

การปลดปล่อยไนอาซิनाไมด์และคาเฟอีนจากครีมชนิดต่าง ๆ

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บทคัดย่อ

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งานวิจัยนี้เป็นการเตรียมตำรับและศึกษาการปลดปล่อยไนอาซิनाไมด์ (วิตามินบี 3) และคาเฟอีนจากครีมเบสสามชนิดที่แตกต่างกัน คือ vanishing cream, hydrophilic emulsion และ cold cream การปลดปล่อยของสารสำคัญศึกษาโดยใช้ Franz-type diffusion cells และเมมเบรนสังเคราะห์เป็นเยื่อแก้ว ทั้ง vanishing cream และ hydrophilic emulsion เป็นครีมชนิดน้ำมันในน้ำ ที่แตกต่างกันตรงชนิดของของสารก่ออิมัลชันและชนิดของน้ำมันที่ใช้ ทำให้ครีม vanishing cream มีลักษณะที่เหลวกว่า hydrophilic emulsion ส่วน cold cream เป็นครีมชนิดน้ำในน้ำมัน และครีมที่ได้มีความหนืดมากที่สุด ในการศึกษาการปลดปล่อยในหลอดทดลองของไนอาซิनाไมด์และคาเฟอีนจากครีมพื้นชนิด o/w มีจลนศาสตร์การปลดปล่อยเป็นไปตาม Higuchi ส่วนชนิด w/o มีจลนศาสตร์การปลดปล่อยเป็นไปตามสมการอันดับหนึ่ง สารทั้งสองชนิดสามารถปลดปล่อยได้ค่า flux มากและอัตราเร็วสูงที่สุดจากครีมพื้นชนิด vanishing cream และปลดปล่อยได้ค่าน้อยที่สุดจากครีมพื้นชนิด cold cream จากผลการศึกษการปลดปล่อยนี้พบว่าส่วนประกอบและชนิดของครีมพื้นมีผลอย่างมากต่อการปลดปล่อยสารสำคัญจากสูตรตำรับ

คำสำคัญ: ไนอาซิनाไมด์, คาเฟอีน, รูปแบบการปลดปล่อย, ครีม

Abstract

***In Vitro* Release Study of Niacinamide and Caffeine from Different Creams**

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The present study was to formulate and study the release of niacinamide (vitamin B₃) and caffeine from three different cream bases, vanishing cream, hydrophilic emulsion and cold cream. The releases of active components were evaluated using Franz-type diffusion cells with artificial membrane. Both vanishing cream and hydrophilic emulsion are the same in o/w type with difference in emulsifying agent and oil components. The vanishing cream is more liquid than hydrophilic emulsion where as the cold cream is w/o type with the most inflexible. *In vitro* releases of niacinamide and caffeine from three cream bases showed the similar kinetics. Both niacinamide and caffeine showed the highest release amounts and the fastest rates in vanishing cream. The lowest release amounts and release rates were found in cold cream. The results of the study suggest that the components and types of cream bases strongly affect the release of the actives from the formulations.

Keywords: Niacinamide, caffeine, release profile, cream, whitening

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Introduction

Hyperpigmentation is a type of skin darkened by the over release of melanin by skin cells. It may cause from over exposure to the sun light, hormone imbalance, skin disorders

and post inflammation. Hyperpigmentation is commonly harmless but makes the skin unattractive. In case of post inflammation including acne, eczema and contact dermatitis,

the treatment challenging is reduction the hyperpigmentation without causing undesirable hypopigmentation and irritation (Woolery-Llord, 2011). A variety of topical whitening agents are available in inhibiting the different step of melanin production. The most commonly step is tyrosinase inhibitor. Hydroquinone has long been used as the gold standard of the treatment but the long-term use of hydroquinone risk to the hypopigmentation including irritation and erythema that finally leads to post inflammatory hyperpigmentation. However, the short term use of execute causes is still greatly effective. The newer whitening agents as alternative in long term use have been intensively investigated. Most of them are botanical origins such as kojic acid, arbutin, licorice, ascorbic acid and soy (Konda, 2012).

Niacinamide (Vitamin B₃) is a derivative of niacin which is one of the new whitening agents. Topical niacinamide showed benefits for post inflammatory form acne (Niren, 2006). The reduced form of it might promise to act as antioxidant. Other benefits of niacinamide are the increase in collagen production, inhibitory of leucocyte peroxidase system of skin cells. Niacinamide also reduces sebum production (Bissett, 2009). All of these effects showed the evidents to reduce the skin aging and acne (Lupo, 2001). Niacinamide has been used in cosmeceutical products in concentrations ranging from 3.5 – 5.0% (Manela-Azulay, 2009). Caffeine is produced naturally by plants from coffee and tea. Applying caffeine on skin results the antiaging effect. *In vitro* test, caffeine shows the cell protective from UV radiation. Caffeine is cosmetically used in eye gels and cellulite burner due to the increase of micro circulation of skin blood vessels (Herman and Herman, 2012).

In this study, niacinamide and caffeine were combined to increase the efficacy of an alternative whitening preparation. Three different cream bases were prepared with 4%w/w of niacinamide and 2 %w/w caffeine. The release profiles of niacinamide and caffeine were investigated to compare the topical characteristics.

Material and methods

1. Materials

Niacinamide was purchased from Chemico Inter Corporation Co., Ltd. Caffeine and sodium 1-heptanesulfonate were purchased from Fluka, Germany.

Methanol (HPLC grade) was purchased from Fisher Scientific. Other ingredients were pharmaceutical and cosmetic grade.

2. Formulation of niacinamide and caffeine creams

Table 1 shows the ingredients of each formulation. To prepare hydrophilic emulsion, oil phase components (white beeswax, cetyl alcohol, almond oil and stearic acid) were mixed and heated to 70°C. The water phase components (triethanolamine, propylene glycol, caffeine, methyl paraben and propyl paraben) were mixed and heated to 72°C. After that, the aqueous phase was poured into the oil phase with homogenizer until it was cool. Vanishing cream and cold cream were prepared by melting white beeswax, stearic acid and mineral oil to 70°C. The aqueous phase (sodium borate, glycerin (only in vanishing cream), methyl paraben, propyl paraben, caffeine and DI water) were mixed and heated to 72°C. The aqueous phase was subsequently added into the oil phase with homogenizer until it was cool. In all cases, niacinamide was dissolved in sufficient quantity of DI water and poured into the emulsion while it was about 45°C.

3. Drug release study

The release studies were conducted using Franz diffusion cell (PermeGear, USA, 15 mL receptor volume), the membrane (Cellu Sep T1, MW cut off 3500, Membrane Filtration Products, Inc USA) was saturated in phosphate-buffer (pH 7.4) for 24 hours and fitted into the place between two chambers. The receptor phase was phosphate buffer pH 7.4. The temperature was maintained at 32±1 °C. One gram of tested creams was mounted on the donor side of the Franz cell. Samples were withdrawn at different time intervals and were analyzed using HPLC. Each formulation was performed in triplicate.

4. Analysis of released niacinamide and caffeine

The chromatographic analysis was conducted on an Inertsil ODS-3 C18 (4.6 mm × 250 mm). The mobile phase consisted of 0.005 M sodium 1-heptanesulfonate: HPLC grade methanol (70:30). The flow rate was set at 1.0 milliliter per minute and the detecting wavelength was set at 254 nm. The volume for injection was 20 microliters. Calibration curves of niacinamide and caffeine were created by diluting from standard stock solutions and analyzed by HPLC. Correlation coefficient and linear regression equations were obtained by plots of concentration versus peak area.

5. Viscosity measurements

Viscosity measurements were performed at $25 \pm 1^\circ\text{C}$ using Brookfield viscometer (DV-II+, USA) with T-bar type spindle no. S94 at 1.0 rpm

6. pH measurements

The pH meter was calibrated by standard buffer solution. About 5 grams of each formulation was measured directly using the pH meter, at $25 \pm 1^\circ\text{C}$.

Table 1. Components of the formulations

Components	Vanishing cream	hydrophilic emulsion	Cold cream
Oil phase			
Cetyl alcohol	-	5	-
White beeswax	1	2	12
Mineral oil	5	-	56
Stearic acid	10	5	12.5
Almond oil	-	5	-
Water phase			
Propylene glycol	-	5	-
Glycerin	5	-	-
Triethanolamine	-	1.8	-
Sodium borate	2	-	0.5
Methyl paraben	0.01	0.01	0.01
Propyl paraben	0.02	0.02	0.02
Caffeine	2	2	2
Niacinamide	4	4	4
DI water	qs to 100	qs to 100	qs to 100

Results

Niacinamide and caffeine are water soluble they readily release through the membrane within one hour. Figure 1 shows release profiles of niacinamide (A) and

caffeine (B) from different creams rang in order of vanishing cream > hydrophilic emulsion > cold cream.

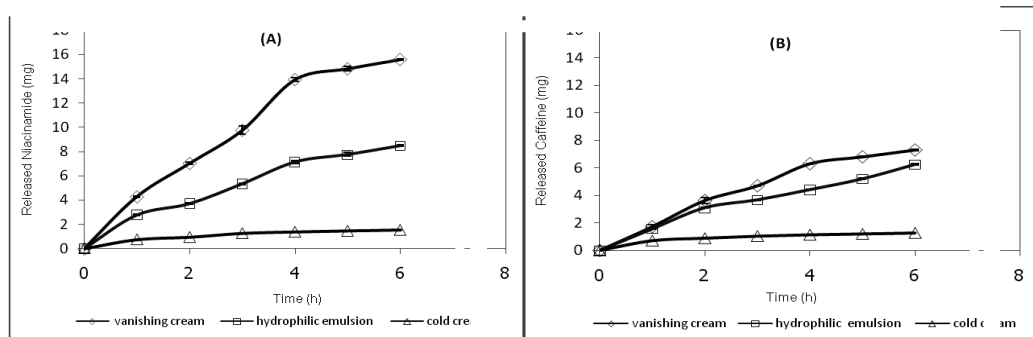


Figure 1. Cumulative amounts (mg) of niacinamide (A) and caffeine (B) released from different creams.

Table 2 demonstrates the characteristics of the niacinamide and caffeine creams. The release fluxes through membrane from all formulations are shown. The pH values are 7.09, 7.28 and 6.61 for vanishing cream, hydrophilic

emulsion and cold cream, respectively. The viscosity is directly related to the components of the formulation. As the results, cold cream is more viscous than vanishing cream about 2 times.

Table 2. Release fluxes in 24 h, viscosity and pH values of different cream bases

Cream base	Flux of niacinamide		Flux of caffeine		pH	Viscosity (cps)
	(mcg/cm ² /h)		(mcg/cm ² /h)			
Vanishing cream	377.1±1.0		175.0±3.1		7.09	482800
Hydrophilic emulsion	196.1±2.6		137.8±1.3		7.28	625600
Cold cream	32.3 ±0.2		25.3 ±0.2		6.61	833400

Table 3 and Table 4 demonstrate the parameters and correlation coefficients obtained from kinetic equations calculated from the steady state regions (4 h for vanishing cream and hydrophilic emulsion and 3 h for cold cream). The release data of both drugs from vanishing cream obeys Zero order kinetic, which their rate limiting step of the release is likely diffusion through the cream base. On the contrary, the release data of both drugs from cold cream follows Higuchi equation with R² of 0.9933 and 0.9862 for niacinamide and caffeine, respectively. The release kinetics of both drugs

from hydrophilic emulsion are anomalous and reveals the low R² of all models.

Various factors might be involved on the release of both drugs. The solubility of niacinamide and caffeine in the outer phase of emulsion as well as the water content in the formulation which strongly influence the thermodynamic activity of each drug. The types and concentrations of emulsifiers used in the formulations have been studied and were found to affect the drug releases.

Table 3. *In vitro* release kinetics of niacinamide from different cream bases (n=3)

Cream base	Zero order		First order		Higuchi model	
	k	R ²	k	R ²	k	R ²
Vanishing cream	3.33	0.9920	0.044	0.9871	6.52	0.9305
hydrophilic emulsion	1.67	0.9778	0.020	0.9819	3.37	0.9564
Cold cream	0.39	0.9208	0.004	0.9231	0.70	0.9933

Table 4. *In vitro* release kinetics of caffeine from different cream bases (n = 3)

Cream base	Zero order		First order		Higuchi model	
	k	R ²	k	R ²	k	R ²
Vanishing cream	1.56	0.9927	0.040	0.9958	3.06	0.9405
hydrophilic emulsion	1.09	0.9558	0.026	0.9674	2.23	0.9762
Cold cream	0.32	0.8548	0.007	0.8590	0.60	0.9867

Conclusion

In this study, three creams were formulated with 4%w/w niacinamide and 2%w/w caffeine for whitening and firming aspects. On the basis of the release studies it was found that the different cream bases system remarkably altered the release of both ingredients. In case of vanishing cream, the highest amounts of both niacinamide and caffeine were detected, while cold cream provided the least extent of both niacinamide and caffeine due to the low solubility in the semisolid matrix. The release studies suggested that different cream bases obviously affect the drug distribution in the dosage form, drug release and might subsequently affect the absorption through skin after application.

References

- Bissett DL. Common cosmeceuticals. *Clin Dermatol* 2009; 27: 435-445.
- Herman A, Herman AP. Caffeine's mechanisms of action and its cosmetic use. *Skin Pharmacol Physiol* 2012; 26(1): 8-14.
- Konda S, Geria AN, Halder RM. New horizons in treating disorders of hyperpigmentation in skin of color. *Semin Cutan Med Surg* 2012; 31: 133-139.
- Lupo MP. Antioxidants and Vitamins in Cosmetics. *Clin Dermatol* 2001; 19: 467-473.
- Manela-Azulay M, Bagatin E. Cosmeceuticals vitamins. *Clin Dermatol* 2009; 27, 469-474.
- Niren NM. Pharmacologic doses of nicotinamide in the treatment of inflammatory skin conditions: A review *Cutis* 2006; 77: 11-16.
- Woolery-Lloyd H, Kammer JN. Treatment of hyperpigmentation. *Semin Cutan Med Surg* 2011; 30: 171-175.