

Aminoethylethanolamine: a new allergen in cosmetics?

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Amphoacetates are organic compounds used in many industrial applications and in cosmetic formulations for the skin, hair and mucosa, as surfactants, mild foaming and cleansing agents in concentrations ranging from 0.1% to 50%. Despite the fact that they have been in use for many years, cases of contact allergy to them are extremely rare. We describe 4 patients who developed an eczematous reaction after use of detergents containing amphoacetates. Patch testing showed positive reactions to sodium lauroamphoacetate (Miranol[®] HM Special, Rhodia, England) as is or diluted at decreasing concentration (10%, 5% and 1%) in water and to aminoethylethanolamine (AEE) at the concentration of 1% in various vehicles (ethanol, acetone, and sodium lauryl ethersulfate 1% aqueous solution) and at decreasing concentrations ranging from 1% to 0.005% in water. AEE is one of the reagents used in the synthesis of amphoacetates. This molecule, that is structurally an ethylenediamine derivative, has sensitizing power and is reported as a cause of occupational contact allergy in cable jointers. Combined eczematous reactions to AEE and sodium lauroamphoacetate can be consequent to the presence of the former substance as an impurity in amphoacetates-containing products, as demonstrated by ion chromatography-mass spectrometry analysis.

Key words: amphoacetates; aminoethylethanolamine; sodium lauroamphoacetate; cosmetics; detergents; ion chromatography-mass spectrometry; impurities. © Munksgaard, 2001.

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Coco- (and lauro-) amphoacetates, amphopropionates, amphodiacetates and amphodipropionates are organic compounds called in the past imidazolinic tensioactives. These compounds are usually amber-coloured fluids with a characteristic fruity smell. They are soluble in water but insoluble in common organic solvents. Amphoterics are used in industrial applications and in cosmetic formulations for the skin, hair and mucosa as surfactants, mild foaming and cleansing agents in concentrations ranging from 0.1% to 50% (1). They are also used in pharmaceutical products for the treatment of glaucoma and hemorrhoids, in disinfectants for contact lenses and in materials for bandages.

Amphoacetates are surfactants with a generally low irritation capacity; indeed they behave as "true" amphoterics (unlike alkylamidobetaines and amine oxides that are considered to be "pseudoamphoteric"), as they contain amine and carboxyl groups in their molecules, both groups being able to exchange protons. Experimental

studies on animals and man have shown that amphoacetates are usually skin-safe cosmetic ingredients (1). In fact, even though they have been in use for many years, cases of sensitization to amphoacetates are extremely rare. We describe 4 cases of contact allergy to amphoacetates and aminoethylethanolamine (AEE), a reagent used in the synthesis of these amphoteric compounds.

Patients and Methods

Case no. 1

A 44-year-old non-atopic woman presented with dermatitis of the face of 20 days duration. She attributed her symptoms to the use of a face detergent containing sodium lauroamphoacetate.

Case no. 2

A 45-year-old man, with a past history of allergic rhinitis, presented with diffuse eczema after re-

Table 1. Patch test results

Substances	Patient nos.			
	1	2	3	4
standard series	—	—	—	—
ethylenediamine	—	—	—	++
sodium lauroamphoacetate ^{a)}				
as is	++	++	++	++
10% aq.	++	++	++	++
5% aq.	++	++	++	++
1% aq.	++	++	++	++
aminoethylethanolamine 1% ^{b)}	++	++	++	++
other amphoteric ^{c)}				
as is	NT	NT	NT	++
10% aq.	NT	NT	NT	++
5% aq.	NT	NT	NT	—
1% aq.	NT	NT	NT	—

a) Miranol® HM Special, Rhodia, England.

b) 1% solutions in water, ethanol, acetone, and 1% sodium laurylthethersulfate aq. solution.

c) Miranol® Ultra L32, Miranol® C2M, Miranol® Ultra C32, Rewoteric® AM2CNM, Empigen® CD, Dehyton® G.

Table 2. Patch test results with decreasing concentrations of aminoethylethanolamine in water

Substance concentrations	Patient nos.			
	1	2	3	4
0.5	++	++	++	++
0.1	++	++	++	++
0.05	+	—	—	+
0.01	+	—	—	+
0.005	—	—	—	+

peated use of a detergent containing sodium lauroamphoacetate.

Case no. 3

A 69-year-old woman developed severe eczema on the face after use of a face wash containing sodium lauroamphoacetate.

Case no. 4

A 53-year-old non-atopic woman with dermatitis of the face reported intolerance to various detergents containing amphoteric acetates.

Patch testing

Patch testing was performed by the internationally accepted method (2) using Finn Chambers®, Scanpor® tape and 2 days (D) occlusion. Readings were made on D2, D3, D4, and D7.

We carried out patch tests with the European standard series, sodium lauroamphoacetate (Miranol® HM Special, Rhodia, England, containing 35±2% active ingredient) and AEE (Aldrich, Mil-

waukee, WI, USA). Sodium lauroamphoacetate was tested as is and with serial dilutions in water (10%, 5% and 1%). AEE was tested at the concentration of 1% in different vehicles (ethanol, acetone, and sodium laurylthethersulfate 1% aqueous solution) and at decreasing concentrations ranging from 1% to 0.005% in water. The various vehicles were selected in order to obtain acceptable transdermal delivery of AEE. Patient no. 4 was tested with other amphoteric: Miranol® Ultra L32, Miranol® C2M and Miranol® Ultra C32 (Rhodia, England); Rewoteric® AM2CNM (Witco, UK); Empigen® CD (Albrigh & Wilson, UK); Dehyton® G (Henkel KgaA Düsseldorf, Germany); as is and with serial dilution in water (10%, 5% and 1%).

Sodium lauroamphoacetate and AEE were tested at the same above-mentioned conditions in 20 control subjects.

Determination of AEE in amphoteric acetate

The concentration of AEE (Aldrich, Milwaukee, WI, USA) was monitored by ion chromatography-mass spectrometry (IC-MS). The IC system was a 1050-Ti pump (Agilent Technologies, Palo Alto, CA, USA) equipped with a AS14A 50×4 mm column (Dionex, Sunnyvale, CA, USA) and a CSRS-U suppressor, working in recycled mode. The MS system was an API 165 single quadrupole mass spectrometer (Applied Biosystems/MSD Sciex, Foster City, CA, USA) equipped with a turboion-spray interface. Samples, diluted 1/10 with double distilled water and injected by a Gilson 234 auto-sampler (Gilson, Middleton, WI, USA) equipped with a 9010 Rheodyne valve and a 50 µl loop, were eluted at 1 ml/min by the following elution program: 50% of water (18.2 MΩ, 4 µg/l of organic

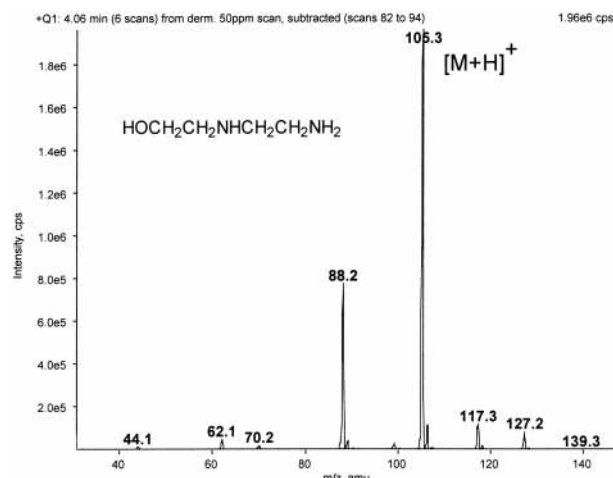
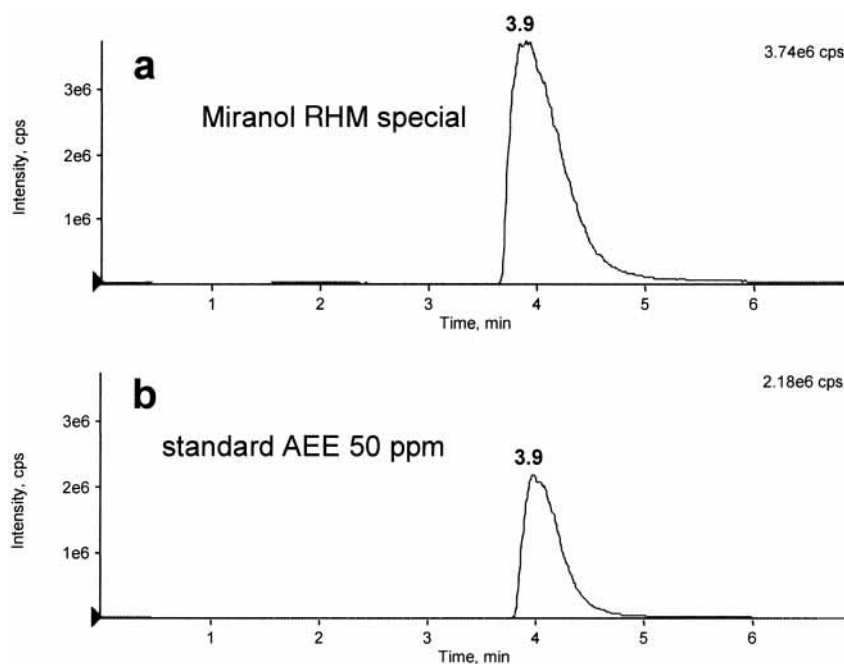


Fig. 1. HPLC-MS spectrum of aminoethylethanolamine.

Fig. 2. HPLC-MS chromatogram of Miranol® HM Special (a) and a standard solution 50 ppm of aminoethylethanolamine (b).



carbon) and 50% of an aqueous solution of methanesulfonic acid (Aldrich) 20 mM for 1.5 min then in 0.1 min to 100% of the methanesulfonic acid solution which was held for 5.4 min. The flow from the IC system was split to allow 200 μ l/min to enter the turboionspray interface, whose experimental conditions (positive ions) were as follows: nebulizer gas (air)=1.2 l/min, curtain gas (nitrogen)=1 l/min, turboion-spray gas (nitrogen at 400°C)=6 l/min, needle voltage=+5200 V, orifice voltage=+10 V and ring voltage=+140 V. In order to get the AEE spectrum the MS quadrupole was scanned from 30 to 200 a.m.u. in 1 s while, for measuring the concentration of AEE, the MS quadrupole was set to monitor the $[M+H]^+$ ion at 105.2 a.m.u and a calibration plot, which turned out to be linear, was built using 3 standard solutions of different concentration.

Results

Results of the patch tests are summarized in Tables 1, 2. All patients showed positive reactions to sodium lauroamphoacetate (Miranol® HM Special) at all the tested concentrations and to AEE 1% in all vehicles. Patient no. 4 showed positive reaction to other amphoteric only when tested undiluted and to the highest concentration (10%). She also showed a positive reaction to ethylenediamine 1% pet. in the standard series.

Patch tests with decreasing concentrations of AEE in water are reported in Table 2. Except for 6 control subjects responding with an irritant reac-

tion to sodium lauroamphoacetate as is, the other control subjects gave no reactions to any concentration of the substances tested.

Fig. 1 reports the mass spectrum of AEE introduced in the HPLC-MS system as a standard solution. The peak at mass/charge (m/z) 105.3 belongs to the protonated molecule ($[M+H]^+$), while that at m/z 127.2 is due to the $[M+Na]^+$ adduct, which is very likely to occur during ionization in HPLC-MS with turboionspray interface (3). The mass spectrum also shows a main fragment ion at m/z 88.2 due to the loss of NH_3 from the $[M+H]^+$ ion. Because of the abundance of the m/z 105.2 ion, it was chosen for the quantitative determination of AEE in the amphoacetates samples. Fig. 2 shows the HPLC-MS chromatogram of Miranol® HM Special (a) and that of a standard solution of AEE (b) obtained by monitoring just the m/z 105.2 ion.

Table 3. Concentrations of aminoethylethanolamine (AEE) in amphoteric samples

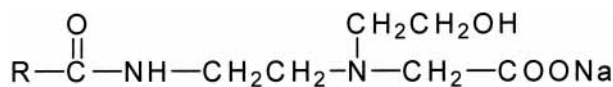
Amphoterics	AEE concentration (ppm)
Miranol® HM Special ^{a)}	1130 $\pm$ 50
Miranol Ultra L32 ^{a)}	6.6 $\pm$ 0.3
Miranol® C2M ^{a)}	4.9 $\pm$ 0.2
Miranol Ultra C32 ^{a)}	15.3 $\pm$ 0.8
Rewoteric® AM2CNM ^{b)}	6.0 $\pm$ 0.3
Empigen® CD ^{c)}	5.5 $\pm$ 0.3
Dehyton® G ^{d)}	6.0 $\pm$ 0.3

^{a)} Rhodia, UK.

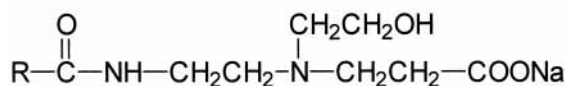
^{b)} Witco, UK.

^{c)} Empigen® CD, Albright & Wilson, UK.

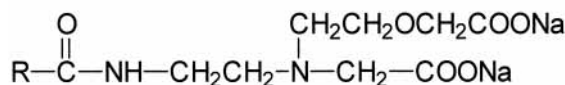
^{d)} Dehyton® G, Henkel KgaA, Düsseldorf, Germany.



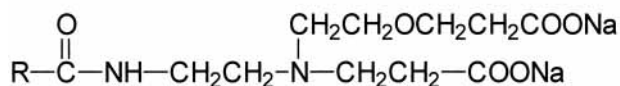
Cocoamphoacetate or lauroamphoacetate



Cocoamphopropionate or lauroamphopropionate



Cocoamphodiaceate or lauroamphodiaceate



Cocoamphodipropionate or lauroamphodipropionate

R = lauric or Coco fatty acid chains

Fig. 3. Chemical formulae of amphoacetates and amphopropionates.

The concentrations of AEE detected in all investigated samples are reported in Table 3. It is worth noting that the Miranol[®] HM Special sample used for patch testing contained the highest amount of AEE. This may be due to some faults in the purification process of this sample.

Discussion

Coco- (and lauro-) amphoacetates, amphopropionates, amphodiaceates and amphodipropionates are amphoteric compounds obtained by a condensation reaction between fatty acids and AEE. Imidazolines are formed as intermediate products. Coco- or lauryl-imidazolines are then set to react with monochloroacetic or monochloropropionic acid in the presence of sodium hydroxide to form the sodium salts of either mono- (coco- or lauryl-) amphoacetate or amphopropionate and di-carboxylated amphoacetates and their blends (1). The most representative structural formulae of amphoacetates are shown in Fig. 3, though blends of several structures are actually present in industrial materials together with the starting raw materials and other reaction by-products. Despite the fact that they have been in use for many years, cases of sensitization to amphoacetates are extremely rare. Only 1 report, in fact, by De Groot in 1996, described a case of contact allergy to dis-

odium cocoamphodipropionate, structurally very similar to lauroamphoacetate, in a 28-year-old woman with atopic dermatitis of the hands, aggravated by sensitization to disodium cocoamphodipropionate contained in a disinfectant solution for contact lenses (4).

The 4 patients whom we observed had positive reactions to the sodium lauroamphoacetate sample (Miranol[®] HM Special, Rhodia), containing 36.7% active ingredient and 9.12% amidoamines as main impurity. Further investigations showed that AEE, a reagent used in the synthesis of amphoacetates, also gave positive reactions in these patients. The AEE molecule, having a structure similar to ethylenediamine, has sensitizing potential and is a well-known cause of occupational asthma (5, 6). The cases of contact allergy reported in the literature are all of an occupational nature and were observed in cable jointers (7, 8). AEE is also used in the chemical industry, for the synthesis of polymers and copolymers, in the pharmaceutical industry, in agriculture, and in the paper, rubber and textile industries.

Combined eczematous reactions to AEE and sodium lauroamphoacetate could not be attributed to cross-reactivity, bearing in mind the different structures of the 2 molecules. Indeed, in amphoacetates one amino group of AEE is transformed into an amido group. Despite its generally low content in the samples we examined, the sensitizing potential of AEE could be enhanced by the carrier and barrier damage effect of amphoacetates. In fact, since AEE is held to be the main allergen in amphoacetates, positive reactions were obtained to AEE at lower concentrations in amphoacetates than in water. Furthermore, we cannot exclude the possibility that other substances, like amidoamines (contained in high quantities in the sample used for the tests but not easy to employ as a hapten due to their known instability) may also be sensitizing or, in view of their irritant potential, may enhance the penetration of AEE. Further studies using purified products and individual impurities to be subjected to chromatographic and spectrophotometric investigations may help to clarify this issue.

The problem of sensitizing impurities deriving from the synthesis or the manufacturing process is not well known; it is often suspected but not much studied because of its unpredictability. In addition to the above reported occurrence, another example of impurities deriving from the synthesis of surfactants in cosmetic products is represented by 3-dimethylaminopropylamine, an intermediate substance in the synthesis of betaines (9–12). Therefore, as preventive measures, the detection of such

sensitizing impurities, which cosmetic and detergent manufacturers should then scrupulously maintain at very low tolerance limits in the various products, is a very important aim. The combination of patch testing and chemical analysis is a useful method in identifying the allergenic impurities in final products.

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