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DETERMINATION OF BISPHENOLS AND PHTHALATES (ENDOCRINE DISRUPTING CHEMICALS) BY USING ADVANCED ANALYTICAL TECHNIQUES, PHOTOCATALYTIC METHODS, ELECTROCHEMICAL METHODS AND BY FLUORESCENCE POLARIZATION IMMUNO ASSAY

Potla Aparna[1], Dr. Kuna Mangamma*

[1]Student, Department of Pharmaceutical Analysis and Quality Assurance, School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, East Godavari, 533004, India.

*M.Pharmacy(Ph.D), Assistant Professor, Department of Pharmaceutical Analysis and Quality Assurance, School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, East Godavari, 533004, India.

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***Corresponding Author**
Dr. Kuna Mangamma
M.Pharmacy(Ph.D), Assistant Professor, Department of Pharmaceutical Analysis and Quality Assurance, School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, East Godavari, 533004, India.

ABSTRACT

Bisphenols and phthalates are endocrine disrupting chemicals which are found in food containers and plastic beverages. The aim of this review article is while taking into account of bisphenols and phthalates present in water samples, food containers, canned foods, beverages, plastics determined by using various techniques like analytical, catalytical, electrochemical and Immuno assay methodologies. while using liquid chromatography (LC), gas chromatography-mass spectrometry (LC-MS), capillary electrophoresis (CE), gas chromatography-mass spectrometry (GC-MS), enzyme linked immunosorbent assay (ELISA) and solid phase micro extraction, the major drawback of these methods were requires complicated pretreatment process, expensive instrumentation and poor detection. The methods which are used should detect the compounds at low levels. In this review, an overview of the most significant methodologies were considered.

KEYWORDS: Bisphenols, phthalates, endocrine disruptor, analytical, catalytic, elctrochemical, Fluorescence polarization immuno assay, food packaging materials.

INTRODUCTION

Pharmaceutical pollutants are generally considered as chemical contaminants, which were migrated from many sources, they may be organic or inorganic. contamination of chemical substances with food is a global issue. which pose a major risk to both humans as well as animals. The main source of these pollutants are industries, factories, agriculture and transport. These pollutants mainly affect the environment like food, air, water and soil. There is a major risk of these pollutants which reaches humans through inhalation, contact, ingestion, which adversely affect the humans health. Now a days getting pure food without any contamination has become imaginable.

These pharmaceutical pollutants belongs to many groups including metals/metalloids, dimethyl phthalate (DMP), bisphenols (A,B,F,S), polycyclic aromatic hydrocarbons (PAHs), persistent organic pollutants, perfluorinated compounds pharmaceutical and personal care products (PPCPs), electronic waste, plastics, nanoparticles, radioactive elements, food packaging materials, mercury, dioxins, alkylphenols, triclosan, alkylphenol, ethoxylates, parabens, pesticides etc,. These chemical contaminants are called endocrine disruptor chemicals (EDCs). EDCs are defined as a group of molecules identified as endocrine disruptors is highly heterogeneous and includes synthetic chemicals used as industrial solvents /lubricants and their products. Some EDCs, which may cause endocrine disorders in animals and humans.

This review article is restricted to pharmaceutical pollutants present in food samples and water and their methodologies (Bisphenols and phthalates); it does not address any biological or physical hazards of chemical contaminants. Food packaging methods may be a source of contamination. In this particular scenario we need to discuss ‘migrants’- these are substances which are transferred or leached from food packaging materials to food stuff.

The transfer of chemicals from food packing materials to food is called migration. For the plastic materials two types of migration limits are established to avoid contamination of chemical substances with the food and to ensure protection to the consumer's health. The 2 types of migration limits are Overall migration limits (OML) and Specific migration limits (SML). An overall migration limit of 60 mg of substance per kg of food stuff: which is applied to all chemicals which are transferred from the food contact materials to food stuff. A specific migration limit (SML) which applies to individual authorized substances and is fixed on the basis of Toxicological evaluation of the substance / chemicals.

Whenever the consumer intake such type of food products, there is more chance of exposure of chemical contaminants which are migrated from food packaging materials. The level of exposure depends upon the route of administration, route of exposure, the consumer's personal characteristics like age and health condition. Chance of exposure of these chemical contaminants is more incase of prenatal neonates and nursing neonates. For example if the mother consumed intentionally any kind of chemical pollutants, that are secreted in breast milk, which shows toxic effects on the nursing neonates.

In the food industry packing materials are used to protect food stuff from physical, chemical and microbiological during its distribution and storage and handling. There should be no food contact materials that are inert. In case any contamination with food may lead to release of hazardous chemical packing components which may severely affect the consumers. The reaction occurs like permeation, Sorption, corrosion etc,. The major food packaging material contaminants are Bisphenols and Phthalates, which are harmful chemical contaminants which show severe effects on the endocrine system, immune system, reproductive system, and cardiovascular system. In this review we are discussed briefly about the bisphenols and phthalates and their analytical methodologies, catalytic methods, electro chemical methods and fluorescence polarization immuno assay.

Bisphenols

Bisphenol A (BPA) belongs to a family called bisphenol. It is industrially produced and also known as endocrine disruptor. It is mainly used as components of epoxy resins and polycarbonate plastics. Bisphenols are also considered as endocrine disruptor chemicals (EDC), which alters the functioning of endocrine system. In the environment there are many number of Endocrine disruptor chemicals which affects the food products and also causes hazardous risk to human health. In case of addition of these chemicals with food products there is a chance to show effects like additivity and synergism.

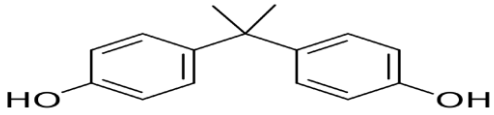
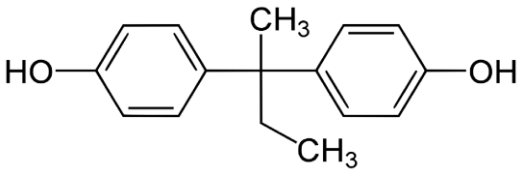
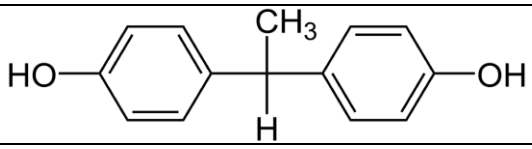
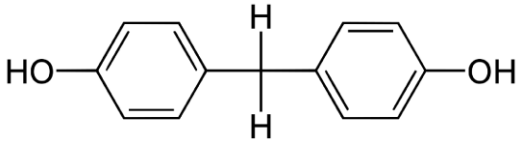
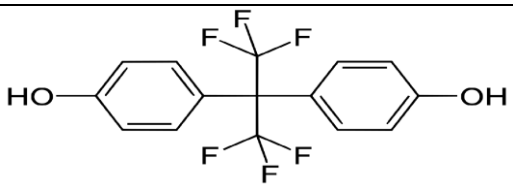
This BPA based plastics used in the fields of food contact material manufacturing such as crockery, thermic paper, and packaging. Through diet there is a chance of human exposure (food and food contact materials). BPA shows hazardous effects in humans like immune, reproductive, developmental, cardiovascular effects. BPA is considered to be on the list of European chemical agencies (ECHA) in 2017. Further use of BPA in food contact materials is restricted in recent regulations. The current Tolerable daily intake (TDI) levels for

bisphenol A is 4 µg kg^{-1} body weight per day, which is given by European food safety authority (EFSA).

Bisphenol A (2,2-bis (4-hydroxy phenol) propane; BPA. It was synthesized in 1891, but it was not used extensively at that time. The production of BPA increased in the 1950's and it has gradually increased by 3.8 million tons year from the year of 2016. Most of BPA is used in food contacting materials such as returnable beverage bottles, infant feeding bottles, storage containers, tableware (plates and mugs) and in manufacturing of epoxy resins which are used in surface coating for food and beverage cans and vats.

Bisphenol B (2,2-bis(4-hydroxy phenol) butane; BPB) It is a phenolic resin and also considered as food contaminant and potential migrant. It is an analogue of BPA. The analogies have the similar chemical structure binding ability for estrogen receptor (ER), which shows toxicological effects in animals. For metabolic activation, it requires both cytosolic and microsomal fractions, this observed in not only rat liver, but also mouse, monkey and human. The other bisphenols which replace BPA are Bisphenol F (BPF), Bisphenol S (BPS) and Bisphenol AF (BPAF).

Table 1: Some of bisphenols with structural similarities.

Name	Structural Formula
Bisphenol A	
Bisphenol B	
Bisphenol E	
Bisphenol F	
Bisphenol AF	

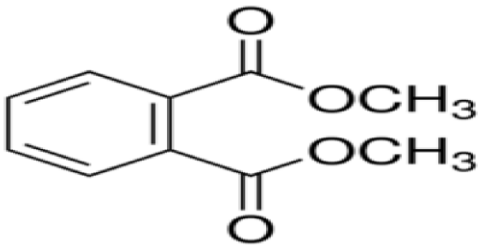
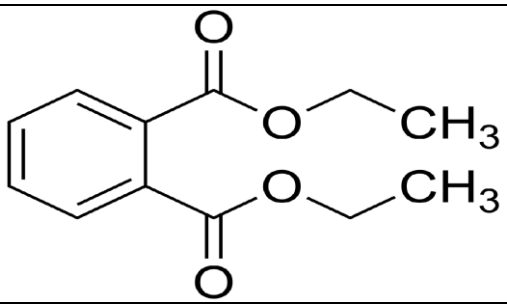
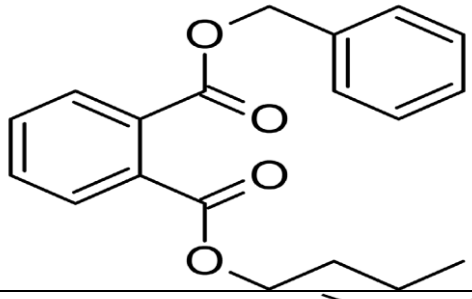
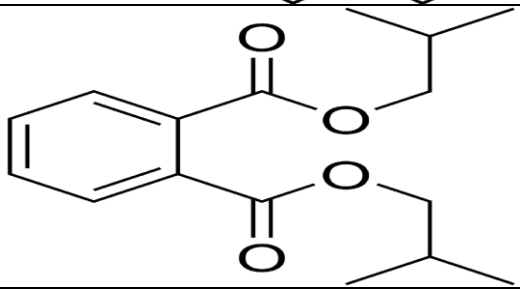
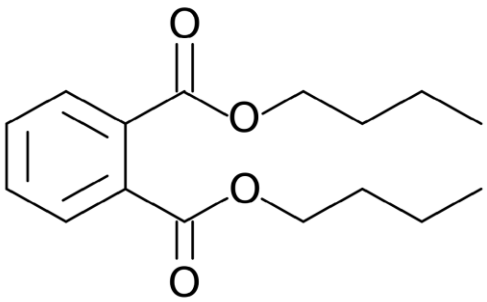
Phthalates

Phthalates or phthalate esters are esters of phthalic anhydride. Phthalates are mainly used as substance added to the plastics i.e., plasticizers. Phthalates are added to increase their flexibility, durability, longevity and transparency. They are used to soften the poly vinyl chloride (PVC).

In the United states, European union, Canada the low molecular weight phthalates are replaced by high molecular weight phthalates due to some health concerns. Low molecular weight phthalates derived from C3-C6 alcohols where as high molecular weight phthalates are derived from carbon skeleton having more than 6 carbons.

The majority of people are exposed to some level of phthalates due to its universality. For example-most of the americans are tested by the center for disease control and prevention have identified many number of metabolites in their urine. Some studies have proved that high doses of phthalates have been shown to cause birth defects and hormonal imbalance. Phthalates are used in packaging materials of food stuff (food containers, wrappers), personal care items containing phthalates include hair spray, nail polish, liquid soap, hair spray, floor tiles, adhesives etc.

As we already discussed above, any substance which interferes with the hormonal mechanisms is said to be an endocrine disruptor, in the scientific field, Phthalates are widely classified as endocrine disruptors. The usage of plastic is gradually increase from the last decades, this leads to increase in human exposure to toxic substances. Large exposure to phthalates will shown major effect on reproductive system, cardiovascular system.

Name	Structure
Di methyl phthalate	
Diethyl phthalate	
Butyl benzyl phthalate	
Di-iso-butyl phthalate	
Di-n-Butyl phthalate	

List of some pharmaceutical pollutants (endocrine disruptors) which contaminates food stuff.

S.No	Industrial Chemical	Human Exposure	Chemical Contaminant	Uses
1	Phthalates	Chocolate, cookies, snacks, milk, vegetables, wine, beer, butter, cheese, baby food, migration from food packaging	-Dimethyl phthalate -Diethyl phthalate -Di-n-butyl phthalate -butyl benzyl phthalate -butyl decyl phthalate	Production of plastics and resins
2	Phenols	Cereal, fish, meat, milk, canned food and honey, baby food, migration from packaging as coating in food cans, beverages	Bisphenol-A Bisphenol-B Bisphenol-F	Production of plastics, resins, disinfectants preservatives
3	Dioxins and furans	Vegetable oils, crustaceans, fat and liver of hens, eggs/ fish, meat, butter	Polychlorinated benzo-p-dioxins Furans (Fs)	Paper and pulp productions, chlorophenols and herbicides forming during combustion
4	Poly chlorinated biphenyls	Mussel, crustaceans, fish, vegetables, meat, hens and pork fat, milk cheese, butter, margarine This substance is stored in animal fat	PCB'S	Wisely used in industries (in hydraulic system, electrical systems, glue, coats, plastics, paints
5	Poly brominated diphenyl ethers (PBDEs)	This substance is stored in animal fat, Exposure indirectly through food by emission through the waste stage	PBDEs	Used in textiles, plastics, Building material, electronic equipment

Bioaccumulation of endocrine disruptor chemicals in marine ecosystem leads to shows impact on both human and marine life. In the last decades the evaluation of endocrine disrupting compounds has been widely increased because of over usage in industries and household applications. The fact is that these pollutants enters into the environment through waters and it is the most affected compartment. Determination of this pollutants present in aqueous samples is done by using several analytical methodologies.

From the last few decades for the analysis of such endocrine disrupting chemicals are examined by using liquid chromatography (LC), gas chromatography-mass spectrometry (LC-MS), capillary electrophoresis (CE), gas chromatography-mass spectrometry (GC-MS),

enzyme linked immunosorbent assay (ELISA) and solid phase micro extraction. But drawback of these methods were requires complicated pretreatment process, expensive instrumentation and poor detection. The methods which are used should detect the compounds at low levels. In this review, an overview of the most significant methodologies were considered.

Detection of bisphenols by using advanced analytical techniques

1. Hollow fiber liquid-phase microextraction-Gas chromatography-mass spectrometry

Metabolites of Bisphenols and phthalates are the compounds which are suspected to produce endocrine system dysfunction in humans and animals. Evaluation of these compounds present in food, water, air samples is done by using several techniques to estimate the human exposure. Different miniaturized extraction techniques have been used in recent years.

The analysis of bisphenols and phthalates present in urine requires prior conjugate metabolite hydrolysis and sample preparation. Hydrolysis is done by using some specific enzymes like β-glucuronidase and α-glucuronidase. Koch et al. And Holm et al. reported that incubation of the sample at 37°C temperature for 90 min is sufficient for complete hydrolysis. Hydrolysis is stopped by adding some acids e.g., phosphoric acid and acetic acid. After hydrolysis the analytes are extracted by using many analytical methodologies. In recent trends Hollow fiber liquid-phase microextraction (HF-LPME) blew up in the extraction of bisphenols and phthalates. HF-LPME consists of a hollow, porous and hydrophobic fibers that are impregnated with organic solvents (acceptor phase). The fiber is placed with in the sample which acts as Donor phase. For the migration of analytes from the matrix to acceptor phase continues stirring is required. After extraction of those analytes from the sample, the analysis is performed liquid chromatography.

Whereas Determining analytes with gas chromatography requires a derivatization step, which consumes more time. In Order to fast up the derivatization step N,O-bis (trimethylsilyl) trifluoroacetamide (BSTFA), containing 1% trimethyl chlorosilane (TMCS) was used to determine the Bisphenols and mono esters, in accordance with the Basheer et.al,.

HF-LPME proved to be an efficient method to extract BPA and phthalates metabolites present in urine by means of GC-MS. This method acts as an alternative method for biomarker analysis.

2. Determination of phthalate plasticizers in palm oil using online solid phase extraction - liquid chromatography (SPE-LC)

The phthalates have high affinity with oily environment and analyzing these chemicals in food matrices is difficult because of the trace amount of the analyte and interference from the matrix. The phthalate plasticizers present in palm oil is well determined by using solid phase extraction (SPE) technique using a large volume (3.5 mL) injection was developed for the analysis. A sample preparation involving methanol: Acetonitrile (1:1) as the extraction solvent and alumina as the fat retainer was performed prior to usage of the online SPE-LC system. This system consist of the two columns, C_{16} for the solid phase extraction and C_{18} as the analytical column and photodiode array detector. A screening on few samples in the retail market revealed the presence of dibutyl phthalate (DBP) and butyl benzyl phthalate (BBP) in the palm oil. The advantage of Online SPE is the SPE column can be washed and reused, and the high pressure pump also plays a key role. Moreover a cycle of SPE column enrichment, impurity removal and column equilibrium can be achieved consistently.

3. Determination of variety of endocrine disrupting compounds present in environmental samples by liquid chromatography coupled with mass spectrometry

The combination of chromatography and MS can separate the mixture into its individual components and subsequently analyse each compound in the mixture both qualitatively and quantitatively. The analysers used is triple quadrupole (QqQ MS), time of flight (TOF-MS) or linear ion trap (LIT-MS) is required to improve the sensitivity and identification of the target analytes. These compounds present in beverages and canned foods were first concentrated using a Solid phase micro extraction (SPME). Other than SPME liquid phase micro extraction, dispersive liquid-liquid micro extraction has also been used.

Wang and schnute reported an ultra high performance liquid chromatography /tandem mass spectrometry (UPLC/MS) is used for the simultaneous quantification of nonyl phenols (NP) and BPA. All targeted analytes are chromatographically separated with in 3 minutes.

A rapid liquid chromatography-tandem mass spectrometry (LC-MS) method was developed for the simultaneous estimation of bisphenol A ether derivatives. This method was applied to the determination of these compounds in canned soft drinks and canned foods. OASIS HLB solid phase extraction (SPE) cartridges were used for the analysis of soft drinks where as solid canned foods were extracted with ethyl acetate.

Thus mass spectrometric techniques is one of valuable detection technique because it provides the information of the molecular structure of the compounds and because it is highly sensitive and selective.

Photo catalytic method

1. By using Fe_3O_4/BiOI/BioBr photocatalyst

The environment and human health is severely affected by the chemical contaminants. To detect these chemicals many methods have been developed, like biological methods, electrochemical methods, ozone oxidation, membrane separation technology etc. Among all these methods photocatalytic technology considered as best method. It is an environmental pollutant treatment method having many advantages like energy saving, simple process, no secondary pollution, high mineralization efficiency. Last few years, number of photocatalysts studies have been done and some of them are successfully industrialized. In Order to degrading the chemical pollutants present in wastewater, there is a necessity to develop new highly efficient and easily separated visible-light-responsive photocatalysts. Most of the semiconductors like TiO_2, ZnO, Cds, ZnS, etc having low photolytic activities, poor utilization of visible light, low separation rate of photogenerated electronic-hole pairs, shows difficulty in separation of pollutants from water body.

Inorder to diminish these problems many methods have been developed. The problems arisen with the single semiconductors is devoid by the construction of heterojunction photocatalysts. Example of heterojunction photocatalysts are $BiVO_4/TiO_2$, ZnS/cdS, BiOI/BioBr, $BiVO_4/Bi_2Ti_2O_7$etc. The best magnetic material is Fe_3O_4 having the properties like excellent magnetic properties (58.0 emu g^{-1}), high theoretical capacity (924 mA h g^{-1}), high electrical conductivity (2×10^4 S m^{-1}) and low cost. Fe_3O_4 can acts as an electron transporter to inhibit recombination of photo generated electron-hole pairs based on above advantages.

The combination of photocatalysts with Fe_3O_4 results in enhancement of specific surface area can increase the active site of the catalyst, the existence of Fe-OH can increase the adsorptive capacity of photocatalysts, excellent magnetic character will facilitate the recycling of the photocatalysts.

The hetero injector BiOI/BioBr is combined with Fe_3O_4 has the capacity to treat organic waste water under visible light. Gao et al. have prepared Fe_3O_4/BiOI/BioBr in 0.5:2:2 ratios respectively. This nanocomposite material is synthesized by precipitation method. This

method own its high crystallinity, uniform particle size, distribution and high yield, solvothermal approach attract to this method more and more. The samples are characterized by scanning electron microscope (SEM), X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD), Brunauer-Emmett-Teller (BET), UV-Vis diffuse reflectance spectroscopy (UV-vis DRS) and Photoluminescence analysis (PL).

The preparation method of photo catalytic material is as follows

Bismuth (III) nitrate pentahydrate (2mmol) and Fe_3O_4 (2mmol) is in 100 ml of water, weigh accurately 5 ml of acetic acid and add to it with simple magnetic agitation for 30 min. followed by add aqueous solution of NaBr add 0.3 gram of sodium acetate of potassium iodide, continue the magnetic stirring for 2 hr. The solid matter is washed with deionized water and ethanol for 5 times, which are dried by using 60 DEG C of vacuum for 12hrs.

This material is used for degrade the interaction of interferent-tetrabromobisphenol A solution, it is a halogenated derivative of Bisphenol A. The present invention uses coprecipitation first by BiOI/BioBr and Fe_3O_4 is combined to obtain a kind of visible light responded magnetic photocatalyst.

Electrochemical method

1. By diamond-based electrochemical aptasensor realizing a femtomolar

For the detection of Bisphenol A, electrochemical methods are most attractive alternative methods due to advantages of small amount of reagent required, wide dynamic range, good sensitivity and selectivity, simplicity and low cost. Glassy carbon, Au, Graphene are used as electrode materials, which were utilized and chemically modified to enhance the detection limitations. However, due to the relatively weak electroactivity of BPA and the deposition of oxidation product on the electrode surface, decrease of sensing efficacy and poor repeatability were widely reported. To decrease the the limit of detection of BPA, conductive boron-doped diamond (BDD) has been proposed. The BDD have unique characteristics such as electrostatic capacity, very low background current, wide potential widow in aqueous solutions, chemical inertness, high current density, excellent electrochemical stability, high resistance to fouling etc.

BPA can be examined at low levels (2.1×10^{-7} mol L^{-1}) by using hydrogen terminated BDD electrode, which showing high relatively low sensitivity was reported. When it is modified with tyrosinase, which has specific interaction with BPA, the detection limit of BDD-based

electrode was increased to 1×10^{-11} mol L^{-1}. It is essential to develop a sensor with good stability, high specificity and good repeatability.

The preparation method of Au-NPs/BDD electrode

The poly crystalline BDD films were deposited on p-type silicon (100) substrates by microwave plasma chemical vapor deposition (CVD) system. The BDD film was coated with thin Au11 layer (20nm thickness) by sputtering method is done in order to fabricating Au-NPs/BDD structure. After that by using a de-wetting process the Au-NPs on BDD substrate were fabricated. Where oxidation in air at 800°C for 1 min was performed.

The preparation of MAABD electrode

Aptamers are short single-stranded oligonucleotides that can be bonded to a wide range of targets with high affinity. The 63 mer single-strand synthetic aptamer with thiol-modification was grafted on the Au-NPs/BDD substrate through the Au-S bonds and was incubated at 37°C overnight. By using Tris-HCl buffer, the sensor was washed and stored in refrigerator at 4°C. On the AA/BDD surface without aptamers, the mercaptoethanol molecules was absorbed. 100 µL of 1 mmol L^{-1}MCH was immobilized onto the Aptamers/Au-NPs/BDD (AA/BDD) electrode for 60 min at room temperature. Then rinsing of electrode is done by using ultrapure water and 100 mmol L^{-1}Tris-HCl to remove the unhybridized MCH to fabricate the MCH/Aptamers/Au-NPS/BDD (MAABD) electrode. Now it shows specific absorption of BPA for detection.

By using electrochemical impedance spectroscopy (EIS), electrochemical measurements were recorded. Characterization of BDD was done by using X-ray diffraction (XRD) (crystal structure), Raman spectroscopy (vibrational character) and SEM (surface morphology).

Detecting BPA trace in milk by MAABD aptasensor

Detection of BPA in various food and life products was investigated with the help of MAABD aptasensor due to its high performance in practical applications. The detection of BPA in milk is done with and without adding BPA. Trace amounts of BPA (10^{-12} mol L^{-1}) were added to the filtrate milk output after the preparation steps, and the sensor was able to detect BPA with recoveries 92-108% with relative standard deviations less than 9.2%. Tris HCl buffer is added to milk with different concentrations. To avoid passivation of diamond-aptamer electrode, the raw mixed BPA/milk solutions were firstly treated following centrifugation and filtration process.

The constructed aptasensor exhibits good linearity from 1.0×10^{-14} to 1.0×10^{-9} mol L^{-1}. The detection limitation of 7.2×10^{-15} mol L^{-1} was achieved, which can be attributed to the synergistic effect of combining BDD with Au-NPs aptamers and MCH. BPA traces were examined in the Tris-HCl buffer and in milk revealed that this method has good stability, high sensitivity and selectivity.

Fluorescence polarization immunoassay

1.By A camelid VHH-based fluorescence polarization immunoassay

Tetrabromo bisphenol A, it is classified as endocrine disrupting chemical because its molecular structure is similar to that of thyroxine. which is a brominated flame retardants (BFR) having IUPAC name as (2,2-bis-(3,5-dibromo-4-hydroxyphenyl)-propane; TBBPA). which are used in different type of industries and many consumer products to prevent fire-related injuries and property damage.

TBBPA is generally examined by using techniques like chromatographic techniques such as HPLC-MS/MS, UPLC-MS/MS And GC-MS. Using these methods has been some drawbacks like expensive instrumentation, tedious, complicated clean-up procedures of the samples prior to analysis and time consuming. In recent years ELISA has been widely accepted for routine analysis. ELISA is a heterogeneous method, requires more time to complete the steps like washing, extensive pipetting and incubation period. Fluorescence polarization immunoassay (FPIA) is a homogeneous method (without separation) is an alternative best approach for ELISA. FPIA method meets the requirements of a simple, fast, reliable and cost effective method.

The materials and preparation method

FPIA is a competitive immunoassay method based on the principle changing the polarization of fluorescence (FP). whenever a small fluorescent – labeled hapten (tracer) is bound with specific antibody, the value of FP will increase. The tracer is compete with the antibody for binding incase of sample containing unlabeled analytes, at this time the FP will fall gradually.

In addition to traditional antibodies Camelid species, eg., camels and llamas are used to produce a unique class of IgG known as heavy chain IgG (HcIgG). To retain antigen binding ability, proteolytic, exhibits high chemical, thermal stability a variable domain of heavy chain domain antibody (VHH) isrequired. VHH is an ideal biorecognition.

For the analysis of TBBPA in water different water samples was collected such as from river and tap water, real water samples and are spiked to get final concentrations. without TBBPA in water samples used as negative control. Before subjecting these samples to FPIA, the samples are passed through a 0.45 µm syringe filter. The average recovery and coefficient of variation values of FPIA were in the range of 73-102% and 7-14%, respectively. This method provides specific, sensitive and convenient method for detection of TBBPA.

CONCLUSION

Many food produts which were packed in the plastic containers showed the presence of these two classes and in some cases both. Bisphenols and phthalates both are reported as endocrine disrupting chemicals to trace these chemical contaminants at low limit of detection there is a need to develop new analytical mehods having good sensitivity, selectivity and accuracy. The sensitive quatification of majority of bisphenols and phthales were achieved by using above metioned methods in less period of time when compared to other techniques.

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