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Evaporative destabilization of double emulsions for effective triggering of release

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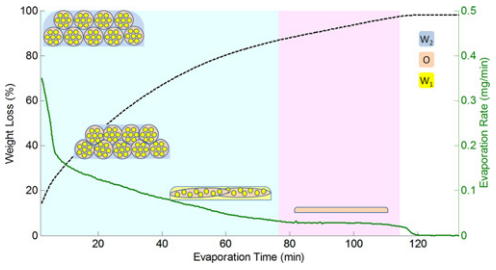
HIGHLIGHTS

- Volatile $W_1/O/W_2$ double emulsions with a cream-like texture were formulated.
- The double-emulsion's evaporation behavior was studied by use of TGA.
- Evaporation results were compared against a mathematical model system.
- Evaporation acts as a trigger mechanism for the release of W_1 phase contents.
- The release rate of the contents can be tuned by composition design.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, volatile water-in-oil-in-water ($W_1/O/W_2$) double emulsions with a cream-like texture were formulated for potential application in dermal delivery. This was achieved by selecting skin-compatible and volatile cyclomethicones, as the oil phase (O) of $W_1/O/W_2$ double emulsions. The double-emulsion's evaporation behavior was studied by use of thermogravimetric analysis (TGA) in order to understand the release mechanism of the internal aqueous phase (W_1). The evaporation rates for the different double emulsions were compared against a model system, in which all three phases were expected to evaporate simultaneously, independently, and at constant rate. Some similar characteristics between the model and the experimental data such as total evaporation time and presence of different evaporation stages were found. Finally, studies showing visual evidence of release and phase separation induced by evaporation were carried out. It was found that the evaporation of $W_1/O/W_2$ double emulsions may act as an effective trigger mechanism for the release of ingredients in the W_1 phase. The release rate of the contents can be tuned by composition design, that is, by selecting oils with the appropriate volatility; the higher the volatility of the oil the faster the release rate of the internal aqueous phase.

1. Introduction

Water-in-oil-in-water double emulsions ($W_1/O/W_2$) are three-phase systems in which oil globules (O) containing tiny droplets of an internal aqueous phase (W_1) are dispersed in an external aqueous phase (W_2). $W_1/O/W_2$ double emulsions are traditionally fabricated by a two-step process [1], where a simple emulsion (W_1/O) is prepared and then re-emulsified to form $W_1/O/W_2$, but they have been also recently generated using a more convenient one-step process [2,3]. Double-emulsion formulations have a compartmentalized structure that can provide high capacity of entrapment, protection of fragile substances, combination of incompatible substances in one product, and controlled release [4]. These features can make double emulsions useful for several applications in foods, pharmaceutical, and cosmetics [5–7].

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Double emulsions with controlled-release purposes can be successfully prepared by several approaches [8–13], but an important aspect must be considered when designing such formulations, namely, the trigger-release mechanism. Several mechanisms are known for inducing burst release of double-emulsion contents, such as shear stress [14–16], dilution into hypo-osmotic solutions [17,18] and recently studied in our lab, freeze-thaw cycling [19–21]. Nevertheless, there are almost no studies referring to an important mechanism which is naturally relevant to the use of multiple emulsions for dermal application: evaporation. Effect of evaporation on emulsion systems, such as water-in-oil microemulsions [22], oil-in-water emulsions [23–25] and water-in-oil emulsions [26,27] has been extensively investigated. In concentrated oil-in-water emulsions, the evaporation of the external aqueous phase induced the compression of oil droplets. and subsequently to drop coalescence [24]. However, only one study has mentioned double-emulsion evaporation, specifically of the O/W/O type [28], but the effect that the evaporation of double emulsions has on the burst release of their contents was not addressed.

In this work, volatile water-in-oil-in-water ($W_1/O/W_2$) double emulsions were produced for potential use as dermal cream-like delivery vehicles. Several formulations were prepared with cyclomethicone oils and silicone-based emulsifiers, which are broadly used in cosmetic applications due to their optimal skin compatibility and spreadability [29]. Furthermore, double-emulsion evaporation behavior under thermal conditions akin to the skin (~33 °C) was studied to reveal the path that leads to triggered release of the encapsulated species, herein a model macromolecule. Finally, release studies induced by evaporation were carried out. Elucidating the evaporation process followed by double-emulsion formulations may be key to better understand the release mechanism and properly tune it for the intended application, which may require either immediate or time-dependent release.

2. Experimental

2.1. Materials

Deionized (DI) water, produced from an Elga water purification system (Medica DV25, Woodridge, IL), with resistivity of 18.2 MΩ cm was used in all experiments. Fluorescein isothiocyanate-conjugated bovine serum albumin (FITC-BSA) was chosen as the model macromolecule, which has a molecular size of 67 kDa, and excitation and emission wavelengths of 485 and 520 nm, respectively. FITC-BSA was employed for all experiments except for the release studies where bovine serum albumin (BSA), which has an excitation wavelength of 278 nm, was used as the model protein instead. A 16.66 mM concentration of 4-(2-hydroxyethyl) piperazine-1-ethanesulfonic acid (HEPES) buffer solution of pH 7.4 was used as the aqueous medium for the model macromolecule. The silicone oils, octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5), were obtained from Clearco Products Co., Inc. The silicone-based polymeric surfactants used to stabilize the $W_1/O/W_2$ double emulsions were Abil® EM90, known also as cetyl PEG/PPG-10/1 dimethicone (which means having a 10:1 molar ratio of ethylene glycol to propylene glycol) and Abil® Care 85 named also as Bis-PEG/PPG-16/16 PEG/PPG-16/16 dimethicone (similarly, Abil® Care 85 has a molar proportion 1:1). The structural formulas are shown below in Fig. 1, and clearly show the oil-soluble surfactant as Abil EM90, whereas the Care 85 is more hydrophilic. Tego® Carbomer 341 ER (Acrylates/C10-30 alkyl acrylate crosspolymer) was used as a thickener of the external aqueous phase (W_2). These were kindly provided by Evonik Degussa Corporation (Parsippany, NJ). Polyoxyethylene sorbitan monooleate

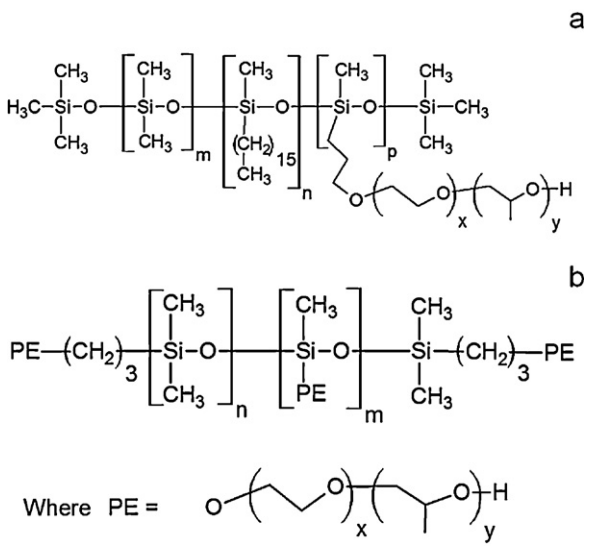

Fig. 1. Structural formulas of the silicone-based polymeric surfactants. (a) Abil EM 90, (b) Abil Care 85.

(Tween 80), used as a cosurfactant in the W_2 phase, and all other reagents and chemicals were purchased from Sigma (St. Louis, MO) unless otherwise stated and were used without further purification.

2.2. Methods

2.2.1. Preparation of double-emulsion formulations

$W_1/O/W_2$ double emulsions were prepared by a two-step emulsification procedure at a volumetric ratio of 2:2:1. The W_1 phase consisted of 5 mg/mL FITC-BSA in HEPES buffer solution at pH 7.4. The composition of the Oil and W_2 phases was varied, leading to the eight different formulations summarized in Table 1. The introduction of a thickener in the W_2 phase was necessary to enhance kinetic stability as preliminary formulations without it were prone to rapid phase separation, given the fact that double emulsions are thermodynamically unstable [30,31].

Briefly, during the first step, 3 mL of the internal aqueous phase (W_1) were added dropwise into 3 mL of the oil phase (O) for about 5 min under vigorous magnetic stirring (710 rpm). Then, a homogenizer (Silverson L4R) with medium-size emulsion screen was utilized to obtain the W_1/O emulsion by applying high-shear homogenization at 1000 rpm for 5 min. During the second step, 5 mL of the freshly prepared W_1/O sample emulsion were added dropwise into 2.5 mL of the external aqueous phase (W_2) under gentle magnetic stirring (315 rpm), prolonging stirring for 5 min after addition ended.

2.2.2. Microscopic and visual observations

After fabrication, samples of each formulation were stored at room temperature (21 ± 1 °C) and also at 5 °C to assess emulsion stability, i.e., to monitor any physical separation of the emulsion phases. Optical and fluorescence microscopy was employed to verify double-emulsion structure. For this, an aliquot of the double emulsion was diluted (20-fold) with 0.2 wt.% Tween 80 in HEPES buffer solution and gently stirred for a few seconds. Subsequently, 5 μL of the diluted emulsion were placed onto a concave glass slide and carefully covered with a coverslip to minimize drying. Samples were observed by use of a Leica DM-IRE2 fluorescence inverted microscope equipped with a Leica DC350F camera (Leica Microsystems Imaging Solutions Ltd, Cambridge, UK). Images were captured onto a computer with Image-Pro Plus image-analysis system,