International Journal of Pharmaceutics 498 (2016) 130–133

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Rapid communication

Double emulsions based on silicone-fluorocarbon-water and their skin penetration

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ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form 30 November 2015
Accepted 9 December 2015
Available online 11 December 2015

Keywords:
Perfluoropolyethers
Double emulsion
Skin permeation
Skin penetration
Stability

ABSTRACT

Double emulsions have significant potential in pharmacy and cosmetics due to the feasibility of combining incompatible substances in one product and the protection of sensitive compounds by incorporating them into their innermost phase. However, a major drawback of double emulsions is their thermodynamic instability and their strong tendency to coalesce. In the present study, the physicochemical stability, the skin permeation and the skin penetration potential of modified semi-solid double emulsions was investigated. The double emulsions were prepared of the cosmetically applied perfluoropolyethers Fomblin® HC/04 or Fomblin® HC-OH, silicone, carbomer and water. Measurement of the droplet size and examination of the microscopic images confirmed their physicochemical stability over the observation period of eight weeks. Franz-type diffusion cell experiments revealed no increase in curcumin permeation due to the employed perfluoropolyethers compared to the respective control formulations. The formulations used as control were O/W macroemulsions with or without a Polysorbate 80/Sorbitane monooleate 80 surfactant combination. Likewise, tape stripping studies showed no penetration enhancing effect of the employed perfluoropolyethers which is desirable as both perfluoropolyethers are commonly applied components in human personal-care products.

Double emulsions are complex systems in which the droplets of the dispersed phase contain smaller dispersed droplets (Garti and Bisperink, 1998). It has been reported that they have significant potential in pharmacy and cosmetics due to the feasibility of combining incompatible substances in one product and the protection of sensitive compounds by incorporating them into their innermost phase. However, a major drawback of double emulsions is their thermodynamic instability and their strong tendency to coalesce (Vasiljevic et al., 2006).

As a result of their insolubility in water or oil, perfluoropolyethers have been demonstrated to be suitable constituents for the preparation of double emulsions (Bonina et al., 1992; Lee et al., 2002). In the present study, the physicochemical stability, the skin permeation as well as the skin penetration potential of modified semi-solid double emulsions that were prepared of the cosmetically applied perfluoropolyethers Fomblin® HC/04 (PFPE HC/04) or Fomblin® HC-OH (PFPE-OH), silicone oil, carbomer and water, were investigated (Table 1). In order to evaluate the influence of PFPE-OH and PFPE HC/04 on the permeation and penetration behavior of an incorporated drug, we used curcumin as model substance. Due to the insolubility of perfluoropolyethers such as Fomblin® either in the water or in the oil phase, we chose the lipophilic compound curcumin (log*P* 3.28) that it is most likely to dissolve in the silicone phase. The inner phase of the double emulsions consisted of perfluoropolyethers and silicone oil.

First, we developed semi-solid double emulsions by mixing the lipophilic phase with the respective perfluoropolyether, followed by adding the hydrophilic phase. For reasons of easier application we also used carbomer to obtain semi-solid systems. The existence of multiple emulsions was evaluated by microscopic studies. Optical light microscopy was employed to confirm the presence and to characterize the morphology of multiple droplets using an Olympus BX53 microscope (Olympus Deutschland GmbH, Hamburg, Germany) equipped with a digital color camera for microscopes (Olympus DP72, Olympus Deutschland GmbH, Hamburg, Germany).

Usually, due to the presence of two thermodynamically unstable interfaces, the prerequisite for preparing stable double or multiple emulsions is the use of a combination of hydrophilic

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http://dx.doi.org/10.1016/j.ijpharm.2015.12.023
0378-5173/

and lipophilic surfactants (Schmidts et al., 2009). For the preparation of the PFPE HC/04 double emulsion we therefore used a Polysorbate 80/Sorbitane monooleate 80 surfactant combination. However, a stable double emulsion could also be prepared without surfactants using PFPE-OH. As also reported by Lee et al., 2002; the slightly polar fluorocarbon PFPE-OH was more effective in maintaining the stability of the double emulsion without additional surfactant than PFPE HC/04. Consistent with the findings of Lee et al., an inner droplet could be identified in the microscopic images in case of the PFPE-OH double emulsion (Fig. 1a) while the core of the PFPE HC/04 double emulsion was partially covered by the outer phase like a crescent (Fig. 1c).

In the following step, assessment of their physicochemical stability was performed by studying the morphology of the multiple droplets and measuring the droplet size over eight weeks. The comparison of the microscopic images of the freshly prepared and the 8-week stored preparations indicated a minor growth of the inner phase and a partial dissolution of the outer phase after 8 weeks of storage (Fig. 1b and d). The droplet size measurements were conducted with a laser diffraction particle size analyzer (Mastersizer 3000, Malvern, Worcestershire, UK). The refractive index, n, was set at 1.293 for the measurement of the double emulsions and 1.402 for the measurement of the macroemulsions. The absorptive index was 0.1 for all preparations. As can be seen in Fig. 2, the droplet sizes of the PFPE-OH double emulsions were larger (87 ± 7 μm) than the droplet sizes of the PFPE HC/04 double emulsions (69 ± 3 μm), but both preparations remained stable during the observation period showing no significant droplet size increase (PFPE-OH: repeated measures ANOVA, $P = 0.17$; PFPE HC/04: one-way ANOVA, $P = 0.25$). The formulations used as control were O/W macroemulsions with (O/W 30T/70S) or without (O/W macro) the surfactant combination (Table 1). The droplet size of the O/W macro was 274 ± 16 μm and 122 ± 5 μm in case of the O/W 30T/70S.

Table 1
Compositions of the double emulsions and the O/W macroemulsions used as control in% (w/w). The formulations used as control were O/W macroemulsions with (O/W 30T/70S) or without (O/W macro) the surfactant combination. The PFPE HC/04 double emulsion and its control formulation O/W 30T/70S contained 2% of a surfactant combination consisting of 30% Polysorbate 80 and 70% Sorbitane monooleate 80. For Franz-type diffusion cell experiments and tape stripping studies, curcumin was incorporated at a concentration of 1% (w/w). T = Polysorbate 80; S = Sorbitane monooleate 80.

Components	Formulation			
	PFPE-OH	O/W macro	PFPE HC/04	O/W 30T/70S
PFPE-OH	15	–	–	–
PFPE HC/04	–	–	15	–
Silicone oil 350	5	5	5	5
Carbomer	0.08	0.08	0.08	0.08
Triethanolamine 50%	0.2	0.2	0.2	0.2
Polysorbate 80	–	–	0.6	0.6
Sorbitane monooleate 80	–	–	1.4	1.4
Water	79.72	94.72	77.72	92.72

Franz-type diffusion cell experiments were conducted using porcine abdominal skin of 700 μm thickness as model membrane and phosphate buffer (0.012 M, pH 7.4) containing 25% (v/v) ethanol as the receptor medium. Fifty milligrams of formulation per square centimeter were applied onto the skin. Samples were withdrawn after 8 and 24 h. Quantification of curcumin concentrations in the samples was done by measuring absorbance at 422 nm on a microplate reader (Tecan™ Infinite 200, Gröding, Austria). Due to the high lipophilicity of the model substance curcumin, the permeated amounts were very low, around 1% of the applied curcumin after 24 h (Fig. 3). Comparison of the permeation rates of the double emulsions with the respective control formulations revealed no increase in curcumin permeation through the employed perfluoropolyethers. However, a trend to

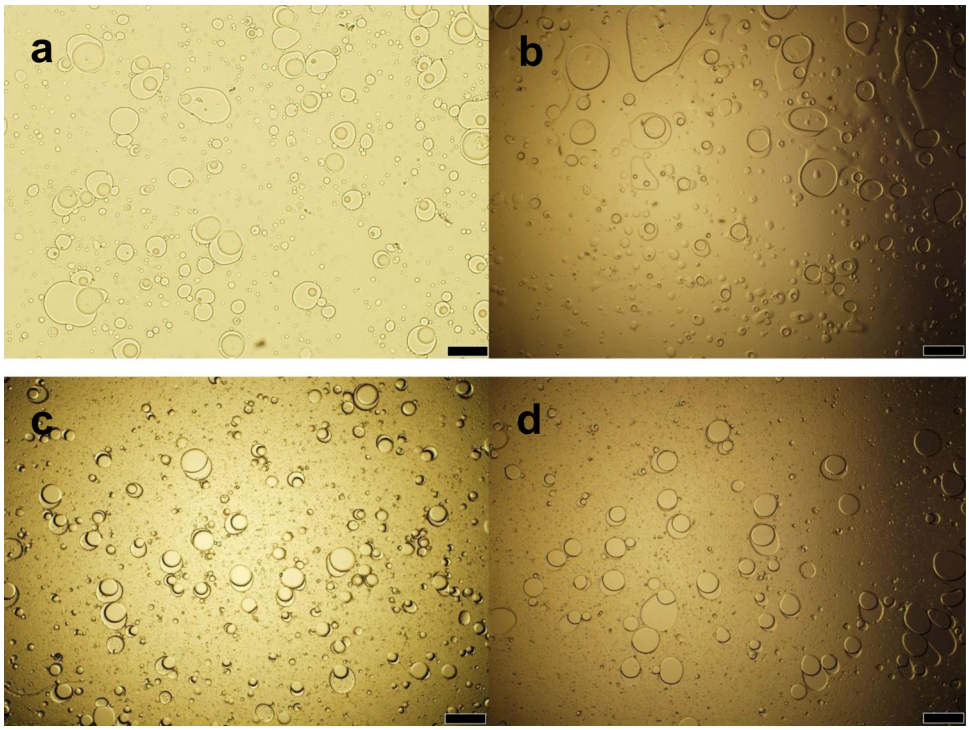

Fig. 1. Microscopical image of the prepared double emulsions used to characterize and assess their stability. Pictures were made directly after preparation and after eight weeks of storage: (1a) fresh PFPE-OH double emulsion; (1b) PFPE-OH double emulsion 8-week stored; (1c) fresh PFPE HC/04 double emulsion; (1d) PFPE HC/04 double emulsion 8-week stored; The indicated scale bars represent 200 μm.