Chapter 9

Use of Mass Spectrometry for the Determination of Formaldehyde in Samples Potentially Toxic to Humans: A Brief Review

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Abstract

The chemical characteristics of formaldehyde make it widely used and important in the global economy. It has applications in the health area and in various industrial sectors. However, formaldehyde is considered toxic substance and is classifed as a persistent organic pollutant. Direct and prolonged contact with formaldehyde can cause serious damage to the body and may even lead to death. It is classifed by several agencies as a human carcinogen and may exhibit mutagenic/teratogenic efects and/or damage the endocrine system. Various matrices have been found to contain formaldehyde at concentrations higher than those permited by global health regulatory agencies. To this end, mass spectrometry can provide a very useful tool, enabling the identifcation and quantifcation of formaldehyde. Although various analytical techniques can be used for the determination and quantifcation of volatile organic compounds, chromatography is one of the most widely used methods due to its precision. Coupled to a detection system such as mass spectrometry, it can be employed for the determination of compounds potentially toxic to humans, including formaldehyde. The purpose of this chapter is to summarize some recent and important studies concerning the quantifcation of formaldehyde using mass spectrometry as a powerful analytical tool.

Keywords: Formaldehyde, mass spectrometry, toxicology, chromatography

1. Introduction

Formaldehyde (FA), the simplest aldehyde, is a carbonyl compound with the molecular formula H_2CO, density of 1.081 g.cm^{-3}, and molecular mass of 30.03 g mol^{-1}. At standard temperature and pressure (STP), it is found in the gaseous state and is colourless and inflammable [1, 2]. It has an irritating odour, is soluble in most organic solvents, and is fairly soluble in water [1]. Formaldehyde is globally one of the top 25 most widely produced chemical substances, due mainly to its high reactivity, absence of colour, commercial purity, and low cost [3].

Commercially available in the solid phase (paraformaldehyde) and as the trioxide [$(CH_2O)_3$], formaldehyde is typically used and stored in 30–50% v/v aqueous solutions, which usually contain methanol as a stabilizing agent (to avoid polymerization) at concentrations that may exceed 15% v/v. Formaldehyde is known by several names, depending on the area of activity where it is used, including formaldehyde, formic aldehyde, formalin, methanal, and methylene oxide, among others [4].

The chemical characteristics of this compound, especially its germicidal activity, make it a product of widespread applicability and important for the global economy [5]. It has uses in the health area (in medical laboratories and hospitals) and in various industrial sectors including civil construction, timber, and paper manufacturing and is employed as a preservative in foods and cosmetics, among other uses [5, 6].

In hospital pathology and anatomical laboratories, formaldehyde is used as a fixative or preservative, in which the biological material is dipped in order to conserve it, and it is also considered a good disinfectant that does not cause excessive hardening of the tissues. Formaldehyde is an excellent medium for the preservation and storage of biopsy and surgical specimens [7].

In civil construction, formaldehyde is employed in the form of urea-methanal coating foams, which are among the most widely used systems for coating buildings [4, 7].

In the timber industry, formaldehyde is used in the production of agglomerates, plywood, laminates, furniture, and adhesives [8]. In the textile finishing industry, it is a constituent of most of the resins used to provide the degree of stiffness and elasticity required to maintain permanent folds while helping to avoid the formation of wrinkles during washing and use of garments [8].

In agriculture, formaldehyde is used as a seed preservative and in the preservation of tubers and fruits. It is employed in the form of disinfectants to eliminate or limit microbiological degradation in the sugar, beer, and leather industries [9].

In the perfume and cosmetics sector, formaldehyde is employed in shampoos, hair creams, deodorants, bath products, creams, and lotions for the skin and can also be found in masks and as makeup for the eyes, in mouth refreshers, cuticle removers, nail polish, and nail hardener, among other products [10, 11].

At the same time, formaldehyde is considered a highly toxic substance and can be characterized as a persistent organic pollutant causing human carcinogenicity and toxicity to aerobic

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and anaerobic microorganisms [4]. Exposure to this substance increases the risk of cancers of the pharynx, nasopharynx, and brain, as well as dermatitis and allergic reactions. Formaldehyde is absorbed through the skin and mucous membranes and is rapidly metabolized by reaction with hydrochloric acid or other inorganic chlorides present in the body, forming bis(chloromethyl)ether, a substance that has carcinogenic effects in humans [12]. Therefore, direct and prolonged contact with formaldehyde causes serious damage to the body and can even lead to death [4, 13].

For these reasons, several agencies have classified this compound as a human carcinogen that may be mutagenic/teratogenic to the endocrine system of humans [1, 4, 10]. These organizations include the Brazilian National Health Surveillance Agency (ANVISA) [14], the International Agency for Research on Cancer (IARC) [12], the National Cancer Institute José Alencar Gomes da Silva (INCA) [6], the United States Occupational Safety and Health Administration (OSHA) [15], and the National Toxicology Program (NTP) [16].

Given the problems caused by the presence of formaldehyde in the human body, it is necessary to develop procedures for the determination of this compound in different sample types, since many matrices can contain formaldehyde at concentrations higher than the levels permitted by global health regulatory agencies. To this end, the mass spectrometry (MS) technique is a very useful tool that enables the detection and quantification of formaldehyde in a wide range of sample types.

Mass spectrometry is an analytical technique that can be used for the structural characterization and quantification of a wide range of molecules [17]. The technique is extensively used by chemists for the analysis of small and volatile organic compounds. It is highly sensitive and can be used to determine substances present at low concentrations, as in the case of doping, food control, environmental contamination, and many other areas of application [18, 19].

In the early stages of the development of mass spectrometry, the sample was introduced into the system by direct vaporization, but with the evolution of chromatographic techniques, the use of a chromatograph to introduce the sample into the mass spectrometer became commonplace (showed in **Figure 1**). In these techniques, the components of the sample are separated and individually introduced into the MS ionization source, generating ions that are then transferred to the analyser for detection and quantification [20]. In the mass spectrometer, the gas phase ions are separated according to their mass to charge ratio (m/z). These ratios are presented in the form of a mass spectrum, which is a graph showing the relative abundance (intensity) of each ion appearing in the form of a peak with defined m/z [21].

This detection technique, when coupled to a chromatograph, enables the construction of a chromatogram of the most important ion fragments, with the elimination of interfering ions, hence increasing the reliability of identification of the components of a sample. Gas chromatography coupled with mass spectrometry (GC-MS) is a powerful analytical tool that is usually used in the analysis of complex gas phase mixtures. However, this limits the technique to the analysis of volatile and semi-volatile compounds of low polarity and low molecular weight. In the case of compounds of higher molecular weight and/or greater polarity and

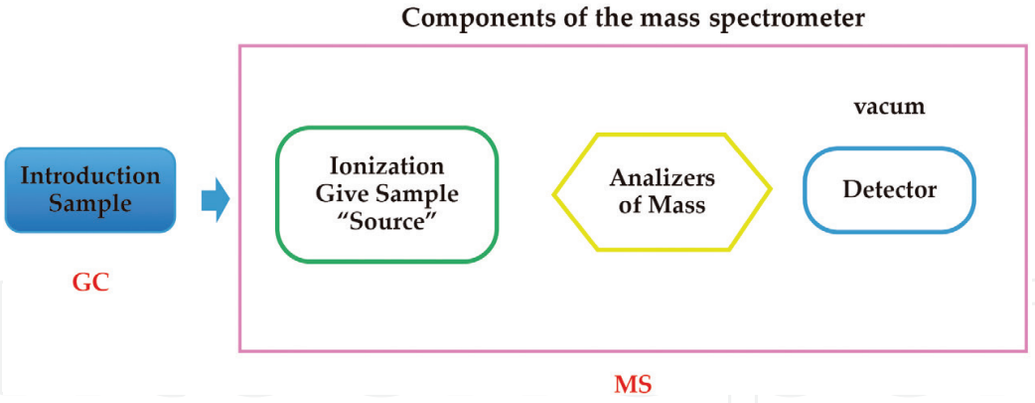

Figure 1. An illustrative figure for mass spectrometer components. Source: Own authors.

lower volatility, the most suitable technique is the coupling of high-performance liquid chromatography and mass spectrometry (HPLC-MS) [20].

Mass spectrometry used as a detection method coupled with gas chromatography offers advantages for the analysis of formaldehyde in different types of samples. These advantages lie in the fact that this technique not only considers the retention time of this compound but also the mass of each of the main fragments generated and the ratio between their intensities, which ensure that the signal is related to the analyte [22].

One of the crucial steps in the analysis of formaldehyde using the mass spectrometry technique involves the use of derivatization reactions. These reactions modify the functional groups of the compound, improving its stability and enabling its detection [9, 10]. The main derivatization agents currently employed in aldehyde analyses include 2,4-dinitrophenylhydrazine (2,4-DNPH) (**Figure 2a**), O-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine (PFBHA) (**Figure 2b**), and pentafluorophenyl hydrazine (PFPH) (**Figure 2c**) [23–29].

In the particular case of formaldehyde, preference has been given to the use of 2,4-DNPH as the derivatization reagent, followed by analysis of the resulting hydrazones (FA-DNPHo) by mass spectrometry [30]. This procedure increases the sensitivity and selectivity of the method. In most DNPH derivatization methods, analysis by HPLC-MS is generally preferred rather than GC-MS. However, in the analysis of FA-DNPHo, the GC-MS system provides greater sensitivity and selectivity, compared to HPLC-MS [30], with gas chromatography providing the benefits of precision and operational simplicity. **Figure 3** shows an illustrative scheme of the identification of formaldehyde in possible sources of contamination and the mass spectral for its identification in the form of Fo-DNPH, using GC-MS, and **Table 1** summarizes some important derivatization studies using mass spectrometry.

The following discussion describes some of the techniques involving chromatography coupled to MS employed for the analysis (detection and quantification) of formaldehyde in different types of samples.

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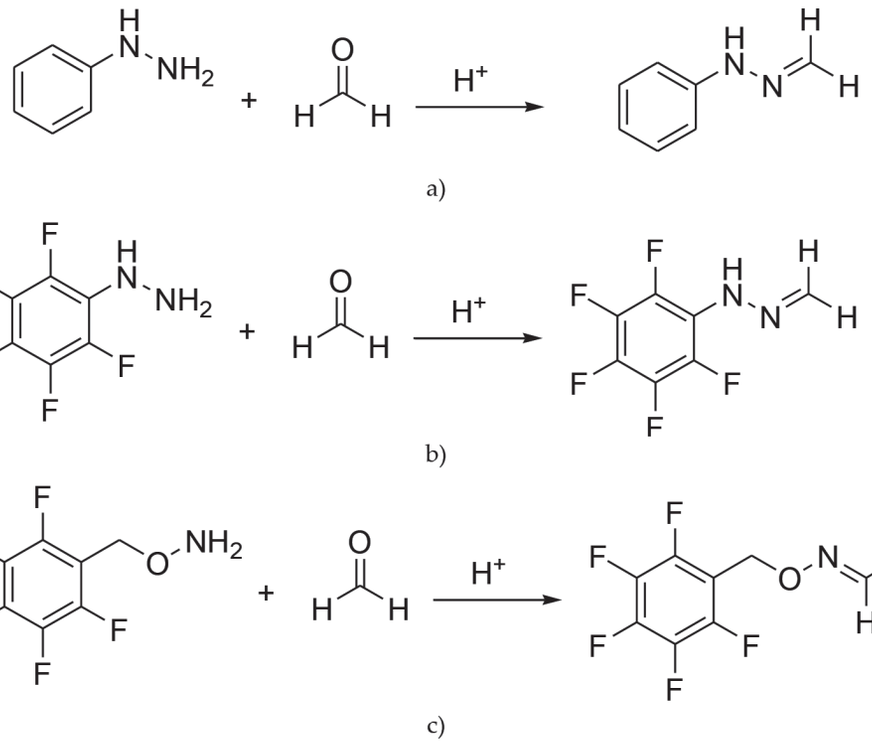

Figure 2. (a) A reaction of formaldehyde with 2,4-dinitrophenylhydrazine to form 2,4 dinitrophenylhydrazone. (b) A reaction of formaldehyde with O-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine to form the oxime. (c) A reaction of formaldehyde with pentafluorophenyl hydrazine to form pentafluorophenyl hydrazone. Source: Own authors, 2017.

Figure 3. An example mass spectrum for FA-DNPHo [spectrum obtained using a gas chromatograph with mass spectrometric detection (CGMS-QP2010 Plus, Shimadzu)]. Source: Own authors, 2017. Google Images [31].

Sample type	Sample analysis	Main results	References
Hair creams	Solubilisation of straightener cream samples, addition of 2,4-dinitrophenylhydrazine in acetonitrile, and direct injection of the prepared samples	All samples had formaldehyde levels above the concentration permitted by Brazilian law.	[32]
Foods	Derivatization with 2,4-dinitrophenylhydrazine	Analysis of free and reversibly bound formaldehyde in 10 squid and squid products.	[33]
Foods	Derivatization with 2,2,2-trifluoroethylene hydrazine	All food samples analysed contained formaldehyde.	[34]
Bio-oil	Derivatization with (2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride	Contained ~2% formaldehyde	[35]
Terpenes α- and β-pinene/limonene/ Δ3–carene	Derivatization with 2,4-dinitrophenylhydrazine and subsequent analysis by high-performance liquid chromatography	Low limits of detection and quantification improved the technique	[36]
Air affected by incense burning	Derivatization on a solid sorbent containing O-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine	The concentration of formaldehyde in a closed room was higher than the concentration in an open place	[37]
Blood	Gas chromatography with mass spectrometry following derivatization with pentafluorophenyl hydrazine	Detection of formaldehyde in rat blood samples	[12]

Table 1. Studies reported in the literature on the analysis of formaldehyde in various types of matrices, using derivatization procedures.

2. Overview of analytical techniques for formaldehyde determination

2.1. Formaldehyde in environmental samples

Several studies have investigated the levels of formaldehyde in samples of air, diesel, water, and other media. The monitoring of formaldehyde in these sample types is very important, due to the likelihood of exposure to part of the population.

Tessini et al. [35] determined aldehydes in bio-oil using HPLC-UV and GC-MS techniques. For analysis using HPLC-UV, the aldehydes were derivatized with 2,4-DNPH in solution, followed by headspace analysis. For analysis by GC-MS, the aldehydes were extracted using

a solid-phase microextraction (SPME) fibre, and the following derivatization in solution with pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA) was analysed. Optimization was performed of the reaction between low molecular mass aldehydes and 2,4-DNPH, forming hydrazones, as well as the HPLC-UV analysis. The best condition found was use of 0.15 μmol of DNPH at 40°C for 30 min. The separation of formaldehyde-DNPH was achieved under the optimized separation conditions, although the presence of interferences was observed. Optimization of the derivatization in solution with PFBHA and analysis by GC-MS resulted in the best conditions being derivatized at 85°C for 60 min, with agitation at 350 rpm. The formation of isomers was observed, except in the case of the derivatization reaction producing the formaldehyde-PFBHA oxime. The selectivity was evaluated by comparison of the mass spectra obtained for the bio-oil sample chromatographic signals with those for a standard solution.

In the study of aldehydes derivatization and extraction on an SPME fibre, evaluation was required of the fibre coating and the optimal HS-SPME conditions for the on-fibre modification. The use of a selective fibre was necessary due to the complexity of the bio-oil matrix, which contains a large quantity of volatile compounds that could interfere in the aldehyde analysis by HS-SPME. The fibres studied were polyacrylate (PA), carboxen/polydimethylsiloxane (CAR/PDMS), and divinylbenzene/polydimethylsiloxane (DVB/PDMS), used for 30 min at temperatures of 30, 40, and 60°C of the aqueous fraction of bio-oil. The best option was found to be DVB/PDMS because at all the temperatures tested, the extraction efficiency was lower for interfering aromatic compounds. The optimization of aldehyde extraction from bio-oil samples, with on-fibre derivatization, was studied using five extraction parameters: PFBHA concentration ($mg.L^{-1}$), temperature for sorption of PFBHA by the fibre (°C), agitation time for sorption of PFBHA by the fibre (min), agitation time for the derivatization reaction (min), and temperature for the derivatization reaction (°C). The best conditions for the extraction of formaldehyde were 1.0 mg L^{-1}, 27°C, 10 min, 20 min, and 35°C, respectively.

No statistical significant difference was observed between the concentrations of formaldehyde, acetaldehyde, and propionaldehyde found in bio-oil samples (n = 5) using either on-fibre derivatization and analysis by GC-MS or derivatization in solution and analysis by GC-MS. The concentration of formaldehyde found in bio-oil is of interest, considering its possible use in industrial production of phenol/formaldehyde resin.

The most commonly used methods for the analysis of airborne carbonyls involve the collection of analytes on solid sorbents coated with a suitable derivatization agent, typically 2,4-DNPH, followed by desorption using solvents.

Pang et al. [25] studied the determination of formaldehyde in airborne samples by GC-MS in comparison with an HPLC method. A novel GC-MS method was described for the analysis of airborne carbonyls based on their PFPH derivatives. The method involved sampling using simple tubes packed with PFPH-coated Tenax TA, followed by GC-MS analysis with liquid injection. The method was considered appropriate for the determination of 23 carbonyl compounds in the range C1–C9 and was applied for the determination of these carbonyls in ambient air and from a strong emission source (cigarette smoke). The technique was subsequently compared with the HPLC-MS method.

In this study, one brand of cigarettes consumed in the UK was tested, with the smoke drawn into a Tedlar bag and diluted to 100 L with nitrogen. The carbonyls in the cigarette smoke were identified and their diluted concentrations in the Tedlar bag were determined. The concentrations of formaldehyde obtained by PFPH-GC-MS were significantly different from those found using DNPH-HPLC-MS, with a mean difference of 2.6% between the two methods. The concentrations of formaldehyde (in ppb) in the diluted cigarette smoke sample were 42.3 ± 2.5 and 45.7 ± 4.3 for the PFPH and DNPH methods, respectively, considering three sampling periods. The mean weight of each cigarette was 0.82 ± 0.02 g, with combustion producing 10 mg of tar, 0.9 mg of nicotine, and 10 mg of carbon monoxide. Only formaldehyde, acetaldehyde, butyraldehyde and valeraldehyde were detected in the ambient air samples, using both PFPH and DNPH methods. In comparative field tests with the classical DNPH–HPLC method, it was concluded that there were similarities between the two methods for the same carbonyls, although more carbonyl species were detected by the PFPH-GC-MS method. The PFPH-GC-MS method provides better separation for carbonyls with similar molecular structures, is highly sensitive, and provides mass spectrometric identity confirmation by the acquisition of structural information.

In recent years, there has been increasing attention given to the presence of aldehydes as disinfection and oxidation by-products formed during drinking water treatment processes. Studies show that formaldehyde, acetaldehyde, glyoxal and methylglyoxal are the major organic by-products produced during the ozonation of natural water.

Tsai and Chang [28] analysed aldehydes in three different types of samples (double distilled water, well water, and chlorinated tap water) using the SPME technique with on-fibre derivatization. Poly(dimethylsiloxane)/divinylbenzene fibres were used, with O-2,3,4,5,6-(pentafluorobenzyl)hydroxylamine hydrochloride being first loaded onto the fibre. The aldehydes present in the samples were transferred into the headspace by agitation and extracted (the extraction was conducted for 10 min) by SPME with on-fibre derivatization. GC-MS was used for analysis of the oximes formed and the adsorption-time profiles were examined. It was observed that the equilibrium times (10 min) were similar for most of the oximes formed on the fibre, with the exception of the formaldehyde oxime. The reason for the different adsorption time profile of formaldehyde was not clear. It was also observed that there were syn- and anti-isomers of the oximes because aldehydes are asymmetrical carbonyl compounds (except formaldehyde). Investigation was made of the effects of salt additions (0, 10, and 20% NaCl) to samples of double distilled water, with only formaldehyde showing increased extraction as the concentration of salt added was increased. Similar results were observed for the addition of salt to well water and chlorinated tap water. The influence of different extraction temperatures (without heating, 40 and 60°C) was also investigated. The formaldehyde peak area increased in line with the temperature. It was concluded that the analysis of aldehydes in water by SPME with on-fibre derivatization provided acceptable precision and sensitivity, with simple and fast procedures. The proposed method was suitable for the routine analysis of water samples.

Ho and Yu [37] determined formaldehyde and other carbonyl compounds in environments affected by incense burning in Chinese homes and temples. The sample air was trapped on a solid sorbent containing O-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine for

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the derivatization of formaldehyde and other compounds, followed by thermal desorption and GC/MS analysis. The concentration of formaldehyde in a worship room (at a range of 340–346 ppbv) was higher that the concentrations in a temple yard (at a range of 154–247 ppbv) and outside the temple (11.1 ppbv). These results were correlated with the intensity of incense burning in the environment. The lowest concentration outside the temple could be explained by faster dispersion in the air of this environment. In the home, the sample was collected during and after incense burning (1 and 2 h). The level of formaldehyde decreased once the burning ended, proving that burning incense emits carbonyl species. In this work, formaldehyde was the most abundant carbonyl compound emitted from incense burning. The study showed that it is necessary to quantify the emission rates of toxic aldehyde species from various brands of incense.

Figure 4 illustrates environmental samples as sources of formaldehyde.

2.2. Formaldehyde in food samples

Chemical contamination is one of the leading causes of foodborne illnesses. Research involving food safety is necessary to preserve the health of the human population and ensure safe food production, distribution, and preparation. The development of new methods of risk analysis needs to include consideration of potentially susceptible populations as well as the combined low-level exposure to several different chemicals. The US Environmental Protection Agency [40] has established an acceptable daily intake (ADI) for formaldehyde of 0.2 $mg.kg^{-1}$ body weight, with the potential adverse health effects increasing at intakes higher than the ADI.

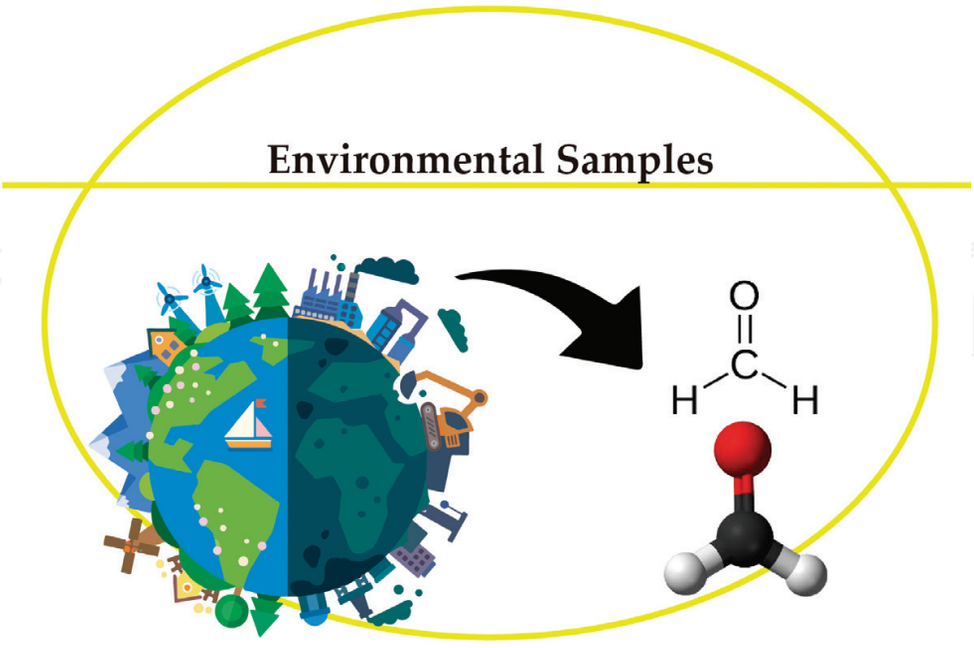

Figure 4. Environmental samples as sources of formaldehyde. Own authors, 2017, Deposit Photos [38], and Info Escola [39].

In 2012, Shin and Lim [34] developed a headspace solid-phase micro-extraction gas chromatography-mass spectrometry (HS-SPME GC-MS) method for the detection of formaldehyde in traditional Korean fermented foods and applied the new method to real sample analysis. The focus of the research was the validation of a robotic sample preparation and detection methodology. Derivatization was performed by the reaction of FA with TFEH (2,2,2-trifluoroethylhydrazine), a highly volatile hydrazine, using food samples contained in headspace vials. The volatile formaldehyde-TFEH formed was vaporized, simultaneously adsorbed on a fibre, and then desorbed into the GC-MS system. The limits of detection (LOD) and quantification (LOQ) for FA were 0.1 and 0.3 $\mu g.kg^{-1}$, respectively. The accuracy and precision of this method were very good, with relative standard deviation less than 10%. The standard curve obtained by computing a least squares regression between the FA concentration and the peak area ratio of FA-TFEH to acetone-d6-TFEH (as internal standard) demonstrated a linear relationship, with a correlation coefficient value of 0.999. The developed method was employed to analyse the concentrations of formaldehyde in 20 samples of traditional Korean foods including kimchi, water radish kimchi, soya bean paste, red pepper paste, soya sauce, and bean-paste soup. All the samples presented detectable levels of formaldehyde in the range from 0.104 to 13.048 $mg.kg^{-1}$. The Korean traditional fermented foods generally contained low levels of formaldehyde, although a red pepper paste sample exceeded the 10 $mg.kg^{-1}$ limit for crustaceans established by the Italian Ministry of Health.

Bianchi et al. [26] determined the formaldehyde contents of different fish and shellfish maintained under different conditions. Validation was performed of an SPME-GC–selective ion monitoring (SIM)-MS method using a CAR-PDMS fibre, based on in-situ on-fibre derivatization with PFBHA, and 12 species of fresh, frozen, stored-on-ice, boiled, roasted, and canned fish were analysed. The fibre was exposed to the headspace of a vial containing an aqueous solution of PFBHA. Fish and fish products fulfil an important role in human nutrition as a source of biologically-valuable proteins, fats, and fat-soluble vitamins, with frozen and fresh fish being the most widely sold products. In fish and crustaceans, formaldehyde is known to form post mortem from the enzymatic reduction of trimethylamine-N-oxide (TMAO) to formaldehyde and dimethylamine [41, 42]. It accumulates during frozen storage, reacts with proteins, and consequently causes protein denaturation and muscle toughness [41].

The performance of the SPME-GC-MS method developed by Bianchi et al. [26] was demonstrated in the determination of formaldehyde at trace levels, with LOD and LOQ values at 17 and 28 $\mu g.kg^{-1}$, respectively, obtained using a blank trout sample. The precision of the method was evaluated in terms of repeatability and between-day precision, with CV% values lower than 3.2% and 9.7% obtained, respectively. No significant differences, at the 95% confidence interval, were found among the mean values for data obtained over 3 days ($p = 0.127$). An extraction recovery of 94.8 ± 1.7% ($n = 3$) was obtained after spiking blank fish samples with formaldehyde at 2.5 $mg.kg^{-1}$. The data obtained for the various samples generally indicated that no adverse effects on human health would be expected due to consumption of the fish and shellfish. However, higher formaldehyde levels were found in species belonging to the Gadidae family, while the freshwater fish and crustaceans generally presented lower values. Evaluation was also made in the influence of cooking, which acted to reduce the formaldehyde contents of the samples analysed.

Wang and co-authors [24] applied HS-SPME analysis of low molecular mass (C1–C10) aldehydes to aqueous solutions of dry white wine, fish, and particle board samples, using PFPH and PFBHA for on-fibre derivatization using fibres coated with PDMS-DVB. Background contamination peaks were observed, most notably for formaldehyde, as found previously in a number of other studies. Using PFBHA, typical formaldehyde concentrations observed were in the region of 25 $\mu g.L^{-1}$. The concentrations obtained using PFPH were significantly higher, at approximately 65 $\mu g.L^{-1}$, indicating a higher level of impurity in the derivatization reagent. Further precautions would be necessary in order to improve the sensitivity and accuracy of the methods for the determination of formaldehyde at low concentrations. Of all the aldehydes studied, formaldehyde showed a steadier increase in derivative formation with extraction time, in the range tested, using both derivatization reagents. This could be explained by the greater affinity of formaldehyde towards the aqueous phase, compared to the other aldehydes studied. Another observation was that formaldehyde presented by far the lowest extraction efficiency, compared to the other aldehydes, with approximately 50% remaining for the second extraction. This was also probably linked to the affinity of this substance for the aqueous phase, which reduced the rate at which it was transferred from the sample to the fibre. The detection limit, linear range, and reproducibility for formaldehyde using the PFPH method were 65, 65–250 $\mu g.L^{-1}$ ($R^2 = 0.9910$), and 10.7%, respectively. The corresponding values for the PFBHA method were 25, 25–250 $\mu g.L^{-1}$ ($R^2 = 0.9955$), and 10.5%, respectively.

The developed PFBHA method was applied to the three different sample matrices (particle board, white wine, and fish). In the case of the particle board sample, it was no surprise to find that the predominant aldehyde was formaldehyde, due to its use as an adhesive in the material. The formaldehyde could not be quantified because the concentration was significantly above the linear range of the method. No formaldehyde was detected in the wine samples. In the raw fish sample, the formaldehyde concentration was again too high for quantification.

The authors concluded that in aldehyde headspace analysis by SPME-GC-FID, use of the PFBHA reagent provided superior on-fibre derivatization, compared to PFPH, under the conditions employed, with detection limits from the low- to sub-microgram level per litre. The automated method was successfully applied to a variety of sample types and could handle samples containing elevated levels (10,000 $\mu g.L^{-1}$) of formaldehyde. GC-MS analyses were performed and compound identifications were made using spectral libraries supplied with the software.

Formaldehyde can occur naturally (endogenously) in many foods and is sometimes used illegally as a food preservative in aquatic products. Due to this, many countries have investigated the form and content of formaldehyde, especially in seafood [34]. For example, the European Commission released an alert notification after finding that shiitake mushrooms from China contained 300 mg/kg of formaldehyde and suggested the possibility that the aldehyde had been added deliberately [33 apud 43]. Yeh and co-authors [33] analysed free and bound formaldehyde in squid and squid products by GC-MS and performed comparative studies with HPC-UV. A comparison was made of free formaldehyde with free and reversibly bound formaldehyde, and similar results were obtained using HPLC-UV and GC-MS.

The GC-MS method provides additional information on the structure of the compound, for example, using mass fragmentation data for identity confirmation. The HPLC-UV method is not

specific to the compound studied and is more liable to matrix effects. In the study by Yeh et al. [33], exposure to formaldehyde due to the consumption of squid and squid products was found to be less than 0.2 mg/kg/d, which is the oral reference dose suggested by the United States EPA.

Figure 5 illustrates foods as source of formaldehyde.

2.3. Formaldehyde in pharmaceutical and related samples

Excipients are substances added to pharmaceuticals in order to ensure the stability and biopharmaceutical properties of the products as well as to improve the organoleptic characteristics and hence increase the patients' acceptance of the formulations. Excipients can be variously classified as follows: preservatives, colourants, flavourings, sweeteners, thickeners, emulsifiers, stabilizers, antioxidants, diluents, humectants, solvents, absorption promoters, and extended release matrices [43].

In 2004, Riveiro and Topiwala [45] developed and optimized an analytical methodology for the extraction of formaldehyde present in cosmetics (shampoos and liquid soaps), using in situ derivatization followed by solid-phase headspace microextraction. The headspace derivatization process was carried out on a PDMS-DVB-coated fibre, followed by extraction for 15 min at 35°C, resulting in an efficiency of around 80%. Sodium chloride was identified as the best salt for the salting-out process. The best analyte desorption time was 5 min, giving an efficiency of 99.8%. The precision, recovery, and detection limit were determined for all the samples. The relative standard deviations were less than 10% for all the cosmetics samples, with recoveries between 89.00 and 101.23%, and the limit of detection was 0.39 $\mu g.L^{-1}$. The proposed method was considered suitable for use in the routine analysis of cosmetics products, offering the advantages of speed and no requirements for the use of large volumes of solvents.

Figure 5. Foods as sources of formaldehyde. Source: Own authors, 2017, Sabor Saudável [44], Info Escola [39].

Del Barrio et al. [46] reported that formaldehyde is a common impurity in many excipients, such as polysorbate, povidone, and polyethylene glycol 300 and that it can form crosslinks with gelatin, leading to incomplete capsule shell dissolution and subsequent drug release problems. Due to oxidation on contact with air, formaldehyde is partially converted to formic acid. Hence, these impurities can coexist in many excipients and can react with active drugs, affecting their stability, so for this reason, it is very important to develop rapid, sensitive, and reliable analytical methods to simultaneously determine formaldehyde, formic acid, and formic acid esters.

Del Barrio et al. [47] developed and validated a GC-MS method for the simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients. An alcohol was selected as the reagent, because both formic acid and formaldehyde can readily react with alcohols, in the presence of an acidic catalyst, to give the corresponding ester and acetyl compounds, respectively, which are volatile and suitable for GC determination. Besides that, the alcohol was used as a solvent to dissolve or disperse the excipients and assist completion of the derivatization reactions. Following evaluation trials, ethanol was selected as the derivatization reagent and solvent, while p-toluenesulfonic acid was used as the catalyst.

Using the SIM mode, the performance of the GC-MS method was evaluated in terms of linearity, range, detection limit, precision, and accuracy, and this mode was subsequently used in the screening of pharmaceutical excipients. Using this method, it was found that almost all the excipients contained varying levels of formic acid and formaldehyde. The good recoveries of both analytes (within the range of 80–120%) indicated that matrix effects were insignificant for the excipients tested. A total of 28 excipients were screened, covering a range of formulations varying in grade, batch, and/or vendor.

Hair products are among the most widely used cosmetics, and the market is growing in Brazil. With an average annual growth of 11% over the last 10 years, Brazil has achieved third place in the world ranking for consumption of cosmetics. Formaldehyde is the chemical compound most widely used in hair products to alter the protein structure of the hair and provide smoothing. In 2001, the National Health Surveillance Agency, which is a branch of the Brazilian Ministry of Health, issued a decree to control the use of formaldehyde, restricting it to a maximum concentration of 0.2% in cosmetics.

Lobo et al. [32] developed a method for the quantification of formaldehyde in hair straightening creams collected at various salons of a city in Brazil, using 2,4-DNPH as a derivatization reagent and analysis by GC-MS. The pH is an important factor in this reaction, due to competition between the nucleophilicity and basicity of 2,4-DNPH. The compound formed is formaldehyde-2,4-dinitrophenylhydrazone, and the mass spectrum for a well-defined peak identified in the chromatogram corresponded to the reference spectrum available in the National Institute of Standards and Technology (NIST) database. Identification of formaldehyde-DNPH was confirmed by the presence of the molecular ion ($m/z = 210$) and its characteristic fragmentation pattern.

In this work, the optimization studies included comparison of the sensitivities of two different procedures, with either external calibration or the use of standard additions. Significant interference from the sample matrix was observed (with decreased sensitivity) so the standard additions method was selected for quantification of formaldehyde in the hair cream samples. As expected, the sensitivity values were significantly different for the two calibration procedures adopted.

The LOD and LOQ values were calculated for each analytical curve of each sample. The values obtained were less than or equal to 0.0165 and 0.055 mg.L^{-1}, respectively. The standard deviation and relative standard deviation obtained were lower than or equal to 81.36 and 18.67%, respectively. The recoveries of known amounts of standards from blank cream samples were in the range from 88 to 115%. Satisfactory results were obtained for formaldehyde-2,4 DNPH standard solutions, enabling the determination of formaldehyde in the real samples. The levels of formaldehyde found in some hair cream samples exceeded the limit permitted according to Brazilian law, giving rise to health concerns, especially for users of these products in hair salons.

Use of dental prostheses on a daily basis can, in some individuals, lead to allergies associated with certain chemicals used in the production of the devices, including methyl methacrylate, ethylene glycol dimethacrylate, hydroquinone, and especially formaldehyde. Mikai and Fuji (2006) [47] carried out a study to evaluate the presence of these substances in several types of denture samples. The materials were prepared by washing, using appropriate agents, and were then sliced into 10-mm-wide portions that were completely immersed in 10 mL of methanol in borosilicate tubes. The tubes were shaken 80 times for 1 min. The procedure was repeated over 4 weeks, with the samples kept in the dark at 37°C. Finally, the eluate was removed, filtered through a 0.2-μm pore size membrane and analysed using GC-MS and HPLC. The results showed that all the samples contained formaldehyde in their compositions, and it was concluded that this substance was a strong candidate for causing allergies.

Figure 6 illustrates cosmetics as source of formaldehyde.

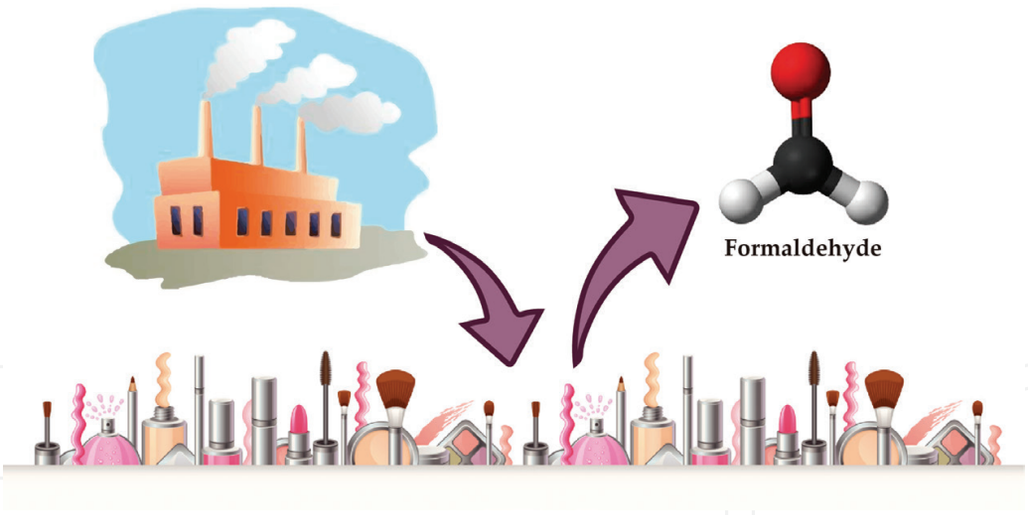

Figure 6. Cosmetics as source of formaldehyde Source: Own authors, 2017; Dreamstime, 2017 [48], Clip Art, 2017 [49], and Info Escola, 2017 [39].

3. Conclusion

Formaldehyde is a substance widely used for many purposes worldwide. However, it is considered carcinogenic by international agencies. The present chapter describes some important work on the determination of formaldehyde in different sample types using

mass spectrometry. This brief discussion demonstrates that mass spectrometry can make a valuable contribution to the determination of commonly encountered toxic compounds such as formaldehyde.

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References

[1] Cetesb. Toxicological Information Sheet. Formaldehyde [Internet]. Available from: http://www.cetesb.sp.gov.br/userfiles/file/laboratorios/fit/formaldeido.pdf [Accessed: 2 June 2016]

[2] Portal Educação. Formol or Formaldehyde [Internet]. Available from: https://www.portaleducacao.com.br/farmacia/artigos/357/formol-ou-formaldeido [Accessed: 9 October 2016]

[3] Vieira IIF, Dantas BPA, Ferreira FCP, Carvalho RBAC, Freire IB, Neto EJS. Efeitos da utilização do formaldeído em laboratório de anatomia. Rev. Ciênc. Saúde Nova Esperança. 2013;**11**(1):97-105

[4] Viegas SPC. Estudo da exposição profissional a formaldeído em laboratórios hospitalares de anatomia patológica [PhD thesis]. Lisbon: Universidade Nova de Lisboa; 2010

[5] Alves CA, Acile SDG. Formaldeído em escolas: uma revisão. Química Nova. 2010;**25**(10): 2025-2029

[6] Instituto Nacional do Câncer (INCA). Formol or Formaldehyde [Internet]. Available from: http://www.inca.gov.br/conteudo_view.asp?id=795#topo [Accessed: 6 August 2016]

[7] Belo CAVF. Avaliação da exposição profissional ao formaldeído e xileno no serviço de anatomia patológica dos hospitais da Universidade de Coimbra [Master's thesis]. Portugal: Universidade de Coimbra, Portugal; 2011

[8] Carvalho MZ. Abordagem multivariada do comportamento das propriedades físico-químicas e caracterização de adesivos naturais à base de taninos. Lavras [PhD thesis]. Brazil: Universidade Federal de Lavras; 2016

[9] Rossi F. O uso de formaldeído na alimentação de cães e gatos. Curitiba. Brazil: Universidade Federal de Tuiuti do Paraná; 2014

[10] Lonta LMP. Efeitos tóxicos do formaldeído em escova progressiva: 10° Congresso de Pós-Graduação: Qualificação e expansão da educação superior no contexto do Plano nacional da educação. 2012. UNIMEP (Universidade Metodista de Piracicaba).

[11] Lorenzini, S. Efeito adverso da exposição ao formaldeído em cabelereiros. 2012. 77 pp. PhD thesis, Rio Grande do Sul, Programa de pós-graduação em ciências pneumológicas, Universidade do Rio Grande do Sul, Brazil.

[12] Iarc M. Analytical methods for formaldehyde. Chemical and Physical Data. 1995;**88:**39-93

[13] Abreu VM, Azevendo MGB, Falcao JSA. Cosmetovigilância em alisantes capilares: Determinação do teor de formaldeído por espectrofotometria e avaliação do rótulo. Rev. Ciênc. Farm. Básica Apl. 2015;**36**(1):51–58

[14] Agência Nacional de Vigilância Sanitária (ANVISA). Resolução – RDC N° 15, de 26 de março de 2013. Available from: http://www.cosmeticsonline.com.br/ct/painel/fotos/assets/uploads/regulatorios/ae972-Rdc-15.pdf [Accessed: 9 October 2016]

[15] Occupational safety and health administration (OSHA). 2011. Hair smoothing products that could release formaldehyde [Internet]. Available from: https://www.osha.gov/SLTC/formaldehyde/hazard_alert.html [Accessed: 10 October 2016]

[16] Report on carcinogens background document for formaldehyde. 2009. National Toxicology Program (NTP) [Internet]. Available from: http://ntp.niehs.nih.gov/ntp/roc/2009/november/background/formaldehydedraftbackgrounddocument.pdf [Accessed: 10 October 2016]

[17] Cunha MM, Rodrigues CR, Ferreira VS, Rodrigues AR, Lemes SR, Chaves DA, Mesquita MM, Araujo LA, Junior NJS, Melo-Reis PR. Eficiência do método de espectrometria de massas em drogas de abuso. Estudos. 2015;**42**:409-423

[18] Colnago LA, Almeid FCL, Valente AP. Espectrometria de massas RMN multidimensional e multinuclear: Revolução no estudo de macromoléculas biológicas. Química Nova na Escola. 2002;**16**:9-14

[19] Cunha RB, Castro MS, Fontes W. Espectrometria de massas de proteínas. Biotecnologia Ciência & Desenvolvimento Ano IX. 2006;**16**:40-46

[20] Lancas FMA. Cromatografia líquida moderna e a espectrometria de massas: finalmente "compatíveis"? Scientia Chromatographica. 2009;**1:**35-61

[21] Wilson K, Walker J. Principles and Techniques of Biochemistry and Molecular Biology. Cambridge University Press; 2009. p. 352

[22] Silva TO. Estudo de emissão de aldeídos e outros COV por óleos de dendê e soja em diferentes condições, sob aquecimento a temperatura de processos de fritura [Master's thesis]. Salvador: Universidade Federal da Bahia; 2017

[23] Sowinski P, Wardencki W, Partyka M. Development and evaluation of headspace gas chromatography method for the analysis of carbonyl compounds in spirits and vodkas. Analytica Chimica Acta. 2005;**539:**17-22

[24] Wang Q, O'Reilly J, Pawliszyn J. Determination of low-molecular mass aldehydes by automated headspace solid-phase microextraction with in-fibre derivatisation. Journal of Chromatography A. 2005;**1071:**147-154

[25] Pang X, Lewis AC, Hamilton JF. Determination of airborne carbonyls via pentafluorophenylhydrazine derivatisation by GC-MS and its comparison with HPLC method. Talanta. 2011;**85:**406-414

[26] Bianchi F, Careri M, Musci M, Mangia A. Fish and food safety: Determination of formaldehyde in 12 fish species by SPME extraction and GC-MS analysis. Food Chemistry. 2007;**100**:1049-1053

[27] Dong JZ, Moldoveanu SC. Gas chromatography–mass spectrometry of carbonyl compounds in cigarette mainstream smoke after derivatization with 2,4-dinitrophenylhydrazine. Journal of Chromatography A. 2004;**1027**:25-35

[28] Tsai SW, Chang CM. Analysis of aldehydes in water by solid-phase microextraction with on-fiber derivatization. Journal of Chromatography A. 2003;**1015**:143-150.

[29] Chi Y, Feng Y, Wen S, Lu H, Yu Z, Zhang W, Sheng G, Fu J. Determination of carbonyl compounds in the atmosphere by DNPH derivatization and LC-ESI-MS/MS detection. Talanta. 2007;**72**:539-545

[30] Jeong HS, Chung H, Song SH, Kim CII, Lee JG, Kim YS Validation and determination of the contents of acetaldehyde and formaldehyde in foods. Toxicology Research. 2015;**31**(3):273-278

[31] Google Images. 2017 [Internet]. Available from: https://www.google.com.br/imghp [Accessed: 24 March 2017]

[32] Lobo FA, Santos TM, Vieira KM, Osorio VM, Taylor JG Determination of formaldehyde in hair creams by gas chromatography-mass spectrometry. Drug Testing and Analysis. 2015;**7**:848-852

[33] Yeh TS, Lin TC, Chen CC, Wen HM. Analysis of free and bound formaldehyde in squid and squid products by gas chromatography-mass spectrometry. Journal of Food and Drug Analysis. 2013;21:190-197

[34] Shin HS, Lim HH. Simple determination of formaldehyde in fermented foods by HS-SPME-GC/MS. International Journal of Food Science and Technology. 2012;**47**:350-356

[35] Tessini C, Muller N, Mardones C, Meier D, Berg A, Von Baer D. Chromatographic approaches for determination of low-molecular mass aldehydes in bio-oil. Journal of Chromatography A. 2012;**1219**:154-160

[36] Bergh VV, Coeckelberghs H, Vankerckoven H, Compernolle F, Vinckier C. Study of the carbonyl products of terpene/OH radical reactions: Detection of the 2,4-DNPH derivatives by HPLC-MS. Analytical and Bioanalytical Chemistry. 2004;**379**:484-494

[37] Ho SSH, Yu JCZ. Concentrations of formaldehyde and other carbonyls in environments affected by incense burning. Journal of Environmental Monitoring. 2002;**4**:728-733

[38] Deposit Photos. [Internet] 2017. Available from: <http://br.depositphotos.com/> [Accessed 24 March 2017]

[39] Info Escola. [Internet] 2017. Available from: http://www.infoescola.com/ [Accessed: 24 March 2017]

[40] US Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS) on Formaldeyde. Washington, DC: National Center for Environmental Assessment, Office of Research and Development; 1999

[41] Sotelo CG, Pineiro C, Perez-Martin RI. Denaturation of fish proteins during frozen storage: Role of formaldehyde. Lebensmittel Untersuchung und Forschung. 1995;**200**:14-23

[42] Badii F, Howell NK. Changes in the texture and structure of cod and haddock fillets during frozen storage. Food Hydrocolloids. 2002;**16**:313-319

[43] Rapid alert system for food and feed (RASFF). Alert notification 2001/106, presence of formalin in fresh mushrooms from China (EC) [Internet]. Available from: https://webgate.ec.europa.eu/rasff-window/portal/index.cfm? [Accessed: 24 March 2017.

[44] Sabor Saudável, 2017. Available At: <Https://Saborsaudavelalimentos.Wordpress.Com/>. Accessed On: March 24, 2017.

[45] Riveiro R. T., Topiwala V. Quantitative Determination Of Formaldehyde In Cosmetics Using A Combined Solid-Phase Microextraction–Isotope Dilution Mass Spectrometry Method. Journal Of Chromatography A 1029 (2004) 217–222.

[46] Del Barrio M. A., Hu J. Zhou P., Cauchon N. Simultaneous Determination Of Formic Acid And Formaldehyde In Pharmaceutical Excipients Using Headspace Gc-Ms. Journal Of Pharmaceutical And Biomedical Analysis 41 (2006) 738–743.

[47] Mikai M., Koike M., Fuji H. Quantitative Analysis Of Allergenic Ingredients In Eluate Extracted From Used Denture Base Resin. Journal Of Oral Rehabilitation 33 (2006) 216-220.

[48] Dreamstime, 2017. Available from: ttps://Pt.Dreamstime.Com/ [Accessed: 24 March 2017]

[49] Clip Art, 2017. Available from: http://Pt.Clipartlogo.Com/ [Accessed: 24 March 2017].

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