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Review

An Overview of Analytical Methods for Bisphenol A

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Abstract

Our food preparation and eating habits have gradually changed due to the pace of business life. Which have paved the way for the rapid development of ready-made food and plastic production industries. Various packets used for storing and selling ready-made foods and disposable plastic products contain Bisphenol A (BPA) which is very dangerous for health. This substance which can be transferred to the food not only acts like a hormone in the human body but also causes various diseases such as cancer, diabetes and obesity. The sensitive determination of this substance has gained importance in foods, human body fluids and tissues. For this purpose, researchers have developed various chromatographic, electrochemical and spectroscopic methods for BPA determination. In this review, the purpose of use, usage areas, exposure routes of BPA and its harms, methods developed to determine substance in question and pros and cons of various methods are discussed.

Keywords: Bisphenol A, Chromatography, Spectroscopy, Electrochemistry, Human health, Solid-phase extraction, Molecularly imprinted polymers

Introduction

Bisphenols (BPs) are compounds containing two hydroxyphenyl groups and have different names according to the reactant group in which hydroxyphenyl groups react [1]. For example, BPA substance which is called as bisphenol A and the member of BPs is synthesized by condensation of 2 moles of hydroxyphenyl and 1 mol of acetone [2] (Fig. 1a).

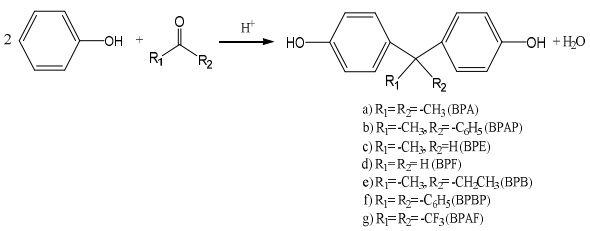

Figure 1. **General synthetic pathway of BPA derivatives**

The synthesis reaction of BPA is known as the Friedel-Crafts hydroxyalkylation reaction. The acid catalyzed condensation of acetone with 2 mol of phenols to produce BPA is an important monomer in the polycarbonate plastics and epoxy resin products. This condensation reaction takes place in two base steps and needs a strong acid like HCl. The first step is the reaction between acetone and one mole of phenol in order to give the corresponding ion. The second step is the reaction between this intermediate ion and the second mole of phenol to produce BPA. In this review, the steps of the reaction mechanism are shown in 5 steps as following (Fig. 2).

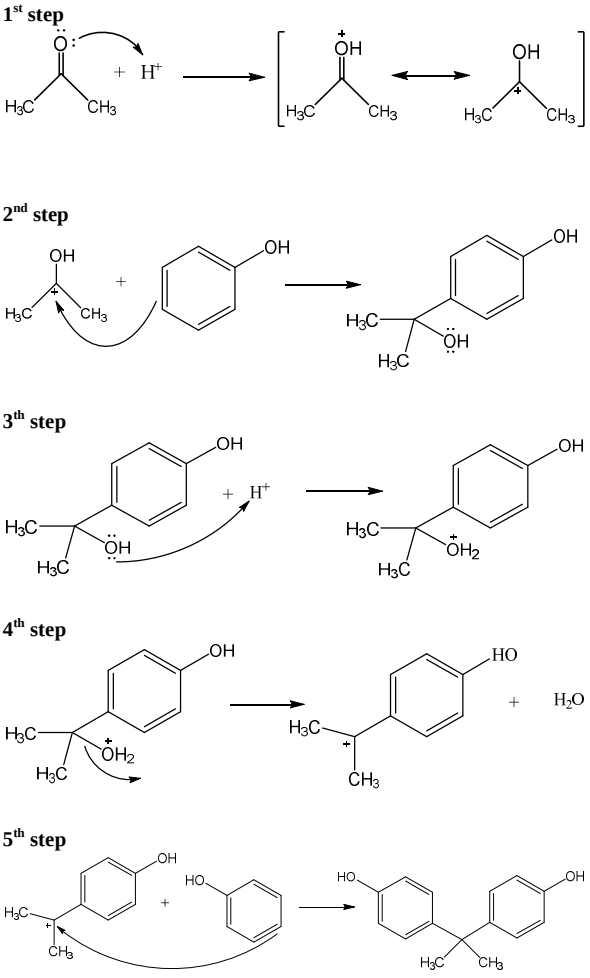

Figure 2. **Reaction mechanism of BPA**

In the first step, the reaction begins with the attack of nucleophilic acetone to hydrogen in the acid catalyst. The second step continues with the reaction between this intermediate carbocation and a phenol molecule. The third step is very similar to the first one in terms of an acid-catalyzed reaction of a nucleophilic hydroxyl group to give the protonated hydroxyl group. The fourth step corresponds to the formation of new carbocation by the elimination of one mole of water from the skeleton. In the final step, the intermediate carbocation reacts to the second mole of phenol by the nucleophilic reaction to get the formation of BPA as target compound.

If the reactant is acetophenone instead of acetone, this compound is called bisphenol AP [3] (Fig. 1). BPs are substances used to harden plastics and increase their durability and they can contaminate from the plastic container to food in it due to the ambient temperature [4]. BPs have various members such as bisphenol B (BPB), bisphenol E, bisphenol F (BPF), bisphenol AP (BPAP), bisphenol BF (BPBP), bisphenol AF (BPAF) (Fig. 1c-g), bisphenol S (BPS), tetrabromobisphenol A (TBBPA), bisphenol Z (BPZ), and 9,9-bis(4-hydroxyphenyl)-fluorene (BHPF) (Fig. 3a-d) but their most recognized member is BPA [5-7].

BPA [2,2-bis(4-hydroxyphenyl) propane] is a synthetic additive and monomer used in the manufacture of various polymers, polycarbonates and epoxy resins [8-11]. Although the synthesis of BPA was first made by Alexander P. Dianin in 1891, the first scientific report on the synthesis was prepared by Thomas Zincke [12, 13]. Reaction of 2 moles hydroxyphenyl and 1 mol acetone [2, 14] valid for the synthesis of BPA is seen in Fig. 1a.

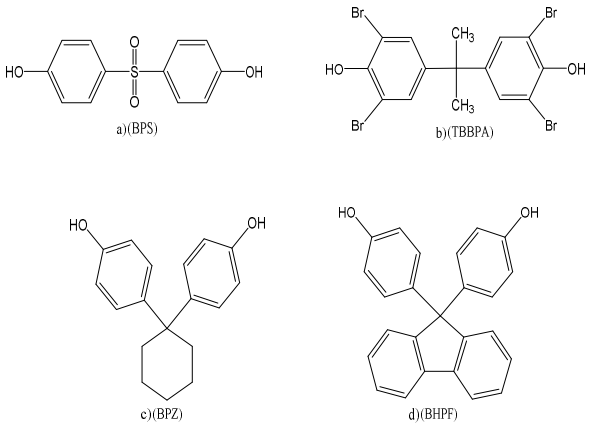

Figure 3. **Some analogues of BPA**

BPA is a very widely used plastic additive substance and monomer in the world because it is resistant to heat and breakage and provides transparency [15]. Plastic products

are an indispensable part of our lives due to their advantages such as long-term storage, ability to heat food and usable and easy for food consumption. Plastic plates, glasses, forks and spoons, which are preferred in the form of disposable, provide quite functionality at workplaces or various celebrations. Plastic containers used for food preparation and storage or heating in the microwave are also very preferred products in our homes [16, 17]. However, foods that are kept in these plastics or heated for a short time in a microwave create a great danger to people and expose them to BPA in the daily diet. While the United States Environmental Protection Agency (USEPA) evaluated the reference dose as 50 µg/kg/day for BPA [16], European Food Safety Authority (EFSA) recommended its indefinite tolerable reference dose (RfD) as 4 µg/kg/day [9, 15, 18-21]. Since BPA is a synthetic hormone mimetic and causes various diseases such as diabetes, heart problems and cancer. Scientists have so far prepared various reports for the sensitive and selective determination methods of BPA in complex samples (human blood serum, urine, breast milk, etc.) [7, 22, 23].

The Uses of Bisphenol A

With the progress in the plastics industry, BPA has become a widely used substance in daily life. Outdoor lighting armatures, PVC plastic windows, baby bottle, microwave ovenware, food packages, storage containers, detergents, DVD, CD, thermal papers, toys, glasses, eye lenses, medical equipment, tickets, water demijohn, water bottle, water pipes, sports equipment, work safety helmets, dental filling materials, automotive parts, canned food and milk cans contain BPA due to the use of BPA monomer especially in the production of epoxy and polycarbonate resins [8, 16, 17, 24].

The function of BPA in polycarbonate plastics is to add hardness and transparency to the products. It also gives properties such as strength and heat resistance [25]. In addition, due to the high refractive index of polycarbonate plastics, it refracts light more than glass and is used as an alternative to it [26]. Owing to these properties, these plastics are used in a wide range such as bullet proof glasses, eyeglass, medical devices, automotive parts, greenhouses, digital floppy disks, police shields, cd and outdoor lighting fixtures. Besides, due to their heat resistance, they are used in kettle, coffee machine, hair dryer and flame retardants [8].

Epoxy resins containing BPA are used on surfaces that require high chemical and mechanical resistance. They have high chemical resistance against solvents, acids and bases. They are also preferred in surface coating processes because of their non-slip and smoothness structures as well as their easy non-wear properties. For example; they are used for lining the inner surface of industrial food and beverage containers and thermal papers [27].

Ways of Exposure to BPA and Its Effects on Health

Very common use of BPA increases human contact with BPA in daily life. As a result of the interaction between the foodstuff and the packaging, BPA passes to the foodstuffs [4, 28]. This means that people are exposed to BPA through the digestive system. In addition, baby food stored and sold in epoxy-coated boxes, fluids given in plastic bottles and baby food prepared in polycarbonate bottles expose babies to BPA. The level of this exposure depends on the contact surface of the food and package, the duration of contact, the temperature, the pH of the food, and several factors such as physical and chemical properties of the package [10,

29, 30]. Furthermore, as a result of the blows received by canned and beverage cans, the transition of BPA to food increases. Especially, low but measurable amount of BPA can be detected in most of the beverages and cans. BPA also passes to people through skin and respiration, besides food and beverages in contact with plastic. For example, BPA is transmitted to the body via skin by contact with thermal papers and cash register receipts [15].

Although the plastic industry claims that the BPA levels found in plastic containers and cans do not harm human health, scientific studies have shown that BPA exposure can cause some health problems. Since BPA has effects like estrogen hormone, it causes considerable damage to individuals' hormone system. For example, it has been foreseen that it may cause a decrease in sperm count in men [6]. It is also believed that it affects men body development and behaviors, while it increases the risk of menstrual irregularity and breast cancer in women and affects brain and intelligence development in infants. In addition to metabolic disorders such as obesity, hypertension and diabetes, BPA invites many diseases such as heart problem, cancer, asthma, chronic fatigue, liver enzyme disorders, neurological disorders and preterm birth [9, 21, 27, 31].

BPA harms not only human beings but also the environment, plants and animals. Plastic and plastic-containing products that we throw into the environment instead of recycling cause pollution in soil, stream, lake and sea. BPA, which is transported to the soil through plastic wastes, prevents the nitrogen fixation in the roots of the plants and causes a decrease in the reproduction of animals. For example, scientists think that reduction in reproduction of many aquatic creatures, especially fish is due to BPA pollution from plastic wastes in the sea [32, 33].

BPA Determination Methods

Studies on whether BPA has harmful effects on humans and animals have revealed that its determination in foods, environmental samples and human body fluids is important [15]. But the trace level of BPA in various complex samples is determined by using sensitive analytical method. For this purpose, scientists recovered BPA from samples by using various extraction techniques and worked on BPA determination with many different methods. They are various chromatographic methods such as gas chromatography-mass spectrometry GC-MS [34], high performance liquid chromatography-UV/Vis detector (HPLC-UV) [35, 36], liquid chromatography-tandem mass spectrometry (LC-MS/MS) [5, 37] and ultra high pressure liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) [38, 39], electrochemical methods such as amperometry [40, 41] and voltammetry [42, 43], and spectrometric methods such as fluorescence (FL) [44, 45] and chemiluminescence (CL) [46] detection. Among these methods, the most widely used is GC or LC. To analyze BPA in complex samples such as food and body fluids, using MS-based ones as detectors in GC or LC devices shows more accurate results than the others. Detectors such as MS, MS/MS as well as UV, ECD (electrochemical) and FL are also used for BPA determinations with LC device [47]. However, interference effects that may occur in the analysis of complex samples made with non-mass-based detectors such as UV, ECD and FL may cause erroneous results. In addition, simultaneous detection of free BPA and conjugated BPA in the sample separately with the LC-MS method is possible due to the mass-based determination. Battal *et al.*, [48] analyzed BPA in BPA spiked urine samples by LC-MS / MS method and determined both conjugated and free BPA with good separation at retention time of 3.67

and 6.33, respectively. In the mentioned study, LOD and LOQ value for conjugated BPA was 0.10 and 0.33 ng.mL^{-1}, respectively, while these values sequentially were determined as 0.03 and 0.08 ng.mL^{-1} for free BPA. Although LC-MS/MS gives more detailed information about BPA ions, LC-MS/MS and LC-MS showed similar results in terms of sensitivity in literature studies. Sajiki *et al.,* in the BPA analysis performed by LC-MS in blood and water samples, found LOD and LOQ value as 0.1 ng.mL^{-1} and 0.3 ng.mL^{-1}, respectively [49]. In addition, Rocha *et al.* in the BPA analysis performed by LC-MS/MS in urine samples, found LOD and LOQ value as 0.1 ng.mL^{-1} and 0.4 ng.mL^{-1}, respectively (Table 1) [50]. After reviewing the results of both studies, it was noticed that LOD values of LC-MS and LC-MS/MS methods are the same. LC-FL is a commonly used LC method. Due to the relatively weak chromophore group of BPA, FL detector gives more sensitive results than UV detector, that's why UV detectors are less preferred. In the BPA analysis with a HPLC device equipped with a UV detector which was performed by Dang *et al.,* [51], the LOD value was found as 0.6 µg.mL^{-1} and they applied this method to the BPA analysis in the receipt and carbon paper samples. Sun *et al.,* [52] used a HPLC device with FL detector for the determination of BPA in breast milk and found the LOD value as 0.11 ng.mL^{-1}. According to these results, HPLC-FL reveals more sensitive results than HPLC-UV. Sajiki *et al.,* [49] found the LOD value as 0.11 ng.mL^{-1} in BPA analysis by the LC-ECD method. Although sensitive results can be obtained using electrochemical detectors, there is less application for BPA determination in complex samples by LC-ECD. Since the derivatization step required for the GC methods is not required in the LC methods, the LC methods are the most preferred methods in the determination of complex samples [47, 53].

Although GC-MS has a derivatization step, it is a highly preferred method for BPA determination, because it has high resolution and low detection limit compared to the LC-MS method [8]. In some studies for BPA analysis with the GC-MS method, N,O-bis (trimethylsilyl)trifluoroacetamide (BSTFA) [54-56], N, O-bis(trimethylsilyl)trifluoroa-cetamide (BSTFA) and trimethylchlorosilane (TMCS) [55, 57] and acetic anhydride (AA) [58] were used as derivatization agents.

In 2000's, enzyme linked immunosorbent assay (ELISA) method, which produces a rapid response for BPA determination, was developed and used commercially. In biological samples, commercial ELISA kits can be used for the determination of BPA, but the ELISA method is not suitable for the determination of free and conjugated BPA separately, because they may interfere with each other, so total BPA can be determined by ELISA method. This situation is one of the problems that may occur in the ELISA method. In addition, homologous structures of BPA have an interference effect in ELISA method. Therefore, a more accurate approach is to confirm ELISA results by GC-MS or LC-MS method. It is not also appropriate to determine low amounts of BPA since the detection limit of the ELISA method is higher than other methods [12, 59]. Furthermore, pre-treatment steps such as solvent extraction and solid phase extraction are required for the determination of BPA in complex samples. However, ELISA method can be used as a method with fast results for samples that do not require pre-treatment step, such as water samples [47]. Since LC and GC methods are very expensive and time-consuming despite their high accuracy and sensitivity, ELISA method is very useful for measuring total BPA in such samples [59].

As seen in Table 1, different samples such as canned food, baby food, breast milk, colostrum, blood and water samples have been studied in various literatures to determine BPA, and all methods have performed well in terms of sensitivity. However, some studies have used separation pretreatment steps such as solvent extraction and solid-phase extraction prior to analysis for complex or solid samples.

Table 1. **Analytical methods for the determination of BPA in various samples.**

Detection Methods	LOD	LOQ	Linear Detection Range	Sample Type	Extraction Technique	Ref.
UHPLC-MS/MS	0.2 ng.mL^{-1}	0.6 ng.mL^{-1}	0.6–40 ng.mL^{-1}	Urine	Dispersive liquid–liquid microextraction	[38]
FL	1.0x10^{-6} mol.L^{-1}	-	6.0x10^{-6}–1x10^{-3} mol.L^{-1}	BPA solution in water	-	[44]
FL	7.0x10^{-8} mol.L^{-1}	-	7.90x10^{-8}-1.66x10^{-5} mol.L^{-1}	BPA solution in water	-	[45]
CL	0.08 μM	-	0.3–80 μM	Baby bottle, beverage bottle, polycarbonate container and mineral water bottle	Reflux	[46]
ELISA	0.05 ng.mL^{-1}	0.17 ng.mL^{-1}		Water and plasma	Without any sample treatment	[49]
LC-MS	0.10 ng.mL^{-1}	0.30 ng.mL^{-1}		Water and plasma	Without any sample treatment	[49]
LC-ECD	0.11 ng.mL^{-1}	0.35 ng.mL^{-1}		Water and plasma	Without any sample treatment	[49]
LC-MS/MS	0.1 ng.mL^{-1}	0.4 ng.mL^{-1}	0.5–20 ng.mL^{-1}	Urine	Dispersive liquid-liquid microextraction	[50]
HPLC-UV	0.6 μg.mL^{-1}	2 μg.mL^{-1}	2–10 μg.mL^{-1}	Receipts and carbon paper	Extraction with methanol	[51]
HPLC-FL	0.11 ng.mL^{-1}	-	0.2–5 ng.mL^{-1}	Human breast milk	Liquid-liquid extraction and SPE	[52]
GC-MS/MS	0.32 μg.kg^{-1}	1.06 μg.kg^{-1}	0.5–500 μg.kg^{-1}	Cellulose, paper and board	Solvent and Folch extraction	[56]
HPLC-FL	3 ng.g^{-1} in ped foods and 2 ng.mL^{-1} in water	-	50–1000 ng.mL^{-1}	Canned cat and dog foods and empty cans	Extraction with acetonitrile and SPE	[68]
ELISA	0.3 ng.mL^{-1}	-	1.56–100 ng.mL^{-1}	Human colostrum	SPE	[69]
Amperometry	10 nM	-	1-400 μM	Water samples from baby bottles	Without any sample treatment	[70]
UV-Vis	20 nM	-	0.1–100 μM	Water samples from baby bottles	Extraction with water at 40 and 100 °C	[71]
GC-MS	0.13 μg.L^{-1}	0.43 μg.L^{-1}	1–50 μg.L^{-1}	Children's Urine	Micro-QuEChERS extraction	[72]
LC-MS/MS	0.0090 ng.mL^{-1}	0.028 ng.mL^{-1}	0.05–5 ng.mL^{-1}	Human blood serum	Liquid-liquid extraction	[73]
HPLC-DAD	0.003 μg·L^{-1}	0.01 μg·L^{-1}	0.01–15 μg·L^{-1}	Pond and sewage water samples	MIP micro SPE	[74]
Square wave voltammetry	0.03 μM	-	0.1–0.9 μM and 1–20 μM	River and drinking water samples	Without any sample treatment	[75]
Square wave voltammetry	0.015 μM/L^{-1}	0.051 μM/L^{-1} $^{-1}$	0.03–1.6 μM/L^{-1}	Water samples from baby bottle, baby bottle nipple, pacifier and disposable cup	Extraction with water at 70 °C	[76]
Differential pulse voltammetry	0.02 μM	-	0.1–2.5 μM and 2.5–50 μM	Mineral water bottle, polycarbonate bottle and baby bottle	Extraction with acetonitrile at 60 °C	[77]

Before analyzing BPA in complex solid or liquid samples such as food and body fluids, it may be necessary to apply a solvent extraction technique such as liquid-liquid or solid-liquid extraction to the sample [60, 61]. While solvent extraction is sometimes necessary for liquid samples, solvent extraction must be applied for solid samples [56, 62]. In some cases, the extraction may even need to be supplemented by the use of microwave. However, the extracts obtained from complex samples by the extraction contain other compounds as well as BPA. In this case, depending on the device on which the analysis will be performed, BPA in these extracts needs to be purified and concentrated with the help of a solid phase extraction cartridge. Silica gel activated charcoal and octadecyl (C18) and octyl-silica (C8) are the most used adsorbents in SPE cartridges [63, 64]. In addition, molecularly imprinted polymers (MIPs) synthesized with superior selectivity properties are used as adsorbents in SPE cartridges. MIPs are high selectivity polymers and synthesized specifically for any target molecule. In their synthesis, while the target analyte and a monomer/monomers are mixed in a solvent, a resistant and rigid polymer is obtained by adding a crosslinker to the complex that is formed during this reaction. When the target analyte is extracted from the resulting polymer, selective cavities remain in the polymer. These cavities are specific to the target analyte in terms of size and sharp and also have functional groups that can catch the target analyte. MISPE cartridges are obtained by filling these polymers into SPE cartridges as adsorbents. The target analyte in the extract which passed through the MISPE cartridge is bound to these selective cavities. So, MISPE allows to purify and concentrate the analyte [65-67]. Consequently, MISPE cartridges are very successful in capturing BPA selectively even from complex samples containing various compounds because of their selectivity. In addition, the interference effects of BPA analogs are very limited. Other advantage of these selector cartridges is being useful for determining the amount of BPA since this substance can't be determined by other technologies due to being below the detection limit in the sample. Moreover, MISPE cartridges can be used by washing over and over, as they are highly resistant to acids, solvents and various conditions.

Pros and Cons of Various Analytical Methods

The primary source of BPA transition to human body is industrial foods and beverages. Another source of transition is disposable plastic materials and various plastic containers used for food consumption and storage in daily life. On the other hand, thermal papers, CD, DVD, detergent and toys are other passage ways of BPA when people contact with them. In addition, people are exposed to BPA in the field of health. For example, fillings and various materials used in dental treatments and various medical sets such as blood and serum sets used in surgeries contain plastic materials. Furthermore, solid and liquid wastes of plastic factories also contain BPA and the release of these wastes to the environment causes soil and surface waters to be contaminated with BPA. Contaminated water and soil threaten the health of all beings in terms of BPA. For these reasons, many complex samples such as surface water, wastewater, foods, drinks, blood, urine, baby food and breast milk need to be examined for the amount of BPA. Sensitive and accurate BPA analysis of complex samples is very important and this is only possible using appropriate separation and analysis techniques.

In order to perform an accurate and sensitive BPA analysis in complex matrices, BPA in the sample must first be purified and

concentrated. Because the amount of BPA in the sample may be below the limit of determination, or compounds with a similar structure may interfere with the amount of BPA in analysis. Such problems can be overcome by extracting the BPA in the sample by solid-liquid and liquid-liquid extraction or solid phase extraction techniques (such as C18 and MIP cartridges). In this regard, MIP cartridges work well in selective extraction of BPA.

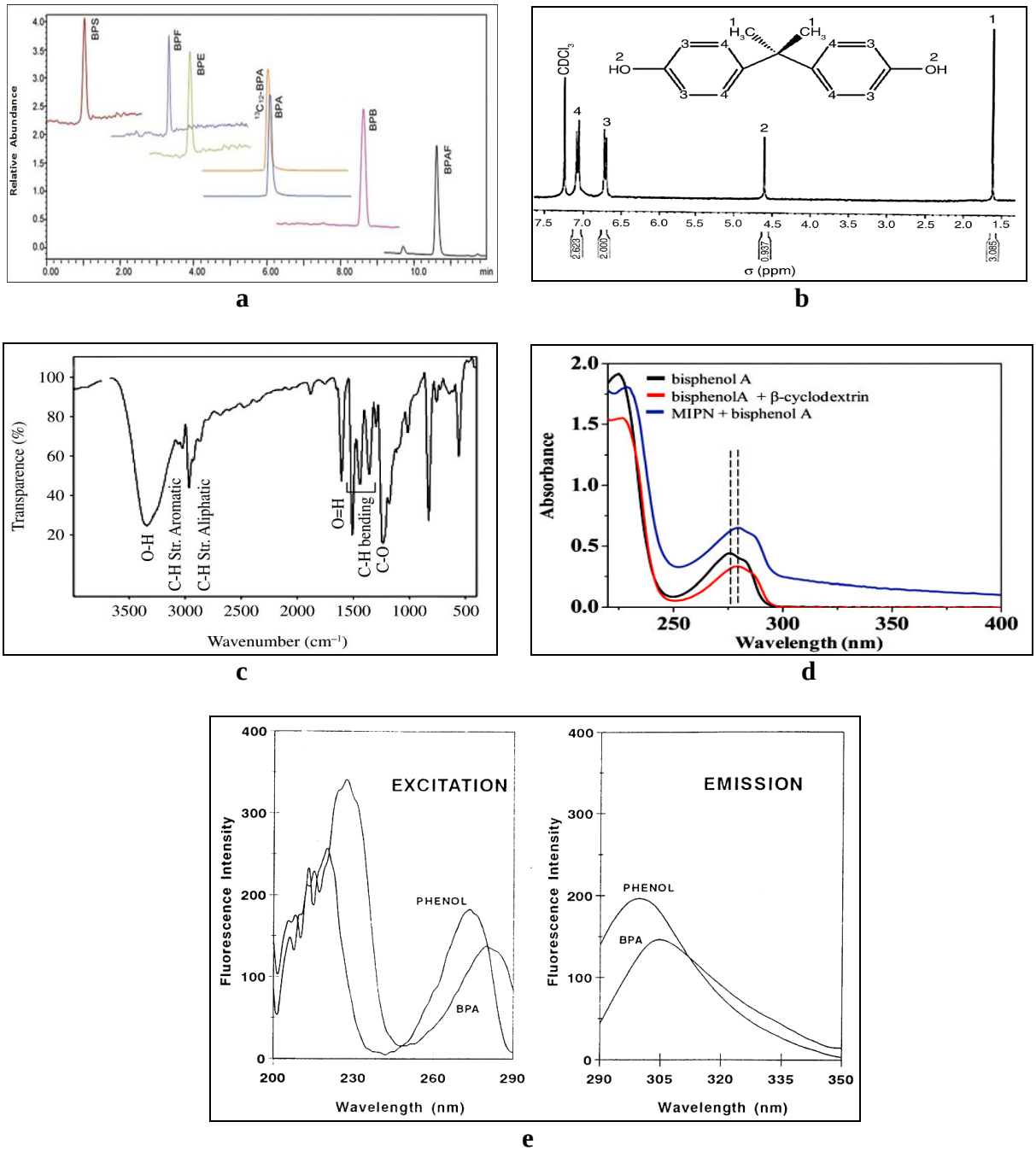

***Figure 4*a. LC-MS/MS Chromatogram [78], b. ^{1}H-NMR Spectrum [79], c. FTIR Spectrum [80] d) UV-Vis absorption spectrum [81] e. Excitation and emission spectrum of BPs [82]**

Method selection is also very important for analyzing purified and concentrated samples. Each method has some advantages and disadvantages. For example, although both electrochemical and chromatographic techniques give sensitive results in BPA determination, they have different pros and cons compared to each other. In spite of the fact that electrochemical techniques are low cost, there may be interference problems in measurements by this technique, in contrast chromatographic techniques are costly but they have the advantage of selective and accurate determinations, especially when combined with an MS detector. While UV-Vis and FL spectroscopy methods are suitable for the determination of BPA in non-complex samples such as water, but unsuitable for complex matrices (Fig. 4) A good pre-separation technique should be applied for determinations with these devices. Although the ELISA technique gives rapid results for the determination of the total BPA amount, it is insufficient for determining the free and bound BPA separately. For this reason, ELISA is a suitable method to use in preliminary research of the amount of BPA but its results must be checked with a second reliable method. Total amount of BPA can also be measured by UV-Vis, FL, amperometry and voltammetry methods and similar compounds may interfere to the measurement results because techniques at issue aren't based mass. For these reasons, results obtained with non-mass-based techniques must be supported by any MS-based chromatographic method.

Conclusion

The use of BPA in the production of various plastics and food packaging materials we use in our daily lives is quite common. For this reason, people are exposed to this substance even through the water they drink. Various studies show that this compound is associated with serious health problems such as infertility, heart disease, diabetes, cancer and hormonal disorders. BPA behaves like an estrogen or other hormones in the human body and prevents natural hormones from secreting and functioning therefore it can be named as a pseudo-hormone. As previously explained, complete avoidance of this substance is impossible so, to avoid such kind of health problems, we need to reduce our exposure to the substance at issue as much as possible. In order to protect from BPA and its damages, first, we should not use plastic products containing BPA, for example instead of plastic bottles or cardboard boxes, glass bottles should be preferred for drinks. In cases we must use plastic bottles, they should be used only once. Additionally, water in plastic bottles exposed to sunlight or heat should never be drunk. Using BPA-free bottles for babies will ensure that intelligence and brain development continue normally in infants. If we use plastic products, we should also avoid putting them in the microwave or freezer and deformative usage. But since BPA exposure pathways are not limited to these, appropriate methods are needed to determine the amount of BPA that can be found in different samples. For this purpose, various techniques such as chromatographic, spectrophotometric, fluorometric and electrochemical have been developed, among which, researchers have focused on chromatographic techniques. Although chromatographic techniques are high cost, they are preferred due to their accuracy and low detection limit. In BPA analysis, MS-based methods give the best results even for complex samples in terms of accuracy, sensitivity and selectivity. Therefore, chromatographic technique with MS detector is mostly used to determine BPA. Results from other non-MS-based methods need to be validated with MS-based methods for accuracy and precision. Due to the various interference effects, the ELISA method can be a more suitable approach for qualitative

purposes rather than quantitative analysis for complex samples. However, in general, it is necessary to apply pretreatment techniques such as extraction, purification and concentration prior to analysis for the determination of BPA which is present in traces or complex samples.

Unfortunately, recently despite the constant proof of this by the publications that this substance causes hormone problems, there is no restriction on the use of the substance at issue. However due to increased publications about obesity and other diseases, we think that there will be limitations on the use of substance in question or that another substance will replace it.

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