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# Surfactant-Free O/W-Emulsion as Drug Delivery System

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***Abstract*—**Most of the drugs used for pharmaceutical purposes are poorly water-soluble drugs. About 40% of all newly discovered drugs are lipophilic and the numbers of lipophilic drugs seem to increase more and more. Drug delivery systems such as nanoparticles, micelles or liposomes are applied to improve their solubility and thus their bioavailability. Besides various techniques of solubilization, oil-in-water emulsions are often used to incorporate lipophilic drugs into the oil phase. To stabilize emulsions surface active substances (surfactants) are generally used. An alternative method to avoid the application of surfactants was of great interest. One possibility is to develop O/W-emulsion without any addition of surface active agents or the so called "surfactant-free emulsion or SFE". The aim of this study was to develop and characterize SFE as a drug carrier by varying the production conditions. Lidocaine base was used as a model drug. The injection method was developed. Effects of ultrasound as well as of temperature on the properties of the emulsion were studied. Particle sizes and release were determined. The long-term stability up to 30 days was performed. The results showed that the surfactant-free O/W emulsions with pharmaceutical oil as drug carrier can be produced.

***Keywords*—**Emulsion, lidocaine, Miglyol, size, surfactant, light scattering, release, injection, ultrasound, stability.

## I. Introduction

THE numbers of the poorly water-soluble drugs in pharmaceutical filed constantly increase. About 40% of all newly discovered drugs are lipophilic [1]. Drug delivery systems such as nanoparticles, micelles or liposomes are necessary to improve their solubility and thus their bioavailability. Besides various techniques of solubilization, oil-water-emulsions are often used to incorporate lipophilic drugs into the oil phase. If the oil droplets are small enough (2-5 µm), particles are able to permeate through the gastrointestinal barrier [2]. To stabilize emulsions surface active substances (surfactants) are generally used. Surfactants are of biological or synthetic origin. Polysorbates are widely used to stabilize pharmaceutical or cosmetic carrier system. An alternative to the use of surfactants is the formation of O/W-emulsion without any addition of surface active agents [3].

The surfactant-free emulsion or SFE was already developed by other researchers [4]-[6] but those emulsions were mostly used in other fields and not as drug delivery systems.

One of the suitable production methods is shown to be ultrasound [4]. It was used to disperse oil in water and stabilize the surfactant-free emulsion (SFE).

The aim of this study was to produce and characterize SFE as drug carrier system by varying the production conditions, measuring the long-term stability and the delivery of incorporated lidocaine base as a model drug. To produce different emulsions a 20 kHz lab scale ultrasonic device was used.

## II. Materials and Methods

The neutral oils Miglyol 810N und 829 (Sasol GmbH, Germany) were used as a disperse phase (Figs. 1 (a), (b)). De-ionized water was delivered by a lab device. Lidocaine base was purchased from a company (Fagron GmbH, Germany). Emulsions were formed by using an ultrasonic device Sonoplus HD operating with a sonotrode MS 73 (Bandelin GmbH, Germany). A total volume of 5 ml dispersion containing 0.25-2.0%v/v oil was sonicated for various times at generator power of 12.2 W.

The size of the emulsion droplets was measured by static laser light scattering method (Mastersizer S, Malvern, UK) and calculated on the basis of the volume (D4,3) or surface distribution (D3,2).

The calibration curve for the solubility of lidocaine base in water was determined by diluting a basic solution to concentration between 0.1 and 0.5 mg/ml and measuring the absorption at 263 nm. The chemical structure of lidocaine base was shown in Fig. 1 (c). Lidocaine base has a molecular weight of 234.34 g/mol, pKa of 8.01, and water solubility of 4.1 g/L.

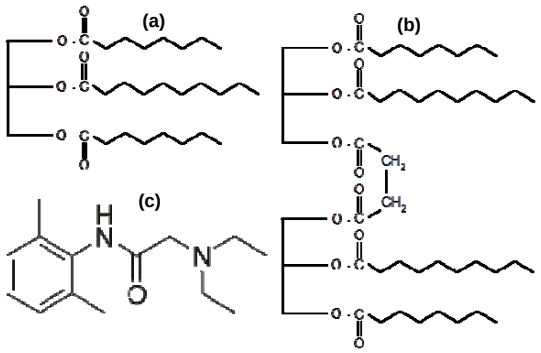


Fig. 1 The chemical structure of (a) Miglyol 810N, (b) Miglyol 829, (c) lidocaine base

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Lidocaine base was dissolved in the oil phase before emulsification. Aliquots of 200 mg Lidocaine base were dissolved in 10 ml of oil with a magnetic stirrer at 40°C for 30 min. The solution was cooled down to room temperature and the solution was checked for crystals by naked eyes.

The Nernst distribution constant of lidocaine between Miglyol and water was determined by covering a solution of 225 mg/ml lidocaine base in oil with water. After 48 h the amount of lidocaine in water was measured by an UV-spectrometer (V630, Jasco, Germany).

The release of lidocaine from O/W emulsion was studied by using the dialysis method. Aliquots of the emulsion (5 ml) were poured into a dialysis tubing (10,000 cut-off). The tube containing emulsion was put into the vessel of a standard dissolution tester with baskets and sealed (PT-DT70 Pharmatest, Hainburg, Germany) and 400 ml water was used as a release medium. The setup of this method was shown in Fig. 2. The kinetics of release was automatically measured.

All presented data are the mean of at least three measurements.

Fig. 2 Setup of the release test using dialysis tube and dissolution tester

## III. Results and Discussion

### A. Solubility of Lidocaine Base in Miglyol

The fit of the calibration curve (absorbance between 0.1 and 0.9) with the equation "y = 2.0884x - 0.0238" for lidocaine base soluble in de-ionized water showed a good correlation coefficient of $R^2 = 0.9985$ (Fig. 3). The slope was used to determine the lidocaine concentration in water.

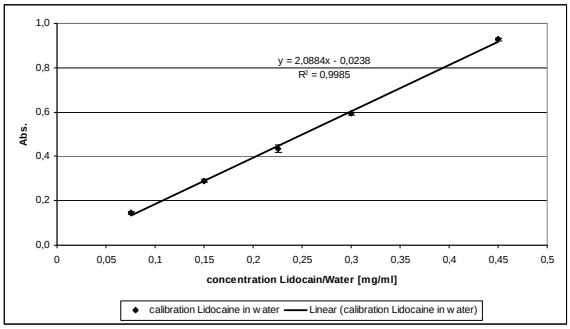


Fig. 3 Calibration curve of lidocaine base in water

The saturation point of lidocaine base in oil Miglyol at room temperature was about 290 mg/ml. According to Nernst distribution law the distribution constant oil-water was calculated to be 58 ± 1. From this result only a small UV signal was expected during tests of release.

### B. Oil Injection and Energy Input

The results showed that the method of oil injection into the water phase and the energy input to disperse the oil distinctly influence the properties of the emulsion (Fig. 4).

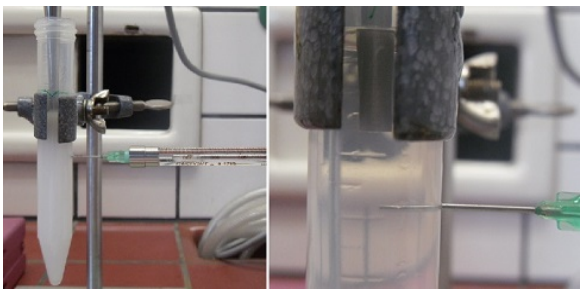

Fig. 4 Oil injection method

Water was poured into a tube and covered with oil (0.5 %v/v). A total volume of 5 ml was sonicated for various times at a generator power of 12.2 W. The particle size (D4,3 and D3,2) reached a plateau within the error of about D4,3 = 2.15 µm and D3,2 = 1.80 µm after 60s (Fig. 5). However, free oil was observed after emulsification. To avoid incomplete homogenization oil was injected by a syringe directly under the tip of the working sonotrode. This method had the highest reproducibility of emulsion formation.

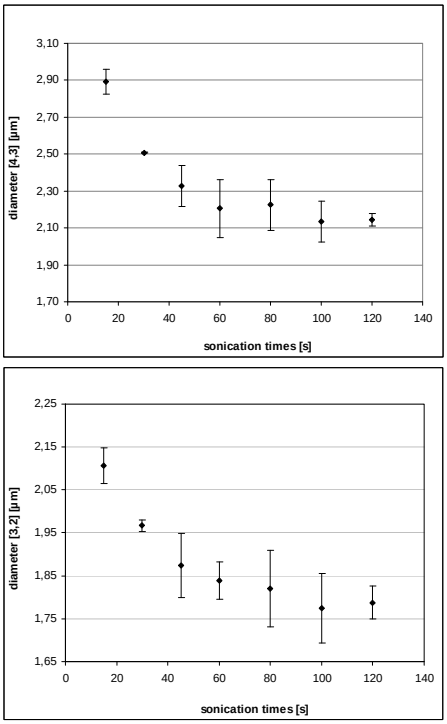


Fig. 5 Particle size distribution (D4,3 and D3,2) in dependence on sonication times

### *C. Oil Concentrations*

The effect of particle size and storage stability of emulsion by the oil concentration was tested at constant energy input of 204 W/ml in a range between 0.25-2.0% oil (Fig. 6). The particle sizes increase if the oil concentrations was increased. The application of the side injection method caused in only slight increase in D3,2 which led to an homogeneous and complete distribution of the oil. Emulsion with 0.75% oil and more were instable over the time. Free oil was already observed after 1 day at room temperature as well as at the lower temperature (refrigerator, 10°C).

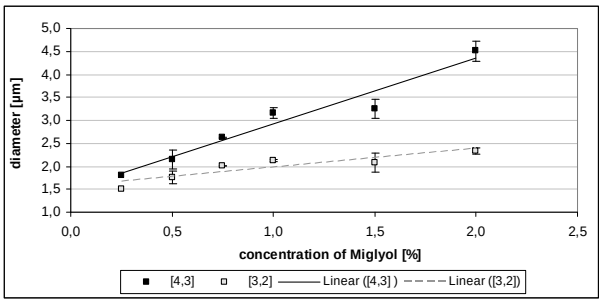


Fig. 6 Particle size distribution in dependence on oil-concentrations

It is interesting to note that the emulsion formation was possible but not stable within 1h when buffer (phosphate buffer at pH 3, 6.8 and 8) was used as a continuous phase. The initial particle size was measured between 4-6 µm (D3,2) and 6-9 µm (D4,3).

A small dependence of the particle size on temperature during homogenization was observed (Table I). The sizes seemed to have a reduction if the temperatures were increased. However, more data are necessary to proof the trend.

TABLE I
PARTICLE SIZE DISTRIBUTION DEPENDENCE ON TEMPERATURES

| Particle size / Temperature | | 35°C | 20°C |
|---|---|---|---|
| D (3,2) | [µm] | 1.76 | 1.82 |
| Standard deviation | [µm] | 0.14 | 0.06 |
| Deviation | [%] | 7.94 | 3,05 |
| D (4,3) | [µm] | 2.16 | 2.28 |
| Standard deviation | [µm] | 0.21 | 0.05 |
| Deviation | [%] | 9.58 | 2.36 |

### *D. Drug Release Test*

The release of lidocaine from emulsion was tested by using the concentration of 224.4 g lidocaine soluble in one liter of oil. The solution was used for emulsification (1% and 2% of disperse phase) at an energy input of 225 W/ml. About 70% of lidocaine was recovered after 200 min of the release test (Fig. 7). An amount of 400 ml water was necessary to cover the dialysis tube. Thus, only a small concentration of lidocaine in water was found and further interpretation of release kinetics by using mathematical model was not possible.

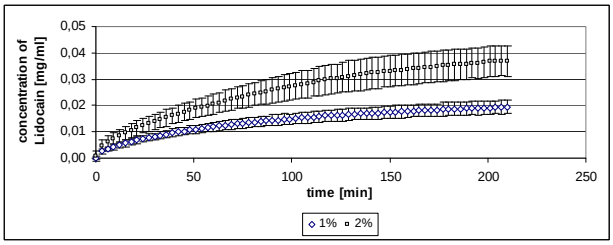


Fig. 7 Release of lidocaine base from emulsions in water

The storage stability of 0.5 and 1.0% lidocaine emulsions (22.4% lidocaine content)) was tested by measuring the particle size for 1 month (Fig. 8). Miglyol 829 seemed to give more stable emulsion and Miglyol 810N seemed to give smaller drop sizes. The particle sizes of these two types of emulsions (0.5 or 1% oil) were constant during 30 days. An addition of the model drug lidocaine base caused in destabilization of the emulsion from Miglyol 810N, especially during the first 7 days after an addition of the drug. However, after this time the particle size seemed to be recovered and stable during 30 days.

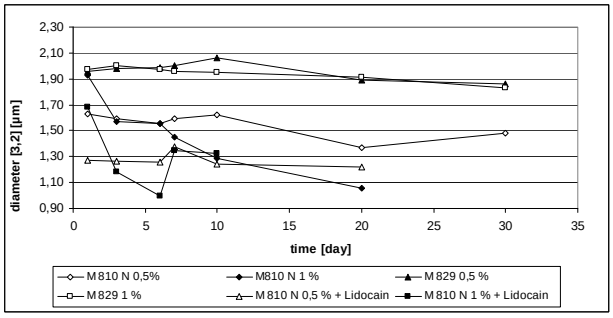


Fig. 8 Particle size during storage up to 30 days

## IV. SUMMARY

The production of O/W emulsion without any addition of the surfactant was possible in the range of 0.5-1% of the disperse oil phase. Moreover, the incorporation of a poorly water soluble drug (lidocaine base) did not influence emulsion properties such as particle size distribution and it has only small influence on the storage stability. Higher oil concentrations (more than 2%) could not be realized because of the particle instability (coalescence). In order to deeply understand the release kinetic the release conditions have to be changed to improve the reproducibility of the data. It is possible to produce the surfactant-free O/W emulsions with pharmaceutical oil as drug carrier. Further studies are in progress to investigate the drug release kinetics and to increase the oil content.

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