Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University, Kiel, Germany

Parameters with influence on the droplet size of w/o emulsions

K. Lindenstruth, B. W. Müller

Received July 19, 2003, accepted August 21, 2003

Prof. Dr. h.c. B. W. Müller, Department of Pharmaceutics and Biopharmaceutics, Kiel University, Gutenbergstraße 76, 24118 Kiel, Germany
bwmueller@pharmazie.uni-kiel.de

Pharmazie 59: 187–190 (2004)

The aim of this study was to show that for w/o emulsions a modulation of components and parameters is necessary. Therefore several w/o emulsions were produced according to a 2^4 factorial design to get the information that pressure and temperature as production parameter have less influence on the droplet size than the substance components olive oil and lecithin. Furthermore an interaction between surfactant and oil component was observed which resulted in an increase of droplet size. With the following experiments the interfacial tension and the viscosity as physicochemical parameters were determined but gave no explanation for the phenomenon of an increasing droplet size if olive oil and lecithin are part of the formulation. So the influence of substance components was examined in more detail with the successive addition of oleic acid or oleyl alcohol to MCT and due to this the presence of unsaturated substances in olive oil could be determined as a possible reason for interactions with lecithin.

1. Introduction

W/O emulsions as disperse systems contain water droplets in a continuous oil phase and their droplet size and distribution are important criteria which describe the formulation quality. To prevent signs of instability an appropriate production process and the right composition of oil and surfactant phase has to be chosen.

For lipid emulsions many studies have investigated the production parameter (Bock et al. 1994, Bock 1994, Lucks 1993, Takamura et al. 1983) or have shown the influence of substance components on the emulsion quality (Buszello et al. 2000, Buszello 1998, Jumaa et al. 1998 a–c, Muchtar et al. 1989, Singleton et al. 1962). Some studies also have shown that it is necessary to adapt the production parameters and substance components to one another to avoid a wide distribution of droplet size (Jumaa et al. 1998d, Jumaa 1999). This is necessary for the long term stability in order to prevent coalescence and phase separation. For the formulation of emulsions with fine dispersity and acceptable stability several factors have to be considered. At first a division in substance components and production parameters is possible. Substance components could be grouped into oil component, water phase and the surfactants which are necessary to build a stable interfacial film and reduce the interfacial tension between the two non-miscible phases. Only the addition of a suitable emulsifier enables that a fine dispersity after production could be maintained during storage and coalescence could be prevented.

The objective of this study was to investigate parameters which influence the droplet size of w/o emulsions and to show that a modulation of components and parameters is necessary. Furthermore interactions which were observed between surfactant and oil component should be examined and interpreted to gain a better understanding of possible instability reactions.

2. Investigation, results and discussion

The paretodiagram (Fig. 1) shows that the substance components have a significant influence on the droplet size. It also can be shown that the production parameters have less influence than the oil or surfactant component. The addition of lecithin leads to a stronger increase of droplet size than the addition of olive oil. Furthermore interaction between the oil component olive oil and lecithin as surfactant component was observed. This is illustrated by the surface plot in Fig. 2. The plots of the other temperature/pressure combinations are not shown. The aim of the following experiments was to provide an explanation for the observed phenomenon.

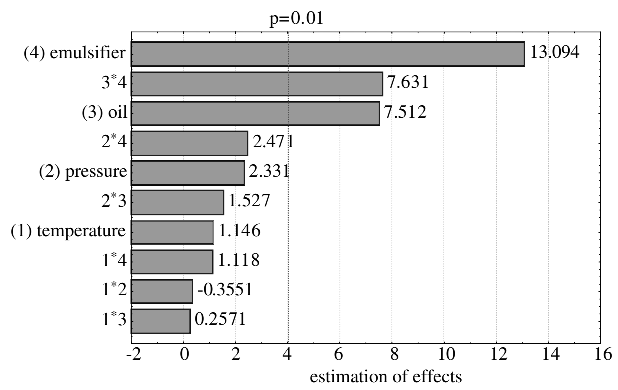

Fig. 1: Paretodiagram for D99-values of 2^4 factorial design

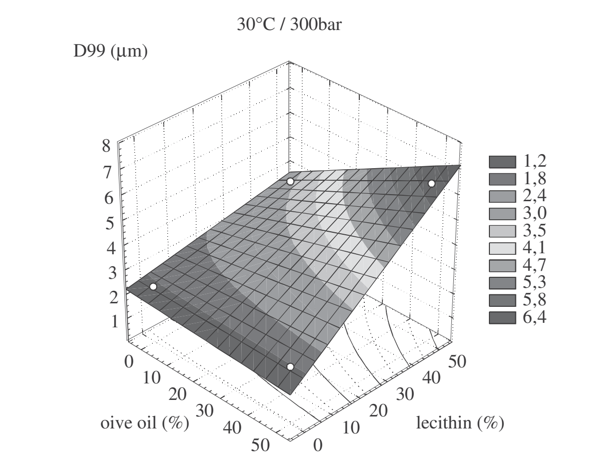

Fig. 2: D99-values at 30 °C and 300 bar

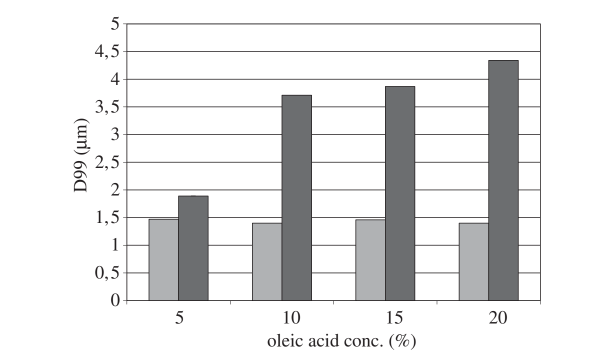

Fig. 4: Influence of oleic acid on the droplet size of w/o emulsions
▪ without lecithin; ▪ with lecithin

The measurement of interfacial tension for the samples without surfactant resulted for MCT in a value of 25.81 mN/m. For olive oil the lowest value was observed (13.15 mN/m) and the interfacial tension of the binary mixture MCT/olive oil gave a value between the single components (18.56 mN/m). This indicates that different oil phases influence the interfacial tension. The interfacial tension of the samples with surfactant showed no difference if Cremophor WO7 was used alone, the surfactant mixture consisting of Cremophor WO7 and Epikuron 105 was used or half of MCT was substituted by olive oil. All values were below 0.2 mN/m. It could be shown that the presence of lecithin and olive oil does not result in an increase of interfacial tension, but the measurement of droplet size shows significantly higher values if both components are present. So a correlation between droplet size and interfacial tension could not be observed and this physico-chemical parameter gives no explanation for the observed phenomenon. Further experiments were carried out to determine the viscosity of the oil/surfactant mixtures. Fig. 3 shows that the addition of Cremophor WO7 to several oil components results in an increase of viscosity. After replacing 50% of Cremophor WO7 against lecithin, the viscosity only increases slightly in comparison to the oils without surfactant. An explanation of the interaction phenomenon illustrated in Fig. 2 was not obtained because it was expected that the simultaneous presence of lecithin and olive oil leads to an increase in viscosity. This could be explained as follows: during the emulsifying process the energy is not high enough to obtain water droplets which are as small as without lecithin or olive oil. It can clearly be shown that in mixtures with Epikuron as lecithin the particle size increases with an addition of olive oil. A correlation between droplet size and viscosity seems to be considerable, as shown in Fig. 2. Regarding only the three right bars in Fig. 3 the given explanation could be true, because with lecithin and olive oil the viscosity is much higher than without olive oil. However, the viscosity of the mixtures without lecithin (the three middle bars) shows higher values than if lecithin is added to the oil/surfactant mixture. So also the viscosity gave no correlation to the droplet size and the explanation is not valid.

Hence, other factors which promote the rise of water droplet diameter should be considered. The phenomenon of increasing values of droplet size was visible only if olive oil and lecithin were used. Without one of these components the described effect was not seen.

So the chemical composition of olive oil with regard to its fatty acids was examined. The composition of olive oil as a nature product in comparison to MCT is heterogeneous regarding the fatty acids. Olive oil as a vegetable oil consists of 74% of oleic acid (Lamotte 2000). The acid value of 0.34 shows that oleic acid can be found as free fatty acid in olive oil but also in esterified form. The influence of oleic acid on the droplet size should be considered in the following experiments. Therefore several emulsions with increasing concentrations of oleic acid added to MCT were produced. The emulsifier Cremophor was used alone or in binary mixture with Epikuron. The production parameters were kept constant at 45 °C und 500 bar.

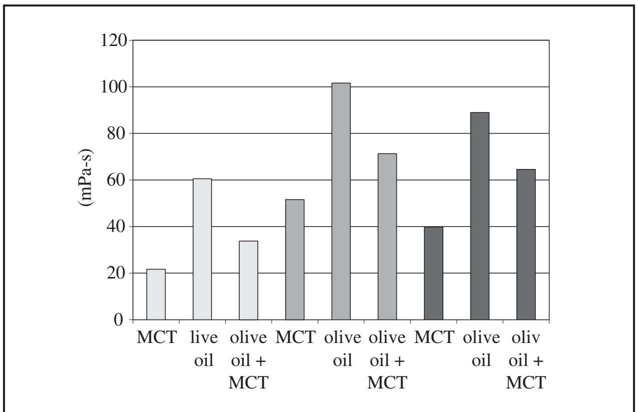

Fig. 3: Determination of viscosity
□ without surfactant; ▪ with Cremophor; ▪ with Cremophor and lecithin

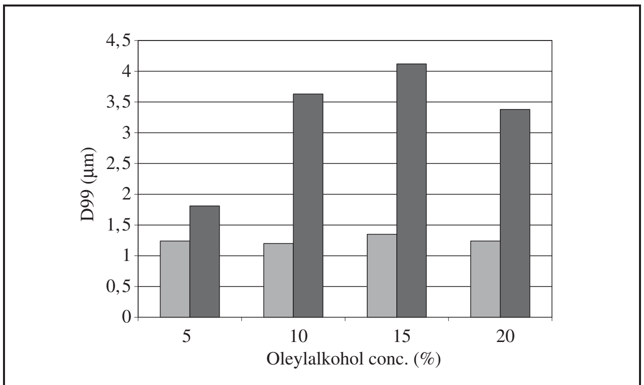

Fig. 5: Influence of oleyl alcohol on the droplet size of w/o emulsions
▪ without lecithin; ▪ with lecithin

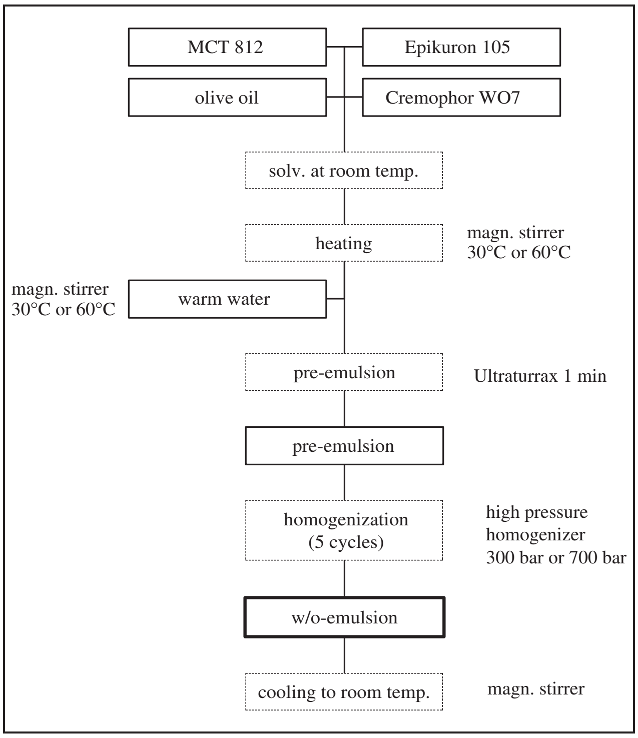

Fig. 6: Flow-chart of production process

Fig. 4 shows the produced droplet sizes expressed as D99 values and it is obvious that increasing concentrations of oleic acid lead to larger droplets when lecithin exists in the formulation. Oleic acid is a single unsaturated fatty acid. Due to its double bond the required space is higher and the liquid-cystalline emulsifier film of lecithin is disturbed. In the absence of lecithin an increase in droplet size could not be observed. To examine the influence of the double bond, the experimental conditions were kept constant but oleyl alcohol was used instead of oleic acid and a series of emulsions was produced. Oleyl alcohol has a similar structure to oleic acid but no acid function. So ionic interactions between lecithin and oleyl alcohol can be ruled out. The results in Fig. 5 show a similar trend of increasing droplet size as with oleic acid in Fig. 4. If lecithin is not part of the surfactant component, the size of water droplets stays constant with increasing concentrations of oleyl alcohol.

With an acid value of 0.34 not only the free fatty acid in olive oil would be the reason for the phenomenon described. The addition of 20% glycerolmonooleat shows values of droplet size (D99) of about 4 µm. Such substances could also have an influence and act as cosurfactants. This was shown by the measurements of interfacial tension. The samples without surfactant showed lower values of droplet size if olive oil was part of the oil component. If lecithin and Cremophor were used the effect was covered. However, an interaction of the additional substances at the interface oil/water is considerable and the described results confirm the hypothesis that unsaturated components in olive oil, free or esterified, prevent the formation of a uniform film of lecithin at the interface oil/water.

In conclusion, this study shows that the experimental design is suitable for evaluating the parameters which influence the emulsifying process. It was shown that the substance components display a stronger effect compared to the production parameters. Furthermore it could be shown that it is necessary to combine only oil components and surfactant components which do not interact, because this will lead to an increase in droplet size and may also cause coalescence and phase separation. Such an interaction between surfactant layer and oil component was shown with unsaturated fatty acids e.g. oleic acid. A correlation between the droplet size and an increasing concentration of oleic acid was observed, due to the fact that the unsaturated compound has a negative influence in the structure of the surfactant film. As a consequence unsaturated components in an oil phase should be avoided if a dispersed phase with small droplet sizes is needed e.g. after the first emulsification step for the production of multiple emulsions.

3. Experimental

3.1. Materials

Miglyol® 812 (MCT) was supplied by Condea Chemie GmbH (Witten, Germany) and olive oil was provided by Henry Lamotte (Bremen, Germany). Cremophor®WO7, a hydrogenated castor oil which has 7 mol ethylene oxide added to it, was obtained from BASF AG (Ludwigshafen, Germany) and the soya lecithin Epikuron®105 was obtained from Lucas Meyer GmbH (Hamburg, Germany). Oleic acid was purchased from Merck KGaA (Darmstadt, Germany) and oleyl alcohol was obtained from Cognis GmbH (Düsseldorf, Germany). Glycerolmonooleat was purchased from Fluka Chemie GmbH (Buchs, Switzerland). Double distilled water was used.

3.2. Methods

3.2.1. Emulsion preparation

The emulsions were prepared using 30% water phase and 70% oil phase containing 20% of the lipophilic surfactant. Both phases were heated separately, mixed after reaching the production temperature and then pre-emulsified using an Ultra-Turrax T25 (Janke & Kunkel, Staufen, Germany) for 1 min. Finally this preliminary emulsion was submitted to a high pressure homogenizer (Micron Lab 40, APV Gaulin, Lübeck, Germany). The following flow-chart describes the way of production (Fig. 6)

3.2.2. Emulsion characterization

The emulsions were characterized by a laser diffraction analyzer (HELOS, Sympatec, Clausthal, Germany) with a 20 mm lens which permits a detection of particles between 0.18 and 35 µm. For the determination of viscosity an Ubbelohde capillary viscosimeter (Schott, Hofheim, Germany) was used and the oils alone, the oil mixtures and the oil/surfactant mixtures as well were examined. The same samples were analyzed with an electronic tensiometer K122 (Krüss, Hamburg, Germany) employing the Wilhelmy plate method to measure the interfacial tension.

3.2.3. Experimental design

A 2^4 factorial design was used to investigate the parameters which have an influence on droplet size. The test arrangement can be described as follows: as production parameters the temperature was varied between 30 and 60 °C and for the pressure, values of 300 and 700 bar were chosen. The oil phase as third factor consisted of MCT alone or MCT + olive oil in a binary mixture (1 + 1). As surfactant, Cremophor®WO7 alone or in mixture with Epikuron®105 (1 + 1) was used. The concentrations used and the phase ratio were left constant. For the statistical analysis the program Statistica® was used.

References

Bock T (1994) Emulsionen als parenterale Arzneistoffträger – Herstellung, Charakterisierung und Optimierung. Ph.D. thesis, Kiel.

Bock TK, Lucks JS, Kleinebudde P, Müller RH, Müller BW (1994) High pressure homogenisation of parenteral fat emulsions – influence of process parameters on emulsion quality. Eur J Pharm Biopharm 40: 157–160.

Buszello K (1998) Grenzflächenmodifikationen von O/W Emulsionen als potentielle Trägersysteme für ein Drug Targeting. Ph.D. thesis, Kiel.

Buszello K, Harnisch S, Müller RH, Müller BW (2000) The influence of alkali fatty acids on the properties and the stability of parenteral o/w emulsions modified with solutol HS 15. Eur J Pharm Biopharm 49: 143–150.

Jumaa M, Kleinebudde P, Müller BW (1998a) Mixture experiments with the oil phase of parenteral emulsions. Eur J Pharm Biopharm 46: 161–167.

Jumaa M, Müller BW (1998b) Influence of the non-ionic surfactant PEG-660-12-hydroxy stearate on the surface properties of phospholipid monolayers and their effect ionic lipid emulsion stability. Colloid Polym Sci 277: 347–353.
Jumaa M, Müller BW (1998c) The stabilization of parenteral fat emulsion using non-ionic ABA copolymer surfactant. Int J Pharm 174: 29–37.
Jumaa M, Müller BW (1998d) The effect of oil components and homogenization conditions on the physicochemical properties and stability of parenteral fat emulsions. Int J Pharm 163: 81–89.
Jumaa M (1999) Wirkstoffhaltige Fettemulsionen zur parenteralen Applikation. Ph.D. thesis, Kiel.
Lamotte (2000) Analytical specification of olive oil. Bremen, Germany.
Lucks JS (1993) Parenterale Fettemulsionen als Arzneistoffträger – Herstellung, Charakterisierung und Stabilität. Ph.D. thesis, Kiel.
Muchtar S, Jacobs GP, Benita S (1989) Intravenous fat emulsion. Tenside Surf Det 26: 347–351.
Singleton WS, White JL, DiTrapani LL, Brown ML (1962) An emulsifier system for experimental intravenous fat emulsions. J Amer Oil Chem Soc 39: 260–263.
Takamura A, Ishii F, Noro S, Koishi M (1983) Effect of homogenization conditions on the physicochemical properties of emulsion bases. Chem Pharm Bull 31: 2786–2792.