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Monoacyl-phospatidylcholine based drug delivery systems for lipophilic drugs: Nanostructured lipid carriers vs. nano-sized emulsions

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ABSTRACT

Monoacyl-phosphatidylcholine (MAPL) offers beneficial properties as surfactant for production of nanostructured lipid carriers (NLC). A MAPL-based NLC system was modified to evaluate the effect of different formulation parameters on the skin permeation and penetration of the incorporated lipophilic model drugs flufenamic acid and fludrocortisone acetate. Increased viscosity and increased MAPL content were investigated regarding their effect on formulation properties, physico-chemical long-term stability and skin permeation. In addition, a MAPL-based oil-in-water nano-sized emulsion was developed for the first time and investigated for comparison. Results showed high storage stability of both NLC and emulsions based on surfactant mixtures with 65% w/w of MAPL; mean particle sizes and zeta potential values remained stable over 16 weeks. Diffusion cell and in vitro tape stripping studies on porcine skin showed that these NLC systems were superior to the corresponding nano-sized emulsions in terms of skin permeation. Neither increased viscosity nor higher MAPL content proved to be an additional benefit for skin permeation of the model drugs. In conclusion, MAPL-based NLC are an interesting carrier system for lipophilic drugs irrespective of the system's viscosity and superior to corresponding nanoemulsions.

1. Introduction

Drug delivery via the dermal route may be a challenging task. Different approaches to optimise skin penetration of drugs exist; one of those is the development of tailor-made innovative carrier systems [3,21,23,34]. A substantial amount of valuable data has been reported for such systems, starting with the development of solid lipid nanoparticles in the 1990s [6,24]; and the next-generation carrier system termed nanostructured lipid carriers (NLC)[1] [22,25,26].

For the production of such carrier systems, phospholipids are a well-established alternative to synthetic emulsifiers; they are frequently employed in dermal, intravenous and oral pharmaceutical formulations [28,32,33]. A regular phospholipid molecule consists of a glycerol backbone with two fatty acid esters in position 1 and 2 and a phosphatidylcholine group in position 3. A recent study has shown the traceability of phosphatidylcholine in porcine skin by vibrational spectroscopy [35]. However, few data exists on dermal formulations based on the more hydrophilic 1-monoacyl-phosphatidylcholine (MAPL)[2], where one fatty acid ester is replaced by an hydroxyl group through enzymatic reactions [9,14]. MAPL offers interesting properties for development of colloidal carrier systems such as MAPL-based self-emulsifying drug delivery system for oral delivery [12,31].

Previous work within our group has led to interesting findings regarding the role of MAPL and total lipid content within NLC formulations [36]. An optimised formulation (NLC65, see Table 1) for the delivery of lipophilic drugs was developed by using the surfactant mixture S LPC65, which consists of roughly 65% w/w of MAPL. Several points of interest arose during this work which we address in this follow-up study.

The aim of this study was to develop different MAPL-based NLC systems and nano-sized emulsions for lipophilic drugs and to investigate differences and similarities in physico-chemical stability and skin permeation. On the one hand, we wanted to elucidate whether the skin permeation of the model drugs flufenamic acid and fludrocortisone

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[1] NLC-nanostructured lipid carriers.
[2] MAPL-monoacyl-phosphatidylcholine.

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Table 1
Basic composition of MAPL-based systems in % w/w and abbreviations: nanostructured lipid carriers with 65% w/w MAPL content (NLC65), NLC with increased MAPL content of 80% w/w (NLC80) and nano-sized emulsions (NE65). Blank and drug-loaded systems with either flufenamic acid or fludrocortisone acetate were produced.

Constituents	NLC65	NLC80	NE65
Surfactant	5% S LPC65	5% S LPC80	5% S LPC65
Lipid phase	2.22% olive oil	2.22% olive oil	20% olive oil
	7.77% Precirol ATO5	7.77% Precirol ATO5	–
Water	ad 100%	ad 100%	ad 100%
Model drug	1% (w/w)		
	flufenamic (*fluf*) acid or fludrocortisone acetate (*fludro*)		

acetate could be modified by increased viscosity of the original NLC65 formulation (NLC65Gel). On the other hand, we wanted to compare the original NLC65 system with a corresponding NLC system with higher MAPL content (NLC80) and a corresponding MAPL-based nano-sized emulsion (NE65). Incorporation efficiency and drug content were monitored additionally to the physico-chemical properties of the systems. For the latter, photon correlation spectroscopy[3] (PCS), pH and rheology measurements as well as cryo transmission electron microscopy[4] (cryo TEM) were employed. To investigate the impact of the modified formulation properties (modification of viscosity, MAPL content or lipid core properties) on the skin permeation of the model drugs, diffusion cell studies were performed. To confirm the results in a finite-dose experimental setup, additional in vitro tape stripping experiments using porcine ear skin were conducted.

2. Material and methods

2.1. Materials

The monoacyl-phosphatidylcholine containing phospholipid mixtures *S-LPC65* and *S-LPC80* (65% or 80% w/w MAPL content) as well as purified olive oil (Ph.Eur.) were kindly provided by Lipoid GmbH (Ludwigshafen, Germany). Precirol®-ATO5 (glyceryl distearate/glyceryl palmitostearate) was provided by Gattefossé (Nanterre Cedex, France); Carbopol® 980 was provided by Lubrizol (Wickliffe, OH, USA).

Flufenamic acid (CAS 530-78-9), fludrocortisone acetate (CAS 514-36-3), TRIS[5] trizma base (EC 201-064-4) and potassium sorbate (CAS 24634-61-5) were purchased from Sigma Aldrich (St. Louis, USA). Aqueous phosphate buffer pH 7.4 (Ph.Eur.) was composed of 2.38 g of Na_2HPO_4 x 12 H_20, 0.19 g of KH_2PO_4 and 8 g of NaCl per 1000 ml of purified water. Porcine abdominal skin and pig ears were obtained from a local abattoir (Johann Gantner GmbH, Hollabrunn, Austria). All further chemicals were of analytical reagent grade and used without further purification.

2.2. Formulation composition

The basic composition of the investigated formulations NLC65, NLC80 and NE65 is given in Table 1. Amount and nature of surfactant and lipid phase is given for comparison. The gelified NLC65Gel formulation generally exhibited similar properties as the original NLC65 system; thus, it is only described separately where necessary.

2.2.1. Production of nanostructured lipid carriers

Nanostructured lipid carriers NLC65 and NLC80 were produced as recently described [36]. The aqueous phase and the lipid phase were prepared separately by stirring them at 70 °C. Next, the phases were mixed rapidly. After 1 min of pre-homogenisation with an ultraturrax Omni 5000 (Omni International, NW Kennesaw, USA) they were subjected to ultrasound treatment of two times 10 min with a Bandelin Sonopuls MS 73 (Bandelin electronic GmbH & Co. KG, Berlin, Germany) at 70 °C to achieve a mean energy input of 30 kJ. In case of drug-loaded NLC, the drug was dissolved in the oil phase (flufenamic acid 1% w/w and fludrocortisone acetate 1% w/w).

For the gelified NLC65Gel formulations, Carbopol® 980 (0.3% w/w) and trometamol (per 1 g Carbopol/0.167 g TRIS) were added to NLC65 systems after production. Potassium sorbate (0.1% w/w) was added as a preservative.

2.2.2. Production of nano-sized emulsion

The composition of the nano-sized emulsion was based on previous work [17]. The surfactant S LPC65 was mixed with a magnetic stirring bar in the aqueous phase. Potassium sorbate (0.1% w/w) was added for preservation. Olive oil was added at 70 °C; the mixture was homogenised with an ultraturrax Omni 5000 (Omni International, USA) for 4 min. The resulting emulsion was further treated with a high pressure homogeniser Emulsiflex C3 (Avestin Inc., Ottawa, ON, Canada) preheated with boiling distilled water. The emulsion was then exposed to 1000 bar of pressure for 10 cycles under high shear stress resulting in a white-creamish liquid nano-sized emulsion[6] (NE65).

2.3. Physico-chemical characterisation and stability evaluation

The parameters of interest were measured directly after production and were monitored fortnightly over an observation period of 16 weeks. Since preliminary studies have shown that refrigerated storage led to improved physical stability of the produced systems, all placebo and drug-loaded formulations were stored in airtight containers at 8 °C.

2.3.1. Mean particle size and PDI

The mean particle size and the polydispersity index[7] (PDI) of all formulations were determined by PCS using a Zetasizer Nano ZS (Malvern Instruments, Malvern, United Kingdom) at 25 °C. Samples were diluted with freshly distilled water 1:100 (v/v) containing sodium chloride (0.01 mmol). For NLC65Gels, the samples were centrifuged (12,000 rpm, 6 min, Hermle Z323K, Wehingen, Germany) and the supernatant was analysed.

2.3.2. Zeta potential

The zeta potential[8] (ZP) of the nanoparticulate systems was determined by laser Doppler electrophoresis using a Zetasizer NanoZS (Malvern Instruments, Malvern, United Kingdom) at 25 °C. Samples were diluted with distilled water (1:100 v/v) containing sodium chloride (0.01 mmol). For NLC65Gels, the samples were centrifuged (12,000 rpm, 6 min, Hermle Z323K, Wehingen, Germany) and the supernatant was analysed.

2.3.3. pH value

The pH value of the formulations was determined at room temperature (25 °C) in regular intervals to detect chemical destabilisation using a pH meter (Orion 420 A, Thermo Scientific Orion, Waltham, Massachusetts, USA).

2.4. Cryo transmission electron microscopy

The morphology of selected formulations was analysed using cryo TEM. Samples were diluted with distilled water (1:100 v/v) containing sodium chloride (0.01 mmol) to achieve results comparable to the data

[3] PCS-photon correlation spectroscopy.
[4] cryoTEM-cryo transmission electron microscopy.
[5] TRIS-trometamol.
[6] NE-nano-sized emulsion.
[7] PDI-polydispersity index.
[8] ZP-zeta potential.