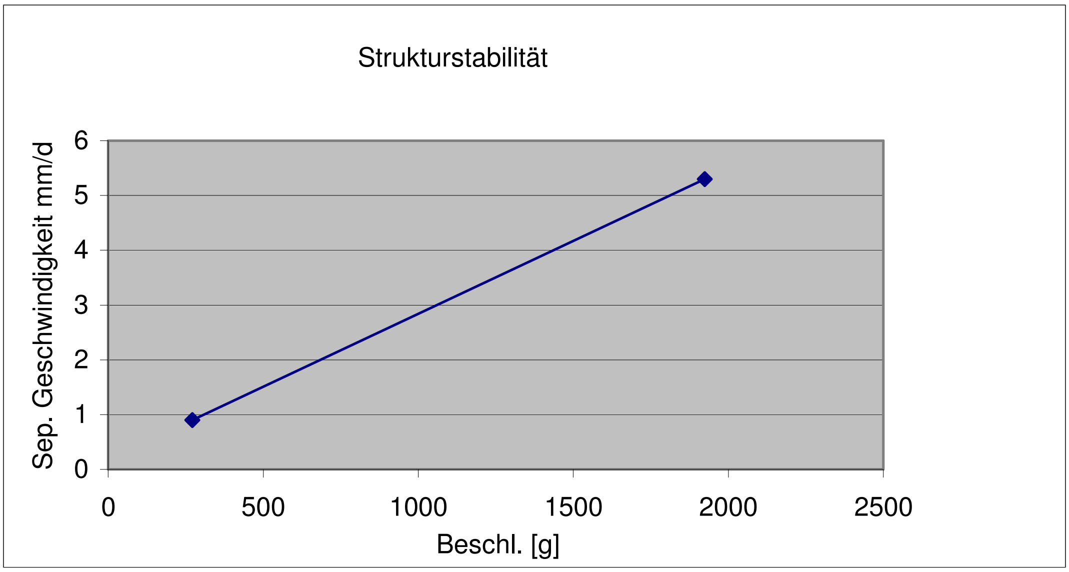


The images already show certain regularities that allow estimate circumstances of the stability of the emulsions. Based on these curves the software then calculates typical data, e.g. separation-speed of the creaming process.

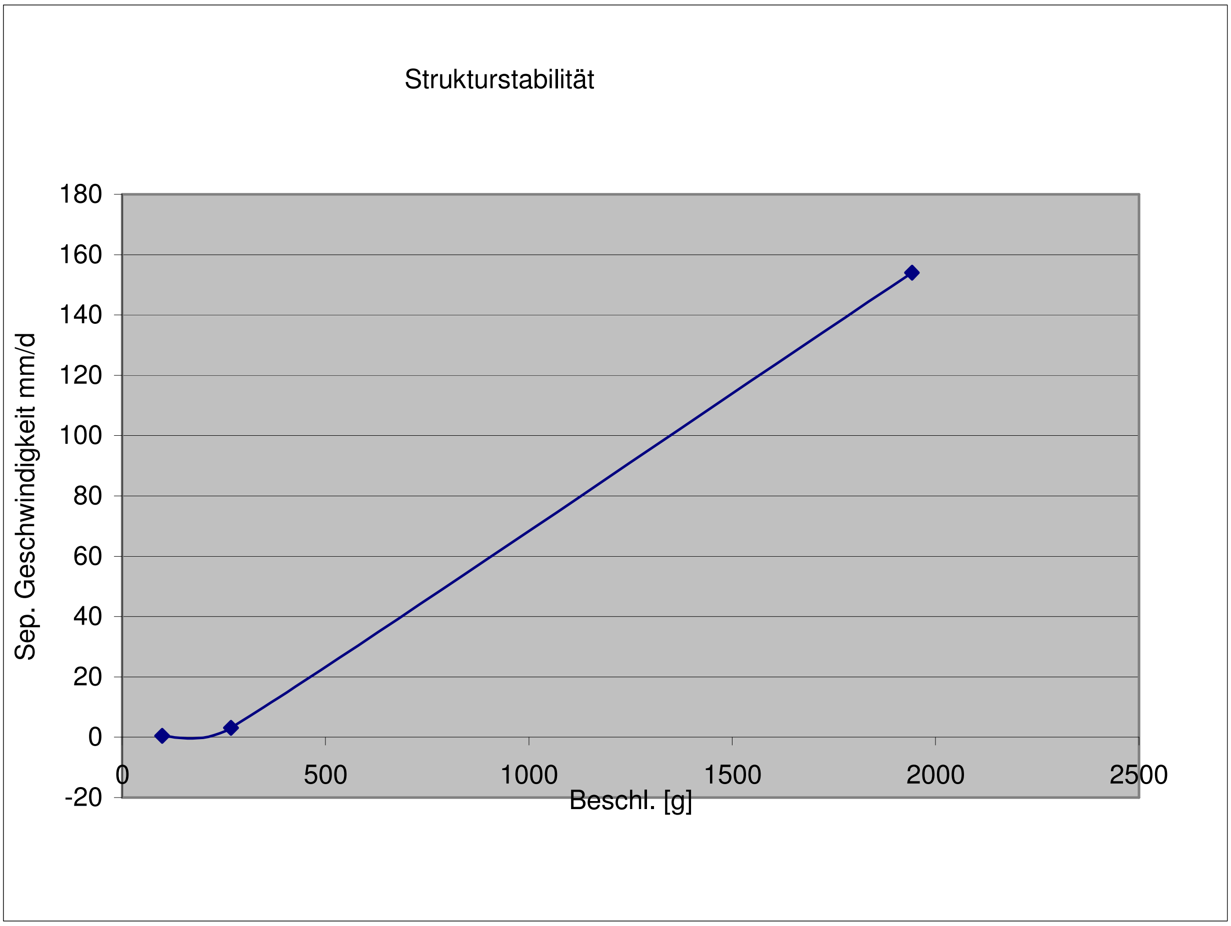
3) Quantifying instabilities

By evaluating the transmission-profiles separation-speeds are calculated and converted into values that would result at normal gravity condition on the earth, i.e. 1g. If, for example several variants of a recipe are measured synchronously by this way (up to 12 samples can be measured in one run), comparing the results already creates valuable rating data on the stability of these formulations. The speed of the centrifuge can be adjusted for gravity-values up to 2300 g.

If two or more gravity-values are applied, more detailed information can be gained. If this procedure is run, the total load of gravity and applied time gives the same value. For example one run is at 1940 g over 50 minutes, a second at 270 g over 6 1/4 hours and a third at 100 g over 16 2/3 hours. Then several separation-speeds are gained, respectively. If these values are plotted against the g-values a diagram as given below is gained:



The line passing both points aims to the centre of the graphic. This means that the separation-effect will occur at any gravity, thus also at 1g on earth. So, this product definitely is physically instable.



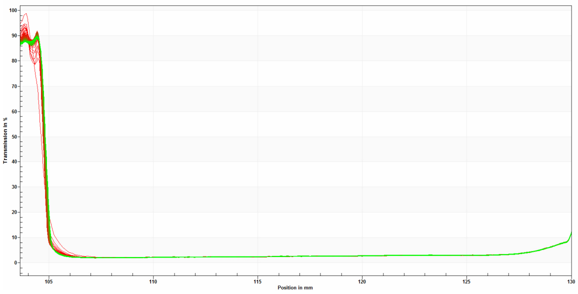
The behaviour of this product is different. The curve aims to a point significantly above the zero point of the x-scale. This means that the separation effect starts not until a certain threshold-value. This product thus is physically stable.

The physical background of this behaviour is the stabilisation by structure-forming substances in the liquid phase (e.g. polymers, Xanthan, cellulose). In their swelled state they form a network in the product that keeps the particles at their place. If, however, a force above the threshold value that destroys the network is applied the particles are able to migrate according to their density-parameters.

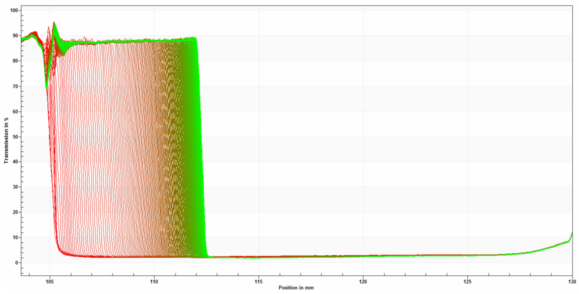
4) Survey of influences of temperature on the stability of emulsions

If the storage-stability of cosmetic or technical emulsion-products is to be evaluated, often also influences of temperature have to be regarded. Diffusion-controlled processes in an emulsion, like Ostwald-ripening or coalescence are temperature-dependent, thus able to reduce the stability of the emulsion significantly. Therefore in common storage-tests various temperature-conditions are applied and the effects onto the emulsion are observed macroscopically or microscopically respectively.

Due to their high sensitivity the optical centrifuge allows a fast acquisition of stability data. So, a mechanism proposed is a twin-temperature-change (1 day each 40°C / 5°C / 40°C / 5°C) followed by the centrifugation of this sample synchronously with an identical sample stored at room-temperature. Products being instable toward such temperature-changes easily are detected by this method as can be seen in the following images:



Cream at RT



Cream after 2 Temperature-changes

As the pictures show the product apparently being stable at room-temperature becomes instable after only two temperature changes. This effect also an end-user would see who brings this cosmetic product into the temperature-changes between his cold car and his warm bathroom.

5) The upscaling-problem

Adjusting the particle-sizes especially of emulsions to definite values is highly important at production of cosmetic products. A problem rising often is that laboratory formulations are highly stable, while production-batches become problematic with respect to their galenic stability.

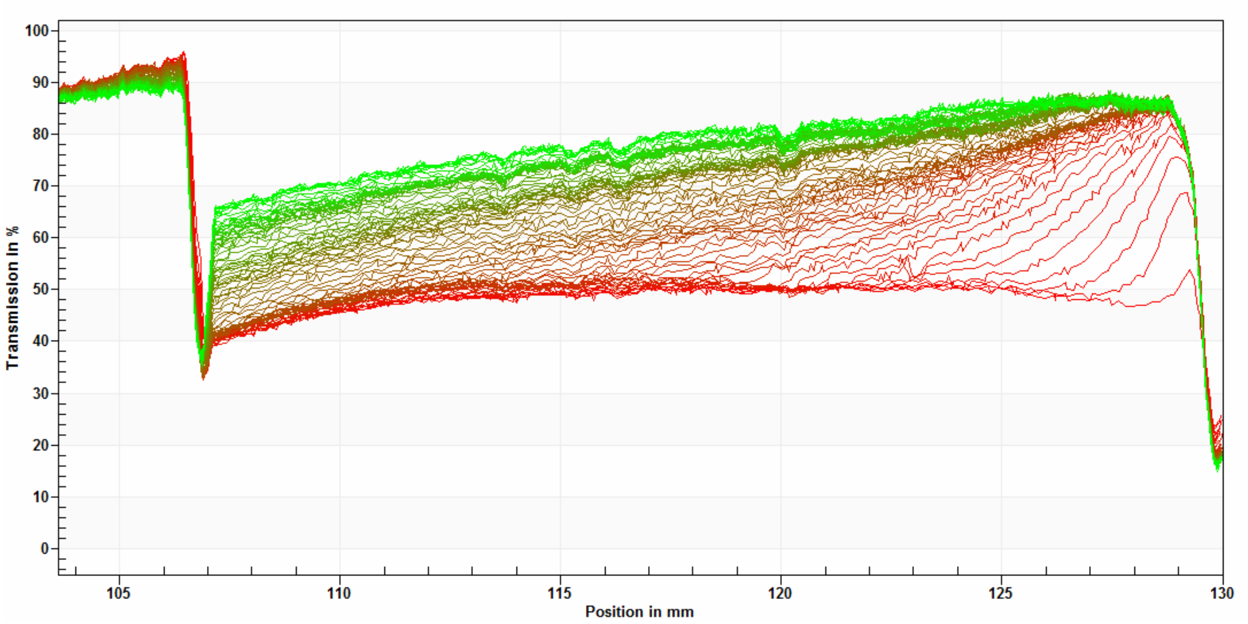
The reason for that is the adjustment of the particle-sizes: The small laboratory-batch produced using a laboratory dispersing machine is physically stable because by this machine a lot of sheering-energy is brought into the emulsion resulting – together with high speed of rotation and very small sheer-slits – in small particles of the dispersed phase. At a bulk-production machine of 200 kg or more the adequate energy cannot be brought into the product, thus only larger particles are formed. If the emulsifying power (or concentration) of the emulsifying agents is not strong enough, stability cannot be reached any longer.

The optical centrifuge allows the early recognition of this problem. Two ways can be chosen: a) a small batch of ca. 2 – 5 kg can be produced on a small technical device, that often are compatible to larger systems regarding the sheer-parameters or b) another laboratory batch will be mixed using a normal stirrer instead of the dispersing machine.

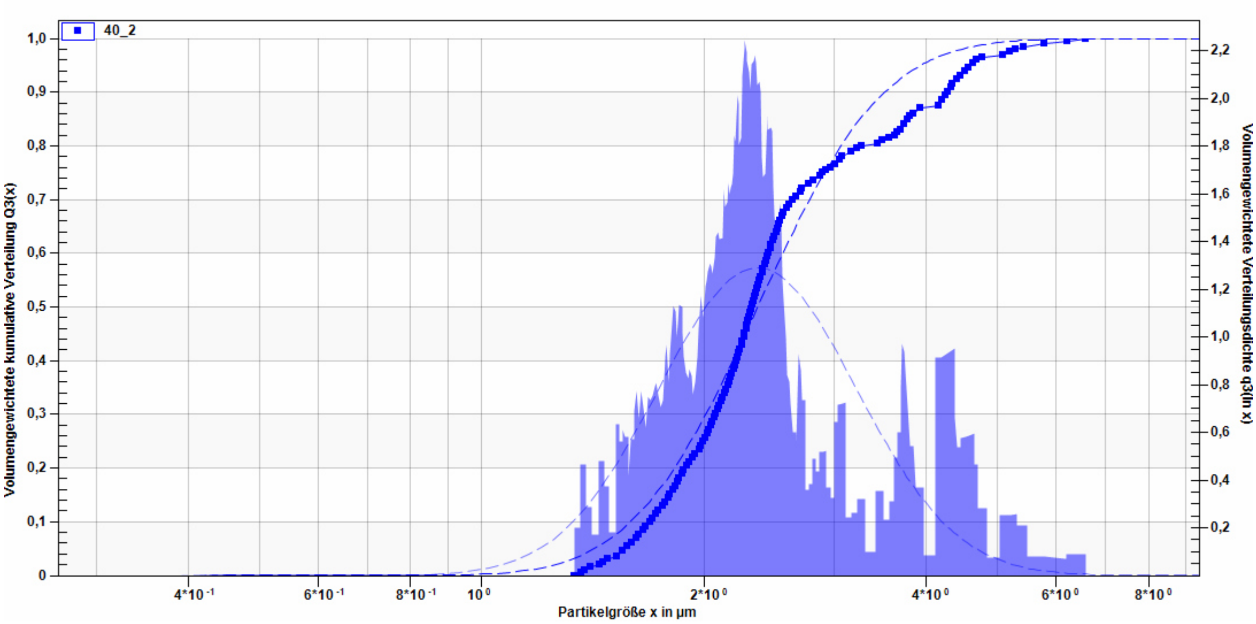
If such samples are surveyed in the optical centrifuge, galenic deteriorations due to the different particle-sizes easily and quickly are detected.

6) Determination of particle-sizes

With the optical centrifuge particle-size-distributions of emulsified particles can be measured. In this case the product will be diluted in the outer phase, thus definitely disturbing emulsion-stability. When this dilution is centrifuged under low g-values sedimentation or creaming will occur. So, typical profiles are gained as the following image shows:

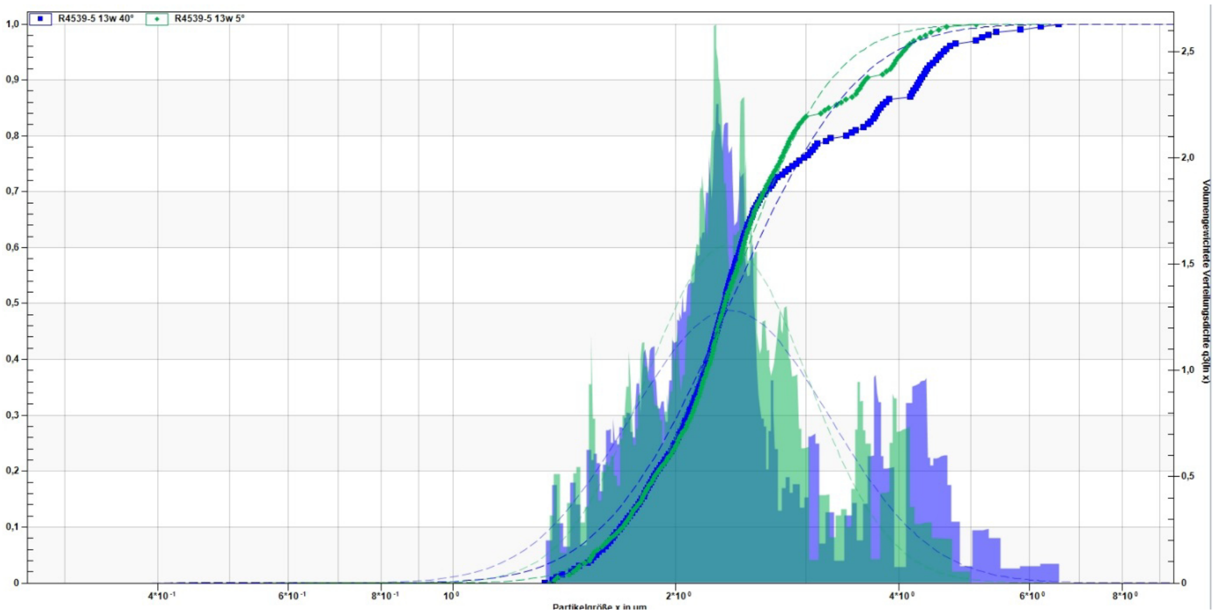


Out of these curves and data of densities, refractive indices and viscosity particle-size distributions can be calculated. The following graph shows an example.



The S-like curve shows the integral particle-size distribution, while the peak-diagram is the first derivation of this curve, giving the frequency distribution curve. Particle-sizes can be measured in the range between 50 nm and 500 µm.

The procedure especially is suitable for measurement of relative sizes. So, for example, the upscaling-issue as described above can be surveyed, or the effect of temperature onto the particles. Changing particle-structures can be seen distinctly. The following graph gives an example for this:



The graph shows the comparison of a cosmetic product after 13 weeks of storage at 40°C and at 5°C. The diagram demonstrates that at the higher temperature an increased fraction of larger particles has formed (blue curve and peaks).

7) Limits of the system

With the data gained by the optical centrifuge only actual states of the product are recorded. When data are extrapolated into the future the assumption must be applied that no slow chemical changes occur during the long-term period. A typical example for such chemical changing are drifts in pH-values that can be evoked by hydrolytic phenomena. If then e.g. a polyacrylate is used as a thickening agent, viscosity can break down dramatically. So, if a development has defined the final formula, performing accompanying classical storage-tests with measuring of typical parameters like pH, viscosity and organoleptic properties can be recommended