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Research paper

Novel concentrated water-in-oil emulsions based on a non-ionic silicone surfactant: Appealing application properties and tuneable viscoelasticity

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ABSTRACT

Silicone excipients are non-irritating ingredients that are extensively used in topical formulations. In the present study, innovative water-in-oil emulsions with a high water content stabilised by a non-ionic silicone surfactant were developed. Effects of formulation composition on its properties and stability were investigated. It was possible to prepare highly stable emulsions with a water volume fraction of up to 80%. The emulsions exhibited desirable application properties such as non-sticky and cooling qualities. A dependency of the viscosity on the water fraction was found; this offers the opportunity to create emulsions with fine-tuned rheological properties.

Furthermore, it could be shown in skin studies that the *in vitro* release of a hydrophilic model drug is influenced by the configuration of the oil phase. The penetration of the silicone surfactant and the other deployed additives was monitored using combined tape stripping and ATR-FTIR experiments, revealing that the compounds remain in the superficial layers of the stratum corneum, thus minimising the risk for skin irritation.

1. Introduction

There is a wide range of scientific literature dealing with emulsion formulation and characterisation; however, the majority is focusing on oil-in-water (O/W) emulsions. In the field of water-in-oil (W/O) emulsions, wherein an aqueous phase is dispersed in an oil phase, the research seems to be much scarcer. One explanation for the limited number of studies might be that in the past, W/O emulsions were more difficult to prepare due to a lack of applicable surfactants, especially if aiming for high water content. Concerning the analysis of W/O systems, a dilution with water is not possible owing to the immiscible property of ambient oil phase and water. This represents a major challenge as many analytical techniques cannot be deployed.

Despite these difficulties, W/O emulsions offer distinct advantages for dermal application. When applied, a continuous film is formed immediately due to the direct contact of the external oil phase with the skin surface; this oil film helps maintaining the flexibility and hydration of the skin [1]. W/O emulsions offer the possibility to include a hydrophilic active pharmaceutical ingredient (API) within the inner water phase; thus, the API is protected against extrinsic impacts by the continuous oil film.

Silicone surfactants, based on a polysiloxane backbone composed of alternating silicon and oxygen atoms, are predestined for the stabilisation of W/O emulsions. The properties of the emulsifier can be adapted by modifying the functional groups attached to the siloxane polymer chain [2]. Using silicone surfactants, it is possible to stabilise a particular large portion of aqueous phase. The high water content facilitates the incorporation of a large proportion of water-soluble API; additionally, it imparts a sensation of coolness when applied.

Silicones have been used in personal care products over many decades; they can be considered safe for topical use as they are non-toxic and do not affect the microstructure of stratum corneum (SC) lipids [3]. A recent study found that despite their water-resistant properties, silicone excipients act non-occlusive [4]. Unlike other W/O surfactants, silicone emulsifiers do not need waxes for additional stabilisation; this makes the formulations more appealing for the user [1]. Consequently, W/O emulsions stabilised by silicone surfactants offer excellent properties for widespread cosmetic and pharmaceutical application.

The objective of this study was to develop and characterise new skin-friendly W/O emulsions with the non-ionic silicone surfactant Dow Corning® Emulsifier 10 as stabiliser. The influence of the formulation

Abbreviations: O/W, oil-in-water; W/O, water-in-oil; API, active pharmaceutical ingredient; SC, stratum corneum; ATR, attenuated total reflection; FTIR, Fourier transform infrared spectroscopy

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composition on its properties and stability should be elucidated. To this end, oils with different polarities were chosen as constituents of the continuous phase. In order to assess the role of emulsifier concentration and water volume fraction, the emulsions were stabilised by 2–4% emulsifier at different water-to-oil ratio. The produced emulsions were characterised in terms of appearance, skin feel, rheological behaviour and stability.

Furthermore, it was of interest to investigate the performance of the emulsions in terms of dermal drug delivery. Novel W/O emulsions that are able to deliver APIs through the SC may serve as useful new dermal drug delivery option; previous carrier systems designed for incorporation of hydrophilic actives, such as liposomes, have drawbacks regarding their storage stability [5,6]. In this study, two different model drugs were incorporated into the developed emulsion systems and *in vitro* Franz-type diffusion cell experiments were carried out using porcine skin. In doing so, the effect of the oil component and formulation composition on the percutaneous permeation of the model drugs was investigated.

Besides the interaction of an incorporated API with the skin, the behaviour of the non-active ingredients of the formulation when applied onto skin should be considered as well. There have been some efforts to analyse the interaction of silicone components with the skin tissue [7,8]; however, the penetration behaviour of the silicone content is not yet fully elucidated. To determine the penetration depth of the silicone additive Emulsifier 10, *in vitro* skin studies were conducted using a combination of the tape stripping technique with ATR-FTIR (attenuated total reflection-Fourier transform infrared) spectroscopy. Thus, knowledge about the skin irritation potential of the silicone surfactant could be obtained as skin irritation is presumably linked to the spatial distribution of a surfactant in the SC [9]. Additionally, the penetration of the two deployed oils into the skin has been investigated.

2. Materials and methods

2.1. Materials

Dow Corning® Emulsifier 10, a silicone surfactant with a hydrophilic lipophilic balance (HLB) value of 2.2, was kindly donated by Biesterfeld Spezialchemie (Hamburg, Germany). Liquid paraffin, isopropyl myristate and sodium chloride were obtained from Herba Chemosan Apotheker-AG (Vienna, Austria). Bodipy 493/503 (4,4-difluoro-1,3,5,7,8-pentamethyl-4-bora-3a,4a-diaza-s-indacene) was purchased from Invitrogen (Eugene, OR, USA) while fluorescein sodium salt, curcumin and Atto 594 were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Abdominal porcine skin was bought from a local butcher, pig ears were obtained from a local abattoir (EU-Schlachthof Gantner, Hollabrunn, Austria) and stored at −24 °C up to a maximum of 6 months. Tesa film crystal clear polypropylene tape (product number 58247-00000, Hamburg, Germany) was used to remove the layers of the SC during tape stripping experiments.

2.2. Preliminary experiments and formulation development

To investigate the effect of chemical differences in the oil phase on emulsion formation and characteristics, two oils with different polarities were chosen for the preparation of the W/O emulsions; isopropyl myristate and liquid paraffin, with polarity indexes (mN/m) 24.2 and 38.3, respectively. In preliminary experiments, it was investigated whether it was possible to produce suitable and stable enough systems with both selected oils. Subsequently, the applicable ratio of ingredients was identified.

Taking into account the results of our preliminary investigations, six formulations were selected for further examination. The final emulsions were stabilised by 2–4% emulsifier at water-to-oil ratio of 20–80% and 18–37%; the composition of the selected emulsions is given in Table 1.

Table 1
Composition of the investigated W/O emulsions in% (w/w).

Emulsion	Excipients			
	Emulsifier 10	Liquid paraffin	Isopropyl myristate	Water phase[a]
PAR_2/18	2	18	–	80
PAR_4/36	4	36	–	60
IPM_2/18	2	–	18	80
IPM_2/28	2	–	28	70
IPM_3/27	3	–	27	70
IPM_3/37	3	–	37	60

[a] Composed of distilled water containing 1% (w/w) sodium chloride.

2.3. Emulsion preparation

The emulsions were prepared by first mixing Emulsifier 10 with the selected oil. Subsequently, the water phase, consisting of freshly distilled water and 1% sodium chloride for formulation stability, was added to the oil phase under moderate stirring (750 rpm). Specifically, the water had to be added slowly to the oil phase so that the emulsifier could thoroughly coat the water droplets. In a last step, the mixture was subjected to an ultraturrax (Omni 5000, Omni International, Kennesaw, USA) at 2500 rpm for 4 min to obtain the final W/O emulsion. The production process was consistently carried out at room temperature.

Additionally, emulsions with model drugs were produced; fluorescein sodium salt and curcumin were used as hydrophilic and hydrophobic model drugs, respectively. To this end, emulsions were loaded with either 0.1% (w/w) of fluorescein sodium salt or 3% (w/w) of curcumin by adding the drug in powder form to the water or oil phase before merging them.

2.4. Emulsion characterisation and stability monitoring

The produced emulsions were characterised immediately after preparation and monitored over an observation period of 20 weeks. In order to detect any instability such as creaming or phase separation, they were investigated for the presence of structures visible to the eye. Likewise, each sample was characterised regarding consistency and skin feeling.

The pH value of the emulsions was determined using a pH meter (Orion 420A, Bartelt, Austria) with an Orion ROSS micro pH electrode (8220BNWP). The rheological properties were likewise investigated in regular intervals over a period of 20 weeks with a cone-and-plate system. Optical light and fluorescence microscopy was employed to gain detailed insight into the structures of the formulations.

The developed emulsions were prepared and analysed in triplicate (n = 3); they were stored in sealed glass containers at 4 °C in a refrigerator.

2.5. Optical microscopy

Optical microscopy was applied to characterise the morphology of the emulsions and to observe structures in the micrometer size range. The examinations were carried out using an epifluorescence microscope (Zeiss Axio Observer.Z1 microscopy system, Carl Zeiss, Oberkochen, Germany) equipped with phase contrast and differential interference contrast (DIC). A small amount of each sample was placed on a microscopy slide, covered and observed immediately. Images were processed using AxioVision software Rel 4.8.2 (Carl Zeiss, Oberkochen, Germany).

Selected emulsions were investigated by fluorescence microscopy. Therefore, the fluorescent dyes Atto 594 and Bodipy were incorporated into the formulations as visual markers for either aqueous or oil phase. These fluorescent labels were chosen according to their excitation and emission maxima; besides optical considerations, the solubility in water