European Journal of Pharmaceutics and Biopharmaceutics 87 (2014) 178–186

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Evaluation of Shirasu Porous Glass (SPG) membrane emulsification for the preparation of colloidal lipid drug carrier dispersions

Sonja Joseph, Heike Bunjes *

Technische Universität Braunschweig, Institut für Pharmazeutische Technologie, Braunschweig, Germany

ARTICLE INFO

Article history:
Received 29 September 2013
Accepted in revised form 30 November 2013
Available online 9 December 2013

Keywords:
Nanoemulsions
Solid lipid nanoparticles
Colloidal lipid dispersions
SPG (Shirasu Porous Glass) membranes
Direct membrane emulsification
Premix membrane emulsification

ABSTRACT

Aqueous colloidal drug carrier dispersions based on nonpolar lipids are usually prepared by high energy dispersion techniques, like high-pressure homogenization. Homogenization generates high shear forces and may thus not be suitable for the processing of sensitive pharmaceutical ingredients, e.g., proteins. This study investigated the general possibility to prepare lipid nanoparticle dispersions by direct and premix Shirasu Porous Glass (SPG) membrane emulsification as alternative low energy and low shear method. The influence of different emulsifiers (polysorbate 20, sorbitan oleate, poloxamer 188, sodium dodecyl sulfate, sucrose laurate), the type of lipid phase (medium chain triglycerides, soybean oil, trimyristin, glyceryl behenate, lauroyl macrogolglycerides), the pore size of the SPG membrane (0.1, 0.2, 0.3, 0.5, 1.1 μm) and the emulsifying pressure on the particle size of the resulting dispersions was investigated. The particle size was primarily controlled by the pore size of the membrane and the emulsifying pressure. Very narrow particle size distributions with membrane pore size/mean particle size ratios of 1:0.4–1:8.2 and 1:0.4–1:2.1 were observed for the direct and the premix membrane emulsification method, respectively. Due to the comparatively lower process pressures of at maximum 10 bar SPG membrane emulsification is an interesting alternative method to high-pressure homogenization.

1. Introduction

Colloidal lipid dispersions such as nanoemulsions and solid lipid nanoparticles are under intensive investigation as carrier systems for poorly water soluble drugs, e.g., with regard to parenteral and peroral administration [1]. These dispersions of colloidal particles with a core of nonpolar liquid or solid lipids are stabilized with physiologically compatible emulsifiers. Usually, they are prepared by droplet disruption techniques like high-pressure homogenization or ultrasonication or by different precipitation methods [2–4]. High shear forces during high-pressure homogenization may not be suitable for the processing of sensitive substances, e.g., proteins [5,6]. Ultrasonication may lead to heating phenomena as well as to radical formation resulting, for example, in oxidation of sensitive substances [7]. As an alternative, precipitation methods use water miscible organic solvents or mixed micellar systems to bring the matrix lipids into homogeneous solution from which they are precipitated into colloidal particles. However, solvent residues and the excess of micelle forming solubilizers need to be removed from the dispersions to avoid physicochemical instabilities and toxicological problems. As a further drawback of the common preparation techniques, the particle size distributions obtained are often rather polydisperse [1].

In an approach to overcome problems associated with the high energy input of the conventional droplet disruption processes, membrane emulsification techniques have received growing interest as alternative low energy input processes for the preparation of drug carrier systems with very narrow particle size distributions. Since the preparation of oil-in-water emulsions by the so called "direct membrane emulsification" process was reported around 1990 [8], SPG (Shirasu Porous Glass) membranes have been the most commonly used membranes for this technique. These hydrophilic membranes are manufactured by a phase separation process of calcium aluminum borosilicate glass and subsequent acid leaching [9,10]. To produce an O/W emulsion by direct membrane emulsification, the liquid lipid is forced through the pores of a membrane into the continuous aqueous phase (Fig. 1), which is recirculated by agitation with a stirrer or pump. Lipid droplets grow at the pore openings of the membrane surface and are stabilized by emulsifiers present in the continuous phase. When the droplets reach a certain size they are detached from the membrane [11]. While direct membrane emulsification is based on droplet formation from a lipid bulk phase, membranes can also be used for droplet disruption. In the "premix membrane emulsification" process developed by Suzuki et al. [12], a coarse pre-emulsion is forced through the pores of a membrane yielding smaller droplets

* Corresponding author. Technische Universität Braunschweig, Institut für Pharmazeutische Technologie, Mendelssohnstraße 1, D-38106 Braunschweig, Germany. Tel.: +49 531 3915657; fax: +49 531 3918108.
E-mail address: Heike.Bunjes@tu-braunschweig.de (H. Bunjes).

0939-6411/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejpb.2013.11.010

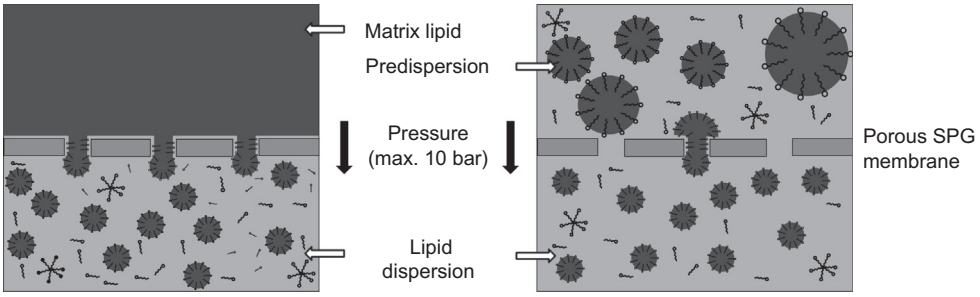

Fig. 1. Principle of direct (left) and premix (right) SPG membrane emulsification.

(Fig. 1). To obtain more uniform particles the emulsified lipid dispersion can be repeatedly extruded through the membrane [13]. In order to obtain solid lipid particles, the corresponding matrix lipids are processed above their melting point and the resulting droplets are subsequently cooled below the recrystallization temperature for solidification [14].

A general advantage of all kinds of membrane emulsification techniques is the possibility to prepare products with well defined monodisperse particle size distributions, which is highly desirable for pharmaceutical formulations. In order to prepare uniform particle size products, "the porous membrane must have a narrow pore size distribution and be strong enough not to deform or compact, even if pressure is applied" [8]. The resulting particle size of aqueous lipid dispersions is controlled by the pore size of the hydrophilic SPG membranes. Typical ratios of average pore size to average particle size are in the range of 1:2–1:10 for the direct process [11] and 1:0.7–1:4.4 for the premix process after one membrane passage [15,16] depending on the amount of emulsifier [15]. Disadvantages of the direct membrane emulsification technique are low flow rates through the membranes and hence low productivity and long production times. Therefore, only formulations with low disperse phase fraction are usually obtained [17]. Furthermore, the commonly used SPG membranes are rather expensive, fragile and time-consuming to purify. The premix membrane emulsification process uses slightly higher pressures for the membrane passage. Hence, higher production rates are possible as well as the preparation of formulations with higher disperse phase fractions, but slightly broader particle size distributions are obtained by the premix process than by the direct technique after one membrane passage [13].

Most studies on direct SPG membrane emulsification report on microparticulate lipid dispersions and only a few on colloidal ones as yet. A major problem to be expected during the preparation of nanoscaled systems is an increasing process pressure with decreasing membrane pore size. Anyway, an at least 13 h stable flurbiprofen-loaded oil-in-water nanoemulsion based on methylene chloride as lipid phase was described by Oh et al. [18]. First investigations on the preparation of solid lipid nanoparticles by direct membrane emulsification were performed with ceramic [19–21] and SPG membranes [22]. In these investigations Gelucire® 44/14 was used as matrix lipid which has self emulsifying properties [23]. Thus, Gelucire® 44/14 may not undergo the classical droplet formation processes of direct membrane emulsification and the results obtained with this matrix material may not be transferable to the use of nonpolar matrix lipids. The processing of more typical lipid matrices like Compritol® 888 or Precirol® ATO 5 did not lead to small colloidal particles, but particles in the upper submicron-range with poor stability on storage were obtained [22,24]. The preparation of nanoemulsions and solid lipid nanoparticles by repeated premix membrane emulsification has been established with polycarbonate membranes [14,25], but has hitherto apparently not been approached with SPG membranes.

The present study investigated the possibility of preparing pharmaceutical colloidal dispersions of nonpolar lipids such as nanoemulsions and solid lipid nanoparticles by direct and premix SPG membrane emulsification. The major focus was on the question whether these methods can produce lipid dispersions in a particle size range that would allow their intravenous administration (as this would render them applicable also for virtually all other administration routes). The particle size limitations for intravenous administration are very strict [1]; therefore, the study particularly aimed at preparing dispersions with a mean particle size below 500 nm and a particle size distribution completely in the nanometer range (colloidal colloidal dispersions/nanodispersions). The influence of emulsifier, the type and concentration of matrix lipid and the SPG membrane pore size on the particle size and particle size distribution of the resulting dispersions was studied as well as the incorporation of a lipophilic model drug.

2. Materials and methods

2.1. Materials

Medium chain triglycerides (MCT) (Miglyol® 812, Caesar und Loretz, Hilden, Germany) and soybean oil (SBO) (Carl Roth, Karlsruhe, Germany) were used as liquid lipids. For the solid lipid particles trimyristin (TM) (Dynasan® 114, Condea Chemie, Witten, Germany; melting point ~56 °C) and glyceryl behenate (CATO) (Compritol® ATO 888, Gattefossé, Saint Priest Cedex, France; melting point ~70 °C) were used as core materials. Lauroyl macrogolglycerides (G44/14) (Gelucire® 44/14, Gattefossé, Saint Priest Cedex, France; melting point ~44 °C) were also used as matrix material. Sodium dodecyl sulfate (SDS) (Texapon® L100, Henkel & Cie, Düsseldorf, Germany), poloxamer 188 (Pol) (Lutrol® F68, BASF, Ludwigshafen, Germany), sucrose laurate (SL) (Ryoto® sugar ester L-1695, Mitsubishi-Kagaku Food Corporation, Tokyo, Japan), polysorbate 20 (T_{20}) (Tween® 20, ICI Specialty Chemicals, Essen, Germany) and sorbitan oleate (S_{80}) (Span™ 80, Carl Roth, Karlsruhe, Germany) were used as emulsifiers, ubidecarenone (Q_{10}) (Fagron, Barsbüttel, Germany) as model drug and thiomersal (Caesar und Loretz, Hilden, Germany) as preservative. Water was prepared by double distillation. Acetone and isopropyl alcohol (both from Carl Roth, Karlsruhe, Germany) were used as solvents to purify the membranes. Nitrogen gas 5.0 was purchased from Westfalen AG (Göttingen, Germany).

2.2. Methods

2.2.1. Experimental set-up

The experimental set-up used for the study is illustrated in Fig. 2. The external pressure type micro kit (MCTech, Shihung-City, Korea) was equipped with a custom-built, double-walled, temperature controlled pressurized vessel of stainless steel. Thus,

the matrix lipid or the predispersion could be tempered by an attached thermostatic water bath (Haake D1, Thermo Haake, Karlsruhe, Germany) if required. The cylindrical hydrophilic SPG membranes (SPG Technology, Miyazaki-city, Japan) of different pore size (0.1, 0.2, 0.3, 0.5, 1.1 μm) had a length of 20 mm and an outer diameter of 10–11 mm. The thickness of the membrane was in the range of 0.7–0.9 mm. The membranes were clamped with O-rings and were screwed in the membrane module of stainless steel. For the direct membrane emulsification process, the membrane module was placed in a beaker glass (nominal volume 100 ml) containing 80 ml of the emulsifier-containing aqueous phase. The aqueous phase was stirred with 300 rpm by a magnetic stir bar (stir bar-hub 4.5 × 2.7 cm, VWR international, Lutterworth, UK) on a temperature controlled magnetic stirrer (IKA® RCT basic, IKA®-Werke, Staufen, Germany). The stirrer speed of 300 rpm did not lead to bubble or eddy formation but ensured a sufficient mixing of the aqueous phase. Furthermore, an agitator speed of 300 rpm has been described as optimal for such emulsification processes [18]. The concentration of the matrix lipid in the resulting dispersions was determined by measuring the level in the pressurized vessel after preparation. For the premix membrane emulsification setup, the membrane module was placed in an empty beaker glass (nominal volume of 10 ml) containing a small magnetic stir bar, which was run with 300 rpm to stir the emulsified dispersion.

Before the emulsification process was started, the SPG membranes were wetted using the following protocol: The SPG membranes were dipped into a container with water positioned in a desiccator (∅ 15 cm, VWR international, Lutterworth, UK). To remove the air inside all membrane pores, the membranes were treated with reduced pressure (3–15 mbar; vacuum exhauster V1200, KVW-Technik, Neustadt, Germany) for 180 min in an ultrasonic bath (Sonorex Digital DK 512 P, Bandelin electronic, Berlin, Germany) operating with a frequency of 35 kHz and an ultrasonic peak output of 820 W. Afterward, the membranes were clamped into the membrane module and were flushed at 990 kPa successively with 100 ml water and 50 ml emulsifier-containing aqueous phase. After each emulsification process, the membranes were cleaned by flushing the SPG membrane in the membrane module at 990 kPa with 100 ml hot water (~80–90 °C), 50 ml acetone, 50 ml isopropyl alcohol and 100 ml cold water.

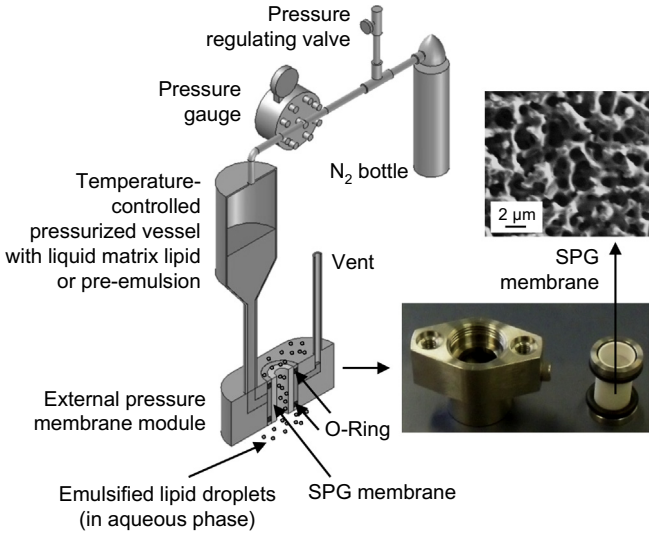

Fig. 2. Scheme of the experimental set-up for membrane emulsification and environmental scanning electron micrograph of an SPG membrane (pore size 1.1 μm).

Formulations with liquid oils were processed at room temperature. Solid lipid particles were obtained by membrane emulsification 10 °C above the melting point of the matrix lipid and subsequent crystallization of the resulting emulsion droplets by dipping the sample containers into an ice-water mixture for 2 h. All samples were stored at room temperature.

2.2.2. Preparation of emulsions and solid lipid particles by direct SPG membrane emulsification

Different combinations of emulsifier-containing aqueous phases and matrix lipids were used in the experiments. The aqueous phases were prepared by dissolving the emulsifier (5% SDS, 5% poloxamer 188, 15% sucrose laurate, 1 or 2% polysorbate 20) in double distilled water containing 0.01% thiomersal as preservative (all concentrations w/w). Comparatively high concentrations of the stabilizing agents in the aqueous phases were chosen as derived from the literature for SDS and polysorbate 20 [26–28] in order to prevent a lack of emulsifier during the droplet formation process. For the first basic studies using sucrose laurate a concentration of 15% was applied according to the premix membrane emulsification studies in the literature [14]. The concentration of poloxamer 188 was chosen closely following the concentration of SDS. The matrix lipids were used as such, soybean oil additionally with 0.5% (w/w) sorbitan oleate. To investigate the effect of drug loading, additionally 5% (related to the matrix lipid) of the model drug ubidecarenone was dissolved in molten trimyristin and was further processed together with the matrix lipid. The compositions under investigation by direct membrane emulsification are given in Table 1.

For the preparation of lipid dispersions, the aqueous phase was stirred continuously and the lipid phase (~10 ml) was placed in the pressurized vessel. As the first process step of direct SPG membrane emulsification, the required emulsifying pressure was determined for all membranes and formulations, respectively, by successively increasing the pressure of the nitrogen gas. Steps of 5 kPa each of 10 min were chosen for membranes with pore sizes of 0.2, 0.3, 0.5 and 1.1 μm and steps of 20 kPa each of 30 min were chosen for those with a pore size of 0.1 μm. The critical emulsifying pressure is reached when the lipid phase starts to pass the membrane and lipid droplets are detached. The emulsifying pressure for the following preparation step was set to 5 kPa (for the 0.2,

Table 1
Overview of the lipid dispersions under investigation by direct and premix SPG membrane emulsification.

Stabilizer	Lipid phase						
	MCT	SBO	SBO/S_{80}	TM	TM/Q_{10}	G44/14	CATO
Direct membrane emulsification[a]							
SDS	5%	5%	–	5%	5%	–	5%
Pol 188	–	–	–	–	–	–	5%
T_{20}	2%	–	1%	–	–	2%	–
SL	–	–	–	15%	–	–	–
Premix membrane emulsification[b]							
SDS	7.5%[1,2]	–	–	7.5%	–	–	–
Pol 188	–	–	–	7.5%[1,2]	–	–	–
T_{20}	–	–	–	7.5%	–	–	–
SL	–	–	–	–	–	–	–

Stabilizer: SDS = sodium dodecyl sulfate, Pol 188 = poloxamer 188, T_{20} = polysorbate 20, SL = sucrose laurate. Lipid phase: MCT = medium chain triglycerides, SBO (/S_{80}) = soybean oil (/sorbitan oleate), TM = trimyristin, TM/Q_{10} = trimyristin/ubidecarenone, G44/14 = lauroyl macrogolglycerides, CATO = glyceryl behenate.
All concentrations are w/w.
[a] Concentrations given refer to the stabilizer concentration in the aqueous phase. The concentration of the matrix lipid was 1–5%.
[b] Concentrations given refer to the stabilizer concentration in the aqueous phase. The concentration of the matrix lipid was 10%. Dispersions with 5%[1] and 2.5%[2] matrix lipid were also prepared keeping the lipid-to-emulsifier ratio constant.

0.3, 0.5 and 1.1 μm-membranes) or 20 kPa (for the 0.1 μm-membrane) above the determined critical pressure according to Nakashima et al. [8]. The experiments were stopped when 1–5% lipid phase had been emulsified into the aqueous phase, and thus, the determination of particle size was possible.

2.2.3. Preparation of nanoemulsions and solid lipid particles by premix SPG membrane emulsification

Usually, the matrix lipids were used in a concentration of 10% with an emulsifier concentration of 7.5% in analogy to previous investigations [14]. The mass ratio of matrix lipid to stabilizing agent was quite high (4:3 (w/w concentrations)) in order to prevent a lack of emulsifier during the droplet disruption process. Emulsions were prepared from medium chain triglycerides and SDS, solid lipid nanoparticles from trimyristin and SDS, poloxamer 188 or polysorbate 20, respectively. An overview of the compositions under investigation by premix membrane emulsification is also given in Table 1. All samples were preserved with 0.01% (w/w) thiomersal in the aqueous phase. 10 ml of the mixture of the matrix lipid and the surfactant-containing aqueous medium was predispersed with an Ultraturrax® IKA T18 (IKA®-Werke, Staufen, Germany) at 16,000 rpm for 30 s (10 °C above the melting point of matrix lipid when processing solid lipids). The resulting pre-emulsion was forced once through the pores of the SPG membrane with an emulsifying pressure of 900 kPa.

2.2.4. Particle size determination

In order to obtain an estimate of the particle size distribution the samples were investigated in a laser diffractometer with PIDS (Polarization Intensity Differential Scattering) technology (LS 13 320, Beckman-Coulter, Krefeld, Germany). Three measurements of 90 s each were performed and used to calculate the volume distributions as well as the corresponding d_{10}-, d_{50}- and d_{90}-values using the Mie theory assuming a refractive index of 1.46 for the particles, 1.33 for the aqueous dispersion medium and 0.01 for the imaginary part of the refractive index.

Additionally, the quality of the dispersions was assessed at different magnifications in an optical microscope (Leica DMLM; Leica Microsystem, Wetzlar, Germany) equipped with an Olympus DP12 digital microscope camera (Olympus America, Melville, New York, USA).

2.2.5. Determination of viscosity

The dynamic viscosity of the lipid phases was determined with the Bohlin Rheometer CV0 50 (Bohlin Instruments, Cirencester, UK) equipped with a temperature-controlled cone and plate. The angle of the rotating cone was 1° and the cone diameter was 40 mm. Each sample was investigated for 120 s at its corresponding process temperature (25 °C for the liquid lipids and 10 °C above the melting point of the solid lipids) in triplicates after equilibration of 5 min at the required temperature. The shear stress was increased from 0.8 Pa to 2000 Pa during the measurement and 120 points of measurements were taken for each run. The results of the three measurements were used to calculate the mean value with its standard derivation. All matrix lipids displayed Newtonian flow.

2.2.6. Determination of interfacial tension

The interfacial tension of medium chain triglycerides and aqueous phases containing 1% (w/w) sucrose laurate, SDS or poloxamer 188 was determined at 25 °C ± 1 °C using the K100 tensiometer (Krüss GmbH, Hamburg, Germany) equipped with a Wilhelmy plate (19.9/0.2/10.0 mm, width/thickness/height) and a sample container with a volume of 43.5 ml. Before each measurement, the plate and glass container were cleaned by abundant rinsing with isopropanol and deionized water followed by heating in a flame. 20 values were collected within a maximum time of 500 s for one measurement. The interfacial tension is given as the mean of three measurements with its standard deviation. The density of the medium chain triglycerides (0.9408 g/cm^3 ± 0.0001 g/cm^3), which was necessary for the interfacial tension calculation, was determined in triplicates by means of a density meter DMA46 (Anton Paar K.G., Graz, Austria) at 25 °C ± 1 °C.

3. Results and discussion

3.1. Direct membrane emulsification

In a screening study with different matrix lipids and emulsifiers, dispersions with well-defined and often very narrow size distribution could be prepared with all membranes under investigation (Fig. 3, left). Particle size distributions completely in the submicron range were, however, only obtained using the membrane with the smallest pore size. Due to low flow rates of the disperse phase the process times were quite long (e.g., 20–60 min for the emulsification of about 1 ml lipid phase). Therefore, only 1–5% lipid phase was emulsified into the aqueous phase as thus the determination of particle size became possible. Long process times increase the risk of membrane fouling as the lipid phase starts to spread over the membrane surface leading to multimodal particle size distributions.

3.1.1. Influence of emulsifying pressure and membrane pore size

The emulsifying pressure is the most sensitive process parameter of direct SPG membrane emulsification. The minimum pressure required to force the lipid phase through the membrane into the aqueous phase (critical pressure p_c) increases with decreasing pore size. It can be estimated from the capillary pressure [8] described by Laplace's law, assuming that the pores are ideal cylinders (Eq. (1)).

$$p_c = (4 \cdot \gamma_{O/W} \cdot \cos\theta)/d_M \quad (1)$$

$\gamma_{O/W}$, θ and d_M represent the interfacial tension between lipid and water phase, the lipid/membrane contact angle and the nominal pore diameter of the SPG membrane, respectively. However, the emulsifying pressure used in the process may be slightly higher than the predicted critical pressure. According to Nakashima et al. there is a range of optimal emulsifying pressure above the critical pressure. Emulsifying pressures above this range can lead to the formation of large particles and broad size distributions [8]. According to Darcy's law (Eq. (2)), the flux of the disperse phase through the membrane (J_d) increases with the emulsifying pressure (p_e) [29,30].

$$J_d = (p_e \cdot K)/(\eta \cdot l) \quad (2)$$

K, η and l represent the membrane permeability, the viscosity of disperse phase and the membrane thickness, respectively. Thus, an increasing emulsifying pressure results in a faster droplet formation and further in an increasing number of active pores [31]. The resulting higher throughputs [32] should lead to shorter process times.

In the present study, the critical pressure was determined in a quite time-consuming process for each membrane and formulation. As expected, it was mainly determined by the membrane pore size. The emulsifying pressure (Fig. 3, right) was adjusted 5–20 kPa above the respective critical pressure according to Nakashima et al. [8]. To rule out any potential influence of membrane thickness on the emulsifying process, membranes with similar thicknesses were used for the present study. Smaller particle sizes were usually obtained with decreasing membrane pore size (Fig. 3, left). In this study, ratios of membrane pore size to mean particle size were in a range from 1:2.8 to 1:8.2 and in agreement with those

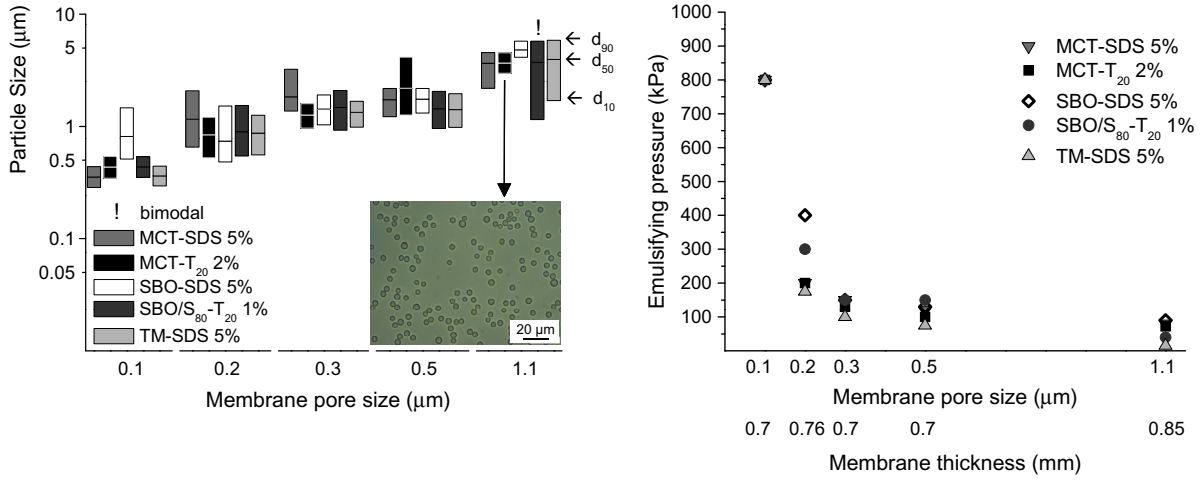

Fig. 3. Particle size distributions (left) and corresponding emulsifying pressures (right) observed in a formulation screening by direct SPG membrane emulsification with different membrane pore sizes. Particle size distributions are shown as floating columns ranging from the d_{10} over the d_{50} to the d_{90} values. Micrographs confirmed the narrow size distributions, shown here for the formulation containing 5% medium chain triglycerides and 2% polysorbate 20 observed after a direct emulsification process.

reported earlier for microparticulate lipid dispersions (typically 1:2–1:10 [11]). Uniform colloidal particles could only be obtained with the smallest membrane pore size of 0.1 µm. Since the maximum pressure of the device was limited to 1000 kPa, membranes with smaller pores could not be used due to higher expected emulsifying pressures.

The influence of the emulsifying pressure on the particle size was investigated using a 0.3 µm-membrane which did not yield colloidal dispersions under the commonly chosen preparation conditions (emulsifying pressure slightly higher than the critical pressure) (Fig. 3, left). Under such regular conditions, narrow particle size distributions in the micrometer range with mean ratios of membrane pore size:mean particle size of 1:2–1:10 are expected for simple oil-in-water emulsions [11]. The mean particle sizes (d_{50} ~1.5 µm) of dispersions prepared with the 0.3 µm-membrane under common preparation conditions in this study were in the expected range (Fig. 3, left). For SDS-stabilized trimyristin dispersions, a slight increase in emulsifying pressure led to the formation of very small particles and broader size distributions (Fig. 4). The particle sizes were even smaller than those observed upon conventional processing with smaller membrane pore sizes (0.1 µm). The incorporation of the model drug ubidecarenone did not influence the required preparation conditions and the particle size. However, at increased pressure a broader size distribution was observed (Fig. 4).

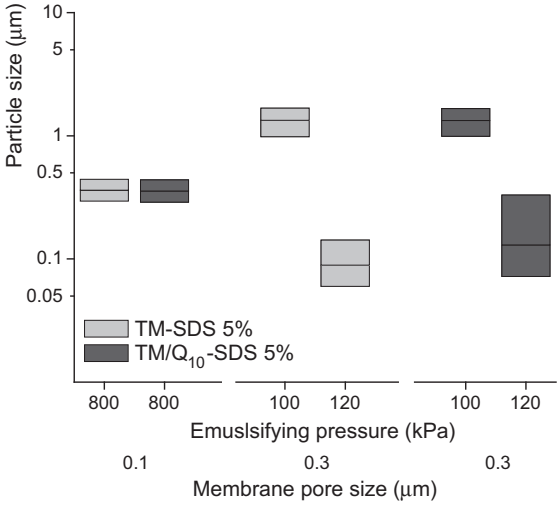

Fig. 4. Particle size distributions of SDS-stabilized unloaded and Q_{10}-loaded trimyristin solid lipid nanoparticles as obtained by direct SPG membrane emulsification (with variation of the emulsifying pressure at the membrane with a pore size of 0.3 µm).

In direct membrane emulsification, the variation of the emulsifying pressure leads to alterations in the droplet formation processes. Upon processing close to the critical pressure individual droplets are formed at the opening of the pores at the membrane surface and are detached when they reach a certain size [33,34]. The droplet formation process is very slow but the droplets – which are larger than the membrane pores – are very uniform in size. An increase in the emulsifying pressure increases the flux of disperse phase and finally leads to a release of thin lipid jets at the pore openings [34–37]. These lipid jets collapse to droplets of different sizes resulting in broader size distributions. Small particles can be observed when small droplets of collapsing lipid jets are covered by rapid stabilizing emulsifiers before coalescence occurs yielding larger particles [38]. Furthermore, Vladisavljević et al. postulated the formation of smaller droplets than the membrane pore size at higher emulsifying pressures [38]. Capillary instabilities are responsible for the breakup of oil threads within the membrane pores wetted by the aqueous phase. Smaller particles are observed in particular when using lipid phases with higher viscosities [39]. Thus, the preparation of nanoparticles with sizes smaller than the pores of the membrane is, in principle, possible by direct SPG membrane emulsification.

In the majority of cases in this study, a slight increase in the emulsifying pressure led to difficulties in controlling the process conditions and resulted in larger particles and polydisperse size distributions than when using common process conditions as also commonly reported in the literature [26,28,40,41]. However, SDS-stabilized glyceryl behenate particles (d_{50} = 80 nm, Fig. 5) and sucrose laurate-stabilized trimyristin particles (d_{50} = 72 nm, Fig. 6) prepared under common process conditions with a 0.2 µm- and 0.1 µm-membrane, respectively, were much smaller than expected according to the usual pore to particle size ratio. Also here, the formation of lipid jets might be the cause for the formation of very small particles. The formation of lipid jets may occur in particular with small membrane pore sizes which require in a rather high critical pressure. As soon as this pressure is overcome the high emulsifying pressure is likely to result in a high flow velocity of

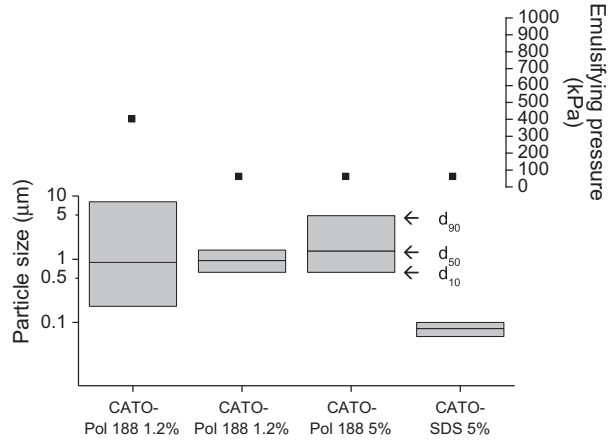

Fig. 5. Particle size distributions and emulsifying pressures of glyceryl behenate (CATO) dispersions containing different emulsifiers observed upon direct SPG membrane emulsification with a pore size of 0.2 µm.

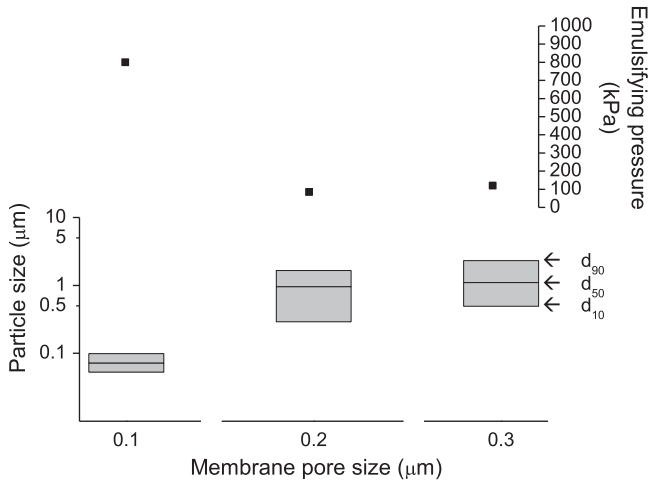

Fig. 6. Particle size distributions and emulsifying pressures of sucrose laurate-stabilized trimyristin particles observed upon the direct emulsification process with different SPG membranes.

the lipid through the membrane pore which does not allow the formation of single droplets at the pore opening but will favor jet formation.

Due to the high resistance of the membranes, which caused high process pressures, the SPG membranes often ruptured in the device, in particular the membranes with the small pore sizes (0.1 and 0.2 µm). The differences in membrane stability may be caused by the different required emulsifying pressures (10–180 kPa and 200–800 kPa for 1.1–0.3 µm- and 0.2–0.1 µm-membranes, respectively). Moreover, the extensive contact with organic solvents during the purification process may render the glass membranes more brittle and may promote ruptures during the time-consuming preparation process at high emulsifying pressures.

3.1.2. Influence of emulsifier

In this study, many experiments were performed with SDS as this emulsifier has often been used for membrane emulsification [10,11]. Since SDS is, however, not a good option for many pharmaceutical applications, the investigations were extended also to surfactants that are more likely to be used, e.g. in parenteral formulations.

The type and concentration of emulsifier affected the particle size and size distribution. Fig. 5 exemplifies the results of emulsification through 0.2 µm-membranes for solid lipid particles containing glyceryl behenate as matrix lipid. Based on the preparation conditions described by D'oria for colloidal particles, the dispersions containing 1.2% poloxamer 188 were processed at 400 kPa [22]. Additionally, the same formulation was processed at 60 kPa after a critical pressure of 55 kPa had been determined. A narrower size distribution was observed at the lower emulsifying pressure, but the mean particle size remained unchanged at about 1 µm. A higher concentration (5%) of the emulsifier poloxamer 188 did not lead to the formation of smaller particles either. However, remarkably small glyceryl behenate nanoparticles with narrow size distribution were observed after replacement of the emulsifier poloxamer 188 with 5% SDS although the critical pressure remained unchanged at 55 kPa.

Sucrose laurate has previously been used very successfully for the preparation of lipid nanoparticles by premix membrane emulsification [14] and was thus investigated for the preparation of solid lipid particles by direct membrane emulsification in this study (Fig. 6). As also observed for other emulsifiers in this study, the use of membranes with 0.2 or 0.3 µm pore size did not yield sucrose laurate-stabilized particles in the colloidal range. Only with the 0.1 µm-membrane sucrose laurate-stabilized trimyristin nanoparticles were obtained.

Influences of the emulsifier on the size of droplets prepared by direct membrane emulsification have been reported earlier [27,28,37,38]. The droplet size of the disperse phase depended mainly on the adsorption speed of emulsifier at the lipid–water interface. Smaller droplets were observed in dispersions with emulsifiers lowering the interfacial tension more quickly, like, e.g. SDS compared to β-casein or 11S soya globulin [42], to dodecyl alcohol-10-glycol ether or spray-dried whey protein [28] or to polysorbate 20 [27,28]. In the present study, also some correlation of the particle size with the (equilibrium) interfacial tension was observed: Preliminary investigations on the interfacial tension between medium chain triglycerides and selected aqueous phases revealed the lowest value for a solution of sucrose laurate (2.96 ± 0.16 mN/m) followed by SDS (3.69 ± 0.34 mN/m) and poloxamer 188 (15.66 ± 0.16 mN/m). Accordingly, sucrose laurate-stabilized trimyristin particles were smaller (d_{50} = 72 nm, Fig. 6) than SDS-stabilized trimyristin particles (d_{50} = 360 nm, Fig. 3, left) when prepared with a 0.1 µm-membrane (and an emulsifying pressure of 800 kPa) and SDS-stabilized glyceryl behenate particles were smaller (d_{50} = 80 nm, Fig. 5) than those stabilized with poloxamer 188 (d_{50} = 950 nm, Fig. 5) when prepared with a 0.2 µm-membrane (and an emulsifying pressure of 60 kPa). However, an influence of the interfacial tension on the emulsifying pressure as predicted by Laplace's law (Eq. (1)) could not be observed.

The particle size is also influenced by the charge of the hydrophilic group of the emulsifier, which determines the droplet charge, due to electrostatic interactions with the negatively charged SPG membrane surface [27,38]. Strong electrostatic repulsions can be observed between negatively charged droplets and the hydrophilic SPG membrane resulting in a fast droplet detachment [38]. Due to the absence of electrostatic repulsions uncharged particles are less quickly detached from the membrane and thus have a more time to grow at the membrane pore [27]. This may be a further reason why the glyceryl behenate particles stabilized with the quickly adsorbing anionic emulsifier SDS were smaller than the particles stabilized by the larger nonionic polymer poloxamer 188.

Compared to the low concentration of emulsified lipid phase, the emulsifiers were applied in quite high concentrations. This was done to prevent a lack of surfactant during the droplet

formation process in direct membrane emulsification. Since for pharmaceutical applications, especially with regard to parenteral administration, delivery systems with low concentration of surfactant are desirable, studies to reduce the emulsifier concentrations are in the focus of further investigations.

3.1.3. Influence of the type of matrix lipid

Usually, nonpolar lipids were used as matrix materials in this study. However, also the more polar substances lauroyl macrogolglycerides (Gelucire® 44/14) and glyceryl behenate (Compritol® ATO 888) have been reported to form particles in the upper colloidal range (lauroyl macrogolglycerides) [19–22] or in the lowest micron range (glyceryl behenate) upon direct membrane emulsification [22,24]. Thus, some experiments were also performed with these lipids. Lauroyl macrogolglycerides in combination with 2% polysorbate 20 yielded dispersions of very small particles (d_{50} = 70 nm) upon direct emulsification with a membrane of 1.1 μm pore size at an emulsifying pressure of 10 kPa. Since this lipid matrix is classified as self-emulsifying by the manufacturer and in the literature [23], this property was investigated by simply adding the molten matrix lipid at 55 °C to a polysorbate 20 (2%) containing aqueous phase on a magnetic stirrer at 300 rpm. After cooling to 5 °C, the particle sizes were in the same range (d_{50} = 70 nm) as after membrane emulsification. For the preparation of lauroyl macrogolglyceride nanoparticles, a technical dispersion process was thus not required due to the self emulsifying properties of the lipid. Thus, it has to be assumed, that the colloidal particles observed after membrane emulsification of lauroyl macrogolglycerides (Gelucire® 44/14) [19–22] do not result from the classical membrane emulsification process according to Nakashima et al. [8].

With the exception of glyceryl behenate, all other lipids yielded dispersions of similar particle sizes (d_{50} around 1 μm) as exemplified in Fig. 7 for SDS-containing formulations using a membrane with a pore size of 0.2 μm. Using glyceryl behenate some peculiarities have to be taken into consideration: The lipid consists of a mixture of approximately 15% mono-, 50% di- and 35% triglycerides of behenic acid (C_{22}) and is more polar than the other lipids used in this study which may result in special effects at the droplet interface. Furthermore, due to its high melting point (~70 °C) and low supercooling tendency (crystallization temperature in dispersion ~65–60 °C) glyceryl behenate bears the risk of lipid crystallization during emulsification. Thus, the lipid was excluded from further studies.

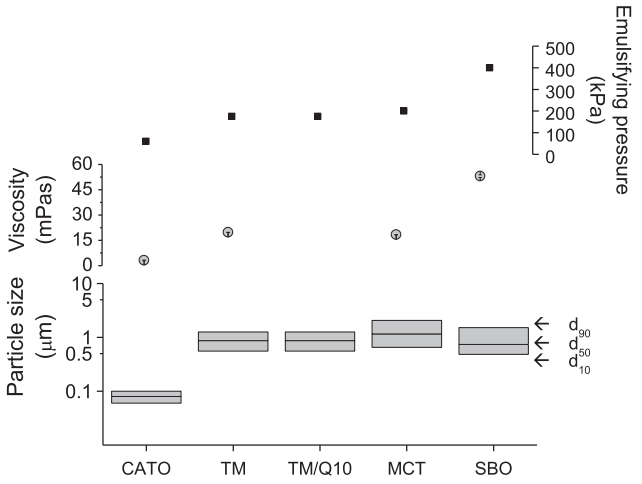

Fig. 7. Particle size distributions and emulsifying pressures of SDS (5%)-stabilized lipid particles observed upon direct emulsification with a 0.2 μm SPG membrane in comparison to the viscosity of the respective matrix lipid of the dispersions obtained at the corresponding process temperature.

To investigate if the differences in emulsifying pressures in direct membrane emulsification (Fig. 3, right) might be related to the viscosity of the matrix lipids, the viscosities were determined at the respective process temperature (Fig. 7). The considerably higher viscosity of soybean oil (53.1 ± 0.77 mPa s, 25 °C) than that of medium chain triglycerides (18.4 ± 0.88 mPa s, 25 °C) and trimyristin (19.8 ± 0.05 mPa s, 65 °C) corresponded to a higher required emulsifying pressure for soybean oil (400 kPa) compared to those for the other two matrix lipids (200 kPa and 175 kPa for medium chain triglycerides and trimyristin, respectively) (Fig. 7). The lowest viscosity was observed for glyceryl behenate (3.20 ± 0.03 mPas, 80 °C), which required the lowest emulsifying pressure (60 kPa) and yielded very small particle sizes. Presumably, the very low viscosity of this matrix lipid supports the formation of liquid lipid jets discussed in Section 3.1.1. However, the influence of the matrix lipid viscosity on the particle size could not be clarified in this study.

Systematic studies on the effect of disperse phase viscosity in the direct membrane emulsification process have shown increasing particle sizes with decreasing matrix lipid viscosity [26,27]. More viscous lipid phases may decrease the supply rate during droplet formation resulting in smaller particles [27] due to easier droplet detachment from the membrane pore [43]. All studies postulated a high viscosity of the disperse phase to facilitate the preparation of monodisperse particle size distributions.

3.2. Premix membrane emulsification

As the formation of small colloidal particles with narrow size distribution was not frequently observed when using the direct emulsification procedure, premix membrane emulsification with SPG membranes was tested as alternative. Generally, the premix process worked much better for the preparation of nanoemulsions and solid lipid nanoparticles than direct membrane emulsification. It allowed manufacturing particles in the lower nanometer range with very narrow size distribution in relatively short time (10 ml of premix were emulsified within at maximum 8–30 min.) and at comparatively high concentrations of matrix lipid (Fig. 8). Dispersions containing 10% lipid were extruded without any problems in most cases. Very remarkably, a single premix emulsification step with nanoporous SPG membranes led to smaller particles and narrower size distributions than 11 or 21 membrane passages through common tracked etched polycarbonate membranes [14]. Obviously, there is a strong influence of the membrane morphology on the resulting particle size distribution. Furthermore, in spite of the comparatively high pressure applied membrane ruptures were less frequently observed than upon direct emulsification.

In premix membrane emulsification, droplet disruption occurs within the membrane pores. In a visualization of droplet break-up mechanisms localized shear forces led to snap-off effects and interfacial tension effects (Rayleigh and Laplace instabilities) as well as steric hindrance between droplets seemed to be responsible for the droplet disruption processes [44]. Smaller particles than the membrane pore size can be achieved upon premix membrane emulsification at higher shear stresses resulting in a more intensive droplet disruption due to collisions between the droplets and the membrane pore wall [13]. Presumably as a result of their much higher thickness (700–900 μm) and tortuous pore structure the SPG membranes led to more intensive colloidal droplet disruption than the thinner membranes, like e.g., the polycarbonate membranes (10 μm) used in previous studies [14,45]. In a model setup, droplet break-up in coarse dispersions was more effective in devices with branchings and junctions than in those with straight channels [44]. However, for an effective droplet break-up

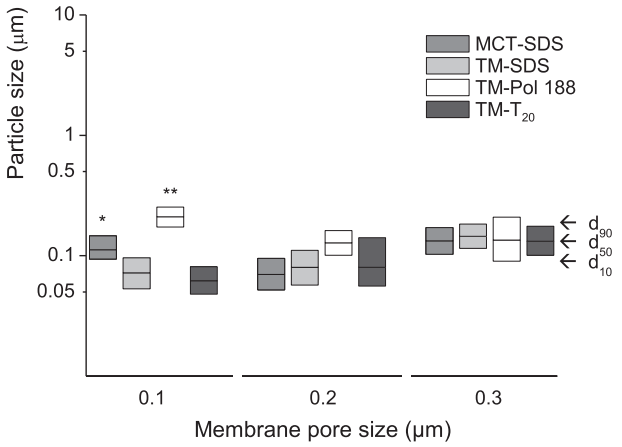

Fig. 8. Particle size distributions observed after one membrane passage in a formulation screening by premix SPG membrane emulsification with different membrane pore sizes. The predispersions used in the premix emulsification setup usually contained 10% matrix lipid (*5% matrix lipid, **2.5% matrix lipid).

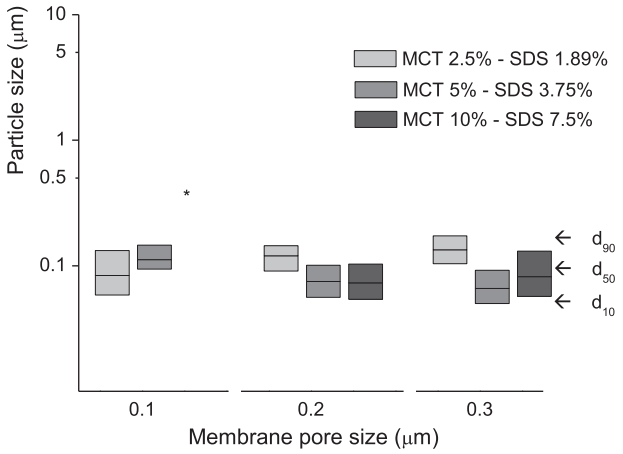

Fig. 9. Particle size distributions of SDS-stabilized colloidal emulsions containing different concentrations of matrix lipid (MCT) observed upon premix membrane emulsification with different membranes at an emulsifying pressure of 900 kPa (*MCT 10% – SDS 7.5% was not processable with a 0.1 µm SPG membrane).

the process pressure might have to be increased with increasing membrane thickness to compensate for the increasing flow resistance of the membrane thus maintaining a sufficient flow rate [44].

3.2.1. Influence of process parameters

As discussed for direct membrane emulsification, the flux through the membrane increases with the emulsifying pressure (Eq. (2)). A comparatively high pressure (close to the limit of the device) of 900 kPa was chosen in order to achieve short process times and thus preventing creaming of the predispersion in the pressurized vessel. In addition, the high flux results in a more effective droplet disruption due to higher shear stress on the dispersion inside the pores [39].

With decreasing membrane pore size smaller particle sizes were obtained (Fig. 8) but the effect of pore size was much less pronounced than in direct membrane emulsification (Fig. 3, left). After one membrane passage, the ratios of membrane pore size to mean particle size were in a range from 1:0.4 to 1:2.1 in good agreement with literature data for microparticulate lipid dispersions (1:0.7–1:4.4 [15,16]). Membrane pore sizes up to 0.3 µm could be employed for the preparation of monodisperse colloidal dispersions.

3.2.2. Influence of emulsion composition

As the viscosity of the formulations increased with the concentration of lipid phase some predispersions with 10 and 5% matrix lipid were not processable under the conditions applied (emulsifying pressure 900 kPa) because they did not pass the 0.1 µm-membrane (Figs. 8 and 9). An increase in the concentration of matrix lipid had, however, only minor effects on the resulting particle size distributions (Fig. 9). A tendency toward slightly smaller particles was observed for the formulations with a higher matrix lipid concentration. These results are in agreement with those obtained for differently stabilized (poloxamer 188, sucrose laurate) trimyristin solid lipid nanoparticles prepared by repeated premix membrane emulsification using polycarbonate membranes [14]: With increasing matrix lipid concentrations increasing emulsifying pressures were observed as well as a tendency toward narrower particle size distributions, but the mean particle size remained unchanged. According to Darcy's law (Eq. (1)), increasing viscosities require increasing emulsifying pressures to provide the flow through the pores of the membrane due to an increasing flow resistance of the liquid. The viscosity of the predispersion is also affected by the type and concentration of emulsifier. In premix membrane emulsification, the formed aqueous "lubrication layer" in the membrane pores become thicker with increasing viscosity of the continuous phase [39]. As a consequence, the droplets of disperse phase passing the membrane pore become thinner and elongated during their passage through the membrane resulting in a break-up to smaller droplets. Furthermore, an earlier droplet break-up inside the membrane pores was observed [38]. Vladisavljević et al. also observed decreasing particle sizes with increasing continuous phase viscosity upon repeated premix membrane emulsification [46].

4. Conclusions

Colloidal lipid particles of pharmaceutically relevant matrix lipids with narrow size distributions can be obtained by SPG membrane emulsification techniques when optimized formulations and preparation parameters are used. Direct emulsification under conventional conditions did, however, only lead to colloidal dispersions when membranes with 0.1 µm pore size were used and the resulting particles were still rather large. Moreover, direct membrane emulsification suffered the drawback of long process times. Generally, premix emulsification worked much better for the preparation of nanoemulsions and solid lipid nanoparticles with particles in the lower nanometer range than the direct preparation technique. Remarkably narrow particle size distributions with a mean particle size around 100–200 nm were obtained with the premix membrane emulsification process even after only one membrane passage. In this regard, the very short preparation time and thus the short stress to the dispersion represent a major benefit.

Due to the lower energy input and lower process pressures (max. 10 bar), SPG membrane emulsification is an interesting alternative method to high-pressure homogenization for the production of these types of drug carriers as well as for special products, which require a high quality with regard to narrow size distributions. However, the direct process does not seem to be a good option for standard processing of nanoparticles due to long preparation times and low yield.

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG) in the research group F856 mikroPART.

The authors would like to thank Carmen Gröchtemeier and Holger Kubiak (Technische Universität Braunschweig, Institut für Pharmazeutische Technologie, Germany) for technical assistance in the determination of viscosity and the construction of the double-walled pressurized vessel for the membrane emulsification device, respectively. Furthermore, the authors are grateful to Simone Schulze (Technische Universität Braunschweig, Institute for Chemical and Thermal Process Engineering, Germany) for taking the environmental SEM image as well as to Condea Chemie, Gattefossé, Henkel & Cie, BASF and Mitsubishi-Kagaku Food Corporation for providing raw materials. The authors would also like to express their gratitude to Judith Kuntsche (Syddansk Universitet, Department of Physics and Chemistry, Odense, Denmark) for fruitful discussions on the manuscript.

References

[1] H. Bunjes, Lipid nanoparticles for the delivery of poorly water-soluble drugs, J. Pharm. Pharmacol. 62 (2010) 1637–1645.
[2] S. Joseph, H. Bunjes, Solid lipid nanoparticles for drug delivery, in: D. Douroumis, A. Fahr (Eds.), Drug Delivery Strategies for Poorly Water-Soluble Drugs, John Wiley & Sons, Chichester, 2013.
[3] H. Schubert, R. Engel, Product and formulation engineering of emulsions, Chem. Eng. Res. Des. 82 (2004) 1137–1143.
[4] W. Mehnert, K. Mäder, Solid lipid nanoparticles: production, characterization and applications, Adv. Drug Delivery Rev. 47 (2001) 165–196.
[5] J. Floury, A. Desrumaux, J. Legrand, Effect of ultra-high-pressure homogenization on structure and on rheological properties of soy protein-stabilized emulsions, J. Food Sci. 67 (2002) 3388–3395.
[6] P. Paquin, Technological properties of high pressure homogenizers: the effect of fat globules, milk proteins, and polysaccharides, Int. Dairy J. 9 (1999) 329–335.
[7] F. Chemat, I. Grondin, P. Costes, L. Moutoussamy, A.S.C. Sing, J. Smadja, High power ultrasound effects on lipid oxidation of refined sunflower oil, Ultrason. Sonochem. 11 (2004) 281–285.
[8] T. Nakashima, M. Shimizu, M. Kukizaki, Membrane emulsification by microporous glass, Key Eng. Mater. 61–62 (1991) 513–516.
[9] T. Nakashima, M. Kawano, M. Shimizu, Articles of porous glass and process for preparing the same, US Patent No. 4,657,875, 1987.
[10] T. Nakashima, M. Shimizu, M. Kukizaki, Particle control of emulsion by membrane emulsification and its applications, Adv. Drug Delivery Rev. 45 (2000) 47–56.
[11] S.M. Joscelyne, G. Trägårdh, Membrane emulsification – a literature review, J. Membr. Sci. 169 (2000) 107–117.
[12] K. Suzuki, I. Shuto, Y. Hagura, Characteristics of the membrane emulsification method combined with preliminary emulsification for preparing corn oil-in-water emulsions, Food Sci. Technol. Int. 2 (1996) 43–47.
[13] G.T. Vladisavljević, M. Shimizu, T. Nakashima, Preparation of monodisperse multiple emulsions at high production rates by multi-stage premix membrane emulsification, J. Membr. Sci. 244 (2004) 97–106.
[14] S. Joseph, H. Bunjes, Preparation of nanoemulsions and solid lipid nanoparticles by premix membrane emulsification, J. Pharm. Sci. 7 (2012) 2479–2489.
[15] G.T. Vladisavljević, J. Surh, J.D. McClements, Effect of emulsifier type on droplet disruption in repeated shirasu porous glass membrane homogenization, Langmuir 22 (2006) 4526–4533.
[16] G.T. Vladisavljević, D.J. McClements, Modification of interfacial characteristics of monodisperse droplets produced using membrane emulsification by surfactant displacement and/or polyelectrolyte electrostatic deposition, Colloids Surf., A 364 (2010) 123–131.
[17] G.T. Vladisavljević, R.A. Williams, Recent developments in manufacturing emulsions and particulate products using membranes, Adv. Colloid Interface Sci. 113 (2005) 1–20.
[18] D.H. Oh, P. Balakrishnan, Y.-K. Oh, D.-D. Kim, C.S. Yong, H.-G. Choi, Effect of process parameters on nanoemulsion droplet size and distribution in SPG membrane emulsification, Int. J. Pharm. 404 (2011) 191–197.
[19] P. Czermak, T. Steinle, M. Ebrahimi, T. Schmidts, F. Runkel, Membrane-assisted production of S1P loaded SLNs for the treatment of acne vulgaris, Desalination 250 (2010) 1132–1135.
[20] C. Charcosset, A. El-Harati, H. Fessi, Preparation of solid lipid nanoparticles using a membrane contactor, J. Controlled Release 108 (2005) 112–120.
[21] A.A. El-Harati, C. Charcosset, H. Fessi, Influence of the formulation for solid lipid nanoparticles prepared with a membrane contactor, Pharm. Dev. Technol. 11 (2006) 153–157.
[22] C. D'oria, C. Charcosset, A.A. Barresi, H. Fessi, Preparation of solid lipid particles by membrane emulsification – influence of process parameters, Colloids Surf., A 338 (2009) 114–118.
[23] A. Svensson, C. Neves, B. Cabane, Hydration of an amphiphilic excipient, Gelucire® 44/14, Int. J. Pharm. 281 (2004) 107–118.
[24] Y. Li, H. Fessi, C. Charcosset, Preparation of indomethacin-loaded lipid particles by membrane emulsification, Adv. Sci. Lett. 4 (2011) 591–595.
[25] J. Drew, A. Liodakis, R. Chan, H. Du, M. Sadek, R. Brownlee, W.H. Sawyer, Preparation of lipid emulsions by pressure extrusion, Biochem. Int. 22 (1990) 983–992.
[26] N.C. Christov, K.D. Danov, D.K. Danova, P.A. Kralchevsky, The drop size in membrane emulsification determined from the balance of capillary and hydrodynamic forces, Langmuir 24 (2008) 1397–1410.
[27] M. Kukizaki, Shirasu porous glass (SPG) membrane emulsification in the absence of shear flow at the membrane surface: influence of surfactant type and concentration, viscosities of dispersed and continuous phases, and transmembrane pressure, J. Membr. Sci. 327 (2009) 234–243.
[28] V. Schröder, O. Behrend, H. Schubert, Effect of dynamic interfacial tension on the emulsification process using microporous, ceramic membranes, J. Colloid Interface Sci. 202 (1998) 334–340.
[29] H. Teng, T.S. Zhao, An extension of Darcy's law to non-Stokes flow in porous media, Chem. Eng. Sci. 55 (2000) 2727–2735.
[30] C. Charcosset, I. Limayem, H. Fessi, The membrane emulsification process – a review, J. Chem. Technol. Biotechnol. 79 (2004) 209–218.
[31] G.T. Vladisavljević, H. Schubert, Influence of process parameters on droplet size distribution in SPG membrane emulsification and stability of prepared emulsion droplets, J. Membr. Sci. 225 (2003) 15–23.
[32] G.T. Vladisavljević, H. Schubert, Preparation of emulsions with a narrow particle size distribution using microporous α-alumina membranes, J. Dispersion Sci. Technol. 24 (2003) 811–819.
[33] A.J. Abrahamse, A. van der Padt, R.M. Boom, W.B.C. de Heij, Process fundamentals of membrane emulsification: simulation with CFD, AIChE J. 47 (2001) 1285–1291.
[34] M. Stölting, Partikelbildung unterhalb des Strahlbereiches bei konstantem Volumenstrom, Chem. Ing. Tech. 52 (1980) 598–599.
[35] M. Pathak, Numerical simulation of membrane emulsification: effect of flow properties in the transition from dripping to jetting, J. Membr. Sci. 382 (2011) 166–176.
[36] W. Jing, J. Wu, W. Xing, W. Jin, N. Xu, Emulsions prepared by two-stage ceramic membrane jet-flow emulsification, AIChE J. 51 (2005) 1339–1345.
[37] U. Lambrich, H. Schubert, Emulsification using microporous systems, J. Membr. Sci. 257 (2005) 76–84.
[38] G.T. Vladisavljević, I. Kobayashi, M. Nakajima, R.A. Williams, M. Shimizu, T. Nakashima, Shirasu Porous Glass membrane emulsification: characterisation of membrane structure by high-resolution X-ray microtomography and microscopic observation of droplet formation in real time, J. Membr. Sci. 302 (2007) 243–253.
[39] M. Kukizaki, Preparation of solid lipid microcapsules via solid-in-oil-in-water dispersions by premix membrane emulsification, Chem. Eng. J. 151 (2009) 387–396.
[40] G.T. Vladisavljević, U. Lambrich, M. Nakajima, H. Schubert, Production of O/W emulsions using SPG membranes, ceramic α-aluminium oxide membranes, microfluidizer and a silicon microchannel plate – a comparative study, Colloids Surf., A 232 (2004) 199–207.
[41] R. Katoh, Y. Asano, A. Furuya, K. Sotoyama, M. Tomita, Preparation of food emulsions using a membrane emulsification system, J. Membr. Sci. 113 (1996) 131–135.
[42] S. Berot, S. Giraudet, A. Riaublanc, M. Anton, Y. Popineau, Key factors in membrane emulsification, Chem. Eng. Res. Des. 81 (2003) 1077–1082.
[43] D.-X. Hao, F.-L. Gong, G.-A. Hu, Y.-J. Zhao, G.-P. Lian, M. Guang-Hui, Z. Su, Controlling factors on droplets uniformity in membrane emulsification: experiment and modeling analysis, Ind. Eng. Chem. Res. 47 (2008) 6418–6425.
[44] E. van der Zwan, K. Schroën, K. van Dijke, R. Boom, Visualization of droplet break-up in premix membrane emulsification using microfluidic devices, Colloids Surf., A 277 (2006) 223–229.
[45] S. Joseph, H. Bunjes, Influence of membrane structure on the preparation of colloidal lipid dispersions by premix membrane emulsification, Int. J. Pharm. 446 (2013) 59–62.
[46] G.T. Vladisavljević, M. Shimizu, T. Nakashima, Production of multiple emulsions for drug delivery systems by repeated SPG membrane homogenization: influence of mean pore size, interfacial tension and continuous phase viscosity, J. Membr. Sci. 284 (2006) 373–383.