PARAMETERS INFLUENCING OSTWALD RIPENING OF NANOEMULSIONS PRODUCED BY PREMIX MEMBRANE EMULSIFICATION

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ABSTRACT

Premix membrane emulsification is a promising method to produce colloidal lipid carrier systems, e.g. triglyceride nanoemulsions, with small particle sizes and narrow particle size distributions for intravenous administration. The stability of these systems can be affected by Ostwald ripening. The process of Ostwald ripening in emulsions of medium chain triglycerides stabilized with sucrose laurate was monitored by particle size measurements with photon correlation spectroscopy. Two different preparation methods were used and the concentration of free emulsifier measured to learn more about the influencing parameters.
The concentration of free sucrose laurate turned out to be the main influencing parameter and should be about zero to minimize Ostwald ripening in the emulsions.

Keywords: Premix membrane emulsification, Ostwald ripening, triglyceride emulsion

INTRODUCTION

Premix membrane emulsification is a promising method to produce colloidal lipid carrier systems for intravenous administration with small particle sizes and narrow particle size distributions. In this procedure, a coarse pre-emulsion is repeatedly extruded through a nanoporous membrane leading to droplets in the nanometer range.

In a previous study triglyceride oil nanoemulsions with particle sizes below 100 nm could be prepared with aluminium oxide membranes (Anodisc™ 0.02 µm) and sucrose laurate (SL) as a nonionic emulsifier. The long-term stability of these nanoemulsions depended on the concentration of the emulsifier. The more sucrose laurate was used in the formulations the faster was the particle size growth induced by Ostwald ripening [El-Hawari, 2018]. Ariyaprakai and Dungan could also observe a negative effect of an excess of emulsifier [Ariyaprakai, 2010].

Ostwald ripening is the process where large droplets grow at the expense of smaller ones due to the higher solubility of the smaller particles. Simultaneously the particle size distribution gets narrower which is a major characteristic of Ostwald ripening.

The aim of this study was to investigate the relationship between the emulsifier concentration, the concentration of free emulsifier (emulsifier in continuous phase, not bound to any interfaces) and Ostwald ripening to be able to forecast the composition of nanoemulsions that have a good stability and to learn more about the parameters influencing Ostwald ripening in the emulsions.

RESEARCH CONCEPT

The nanoemulsions were produced by premix membrane emulsification with an instrumented small scale extruder [Gehrmann, 2016]. The extruder consists of a high pressure syringe pump connected to a membrane holder and a computer to control the flow rate. A coarse premix emulsion dispersed with an Ultra-Turrax (IKA T25 digital, S25N-10G, Ika-Werke) at 10.000 rpm for 2 min was processed 27 times through Anodisc™ membranes (0.02 µm pore size, d= 41 mm) with a constant flow rate of 0.4 ml/s. The

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emulsions consisted of 10 % Miglyol® 812 (MCT) and various concentrations of sucrose laurate (1.5-10 %) in double distilled water. Sodium azide (0.05 %) was added as a preservative.

Two different production methods were used, termed "general method" and "addition method" in the following. In the general method the whole emulsifier was added to the aqueous phase at the beginning of the production. Using the addition method only 1.5 % emulsifier was added in the beginning and the difference to the defined concentration was added to the already prepared nanoemulsion under stirring for 2 hours. The emulsions were stored for 18 weeks under nitrogen at 20°C and the particle size and particle size distribution was measured at particular times.

The particle size (Z-Average diameter) and particle size distribution width (expressed as polydispersity index (PDI)) were determined using photon correlation spectroscopy (PCS) (Zetasizer Nano ZS, Malvern Instruments) at 25 °C and a backscattering angle of 173°. The emulsions were diluted to an attenuator of 6-8 and measured three times for 5 min with 5 min equilibration time. The mean number average diameter was determined applying the Mie theory (n_{lipid}= 1.45, n_{imag}= 0.01, n_{contin}= 1.33) and used for the calculation of the Ostwald ripening rates. The Ostwald ripening rate ω was calculated from the cube of the number average droplet radius as a function of time [Kabalnov, 1994].

The concentration of free emulsifier in the continuous phase of the nanoemulsions was measured after filtering 5 ml of the respective nanoemulsion through Vivaspin® 6 tubes (Sartorius, MWCO 300 kDa) with the aid of centrifugation for about 20 min (500xg, 22°C). Receiving a small volume of the continuous phase, without lipid droplets, the refraction index (Abbemat WR, Anton Paar) was measured and the SL concentration determined with the aid of a calibration curve.

The critical micelle concentration (CMC) was measured by the surface tension method with a Wilhelmy plate at 25°C (Tensiometer K100, KRÜSS GmbH). A solution of SL was stepwisely added to double distilled water and the values were plotted on a logarithmic scale against the surfactant concentration. The CMC was determined at the intersection of the linear fits.

RESULTS

With the general method all emulsions were successfully prepared but with different initial particle sizes, all smaller than 100 nm depending on the SL concentration. The initial particle size got smaller with higher SL concentrations using the same production parameters. The reason is that more emulsifier has a better stabilisation effect during the emulsification process and therefore smaller particles can be generated. Upon storage the droplet sizes increased up to a maximum of 135 nm (depending on SL concentration). The Ostwald ripening rates were linearly related to the SL concentration (Fig. 1) and in good agreement with results from earlier studies [El-Hawari, 2018]. When using the general method for emulsion preparation the Ostwald ripening rates are affected by the different initial particle size which is likely to have an influence on the results.

To tackle this problem an alternative processing method, the addition method, was tested. The particle size of the nanoemulsions was measured before and shortly after the second addition of SL. No significant alterations of the droplet sizes could be detected under these circumstances. After longer storage times a similar particle size growth as in emulsions prepared by the general method as well as decreasing PDI values could be measured. The Ostwald ripening rates were calculated and compared with that for emulsions prepared with the general method (Fig. 1). A linear relationship could also be determined for the addition method.

To obtain more detailed information about the parameters influencing Ostwald ripening the concentration of free SL was determined. The Ostwald ripening rate had a linear relationship to the concentration of free SL. The more free SL was available in the continuous phase the faster was the Ostwald ripening (Fig. 2). With regard to the overall as well as to the free SL concentration the slope of the linear fit for emulsions prepared with the two different methods are not completely equal.

The CMC (mean of three independent measurements) of SL was determined as 0.015%.

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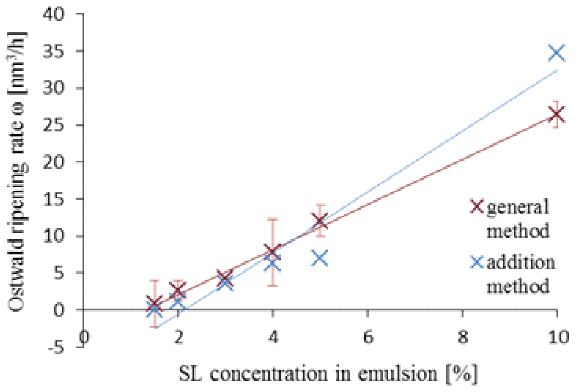

Fig. 1: Comparison of Ostwald ripening rates calculated for emulsions obtained by the general and the addition method at different SL concentrations.

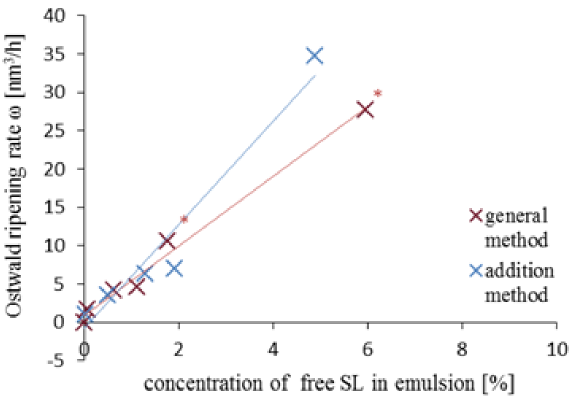

Fig. 2: Linear correlation between Ostwald ripening rates and the concentration of free SL for emulsions prepared with the general and the addition method. * values are affected by the presence of lipid droplets in the filtrate.

DISCUSSION

Ostwald ripening similarly occurred in the emulsions prepared by the two methods but somewhat unexpectedly the correlation between Ostwald ripening rate and SL concentration was not the same. The smaller slope observed for emulsions prepared by the general method may be a consequence of the different initial particle sizes of the emulsions prepared with different emulsifier contents.

Nevertheless, the higher the concentration of free SL the higher were the Ostwald ripening rates independent of the method. In these experiments the concentration of free SL seems to be the major factor determining the rate of Ostwald ripening. Different mechanisms have

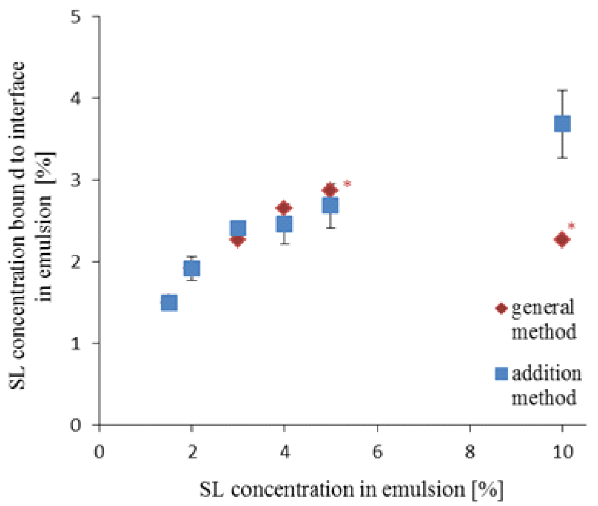

Fig. 3: Correlation between the amount of SL bound to the interfaces and the overall SL concentration for emulsions prepared by the general and the addition method. * values are affected by the presence of lipid droplets in the filtrate.

been discussed how the transport of lipid through the continuous phase may be going on. One possibility is the transport in micelles [Binks, 1999, Weiss, 2000]. The results obtained for the concentration of free SL were, except for emulsions containing 1.5 % SL, above the critical micelle concentration (CMC= 0.015 %). Transport in micelles thus seems to be a likely possibility but further investigation is necessary to prove the underlying mechanisms.

It is also an interesting point that the amount of SL bound to the interfaces (calculated from the difference of absolute concentration and free SL concentration) increased with higher SL concentration (Fig. 3). The curve progression leads to the assumption that at higher SL concentrations, a saturation of the interfaces will likely be reached. With regard to the storage stability nanoemulsions with less SL, e.g. 1.5 %, and therefore less SL bound to interfaces, were better stabilized against particle size growth as reflected by a low Ostwald ripening rate (Fig. 1). Higher surface coverage with emulsifier molecules does thus not have a protecting effect against Ostwald ripening of nanoemulsions.

CONCLUSIONS

For the emulsions under investigation here the free concentration of emulsifier is a main influencing parameter for the rate of Ostwald ripening probably by

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its effect on micellar transport. In order to achieve long-term stable nanoemulsions the concentration of free SL should be about zero to minimize the Ostwald ripening rate. It seems to be of little importance for the speed of Ostwald ripening whether the emulsifier SL is completely added before processing (general method) or in two parts, before and after emulsification (addition method). The different initial particle sizes resulting from preparation with the general method probably affected the results obtained for the Ostwald ripening behaviour. The addition method can serve as an easy and time-saving method to produce nanoemulsions with the same particle size but different SL concentrations.

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