ENGINEERING OF CONCENTRATED EMULSIONS AS A DRUG CARRIER SYSTEM FOR PHARMACEUTICAL APPLICATION

Lihong Tong[1,2], Mont Kumpugdee-Vollrath[1], Jens-Peter Krause[1], and Pornsak Sriamornsak[2]

[1]Beuth Hochschule fuer Technik Berlin - University of Applied Sciences, Faculty of Mathematics-Physics-Chemistry, Department of Pharmaceutical Engineering, Luxemburger Str. 10, 13353 Berlin, Germany
[2]Silpakorn University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Pharmaceutical Biopolymer Group (PBiG), Nakhon Pathom 73000, Thailand

Introduction

Emulsions normally contained two phases, i.e. water and oil phases. In order to stabilize the system, some emulsifiers should be added. Different types of emulsions can be prepared, e.g. simple emulsions as well as multiple emulsions. These systems are normally thermodynamic instable. The phase separation can happen during the storage, which is not suitable for using as pharmaceutical products. Many researchers have, therefore, tried to find the more stable systems, e.g. microemulsions, nanoemuslions or nano-structure liquid carrier systems [1]. However, these systems can be mostly prepared by using special equipments, e.g. high pressure homogenizer or high amount of emulsifier should be added. Further disadvantage of the normal emulsions is, because of the high viscosity, they can contain maximal 30% w/w of the dispersed phase. The internal phase can be used as a reservoir for the drug substance to carry it to the target organ. However, if the high amount of drug loading (>30% w/w) is required, the normal emulsion may cause a problem in the step of drug incorporation. Therefore, this project was performed to show the possibility of engineering the oil-in-water (o/w) concentrated emulsions with a higher drug loading capacity (up to 70% w/w) and a good stability by using a natural substance, i.e. plant protein as an emulsifier.

Experimentals

Materials
The semi-synthetic neutral oil (Miglyol 812) was a gift from Sasol, Germany. The model drug was lidocaine base with the chemical formula $C_{14}H_{22}N_2O$ and molecular weight 234.3 g/mol, which was bought from Sigma, Germany. Lidocaine base is a water-insoluble drug and normally used as a local anaesthetic drug. The soybean protein was a gift from Hahn, Germany with 90% protein content. The phosphate buffer pH 8 was prepared after Soerensen [2]. All chemicals were used as received without any purification.

Preparation of Emulsions
In order to prepare the concentrated emulsions, 100 grams of original emulsions (or pre-emulsion) with 30% w/w of Miglyol 812 and 70% w/w phosphate buffer pH 8 were prepared separately using an ultrasonic probe (HD 70, BANDELIN electronic GmbH & Co. KG, Germany) and a high pressure homogenizer (EmulsiFlex-C5, Avestin Europe GmbH, Germany). Soybean protein at the level of 1%, 2% and 3% w/w was applied as a stabilizer. It is important to control a pre-emulsion with the soluble soybean protein at pH 8 in order to get smaller droplets with stable interface protein films. The homogenization time by the ultrasonic probe was 2 min. If the high pressure homogenizer was used, the emulsion was pressed five or eight times through the machine in order to produce the pre-emulsion. The pre-emulsion was centrifuged by a high speed centrifugation machine (Minifuge RF, Heraeus SEPATECH GmbH, Germany) at 5400 min^{-1} for 30 min in order to obtain the concentrated emulsions.

Characterizations of Emulsions
A) Particle size and particles size distribution
The particle size distribution of the pre-emulsion and the concentrated emulsions were determined by a laser light scattering method (Mastersizer-S, Malvern, UK). For this purpose the concentrated emulsions were diluted with 10% w/w sodium dodecyl sulfate (SDS, Carl Roth, Germany). During the measurement with a light scattering method, a 5% w/w SDS was used instead of de-ionized water as the background to avoid the agglomeration between the emulsion-drops.

B) Emulsifying activity index (EAI)
The EAI of soybean protein was measured after the principle of Pearce and Kinsella [3].

The excess amount of the un-adsorbed soybean protein was removed by washing the emulsions many times with phosphate buffer. By this procedure the correct amount of protein for emulsifying the emulsions can be calculated by the following equation.

$$\tau = \frac{2.303 \bullet A \bullet DF}{L} \quad (1)$$

$$EAI = \frac{2 \bullet \tau}{E \bullet 1000 \bullet \varphi} \quad (2)$$

τ = Turbidity
A = Absorption
DF = Dilution factor
L = Thickness of cuvette (1 cm)
EAI = Emulsifying activity index
E = Real amount of emulsifier ($mg.ml^{-1}$)
φ = Amount of oil phase in emulsion ($ml.ml^{-1}$)

C) Dynamic interfacial tension
The interfacial tension of soybean protein against the natural oil Miglyol 812 was studied using the Pendent Drop Apparatus (FTA 1000B, First Ten Angstrom, USA)

Results and Discussion

A) Effect of the homogenizer-types
The size distribution of the concentrated emulsions produced by an ultrasonic probe is monomodal. In contrast, the concentrated emulsions prepared by a high pressure homogenizer showed many peaks, which mean that the emulsions have a broad size distribution. The best formulation for production of the drug carrier system was 30% oil: 60% water: 10% drug – volume fraction). After incorporation of the drug lidocaine the size distribution was monomodal at about 1.1 µm, which was not significantly different from the bare concentrated emulsions.

B) Effect of pH on the washing process
The three pH-values, i.e. 5, 8 and 10, were used. The results showed that the washing process was not pH-dependent. The emulsifier-film occurred from the soybean protein at the interface was stable during the time.

C) Effect of protein concentrations
The turbidity was calculated to be 2.87×10^5 m^{-1} and the EAI was 136 m^2g^{-1}.

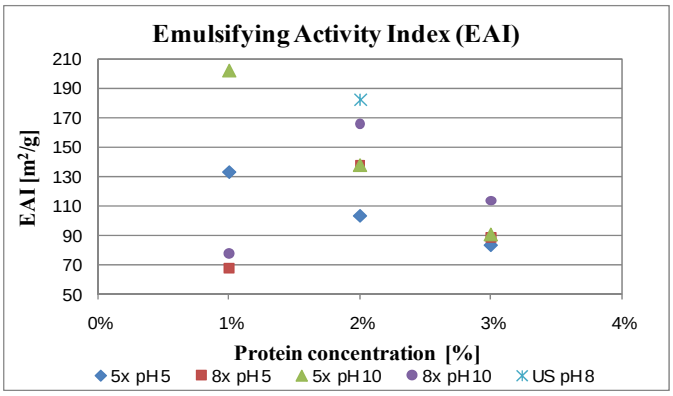

Fig. 1 EAI of soybean protein depending on the protein concentration and pH. x means the numbers of the cycle of a high pressure homogenization and ж means homogenization by an ultrasonic probe.

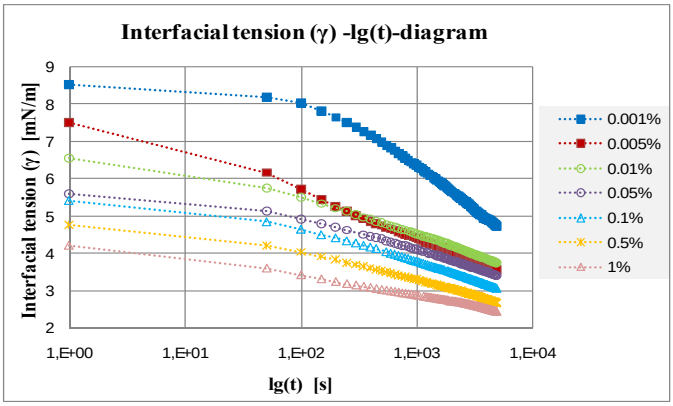

Fig. 2 Dynamic interfacial tension of soybean protein against Miglyol 812 depending on the time and protein concentrations.

Conclusions

The concentrated emulsions with small sizes in micrometer range can be prepared by a simple method i.e. preparation of pre-emulsion and then washing with buffer afterward centrifugation at least two cycles. The homogenization by an ultrasonic probe gives better emulsion with smaller particle size distribution than the complicated high pressure homogenizer. The water insoluble model drug lidocaine base can be incorporated into the concentrated emulsions and the particle sizes were not changed. The interfacial properties show that the soybean protein can be used effectively as an emulsifier to produce the stable concentrated emulsions.

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