Abstracts

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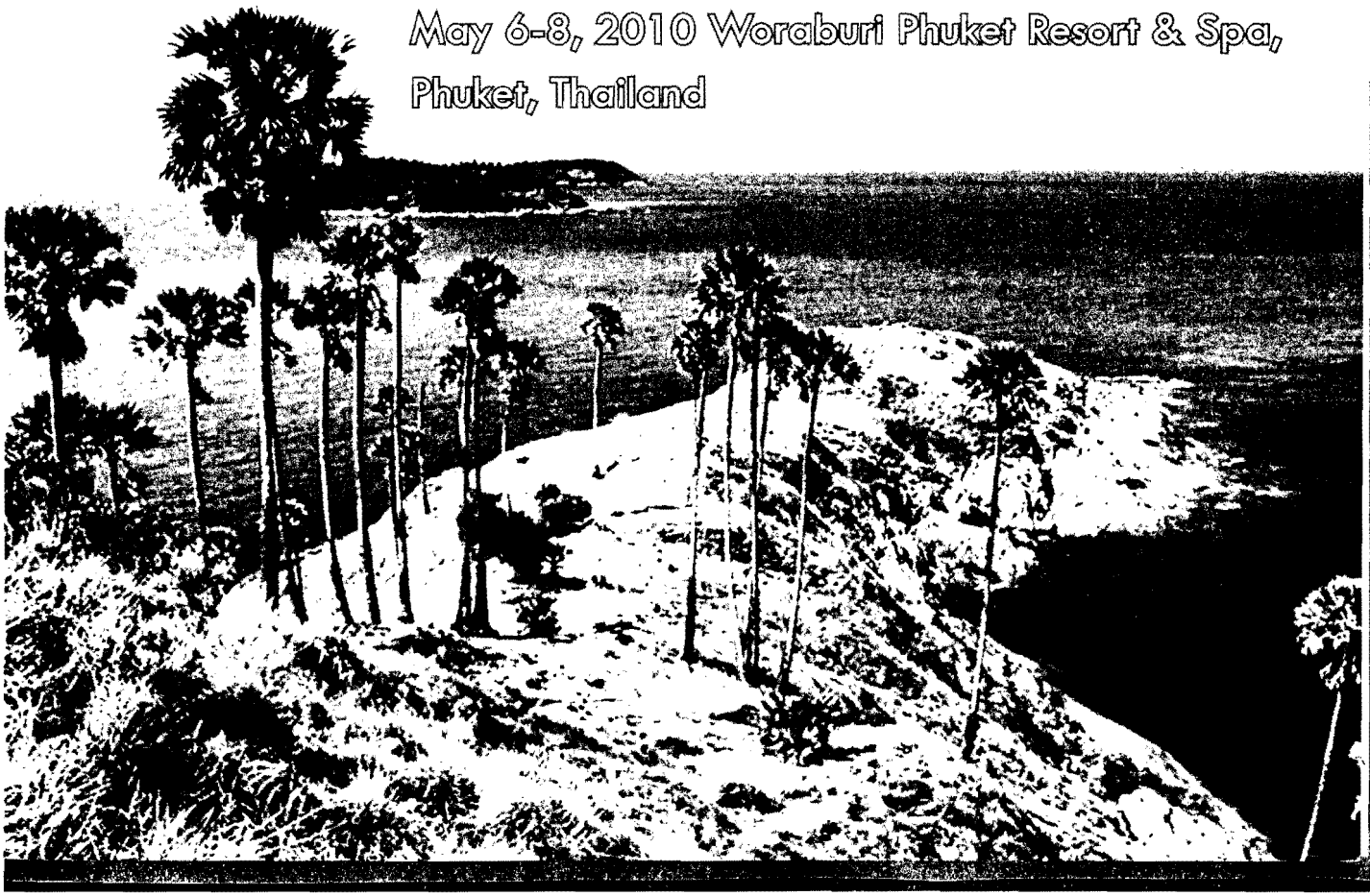

Kinetics of *in vitro* release of nicotinamide from non-ionic microemulsions

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The aim of present investigation was to study the in vitro release kinetics of nicotinamide from non-ionic microemulsions (MEs) formulated with cosmetic acceptable ingredients. Oleth-10, isopropyl alcohol (IPA), soybean oil and water were used as surfactant, cosurfactant, oil phase and aqueous phase, respectively. Two water-in-oil (w/o) microemulsion formulations designated as ME-1 and ME-2 were selected from the microemulsion region of water/soybean oil/9:1 oleth-10:IPA system to incorporate with 3% w/w nicotinamide. Both formulations were composed of the same concentration of water but different concentration of soybean oil and surfactant/cosurfactant mixture. The cumulative amount of nicotinamide released through the cellulose acetate membrane was performed using modified Franz diffusion cells and then plotted with time or square root of time in order to characterize the release kinetics of nicotinamide from the MEs. The results demonstrate a good correlation or higher values of correlation coefficients for Higuchi model rather than first order model for both studied MEs. The mechanism of release of a hydrophilic compound from w/o MEs is likely to be dependent on diffusion or partition process.

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Summary

The aim of present investigation was to study the *in vitro* release kinetics of nicotinamide from non-ionic microemulsions (MEs) formulated with cosmetic acceptable ingredients. Oleth-10, isopropyl alcohol (IPA), soybean oil and water were used as surfactant, cosurfactant, oil phase and aqueous phase, respectively. Two water-in-oil (w/o) microemulsion formulations designated as ME-1 and ME-2 were selected from the microemulsion region of water/soybean oil/9:1 oleth-10:IPA system to incorporate with 3% w/w nicotinamide. Both formulations were composed of the same concentration of water but different concentration of soybean oil and surfactant/cosurfactant mixture. The cumulative amount of nicotinamide released through the cellulose acetate membrane was performed using modified Franz diffusion cells and then plotted with time or square root of time in order to characterize the release kinetics of nicotinamide from the MEs. The results demonstrate good linear relationships or higher values of coefficient of determination for Higuchi model rather than first order model for both studied MEs. The mechanism of release of a hydrophilic compound from w/o MEs is likely to be dependent on diffusion or partition process.

Introduction

In Asia, light or fade skin is preferable; therefore skin lightening products are popular. Among a lot of skin lightening agents, nicotinamide is one of widely used and well-known compound. It can inhibit melanosome transfer from melanocytes to keratinocytes. Therefore, it provides safety mechanism since inhibition process occurs after melanogenesis within melanosome and does not affect intrinsic biosynthesis of melanin production. In addition, it can be applied for moisturizing and treatment of acne vulgaris (Hakozaki et al., 2002; Soma et al., 2005; Solano et al., 2006; Kaymak & Onder, 2008). Nicotinamide, which is also called niacinamide, is one of two principal forms of vitamin B3. It is also called vitamin B3. Another form of vitamin B3 is nicotinic acid (niacin). Nicotinamide plays an important role in the body as a precursor of two important coenzymes, i.e., nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) to generate energy inside the cells. These coenzymes are involved in many intracellular oxidation-reduction reactions. For the stability, nicotinamide is resistant to heat, air, and oxidants, but it is hydrolyzed in strong acidic and alkaline solutions (Draelos, 2000; Leskova et al., 2006). Since nicotinamide is hydrophilic, it is difficult to penetrate into the skin due to the lipid bilayer structure of the stratum corneum (Hakozaki et al., 2006; Nicoli et al., 2008). To improve the skin penetration of nicotimide, advanced vehicles are necessary. Microemulsions (MEs) are one of the interesting novel vehicles using in cosmetics. They are optically transparent, low viscous, and thermodynamically stable dispersions of oil and water stabilized by the interfacial film of a surfactant, usually in combination with a cosurfactant. Recently published report has informed about proposed mechanisms of MEs in skin penetration enhancement (Boonme, 2007). For example, a large amount of active ingredient can be incorporated in the formulation due to high solubilization power. The thermodynamic activity of the active ingredient in the MEs can be modified to favor partitioning into the stratum corneum. The surfactants in the MEs may reduce the diffusional barrier of the stratum corneum. MEs can act as active ingredient reservoirs where loaded active ingredient is released from the internal phase to the external phase and then to the skin. The nano-sized droplets in range of about 10-140 nm dispersed in the continuous phase of the MEs can move easily through the stratum corneum and carry the active ingredient through the skin barrier. If the water content in the MEs is high enough, percutaneous absorption of active ingredient can increase due to the hydration effect of the stratum corneum. Nowadays, MEs have been applied as the vehicles for numerous cosmetic active ingredients such as whitening agents, antioxidants, moisturizers, sunscreens and others in order to increase the product efficiency and respond to the consumers' demand (Boonme, 2007; Boonme, 2009; Boonme et al., 2009). The aim of this study was to investigate the *in vitro* release kinetics of nicotinamide from microemulsions formulated with cosmetic acceptable ingredients.

Materials and Methods

Materials

Nicotinamide was purchased from Fluka (Buchs, Switzerland). Soybean oil was obtained from Thai Vegetable Oil Public Company (Nakornphathom, Thailand). Oleth-10 (polyoxyethylene-10-oleyl ether) was obtained from Uniquema (New Castle, DE, USA). Isopropyl alcohol (IPA) was purchased from Anala R®, VRW International Ltd (Poole, England). Sterile water for injection was supplied by Thai Otsuka Pharmaceutical Co., Ltd (Samutsakorn, Thailand). All chemicals were of pharmaceutical grade and used as received without further purification. Other chemicals used in release study and analysis were purchased from local suppliers and of analytical grade.

Microemulsion preparation

In our previous study, the system of water/soybean oil/9:1 oleth-10:isopropyl alcohol (IPA) provided the largest microemulsion region among several investigated systems (Suksawad et al., 2009). Therefore, two MEs designated as ME-1 and ME-2 from this system were further investigated in this study as illustrated in Figure 1. ME-1 was composed of 10% w/w water, 18% w/w soybean oil and 72% w/w 9:1 oleth-10:IPA mixture. ME-2 was composed of 10% w/w water, 25% w/w soybean oil and 65% w/w 9:1 oleth-10:IPA mixture. Both formulations were water-in-oil (w/o) type (Suksawad et al., 2009). Nicotinamide at concentration of 3% w/w was incorporated in the MEs as a part of water phase. The nicotinamide MEs were prepared by adding an appropriate amount of each component in the tube and constant mixing under magnetic stirring until the clear liquid samples were obtained. The samples were stored at room temperature at least 24 hours to achieve equilibrium before further *in vitro* release study.

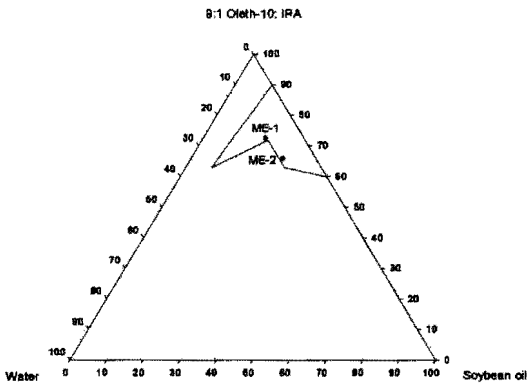

Figure 1 Microemulsion region in system of water/soybean oil/9:1 oleth-10:IPA (Suksawad et al., 2009) and selected formulations in this study, i.e., ME-1 and ME-2.

In vitro release study

In vitro release studies were performed using modified Franz diffusion cells (Hanson Model 57-6 M, Hanson Research Corporation, CA, USA). The diffusion area of each cell was 1.77 cm^2 and the receptor compartment volume was 11 mL. The diffusion cells were connected with a circulating water bath and the temperature was controlled at 37°C. Isotonic phosphate buffer pH 7.4 (IPB) was used as a receptor fluid and stirred by an externally driven Teflon-coated magnetic bar at 200 rpm. Cellulose acetate membrane was placed on the receptor compartment and then the donor compartment was connected with a clamp. One gram of each formulation was applied onto the membrane surface of each donor compartment. The donor compartment was covered with parafilm and the sampling arm was covered with the aluminum foil. At suitable time intervals (0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours), 0.5 mL of receptor fluid was taken from the middle of receptor compartment and immediately replaced with an equal volume of fresh IPB. The withdrawn samples were analyzed for nicotinamide concentration by high performance liquid chromatography (HPLC). For each formulation, the experiment was performed in triplicate. The cumulative drug release (Q_t) was calculated from Equation 1:

$$Q_t = V_r C_t + \sum_{i=0}^{t-1} V_s C_i \quad (1)$$

where C_t is the drug concentration of the receptor fluid at each sampling time, C_i is the drug concentration of the i^{th} sample, and V_r and V_s are the volumes of the receptor fluid and the sample, respectively (Sintov & Shapiro, 2004). In this study, two possible mathematical equations were employed to model the release

Formulations	First order model	Higuchi model
ME-1	0.878	0.961
ME-2	0.940	0.968

The obtained correlation coefficients were summarized in Table 1. It was found that the release profiles of both ME-1 and ME-2 were fitted with Higuchi model rather than first order model (coefficient of determination > 0.96). The linear relationship between cumulative amount of drug released versus square root of time suggested that the transport of drug was controlled by diffusion through MEs (Kapoor & Chauhan, 2008). Nicotinamide is a hydrophilic compound. Therefore, it was proposed to deposit in water internal phase of w/o MEs. It had to diffuse or partition from water droplets to oil continuous phase of MEs before releasing through the cellulose membrane.

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