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Characterization and release kinetics of nicotinamide microemulsion-based gels

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Synopsis

The aim of this study was to investigate physicochemical characteristics and to determine *in vitro* release kinetics of prepared nicotinamide microemulsion-based gels (MBGs). Nicotinamide microemulsions (ME) were composed of 3% w/w nicotinamide, 7% w/w water, 25% w/w soybean oil, and 65% w/w of 9:1 oleth-10:isopropyl alcohol mixture. A water-in-oil (w/o) type ME was converted to three MBGs. ME was combined with 5% w/w of colloidal silica to obtain MBG-1, with 5% w/w of 0.5% w/w carbomer solution to obtain MBG-2, or with a mixture of 3% w/w of 0.5% w/w carbomer solution and 2% w/w of PEG-40 hydrogenated castor oil to obtain MBG-3. The results indicated that MBG-1 was a clear gel with plastic flow while MBG-2 and MBG-3 were turbid gels with Newtonian flow. MBG-1 was physically and chemically stable at 4ºC as well as at ambient temperature (approximately 30ºC) during the 2-month study period. The color darkened when stored at 60ºC. The release kinetics of MBG-1 was best fitted to zero order model. The *in vitro* release of nicotinamide from MBG-1 through cellulose membrane was compared with that from the ME and an oil-in-water (o/w) commercial cream (CC). The rank order of release rate of nicotinamide from different formulations was MBG-1 > ME > CC.

INTRODUCTION

Nowadays, white skin is preferable for Asian people since they think that whiteness means beauty and attractiveness. This belief is influenced by skin color of famous Asian singers and actors. For this reason, skin whitening products gain widespread acceptance and provide high income in cosmetic markets of Asia. Among many skin whitening agents, nicotinamide, commonly known as vitamin B3, is a widely used and well-known compound that can inhibit melanosome transfer from melanocytes to keratinocytes (1). It provides a safe mechanism since the inhibition process occurs after melanogenesis within the melanosome and does not affect intrinsic biosynthesis of melanin production, considered to be safe and effective for use in skincare products for anti-aging, anti-inflammatory, and depigmentation effects. Benefits of topical nicotinamide on the skin have been reported

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(2–4). However, its hydrophilicity provides difficult penetration into the basal layer of the epidermis, its target site, due to the barrier function of the stratum corneum (5). Hence, novel formulations are necessary.

Microemulsions (MEs) are novel carriers used in cosmetics and cosmeceuticals. They are thermodynamically stable, transparent, low-viscosity dispersions of oil and water stabilized by an interfacial film of a surfactant and usually in combination with a cosurfactant such as a short-chain alcohol and a polyhydroxy compound. Many advantages can be obtained from topical MEs including enhanced aesthetics, thermodynamic stability, high solubilization power, ease of preparation, and skin penetration enhancement (6–9). Several researches have shown that MEs are effective vehicles for skin whitening agents such as ascorbyl palmitate (10), sodium ascorbyl phosphate (11), arbutin (12), kojic acid (12), and ascorbic acid (13). Application of MEs in skin whitening products was recently reviewed (14).

In our previous study (15), phase behavior of systems composed of oleth-10, water, various oils, and various cosurfactants was investigated. The oils studied were silicone oil and soybean oil. The studied cosurfactants were isopropyl alcohol (IPA), propylene glycol, and sorbitan monooleate (Span 80). Various ratios of surfactant and cosurfactant were also studied. It was found that among investigated systems, the system of soybean oil, water, and 9:1 mixture of oleth-10 and IPA provided the largest ME region. In a subsequent study (16), two ME formulations designated as ME-1 and ME-2 were selected from this system to be incorporated with nicotinamide and then characterized for physicochemical properties and *in vitro* release profiles. The concentrations of nicotinamide, water, soybean oil, and surfactant mixture in ME-1 were 3% w/w, 7% w/w, 18% w/w, and 72% w/w, respectively. Those in ME-2 were 3% w/w, 7% w/w, 25% w/w, and 65% w/w, respectively. Both ME-1 and ME-2 were of water-in-oil (w/o) type. They had similar physicochemical characteristics (i.e., conductivity, viscosity, class of flow, and particle size), stability, and *in vitro* release profiles.

MEs can be used directly as drops or sprays; however, they might not be suitable in some cases because of low adhesion. Conversion to gel form can overcome this problem. This study aimed to characterize physicochemical properties and to investigate *in vitro* release kinetics of the prepared nicotinamide ME-based gels (MBGs).

EXPERIMENTAL METHODS

MATERIALS

Nicotinamide was obtained from Fluka (Buchs, Switzerland). Soybean oil was obtained from Thai Vegetable Oil Public Company (Bangkok, Thailand). Oleth-10 (Sympatents-AO/100®) was obtained from Kolb Distribution Ltd. (Hedingen, Switzerland). IPA was obtained from VRW International (Arlington Heights, IL). Colloidal silica was obtained from Sigma-Aldrich (St. Louis, MO). Carbomer (Carbopol® Ultrez 21) was obtained from Lubrizol (Wickliffe, OH). Triethanolamine (TEA) was obtained from P.C. Drug Center (Bangkok, Thailand). PEG-40 hydrogenated castor oil was obtained from BASF (Morris County, NJ). Isotonic phosphate buffer pH 7.4 (IPB) was prepared in-house and composed of disodium hydrogen phosphate (Carlo-Erba, Milan, Italy), sodium dihydrogen orthophosphate (BDH Chemicals Ltd., East Yorkshire, UK), and sodium chloride (Carlo-Erba, Milan, Italy).

Acetonitrile, triethylamine, and methanol, which were used in high performance liquid chromatography (HPLC) assay, were supplied by Lab-Scan Analytical Science (Bangkok, Thailand). Distilled water was used throughout the experiments. All chemicals were of pharmaceutical grade and used without further modification. A commercial cream (CC) containing 3% w/w of nicotinamide was purchased from a local supermarket in Songkhla Province, Thailand. Cellulose acetate membrane (Spectra/Por®3 dialysis membrane, MWCO 3500 Dalton) was obtained from Spectrum Laboratories Inc. (Los Angeles, CA). Polyamide membrane filter was obtained from Sartorius AG (Göttingen, Germany).

PREPARATION OF MICROEMULSION-BASED GELS

ME-2 from our previous study (16), referred to as ME here, was further used for converting to three nicotinamide MBGs designated as MBG-1, MBG-2, and MBG-3 via the formulations as shown in Table I.

CHARACTERIZATION OF MICROEMULSION-BASED GELS

Appearance of the samples was optically observed. Viscosity and class of flow of the samples were measured at five different speeds using a Brookfield DV-III Ultra rheometer (Brookfield Engineering Laboratories Inc., Middleboro, MA) fitted with an LV spindle. Brookfield Rheocalc operating software (version 3.1-1) was used to control the rheometer. The determinations were performed at 32°C, equal to the temperature of human skin. The measurements were performed in triplicate.

STABILITY STUDY

The physical and chemical stabilities of the prepared formulations were investigated by storing the samples at three temperatures—4°C, ambient temperature (approximately 30°C), and 60°C—for 2 months. The 4°C represented the temperature of a refrigerator, the ambient temperature represented the normal usage as well as storage conditions, and 60°C mimicked the temperature on transportation during summer in Thailand. Since the temperature during summer in Thailand is fluctuated high, it is interesting to investigate the changes in the appearance of MBGs when stored at high temperature in this study.

Table I
Formulations of the Investigated MBGs

	% w/w		
Component	MBG-1	MBG-2	MBG-3
ME	95	95	95
Colloidal silica	5	—	—
Carbomer (0.5% w/w solution in water, adjusted the pH to 6 with TEA)	—	5	3
PEG-40 hydrogenated castor oil	—	—	2

The chemical stability at 60°C was not anticipated since in the guideline for accelerated stability test of new drug substances and products suggested by International Conference on Harmonization (17), the studied temperature is assigned at 40°C. Physical changes of the samples such as phase separation and clarity were optically observed. Only MBG-1 was selected to investigate for the chemical stability study by determining the amount of non-degraded active compound using HPLC. The 100 µl of the formulation was dissolved with IPA and adjusted the volume in a 10-ml volumetric flask. The 100 µl of this solution was diluted with 80:20 IPA/methanol in a 10-ml volumetric flask. Afterward, the obtained solution was further diluted with the same solvent in a 10-ml volumetric flask and then filtered through a 0.45-µm polyamide membrane filter before HPLC analysis.

IN VITRO RELEASE STUDY

The release of nicotinamide from MBG-1, ME, and CC was investigated using modified Franz diffusion cells (Hanson Model 57-6 M, Hanson Research Corporation, Los Angeles, CA) and a cellulose acetate membrane with an effective diffusion area of 1.77 cm^2. The membrane was cut into 3 × 3 cm pieces, and the obtained pieces were boiled in distilled water to remove the wax. The cleaned membrane pieces were soaked in distilled water, stored in a cool place, and used within a week. The hydrated membrane pieces were mounted between the donor and receptor compartments of the diffusion cells. The receptor compartment was filled with 11 ml of degassed IPB. The diffusion cells were connected to a circulating water bath thermostated at 37°C, giving the membrane surface temperature of 32°C that was equal to human skin temperature. Each diffusion cell was continuously stirred at a speed of 200 rpm using a magnetic bar. After the membrane was equilibrated for 30 min, 1 g of each formulation was placed onto the membrane in the donor compartment. The donor compartment and the sampling arm were covered with Parafilm to prevent water evaporation. At defined time intervals (0.5, 1, 2, 4, 8, 10, 12, and 25 h), 0.5 ml of samples were taken from the receptor compartment and immediately replaced with an equal volume of fresh receptor medium. The withdrawn samples were analyzed for nicotinamide concentration by HPLC. For each formulation, the experiment was performed in triplicate. The cumulative release (Q) of nicotinamide was calculated from equation (1).

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

where C_t is the concentration of active compound in the receptor fluid at each sampling time t, C_i is the concentration of active compound of the i^{th} sample, and V_r and V_s are the volumes of the receptor fluid and the sample, respectively. The release rate was calculated as percent of the initial concentration per hour by linear regression interpolation of the experimental data.

Three possible mathematical equations were employed to fit with the release profiles, i.e., zero order, first order, and Higuchi square root of time equations as shown in equations (2), (3), and (4), respectively.

$$Q = Q_0 - k_0 t \quad (2)$$

$$\ln Q = \ln Q_0 - k_f t \quad (3)$$

$$Q = k_H t^{1/2} \quad (4)$$

where Q is the cumulative amounts of active compound released in time t; Q_0 is initial amounts of active compound in the preformed preparations; and k_0, k_f, and k_H are release rate constants of zero order, first order, and Higuchi model, respectively (18).

HPLC ASSAY

The concentrations of nicotinamide remained in MBG-1 after stability study and released from the investigated samples into the receptor fluid were quantitatively analyzed by HPLC as described by Xu and Trissel (19) with some modifications. The HPLC system (Agilent 1100, Santa Clara, CA) connected with an HPLC column, 5-μm particle size, 150 × 4.6 nm (Chrompack Inertsil ODS, Middelburg, The Netherlands). A mixture of 0.1% triethylamine in 0.067 *M* monobasic potassium phosphate buffer (pH 6.7) and acetonitrile (100:4 v/v) was used as the mobile phase. The injection volume was 20 μl. The samples were detected at 260 nm and integrated with the RF 10A (version 1.1) LC software program. The calibration curve was constructed by running standard solutions of nicotinamide in extraction solvent and in IPB for every series of samples. Validation of the method was performed to ensure that chromatogram of the standard solution of nicotinamide could be separated from chromatogram of the blank MBG extract and that of receptor fluid incubated with cellulose membrane. The calibration curve between 2.5 and 40 μg/ml of nicotinamide was in the linearity range ($r^2 > 0.999$) and coefficients of variation were less than 2%, both intraday and interday.

RESULTS AND DISCUSSION

CHARACTERISTICS OF NICOTINAMIDE MICROEMULSION-BASED GELS

According to optical observation, the rank order of clarity of the prepared MBGs was MBG-1 > MBG-3 > MBG-2. It was found that using colloidal silica provided a transparent gel. The result can be explained that during the gel formation, H^+ ions of water attached to some of the small particles of colloidal silica, resulting in the hydrophilic surface and capability of hydrogen bonding. This structure formed into a three-dimensional network through the branched interaction of hydrogen bonding of hydroxyl groups on silica surface (20,21). Although the water in the system was low, the water cores of ME might serve as compartmentalized media for this reaction due to their dynamic characteristics (22). Colloidal silica was previously reported that it converts sodium ascorbyl phosphate

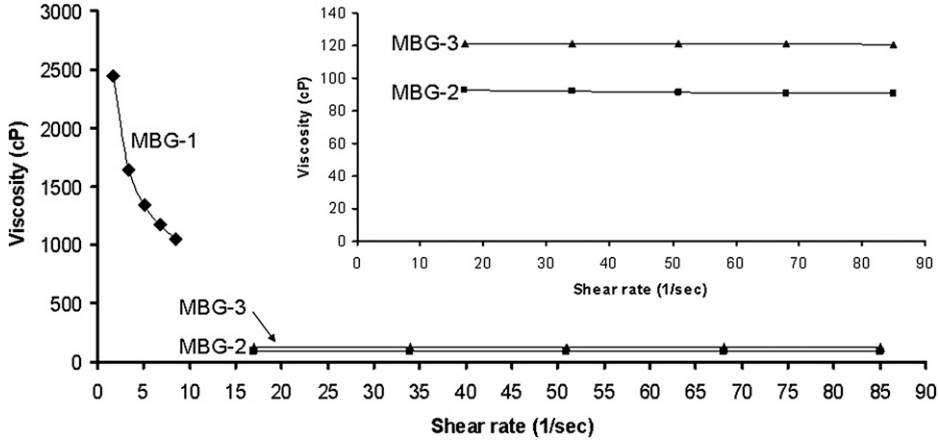

Figure 1. Rheograms of three nicotinamide MBGs.

w/o ME to an MBG (11). Unfortunately, the appearance of MBG-2 was turbid. ME was investigated as w/o type via dilution test and conductivity measurement (16). Hence, incompatibility between hydrophilic carbomer and hydrophobic external phase of ME resulted in turbid MBG-2. Expectably, adding mixture of carbomer and PEG-40 hydrogenated castor oil into MBG-3 had slightly achieved to stabilize the formulation, resulting in the reduction of turbid appearance. However, the appearance of MBG-3 was still hazy.

The rank order of viscosity of the prepared MBGs was also MBG-1 > MBG-3 > MBG-2. Rheological behavior of MBG-1 was plastic flow while that of MBG-2 and MBG-3 was Newtonian flow as demonstrated in Figure 1. Therefore, MBG-1 would not begin to flow until it received a shearing stress which was higher than the yield value. Plastic flow of MBG-1 implied that MBG-1 acted as a semisolid gel at stresses below the yield value and could be spread on the skin when applying.

When colloidal silica was added into the ME with the viscosity of 74.44 ± 0.31 cP, the viscosity of the obtained MBG-1 was significantly higher than that of its counterpart ($p < 0.05$). It can be explained that the interconnected gel network via hydrogen bonds between water and colloidal silica resulted in strong interactions between ME droplets (23,24). Incompatibility between hydrophilic carbomer and hydrophobic external phase of ME resulted in low viscosity of MBG-2. PEG-40 hydrogenated castor oil might increase viscosity of MBG-3 when compared with MBG-2 due to its lipophilicity.

STABILITY OF NICOTINAMIDE MICROEMULSION-BASED GELS

The stability testing of the three MBGs revealed that there was no change in physical appearance of all samples during 2 months of storage at 4°C and ambient temperature. However, the change in color from yellowish to brownish was observed in the stored formulations at 60°C. At 60°C or higher temperature, one or more components in the formulations might decompose. To confirm this assumption, each component in ME formulation, i.e., oleth-10, soybean oil, and nicotinamide aqueous solution, was separately stored at

60°C for 2 days and observed for color change. Indeed, only the color of soybean oil was darker. The result can be explained by the degradation of soybean oil via lipid oxidation, which was catalyzed by high temperature like other natural oils such as coconut oil (25). Although MBG-2 and MBG-3 were physically stable like MBG-1, their appearance was unsatisfactory. Therefore, only MBG-1 was selected to be analyzed with HPLC for the chemical stability study. The content of nicotinamide compared to the initial concentration after 2 months storage was found to be 99.98% when stored at 4°C and 98.18% when stored at ambient temperature. Nicotinamide was entrapped in the internal phase of the MBGs; therefore, it was protected from degradation. It was reported that ascorbyl palmitate was more stable in w/o than in oil-in-water (o/w) MEs composed of identical components since its cyclic ring, oxidation sensitive group, was shielded in the internal aqueous phase (10).

IN VITRO RELEASE OF NICOTINAMIDE FROM THE STUDIED FORMULATIONS

Because of its good appearance and stability, MBG-1 was selected to study for *in vitro* release. Figure 2 shows the *in vitro* release profiles of nicotinamide from MBG-1 with three different mathematical models, i.e., zero order, first order, and Higuchi. The best linearity with the r^2 value of 0.9932 was found in zero order model during the studied period. Hence, the ability of MBG-1 to deliver nicotinamide was independent of the concentration of the active compound..

The release rates of nicotinamide from MBG-1, ME, and CC calculated as percent of the initial concentration per hour are shown in Table II. The release of nicotinamide tended to be in the rank order of from MBG-1 > ME > CC.

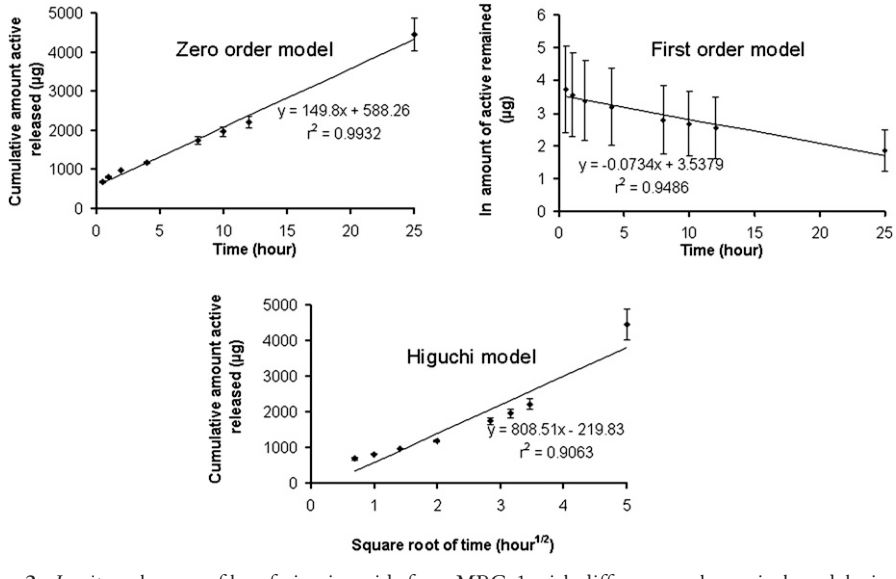

Figure 2. *In vitro* release profiles of nicotinamide from MBG-1 with different mathematical models, i.e., zero order, first order, and Higuchi.

Although CC is o/w formulation and nicotinamide locates in the outer phase, it provided the lowest release rate of nicotinamide. It was found that the viscosity value of CC (6827.87±549.63 cP) was much higher than that of MBG-1 and ME. Release ability was reported to be inversely related to the viscosity of the continuous phase (26). Moreover, the complex partition of nicotinamide among all the compositions may limit the transferring of nicotinamide through the membrane (27).

ME increased the release rate of nicotinamide when compared with CC. The possible mechanisms of ME in enhancing nicotinamide release were that the thermodynamic activity of nicotinamide in the ME could be modified to favor partitioning into the membrane and that the nanosized droplets dispersed in the continuous phase of the ME could move easily and carry nicotinamide through the membrane (7).

MBG-1 exhibited the highest release rate. The structure of colloidal silica is amorphous and composed of submicron-sized spheres, which are 40–60% fused into short chains, very highly branched, 0.1–0.2 microns long. Hence, the formation of three-dimensional networks of particles created the mobility of the network chains in the gel contributing to the loose structure of the matrix, resulting in nicotinamide burn out (28,29). Low affinity between hydrophilic nicotinamide and hydrophobic phase subsequently increased the release of nicotinamide.

As expected, the 3% w/w nicotinamide aqueous solution provided cumulative amount active released markedly higher than MBG-1 (data not shown). However, the aqueous solution was not an appropriate vehicle for topical delivery of any active compound because of the lipophilic nature of the stratum corneum. The release rate of nicotinamide from the aqueous solution drastically increased during 0.5 to 12 h and reached a plateau state after 12 h. The release profile of MBG-1 did not show a plateau state since MBG-1 acted as active compound reservoirs (30).

CONCLUSIONS

It was observed that the order of clarity and viscosity in prepared nicotinamide MBGs was MBG-1 > MBG-3 > MBG-2. All samples were physically stable at 4°C and ambient temperature (approximately 30°C) during the 2 months of storage; a darker color developed when stored at 60°C. Since MBG-1 was desirable according to its appearance and viscosity, it was further analyzed for residual nicotinamide content by HPLC. It was found that MBG-1 was chemically stable. The remaining nicotinamide in MBG-1 after storage at 4°C and ambient temperature for 2 months was 99.98% and 98.18%, respectively. *In vitro* release kinetics of nicotinamide from MBG-1 was best fitted to zero order model. The rank order of release rate of nicotinamide from different formulations was

Table II
Release Rates of Nicotinamide from Different Formulations

Sample	Release rate (percent of initial concentration/hour)
MBG-1	0.30716
ME	0.00029
CC	0.00019

MBG-1 > ME > CC. The addition of colloidal silica as a thickening agent in MBG-1 resulted in high release of nicotinamide due to loose structure of the matrix gel as well as low affinity between the hydrophilic nicotinamide and the external hydrophobic phase of the formulation. On the basis of screening formulations, it was concluded that MBG-1 was a suitable formulation for topical nicotinamide due to its appearance, viscosity, stability, and *in vitro* release characteristics.

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