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Neutral desorption extractive electrospray ionization mass spectrometry for fast screening sunscreen agents in cream cosmetic products

Xinglei Zhang[a,1], Yan Liu[b,1], Jinghua Zhang[b], Zhong Hu[a], Bin Hu[a], Liying Ding[a], Li Jia[b], Huanwen Chen[a,*]

[a] Jiangxi Key Laboratory for Mass Spectrometry and Instrumentation, East China Institute of Technology, Nanchang, Jiangxi Province 330013 PR China
[b] Beijing Center for Physical and Chemical Analysis, Beijing 100089, PR China

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ABSTRACT

High throughput analysis of sunscreen agents present in cream cosmetic has been demonstrated, typically 2 samples per minute, using neutral desorption extractive electrospray ionization mass spectrometry (ND-EESI-MS) without sample pretreatment. For the targeted compounds such as 4-Aminobenzoic acid and oxybenzone, ND-EESI-MS method provided linear signal responses in the range of 1–100 ppb. Limits of detection (LOD) of the method were estimated at sub-ppb levels for the analytes tested. Reasonable relative standard deviation (RSD = 8.4–16.0%) was obtained as a result of 10 independent measurements for commercial cosmetics samples spiked with each individual sunscreen agents at 1–10 ppb. Acceptable recoveries were achieved in the range of 87–116% for direct analysis of commercial cream cosmetic samples. The experimental data demonstrate that ND-EESI-MS is a useful tool for high throughput screening of sunscreen agents in highly viscous cream cosmetic products, with the capability to obtain quantitative information of the analytes.

1. Introduction

Sunscreen agents are commonly added in commercial cosmetic products to protect skin from tanning and/or sunburn, due to their excellent absorption capability at medium-wave ultraviolet (280–320 nm, UVB) and long-wave ultraviolet range (320–400 nm, UVA). Most of the sunscreen compounds are used safely for many years. However, some chemicals such as oxybenzone (MW 228) have been banned for cosmetics due to the carcinogenic toxicity of oxybenzone [1]. Furthermore, in many countries such as China, the type and amount of the sunscreen agents which can be added to the cosmetics has been limited by Hygienic Standard for Cosmetics of China. Thus, analytical techniques available for fast detection of trace sunscreen agents in cream products are highly demanded.

Chemically, cosmetic cream products are complex mixtures composed of many ingredients such as oils, fats, waxes, surfactants, moisturizing agents, emulsifier, preservatives, pigments, fragrances and so on. This makes it difficult for fast detection of a specific sunscreener in the cream matrix. To date, chromatographic techniques [2–9] are the most common methods for detecting the sunscreen agents in the cosmetics. Mass spectrometry (MS) has been coupled to liquid chromatography (LC) for the determination of sunscreen agents with improved sensitivity [4,7]. Sample pretreatments including pre-separation and pre-concentration are generally required for chromatography-based protocols. The sample pretreatment steps make the whole analysis process laborious and time-consuming, resulting in difficulties for fast screening inferior commercial products containing illicit sunscreen agents.

Mass spectrometry is an analytical tool of intrinsically high sensitivity and specificity. The throughput of mass spectrometric methods has been dramatically improved by means of creating analyte ions at the ambient conditions with minimal/no sample pretreatment. As the first example, Cooks et al. introduced desorption electrospray ionization (DESI) [10–12], which tolerates complex matrices, and forms analyte ions from the ejected secondary droplets from the sample surface without prior separation. Later on, various so-called ambient pressure ionization (API) techniques [13,14] including direct-analysis-in-real-time (DART) [15], desorption atmospheric pressure chemical ionization (DAPCI) [16–18], atmospheric-pressure solids analysis probe (ASAP) [19], electrospray laser desorption/ionization (ELDI) [20], plasma-assisted desorption/ionization (PADI) [21], low temperature plasma (LTP) [22,23] and extractive electrospray ionization (EESI) [24–29] were developed for direct analysis of complex samples without sample pretreatment. However, above-mentioned

* Corresponding author at: Department of Applied Chemistry, East China Institute of Technology, Nanchang, Jiangxi Province 330013 P. R. China Tel.: +86 791 3896370; fax: +86 791 3896370.
E-mail address: chw8868@gmail.com (H. Chen).
[1] These authors contributed equally to this work.

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techniques normally are unsuitable for analysis of viscous samples with complex nature. Analytes in the viscous matrices, usually as the heterogeneous liquid phase, cannot be readily desorbed for sensitive ionization/detection due to the high viscosity of the sample.

By directing a nitrogen gas beam into the bulk liquid, analytes in highly viscous liquids such as ionic liquids [30], edible oil samples [31] or on the surfaces of greasy cheese products [32], toothpaste products [33] can be sampled for EESI-MS analysis [34,35]. This strategy separates the extractive ionization process from the sampling process in both space and time, yielding better toleration of the complex matrix and potential ionization efficiency improvement during MS analysis. With a sealable ND device [36], non-volatile compounds (e.g., explosives) at picogram level were detected from the human skin surface, since the material liberated from the sample surface were efficiently transferred to the EESI source, preventing the material loss at the maximal degree. Recently, a geometry-independent neutral desorption (GIND) device [37] was fabricated for better sampling of explosives on various surfaces. In comparison with previous reported ND devices, the GIND device requires no optimization of the ND parameters (e.g., the angles between the gas beam, the surface, and the collecting tube; distances, etc.), allowing easy operation and high throughput analysis. In present study, several illicit sunscreeners in viscous cosmetics, were rapidly detected and identified by EESI-MS coupled with a sealable GIND device without any sample pretreatment.

2. Experiments

2.1. Chemicals and reagents

4-Aminobenzoic acid was bought from Acros organics (New Jersey, USA). Avobenzone (99.5%) was bought from Dr. Ehrenstorfer GmbH (Augsburg, Germany). Bis-ethylhexyloxyphenol methoxyphenyl triazine, octyl 4-methoxycinnamate and UVT-150 were purchased from US Pharmacopeia (USP) (Rockville, MD), 3-(4′-methylbenzylidene) camphor and oxybenzone were bought from Accustandard (New Haven, USA). Octocrilene and UV-360 were bought from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Individual stock standard solutions (1000 mg/L) were prepared in methanol and stored at −20 °C. The cosmetic products including night cream, day cream, anti-sunlight oil were purchased from a local supermarket. No further treatment was performed before samples analysis using ND-EESI-MS.

2.2. Neutral desorption sampling

As reported elsewhere [33], a home-made glass shell (i.d., 20 mm) was utilized as the GIND device (as shown in Fig. 1) to air-tightly cover the sampling area (~50 mm^2). The surface of the viscous cosmetics (~0.1 g) was impacted by a pure nitrogen gas beam (room temperature 20 °C, velocity ~300 m/s, flow rate 2.7 mL/s) ejected from an aperture (i.d. 100 μm) for desorption. The distance between the GIND gas emitter and the gel surface was 1.5 mm. The desorbed analytes were sampled as an aerosol flow (velocity 3.4 m/s, flow rate 2.7 mL/s) into the EESI source using the sample transfer line (Teflon tube, i.d. 3 mm).

A fraction of the commercial cosmetic sample (~100 mg) was deposited on paper or skin surface, and then subjected to GIND sampling without further treatment. The method was extended for sampling of trace cosmetic ingredients of the residues coated on a skin surface.

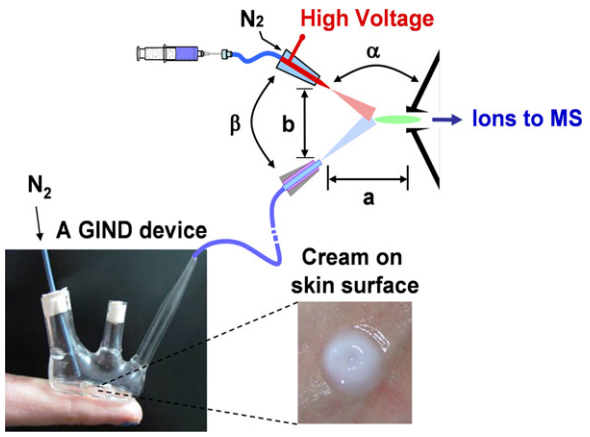


Fig. 1. Schematic diagram of an EESI source with a sealable GIND device (GIND-EESI). The cream sample on the skin surface was sampled by the GIND device (shown in the inset).

2.3. EESI-MS analysis

A home-made EESI source [24–29,33] was coupled to a LTQ XL linear ion trap mass spectrometer (San Jose, CA) for the direct analysis of sampled illicit additives and contaminants in cosmetics. The angle between the sample outlet and the electrospray beam (β, Fig. 1) was 60°. The angle between the electrospray beam and the heated capillary of the LTQ instrument (α, Fig. 1) was 150°, which was equivalent to the one formed by the sample outlet and the heated capillary of the LTQ instrument. The distance between the inlet of the LTQ instrument and the gas outlets (a, Fig. 1) was 15 mm. The distance between the two spray tips (b, Fig. 1) was 6 mm.

A methanol/acetic acid (100:0.1, v:v) solution infused at 5 μL/min was electrosprayed as the extraction solvent to generate the primary ions. The sample plume was directed to intersect the ESI plume for extractive ionization of the analytes. The analyte ions were then guided through the heated capillary of the LTQ mass spectrometer for mass analysis. The temperature of the heated capillary maintained at 300 °C. A positive ion detection mode was used for most experiments, with an ESI voltage of +4.0 kV. The pressure of nitrogen gas was set at 2.0 MPa. The default values of voltages for the heated capillary, ion optics, and the detectors were used without further optimization. For full MS scan, a mass range between 50 and 600 m/z was scanned for each measurement. The mass spectra were recorded with an average time of 30 s and with background subtracted. Collision-induced dissociation (CID) experiments were preformed by applying 10–35% (arbitrary units defined by the LTQ instrument) of the collision energy to the precursor ions isolated with a window width of 1.6 mass/charge (m/z) units.

2.4. Preparation of spiked standard samples

To prepare the series of standard cosmetics samples, analyte-free day cream samples (2.0 g each) were put into several beakers (10 mL, Tianjin Tianbo Glass Instrument Co., Ltd., Tianjin, China), into which a series of standard solutions (400 μL of methanol solutions containing different concentrations of analytes) were added, respectively, to make the standard samples. Samples were kept stirring for 30 min to achieve the homogeneous distribution of analytes inside cosmetics. These mixtures were partially dried under low vacuum conditions (10 mTorr, 25 °C), if necessary, until the final mass loss was 400 mg for each beaker. Due to its volatility, the methanol evaporated easily within minutes while the other ingredients were kept, imposing no significant alteration of its viscosity after the analyte adulteration.

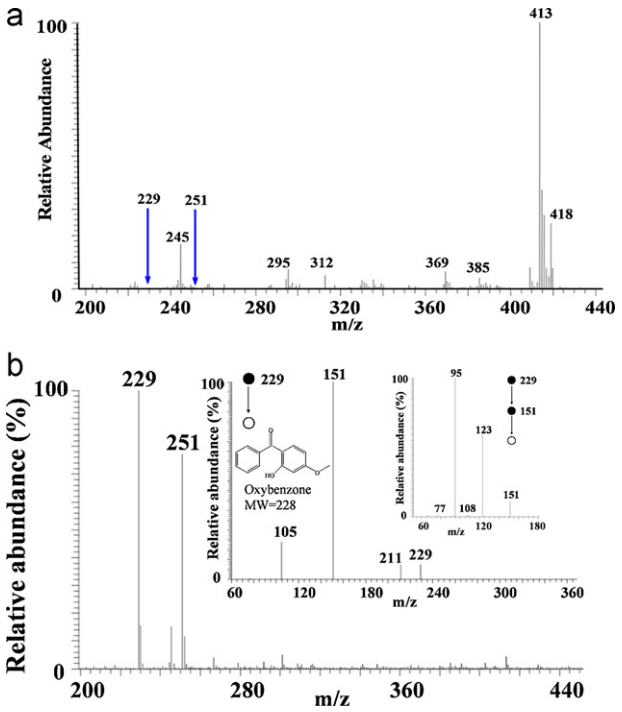


Fig. 2. Typical GIND-EESI mass spectrum recorded from commercial day cream samples. (a) A blank sample; (b) a sample spiked with oxybenzone. The insets show the major fragments obtained in the CID experiments.

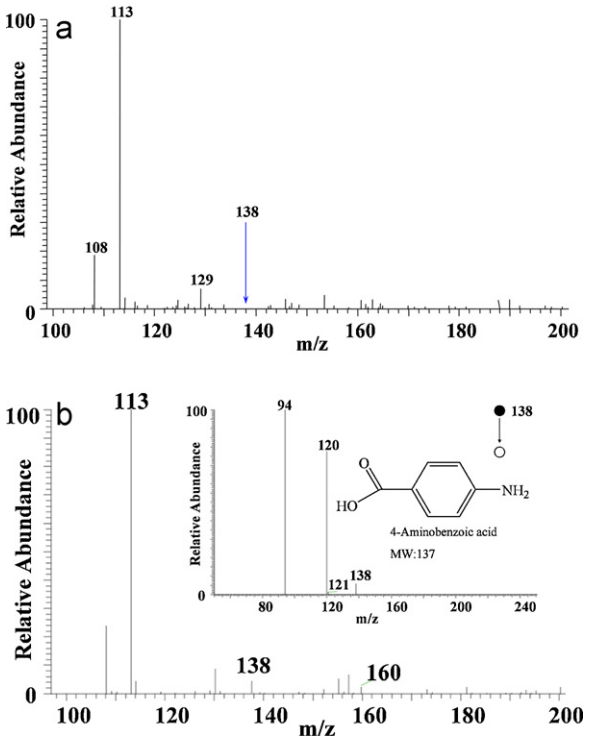


Fig. 3. Typical GIND-EESI mass spectrum recorded from commercial anti-sunlight oil sample. (a) A blank sample; (b) a sample spiked with 4-aminobenzoic acid. The inset shows the MS/MS spectrum of the protonated 4-aminobenzoic acid. The peak at *m/z* 113 was ascribed to the major component of the sample; however, the identification was not attempted.

3. Results and discussion

3.1. Optimization of the working conditions

The pressure of the desorption nitrogen gas is the key parameter for GIND sampling, because GIND is a geometry-independent device, and the optimization of the angles, distance, etc. is not necessary. Thus, the pressure of nitrogen gas was optimized with respect to the measured MS signal of oxybenzone (100 ppb) in a day cream sample. The signal intensity of *m/z* 229 (protonated oxybenzone) increased with elevated pressure of the nitrogen gas for neutral desorption from 1.0 to 2.0 MPa. Further pressure increase (>2.0 MPa) resulted in reduced signal intensities, probably because the analytes were blown away form the extractive ionization region by the high-velocity gas flow without producing sufficient signals. Thus, the pressure of nitrogen gas was selected as 2.0 MPa. As one of the optimized results, the methanol/acetic acid (100:0.1, v:v) solvent was infused at 5 μL/min as the electrospray solvent and the electrospray voltage was kept as 4.0 kV for all the measurements. The elevated temperature of the heated capillary improves the desolvation process. However, when the capillary temperature was set at more than 300 °C, the thermo-induced dissociation of analyte were observed, resulting in the reduced signal intensity. Note that for different cosmetic samples, the sensitivity of this method for detection of a given sun screener varied along with the matrix (i.e., the cosmetics itself); however, the highest sensitivity was achievable only at the optimized conditions, which were the same for different analytes present in various cosmetics samples tested.

3.2. ND-EESI mass spectrum of sunscreen agents in cream samples

A reference mass spectrum (Fig. 2a) was collected using GIND-EESI-MS from a blank day cream sample. Fig. 2b exhibits the GIND-EESI-MS mass spectrum recorded for 1 min from a skin care product spiked by 10 ppb oxybenzone, showing the abundant peaks ascribed to the protonated molecules (*m/z* 229) and the sodiate molecule (*m/z* 251). In comparison with the reference spectrum (Fig. 2a), no signals were detected with significant abundances at either *m/z* 229 or *m/z* 251 although other background peaks were detected at relatively high signal levels (~10^3, cps), indicating that no oxybenzone was detected in the blank sample. The protonated molecules (*m/z* 229) produced major fragments of *m/z* 211, 151 and 105 during CID, by the loss of water, benzene, and $C_7H_8O_2$, respectively (inset of Fig. 2b). The abundant peak at *m/z* 151 showed that the cleavage of benzene was highly favored in the CID process. In the MS^3 spectrum (inset of Fig. 2b), the major fragments of *m/z* 151 further fragmented into ionic species, such as ions of *m/z* 123 and 95 by the loss of CO and CO, successively. These characteristic fragments matched those obtained using the authentic oxybenzone, confirming the detection of trace analytes in the viscous sample.

Fig. 3 shows the typical data obtained from commercial anti-sunlight oil products. In the blank spectrum (Fig. 3a), there are several peaks detected with abundant signal intensities (~10^2, cps), but no much signal appears at *m/z* 138. The outstanding signals were also detected from the anti-sunlight oil sample while the analytes such as 4-aminobenzoic acid was spiked, indicating that these compounds were ingredients of the sample and the addition of the analyte caused no alteration of the matrix of the sample; however, the identification of these signals remains further studies. In Fig. 3b, the GIND-EESI-MS spectrum of a skin care cream sample spiked with 4-aminobenzoic acid (100 ppb) was shown. Among several predominant signals, 4-aminobenzoic acid (MW 137) was clearly seen as the protonated molecule at *m/z* 138. The precursor ions (*m/z* 138) fragmented into ionic species of *m/z* 120 or 94 by the loss of H_2O or CO_2, respectively. A tiny peak at *m/z* 121 was also detectable in the MS/MS spectrum (inset of Fig. 3b) due to the loss of NH_3; the low abundance of this peak indicated this fragmentation pathway

Table 1
Mass spectral data for GIND-EESI-MS analysis of sunscreen agents.

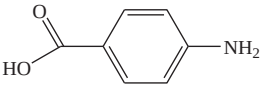
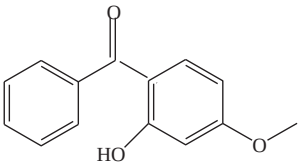
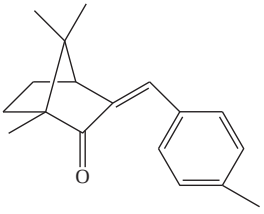
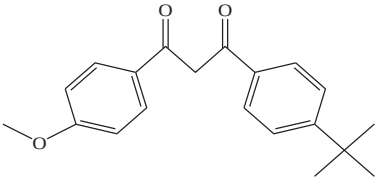
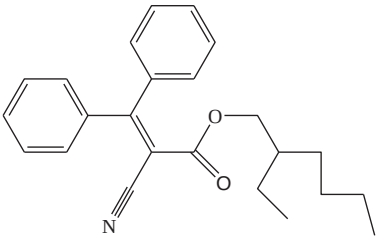
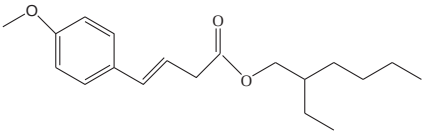
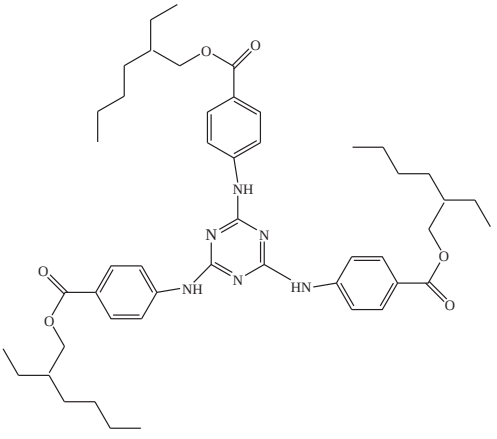
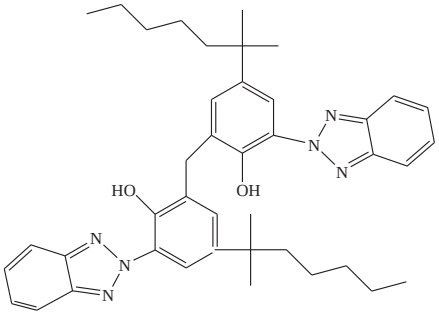
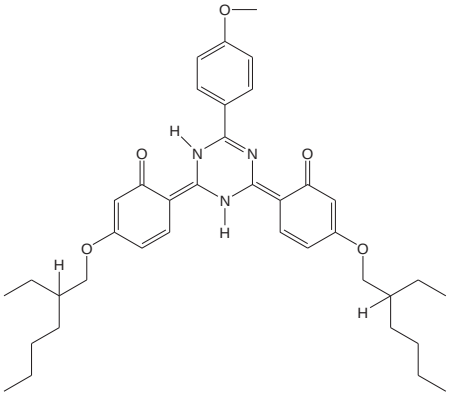
Analytes	Molecular structure	Ions observed (*m/z*)		Product ions MS/MS (*m/z*)
		$[M+H]^{+}$[a]	$[M+Na]^{+}$	
4-Aminobenzoic acid		138	160	120, 94
Oxybenzone		229	251	151, 105
3-(4′-Methylbenzylidene)camphor		255	277	237, 213
Avobenzone		311	333	161, 135
Octocrilene		362	384	250, 232
Octyl 4-methoxycinnamate		291	313	179, 161
UVT-150		824	846	712, 600, 487

Table 1 (*Continued*)

Analytes	Molecular structure	Ions observed (*m/z*)		Product ions MS/MS (*m/z*)
		$[M+H]^+$ [a]	$[M+Na]^+$	
Ultraviolet Absorbent UV-360		660	682	548, 337, 266
Bis-ethylhexyloxyphenol methoxyphenyl triazine		629	651	517, 405

[a] Ions selected for CID processes to yield the fragments listed in this table.

was not favored under present experimental conditions. The abundance of the peak at *m/z* 94 was higher than that of the peak at *m/z* 120, showing the preference of the cleavage of CO_2 rather than H_2O. These data confirmed that the charge was preferably localized on the $–NH_2$ group rather than the –OH group, showing the intrinsic chemistry of the protonated 4-aminobenzoic acid in the gas phase.

Many sunscreen agents have been regulated for their use in skin care products. As demonstrated in the present study, commonly used sunscreen agents were directly detected from the skin care products using GIND-EESI-MS. The targeted analytes were further identified by tandem mass spectrometry. Table 1 shows the detailed data for detection of common sunscreen agents from cosmetic product samples.

3.3. Sensitivity and reproducibility

As the functional ingredients, the illicit additives are used with significant amounts, allowing the final concentration no less than 1 ppb range. It is unlikely to rapidly distinguish the products containing the illicit addictives at ppb level by sensory evaluation. GIND-EESI-MS possesses the merits of high sensitivity, easy sampling and direct analysis, resulting in a powerful analytical platform for sensitive analysis of complex samples of high viscosity. LOD values at sub ppb range (Table 2) were measured for most illicit additives tested using the characteristic fragments obtained in the MS/MS experiments. The data showed that the method established here is sensitive for rapid screening of cosmetics containing illicit additives.

Under optimized experimental conditions, the relative standard deviation (RSD) was obtained by measuring the characteristic fragment abundances (MS/MS) of typical illicit compounds spiked in the cream samples for multiple times. For example, the RSD ($n = 6$) for oxybenzone (20 ppb), 4-aminobenzoic acid (10 ppb) and avobenzone (20 ppb) were 12.2%, 8.4% and 16.0%, respectively. Above mentioned values were acquired during ten measurements of adulterated cream samples containing the analytes at the concentration equal to 50 times of the LOD. The RSD data showed the method provided a reasonable deviation for trace detection of the analytes.

3.4. Quantitative analysis

For practical sample analysis, it is recommended to fast screen the analyte using its characteristic fragments at first. If no positive signals are detected in the MS/MS experiments, the sample tested contains no the analyte. For quantitative analysis, as the matrix in the example is not blank, and thus the method of standard addition has been used. For example, the characteristic fragments of oxybenzone in the MS/MS experiments showed linear responses to their concentrations in the contaminated samples, with a linear equation of $y = 25.2x + 215.5$ ($R^2 = 0.989$) (Fig. 4). However, the

Table 2
GIND-EESI detection limits for illicit sun screener in cosmetics.

Illicit sunscreeners detected	Limit of detection (ppb, S/N = 3)
Phenylbenzimidazole sulfonic acid	10[a]
Bis-ethylhexyloxyphenol methoxyphenyl triazine	0.09
4-Aminobenzoic acid	0.10
Oxybenzone	0.10

[a] Positive ion detection mode was chosen for the detection of this compound. When the deprotonated molecules (*m/z* 274) were selected to be monitored in the negative ion detection mode, the LOD obtained was about 100 times lower than that in negative ion detection mode.

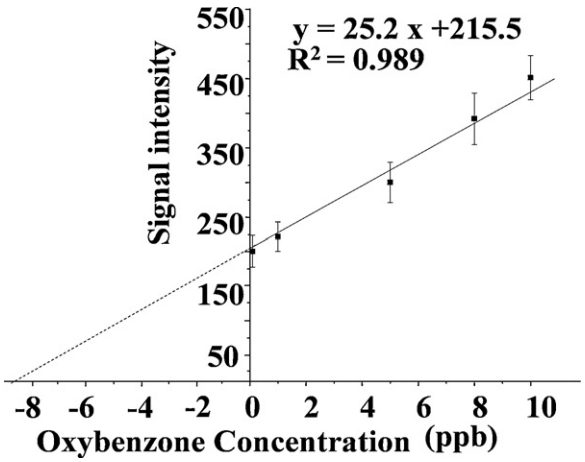


Fig. 4. Quantification of oxybenzone (sunscreen agent) in a commercial cosmetic product. The error bars show the standard deviation (SD) of 10 independent measurements at each concentration.

intercepts of the calibration curves were significantly higher than zero, because the analytes existed in the cream samples with considerable amounts. As shown in Fig. 4, the original concentrations of the analytes were estimated to be 8.6 ppb (oxybenzone). These data showed GIND EESI-MS can be used for rapid detection of illicit additives in cosmetic products, with quantitative information.

Extra experiments were performed to obtain the recovery of typical illicit additives added into the viscous cosmetic samples. As calculated by following the equation Recovery (%) = 100(Amount found − Amount added)/Amount added, the recovery for the oxybenzone (added 5 ppb) in the highly viscous cream was 87.2%. The averaged recovery of most compounds (5 measurements for each sample) added to relatively high concentration levels such as 50–200 ppb were in the range of 90–110%. The relative narrow range of the recovery for measuring various concentration levels of the additives confirms that the GIND-EESI-MS has the capability to fast detect trace illicit additives in actual samples of high viscosities.

Furthermore, different sunscreen agents were added together to a cream sample (50 ppb), resulting in a homogeneously mixed cream sample containing more than one sunscreen agent. This sample mixture was then directly analyzed by the GIND-EESI-MS method. As the result, the individual analytes were successfully detected without no significant signal suppression (data not shown). These data showed that every analyte could be measured using GIND-EESI-MS, although they were present in a single sample with complex matrix. This figure of merits could be ascribed to an advanced feature of GIND-EESI-MS method, which tolerates extremely complex matrices by separating the GIND sampling process from the EESI ionization process in both space and time, resulting in reduced ionization suppression effects.

4. Conclusions

Cosmetic products, as heterogeneous liquid samples possessing high viscosities, are widely used by large populations. Fast detection of trace compounds such as illicit sunscreen agents in cosmetic products is urgently required, due to necessary multi-step time consuming sample pretreatments required by traditional analytical techniques. In the study present, using a sealed geometry independent neutral desorption device (GIND), the analytes were liberated from the matrices, efficiently collected and further transferred for post extractive ionization in a home-made EESI source, without significant loss of the targeted analytes. The illicit sunscreen materials were thereby rapidly detected and identified by tandem mass spectrometry, without requiring any sample pretreatment. For most compounds tested, this method provided acceptable detection limits at sub-ppb range, and reasonable RSD values about 6.8–11.4%. The signals detected linearly responded to the concentrations of the illicit additives in the cosmetic product samples, showing the capability of this method for quantitative analysis. The analysis speed has been improved, and the analysis of 2 samples was completed within 1 min. The experimental data demonstrate that GIND EESI-MS developed here is an attractive analytical tool for high throughput analysis of highly viscous samples, including but not limited to cosmetic products, with high sensitivity, quantitative and quantitative information.

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