Ion mobility quadrupole time-of-flight high resolution mass spectrometry coupled to ultra-high pressure liquid chromatography for identification of non-intentionally added substances migrating from food cans

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Abstract

Sealants, incorporated in the lids of food cans to ensure the can is hermetically sealed, are formu- lated from a wide variety of compounds. These compounds and associated non-intentionally added sub- stances (NIAS) could migrate to the food contained in the can. In this work, ion mobility quadrupole time-of-flight mass spectrometry coupled to ultra-high performance liquid chromatography (UHPLC-IM- QTOF-MS) has been used to obtain ion mobility filtered extracted ion chromatograms. Subsequently, accurate mass precursor ions and their fragments have been used to identify the compounds mi- grating from the sealant to the content of the cans. Moreover, the correlation between the colli- sion cross-section (CCS) values and *m/z* of the compounds was used to increase the level of confi- dence of the identification. Seven compounds were found to have migrated to the food simulants. The compounds bis(2-hydroxy-3-tert-butyl-5-methylphenyl)dicyclopentane,1-tetradecanesulfonic acid, 1- pentadecanesulfonic acid, 1-hexadecanesulfonic acid and naphthalene-2-sulfonic acid (whose migration was over the specific migration limit established by the European Regulation 10/2011/EU) were identified as NIAS in the food simulants studied.

1. Introduction

A sealant is usually composed of a mixture of substances ca- pable of attaching at least two surfaces, thereby filling the space between the surfaces to provide a barrier or protective coating [1] . The lids on food and beverage cans are mechanically seamed onto the can bodies. Although the seam gives a very tight seal, a layer of sealant is incorporated to ensure a hermetic seal [2] . The composi- tion of sealants is complex, containing a polymer, fillers, plasticiz- ers, thixotropic agents, adhesion promoters, catalysts, curing agents and other ingredients [3] . Any of these components could migrate to the food contained in the can and contaminate the contents. Ad- ditionally, non-intentionally added substances (NIAS) could be also present and migrate into the food. NIAS, that are not expected in the manufacture of food contact materials, may be formed during manufacture and use, result from reaction and degradation pro- cesses, or may be present as impurities from the raw materials. There are increasing concerns with regard to the presence of NIAS in food [4] . They have been found to migrate from several food contact materials, such as plastics [5–9] , paper and board [10] , coatings [11] , metals [12] and adhesives [13–15] . NIAS originating from sealants, though, have not been investigated. In the case of sealants, where a high number of constituents are

present in the sealant formulation, the possibility of migration into food is rela- tively high. The study of NIAS is analytically challenging work, since the compounds that may potentially migrate are unknown and no information about their chemical properties or molecular weight are available prior to investigation. The study of non-volatile NIAS is particularly complex, since no compound database is available. High resolution mass spectrometry (HRMS), is an analytical tech- nique particularly suited to confirm the presence of NIAS. The main benefit of HRMS techniques is the ability to obtain full scan spectra with very accurate mass measurements, which allows the analyst to perform the structural elucidation of the unexpected compounds detected [7] . However, even using HRMS, the iden- tification of all NIAS present in a sample is not always possi- ble due to the complexity related to the mass spectral interpre- tation. The technique of ion mobility quadrupole time of flight mass spectrometry coupled to the ultra-high pressure liquid chro- matography (UHPLC-IM-QTOF-MS) enables cleaner spectra to be obtained. Ion mobility spectrometry is a rapid gas phase separa- tion technique that can be combined with MS for high throughput multi-dimensional separations. Generally speaking, ions are guided through a mobility cell containing a buffer gas. Travelling waves are generated within the mobility cell that enable ions to be sep- arated due to their shape, charge and size; compact molecules ex- perience fewer collisions with the drift gas and "surf"the travel- ling wave, whereas ions extended or flat structures are subjected to more collisions and as such are more likely to tumble over the waves [16] . The time taken for the ions to traverse the mobility cell, the drift time, is measured and this can be converted to the collision cross-section (CCS) of the ions; a measurement related to the averaged rotational cross section, shape, total charge and charge distribution of the ion. When UHPLC coupled to IM-QTOF- MS is used, complex matrices can be resolved, since alignment of precursor and fragment ions is performed on both the basis of re- tention time and drift time. Using ion-mobility filtered extracted ion chromatograms, which are cleaner than those obtained from extraction of *m/z* values alone, it is possible to distinguish analytes from matrix interferences [17–22] . The identification of the unknowns is done through the study of the ion fragments obtained by fragmentation on the collision cell. The fitting between the parent ion and the fragments obtained is the key of the identification of a compound. Apart from the mass accuracy needed for this purpose a clean spectrum is very im- portant to distinguish between matrix interferences and ion frag- ments. Therefore, the use of IM-QTOF-MS results in a higher de- gree of confidence in the identification of unknown compounds. In this work, the ion mobility technology has been used in or- der to obtain cleaner spectra, which enables the identification of the NIAS migrating from two different sealants intended to be ap- plied to cans that contain food. **2.**

Materials and methods

2.1. Reagents

The standards 2-methyl-2H-4 isothiazol-3-one, tri- ethanolamine, 1-tetradecanesulfonic acid, 1-pentadecanesulfonic acid, 1-hexadecanesulfonic acid and naphthalene-2-sulfonic acid were purchased from Sigma-Aldrich Química S.A (Madrid, Spain). The compound bis(2-hydroxy-3-tert-butyl-5- methylphenyl)dicyclopentane is an industrial standard with a purity up to 85%. Ethanol, water and methanol of HPLC grade were supplied by Scharlau Chemie S.A (Sentmenat, Spain).

2.2. Samples

Two sealants were studied (sealant 1 and sealant 2). They were provided by Samtack SL (Barcelona, Spain). Both sealants are in- tended to be used to seal food cans. These cans may contain soda or food (for example, fish, meat or vegetables).

2.3. Sample preparation

Sealants do not fall under any specific regulations in Europe. Therefore, migration assays were performed according to the Plas- tics Regulation 10/2011/EU [23] and to the FEICA guidance on
migration testing of adhesives intended for food contact mate- rial, which includes guidance for sealants [24] . Three replicates of the lids with sealant applied and three replicates of lids without sealant (blanks) were placed in contact with ethanol 95% (v/v), ethanol 10% (v/v) and acetic acid 3% (v/v) used as food simulants according the Plastics Regulation 10/2011/EU. The lids were im- mersed into 50 g of the simulants at 60 °C for 10 days since this European regulation establishes this conditions when the contact of the packaging with the food will be longer than 6 months at room temperature. The volume of the smallest cans intended to be used in conjunction with the sealants was used as a worst case scenario. Simulants were directly injected onto the UPLC IMS QTOF. Calibration curves of the standards were prepared using ethanol 95% (v/v), ethanol 10% (v/v) and acetic acid 3% (v/v) as solvents. Three replicates of each concentration was analyzed.

2.4. UPLC IMS QTOF analysis

The analyses were carried out using an Acquity TM UPLC system coupled to an electrospray interface (ESI) on a VION®IMS/QTOF detector, supplied by Waters (Manchester, UK). A UPLC BEH C-18 column of 1.7 µm particle size (2.1 ×100 mm) was used with a flow rate of 0.3 mL/min and a column temperature of 35 °C. The mobile phase was water (phase A) and methanol (phase B), both with 0.1% formic acid. The gradient used was 95–5% of phase A-B ending with 100% of phase B after 13 min. The injection volume was 5 µL. The electrospray interface (ESI) was used in both positive and negative ionization modes, and the mass spectrometer was oper- ated in sensitivity mode with a capillary voltage of 1 kV and a sampling cone voltage of 30 V. The source and desolvation temper- atures used were 120 °C and 500 °C, respectively, and the desolva- tion gas flow was800Lh-1. The system was calibrated and data ac- quired in the range 50–10 0 0 *m/z* . Leucine-Enkephalin, [*M* + + *H*] + *m/z* 556.2765, was used as the lock-mass for real time mass correc- tion. A collision ramp of 20 to 40 eV was applied to generate high- energy fragment ions and argon was used as the collision gas. CCS measurements were determined via a calibration between drift-time and CSS which was performed using polyaniline for which CCS values are known The acquisition mode used was high definition mass spectrom- etry (HDMSE), with a scan time of 0.1 s.

2.5. Software

Data acquired on the VION®IMS/QTOF were processed using UNIFI (v. 1.8.). The software application Toxtree®(v. 2.6.0.) was used for risk assessment. The classification depends on the molecular structure of the compound and maximum values of human exposure for each toxicity class: Class I, II and III, 1.8, 0.54 and 0.09 mg/kg, re- spectively. These values are the result of applying the estimated daily intake (EDI) for each Cramer class (30 µg/kg bw/d, 9 µg/kg bw/d and 1.5 µg/kg bw/d for Class I,II and III respectively) to a 60 kg bw/person that eats 1 kg packaged food /day.

3. Results and discussion

3.1. Identification

Ion mobility coupled to high resolution mass spectrometry (HRMS) affords an additional separation of ions, based on size, shape, and charge. On the equipment used in this work, ion mobil- ity separation (IMS) occurs after introduction of the ions into the source. Ions are transported through a mobility cell by travelling wave generated by a stacked ring ion guide. The residency time of an ion in the mobility cell is dependent upon the number of colli- sions it experiences with the buffer gas in the cell, which in turn is related to the cross section of the ion. The time taken to traverse the mobility cell, the drift time, is measured and a collision cross section (CCS, measured in ˚A2) value for the compound is derived. The CCS represents a unique parameter that is representative of the average rotational cross section of an ion as it travels through the mobility cell. In this work the data have been acquired using HDMSE. In HDMSE experiments, alternating low and high energy scans are acquired. There is no precursor selection in the low energy data and all low energy ions are fragmented in the high energy chan- nel. Precursor and corresponding fragment ions are then aligned based on a combination their retention times and drift times (drift time alignment). This results in clean spectra which are unique to ion mobility data and simplifies the elucidation of unknown com- pounds [25] . Once the samples were acquired and analysed, a comparison of the blanks and the samples was done creating a workflow based on a filter that allowed us to compare the *m/z* that were unique on the samples and the *m/z* that were more than 3 times higher on than samples than on the blanks. Then each *m/z* was studied in this workflow was studied. The discovery tool of UNIFI software was used for elucidation. This tool combines the molecular formula collection, candidates search in databases and fitting of the candi- date with the mass spectra through an algorithm. Carbon, oxygen, hydrogen, nitrogen, chlorine, bromine, phosphorous, fluorine, sul- fur and silicon were selected to elucidate the molecular formula since they were the most common elements found on migrants form food packages. The mass tolerance was set on 2 mDa. Ele- mental compositions sorted with respect to the fit of the experi- mental data to the theoretical isotope distribution (i-FIT) were ob- tained. Then, the Chemspider database is used to search candidates Then, the identification was based on the study of the fitting of the accurate *m/z* ion fragments with parent ion. UNIFI algorithm is based on the probability of chemical bond cleavage and the ac- curate mass tolerance. Once, UNIFI provides the list of most likely candidates, a bibliographic search is done in order to try to fig- ure out which one is more probable that could be present on a food sealant. Finally, the standard of the compound is acquired and compared to confirm the identification. Using this methodology all the migrants could be identified. Fig. 1 a shows the low and high energy spectra of the com- pound 1-tetradecanesulfonic without drift-time alignment. Fig. 1 b. shows the spectra of the same compound with drift-time align- ment. A significant clean-up can be seen, and a large number of background ions associated with the matrix have been removed. The collection of ion-mobility filtered extracted ion chromatograms enable spectra with a high degree of specificity to be generated. Cleaned-up low and high energy spectra were obtained for all compounds detected in each run. Fig. 1 b shows the fragments obtained for the compound 1- tetradecanesulfonic. Comparison with Fig. 1 a shows that if drift alignment would not be applied, the background would be con- fused with fragments of the precursor and confirmation of this compound would not be possible. Table 1 shows each of the sealants for which migration has been studied, *m/z* detected, ESI polarity used in the analysis, el- emental composition, theoretical mass of the elemental composi- tion, CCS measurement, compound name, SML expressed as mg/kg, simulant, migration values (mg/kg), limit of detection and RSD% of the three replicates of the migration analyze The difference between

theoretical mass and mass measured by the equipment ranged between 0.0 and 0.1 mDa, thus demonstrat- ing the high accuracy of the mass measurements.

The compounds found (Table 1) were two intentionally added substances, namely 2-methyl-2H-4 isothiazol-3-one, a common biocide [26] , and triethanolamine that is used to solubilize oils and other ingredients that are not completely soluble in water [27] . They were detected using the positive ESI acquisition mode. In negative ESI mode, several non-intentionally added substances (NIAS) were found. Fig. 2 shows the high en- ergy spectrum of the NIAS bis(2–hydroxy–3–tert–butyl–5- methylphenyl)dicyclopentane. The masses of the fragments detected in the spectrum and the theoretical fragments of the molecule agree to a high level of accuracy. The identification of this NIAS was verified analyzing the pure standard. Therefore, the level of confidence of the identification was considered 100%. This compound could be derived from the reaction products of polymeric antioxidant phenol, 4-methyl-, with dicyclopentadiene and isobutylene, also named as Rubber Antioxidant L AC1L4QWL. This indicates that even when good manufacturing practices are applied and polymeric antioxidants of high molecular weight are used in order to avoid migrating problems, NIAS of lower molecular weight coming from these theoretically safe additives can migrate to the food. This highlights the necessity of using accurate techniques to look for NIAS in migrating extracts from all materials in contact with food. In addition, three alkanesulfonic acids were found in migration simulants from sealant 1. They are NIAS coming from polymeric anionic surfactants based on sodium C14-17 sec-Alkyl sulfonate. Moreover, naphthalene-2-sulfonic acid (Table 1) was a NIAS found in sealant 2. This NIAS could come from the surfactant naphthalene sulfonic acid-formaldehyde polymer, sodium salt. This is also a sul- fonic acid derivative. The identification of sulfonic acid derivatives was also verified with pure standards, and as such we can confirm the presence of these compounds. These findings also highlight the importance of studying NIAS, even when high molecular additives are used in formulations. Fig. 3 a shows the CCS values vs the *m/z* of all migrating com- pounds. It can be seen that the CCS values are correlated with *m/z* . However, although this correlation is very high (R2 = 0.9388), relying on *m/z* alone to predict CCS is insufficient, as many ions have the same *m/z* but a different 3 D structure and thus, CCS value. Moreover, Fig. 3 b shows the CCS of the alkanesulfonic acid compounds identified in migration from sealant 1 vs. their *m/z* . A coefficient of determination of R2 = 0.9999 was obtained, since the CCS value of a given class of compounds is broadly correlated with *m/z* . Nevertheless, when naphthalene-2-sulfonic acid is considered (Fig. 3 c) it can be seen that the correlation decreases (R2 = 0.9729), since its structure has a very different spatial con- formation to the alkanesulfonic acids found in sealant 1. These data allowed us to confirm the presence of naphthalene-2-sulfonic acid in migration coming from sealant 2. It can be concluded that CCS can be used as an additional mea- surement to consider when a non-target identification is being per- formed, as it may enable potential structures to be either con- firmed or discarded based on their spatial conformation.

3.2. Migration results and risk assessment

Table 1 shows the migration results to the simulants studied. The stimulants ethanol 95% (v/v), ethanol 10% (v/v) and acetic acid 3% (v/v) were selected to account for the variety of foods could be packaged in cans. As such, acidic, fatty or even alcoholic foods were able to be modeled. Limits of detection ranged from 0.001 mg/kg to 0.006 mg/kg, confirming the high sensitivity of the system. This makes it not only remarkable in terms of identification, but also in terms of quantification. Sealants are not yet covered by specific European legislation. Nevertheless, they must comply with the Regulation (EC) No 1935/2004 [28] . This Regulation establishes that materials and arti- cles, including active and intelligent

materials and articles, should be manufactured in compliance with good manufacturing practices (GMPs) so that, under normal or foreseeable conditions of use, they do not transfer their constituents to food in quantities which could: (a) endanger human health; or (b) bring about an unaccept- able change in the composition of the food; or (c) bring about a deterioration in the organoleptic characteristics thereof. A risk assessment procedure has to be applied to any food con- tact material [29] . When the compound is listed in the plastics regulation 10/2011/EC [23] and the migration value is below the specific migration limit (SML), it is considered that the compound complies with Regulation 1935/2004/EC. However, when the compound is not listed in the plastics reg- ulation and values of no observed adverse effect level (NOAEL) do not exist, the TTC (threshold of toxicological concern)25 approach can be used. This methodology is a theoretical approach based on a decision-tree that uses the molecular structure of a target sub- stance to assign the substance to one of the three Cramer classes. Each Cramer class is allocated an exposure limit, the estimated daily intake (EDI) (mg/person/day) [30] . The same convention re- garding the daily consumption of 1 kg packaged food per person was considered alsoin this approach [29] . Migration results showed that alkanesulfonic acid had a higher tendency to migrate to the acid simulant due to its acidic nature. The same was observed for naphthalene-2-sulfonic acid. The mi- gration of this compound from sealant 2 was higher than the EDI established by Cramer (0.09). Thus, sealant 2did not comply with the expected safety assessment and was discarded. The two sealants are intended to be used to seal food cans con- taining soda or food, the company was interested on this study to decide which formulation was safer for this application. After con- sidering the migration results presented in Table 1 , it was decided to continue working with sealant 1, since it was demonstrated to be safer that sealant 2. The study performed highlights the importance of identifying the NIAS and quantifying their migration to food, in order to de- cide the products that will be safer for use with food for human consumption.

4. Conclusions

The use the technique UHPLC-IMS/QTOF to study migrants com- ing from food cans provided ion-mobility filtered extracted ion chromatograms. It allowed to distinguish between matrix ions and ion fragments generated on the collision cell that came from the parent ion. This fact, combined with the mass accuracy obtained with the TOF analyser were the keys for being able to identify all the migrants coming from the food cans. Five out of the seven compounds identified were NIAS and one compound identified in this work migrated to the food simulant to a level over the established migration limits by legislation. This highlights the importance of the use of ion mobility techniques that allow to correctly identify the migrants from food packaging.

CRediT authorship contribution statement

Elena Canellas: Conceptualization, Methodology, Software, Val- idation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervi- sion. **Paula Vera:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - orig- inal draft, Writing - review & editing, Visualization, Supervision. **Cristina Nerín:** Conceptualization, Methodology, Software, Valida- tion, Formal analysis, Investigation, Resources, Data curation, Writ- ing - original draft, Writing - review & editing, Visualization, Su- pervision. **Nicola Dreolin:** Conceptualization, Methodology, Soft- ware, Validation, Formal analysis, Investigation, Resources, Data cu- ration, Writing - original draft, Writing - review &

editing, Visu- alization, Supervision. **JeffGoshawk:** Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision.

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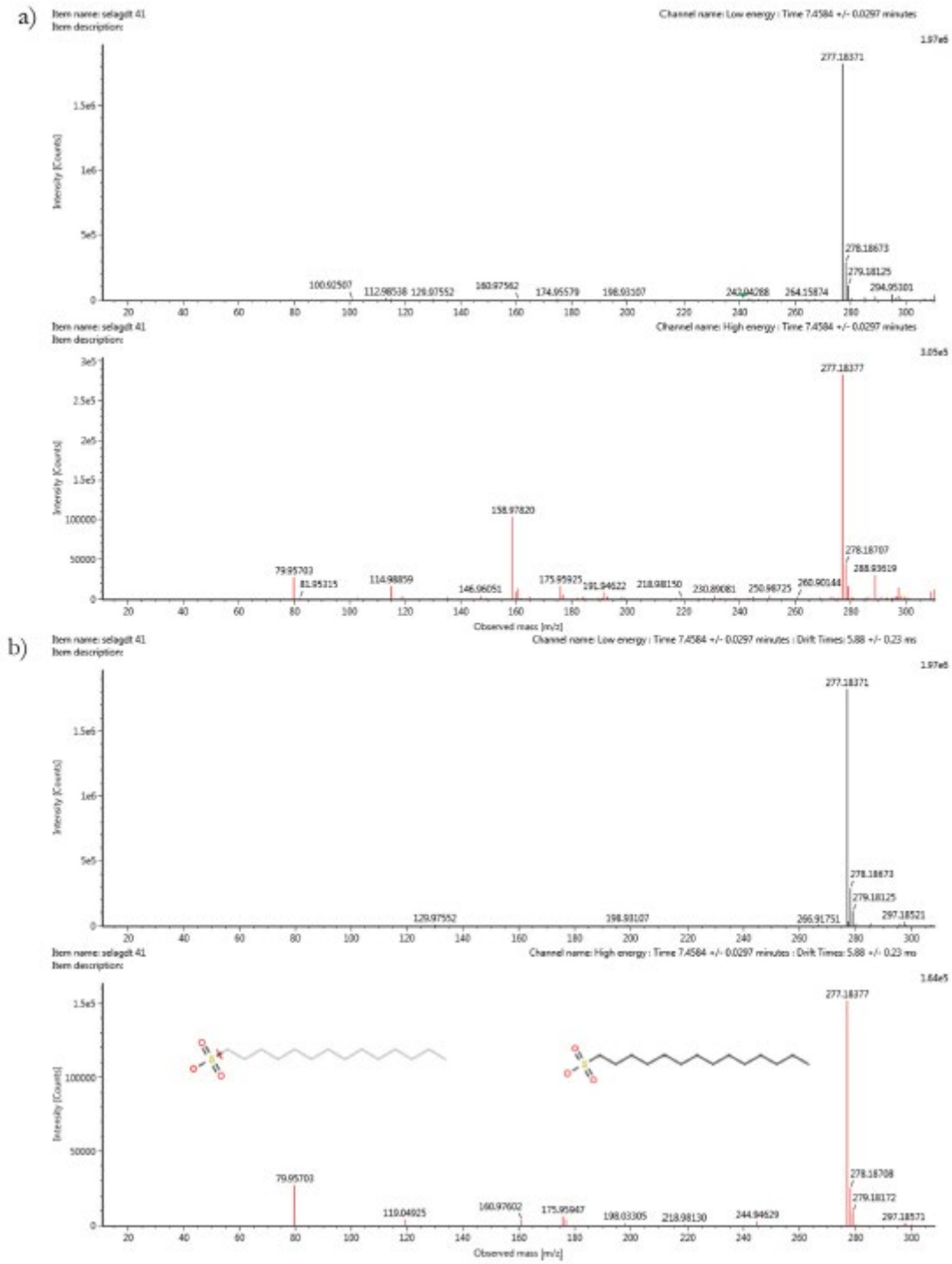

Fig. 1. (a) Spectrum of the compound 1-tetradecanesulfonic at low energy acquisition and high energy acquisition, without drift time alignment. (b) spectrum of the same compound taking into account the drift time alignment.

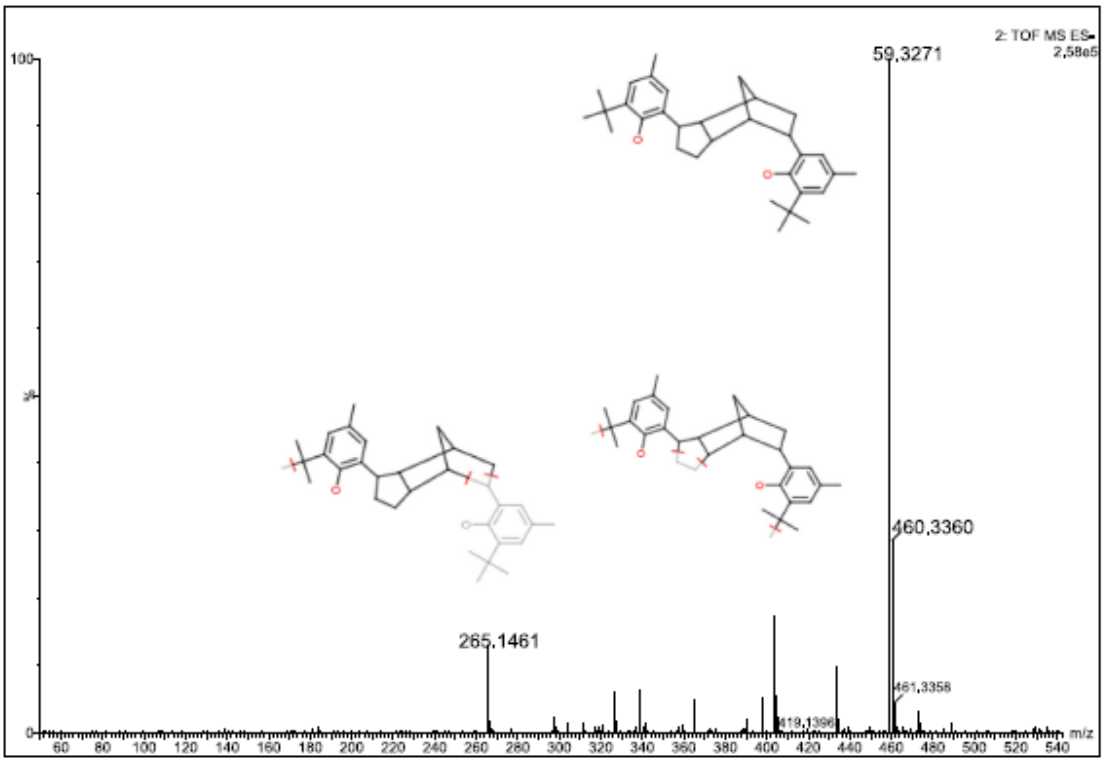

Fig. 2. High energy spectrum of the NIAS bis(2–hydroxy–3–tert–butyl–5-methylphenyl)dicyclopentane.

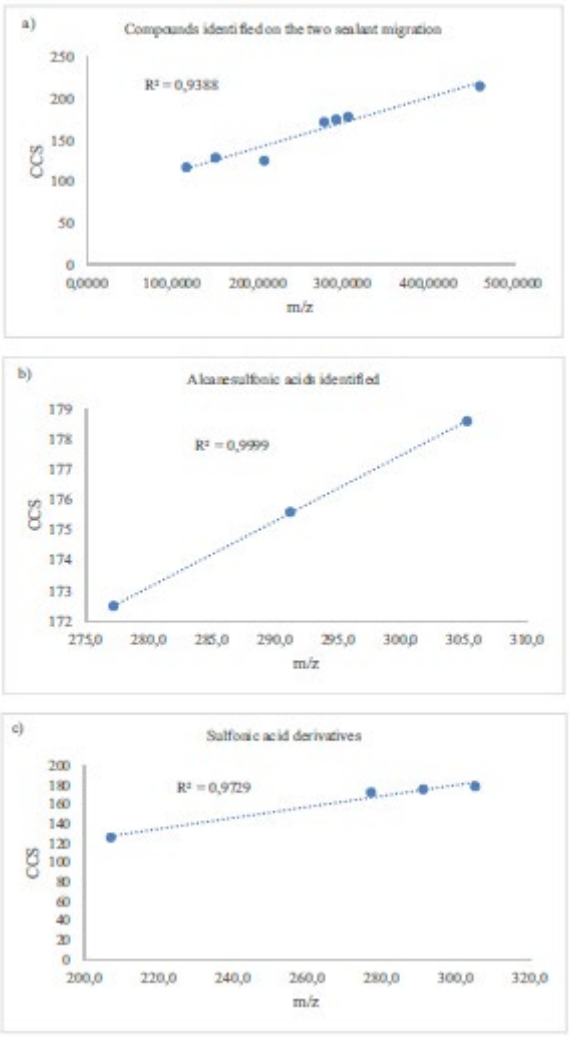

Fig. 3. (a) *m/z* vs CCS of ions detected on the sealant migration (b) *m/z* vs CCS of the alcane sulfonic acids c) *m/z* vs CCS of all the sulfonic acid derivatives.

Table. 1 Number of sealant, *m/z* detected, ESI polarity used in the analysis, elemental composition, theoretical mass of the elemental composition, CCS measured, compound name, SML expressed as mg/Kg, simulant, migration values (mg/Kg), limit of detection and RSD% of the three replicates of the migration analyzed.

Sealant	**m/z detected**	**ESI polarity**	**Elemental composition**	**Theorethical mass**	**CCS**	**Compound**	**SML (mg/Kg)**	**Simulant**	**Results(mg/Kg)**
1,2	116.01589	+	C_4H_5NOS	116.0159	117.7	2-methyl-2H-4 isothiazol-3-one	0.5	95% ethanol 3% acetic acid 10% ethanol	0.06 n.d. (LOD=0.002) 0.04
1	150.11188	+	$C_6H_{15}NO_3$	150.1119	129.2	triethanolamine	0.05	95% ethanol 3% acetic acid 10% ethanol	0.02 (LOD=0.001) 0.01 0.02
1,2	459.3262	-	$C_{32}H_{44}O_2$	459.3263	215.5	bis(2-hydroxy-3-tert-butyl-5-methylphenyl)dicyclopentane	0.09 (class III)	95% ethanol 3% acetic acid 10% ethanol	0.02 0.02 n.d. (LOD=0.005)
1	277.1839	-	$C_{14}H_{29}O_3S$	277.1839	172.5	1-tetradecanesulfonic acid	6	95 % ethanol 3% acetic acid	0.10 0.52 (LOD=0.005)

								10% ethanol	0.30
1	291.19929	-	$C_{15}H_{32}O_3S$	291.1993	175.6	1-pentadecanesulfonic acid	6	50% ethanol 3% acetic acid 10% ethanol	0.15 0.68 (LOD=0.005) 0.39
1	305.21484	-	$C_{16}H_{34}O_3S$	305.2148	178.6	1-hexadecanesulfonic acid	**6**	50% ethanol 3% acetic acid 10% ethanol	n.d (LOD=0.005) 0.20 0.08
2	207.01185	-	$C_{10}H_8O_3S$	207.0119	125.9	naphthalene-2-sulfonic acid	0.09 (class III)	50% ethanol 3% acetic acid 10% ethanol	n.d. (LOD=0.006) 0.50 0.10

n.d. (non detected) LOD (limit of detection)