A Novel Fiber-Optic Photometer for In Situ Stability Assessment of Concentrated Oil-in-Water Emulsions

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ABSTRACT

The purpose of this research was to evaluate a novel fiber-optic photometer for its ability to monitor physical instabilities occurring in concentrated emulsions during storage. For this, the fiber-optic photometer was used to measure transmission of oil-in-water emulsions stabilized with hypromellose (HPMC) as a function of oil volume fraction and droplet size distribution (DSD). To detect physical instabilities like creaming and coalescence, the transmissivity of the samples was studied at 2 different height levels over a certain period of time. The corresponding droplet size distributions were determined by laser diffraction with PIDS. Transmissivity was found to depend on the number of dispersed droplets and thus is sensitive to both the variation of phase volume fraction as well as the emulsions droplet size distribution. At constant DSD, light transmission decreased linearly with increasing oil content within a large interval of phase volume fractions from 0.01 to 0.3. At constant phase volume fraction, an increase in droplet size increased light transmission. Investigation of creaming on emulsions with different droplet size distributions showed changes in the initial delay times and creaming velocities. In contrast to creaming phenomenon coalescence can be identified by height independent changes of the transmissivity. In conclusion, transmissivity of oil-in-water emulsions observed by the novel fiber-optic photometer is sensitive to phase volume fraction, droplet size distribution, and thus can be used as a tool for stability studies on concentrated emulsions.

KEYWORDS: Fiber-optic photometer, Optical analyser, Hypromellose, Emulsion stability, Concentrated dispersion.

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INTRODUCTION

Emulsions are inherently unstable systems. Their shelf life is kinetically controlled and thus the dispersed state can only be maintained for a certain period of time. Usually, a shelf life of at least 2 years is required for a commercially acceptable product. Therefore, methods are desired that allow an estimate of the long-term physical stability during formulation development at the earliest time possible.

Adequate methods have to be sufficiently sensitive to identify even small changes due to physical instability. Furthermore, these methods have to consider that dispersions are in general subtle systems and dilution or mechanical preparation preceding a measurement may induce physical instabilities like creaming or coalescence. All testing, therefore, has to be done preferentially without excessive sample preparation in order to avoid artifacts. This is absolutely mandatory when looking at creaming processes.

However, many analytical techniques are restricted to diluted systems, mostly below 1% (vol/vol), and therefore are not suitable for practically relevant systems. Stability assessment is hence often performed phenomenologically by subjective or time-consuming methods.[1]

Alternatively, several instruments have been introduced during the past few years that allow identification of physical instabilities.[2-6] Although each of these instruments was a step forward, there are still some shortcomings with the existing methods. Measurement of ultrasound velocity has a limited spatial resolution and is disturbed when air bubbles are entrapped in the sample. Measurement of demixing phenomena in an analytical photo-centrifuge using a near infrared charge-coupled device photo sensor (CCD)-line as a detector is restricted to semidiluted systems. The TurbiScan (Formulaction, l'Union, France) offers the possibility of monitoring creaming directly, even in concentrated systems. However, in nontransparent samples only the back-scattered light is analyzed and thus primarily surface and not bulk phenomena are reflected.

There is, therefore, still a need for an alternative method.

The fiber-optic photometer is a new promising candidate in this group of analytical instruments, which at first was

intended to measure sensitively creaming in dispersed systems. Moreover, it would be ideal if the method is also sensitive to changes in particle size.

As a first step, a prototype of this instrument was tested for its applicability in the stability assessment of oil-in-water emulsions. The instrument offers the opportunity to measure time-resolved transmissivity of transparent and opaque dispersions and allows on-line observation of changes in concentrated emulsions without any sample preparation.

The optical density of a dispersed system might be indicative of its physical stability if there is a clear correlation between the number of dispersed droplets and the transmissivity of a sample.

In the present work a novel fiber-optic photometer was used to measure transmission of oil-in-water emulsions as a function of droplet size distribution (DSD) and oil volume fraction Φ. Based on these results, oil-in-water emulsions that were designed to show creaming or coalescence were evaluated. For these studies it was an essential prerequisite that test emulsions could be reproducibly varied in phase volume fraction and/or droplet size. Hypromellose-stabilized emulsions are very well characterized and ideally fulfill these conditions.[7-9] Three sets of test emulsions were used: (1) emulsions with varying Φ and constant DSD, (2) emulsions with constant Φ and varying DSD, and (3) emulsions with varying Φ and varying DSD.

MATERIALS AND METHODS

Emulsions

Emulsions consisted of an aqueous hypromellose solution and medium-chain triglycerides (MCT) (Miglyol 812; Hüls, Troisdorf, Germany). Two types of hypromellose (HPMC) were used: low viscosity-grade hypromellose (sHPMC) (Pharmacoat 904, Shin Etsu, Tokyo, Japan) and medium viscosity-grade hypromellose (mHPMC) (Metolose 90 SH 100, Shin Etsu, Tokyo, Japan). Both were of USP substitution type 2208.[10] To prepare the polymer solution the whole amount of HPMC was dispersed in one third the volume of water at 70°C while stirred. Subsequently the remaining water was added. A transparent, slightly opalescent solution resulted after swelling for 12 hours. Emulsions were processed with a Becomix Laboratory Mixer RW 2.5 (A. Berents GmbH and Co.KG, Stuhr, Germany). For pre-emulsification, the polymer solution was added to the MCT oil phase within 10 minutes at 40°C and homogenized at 3500 rpm. Final homogenization (5900 rpm) was performed at 40°C for 20 minutes. All HPMC contents given below are as percentage with respect to aqueous phase.

Note that the phase volume fraction of original emulsions is denoted by Φ whereas daughter emulsions obtained by dilution are marked Φ_{dil}.

Transmission Photometric Analysis

Similar to conventional instruments, the fiber-optic photometer (Lucina II, Optimags GmbH, Karlsruhe, Germany) measures light transmission through a sample. Reduction of the transmitted light intensity may arise from absorption and scattering phenomena. A novel measuring technique enables the instrument to determine light transmission in concentrated systems without previous dilution of the sample. The experimental setup is shown in Figure 1a. Pulsed laser light is channeled through fiber optics to a test tube, passes the test tube containing the sample, and travels back to the detector. The wavelength of 905 nm is fixed by the emitting photodiode. During measurement, the laser intensity is adjusted in a way that the detector signal reaches a predefined value. This reference value can be set in a range from 3% to 95% of the maximum laser intensity. In the present study the reference value was set to 8% for all samples. With decreasing transmissivity of the sample the incident light intensity has to be increased to reach the adjusted detector threshold. Thus the required laser intensity is proportional to the optical density of the sample. The corresponding
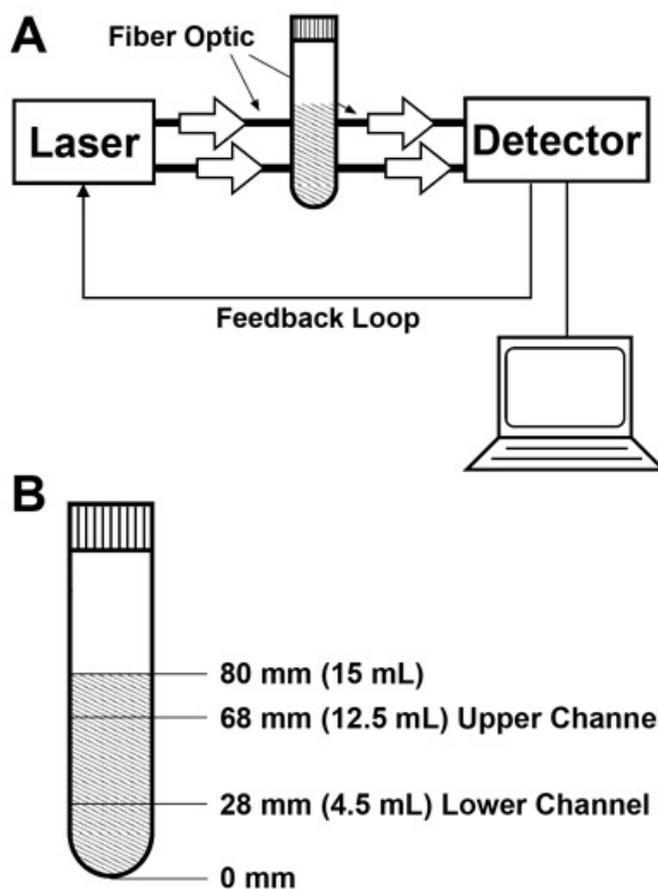

Figure 1. (a) Experimental setup of the fiber-optic photometer. Transmission of pulsed laser light in the test tube is measured in two channels at different levels. (b) Sketch of the measurement channel heights.

control loop acts very fast so that stable detector signal is typically achieved after less than 5 laser pulses (< 3 ms). The transmissivity of a sample can be described by the optical density (OD)

$$OD = \log_{10}(I_0 / I_x) \qquad (1)$$

with initial light intensity I_0, and final light intensity I_x after passing through a sample of thickness x. The decreasing of I_x with x is described by the Lambert-Beer law:

$$I_x = I_{0^{e^{-\alpha x}}} \qquad (2)$$

with extinction constant α. The extinction constant $\alpha = \varepsilon c$ is the product of the molar extinction coefficient ε and the mass concentration c. The transmissivity of a sample is the reciprocal of its OD.[11] The photometer has a huge measuring range ($0 < OD < 10$) as compared with conventional photometers ($OD < 3$).

The fiber-optic photometer in general supports simultaneous measurement of 3 independent channels. Proper positioning of the sample and the fiber optics was maintained with a specially designed sample holder. The test tubes were of alkaline resistant (AR) glass with 18 mm outer diameter and 180 mm length (Carl Roth GmbH and Co KG, Karlsruhe, Germany). Sample volume was 15 mL, which corresponds to a height of 80 mm in the test tubes. In the present study only 2 measuring channels positioned at different height levels (Figure 1b) were used to simplify the analysis. Both channels were plotted for height-dependent measurements, eg, to detect creaming. In all other cases only data of 1 channel were shown for clarity. A personal computer was used to control the experimental system, acquire, and visualize the experimental data. The instrument is capable of recording up to 2000 data points per second. Raw data are averaged and can be exported to plain ASCII data files.

All transmissivity data are given as percentage of the maximum laser intensity with laser intensity for a test tube filled with water as offset. Error bars show the standard deviation of 3 independent batches of the emulsions. Test tubes were gently shaken 10 times immediately before the measurements.

Droplet Size Analysis

Droplet size distributions of the emulsions were determined with the laser diffraction analyzer Coulter LS 13320 (Beckmann Coulter, Fullerton, CA) with integrated polarization intensity differential scattering (PIDS) technique. Intensities of PIDS and laser diffraction measurements were combined by a standard algorithm[12] and interpreted with Mie theory. Combination of laser diffraction and PIDS technology enables droplet size measurement in the range of 0.04 μm to

2000.00 μm. The following Mie parameters were chosen[13] real refractive index for the dispersion medium 1.33, real refractive index for the dispersed phase 1.46, and absorption factor for the dispersed phase 0.01. Data were fitted to a model-independent volume distribution.

Each sample was redispersed before measurement by gently turning it upside down 10 times. Emulsions were diluted with distilled water before measurement to obtain a droplet concentration optimal for the analysis.

For clarity, droplet size distributions are expressed by their corresponding d_{10}, d_{50}, and d_{90} values, respectively.

Microscopic Analysis

Visual assessment of the emulsion's droplet distribution was performed with a photomicroscope (Carl Zeiss, Oberkochen, Germany) at magnification of ×100. Concentrated emulsions were compared with corresponding systems after dilution. Photos from initial and diluted emulsions were taken and checked qualitatively for severe changes.

Storage at Cyclic Temperature

Storage at cyclic temperature is a common mean for accelerated stability testing of dispersed systems.[14,15] In this study, storage at cyclic temperature conditions is used to increase the rate of coalescence of the hypromellose stabilized emulsions. Temperature cycle tests (–5°C/+40°C for 12 hours each) were performed in a cooled incubator (Rumed Type 3401; Rubarth Apparate GmbH, Laatzen, Germany). Emulsions were stored in glass jars. Before measurement samples were withdrawn at 40°C and equilibrated at room temperature (22°C ± 2°C) for 2 hours.

RESULTS AND DISCUSSION

Dependency of light transmission on the phase volume fraction

The influence of the phase volume fraction on light transmission was evaluated using oil-in-water emulsions consisting of a 6% aqueous sHPMC solution with oil volume fraction varied from 20% to 60%. All samples showed a narrow DSD, which was not substantially affected by the variation of Φ. The d_{10}, d_{50}, and d_{90} values were (1.27 ± 0.25) μm, (2.38 ± 0.12) μm, (3.79 ± 0.22) μm respectively. In addition, the influence of dilution on the DSD was checked. Two independent methods (light microscopy and laser diffraction) revealed that the DSD remained unchanged within a dilution series (each step lowering Φ_{dil} by 0.1).

The deviations of the DSD between original emulsion and dilutions were found to be negligible. Thus, emulsions stabilized by 6% sHPMC are ideal test systems for evaluating
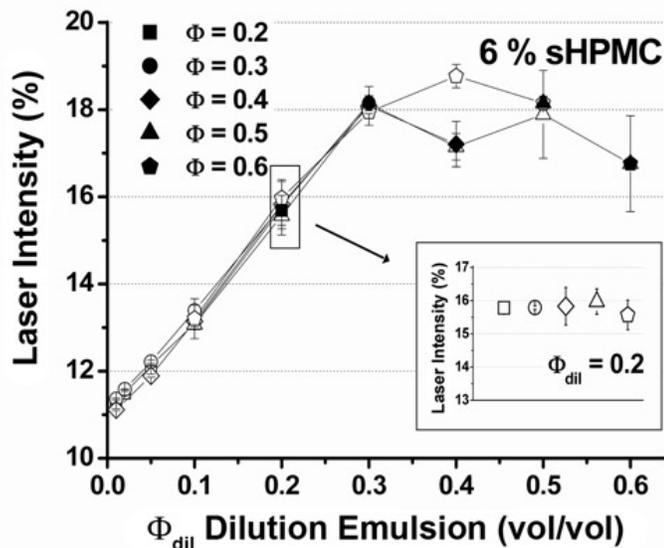
Figure 2. Transmissivity of emulsions with 6% sHPMC. The graphs show dilution series (blank symbols) starting from initial oil volume fractions $\Phi = 0.2$–0.6 (filled symbols). The insert shows dilution step $\Phi_{dil} = 0.2$ for all initial oil volume fractions.

the transmissivity as a function of the emulsion's oil volume fraction.

Figure 2 shows the transmissivity of both the original emulsions (Φ) and diluted samples (Φ_{dil}) prepared from these yielding emulsions with $0.01 < \Phi$ or $\Phi_{dil} < 0.6$. The laser intensity increased linearly with the oil volume fraction in a rather large interval from $\Phi = 0.01$ to 0.3. Increasing laser intensity corresponds to decreasing transmission. Although no consistent theory for multiple scattering systems is available to explain this behavior, light transmission of the emulsions obviously decreases linearly with the oil volume fraction. The results are in accordance with Miller.[16] As the DSD was almost invariable for all samples, light transmission can be directly correlated with the number of oil drops.

Above $\Phi > 0.3$ the response of the fiber-optic photometer was nonlinear and reached a pseudo plateau. At high oil concentration such phenomena may arise from wall effects of the cylindrical test tubes.[17] Part of the laser intensity may not penetrate the sample but reach the detector through the test tube wall. The insert in Figure 2 compares the optical density of all emulsions with a content of 20% oil. The result is constant within the error bars independent of the oil volume fraction of the original emulsion that was used for the preparation of the appropriate diluted emulsion.

As all of these emulsions have essentially the same DSD, it is concluded that for a given DSD the transmissivity solely depends on the oil volume fraction.

In this paper emulsions with $\Phi < 0.01$ are not considered because emulsions with less than 1% oil phase seem to be of no practical importance. Furthermore, from preliminary

studies it is known that at $\Phi < 0.01$ the required laser intensity decreases nonlinearly because multiple scattering was almost negligible. So far, $\Phi = 0.01$ is considered as the practical lower limit of resolution at least for the type of emulsion tested.

Dependency of light transmission on the droplet size distribution

The effect of DSD on the transmissivity was elucidated using oil-in-water emulsions prepared with 2.5% aqueous mHPMC solutions. Figure 3 shows the DSD for such emulsions with varying oil volume fraction in the range of 20% to 60%. All emulsions have a broad DSD with marked tailing at large droplet size. According to Daniels and Rimpler,[18] DSD broadens with increasing initial Φ and the modal value shifts toward larger sizes. In addition, Figure 3 illustrates that dilution of these emulsions has no impact on their DSD because the corresponding d-values for the diluted samples lie within the error bars of the undiluted systems. Thus emulsions stabilized with 2.5% mHPMC are suitable to evaluate the influence of DSD on the optical density if the original emulsions are diluted to a certain oil volume fraction. In addition, the influence of Φ on the transmissivity can be seen from a dilution series (Φ_{dil}) originating from the same emulsion. Transmissivity of these emulsions is shown in Figure 4.

Beyond an oil volume fraction of 0.3, there is a significant change in the slope of the curves (Figure 4) or even nonmonotonous behavior. This is in accordance with the findings reported above (Figure 2). Again a linear decrease of transmission for oil volume fractions in the range from $\Phi = 0.01$
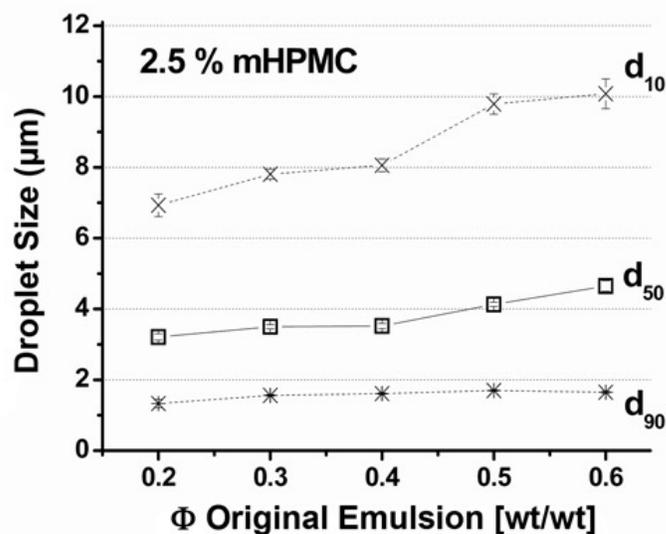

Figure 3. DSD of emulsions with 2.5% mHPMC. Each point represents an average value of initial oil volume fraction and 2dilution steps of 0.1 (0.09 in the last step). Thus the width of the standard deviation is a measure for dilution stability.
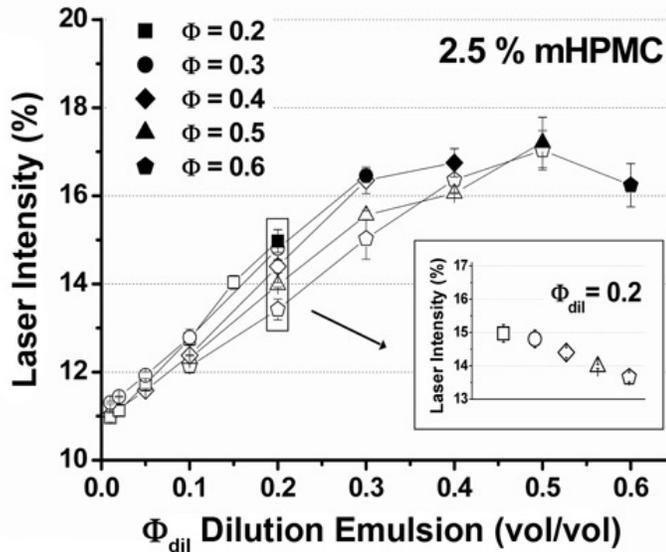
Figure 4. Transmissivity of emulsions with 2.5% mHPMC. The graphs show dilution series (blank symbols) starting from initial oil volume fractions $\Phi = 0.2$–0.6 (filled symbols). The insert shows dilution step $\Phi_{dil} = 0.2$ for all initial oil volume fractions.

to 0.3 was observed. However, the observed slopes vary depending on the oil volume fraction of the original emulsion. The insert in Figure 4 shows that at fixed oil volume fraction after dilution $\Phi_{dil} = 0.2$, the laser intensity decreases linearly with increasing initial oil volume fraction Φ. As the DSD of the diluted systems is almost identical to that of the original emulsions, it follows from the insert in Figure 4 that the transmissivity responds to variation in droplet size. The transmission of emulsions increases while the DSD broadens and shifts to larger droplet sizes.

The correlation of DSD and transmissivity is combined in Figure 5. Note that in general the transmissivity includes both influences of the sample's DSD and the phase volume fraction with a more pronounced effect, in this case coming from Φ.

In order to exclude that the changes in the optical behavior are caused by the different polymers, an additional series of emulsions containing sHPMC was used. All these systems contained 20% MCT but used different concentrations of sHPMC (1% to 6%) for stabilization. These emulsions differed in DSD due to suboptimal stabilization. Figure 6 represents the optical density of these emulsions as a function of their DSD. A dramatic broadening of the droplet size distribution can be observed with reduction of the sHPMC content in the aqueous phase. Light transmission of these emulsions increases in line with the droplet size. The sHPMC concentration does not affect light transmission through the aqueous phase. As expected, the transmissivity for a given phase volume fraction is directly linked to the dispersivity of an emulsion. Thus, it was verified that at constant oil volume
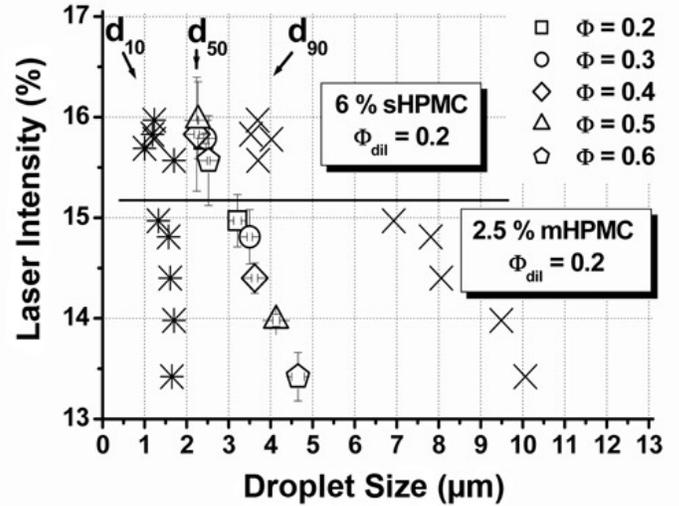

Figure 5. Transmissivity of emulsions with 6% sHPMC and 2.5% mHPMC plotted versus droplet size. Data for constant oil volume fraction $\Phi_{dil} = 0.2$ diluted from initial $\Phi = 0.2$ to 0.6 at preparation are shown.

fraction the signal intensity of the novel fiber-optic photometer for HPMC stabilized emulsion depends solely on the DSD and is independent of the polymer type and concentration. Nonetheless, polymer type and concentration may in turn determine the DSD of an emulsion.

Detection of Creaming

Creaming leads to a time- and height-dependent change of the oil volume fraction within the sample. This results in
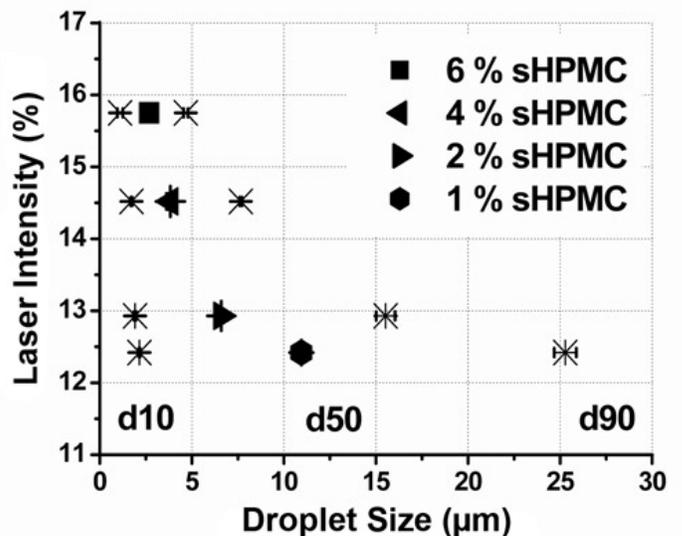

Figure 6. Transmissivity of emulsions with sHPMC plotted versus droplet size. Data for constant oil volume fraction $\Phi = 0.2$ at preparation and variation of sHPMC content in the aqueous phase are shown.
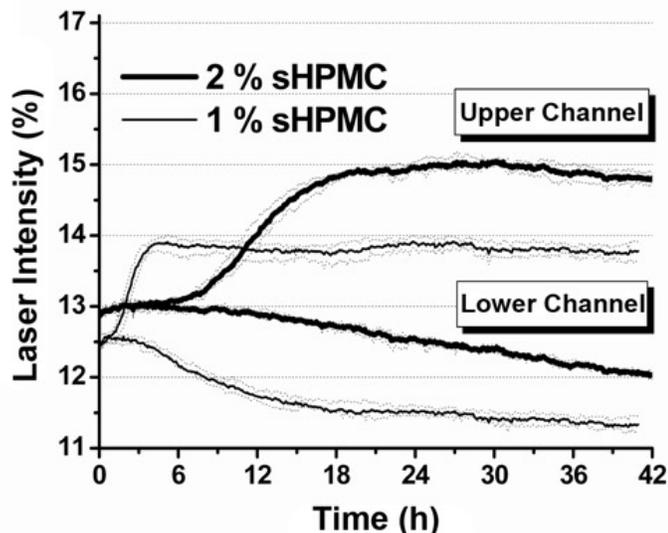
Figure 7. Time-dependent transmission of emulsions with 1% or 2% sHPMC for oil volume fraction $\Phi = 0.2$ at preparation. Dotted lines denote minimal and maximal deviation from mean values.

differences in optical densities when comparing the signals from the 2 channels of the experimental setup (Figure 1b).

Figure 7 shows the time-dependent transmissivity of 20% MCT-in-water emulsions stabilized with 1% or 2% sHPMC, respectively. The 1% and 2% aqueous sHPMC solutions do not sufficiently stabilize emulsions containing 20% MCT. These emulsions had a broad DSD (Figure 6) and creamed rather fast but did not increase in droplet size during the test period.

Figure 7 represents 3 repetitive measurements on each sample with preceding redispersion of the sample. The transmissivities match well at $t = 0$, which indicates both good reproducibility of measurements with the photometer and unchanged DSD after redispersion. As the oil droplets creamed, the lower region of the emulsions became more diluted. This could be observed by an increasing light transmission in the photometer's lower channel irrespective of the polymer content of the emulsions. After 30 hours, a nearly constant transmissivity was reached in the lower channel. Emulsion with 1% sHPMC creams clearly faster than emulsions with 2% polymer, because of their broader DSD, their lower viscosity, and the reduced fraction of small-sized droplets.

In the upper channel, the transmissivity rapidly reached a minimum that did not change further with time. The time required to reach constant light transmission in the upper channel is a measure of the creaming velocity. The final transmissivity depends on the packing density of droplets in the cream layer, which is mainly influenced by the local DSD and repulsive or attractive forces acting between the droplets. These relationships can be clearly seen with the test emulsions: The less-stable emulsions with 1% sHPMC reached constant transmissivity after ~5 hours, whereas systems with

2% sHPMC required more than 24 hours. Furthermore, emulsions stabilized with 2% sHPMC had a narrow DSD with smaller mean droplet size compared with those with 1% sHPMC (Figure 6). This resulted in a closer packing of the oil droplets in the cream layer of emulsions with 2% sHPMC. Accordingly, the cream layer of these emulsions had a higher optical density.

Another indicator for the rate of creaming is the delay time from $t = 0$ until the signals from the upper and the lower channels split.[19] It increased in line with increasing resistance against creaming.

The results give evidence that transmissivity measurements at 2 height levels are adequate to characterize time-dependent changes in the present emulsions. The influence of the polymer concentration on the rate of creaming is well resolved.

Detection of Coalescence

Emulsion with 6% sHPMC and an oil volume fraction Φ of 0.2 are stable when stored at room temperature (25°C) and thus showed no change in DSD within 2 years of storage. Therefore, cyclic temperature storage conditions were used to increase the rate of coalescence. This gave access to a series of emulsion systems with steadily increasing droplet sizes. Figure 8 depicts the emulsion's transmissivity together with its DSD during storage at cyclic temperatures. As the droplet size increases with time, the optical density of the emulsions decreases. This decrease in optical density was most pronounced during the first days of storage whereas a marked increase in droplet size became evident after 5 days.
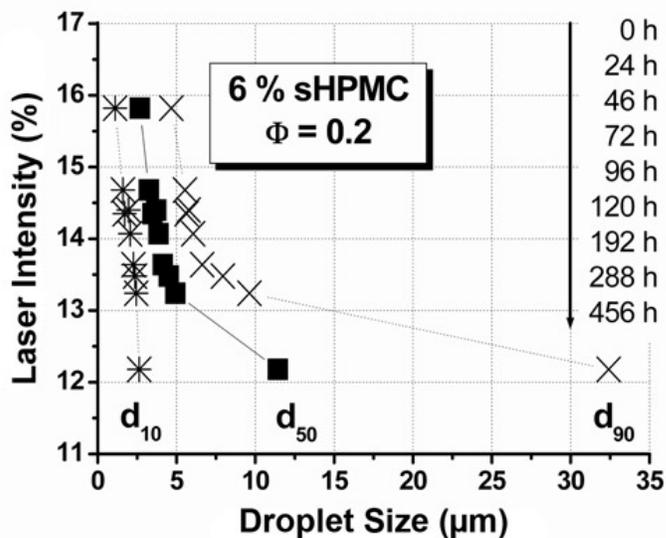

Figure 8. Transmissivity of emulsions with 6% sHPMC plotted versus droplet size. Time-dependent data for storage under stress conditions and constant oil volume fraction $\Phi = 0.2$ at preparation are shown.

Expectedly, the transmissivity was sensitive to the number of droplets, which rapidly decreased through the coalescence of small-sized droplets during initial storage. However, this had only a little influence on the drop volume distribution, which is represented by the droplet size measurements.

In contrast to the creaming phenomenon discussed above, coalescence is height independent. Both the upper and lower channels showed the same transmissivity. This allows one to clearly distinguish between either of these physical instabilities occurring in emulsions. For emulsions that show both physical instabilities, the following strategy with 2 repetitive measurements is suggested: after measuring the sample at the end of a storage period without manipulating it, a second assessment is performed after gently redispersing the sample. Following this measuring regime, the first measurement is indicative of creaming, whereas the second one identifies additional coalescence.

CONCLUSION

In conclusion, the novel fiber-optic photometer allows one to easily measure light transmission in concentrated oil-in-water emulsions (Φ = 0.01 to 0.3). The signal is primarily sensitive to the number of oil droplets. Therefore, changes in the oil volume fraction as well as changes in the DSD can be detected. Measurements at different height levels and before and after redispersion are necessary to distinguish between these two phenomena. Following such a strategy, the instrument has proven to be a valuable tool for stability studies because it allows identificaiotn of both creaming and coalescence.

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