

Effects and Detection Methods of Potential Toxic Chemicals in Cosmetics: Metals, Phenoxyethanol and Aloe Vera

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Abstract. Cosmetics are widely used, but some components can be toxic at a certain dose. Thus, it is emerging to understand the toxic chemicals in cosmetics and their potential impact. This review introduces common cosmetics components with toxicity including metals, phenoxyethanol and Aloe vera. Toxic effects include some local effects, such as osteomalacia caused by metals, eye irritation, skin irritation and allergy caused by phenoxyethanol, as well as colonic mucosa caused by Aloe vera. Toxic chemicals in cosmetics are usually absorbed via the skin, and degraded in liver, then exerted through kidney and forceps. Methods to determine potential toxins includes determining heavy metals in skin-whitening cosmetics, fluorescence-based assay and the first voltametric method of phenoxyethanol determination. Future research may focus on exploring the effects of accumulation of toxic components and mechanisms of the toxicities to prevent toxic effects, as well as improving the efficiency of testing to better monitor the commercial cosmetics.

Keywords: Cosmetics, toxin, metal, phenoxyethanol, Aloe vera.

1. Introduction

Cosmetics have been widely used by people to clean, improve or change the appearance of the skin, hair, teeth and nails. However, a wide range of chemicals many cosmetic products have been displaying toxicity, such as metals, phenoxyethanol, Aloe vera, etc. [1]. Metals are often used in different kinds of cosmetics as pigments and UV filters [2]. It has been reported different types of metals and their concentrations in cosmetics. Phenoxyethanol, is an organic compound often used in skin care products, can be made from ethylene glycol and phenol ether, commonly used in skin care cream and sunscreen. Phenoxyethanol is a colorless oily liquid with antibacterial efficacy and is often used as a biological buffer substitute for highly toxic sodium azide because 2-phenoxyethanol is less toxic and chemically not active against Copper (Cu) and lead. It is often acted as antiseptic in cosmetics [3]. Moreover, nowadays, there are more and more people use herbal products. Aloe vera have a long history as a component of cosmetics and medicines, providing people more health benefit. While, recently, it was found that the production of Aloe vera may have toxicity, genotoxicity and carcinogenicity [4].

The components in cosmetics may be absorbed from skin and may be eaten directly from mouth. For example, the metals in lipsticks may have a risk of direct oral ingestion when people lick their lips or eat food and the toxins in eye shadows may also be absorbed by skin and eyes [2].

The test methods of toxins in cosmetics are also important, which are great for testing the safety of cosmetics. ICP-AES is the most useful methods. It is a method for qualitative and quantitative analysis of the elements based on the characteristic line emitted when the tested atoms in the excited state return to the ground state [5]. Another method is fluorescence-based assay. Fluorescence is the radiation excited when the material absorbs the electromagnetic radiation, and the excited atoms or

molecules reemit it at the same or different wavelength as the excitation radiation wavelength [6]. Fluorescence-based assay is also an effective way to test the toxicities in cosmetics.

This review discusses the sources, absorption and metabolism of toxic components in cosmetics, including metals, phenoxyethanol and Aloe vera. Moreover, the advantages and disadvantages of test methods are discussed.

2. Sources and properties

2.1. Metals

2.2.1. Sources of metals

The sources of the metals include plants, UV filters and pigments, crude oil, et al. When producing cosmetics, the use of plants contaminated with metals will lead to herbal products pollution [7]. Many reports show that many herbs used in cosmetic are sometimes contaminated with metals. Many metals may act as UV filters, so they are often used in face and body care products, and they are also the pigments in coloured cosmetics [2]. Different colours are corresponded to different metals and the metals in coloured cosmetics are often higher than other cosmetic products. The EU also have regulations on the concentration of metals in cosmetics. Many cosmetic preparations will also use derivatives of crude oil such as paraffin, mineral oils, aliphatic hydrocarbons and silicones [2]. These ingredients do harm to human health and furthermore some metals such as Cadmium (Cd), Chromium (Cr) and Cu may exist in it.

2.2.2. Properties of metals in different cosmetics

The use of makeup has become popular, and even on a daily basis sometimes. These cosmetics are usually left on the skin for a whole day and some of them may be used repeatedly such as lip glosses and lipsticks. Not only could these metals have direct oral ingestion with food, they also may be absorbed by skin. Different countries have different regulations of the concentration of metals in cosmetics. To human's health, the EU law or other regulations restrict the concentration of the metals in cosmetics in this order: Iron (Fe) > Cu > Al (Aluminum) > Cr > Lead (Pb) > Nickel (Ni) > Cobalt (Co) > Cd > Mercury (Hg) [2]. The metal at the highest order shows highest concentration compared to others and is often regarded as less toxicity than others.

Al and some heavy metals have also been found in various kinds of face and body care products. Some heavy metals such as Hg may sometimes be used in some cosmetics such as face cream because Hg can lighten the skin [8]. Moreover, Al is often found in antiperspirants because its compounds can block the sweat ducts. The action of Aluminum compounds involves the formation of a physical plug consisting of a combination of metal-proteoglycan precipitate and damaged cells at the top of the duct, thus preventing sweat escape to the body surface. Table 1 shows the concentration of metals in these products [2].

Many metals have been found in many kinds of hair cosmetics which include conditioners, pomades, dyes and shampoos. When structure of hair is damaged, it is easier to bind the metal. Higher concentrations of Cd, Ni, Fe, Antimony (Sb), Cu, and Manganese (Mn) have been found in stained hair as compared to unstained hair [2]. Based on other literature Table 2 shows the concentration of metals in these products.

Table 1. Concentration of metals in face and body products [2]

Metal	Pb	Hg	Fe	Al	Ni	Cd	Cu	Cr
Concentration (g/kg)	0 – 790	0 – 65.133	0 – 2.469	0 – 0.062	0 – 0.029	0 – 0.028	0 – 0.019	0 – 0.006

Table 2. Concentration of metals in hair cosmetics [2]

Metal	Fe	Ni	Co	Pb	Cu	Cr	Cd
Concentration (g/kg)	0 – 0.421	0 – 0.072	0 – 0.025	0 – 0.018	0 – 0.013	0 – 0.011	0 – 0.007

2.2. Phenoxyethanol

Nowadays, phenoxyethanol is widely used in cosmetic industry but exerts toxic effects [9]. The structure of phenoxyethanol is shown in Fig. 1. Compared with other cosmetic chemical preservatives, phenoxyethanol has weak inhibition on resident bacteria in normal skin and can be used as a preservative for large flushing and residual cosmetics. It is also a fragrance ingredient which is used in some fragrance mixtures. The precious study has demonstrated that phenoxyethanol may cause repeated dose toxicity, which contains oral route, inhaled route and topical route. [3]

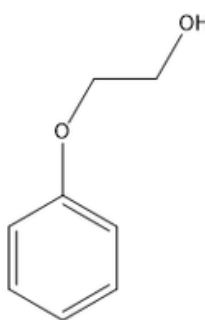


Figure 1. phenoxyethanol

Moreover, phenoxyethanol also has neurological effects and local effects. In subchronic animal studies, phenoxyethanol was not found to have any neurotoxic effects regardless of the route of administration used [3]. Moreover, other research also shows that Phenoxyethanol is irrelevant to neurological effects, eye irritation, skin irritation and allergy. [3]

2.3. Aloe vera

Aloe vera contains antioxidants, which may increase the shelf-life and nutritional value of food; therefore, it is widely used in cosmetic, pharmaceutical and food industry [4], but the widespread human exposure and its potential toxic and carcinogenic activities raise safety concerns. The researchers have proved that *Aloe vera* and some of their products may have toxicity, genotoxicity, and carcinogenicity [10]. In addition, different parts of the *Aloe vera* have different chemical composition.

The leaf extract of *Aloe vera* contain over 200 compounds. The raw leaf consists of 98.5% water and the rest are some nutrients (eg. amino acids, carbohydrates, minerals and vitamins) and non-nutrients such as organic acids, phenolic compounds, anthraquinones, and phytosterols [10]. The *Aloe vera* latex or exudate contains nearly 80 chemicals and most of them are phenolic in nature, mainly anthraquinone C- glycosides, anthrones, and free anthraquinones [11]. Moreover, the other ingredients are aloin B, aloeresin B, aloeresin A and other anthraquinones and chromones which include aloe-emodin, aloeresin E, aloenin [12]. The *Aloe vera* gel is present in the parenchymal cells of the fresh *Aloe vera* leaf pulp. The gel contains a high level of water (99%–99.5%) [13]. The other components include 35% dietary fibers, 27% soluble sugars, 24% ash, and small amounts of lipids, proteins, enzymes, and mineral elements [10].

3. Absorption and accumulation of toxin in cosmetics

3.1. Absorption

As most cosmetics work on face, cosmetics usually are absorbed via the skin. Skin is an open system and it's our channels for exchanging materials with external stimuli. Thus, there are many ways for toxin in cosmetics enter our bodies. For example, foreign matter can transmit the skin through gap between cuticle and cells, or through the pores of sweat glands and hair follicles. In addition, some toxins in lipstick can also have direct oral ingestion with food [14]. When those toxins accumulate to a certain amount in our bodies, many symptoms can be caused, especially on the face, including skin allergy, osteomalacia, etc. [2, 3]. However, when heavy metal elements accumulate to the organs, even the whole body may be affected and cause serious damage.

3.2. Metabolisms of toxin

3.2.1. Metals

Among the metals, heavy metals such as lead, mercury, cadmium, arsenic and nickel, also aluminium as light metal doesn't are usually detected in many types of cosmetics [2]. In fact, metals like antimony, arsenic, cadmium, chromium, cobalt, mercury, nickel and lead are prohibited ingredients in cosmetics because they are considered unsafe [19].

The metals enter human body through several ways. Firstly, they can be simply accumulated in the skin. Secondly, when we cover cosmetics on our skin, metals such as Cr, Ni, As can bound with the keratin, which is composed of dead cells. Other metals such as Pb, Hg, Al, Cd can be absorbed to the blood circulation and spread to the whole body with the blood flowing [2]. The former may form deposits at deeper layers of the stratum corneum causing illness like allergic contact dermatitis, and the in the latter case metals can enter various organs and accumulated with blood circulation. Table 3 shows biological half-life of some metals mentioned above.

Table 3. Biological half-life of metals

Metal	Half life	References
Cr	4-10 hours	[15]
Pb	27-30 days	[16]
Hg	60 days	[17]
Al	7-50 years	[18]
Cd	30 years	[19]

3.2.2. Phenoxyethanol

Phenoxyethanol has been widely used as a preservative in cosmetic products for decades because of its large spectrum of antimicrobial activity. Research shows that after exposure only minority of phenoxyethanol remain in the skin and most was recovered in the receptor fluid, which means it doesn't bind to the skin or accumulate in the skin [3].

Phenoxyethanol can be metabolized rapidly in the skin or in the liver and is more efficient in the liver. After a two-step oxidation process by cytosolic alcohol dehydrogenase and aldehyde dehydrogenase, it mainly forms 2-phenoxyacetic acid. This oxidation process is primarily found in human urine [3].

To study about the repeated dose toxicity of phenoxyethanol, scientists did researches on animal models via inhalation (rats), oral administration (mice and rats) and dermal routes (rabbits) [3]. The result shows that after oral exposure to high doses of phenoxyethanol, the systemic effects like haematological and liver effects can be observed. However, the dose is much higher than when it is used as cosmetic ingredient.

3.2.3. Aloe vera

Chemical analysis reveals that the *Aloe* plant contains various polysaccharides and phenolic chemicals, notably anthraquinones [10]. *Aloe vera* includes *Aloe vera* whole leaf extract, *Aloe vera* latex or exudate and *Aloe vera* gel. Study noted that emodin in *Aloe vera* can cause the expansion of female uterine blood vessels and then progresses to inflammation [10].

4. Symptoms of adverse effects

4.1. The harm of metals

Heavy metals are harmful to people's body when heavy metals accumulated mainly because of their effects of irreversibly change the structure of proteins, especially some key proteins. Al, as a type of light metal, usually be found in a series of cosmetics. It is a metal characterized by high toxicity and under prolonged exposure it accumulates in the bone tissue leading to osteomalacia. Through investigation, after using cosmetics with metals, people may also exhibit symptoms like allergic contact dermatitis caused by Ni, Fe and Cr, severe eye keratitis caused by Cd, chronic intoxication with Hg caused by Hg in some creams [2].

4.2. The harm of phenoxyethanol

Some studies showed that phenoxyethanol may cause skin allergy after one topical contact with cosmetic products. In addition, phenoxyethanol may also cause eye irritation and skin irritation theoretically, which have not been observed on adults [3].

4.3. The harm of Aloe vera

Anthraquinones cause hepatorenal toxicity because too much ingestion of *Aloe vera* has to do with pigmentation of colonic mucosa, then anthraquinones may cause melanosis of colonic mucosa. In clinical trials *Aloe vera* also cause discomfort, pain and the development of hypersensitive reactions. Some symptoms on skin include generalized eczematous and papular dermatitis and pruriginous erythema [10].

5. Tests and analysis of toxin in cosmetics

Detection methods have been developed to predict or determine potential toxins in cosmetics that may cause a damage to people's body (Table 4). Three main methods are discussed, including fluorescence-based assay, determining heavy metals in skin-whitening cosmetics, as well as the first voltammetric method of phenoxyethanol determination.

Table 4. Methods to test toxins in cosmetics

Method	Purpose	References
Fluorescence-based assay	More than one kind of toxic chemicals in cosmetics	[21]
ICP-AES (inductively coupled plasma atomic emission spectrometry)	Heavy metals in skin-whitening cosmetics	[25]
First voltammetric method	Phenoxyethanol	[29]

5.1. Fluorescence-based assay

Fluorescence-based assay is a widely used as a novel tool for screening toxic chemicals, which can be applied to detect various toxins based on the changes of their fluorescence spectra. The fluorescence-based assay has been improved by applying computerized cell-based system. For the fact that researchers don't need animals in fluorescence-based assay, researchers only need to make a combination of dyes with the cells of human skin which can have characteristic response to toxin. and analyze the changes of spectra. Therefore, fluorescence-based assay is less expensive, much fast

and of high efficiency. The method of fluorescence-based assay roughly consisted of composition of dye assay, sample preparation and the measurements of fluorescence. Different toxins in this method can be reflected in the pattern of dyes and also amount number of substances can be screened in a short time and effectively in only one time [21]

5.2. Inductively coupled plasma atomic emission spectrometry (ICP-AES)

Because some of the heavy metals are applied to the skin cream, which might do harm to people's body, people all over the world are concerned about their safety [22-24], it is important for researchers to make some assessments on these cosmetics, thus guaranteeing the customers' safety.

5.2.1. The function of the ICP-AES

The ICP-AES, which is short for inductively coupled plasma atomic emission spectrometry, and microwave digestion is the method for determining the heavy metals in skin-whitening cosmetics. This method can detect the concentration of the heavy metals including Cd, Bi, Hg, Ti, Pb and As in cosmetics, based on which, the defective products can be picked out, avoiding posing the risk to people's body [25].

5.2.2. The procedure of ICP-AES

In this method which is called ICP-AES, the researchers used the analytical grade or high-performance liquid chromatography. Some preparations on samples ought to be made before the experiment. The samples were chosen from different pharmacies and beauty aid stores [25]. Every 0.1-0.25g of samples were mixed with the solvents to react and were added to digested solution. After that, statistics can be figured out and be analyzed from several aspects, including validation of the method, limit of detection, precision and the final analysis. Based on the equation (1) of the recovery percentage, researchers compared the real statistics with the certified ones, which are close to each other. That means this method is pretty feasible [25]. The concentration which are below the limit of detection can't be detected in the experiment. What's more, to make the standard addition quantification more precise, the researchers also added five standard solutions to spike each sample. There is an allowable limit which is set by WHO for every kind of metal. Once the results of these metals are beyond the allowable limit (The allowable limit for As, Cd, Hg, Pb is 10mg/L, 0.3mg/L, 1.0mg/L, 10.0mg/L respectively), the product is unqualified [25].

$$R = [(amount\ after\ spike - amount\ before\ spike) / amount\ added] \times 100\% \quad (1)$$

5.2.3. The analysis of the results

According to the WHO, the allowable limit for As, in cosmetics are 10 mg/kg. Among the 15 analyzed samples, seven of these samples are detected. The sample no.11 has the utmost As level and is beyond the allowable limit. And nine of Cd samples are below the LOD, and other six samples have relatively lower concentration than that of other five heavy metals. The allowable limit for Cd is 0.3mg/L. Thus, about 11 samples are qualified. The other three metals (Hg, Pb, Bi) left (Table 5) are also evaluated in this way. Therefore, the researchers can reach the conclusion that this method is a good way to detect the concentration of heavy metals in skin-whitening cosmetics before these products being marketed [25].

Table 5. The number of the samples which contains Hg, Pb, Bi in an example analysis [25]

	Hg	Pb	Bi
<LOD	5	4	10
>LOD	10	11	5

LOD=limit of detection; <LOD = below LOD; >LOD = above LOD

5.3. First voltametric method

To detect the potential toxin named phenoxyethanol in cosmetics, first voltametric method has been used, which is a developing alternative to chromatography. Before this method is invented, many other chromatographic methods have been put into practice, like high performance liquid

chromatography in reverse phase (RP-HPLC) [26], micellar electrokinetic chromatography (MEKC) [27]. Compared with the previous methods which need to extract phenoxyethanol first, first voltametric method has the advantages, one of which is omitting the extraction. Since more and more phenoxyethanol are used as preservative, it is important for manufacturers to produce qualified products.

5.3.1. Procedure of the method

The Scientific Committee on Consumer Safety gave some advice that the allowable limit for phenoxyethanol in cosmetics is 1% [28]. Luckily, the newly developed first voltammetric method might be a more precise way to better detect the concentration of phenoxyethanol. Considering the oxidation, reproducibility and sensitivity, first voltammetric method chose to carry the mixture of acetonitrile and acetic acid as supporting electrolyte to do the following experiments. During the process of identification of phenoxyethanol, the repeated curve around 1.6 V presented the high reproducibility of the oxidation of phenoxyethanol, which also can perfectly illustrate the potential of oxidation of phenoxyethanol is approximately 1.6 V vs. Ag/AgCl. The researchers also figured out the equation (2) to calculate the concentration in particular potential. After the test of interferences and reliability, this method was confirmed gradually [29].

$$I_p \text{ (nA)} = 0.01129c \text{ (}\mu\text{mol L}^{-1}\text{)} - 0.009 \quad (2)$$

5.3.2. Advantages

First voltametric method is to detect wider range of phenoxyethanol, and offers relatively lower limit of detection, which can be more sensitive and accurate than HPLC. What is more, because it is difficult to extract phenoxyethanol completely from compounds, HPLC might make more errors [29]. Future research may pay attention to developing this method. Also, the following methods may consider skipping the process of extraction, which can reduce the errors caused by incomplete extraction, and doing experiments by a more reliable method directly to improve the efficiency of testing.

6. Conclusion

With the improvements of the living condition, people are more likely to be fussy about their own appearance, and the industry of cosmetics is prevalent. However, a series of problems regarding safety also accompany. This review discusses several potential toxins in cosmetics, including heavy metals, phenoxyethanol and *Aloe vera*. Heavy metals such as Cr, Pb, Hg, Al and Cd exerted notorious effects when absorbed from skin and/or accumulate in the body, and some of them have long biological half-life. Although phenoxyethanol is widely used as preservative, it also can engender some damage to people. Research on metabolisms and mechanisms helps people better understand how these potential toxins work. Some useful methods, which include fluorescence-based assay, ICP-AES and first voltametric method, are discussed to better make some checks on cosmetics. However, quality of substances in cosmetics still can't be guaranteed completely yet. Even the products on the market, some toxins in cosmetics are also beyond the allowable limits and might pose some risks to customers. Therefore, further research is required on the mechanisms of these substances to quit the bad effects and keep doing experiments to modify the existing methods, in which case, some new methods with more accuracy and efficiency can be developed.

References

- [1] A. Panico, F. Serio, F. Bagordo, et al., Skin safety and health prevention: an overview of chemicals in cosmetic products, *J Prev Med Hyg.* 60 (2019) E50-E57.
- [2] S. Borowska, M.M. Brzóśka Metals in cosmetics: implications for human health, *J Appl Toxicol.* 35 (2015) 551-72.

- [3] B. Dréno, T. Zuberbier, C. Gelmetti, G. Gontijo, M. Marinovich. Safety review of phenoxyethanol when used as a preservative in cosmetics, *J Eur Acad Dermatol Venereol.* 7 (2019) 15-24.
- [4] M. Hęś, K. Dziedzic, D. Górecka, A. Jędrusek-Golińska, E. Gujska. Aloe vera (L.) Webb.: Natural Sources of Antioxidants - A Review, *Plant Foods Hum Nutr.* 74 (2019) 255-265.
- [5] L. Thines, A. Iserentant, P. Morsomme. Determination of the Cellular Ion Concentration in *Saccharomyces cerevisiae* Using ICP-AES, *Bio Protoc.*10 (2020) e3727.
- [6] H.R. Suma, S. Prakash, S.M. Eswarappa. Naturally occurring fluorescence protects the eutardigrade *Paramacrobiotus* sp. from ultraviolet radiation. *Biol Lett.* 16 (2020) :20200391.
- [7] A. Fischer, B. Brodziak-Dopierała, K. Loska, J. Stojko. The Assessment of Toxic Metals in Plants Used in Cosmetics and Cosmetology, *Int J Environ Res Public Health.* 14 (2017) 1280.
- [8] A.A. Alqadami, M. Naushad, M. Abulhassan Abdalla, MR. Khan, et al. Determination of heavy metals in skin-whitening cosmetics using microwave digestion and inductively coupled plasma atomic emission spectrometry, *IET Nanobiotechnol.* 11 (2017) 597-603.
- [9] M.Ç. Akgündüz, K. Çavuşoğlu, E. Yalçın. The Potential Risk Assessment of Phenoxyethanol with a Versatile Model System, *Sci Rep.* 10 (2020) 1209.
- [10] X. Guo, N. Mei. Aloe vera: A review of toxicity and adverse clinical effects, *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 34 (2016) :77-96.
- [11] W. Rebecca, O. Kayser, H. Hagels, KH. Zessin, et al., The phytochemical profile and identification of main phenolic compounds from the leaf exudate of *Aloe secundiflora* by high-performance liquid chromatography-mass spectroscopy, *Phytochem Anal.* 14 (2003) 83-6.
- [12] D. Saccù, P. Bogoni, G. Procida, Aloe exudate: characterization by reversed phase HPLC and headspace GC-MS, *J Agric Food Chem.* 49 (2001) 4526-30.
- [13] J.H. Hamman, Composition and applications of Aloe vera leaf gel. *Molecules.*13 (2008) :1599-616.
- [14] G.E. Flaten, Z Palac, A Engesland, J Filipović-Grčić, et al., In vitro skin models as a tool in optimization of drug formulation. *Eur J Pharm Sci.* 2015 Jul 30; 75: 10-24.
- [15] Information on <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=62&tid=17>
- [16] Information on <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=96&tid=22>
- [17] Information on <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=115&tid=24>
- [18] Information on <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=191&tid=34>
- [19] Information on http://en.volupedia.org/wiki/Biological_half-life
- [20] B. Bocca, A. Pino, A. Alimonti, G. Forte, Toxic metals contained in cosmetics: a status report. *Regul Toxicol Pharmacol.* 2014 Apr; 68 (3): 447-67.
- [21] E. Moczko, E.M. Mirkes, C. Caceres, A.N. Gorban, et al., Fluorescence-based assay as a new screening tool for toxic chemicals, *Sci Rep.* 6 (2016) 33922
- [22] R.F. Davies and G.A. Johnston, New and emerging cosmetic allergens, *Clin Dermatol.* 29 (2011) 311-5.
- [23] Information on <http://www.emedicine.medscape.com/article/814960-overview>
- [24] B. Bocca, G. Forte, F. Petrucci, and A. Cristaudo, Levels of nickel and other potentially allergenic metals in Ni-tested commercial body creams, *J Pharm Biomed Anal.* 44 (2007) 1197-202.
- [25] A.A. Alqadami, M. Naushad, M. Abulhassan Abdalla, M.R. Khan, et al., Determination of heavy metals in skin-whitening cosmetics using microwave digestion and inductively coupled plasma atomic emission spectrometry, *IET Nanobiotechnol.* 11 (2017) 597-603
- [26] C. Roy and J. Chakrabarty, Development and Validation of a Stability-Indicating RP-HPLC Method for the Simultaneous Determination of Phenoxyethanol, Methylparaben, Propylparaben, Mometasone Furoate, and Tazarotene in Topical Pharmaceutical Dosage Formulation, *Sci Pharm.* 81 (2013) 951-67.
- [27] P. Wang, X. Ding, Y. Li, and Y. Yang, Simultaneous determination of eleven preservatives in cosmetics by micellar electrokinetic chromatography, *J AOAC Int.* 95 (2012) 1069-73.
- [28] W. Lilienblum, Opinion of the Scientific Committee on Consumer Safety (SCCS) – Final version of the opinion on Phenoxyethanol in cosmetic products, *Regulatory Toxicology and Pharmacology.* 82 (2016) 156.

- [29] M. Jakubczyk and S. Michalkiewicz, First Voltammetric Method of Phenoxyethanol Determination in Pharmaceutical and Cosmetic Preparations, Journal of The Electrochemical Society. 166 (2019) H291-H296.