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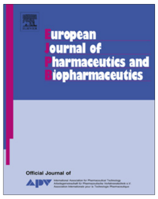

Research paper

Influence of membrane material on the production of colloidal emulsions by premix membrane emulsification

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ABSTRACT

Premix membrane emulsification is a possibility to produce colloidal emulsions as carrier systems for poorly water soluble drugs. During the extrusion of a coarse pre-emulsion through a porous membrane, the emulsion droplets are disrupted into smaller droplets. The influence of the membrane material on the emulsification success was investigated in dependence on the emulsifier. Premixed medium chain triglyceride (MCT) emulsions stabilized with five different emulsifiers were extruded through seven different hydrophilic polymeric membrane materials with pore sizes of 200 nm. The resulting emulsions differed strongly in particle size and particle size distribution with a range of median particle sizes between 0.08 µm and 11 µm. The particle size of the emulsions did not depend mainly on the structure or thickness of the membrane but on the combination of emulsifier and membrane material. Contact angle measurements indicated that the wetting of the membrane with the continuous phase of the emulsion was decisive for achieving emulsions with colloidal particle sizes. The type of dispersed phase was of minor importance as basically the same results were obtained with peanut oil instead of MCT. To prove the assumption that only sufficiently hydrophilic membrane materials led to emulsions with colloidal particle sizes, two membrane materials were hydrophilized by plasma treatment. After hydrophilization, the emulsifying process led to emulsions with smaller particle sizes. The use of an alumina membrane (Anodisc®) improved the process even more. With this type of membrane, emulsions with a median particle size below 250 nm and a narrow particle size distribution could be obtained with all investigated emulsifiers.

1. Introduction

An increasing number of new drug substances is poorly water soluble and thus difficult to effectively administer to patients. To overcome this problem, extensive research on suitable formulation strategies is carried out. A promising option for the formulation of poorly water soluble substances is loading them into colloidal lipid emulsions. These drug carriers can even be administered by direct injection into the bloodstream, provided that the emulsion droplets are smaller than 500 nm, have a narrow particle size distribution and consist of biocompatible components [1]. Recently, premix membrane emulsification (premix ME) was developed as an alternative technique for the preparation of such colloidal emulsions as carrier systems for lipophilic drugs [2]. In this process, a coarse pre-emulsion is extruded through the pores of a membrane, yielding smaller emulsion droplets [3]. The extrusion step can be carried out in several cycles, to lead to a sufficiently narrow particle size distribution [4]. The advantages of premix ME are the possibility of adjusting the particle size of the resulting emulsion by the pore size of the membrane, the very narrow particle size distribution in comparison to high pressure homogenization and the comparatively low process pressure, which makes it an interesting alternative for the processing of sensitive substances [5]. So far, the preparation of colloidal emulsions has only been successful with a few pharmaceutically relevant emulsifiers, which indicates that the process has not been completely comprehended yet. To make use of the advantages of premix ME for the preparation of biocompatible colloidal emulsions, the process has to be controllable and thus entirely understood. One decisive parameter in premix ME seems to be the membrane material. In the literature, the use of different membrane materials has been described for this process. The most commonly used membranes for premix ME consist of Shirasu Porous Glass [3,6–8], polycarbonate [2,9–11] and

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polytetrafluoroethylene [12,13]. These three membrane materials represent the two main groups of membrane structures on the market. Shirasu Porous Glass and polytetrafluoroethylene membranes are branched membranes with interconnected pores whereas polycarbonate membranes are track-etched membranes with cylindrical straight-through pores. Within the investigations described in the literature, the membranes differ not only in chemical composition and structure but also in thickness and pore size. All such properties of the membrane might have an influence on the resulting particle size of the emulsion. The particle size of the emulsion is mainly controlled by the pore size of the membrane with an almost linear relationship between mean particle size and mean pore size. The ratio of mean particle size to mean pore size increases with decreasing pore size and is between 1.25 and 0.68 for pore sizes between 5.4 and 20 μm depending on the preparation conditions [14,15]. Zhou et al. demonstrated with two different kinds of membranes that the pore size distribution does not affect the particle size when using premix ME with repeated extrusion cycles. During premix ME, a narrow pore size distribution of the membrane is not essential for the homogeneity of the emulsion, because when the extrusion through the membrane is repeated, the probability that all emulsion droplets are disrupted inside the smallest pores is increased with every extrusion cycle. Beside the pore size also the thickness of the membrane has an influence on droplet disruption and therefore on the resulting particle size of the emulsion. An increasing thickness of a branched membrane leads to an increased extent of droplet disruption and therefore to smaller particle sizes [15,16]. Whether this is also the case for membranes with cylindrical pores has not been examined yet. Also the chemical properties of the membrane material have an influence on the particle size. The membrane must be wetted by the continuous phase of the emulsion and the contact angle between the dispersed phase and the membrane must be large to obtain small-sized and homogeneous emulsions [3,15]. Therefore, for the successful preparation of O/W emulsions, a hydrophilic membrane should be used. Whether the use of different hydrophilic membrane materials leads to different emulsion qualities, depending on the emulsifier, has not been investigated systematically yet. Trentin et al. indicated that there is a difference in the applicability of three different hydrophilic membranes (nylon, polyethersulfone and nitrocellulose mixed ester) but they did not correlate the result with the emulsifiers used [17]. Schroën et al. discussed that a change in wettability of the membrane, as a result of formulation interaction with the membrane, might be the reason for an unsuccessful preparation of a homogeneous emulsion [18]. Most of the studies concerning premix ME are about emulsions with particle sizes in the micrometer range, but how the membrane material influences the preparation of colloidal emulsions (i.e., with mean particle sizes between 1 and 500 nm) in dependence on the emulsifier properties has not been studied yet. A preliminary investigation with SDS- and poloxamer 188-stabilized emulsions carried out in our group indicated that the suitability of the membrane material for a successful preparation of emulsions with particle sizes smaller than 500 nm depends on the formulation composition [19].

In the present study, the influence of different membrane materials on the resulting particle sizes of emulsions stabilized with different pharmaceutically relevant emulsifiers was investigated systematically. The membranes differed not only in their chemical composition but also in structure, thickness and pore size distribution. Two of them were track-etched membranes with cylindrical pores and a thickness of 10 μm. The others were branched membranes with interconnected pores and a thickness between 120 and 150 μm. An instrumented small scale extruder developed for the preparation of nanoemulsions was used to carry out the process [20]. With this device it was possible to control the flow rate and the extruded volume. Furthermore, the extrusion pressure could be monitored during the whole process. Thus a reproducible, well-monitored process was applied making the investigation of the membrane influence feasible. The specific aim of this study was to investigate under which conditions the preparation of biocompatible emulsions with particle sizes smaller than 500 nm and a narrow particle size distribution, suitable for intravenous administration, is possible.

2. Material and methods

2.1. Characterization of the membrane materials

Seven different polymeric membranes out of polycarbonate (PC; thickness: 10 μm; Nuclepore®, Whatman™, GE Healthcare, United Kingdom), polyester (PE; thickness: 10 μm), polyethersulfone (PES; thickness: 150 μm), polysulfone (PS; thickness: 165 μm), polyvinylidene fluoride (PVDF; thickness: 180 μm), nylon (thickness: 130 μm) and cellulose acetate (CA; thickness: 150 μm) (all from Pieper Filter, Bad Zwischenahn, Germany) with nominal pore sizes of 200 nm were characterized with different microscopic techniques and with mercury porosimetry.

2.1.1. Scanning electron and atomic force microscopy

To investigate the membrane structure, images of the gold sputtered membranes were taken with a scanning electron microscope (SEM; EVO LS25, Zeiss, Germany). The upper side of the membrane and the cross section obtained after cutting with a razor blade was imaged. Before measurement, the membranes were rinsed three times with argon and sputtered with gold at 5 mA for 4 min in a distance of 4 cm in a Balzer Union SDC 030 sputter device. The SEM images were taken with a voltage between 20 and 30 kV at a distance around 6 mm in high vacuum with a secondary electron (SE 1) detector. The appearance in the SEM was verified with an atomic force microscope (AFM; XE-100, Park Systems, Korea). For the AFM images, a cantilever out of silicium nitride was used to scan a surface area of 25 × 25 μm of the membrane in the contact mode.

2.1.2. Porosity and pore size distribution

The porosity and pore size distribution of the membranes were examined by mercury porosimetry (Poremaster 60, Quantachrome, Germany). For this measurement, the membranes were cut into pieces of 1 × 2 cm and filled into the measuring cell. The cell was evacuated and subsequently filled with mercury. With increasing pressure, the mercury was intruded into smaller pores. The applied pressure was increased to around 75,000 kPa, which corresponded to a pore size of 20 nm. The correlation between the applied pressure (p) and the pore radius (r) is given by the Washburn equation [21]:

$$r = \frac{-2\gamma * \cos\theta}{p}$$

Based on convention [22,23] surface tension (γ) and contact angle (Θ) of the mercury were set to 0.48 N m^{-1} and 140°, respectively.

As the volume pore size distribution is based on a model of cylindrical pores, this method is just an approximation. The volume of the intruded mercury was determined by volume flow rate measurement and assumed to be equal to the pore volume. Only mercury data for pore sizes smaller than 6 μm were analyzed to ensure that only the pore volume within the filters was taken into account. To gain reliable results, two different filters of each membrane material were analyzed separately.

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