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Design of lipid microparticle dispersions based on the physicochemical properties of the lipid and aqueous phase

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ABSTRACT

Lipid microparticle (LMP) dispersions may be utilized as novel pharmaceutical dosage forms for different administration routes. The particle size and particle size distribution of the LMPs can be classified to the most crucial specifications for therapeutical and research applications. The size parameters can be adjusted via the physicochemical properties of the inner lipid and the outer aqueous phase. In the present study, ten different solid lipids with incorporated lecithin and four concentrations of the surfactant poloxamer 407 (P407) were utilized for LMP dispersion preparation. Physicochemical properties of the bulk and dispersed lipid matrices as well as features of the P407 solutions were determined. Correlations between the mean particle size (mean) of the LMPs and the span as parameter for the particle size distribution as responses were identified by plotting against the measured physicochemical parameters. Most significant linear correlations were found between the mean and the micellization onset temperature (T_{micell}) in the parent solution and the dynamic viscosity of the emulsifier solution at 25 °C and between the span and the T_{micell} in the LMP dispersion. Consequently, P407 micelles as a reservoir for surfactant monomers and the overall viscosity as a separator between newly-formed lipid droplets are fundamental stabilizing parameters.

1. Introduction

Lipid microparticle (LMP) dispersions are suitable for pharmaceutical applications such as ophthalmologic administration (Wolska and Sznitowska, 2013), inhalation (Scalia et al., 2013), oral intake (Yadav et al., 2009), nasal administration (Dalpiaz et al., 2014), parenteral injection (Yehia et al., 2012), and topical application (Al-Kassas et al., 2009). The utilization of biocompatible and commercially available lipids, the processing via established and scalable emulsification methods, the incorporation of particularly lipophilic drugs, the potentially enhanced physical and chemical stability of these compounds, and the modification of the drug release and/or targeting are favorable for implementation as innovative pharmaceutical dosage forms (Berton et al., 2011). Process and phase parameters may adjust the quality attributes of the final product such as the particle size and particle size distribution.

Defined particle sizes and size ranges are commonly specified for different applications. For instance, a particle size below 10 μm is preconditioned for application to the eye (Ali and Byrne, 2008), whereas a narrow particle size distribution between 0.5 and 5 μm is intended for lung targeting (Jaspart et al., 2007). A consistent target particle size can neither be assigned to promoted nasal nor oral drug delivery. However, generally smaller particles may either increase the nasal uptake due to similarity to viral or bacterial particles and associated induced phagocytosis processes (Sharma et al., 2009) or promote oral bioavailability due to surface enlargement and solubilization (Elgart et al., 2012). For subcutaneous or intramuscular injection, particles below 150 μm may be suitable (Del Curto et al., 2003). Additionally, particle sizes between 1 and 10 μm may hinder the diffusion from the injection site of parenteral depot formulations but are still predisposed to phagocytosis for entry into lymph nodes (Hafner et al., 2013). In dermal drug delivery, particles in the range of 20–40 μm are

Abbreviations: CP15, cetyl palmitate 15; CP95, cetyl palmitate 95; DLS, dynamic light scattering; DSC, differential scanning calorimetry; ΔT, extent of supercooling; FF TEM, freeze fracture transmission electron microscopy; HF, hard fat; OHV, hydroxyl value; GDB, glycerol dibehenate; GDS, glycerol distearate; GMD, glycerol monostearate; GTM, glycerol trimyristate; GTP, glycerol tripalmitate; GTS, glycerol tristearate; HPO, hydrogenated palm oil; LD/PIDS, laser diffractometer with polarization intensity differential scattering; LEC, lecithin; LM, lipid matrix; LMP, lipid microparticle; mean, mean particle size; T_{micell}, micellization onset temperature; P407, poloxamer 407; PDI, polydispersity index; PEG, polyethylene glycol; PEG 12000, polyethylene glycol 12000; PPG, polypropylene glycol; PCL, predominant chain length; $T_{recryst}$, recrystallization onset temperature; SV, saponification value; SAXS, small angle X-ray scattering.

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appropriate for distribution on the skin surface as for sunscreen applications (Scalia et al., 2007), whereas solid lipid particles in the range of 3–5 μm provide the potential for penetration into orifices of hair follicles (Lauterbach and Müller-Goymann, 2014).

Stable and precisely adjusted particle sizes and narrow particle size distributions are also essential for various research applications such as cellular uptake studies (Erni et al., 2002), provoked ischemias in animal models (Tsai et al., 2014), and the prospective introduction of tissue engineering scaffolds (Hacker et al., 2007). In order to understand basic correlations between particle sizes and biopharmaceutical processes such as follicular penetration (Patzelt et al., 2011), enhanced permeability and retention in tumors (Danhier et al., 2010), and drug release (Zaky et al., 2010), sizes have to be set accurately. Thus, understanding the impact of phase parameters and the reciprocity of their physicochemical properties on the size properties is crucial for the design of LMP dispersions in pharmaceutical and biomedical research and development.

In order to investigate different physicochemical properties of the lipid and aqueous phases and their interaction among each other, a range of ten different solid lipids and four concentrations of the block copolymer poloxamer 407 (P407) blended with the high-molecular polyethylene glycol 12000 (PEG 12000) were studied. Lecithin (LEC) was incorporated into the solid lipid in order to enable a potential association of a compound to the dispersed lipid phase and its interfacial layer (Finke et al., 2014). A rotor-stator homogenization process was chosen as a reproducible and established manufacturing procedure with constant process parameters in order to consider the impact of either the lipid or the emulsifier phase on the dispersion formation individually. Various investigations have been performed on the structural properties and formation mechanisms of P407 micelles (Basak and Bandyopadhyay, 2013), mixed micelles of P407 and polyethylene glycol (PEG) (Pragatheeswaran and Chen, 2013), mixtures of P407 assemblies and LEC vesicles (Quirion et al., 2013), and oil emulsions stabilized by block copolymers such as P407 (Torcello-Gómez et al., 2013). However, pharmaceutical formulations are multi-component systems whose structure and formation depend on the interplay of all constituents. For instance, colloidal formulations such as cubic dispersions (Siekmann et al., 2002), nanoemulsions (Ying et al., 2013), and LEC organogels (Bhatia et al., 2013) contain lipids, phospholipids, and P407. Therefore, in the present work a composition with the same basic constituents but with a dispersed phase in the micrometer range differing from previous reports was employed as the object of the study. Correlations between phase parameters of the single initial phases and the final size parameters in the dispersions were evaluated in order to elaborate on underlying mechanisms for generation of pharmaceutical dispersions.

2. Materials and methods

2.1. Materials

Cetyl palmitate 15 (CP15, Kollicream™ CP 15, BASF, Ludwigshafen, Germany), glycerol distearate (GDS, Precirol® ATO 5), glycerol dibehenate (GDB, Compritol® 888 ATO), cetyl palmitate 95 (CP95, Precifac®), glycerol monostearate (GMS, Geleol™), hard fat (HF, Gelucire® 43/01, all Gattefossé, Saint Priest, France), glycerol trimyristate (GTM, Dynasan® 114), glycerol tripalmitate (GTP, Dynasan® 116), hydrogenated palm oil (HPO, Softisan® 154, all Condea, Witten, Germany), and glycerol tristearate (GTS, Dynasan® 118, Sasol, Hamburg, Germany) as the solid lipid and purified LEC (Phospholipon® 90G, Lipoid, Ludwigshafen, Germany) formed the lipid matrix (LM). Poloxamer 407 (P407, Kolliphor™ P407, BASF, Ludwigshafen, Germany) and polyethylene glycol 12000 (PEG 12000, Sigma–Aldrich, Seelze, Germany) were dissolved in water of double-distilled grade in order to obtain the aqueous phase.

2.2. Preparation of the LMP dispersions

The LMP dispersions were produced according to (Lauterbach and Müller-Goymann, 2014). In brief, 30% LEC was solubilized in 70% molten lipid (all by weight) by stirring with a magnetic bar on a hot stirring plate (IKA® RCT basic, IKA®, Stauffen, Germany) at 70 °C or 90 °C in the cases of GDB and GTS to allow for complete solubilization. Each lipid melt was stirred at room temperature until solidification. 20% solid LM was dispersed at 70 °C or 80 °C in the cases of GDB and GTS with the aqueous phase containing P407 and PEG 12000 with an Ultra-Turrax® T25 digital (IKA®, Stauffen, Germany) with 16.000 rpm for 3 min. After cooling to ambient temperature the final dispersions were obtained. In the first experimental series, the solid lipids were varied while keeping the aqueous phase constant to 12% P407 and 3% PEG 12000. In the subsequent study, the LM was unchanged with a weight percentage of 20% and HPO as the solid lipid, whereas the concentration of P407 was varied from 6 to 12% in 2% steps (all by weight). The LM and LMP dispersions were analyzed one day after manufacturing and storage at ambient conditions for their physicochemical properties. The emulsifier solutions were subjected to further analysis after full dissolution and hydration of P407 and PEG 12000.

2.3. Particle size determination

The mean particle size (mean) and the span as the quotient of $(D_{90} - D_{10})/D_{50}$ were determined with a laser diffractometer featuring polarization intensity differential scattering technology (LD/PIDS, LS13 320, Beckman Coulter, Krefeld, Germany). The dispersions were measured by immediate dilution in the water of the measurement cell and the size parameters were calculated from the diffraction pattern via the Fraunhofer approximation and the resulting volume distribution in triplicate.

2.4. Microscopical analysis

The LMP dispersion composed of 20% LM based on HPO, 12% P407, and 3% PEG 12000 was prepared for freeze-fracture transmission electron microscopy (FF-TEM) according to a previous study (Lauterbach and Müller-Goymann, 2014). In brief, after shock-freezing of the sample between two gold holders in melting nitrogen, fracturing in a BAF 400 device (Balzers, Wiesbaden, Germany), shadowing with a 2 nm platinum/carbon layer and a 20 nm pure carbon coating, and cleaning with sulphuric acid and water, the sample was analyzed with a transmission electron microscope (LEO 922 Omega, Zeiss, Oberkochen, Germany).

2.5. Thermal analysis

Each LM was analyzed for melting and recrystallization events by differential scanning calorimetry (DSC) by keeping the sample at 25 °C for 5 min, heating it from 25 °C to 85 °C, keeping it at 85 °C for 5 min, and cooling it from 85 °C to 25 °C each time with a rate of 5 °C/min. The same measurement program was run for the LMP dispersions but starting and ending at 5 °C using a DSC1 (Mettler Toledo, Gießen, Germany) for additional analysis of the phase transition event of P407 micellization. All experiments were run in hermetically sealed off crucibles against an empty reference pan under a nitrogen flow of 40 ml/min in triplicate. The melting, recrystallization ($T_{recryst}$), and micellization onset temperature (T_{micell}) as well as the extent of supercooling (ΔT) as difference