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Research paper

Mixture experiments with the oil phase of parenteral emulsions

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Abstract

The effects of the oil phase as a mixture (binary, ternary) on the emulsion droplet size were investigated. The binary trials were performed with the aid of simplex lattice design with constraints. Droplet diameter was evaluated in terms of the oil phase viscosity and the interfacial tension between oil phase and the aqueous phase. As a result it could be shown that increasing the oil phase viscosity as a function of castor oil concentration led to a greater increase in particle size. At the same time, decreasing the interfacial tension of the oil phase as a function of oleic acid or oleic alcohol was shown to have a negligible effect on the particle size of the dispersed phase. A further aim was to find out a formulation by using a ternary oil phase resulting in a stable emulsion which could pass the autoclaving process. It was ascertained that oleic acid as a part of the oil phase led to proper formulation showing a satisfactory stability.

Keywords: Parenteral emulsions; Oil phase mixture; Viscosity; Interfacial tension; Lattice design

1. Introduction

Lipid emulsions are currently receiving more attention as drug delivery systems for drugs with poor water solubility [1–3]. The influence of different parameters in the emulsification process has been studied by many authors: the classical approach in many experiments is to investigate the effects of the production conditions [4] or the surfactant effects [5,6]. It has been reported that the oil phase volume ratio has a great influence on the mean particle size of the emulsion [7] but usually such studies were carried out using only one single oil. Either medium-chain triglycerides (MCT) [8] or soy bean oil [7,9] were used in these studies.

In this investigation emulsions with different binary or ternary oil mixtures but with a constant oil phase volume ratio were evaluated. The particle size distribution as function of viscosity and interfacial tension (against water) of the oil mixture was studied. The ternary mixtures were varied according to a simplex lattice design with constraints to find out the most suitable oil ratio for an emulsion formulation. Another aim of this study was to develop an emulsion formulation which can pass the sterilization process by autoclaving without being damaged. In this part of the study binary oil mixtures were used.

The oil mixtures consisted of three components, castor oil and MCT and oleic acid. These have already been used previously in parenteral formulations [10–12]. Washington and Davis [13] reported that ζ potential became more negative with the addition of oleic acid due to the accumulation of negatively charged ionized carboxyl groups on the surface. In addition, Yamaguchi and colleagues [5] found that Vt_{max} (maximum total interaction energy) and W (energy barrier for coalescence) were increased respectively by the addition of oleic acid and that this prevented flocculation and coalescence. In two further trials oleic alcohol and oleic acid oleylester were used instead of oleic acid. These trials were performed to prove the importance of the charged ionized carboxyl groups using uncharged molecules of similar structure.

In the last experiments binary oil mixtures of MCT with

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either oleic acid or oleic alcohol were investigated. Synperonic F68, a polyoxyethylen-polyoxypropylen-block-copolymer, was used as emulsifier due to its wide safety margin throughout the study [6,14].

2. Materials and methods

2.1. Materials

Purified castor oil was purchased from Henry Lamotte (Bremen, Germany) and oleic acid of highest quality was purchased from Merck (Darmstadt, Germany). Oleic alcohol (Eutanol-HD) and oleic acid oleylester (Cetiol) were purchased from Henkel (Düsseldorf, Germany). Medium-chain triglycerides (Miglyol 812) were obtained from Hüls (Witten/Ruhr, Germany) and Synperonic F68 was supplied by ICI (Cleveland, UK). Double distilled water was used. All other chemicals were of reagent grade.

2.2. Preparation of emulsion

Emulsions containing 20% oil were prepared as follows: 2% (w/w) of Synperonic F68 was dissolved in water. The oil mixture and the aqueous solution were heated separately to about 50–55°C. The oil phase was added to the water phase and this mixture was pre-emulsified using an Ultra-Turrax T25 (Janke and Kunkel, Staufen, Germany) running at 8000 rev./min for 3 min.

Final emulsification was carried out by passing 40 ml of the coarse emulsion through a high pressure homogenizer (Micron Lab 40, APV Gaulin, Lübeck, Germany) 8 times at a pressure of 10 MPas. The homogenization was performed at a temperature of 40°C.

For the systems with binary oil phases the isotonicity was adjusted using 2.5% (w/w) glycerol and the pH was adjusted to about 7.5 using 0.1 N sodium hydroxide solution. The emulsions were filled into 50 ml vials and autoclaved at 121°C for 20 min.

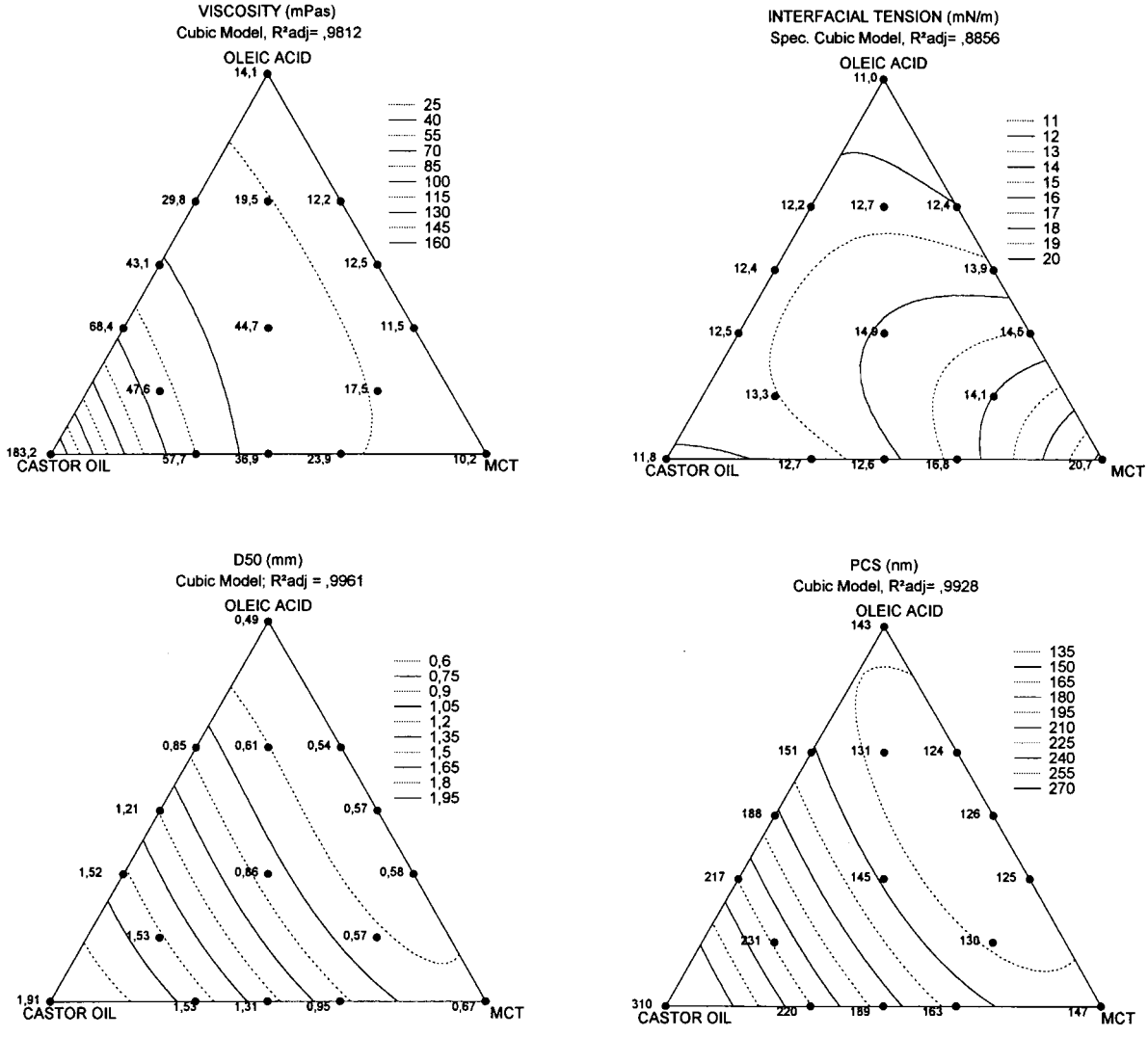

Fig. 1. Contour plot of the mixture consisting of castor oil, MCT and oleic acid.

Table 1

Results of the ternary mixture

Cast oil	MCT	3rd oil	Oleic acid						Oleic acid oleylester						Oleic alcohol					
			IFT (mN/m)	Visco (mPas)	D50 (μm)	D99 (μm)	D_{max} (μm)	PCS (nm)	IFT (mN/m)	Visco (mPas)	D50 (μm)	D99 (μm)	D_{max} (μm)	PCS (nm)	IFT (mN/m)	Visco (mPas)	D50 (μm)	D99 (μm)	D_{max} (μm)	PCS (nm)
0.00	0.00	1.00	10.8	14.6	0.48	1.12	1.5	140	15.8	12.9	0.70	1.59	1.8	159	8.8	26.6	0.84	1.95	2.5	147
0.00	0.00	1.00	11.2	13.5	0.50	1.14	1.5	146	14.9	13.4	0.72	1.64	1.8	160	9.4	25.8	0.83	1.90	2.5	150
0.00	0.33	0.67	12.7	12.3	0.54	1.29	1.5	123	15.2	11.6	0.71	1.63	1.8	153	9.8	17.6	0.71	1.64	1.8	120
0.00	0.33	0.67	12.2	12.1	0.53	1.23	1.5	125	15.8	12.6	0.70	1.60	1.8	154	10.1	16.3	0.70	1.60	1.8	127
0.00	0.50	0.50	14.1	12.3	0.56	1.38	1.5	126	16.2	11.4	0.72	1.65	1.8	152	10.9	17.3	0.62	1.46	1.8	124
0.00	0.50	0.50	13.7	12.8	0.57	1.37	1.5	124	17.6	11.6	0.72	1.64	1.8	153	11.6	16.5	0.61	1.45	1.8	122
0.00	0.67	0.33	14.3	11.8	0.57	1.41	1.8	126	17.2	11.3	0.71	1.60	1.8	152	11.2	12.9	0.62	1.46	1.8	121
0.00	0.67	0.33	14.7	11.3	0.59	1.39	1.8	123	16.8	11.1	0.70	1.59	1.8	150	10.8	12.1	0.64	1.48	1.8	125
0.00	1.00	0.00	21.2	10.1	0.68	1.53	1.8	149	21.2	10.1	0.68	1.53	1.8	149	21.2	10.1	0.68	1.53	1.8	149
0.00	1.00	0.00	20.3	10.3	0.66	1.53	1.8	144	20.3	10.3	0.66	1.53	1.8	144	20.3	10.3	0.66	1.53	1.8	144
0.17	0.17	0.67	12.8	19.4	0.61	1.45	1.5	132	14.8	16.3	0.82	1.79	2.1	161	10.4	36.0	0.69	1.58	1.8	131
0.17	0.17	0.67	12.6	19.6	0.60	1.41	1.5	129	14.2	16.5	0.81	1.76	2.1	158	9.9	34.9	0.68	1.54	1.8	133
0.17	0.67	0.17	14.3	17.3	0.56	1.39	1.8	126	16.1	15.2	0.78	1.72	2.1	154	14.6	20.1	0.68	1.54	1.8	135
0.17	0.67	0.17	14.0	17.8	0.57	1.44	1.8	133	15.9	14.4	0.78	1.72	2.1	154	14.8	18.9	0.67	1.50	1.8	137
0.33	0.00	0.67	11.9	30.1	0.85	1.91	3.6	152	14.4	22.9	1.03	2.41	3.0	155	10.1	37.7	0.83	2.10	3.6	150
0.33	0.00	0.67	12.7	29.6	0.84	1.85	3.6	150	14.8	22.6	1.04	2.40	3.0	161	9.9	38.7	0.86	2.20	3.6	160
0.33	0.33	0.33	15.0	45.0	0.86	2.03	3.6	146	14.5	22.7	0.85	1.96	3.6	150	10.6	23.7	1.05	2.42	3.0	154
0.33	0.33	0.33	14.8	44.5	0.85	2.00	3.6	144	14.1	21.3	0.86	1.95	3.6	149	9.5	23.2	1.05	2.42	3.0	153
0.33	0.67	0.00	16.5	24.1	0.95	2.13	3.6	165	16.2	24.1	0.95	2.13	3.6	165	16.5	24.1	0.95	2.13	3.6	165
0.33	0.67	0.00	17.1	23.7	0.94	2.08	3.6	162	16.8	23.7	0.94	2.08	3.6	162	17.1	23.7	0.94	2.08	3.6	162
0.50	0.00	0.50	12.5	43.7	1.20	2.88	3.6	184	13.0	30.1	1.30	3.00	3.6	203	9.7	53.3	1.19	2.67	3.6	207
0.50	0.00	0.50	12.2	42.5	1.19	2.87	3.6	192	13.4	30.9	1.27	2.96	3.6	195	10.6	52.8	1.21	2.71	3.6	202
0.50	0.50	0.00	12.5	36.5	1.32	3.00	3.6	193	12.6	36.5	1.32	3.00	3.6	193	11.8	36.5	1.32	2.98	3.6	193
0.50	0.50	0.00	12.7	37.2	1.29	2.95	3.6	185	11.8	37.2	1.29	2.95	3.6	185	12.5	37.2	1.29	2.95	3.6	185
0.67	0.00	0.33	12.6	68.1	1.51	3.82	5.0	214	13.1	48.2	1.59	3.87	5.0	219	10.3	69.5	1.62	4.48	6.0	222
0.67	0.00	0.33	12.5	68.7	1.52	3.80	5.0	221	12.5	47.5	1.56	3.80	5.0	226	9.9	67.8	1.65	4.60	6.0	216
0.67	0.17	0.17	13.1	48.3	1.54	3.71	5.0	233	13.5	45.3	1.58	3.85	5.0	223	12.9	59.8	1.37	3.27	4.2	203
0.67	0.17	0.17	13.4	46.9	1.52	3.70	5.0	229	12.9	44.5	1.56	3.82	5.0	210	13.1	58.1	1.37	3.27	4.2	195
0.67	0.33	0.00	12.9	57.1	1.52	3.57	5.0	223	13.2	57.1	1.52	3.57	5.0	223	13.1	57.1	1.52	3.57	5.0	223
0.67	0.33	0.00	12.5	58.2	1.54	3.58	5.0	219	12.5	58.2	1.54	3.58	5.0	219	12.5	58.2	1.54	3.58	5.0	219
1.00	0.00	0.00	12.0	188.5	1.89	7.10	8.6	307	12.0	188.5	1.89	7.10	8.6	307	12.0	188.5	1.89	7.10	8.6	307
1.00	0.00	0.00	11.6	177.8	1.91	7.19	8.6	312	11.6	177.8	1.91	7.19	8.6	312	11.6	177.8	1.91	7.19	8.6	312

2.3. Measurements

The mean particle size of the emulsions was measured by photon correlation spectroscopy using laser light scattering (Malvern spectrometer RR102, Malvern, UK; with Helium-Neon laser λ = 632.8 nm, Siemens, Nürnberg, Germany). The volume distribution of particle size was determined by the use of a laser diffractometer (HELOS, Sympatec, Clausthal-Zellerfeld, Germany) with 20 mm lens. The emulsions were characterized by their D50, D99 and D_{max}, that means 50%, 99% or all the particles (D_{max}) are below the given size. The ζ potential was measured by ZetaSizer 3 (Malvern Instruments, Malvern, UK) using double distilled water with a conductivity of 50 μS/cm. The viscosity of the oil mixtures was measured by an Ubbelohde capillary viscosimeter (Schott, Hofheim, Germany) and the interfacial tension was measured by an electronic tensiometer (K122, Krüss, Hamburg, Germany) employing the plate detachment method. Viscosity and interfacial tension measurements were carried out at a temperature of 40°C corresponding to the homogenization temperature.

2.4. Experimental design

The influence of the oil mixtures on the emulsion formulation was studied using a simplex lattice design with constraints. Binary and ternary terms were used with respect to the oil phase. The composition of the oil phase varied according to Fig. 1. The ternary systems used containing castor oil, MCT and/or oleic alcohol and oleic acid oleylester, respectively. The composition of the oils mixtures in each system is summarized in Table 1. The ratios of water (78%), surfactant (2%) and oil phase (20%) in the formulation were kept constant. Each of the 16 formulations of a trial was produced twice in order to estimate the precision of the production method. The mean particle size and the 50% and 99% quantile of the particle size distribution were used as yield values.

The trials with binary oil phases were characterized by the same parameters before and after autoclaving. Additionally the ζ potential of the emulsions was determined before and after autoclaving.

2.5. Statistical evaluation of ternary mixtures

The results were evaluated using the Program Statistica (Version 5, StatSoft, USA-Tulsa). The results were analyzed according to ternary mixture models of increasing complexity: linear, quadratic, special cubic and cubic model [15]. All four models were fitted stepwise to the 32 results for one yield value. The most simple model which describes the results adequately was chosen for graphical representation. Model selection is based on the significant contribution of the coefficients for the different models.

3. Results and Discussion

3.1. Ternary mixtures

The results for the ternary mixtures are presented in Table 1. Contour plots for the three systems containing oleic acid, oleic alcohol and oleic acid oleylester as third oil component are presented in Figs. 1–3. For each experiment plots of the appropriate model for viscosity, interfacial tension (mN/m) and particle size (PCS and D50) are given. The results for D99 and D_{max} are not shown, because these variables are highly correlated with D50 ($r > 0.93$, $P < 0.001$) in all cases. The value for R^2_{adj} is very high for all contour plots indicating a good description of the experimental results.

For all three ternary mixtures the particle size (D50 and PCS) increased with the fraction of castor oil. The dominating effect of castor oil is also evident from the pattern in the contour plots. The contour plots for viscosity show a similar pattern while the plot for interfacial tension is substantially different. From these results it can be suggested that the viscosity of the ternary mixture is the dominating factor determining the particle size. The interfacial tension between the oil mixture and water is less important. These statements are only valid if the whole factor space is eval-

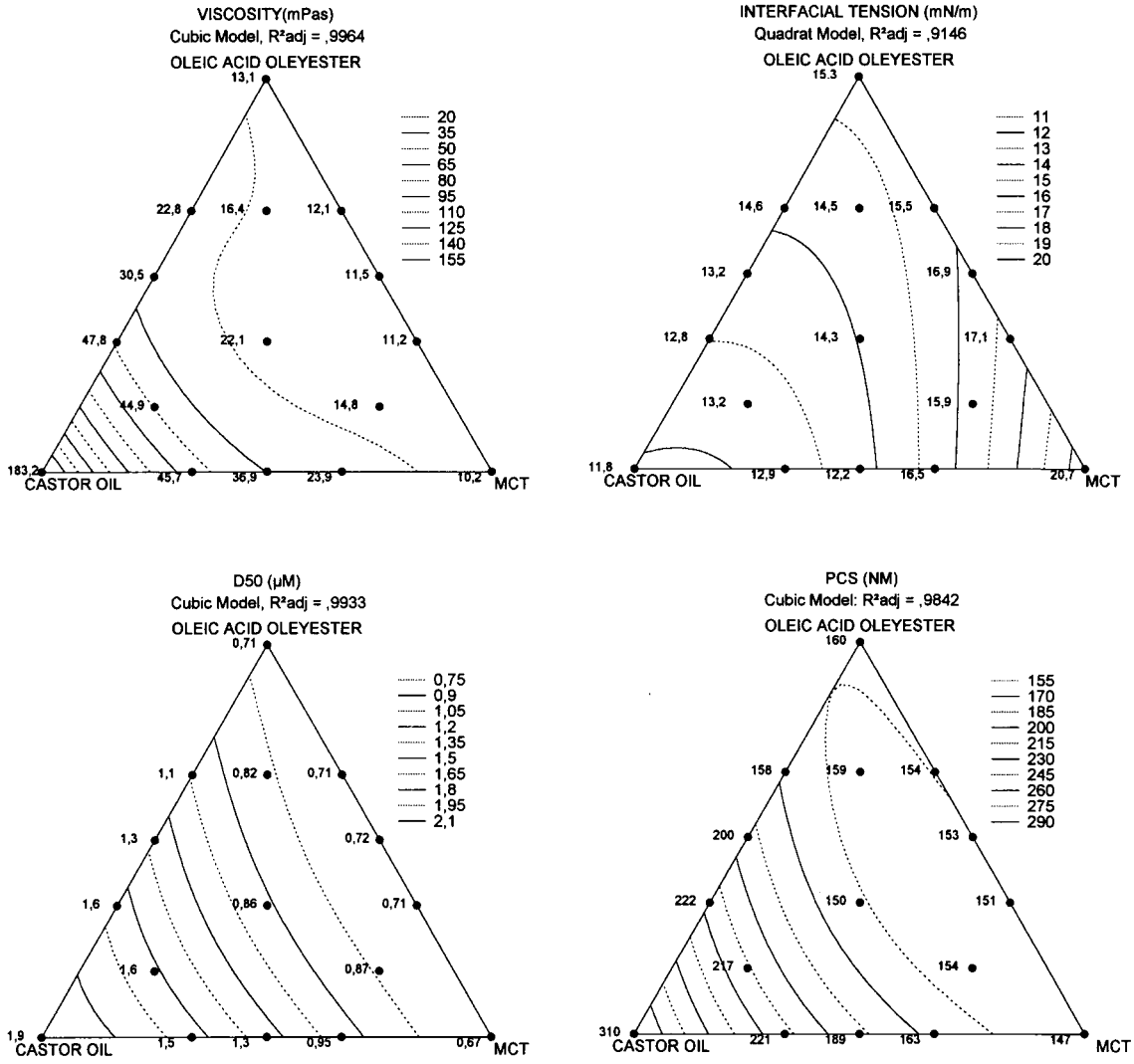

Fig. 2. Contour plot of the mixture consisting of castor oil, MCT and oleic acid oleylester.

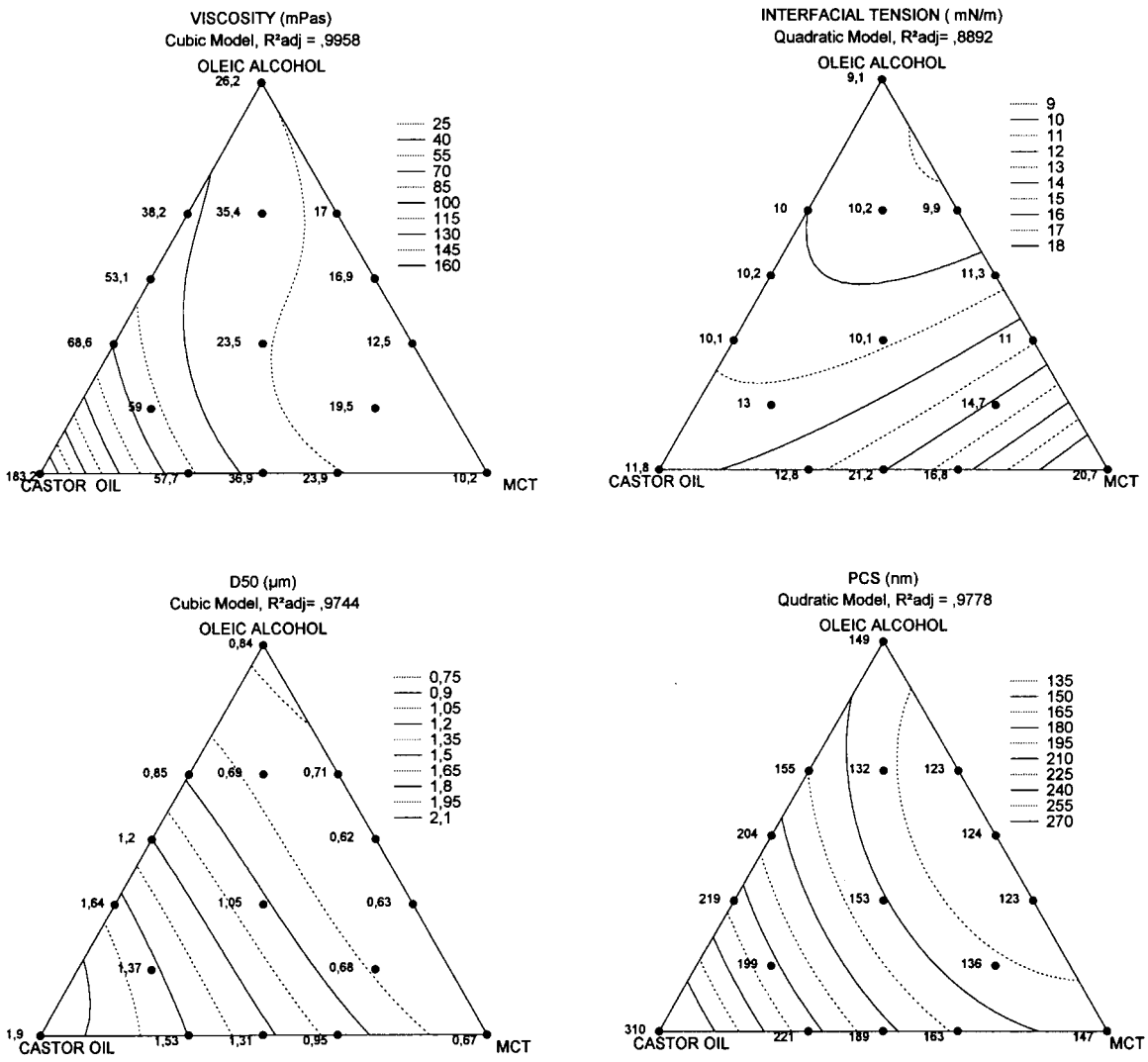

Fig. 3. Contour plot of the mixture consisting of castor oil, MCT and oleic alcohol.

uated. The viscosity of the ternary mixtures is almost dependent on the fraction of castor oil in the mixture. An increasing fraction of castor oil results in a higher viscosity of the oil mixture and in a larger particle size of the emulsion in all three systems studied. The reason for this behavior can be attributed to the factor space: the viscosity varies between 10 and 180 mPas (factor 18) while the interfacial tension differs between 9 and 21 (factor 2.33).

If only binary mixtures without castor oil are analyzed an influence of the viscosity on the particle size is no longer dominant. The three systems behave in different manners. The 30 results for binary mixtures without castor oil show a significant correlation between interfacial tension and viscosity ($r = -0.719$). Thus the particle size of these systems cannot be attributed to a single physico-chemical property. An increase in viscosity can be compensated by a decrease in interfacial tension with respect to the particle size of the emulsion.

The lowest particle sizes determined by PCS were obtained for the systems with oleic acid and oleic alcohol. The lowest values for D50, however, were obtained for the system containing oleic acid. A binary mixture of oleic acid with MCT (2:1) resulted in the emulsion with the smallest particle size. The binary mixtures with oleic acid and MCT obeyed a low interfacial tension and a low viscosity, simultaneously. The respective mixtures with oleic alcohol exhibited a higher viscosity while those with oleic acid oleylester showed a higher interfacial tension. Both factors had an influence on the particle size.

Emulsions with particle size suitable for parenteral administration can be produced with Synperonic F68 as emulsifier. This was possible by the use of binary mixtures of oleic acid with MCT. Binary mixtures of oleic alcohol/MCT and oleic acid oleylester/MCT were inferior. The addition of castor oil led to the formation of coarser emulsions due to its high viscosity. The stability of the emulsions during autoclaving will be studied in a second part of this paper.

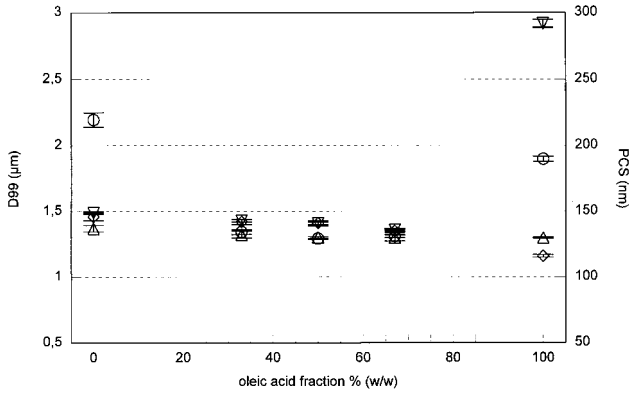

Fig. 4. Effect of the oleic oil fraction on the particle size before and after sterilization (◇, D99 before sterile; ▽, D99 after sterile; △, PCS before sterile; ○, PCS after sterile).

3.2. Binary mixture

Emulsions are thermodynamically unstable systems. In addition, the application of heat required during the sterilization process often accelerates the degradation of an emulsion system.

By using a mixture consisting of MCT with either oleic acid or oleic alcohol, different formulations were investigated to produce a stable emulsion which can pass the autoclaving process without changes in the physical stability in terms of particle size. As shown in Fig. 4, emulsions containing MCT or oleic alcohol either as single oil phase or in mixtures showed a great increase in the mean particle size as well as in the particle size distribution (D99). However, emulsions consisting of MCT and oleic acid in the range of 33% to 67% (w/w) showed no changes before and after autoclaving (Fig. 5).

As can be expected from the results with ternary mixtures, the two components (oleic acid and oleic alcohol) led to a noticeable decrease in the interfacial tension. Thus, the stability of oleic acid emulsions cannot be correlated to the interfacial properties only.

The presence of oleic acid leads to more negative ζ potential due to an accumulation of the negatively charged ionized carboxy groups on the interface resulting in a higher resistance to coalescence of the oil droplets [5,13]. As illustrated in Fig. 6, an addition of oleic acid led to a great increase in negative ζ potential, while the presence of the oleic alcohol resulted in a negligible change. The adjustment of the pH-values with sodium hydoxide induced the formation of sodium oleate which can act an as additional stabilizing factor [16].

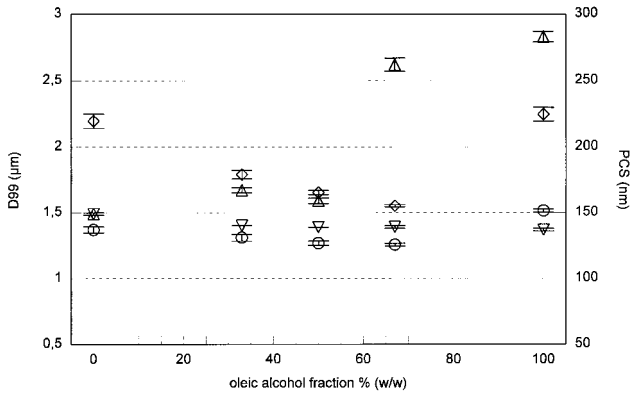

Fig. 5. Effect of the oleic alcohol fraction on the particle size before and after sterilization (□, D99 before sterile; △, D99 after sterile; ○, PCS before sterile; ◇, PCS after sterile).

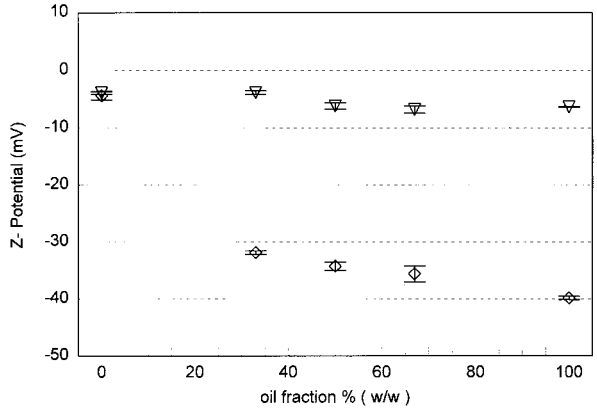

Fig. 6. Effect of the oil fraction on the ζ-potential (◇, oleic acid; ▽, oleic alcohol).

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