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A Green and Rapid Analytical Method for the Determination of Hydroxyethoxyphenyl Butanone in Cosmetic Products by Liquid Chromatography

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Abstract: An analytical method for the determination of hydroxyethoxyphenyl butanone, which is used as an alternative preservative in cosmetic products, has been developed and validated for the first time. The method is based on a simple ultrasound-assisted lixiviation of the analyte from the cosmetic matrix followed by liquid chromatography with UV spectrophotometric detection. Under optimized conditions, the method limit of detection and limit of quantification values were 30 and 90 $\mu g \cdot g^{-1}$, respectively. The method was validated with good recovery values (86–103%) and precision values (RSD 0.2–4.7%). Finally, the proposed analytical method was successfully applied to 7 commercially available cosmetic samples including both lipophilic and hydrophilic matrices, such as moisturizing cream, sunscreen, shampoo, liquid hand soap, and make-up. Additionally, a laboratory-made cosmetic cream containing the target analyte was prepared and analyzed. The good analytical figures of merit of the proposed method, in addition to its environmentally-friendly characteristics, demonstrate its usefulness to perform the quality control of cosmetic products to ensure the safety of consumers.

Keywords: alternative preservatives; hydroxyethoxyphenyl butanone; cosmetic products; liquid chromatography; ultraviolet-visible spectrophotometry

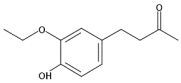
1. Introduction

According to the current European Regulation of Cosmetic Products (EU Regulation 1223/2009) [1], 'cosmetic product' means 'any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors'. Cosmetic formulations generally include a variety of different types of ingredients, such as excipients, active principles and several additives. Some examples of these are perfumes, colorants and preservatives. The list of the currently permitted preservatives in cosmetic products, and their restrictions to be used (including their maximum concentration), are listed in the Annex V of the aforementioned EU Regulation 1223/2009.

During the last years, the cosmetic industries have been continuously looking for new compounds that can perform the preservative function effectively and safely, since the European Commission [2] banned the use of certain parabens in 2014. In fact, some cosmetic ingredients can play more than one role in a cosmetic formulation, leading to cosmetic products that are free of preservatives or self-preservatives [3–5].

In this sense, according to the Inventory of Cosmetic Ingredients (2006/257/EC) [6], hydroxyethoxyphenyl butanone (HEPB), whose detailed information is summarized in Table 1, is used as skin conditioning. However, based on a recent opinion published by the Scientific Committee on Consumer Safety (SCCS) [7], HEPB is intended to be used specifically as preservative in rinse-off, leave-on, and oral care cosmetics in concentrations up to 2%. Nevertheless, the SCCS concluded that only a maximum concentration of 0.7% of HEPB in these kinds of cosmetic products can be considered safe, as potential toxicity due to repeated exposure has been shown [7]. Consequently, the inclusion of HEPB in the Annex V of the EU Regulation 1223/2009, in order to restrict its maximum concentration, is expected to occur.

Table 1. Detailed information of Hydroxyethoxyphenyl butanone (HEPB).

IUPAC Name	CAS Number	Chemical Structure	Molecular Weight	pK_a	Log $K_{o/w}$
4-(3-Ethoxy-4-hydroxyphenyl) -2-butanone	569646-79-3		208.25 g·mol^{-1}	10.19	1.68

Cosmetics products are used on a daily basis by many consumers, contributing to the improvement of their well-being, so these products must be safe for human health. Therefore, procedures to perform the analytical control of cosmetic products by cosmetic companies are necessary to ensure the safety of consumers [8,9]. However, there is no official method to quantify HEPB in cosmetic samples. Furthermore, to the best of our knowledge, there are not published analytical methods regarding its determination.

With regard to the analytical techniques for the determination of preservatives [9], reversed-phase liquid chromatography (LC) coupled with ultraviolet-visible spectrophotometry (UV/Vis) [10–14], and tandem mass spectrometry (MS/MS) [15,16] detectors are the most commonly used. Gas chromatography (GC) [17–19], capillary electrophoresis (CE) [20,21], and micellar electrokinetic chromatography (MCEK) [22–25] methods are also frequent alternatives to LC methods. About sample preparation, different extraction procedures based on solid-phase extraction (SPE) [20,26–28], pressurized liquid extraction (PLE) [29,30], matrix solid-phase dispersion (MSPD) [31–33] and microextraction techniques, such as solid-phase microextraction (SPME) [34,35] and liquid-liquid microextraction (LLME) [11–13,17,19,21], are gaining popularity as clean-up and pre-concentration procedures to overcome the problems associated to the complex cosmetic matrices. However, these sample treatment procedures are frequently tedious, time consuming, and expensive if commercial sorbents, cartridges or fibers are required. Among the different types of cosmetic preservatives studied in the analytical literature, parabens are by far the most frequently analyzed, whereas the number of published papers dealing with the analysis of other preservatives is more limited [9].

To the best of our knowledge, this is the first work addressing a reliable and useful analytical method which has been developed and validated for the determination of HEPB in cosmetic samples. Special emphasis is paid with regard to rapidness and simplicity on sample preparation, besides on accuracy and sensitivity. The sample preparation of the proposed method is based on a green ultrasound-assisted lixiviation of the analyte followed by its determination by LC-UV/Vis. The proposed LC-UV/Vis method provides limits of detection and quantification far below the limits contemplated in the abovementioned SCCS opinion. These characteristics make the proposed method useful to perform the pre- and in-market analytical control of cosmetic products, in order to assure their safety.

2. Materials and Methods

2.1. Apparatus

An Agilent 1220 Infinity LC system including a degasser, a quaternary pump, an autosampler with up to 100 µL injection volume, a thermostated column oven, and a UV/Vis detector was employed. The column was a LiChrospher® 100 RP-18 (250 mm length, 4 mm I.D., 5 µm particle size) from Merck (Darmstadt, Germany).

An ultrasound bath (50 Hz, 360 W) from J.P. Selecta (Barcelona, Spain) was used to ease the lixiviation of the analyte in the preparation of sample solutions.

2.2. Reagents

HEPB (4-(3-ethoxy-4-hydroxyphenyl) butan-2-one) 95% from Enamine (Riga, Lativa) was used as standard.

Deionized water obtained from a Connect water purification system provided by Adrona (Riga, Latvia) was used as solvent to prepare samples and standard solutions.

LC-grade absolute ethanol from Scharlab Chemie (Barcelona, Spain), extra-pure glacial acetic acid from Scharlab Chemie (Barcelona, Spain) and deionized water were used to prepare the mobile phase.

2.3. Samples

Seven commercial cosmetic samples, including three hydrophilic gels (two liquid hand soaps and a shampoo), three lipophilic creams (two sunscreens and a moisturizing cream), and a make-up (foundation) were analyzed. They were from different brands and the names are not shown for reasons of confidentiality. Moreover, a laboratory-made cosmetic cream containing the target analyte was also fabricated and analyzed, using common cosmetic-grade ingredients from Guinama S.L. (Valencia, Spain) such as emollients, hydrating agents, surfactants, preservatives, etc. (see Supplementary Material).

2.4. Proposed Method

2.4.1. Preparation of Standards and Sample Solutions

A stock standard solution containing HEPB at 500 $\mu g \cdot mL^{-1}$ was prepared using deionized water as solvent. From this solution, working calibration solutions (1–100 $\mu g \cdot mL^{-1}$) were prepared by proper dilution with deionized water and then placed into 1.5 mL injection vials for LC-UV/Vis analysis.

Samples were prepared by weighing approximately 0.1 g into a 10 mL volumetric flask and then diluted up to the line with deionized water. After that, the volumetric flask was introduced in an ultrasonic bath and sonicated for several minutes in order to achieve the lixiviation of the analyte from the sample matrix. Finally, it was filtered when needed to remove the non-soluble compounds and placed into 1.5 mL injection vials for LC-UV/Vis analysis.

2.4.2. Chromatographic Analysis

Twenty microliters of the aqueous standard or sample solution were injected into the column set at 35 °C. The elution was performed in isocratic mode, the mobile phase was a mixture of ethanol and aqueous 1% acetic acid solution (23:77, v/v), and the flow rate was set at 0.8 $mL \cdot min^{-1}$. The detection wavelength for signal monitoring was fixed at 279 nm and the runtime was completed in 18 min. Calibration curves were constructed by plotting the peak area of the target analyte versus concentration.

3. Results and Discussion

3.1. Study of the Chromatographic Variables

Preliminary studies were carried out in order to evaluate the different variables that may affect the chromatographic determination, such as the mobile phase composition, the flow rate, the column

temperature and the column length. To carry out these studies, a standard solution containing HEPB at 25 μg·mL^{-1} was used.

With the purpose of obtaining a good chromatographic resolution in as short a time as possible, and taking into account the presence of other matrix compounds when cosmetic samples are analyzed, the effect of the mobile phase was initially studied. In this sense, an aqueous solution of acetic acid (1%, *v*/*v*) was used as the aqueous mobile phase and ethanol was used as the organic modifier. Different ratios of both solvents were tested, obtaining the best chromatographic results at a mixture ratio of 23:77 (*v*/*v*), respectively. In this sense, ethanol was preferred over other possible organic modifiers, such as methanol or acetonitrile, for being a less toxic solvent (environmentally-friendly). Moreover, the high elution power of ethanol allows to achieve good chromatographic separations using less volume of organic modifier in the mobile phase.

Regarding the flow rate, different values between 0.5 and 1 mL·min^{-1} were tested, obtaining the best chromatographic separation at 0.8 mL·min^{-1}. The effect of the column temperature was also studied. Oven temperatures from 30 °C to 50 °C were tested. No significant differences were observed, and thus 35 °C was selected for further analysis in order to set the system at fixed conditions.

However, depending on the sample, a partial overlapping of the analyte with other cosmetic matrix compounds was still observed. In this sense, a Purospher® STAR RP-18 endcapped (125 mm length, 4 mm I.D., 5 μm particle size) column and a LiChrospher® 100 RP-18 (250 mm length, 4 mm I.D., 5 μm particle size) column were compared. When the latter was employed, a better chromatographic resolution was obtained, and thus it was selected for further analysis.

3.2. Study of the Sample Preparation

Samples with different composition and cosmetic form were assayed (liquid hand soaps, shampoo, sunscreen, moisturizing creams, and make-up) and studies were conducted in order to find a preparation procedure that was common for all them. This procedure does not need to achieve the total dissolution of the sample, it is sufficient that it allows the lixiviation of the analyte and the subsequent separation by filtration of the insoluble part of the sample. In order to ease the lixiviation of HEPB from the cosmetic matrices, different mixtures of deionized water and ethanol (from 0 to 50%, *v*/*v*) were tested as sample solvents.

Chromatographic assays showed that bad-shaped peaks were obtained in the LC-UV/Vis analysis when the content of ethanol was equal to or greater than 25% (*v*/*v*), while no significant chromatographic differences were observed when the content of ethanol was lower. At the same time, the solubility assays showed that ethanol is not necessary for the lixiviation of HEPB if the aqueous dispersion/emulsion of samples is sonicated in an ultrasound bath. Thus, deionized water was finally selected as the sample solvent.

3.3. Analytical Figures of Merit of the Proposed Method

Under the selected conditions, method validation was performed by determining a series of quality parameters such as the linearity of the response curve, the limits of detection (LOD) and quantification (LOQ), the repeatability, and the accuracy of the proposed method. These results are summarized in Table 2.

Table 2. Analytical figures of merit of the proposed method.

Slope (mAU min mL·μg^{-1}) [a]	19.0 ± 0.1		
Intercept (mAU min) [a]	−7 ± 6		
R^2 [b]	0.9997		
Instrumental LOD (μg·mL^{-1}) [c]	0.3		
Instrumental LOQ (μg·mL^{-1}) [d]	0.9		
Method LOD (μg·g^{-1}) [c]	30		
Method LOQ (μg·g^{-1}) [d]	90		
Intra-day Repeatability (RSD, %) [e]	2.5 (5 μg·mL^{-1})	0.2 (25 μg·mL^{-1})	0.9 (50 μg·mL^{-1})
Inter-day Repeatability (RSD, %) [e]	1.2 (5 μg·mL^{-1})	1.2 (25 μg·mL^{-1})	4.7 (50 μg·mL^{-1})

[a] Parameters of the calibration curve obtained by simple linear regression. Working range: 1–100 μg·mL^{-1}, n = 10. Expressed as the value ± standard deviation. [b] Coefficient of determination (R^2) of the calibration curve. [c] Limit of detection (LOD) estimated as 3-folds the signal-to-noise ratio. [d] Limit of quantification (LOQ) estimated as 10-folds the signal-to-noise ratio. [e] Precision expressed as relative standard deviation (RSD, %), n = 5.

The experiments shown that linearity reached at least 100 μg·mL^{-1}, with coefficients of determination (R^2) > 0.9997.

The instrumental LOD and LOQ values, calculated as 3- and 10-folds the signal-to-noise ratio, were 0.3 and 0.9 μg·mL^{-1}, respectively. These values correspond to method LOD and LOQ (i.e., in the cosmetic sample) of 30 and 90 μg·g^{-1}, respectively. These low limits of detection and quantification, in addition to the linear range observed, allow the determination of the target compound in a wide range of concentrations.

The repeatability, expressed as relative standard deviation (RSD, %), was evaluated by applying the proposed method to five replicates of aqueous standard solutions containing HEPB at three concentration levels (5, 25, and 50 μg·mL^{-1}) in the same day (intra-day repeatability) and in different consecutive days (inter-day repeatability). Results shown in Table 2 reveal that good precision was achieved (RSD < 4.7%).

In order to evaluate the accuracy of the proposed method, a laboratory-made cosmetic sample (i.e., a moisturizing cream) containing a known amount of the target analyte (specifically, 0.36%, *w*/*w*) was prepared following the usual manufacturing procedures of the cosmetic industry. Then, it was analyzed by triplicate employing the proposed LC-UV/Vis method, and the obtained result was 0.34 ± 0.01%, *w*/*w*. Thus, the relative error was below 6%, showing that the proposed method is accurate.

3.4. Analysis of Commercial Samples

Samples were prepared by triplicate as specified in the proposed method (see Section 2.3) and injected into the chromatographic system under the selected conditions. The results shown that HEPB was only detected in one of the seven commercial samples analyzed, the moisturizing cream (sample 5), as can be seen in Table 3. With the purpose of evaluating the matrix effects, recovery studies were performed. Thus, the samples were prepared by triplicate according to the proposed method, and then spiked with the target analyte at three concentration levels (0.05, 0.25, and 0.50%, *w*/*w*). A good chromatographic resolution was obtained for all the tested samples. The obtained recovery values (Table 3) ranged from 86 to 103%, thus showing that matrix effect was negligible and that external calibration can be used as described in the proposed method. These results also confirm the study of the accuracy previously described.

Table 3. Obtained concentration (%, *w*/*w*) and recovery values (%) in the analysis of cosmetic samples.

	Sample	Concentration (%, *w*/*w*) [a]	Recovery Values (%) [a]		
			0.05%, *w*/*w*	**0.25%, *w*/*w***	**0.50%, *w*/*w***
1	Laboratory-made cream (HEPB at 0.36%, *w*/*w*)	0.34 ± 0.01	86 ± 2	102 ± 5	90 ± 5
2	Liquid hand soap 1	n.d.	98 ± 4	102 ± 2	101 ± 1
3	Liquid hand soap 2	n.d.	100 ± 4	100 ± 1	99 ± 1
4	Make-up	n.d.	93 ± 2	90 ± 1	89 ± 2
5	Moisturizing cream	0.083 ± 0.002	103 ± 8	92 ± 5	91 ± 1
6	Shampoo	n.d.	99 ± 1	100 ± 1	99 ± 1
7	Sunscreen 1	n.d.	97 ± 1	98 ± 1	100 ± 1
8	Sunscreen 2	n.d.	89 ± 2	90 ± 2	87 ± 2

[a] The values are expressed as the mean of three replicates ± standard deviation. n.d.: Not detected.

Figure 1 shows, as example, the chromatograms obtained applying the proposed method to: an aqueous standard solution, a laboratory-made cream containing HEPB, a moisturizing cream, a sunscreen sample, and this same sunscreen sample spiked with HEPB. The unidentified peaks in the chromatograms belong to unknown compounds from the sample matrix.

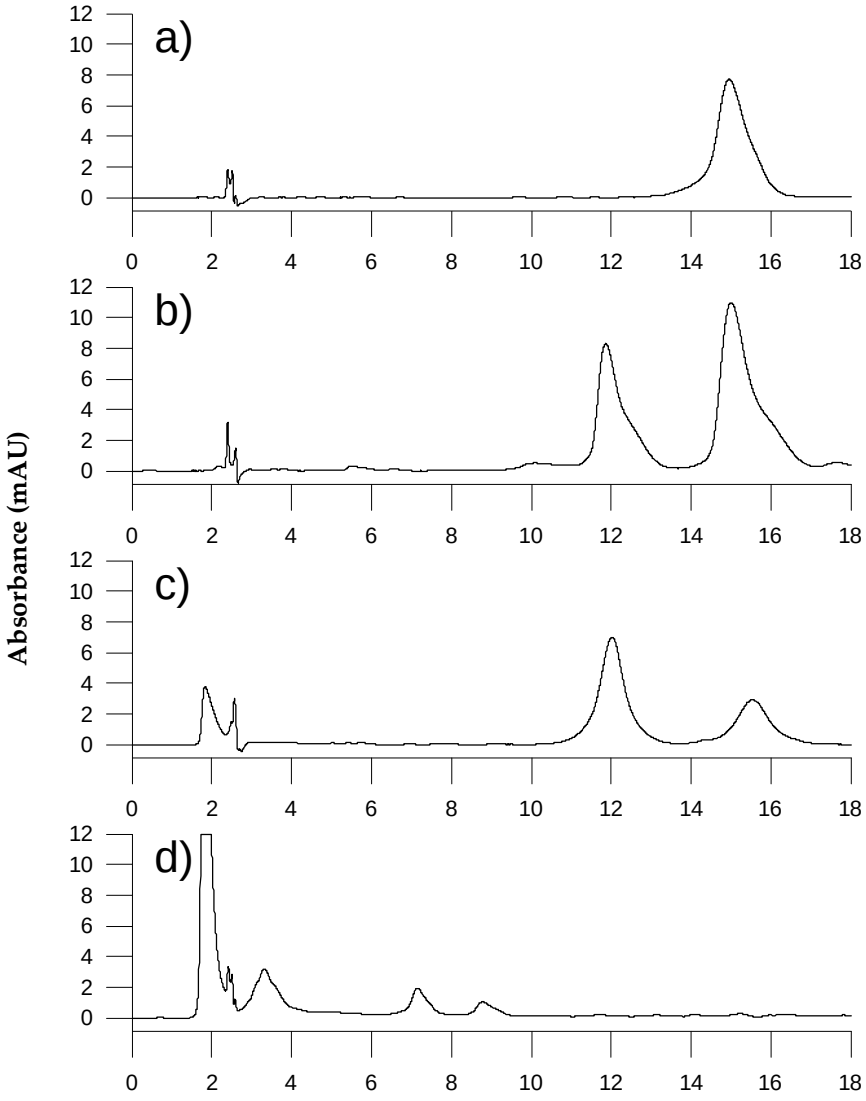


Figure 1. *Cont.*

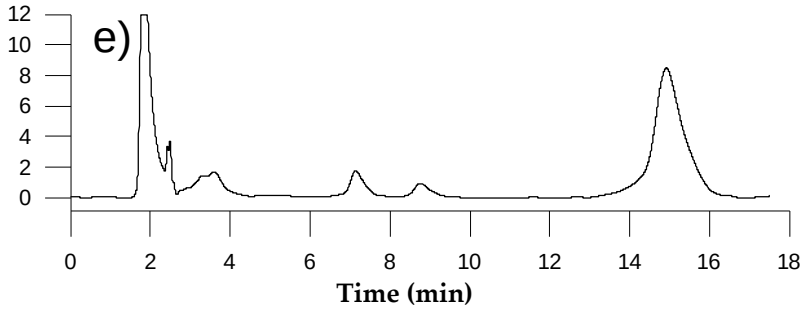


Figure 1. Chromatograms obtained applying the proposed method: (**a**) standard solution (25 μg·mL^{-1}); (**b**) laboratory-made cream containing HEPB at 0.36%, *w*/*w* (sample 1); (**c**) moisturizing cream (sample 5); (**d**) sunscreen (sample 7); (**e**) sunscreen (sample 7) spiked at 0.25%, *w*/*w*.

3.5. Evaluation of the Greenness of the Proposed Method

In order to evaluate the eco-friendly characteristics of an analytical procedure, different tools published in the analytical literature can be used. In this sense, the greenness of the proposed method has been evaluated according to the Analytical Eco-Scale [36], which applies penalty points to those parameters that are not in agreement with the ideal green analysis. The evaluation of the proposed method based on the Analytical Eco-Scale is summarized in Table 4. As can be seen, the obtained score for the proposed method is 85, which represents an excellent green analysis (>75). It should be noted that all the assigned penalty points are due to the LC-UV/Vis measurement (instrument, mobile phase, and wastes), as the proposed sample preparation is completely eco-friendly.

Table 4. Evaluation of the greenness of the proposed method based on Analytical Eco-Scale.

Proposed Method	Penalty Points
Sample preparation	
Dilution with water (10 mL/sample)	0
Ultrasound-assisted lixiviation	0
Instrument	
LC-UV/Vis	1
Mobile phase reagents	
Ethanol (≈3.3 mL/sample)	2
Acetic acid (≈0.1 mL/sample)	4
Wastes	8
Total penalty points: 15	
Analytical Eco-Scale total score: 85	

4. Conclusions

With the aim of providing reliable and affordable analytical methods to improve and facilitate the quality control of cosmetic products, a new LC-UV/Vis method for the determination of an alternative preservative (i.e., hydroxyethoxyphenyl butanone) is presented. To the best of our knowledge, this is the first proposed method where this preservative is determined in different cosmetic formulations.

The method allows the quantification of the target compound in both lipophilic and hydrophilic cosmetic samples with good analytical features, such as accuracy, precision and sensitivity. Moreover, the method is simple, fast, and both user and environment friendly, based on the principles of the so-called Green Analytical Chemistry. For that reason, the proposed method is useful to perform the pre- and in-market analytical control of cosmetic products in order to assure the safety of the consumers.

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