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The effect of oil components and homogenization conditions on the physicochemical properties and stability of parenteral fat emulsions

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Abstract

The stability and physicochemical properties of different parenteral emulsion formulations containing 20% oil phase stabilized with soya lecithin were examined. Oil mixtures of castor oil with either soybean oil or middle-chain triglycerides (MCT) yielded very fine mean particle sizes (130–140 nm), which remained stable over 9 months. Moreover, a further aim was to produce emulsions containing 30% oil phase with small mean particle sizes and moderate viscosity. By optimizing the homogenization process and using only 1.5% soya lecithin, emulsions with 30% oil phase consisting of castor oil and MCT 1:1 with particle sizes in the range of 135–145 nm and moderate viscosity (3.8–3.9 mPa·s) could be prepared. These emulsions showed good stability over 9 months. The stability of these emulsions could be correlated with the decrease in interfacial tension by using castor oil as a component of the oil phase. This study shows the dominating influence of the nature of the oil phase as well as the importance of the homogenizing conditions on processing and stability.

Keywords: Parenteral emulsions; Oil phase; Fat component; Interfacial tension; Emulsion processing; Stability

1. Introduction

At present there is a renewed interest in lipid emulsions of vegetable oils and lecithin for i.v. delivery of drugs with a short biological half-life and poor oral bioavailability (Fortner et al., 1975; Dardel et al., 1976; Singh et al., 1986; Collins-Cold et al., 1990). Their usefulness as carriers stems from their ability to incorporate drugs with a poor water solubility within the dispersal phase. Thus, direct contact of the drug with the body fluids and tissues can be avoided and the drug released slowly over a prolonged period of time, which may lead to a minimization of side effects (Mizushima et al., 1983; Bock and Müller, 1994; Lovell et al., 1994). However, in contrast, the

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Table 1
Effect of different oil phases on the mean particle size (PCS) at room temperature (22°C)

Emulsion	Mean particle size (nm)				
	Before sterilization	After sterilization	1 Month	3 Months	6 Months
Almond oil	144 ± 3.4	143 ± 3.3	144 ± 2.8	143 ± 2.3	145 ± 2.7
Sesame oil	145 ± 2.9	142 ± 3.1	142 ± 2.3	140 ± 2.8	141 ± 3.1
Castor oil	159 ± 4.9	160 ± 4.5	163 ± 4.2	161 ± 3.8	Unstable
Castor oil–soybean oil 1:1	146 ± 2.9	146 ± 2.9	147 ± 3.2	146 ± 2.6	145 ± 2.5
Castor oil–MCT 1:1	144 ± 3.1	145 ± 2.9	141 ± 2.4	142 ± 3.2	143 ± 2.6
Lipofundin®MCT 20%		126 ± 2.4	124 ± 3.1	125 ± 2.5	123 ± 2.2

incorporation of a drug in a lipid emulsion can enhance the activity and the bioavailability (Nakamoto et al., 1975; Mizushima et al., 1982). In addition, increasing the volume of the oil phase promoted the amount of the liposoluble drug which could be incorporated in the emulsion dosage form. Unfortunately, high oil concentrations often lead to an increase in particle size and viscosity of the system (Benita and Levy, 1989; Ishii et al., 1990). The increase in particle size distribution may result from an impoverishment of the surfactant at the interface with increasing surface of the dispersed oil phase. The particle size distribution of parenteral fat emulsions, however, is a critical factor for patient safety because larger particles may cause embolism (Jeppsson et al., 1976; Laval-Jeantet et al., 1982). Hence, more emulsifier should be used; but this will lead to an additional increase in viscosity (Tamakura et al., 1983; Ishii et al., 1990). This would be a disadvantage because the i.v. administration of viscous systems is usually painful. Moreover, the extent of the increase of viscosity depends on the nature of the surfactant (Nielloud et al., 1996).

Variations in the emulsifier system are constrained because parenteral application is normally restricted to two types of emulsifier only: phospholipids and poloxamers. Normally, soya oil, middle-chain triglycerides (MCT), safflower oil and cotton seed oil are used as the oil phase in fat emulsions for total parenteral nutrition (Bivins et al., 1980; Hansrani et al., 1983; Sayeed et al., 1987). The solubility of the drugs in the oil phase is too low to permit use of these emulsions for parenteral drug delivery, which limits their application. Therefore, in this study, attempts were made to use oils with different polarities, such as castor oil, sesame oil, MCT, soybean oil or almond oil themselves or in mixtures in order to prepare emulsions with a capacity for a high drug uptake and good physicochemical properties, such as low viscosity and excellent stability.

Apart from the adjustment of the polarity of the oil phase an attempt was made to increase the ratio of the oil phase up to 30%. Using only 1.5% emulsifier a sharp increase in the viscosity should be avoided and the reported instability of high concentrated emulsions should be eliminated by optimizing the production conditions (Tamakura et al., 1983; Bock, 1994).

2. Materials and methods

2.1. Materials

Purified castor oil, sesame oil, almond oil and soybean oil were obtained from Henry Lamotte (Bremen, Germany) and MCT oil was purchased from Hüls (Witten/Ruhr, Germany). All these oils were of pharmaceutical grade. Lipoid S75 was supplied by Lipoid (Ludwigshafen, Germany) and glycerol was purchased from Merck (Darmstadt, Germany). Double distilled water was used and all other chemicals were of reagent grade.

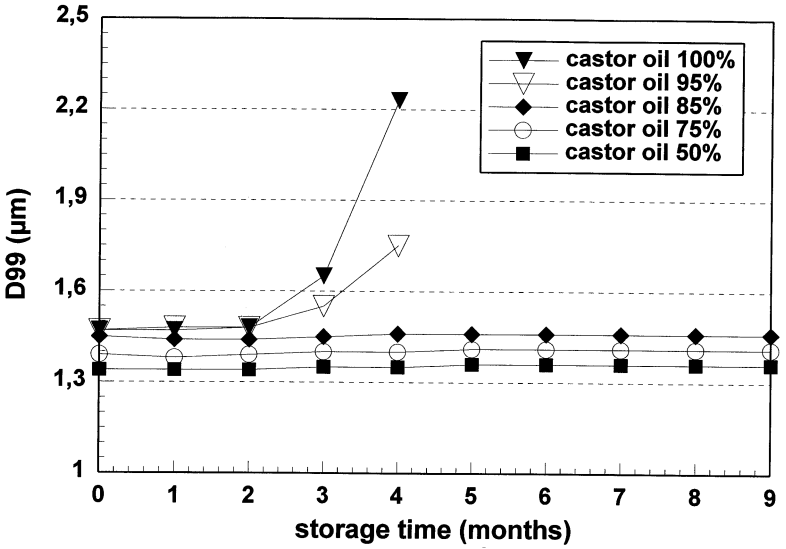

Fig. 1. Influence of the castor oil ratio on the stability of 20% emulsions at 22°C.

2.2. Methods

2.2.1. Preparation of emulsions

The emulsions were prepared as follows. Lipoid S75 (1.5%) was dispersed in the oil phase using an Ultraturax T25 (Jancke and Kunkel, Staufen, Germany) and its solution was completed by warming up the mixture (50–55°C) under slight stirring for 30 min. Under these conditions no degradation of the phospholipid occurs. This emulsifier-oil phase was added to 2.5% aqueous solution of glycerol (for adjustment of isotonicity) of the same temperature. This mixture was pre-emulsified using the Ultraturax at 8000 rpm for 3 min. Final emulsification was carried out by passing the coarse emulsion through a high pressure homogenizer (Micron Lab 40, APV Gaulin, Lübeck, Germany). Warm water was circulated around the homogenization unit to maintain the temperature of the emulsion at 40°C. Different formulations were produced by variation of the homogenization pressure and the number of cycles. Each formulation was produced 3-fold. After the homogenization, the pH of the emulsions was

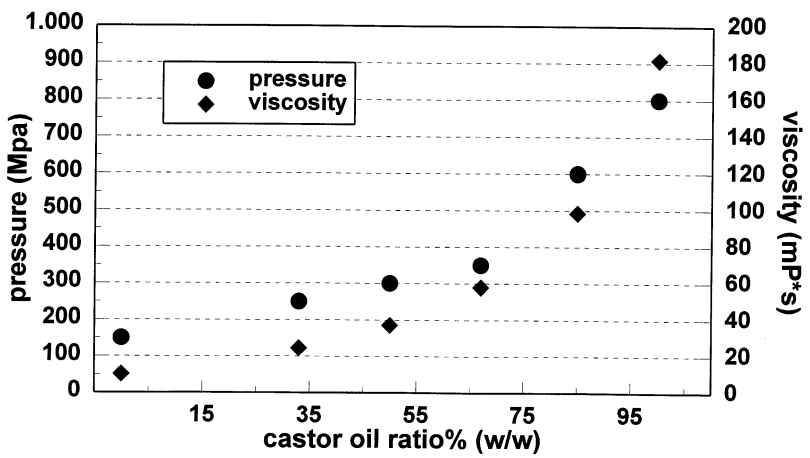

Fig. 2. Effect of the castor oil ratio on the oil phase viscosity and homogenization pressure at 40°C.

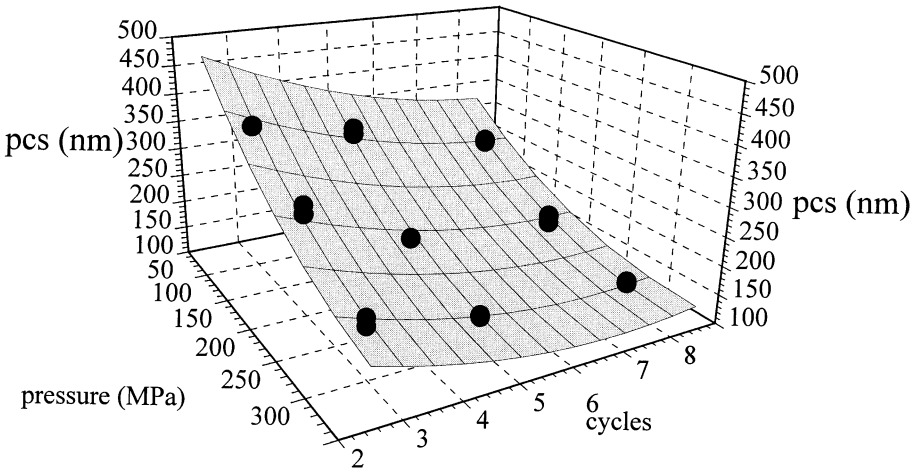

Fig. 3. Influence of the manufacturing process on the mean particle size (PCS) of a 30% emulsion containing castor oil/MCT 1:1.

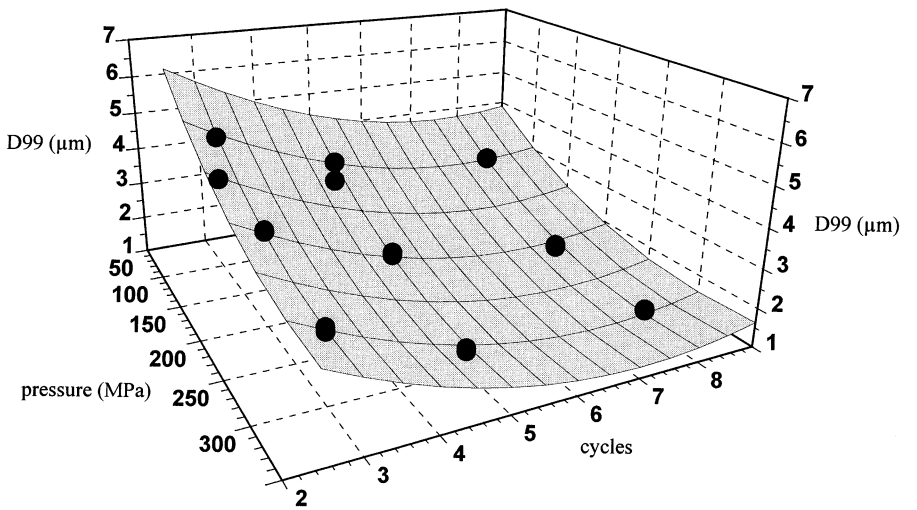

Fig. 4. Influence of the manufacturing process on the D99 values of the 30% emulsions containing castor oil/MCT 1:1.

adjusted to about 7.5 using 0.1 N aqueous sodium hydroxide. The batches of emulsions were filled in 15 ml vials, the vials were sealed and the emulsions were sterilized using steam autoclave (K15T, Keller, Weinhein, Germany) at 121°C for 20 min.

2.3. Emulsion evaluation

2.3.1. Particle size analysis

The volume distribution of particles was measured by laser diffractometry LD (HELOS, Sympatec, Clausthal, Germany) using a 20-mm lens which detects particles from 0.18 to 35 μm thus allowing the large oil droplets to be measured. The mean particle size of the emulsions was measured by photon correlation spectroscopy (PCS) using laser light scattering (Malvern spectrometer RR 102, Malvern, UK) with helium–neon laser $\lambda = 632.8$ nm (Siemens, Germany). Lipofundin® MCT 20%, which is a commercially available emulsion, was used as standard for comparative purposes. The application of two methods for particle sizing is necessary because PCS enables only moderately narrow distributions to be analyzed and shows good precision in the small particle size range. However, if the system shows a

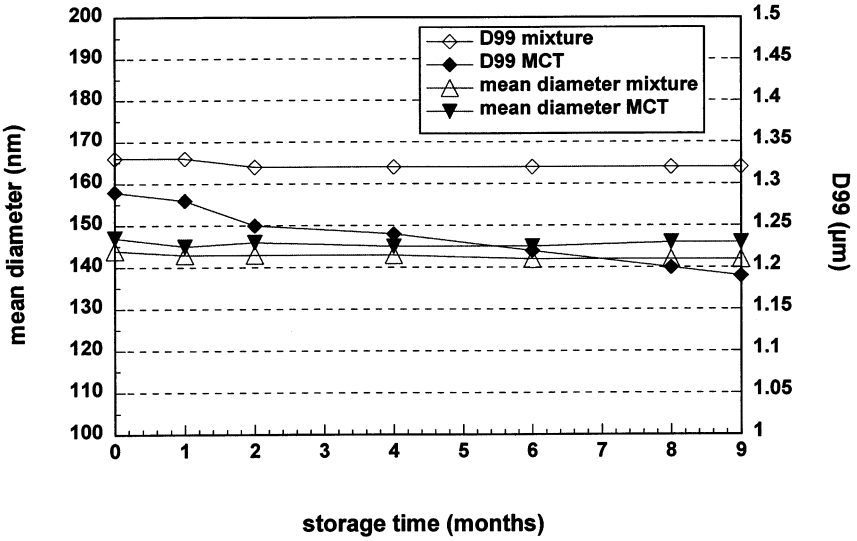

Fig. 5. Effect of the nature of the oil phase on the shelf stability of the emulsions containing 30% oil phase at 22°C.

broad particle size distribution only laser diffraction can detect a small coarse particle fraction beside a large number of smaller ones.

2.3.2. ζ-Potential

The surface charge (ζ-potential) was measured using a ZetaSizer 3 (Malvern Instruments, Malvern, UK). The electrolyte solution used for dilution consisted of double distilled water with a conductivity of 50 μS/cm adjusted by NaCl (0.5 mmol/l). Of each emulsion formulation, 500 μl was diluted by 20 ml electrolyte solution.

2.3.3. Interfacial tension and viscosity

The interfacial tension measurements were carried out at 25°C using an electronic tensiometer K122 (Krüss, Hamburg, Germany) and employing the plate detachment method. The viscosity of the emulsions was measured by an Ubbelohde capillary viscometer (Schott, Hofheim, Germany), while the oil phase viscosity measurements were performed at 40°C corresponding to the homogenization temperature.

2.3.4. Microscopical examination

The microscopic assessment was carried out using a photo microscope, Carl Zeiss (Oberkochen, Germany). The emulsion sample was fixed using gelatin to decrease the Brownian movement of the lipid particle and then exposed for 7 min to light. This enabled the larger lipid globule sizes to be measured.

3. Results and discussions

3.1. Emulsions with 20% oil phase (w/w)

Emulsions with an oil phase of 20% w/w were prepared using either sesame oil, almond oil, castor oil, or a mixture of castor oil with either soybean oil or MCT in the ratio of 1:1. As illustrated in Table 1, these emulsions exhibited no change in the mean particle size before and after autoclaving, with the exception of the castor oil emulsion which showed some macroscopic changes. All emulsions were stored at room temperature and observed for more than 9 months.

These emulsions exhibited D99 particle size (D99 is the volume diameter 99% obtained from LD, that means 99% of the particles are below the given size) in the range 1.35–1.40 μm which was more or less constant over the storage time. In contrast to this, castor oil emulsions showed a great increase in the D99 value after 3 months, accompanied by a visible deterioration. Further-

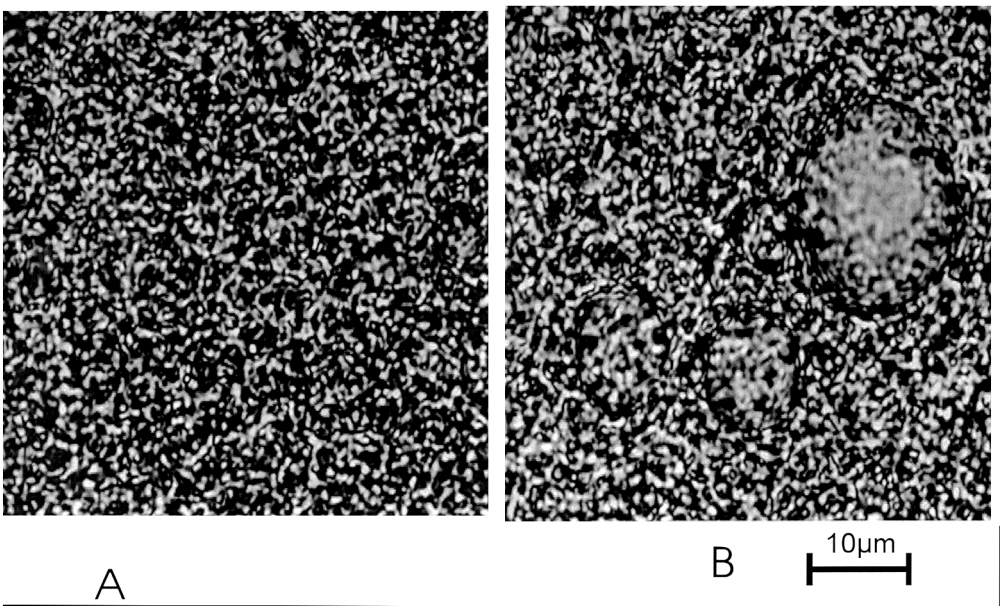

Fig. 6. Photomicrograph of 30% emulsions after 9 months storage at 22°C. (A) Castor oil–MCT; (B) MCT only.

more, the stability of formulations as a function of castor oil ratio in mixtures with MCT was studied. Fig. 1 indicates that increasing the castor oil ratio from 50 to 85% of the oil phase was accompanied by a slight increase in the emulsion particle size and led to instability after a storage time of 3 months in the case of ratios above 80%.

All other emulsions demonstrated good stability over 9 months storage at 22°C as indicated by constant D99 values. In order to reach mean particle sizes below about 150 nm higher homogenization pressures are needed when the castor oil ratio increased. The application of a higher shear stress may be due to a change in the viscosity of the oil phase because castor oil shows a much higher viscosity than MCT oil. Fig. 2 shows the correlation between homogenization pressure and viscosity and the ratio of the castor oil in the oil phase. Oil phases with higher viscosities need higher homogenization pressures to achieve smaller particle size distributions, otherwise at critical viscosity values coarse, unstable, large oil droplets coalesce resulting in a destabilization effect. This was contrary to what might be expected with a high viscosity increase if coalescence was hindered (Bock and Müller, 1994).

3.2. Emulsions with 30% oil phase (w/w)

The above results indicate that the physicochemical properties and the stability of emulsions containing 20% oil phase are greatly influenced by the nature of the oil phase. A higher oil ratio will enable the emulsion system to carry a higher drug concentration. Fig. 2 indicates that a castor oil–MCT ratio of 1:1 showed low viscosities and required only moderate homogenization pressure to obtain acceptable mean particle sizes.

The contour plot in Fig. 3 shows the influence of the preparation conditions on the mean particle size of emulsions containing 30% oily phase (consisting of 1:1 castor oil, MCT). The optimum is achieved by using a homogenization pressure of 30–35 MPa at eight cycles. With these conditions, the maximum size reduction (from 360 to 140 nm) and optimum decrease in polydispersity from 0.5 to 0.15 (the figure is not shown) is obtained.

It is clear from Fig. 4 that the optimum homogenization pressures are between 30 and 35 MPa at eight cycles which leads to a decrease in D99 values from 4.5 to 1.35 μm. This pattern is in full agreement with PCS measurements indicating the absence of the large particles. A homogenization

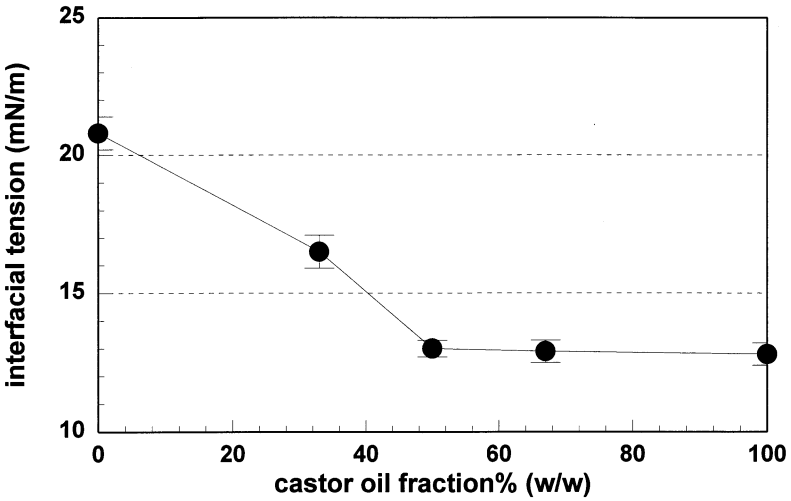

Fig. 7. Influence of the castor oil ratio on interfacial tension.

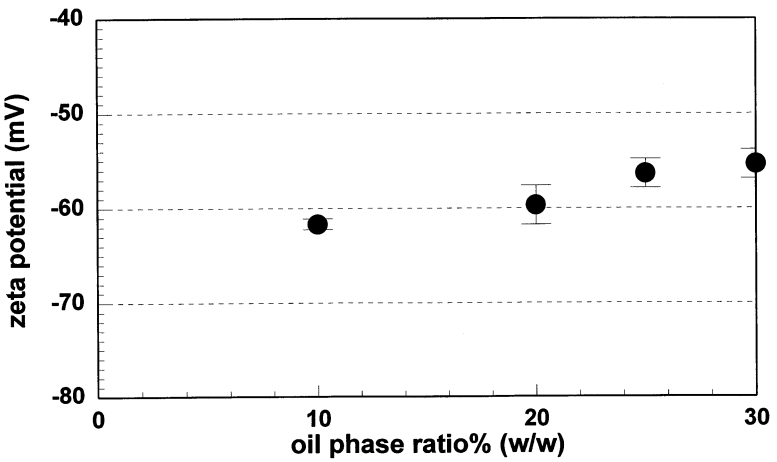

Fig. 8. Influence of the oil phase ratio on the ζ-potential.

pressure higher than 35 MPa leads to a decrease in mean particle size but simultaneously to an increase in particle size distribution. These formulations have only a poor shelf life (Bock and Müller, 1994). All other emulsions showed excellent physical stability with a storage time of more than 9 months at 22°C.

The influence of the nature of the oil phase on emulsion stability is shown in Fig. 5. The mean particle size from both 30% formulations castor oil/MCT and MCT alone showed no changes within a period of 9 months, whereas HELOS values (D99) indicate coalescence of the MCT emulsions. Fig. 6 shows clearly an association of the small oil droplets with large ones.

Increasing the volume of the oil phase and decreasing particle size led to an increase in the interfacial surface. Hence, more emulsifier amount should be added to stabilize the system. However, these emulsions could only be prepared with 1.5% emulsifier. The excellent stability could be interpreted as being due to the presence of castor oil as a part of the oil phase. As shown in Fig. 7 the presence of the castor oil led to a remarkable decrease in the interfacial tension. Increasing the ratio of the castor oil leads to a great decrease in

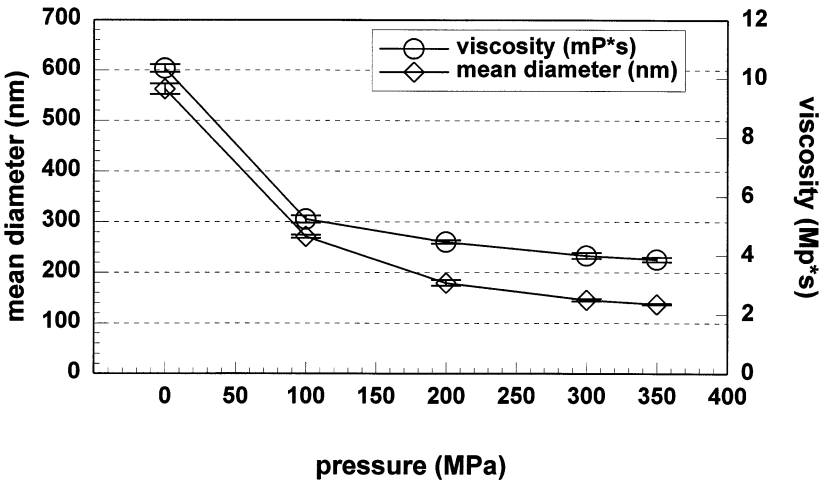

Fig. 9. Effect of the homogenization pressure on mean particle size and viscosity of 30% emulsions containing castor oil/MCT 1:1.

interfacial tension in the initial addition and then levels off at a ratio of more than 50% (w/w).

Surface potentials should play an important role in the emulsion stability due to electrostatic repulsion. Fig. 8 shows the apparent change in the ζ-potential of the oil droplets as the volume of the oil phase increased. The ζ-potential decreased slightly as the volume of the oil phase increased from 20 to 30% (w/w). These results show that the free fatty acids (85–87%), which are contained in the castor oil can act as co-surfactant (Yamaguchi et al., 1995). Rheological properties are important factors affecting the use of parenteral emulsions as drug delivery systems. Fig. 9 shows the effect of the homogenization pressure on the emulsion viscosity and/or the correlation between the viscosity and the mean particle size. The emulsion viscosity decreases sharply with decrease in the mean particle size, when the homogenization pressure is increased up to 30 MPa. At higher values a slight reduction in mean particle size can be observed which is not accompanied with a change in viscosity. This decrease of emulsion viscosity was considered to be caused by destruction of the inner oil phase as a result of increasing the homogenization pressure. These findings are in agreement with the other reported results (Tamakura et al., 1983).

Moreover, increasing the volume of the oil phase usually leads to a remarkable increase in the mean particle size but, in contrast, emulsions prepared by 30–35 MPa pressure and at eight cycles and with different oil phase volumes (20, 25 and 30%) showed a slight increase in the mean particle sizes (from 135 to 150 nm). This may be due to the decrease in interfacial tension as a function of castor oil and the appropriate homogenization conditions.

4. Conclusion

The nature of the oil phase has a great influence on emulsion stability. The free fatty acids contained in the castor oil may act as co-surfactant and appeared to suppress the coalescence and flocculation of lipid particles, which leads to an additional stabilizing factor.

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