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Rapid determination of cocamidopropyl betaine impurities in cosmetic products by core-shell hydrophilic interaction liquid chromatography-tandem mass spectrometry

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ABSTRACT

Cocamidopropyl betaine (CAPB) is a common surfactant widely used in personal care products. Dimethylaminopropylamine (DMAPA) and lauramidopropyldimethylamine (LAPDMA) are two chemicals present as impurities in CAPB and have been reported as skin sensitizers. A rapid and sensitive ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) method, using a core shell hydrophilic interaction liquid chromatography (HILIC) column, has been developed to quantify DMAPA and LAPDMA in cosmetic products. Corresponding stable isotopically labeled analogues of the above native compounds were used as internal standards to compensate for matrix effect and for loss of recovery. Each sample was first screened to determine whether the sample needed to be diluted to minimize matrix effects as well as to fit the calibration range. The concept of matrix effect factor (MEF) was introduced to quantitatively evaluate each sample with a unique matrix using the internal standards. Recoveries at three spiking levels of low, medium, and high concentrations ranged from 98.4 to 112% with RSDs less than 5%. This method has been validated and is the first UHPLC–MS/MS method, which uses core shell HILIC column and stable isotopically labeled internal standards to simultaneously determine these two CAPB impurities in cosmetic products.

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1. Introduction

Cocamidopropyl betaine (CAPB) is a common surfactant used in cosmetic products. As shown in Fig. 1, CAPB is synthesized by reacting fatty acids, often obtained from coconut oil, or coconut oil, with dimethylaminopropylamine (DMAPA), yielding lauramidopropyldimethylamine (LAPDMA) [1]. LAPDMA is subsequently allowed to react with sodium monochloroacetate to produce the end product CAPB. Because of the synthetic route, DMAPA and LAPDMA are two impurities often detected in CAPB and therefore may be present in cosmetic products. Different concentrations of DMAPA and/or LPADMA may be found in commercially available CAPB, depending on the quality of the commercial CAPB [1].

The safety of CAPB was reviewed in 1991 and re-reviewed in 2010 by an expert panel of the Cosmetic Ingredient Review (CIR) [2], an industry-sponsored panel that meets quarterly to conduct safety assessments of cosmetic ingredients and publishes its reports in the literature. Based on a quantitative risk assessment [1–3], the panel concluded that CAPB is safe in cosmetics as long as they are formulated to be non-sensitizing, despite cocamidopropyl betaine (CAPB) being voted Allergen of the Year by the American Contact Dermatitis Society in 2004 [4]. A review of FDA's Voluntary Cosmetic Registration Program (VCRP) database indicates that since December 2005, CAPB has been used in 4400 cosmetic formulations that were registered with the FDA, with many of these products being leave- on and rinse-off products. Further, the CIR panel reports recognized that DMAPA and LAPDMA have the potential to cause allergic contact dermatitis. Generally, one would expect leave-on products to have more contact with the skin, and possibly result in greater chances of inducing sensitization reactions. Moreover, other reports in the scientific literature also describe these chemicals as potential human skin sensitizers [1,3,5].

CAPB is amphoteric because it contains both an acidic and a basic functional group (Fig. 1), whose charges are changed with the pH of solution. Amphoteric surfactants, such as CAPB, affect foaming, wetting, and detergency through a surface action that exerts both hydrophilic and hydrophobic properties [6]. In biochemistry, amphoteric surfactants are used as detergents for purifying, cleansing, and for their antimicrobial effects. The amphoteric properties are the reason CAPB has been widely employed in cosmetic products [7].

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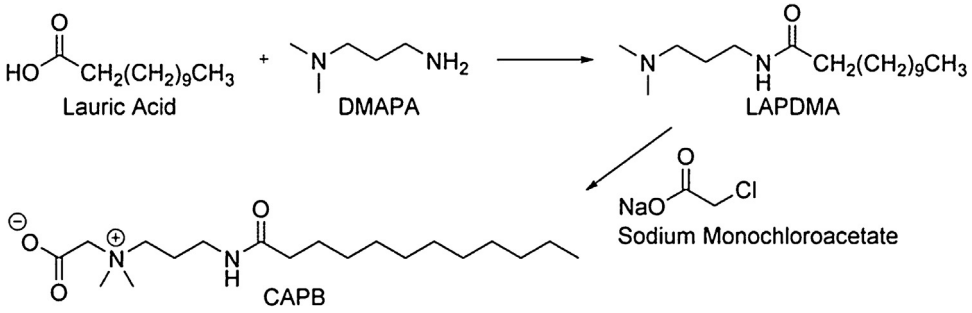

Fig. 1. The synthetic procedures of CAPB.

Because DMAPA contains one primary and one tertiary amine group, it has numerous uses in the production of other chemicals, such as CAPB. Based on the Personal Care Product Council's *International Cosmetic Ingredient Dictionary and Handbook*, DMAPA is an aliphatic amine functioning as a pH adjuster in cosmetic products [7]. Since DMAPA is used to synthesize CAPB, it has been identified as an impurity in many shampoos, cosmetics, and detergents, which use CAPB as an amphoteric surfactant [1,3].

Even though CAPB is extensively used as a surfactant in cosmetic products, only a few analytical methods to determine the possible contaminants DMAPA and LAPDMA have been published. These include ion mobility spectrometry [8], ion chromatography [9], gas chromatography [10] and HPLC via derivatization of DMAPA [11]. A reliable analytical method with high precision and accuracy is needed to monitor and quantify DMAPA and LAPDMA. To date, neither LC methods without derivatization nor LC–MS methods have been published for the determination of DMAPA and LAPDMA in cosmetic products.

In this study, a rapid and sensitive ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) method, using a core shell hydrophilic interaction liquid chromatography (HILIC) column, has been developed. Stable isotopically labeled DMAPA and LAPDMA were used as internal standards (ISs) to compensate for matrix effects and correct for loss of recovery. The method has been validated and successfully used to survey twenty commercial products. The validated data can help assess how successfully the industry has minimized the levels of these CAPB impurities in consumer products. To the best of our knowledge, this is the first UHPLC–MS/MS method, which uses core shell HILIC and stable isotopically labeled internal standards, to simultaneously determine these two CAPB impurities in cosmetic products.

2. Materials and methods

2.1. Chemicals and materials

LC–MS grade acetonitrile (ACN), methanol (MeOH), and water were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Formic acid (FA, 97%, ACS) was obtained from Acros Organic (New Jersey, USA). Ammonium formate, trifluoroacetic acid (TFA, reagent Plus, 99%), DMPAA, and LAPDMA were obtained from Sigma-Aldrich (St. Louis, MO, USA). DMPAA-d_6 and LAPDMA-d_{23} were custom-synthesized by Toronto Research Chemicals (Toronto, ON, Canada). All commercial cosmetic products were purchased from Internet-based vendors.

2.2. LC system

The LC system was a Waters ACQUITY UPLC® (Milford, MA, USA) consisting of a binary solvent manager, a column manger, and a sample manager. The temperature of the sample manager was set to ambient during operation. The separations were carried out using a Phenomenex Kinetex HILIC column (1.7 μm, 50 mm × 2.1 mm i.d., Torrance, CA, USA). The LC eluent was introduced into the electrospray ion source without splitting. The components were eluted by a 5-min gradient program at a flow rate of 0.50 mL/min with an injection volume of 10 μL. The mobile phase A = 10 mM ammonium formate in 95:5 ACN:H_2O and B = 50 mM ammonium formate and 0.2% FA in 5:95 ACN:H_2O. The gradient parameters were: 0–0.7 min, 100% A; 0.7–1.7 min, from 100% A to 100% B; 1.7–2.7 min, 100% B; 2.7–3.2 min, from 100% B to 100% A; and 3.2–5 min, 100% A.

2.3. Mass spectrometry

UHPLC–MS/MS was performed using an AB Sciex QTRAP 6500 (AB Sciex, Foster City, CA, USA) equipped with an IonDrive TurboV source® (electrospray ionization). The UHPLC–MS/MS operation and data acquisition/processing were conducted using AB Sciex Analyst software (version1.6). The IonSpray voltage was set at 4500 V in the positive ion mode. The turbo heater was maintained at 400 °C. Nitrogen was used as curtain gas and collision gas. The curtain gas, ion source gas 1, and ion source gas 2 were set at pressures of 35, 45, and 50 PSI, respectively. The collision gas was set at "Medium". The mass spectrometer was operated in the selected reaction monitoring (SRM) mode. The optimized analyte-dependent SRM parameters are listed in Table 1.

Table 1
Optimized SRM parameters.

Analytes	Formula	Precursorion	Production	DwellTime, ms	DP (V)	EP (V)	CE (V)	CXP (V)	Function
DMAPA	$C_5H_{14}N_2$	103	86	50	40	10	15	10	quantitation
		103	58	50	40	10	24	10	confirmation
DMAPA-d_6	$C_5H_8N_2$-d_6	109	92	50	40	10	15	10	quantitation_IS
		109	64	50	40	10	26	10	confirmation_IS
LAPDMA	$C_{17}H_{36}N_2O$	285	240	10	40	10	25	10	quantitation
		285	183	10	60	10	32	10	confirmation
LAPDMA-d_{23}	$C_{17}H_{13}N_2O$-d_{23}	308	263	10	30	10	28	10	quantitation_IS
		308	206	10	30	10	38	10	confirmation_IS

Note: IS = Internal standard; DP = declustering potential; EP = entrance potential; CE = collision energy; CXP = collision cell exit potential.