Application of nanobiosensor in food-A comprehensive review

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Abstract

Nanotechnology plays a vital role in the development of biosensors. The sensitivity and performance of biosensors are better-quality by using nanomaterials through new signal transduction technologies. The food products which are spoiled exhibit odours, colours or other sensory characteristics which can be easily discerned by consumers. But when the foods are packed, the packaging material prevent sensory exposure from the foods and hence consumers must trust on expiry dates provided by producers based on a set of idealized assumptions about the way that the food is stored or transported. Nanosensors offer solutions to this problem through their unique chemical and electrooptical properties. Nanosensors can be used to determine microbes, pollutants contaminants etc. and ultimately the freshness of the food.This paper review the status of the various types nanobiosensors and their applications in food.

Keywords: Biosensor, E. coli, Staphylococcal enterotoxin, Salmonella, Mycotoxins, GMO.

Introduction

Nanotechnology is a novel branch of science that deals with the invention and alteration of materials to nanosize (10^{-9} m). Various nanomaterials have been discussed to analyze their properties and recent applications in biosensors (Chen Jianrong et al., 2004). The explore in biosensor technology shows a constant increase in relation to the various nanomaterials with the curiosity to be implemented either into transducers or receptors operation parts, so as to enhance their multi detection potential and sensitivity. These nanomaterials are quantum dots nanoparticles, nanotubes or other biological nanomaterials. Mainly biosensors can be an awesome alternative to the traditional methods for the detection of toxins and pathogens in food (Bogue, 2008)

The food quality is essentially based on biochemical composition of food. Biosensors have been designed for the measurement of different components in the food samples. Electrochemical, Optical, calorimetric, immunosensors to screen-printed three electrode systems are various types of biosensors. Monitoring of the quality is one of the most important concerns in the food industry. Particularly, there is a progressive want to develop analytical tools which could grant monitoring of the quality for the entire food processing function, by means of starting materials and final products (Rana et al. 2010).

In food analytical methods for pathogen detection must have the adaptability to identify different analytes, the specificity to differentiate between dissimilar bacteria, and the sensitivity to identify bacteria directly and on-line in real samples without pre-enrichment to meet users' viewpoint. To manufacture and design the tool should also be inexpensive and simple. The Biosensor technology is maintained to satisfy these necessities (Palchetti, Mascini 2008, Ozimek, Pospiech, Narine 2010).

Component of Biosensor

A biosensor is a diagnostic tool that converts a biological reaction into a detectable measurable signal. A number of stages must be realised in developing a biosensor (Fig. 1). *Transduction*, *signal generation* (increase of signal or reduction of noise); *fluidic design* (sample injection and drainage, concentration of sample, reduction of sample consumption, increase of analyte transport, reduction in detection time); *surface immobilization chemistry* (analyte capture efficiency, elimination of nonspecific binding); *detection format* (direct binding, sandwich type binding, competitive binding) and *data analysis* (extraction of information regarding analyte concentration, binding kinetics) (Fan et al .,2008).

The biosensor is made up of three components: the sensor material base has traditionally being made of metal, glass, polymer or even paper, onto which a bioreceptor is coupled. The bioreceptor (enzymes, antibodies, nucleic acid aptamers or single stranded DNA, cellular structures/cells, biomimetic and bacteriophage (phage) (Velusamy et al., 2010), is united in the sensor through a number of immobilizing techniques which can be physical or chemical. Chemical groups that are reactive can include functional groups such as carboxyl, –COOH; amine; –NH_2; and hydroxyl, –OH. As environmental factors can affect biological materials making them very sensitive, they can easily lose their activity when forced to interact with the solid surface. The method for surface attachment of the probe is the most significant step in fabrication of biosensors and requires a high level of control over the surface chemistry present.

The trend in biosensors to date include, enzyme, antibody or antigen based biosensors; gene based sensors and whole cell sensor. Enzyme-based biosensors dominate the market and are mostly based on electrochemical transduction systems with glucose

oxidase sensors dominating the market, the other focus are on chemical determinants (e.g., toxins, pesticides). However, many conjugated polymer based biosensors rely on indirect detection of the target analyte, usually a fluorescently labelled compound and this is especially true for biomolecular macromolecules such as proteins. Fluorescent sensors using boronic acid as a ligand, in a non-enzymatic approach for the detection of saccharides have found applications in microbial detection, as polysaccharides are a component of the bacterial cell membrane (Amin and Elfeky, 2013).

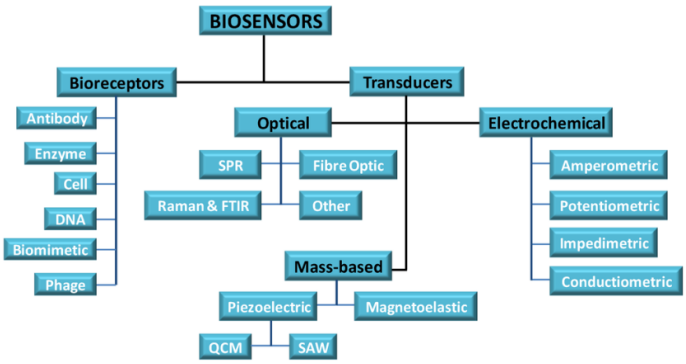

Fig. 1: Components of a biosensor

Microbial Biosensor

A microbial biosensor is a biosensor that uses microorganisms which consists of numerous enzymes as the bioelements (Figure 2). The enzymes in the living cells can produce a response to the analytes specifically and selectively, without neither the necessity of time-consuming and costly purification nor the negative effects of the operating environment (Su et al., 2011). In order to transfer the responses from the recognition elements to the transducers, the immobilization between the bioelements and the transducers must be intimate and stable. Integrating the microorganisms onto the transducer is the basic requirement of achieving a reliable microbial bio-sensor (Lei et al., 2006)

Immobilization determines not only the quality of the signal transferred from the microorganisms to the transducer but also the reusability of the microbial biosensor. Therefore, immobilization plays an important role in developing a microbial biosensor (D'Souza, 2001)

Microbial fuel cells (MFC) have been proposed as a new technique for microbial biosensors which relied on optical transducers as a main transducer in the past decade. With the ability to generate sustainable electricity from biodegradable organic com- pounds through microbial metabolism, MFCs provide high sensitivity and selective sensing capability (Choi and Chae., 2012).

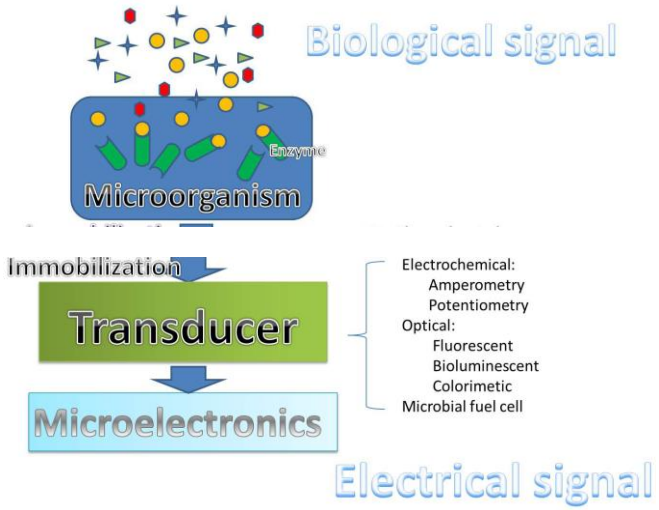

Fig. 2: A schematic representation of microbial biosensor

With the advantages of low cost, stability and a fast response, the applications of microbial biosensor have been widely used in various fields ranging from environmental monitoring, food & fermentation

industry, to clinical diagnostics. For environmental monitoring, it is necessary to find a simple, rapid, cost-effective and field portable screening method to monitor various organic and inorganic chemical contaminants which can be potential risks to human health (Rogers .,2006). The food and fermentation industries need rapid, affordable and reliable methods to ensure the quality of products and process controls (Arora et al., 2011).

Type of Microbial Biosensors

Optical Biosensor

An optical biosensor is a device that makes use of an optical transducer to produce changes in diverse optical properties such as adsorption, fluorescence, luminescence, or refractive index, which are proportional to the concentration of the analytes. Fluorescence, bioluminescence, and colorimeter based biosensors are widely investigated due to their properties of compactness, selectivity, sensitivity, flexibility, resistance to electrical nose and small probe size (Velasco-Garcia., 2009).

Fluorescent Microbial Biosensor

Fluorescent microbial biosensors are widely used in analysis processes, which can emit fluorescent light that is directly proportional to the analytes concentration at a low level. The basis of the fluorescent microbial biosensor is to fuse an inducible promoter to a reporter gene to encode a fluorescent protein which can emit detectable fluorescence in a genetically engineered micrositivity, green fluorescent protein is most commonly used in fabrication of fluorescent microbial biosensors. Recombinant *Escherichia coli* cells which are trans- formed with plasmids, harboring three tandem copies of the *ars* promoter/operator-the gene for *gfp*, were developed for the detection of arsenic. Compared to cells that used plasmids harboring only one copy, the recombinant *Escherichia coli* cells doubled the signal-to-noise ratio and decreased the detection limit form 20 to 7.5µg/L. The recombinant yeast, Green Screen TM, has the ability to emit fluorescence by expressing green fluorescent proteins when it is exposed to genotoxins. Based on this mechanism, a microfluidic chip which retained yeast within the chip was developed for the detection of toxic compounds (Garcia-Alonso et al, 2009).

Bioluminescent Microbial Biosensor

Bioluminescence based microbial biosensors have been extensively used in environmental monitoring for detection of toxicity due to its ability to closely reflect to toxicity (Steinberg et al., 1995). As a proportional response to the concentration of the analytes, the changes in the density of the bioluminescence emitted by the living cells can be measured by the bioluminescent microbial biosensor. According to the mechanism of production of biolumines cence, the method to control the expression of the *lux* gene can be divided into two manners: the constitutive manner and the inducible manner. In the constitutive manner, the bioluminescence caused by *lux* gene-coded luciferase exists constitutively as long as the organism is active. As the density of the bioluminescence can be affected by the additional compounds such as the toxicity, it can be used as a parameter to determine the additional compounds. In the inducible manner, the *lux* gene is fused with a promoter regulated by the concentration of the analytes.

Based on this mechanism, the bioluminescence cannot be detected until the concentration of the analytes approaches a critical value (Su et al., 2011)]. Several bioluminescent microbial biosensors have been developed in recent years. A whole-cell bioluminescent biosensor, based on genetically engineered *Escherichia coli* bacteria, carrying a recA::luc CDBAE promoter-reporter fusion, was developed for the detection of water toxicity. Kuncova *et al*. constructed a biosensor for the detection of water pollutions, based on *Pseudomonas putida* TVAS, harboring chromosomal *tod-lux CDABE* fusion. By immobilizing bioluminescent bacteria, TV1061 strain, in wells of a microtiter plate, Eltzov *et al*. fabricated a microbial biosensor for air toxicity monitoring and achieved a good response to a low concentration of chloroform (6.65 ppb) (Eltzov et al .,2011)

Colorimetric Microbial Biosensor

Colorimetric microbial biosensors make use of the changes in the color of the special compound to determine the concentration of the target analytes. Methyl parathion can be hydrolyzed by bacterium into chromophoric product, p-nitrophenol (PNP), which can be measured by a colorimetric method. Based on this mechanism, colorimetric transducers have been widely used in developing microbial biosensors for the detection of methyl parathion. A colorimetric microbial biosensor based on the immobilization of *Flavobacterium*° sp. in glass fiber filter was constructed for the detection of methyl parathion with a detection limit of 0.3 µM and a lin- ear range from 4 - 80 µM (Kumar et al .,2006)

Kumar *et al*. immobilized *Sphingomonas* bacteria onto the surface of the wells of polystyrene microplates (96 wells) to construct a colorimetric microbial biosensor, which had the same linear range to methyl parathion but achieved an advantage of multiple detections By immobilizing the *Sphingomonas* bacteria on inner epidermis of onion bulb scale, a colorimetric microbial biosensor for detection of methyl parathion was developed and achieved a stable characteristic (Kumar and D'Souza., 2010)

Application of Microbial Biosensor in Food and Fermentation

Fermentation is widely used for the production of foodstuffs and drinks, which requires a carefully performed fermentation system operation. Microbial biosensors are used to monitor the materials in order to control the fermentation process. Because ethanol is very important and necessary in different fermentation process, microbial biosensors have been used for sensitive determination of ethanol in order to monitor the fermentation process. An amperometric biosensor based on *Candida tropicalis* cells immobilized in gelatin by using glutaraldehyde was developed for the determination of ethanol in the range from 0.5mm to 7.5mm (Kim et al., 2009).

The control of food quality and freshness is of growing interest for both the consumer and the food industry (Mello and Kubota 2002). The demand for quick and specific analytical tools is needed for monitoring nutritional parameters and food contaminants. Microbial biosensors work as a rapid and affordable method to assure the quality of products. As an index in the determination of the quality of coffee, caffeine needs to be detected sensitively and rapidly. Babu *et al*. developed an amperometric biosensor for the determination of caffeine by immobilizing *Pseudomonas alcaligenes* MTCC 5264 on a cellophane membrane, which responded linearly to caffeine over a range of 0.1 - 1 mg/mL within 3 minutes (Babu et al., 2007).

D-glucose and D-xylose are the two ideal sweeteners and nutritional agents which are widely used in food. Based on the co-immobilization of glucose oxidase and xylose dehydrogenase displayed XDH-bacteria on multiwalled CNT nanocomposite films modified electrode, a voltametric biosensor was developed for detection of D-glucose and D-xylose (Li et al., 2013). Contaminants also should be carefully detected in order to assure the quality of the products. Zearalenone family mycotoxins are common contaminants in milk, which canlead to mycotoxicoses (Bryden., 2007). In order to declare the quality of milk, genetically modified *Saccharomyces cerevisiae* strain were used as the bioelement of the microbial biosensor for the detection of zearalenone family mycotoxins in milk (Valimaa et al., 2010)

Detection of Food Quality and Safety

Food safety can be defined as systems which ensure food and food products are free from hazards for the end user (Scallan et al., 2011). Ensuring food safety has always been a very important part of government strategies in several countries. Control programs have been established to prevent hazards posed by the entry of undesirable contaminants into the food supply. A `hazard' refers to any biological, chemical or physical property that may cause unacceptable risk. The common contaminants encountered in foods could be from natural sources either biological, chemical, physical or artificially generated. This includes bacteria, viruses and parasites, seafood toxins, mycotoxins and other chemical compounds like veterinary drug residues, pesticides, toxic metals and undesirable products generated during food fermentations. The long term impact of these residues have always been a cause of concern due to their adverse health effects. The safety and quality of food can be ensured through strict enforcement of quality control systems along the food chain at the farm level, processing level and catering level.

Biosensors due to their small size can be easily incorporated into food and dairy manufacturing equipment, packaging systems and online process monitoring equipment (Patel., 2002). They can also be used for food process manufacture monitoring such as HACCP (Hazard Analysis and Critical Control Points). Table **1** gives a list of some of the biosensors developed for food analyses.

Nanobiosensor Samples on Food

A nanoparticle based bioassay is developed by a research group which can rapidly identify *E. Coli* O157:H7 in food. This is one of the most dangerous food-borne diseases which highly infectious strain and also could be fatal, especially in elderly or the children. 60 nm-diametre silica nanoparticles are adoped with fluorescent dye molecules and antibodies which react with antigens on the bacteria surface were then attached to the particles. Each of these nanoparticles contains thousands of dye molecules and nanoparticles are suitable to attach themselves to each bacterium. Then the fluorescent signal arising from the dye when the antibodies and antigens react is effectively amplified, allowing the bacterial concentration to be determined readily using fluorescence microscopy and spectrofluorometric analysis. Figure.3 shows an *E. coli* bacterium and the fluorescence arising from a single bacterial cell. By adding different antibodies to the nanoparticles, the research group was able to identify other spores and bacteria, allowing the technique to confirm for the presence of multiple contaminants simultaneously (Bogue 2005).

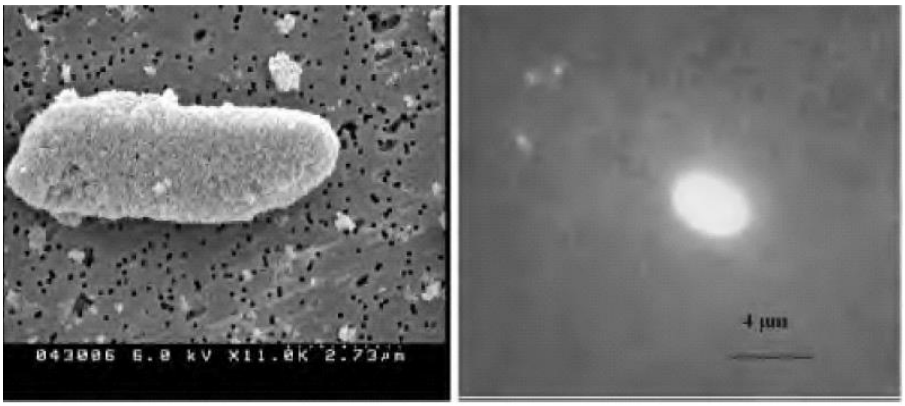

Fig. 3: Electron micrograph of an E. coli bacterium (left) and the fluorescence from a single bacterial cell following incubation with antibody conjugated nanoparticles (right)

To identify airborne bio-warfare agents, the need is to put off mass poisoning through contamination of the food chain and also biosensor technologies under development to detect pathogens in food would play a role in homeland security. Devices that operate in the aqueous phase will be needed because of the requirement of ensuring a contaminant-free water supply. In a probable manner, the most demanding aspect of these requirements is the need to detect several different biological agents simultaneously and the technological key is surely some form of generic sensing platform that may be modified to respond to each of the target species (Bogue 2005).

Table 1: Some Examples of Biosensors Used for Food Safety Analysis

Biosensor Type	Detection Principle	Detection Limit	Food Matrix
Pathogen detection: *S. typhi*	Amperometric	1-10 cells/125 g	Meat
Pathogen detection: *C. jejuni*	SPR/ phage detection	102 cells/ml	Milk
Pathogen detection: *E. coli 0157:H7*	Quantum dots/phage	20 cells/ml	Water
Pathogen detection: *E. coli 0157:H7*	Fluorescent array biosensor	20 cells/ml	Milk
Pathogen detection: *L. monocytogenes*	Resonant crystal	2.5x105 Cells	Milk
Toxin detection: Staphylococcal enterotoxin	SPR mass spectrometry	1 ng/ml	Milk and mushrooms
Toxin detection: Aflatoxin	Fiber optic	2 µgs/kg	Maize
Toxin detection: Aflatoxin B1	Electrochemical	0.03 µgs/kg	Barley
Toxin detection: Staphylococcal enterotoxin	Array immunoassay	0.5ngs/ml	Meat and fruit
Electronic nose Blood hound TM BH 114 Mixed cultures	Conducting polymers	-volatile components	Skimmed milk

Immunosensors in food analysis

When antibodies or antibody fragments are used as molecular detection element for exact analytes (antigens) to form a stable complex, the device is called immunosensor. Depending on the method of signal transduction, immunosensors may be divided into four basic groups: electrochemical, optical, piezoelectric and thermometric (Luppa, et al., 2001). The transducers chosen are directly related to the labelling, enzymatic or not, performed on the antigen or on the antibody. For each particular detection type, a specific labelling is usually performed, even though some labels can be used with different detection methods (i.e. horseradish peroxidase can be employed for an electrochemical

immunosensor and for fluorescent and chemiluminescent detection using a fibre optic sensor).

Applications in food analysis

Pathogenic bacteria and related toxins

Escherichia coli.

A SPR technique has been comprehensively tested for *Escherichia coli* determination. Fratamico et al. (1998) developed an assay for detection of *E. coli* O157:H7 achieving a detection limit of 5–7×107 CFUmL−1. More recently a sandwich SPR-based biosensor was used to detect *E. coli* O157:H7 in different spiked food samples. Milk, apple juice, and ground beef patties spiked with *E. coli* O157:H7, at varying concentrations, were injected onto the sensor surface on which were immobilised antibodies against the pathogen. Uninoculated samples were used as negative control. A significant change in the signal (RU) was observed for spiked samples versus the control and a LOD in the range of 102–103 CFUmL−1 was calculated. However, from the data provided by the authors, it appears that different behavior is obtained with different samples, while there is no complete study of recovery and accuracy presented in the report. A specificity study was conducted demonstrating that response for non-target organisms, *E. coli* K12 or *Shigella* sp. at a concentration of 105 CFUmL−1, was close to the response observed for a negative control. The experiments conducted demonstrates the potential of a SPR assay for direct monitoring of pathogens in food systems; however, real sample application appears to be still insufficient to demonstrate its applicability.

Detection of *E. coli* O157:H7 in ground beef samples was also investigated by Geng et al. (2006) by a sandwich fluorescent antibody-based FOBS which was able to detect the pathogen at a concentration of 103 CFUmL−1. In the case of real sample measurement, which were artificially inoculated at concentration of 1CFUmL−1, a pre-enrichment step of 4h was always needed for the detection. Although this, the method demonstrated a good potentiality for food analysis

Staphylococcal enterotoxin B (SEB).

SEB belongs to a family of 10 major serological types (SEA through SEK) of emetic enterotoxins (SEs) produced by *Staphylococcus aureus*. These 26–30 kDa toxins are monomeric, heat-stable, and potent gastrointestinal toxins (Bergdoll,1991). A method is needed that allows detection of SEs in a quantity below the minimum intoxication level. For SEA, the most potent SE, this is about 2ngg−1. Several approaches based on the use of SPR have appeared in the literature for the detection of SEB (Nedelkov and Nelson, 2003) One of the first examples of the application of SPR for the detection of this analyte in food samples was based on the use of a newly developed dual-channel SPR sensor (Homola et al., 2002)

Salmonella

Detection of *Salmonella* is of outmost importance in the food industry (Thornton et al., 1993) and a rapid, simple, sensitive, specific, online and affordable technique for the detection of such pathogen is urgently needed. A SPR assay was developed as a sandwich model using a polyclonal antibody against *Salmonella* as capture and detection antibody (Mazumdar, et al., 2007). The authors also claim that the presence of milk fat and proteins did not affect the sensitivity of the assay and no negative effects due to the milk matrix were observed. For this reason, no sample preparation or clean-up steps were undertaken. The specificity of the assay was only assessed with an *E. coli* spiked milk sample (1.0×108 CFUmL−1) which did not show any signal. The detection limit obtained in milk is comparable to those of commonly used and approved commercial *Salmonella* detection kits (ca. 1.25×105 CFUmL−1). The authors claim an overall analysis time of only 1h (including the antibody immobilization); however, they did not take in account any pre-enrichment step which, considering the sensitivity of the method, is absolutely necessary.

Mycotoxins

Mycotoxins are defined as "fungal metabolites which, when ingested, inhaled or adsorbed through the skin cause lowered performance, sickness or death in man or animals, including birds". The most important mycotoxins are the aflatoxins (AFs) and ochratoxin A (OTA) that are produced as secondary metabolites by the fungi *Aspergillus* and *Penicillium* and are known to be carcinogenic, mutagenic, teratogenic and immunosuppressive. When aflatoxin B1 (AFB1) is ingested by cows, it is transformed into its hydroxylated product, aflatoxin M1 (AFM1), which is then secreted in the milk. Unfortunately, AFM1 is relatively stable during milk pasteurization and storage as well as during the preparation of various dairy products (Stroka, and Anklam, 2002). Analytical methodology must allow the purpose of aflatoxins at least below the specific regulatory levels. In fact, the European Committee Regulations (ECR) has established the maximum acceptable level of AFB1 in cereals, peanuts and dried fruits for direct human consumption: 4ngg−1 for total aflatoxins (AFB1, AFG1, AFB2, AFG2) and 2ngg−1 for AFB1 alone. The current maximum level for AFM1 in milk is 0.05 ngmL−1, while for OTA is 3_gkg−1 in all cereal products intended for direct human consumption.

Aflatoxins

Responding to the need to achieve high sensitivity and move to the use of disposable probes, several electrochemical immunosensors have recently been reported in literature for the detection of AFB1 in corn and barley (Piermarini et al., 2007) and AFM1 in milk . In exacting, for AFB1 determination, an indirect

competitive electrochemical immunoassay has been developed using disposable screen-printed carbon electrodes. The specificity of the assay was assessed by studying the cross-reactivity of the MAb towards other aflatoxins. The results indicated that the MAb could readily distinguish AFB1 from other toxins, with the exception of AFG1. The proposed system showed a low matrix effect for barley and good recovery when analyzing spiked samples that were treated with an easy procedure: extraction of the analyte with 85% methanol:15% PBS, next centrifugation and dilution 1:1 (v/v) with phosphate buffer. The results obtained were confirmed by HPLC coupled with fluorescence detection. The stability of the modified sensor, up to the blocking step, was also evaluated so as to have a strip ready to use directly in the competition step (Ammida et al., 2006).

Another disposable electrochemical immune sensors has been proposed by Micheli et al. for the detection of AFM1 in milk (Micheli et al., 2005). Amperometric immunonosensor was based on the use of screen-printed electrodes and performed in a direct competitive format. Studies of interference and matrix effects have been performed to evaluate the suitability of the developed immunosensor for AFM1 analysis directly in centrifuged milk without the need of pre-treatment or extraction steps. The proposed system was compared with a conventional method (spectrophotometric ELISA) obtaining similar results but with the advantages of a shorter analysis time and the suitability for "in situ" monitoring.

***GMO* (Genetically Modified Organism)**

Progress in genetic engineering technology has enabled the introduction and expression of novel genes in crop plants in order to produce agronomically useful traits such as insect and disease resistance. In the contest of this development, three transgenic Lepidoptera-resistant maize lines (Bt-11, MON-810, Bt-176), commonly referred to as *Bt*-maize, express the genes for the *Bacillus thurigiensis* toxic proteins Cry 1Ab (Bt-11, MON-810) and Cry 1Ac (Bt-176). In the EU, foods containing ingredients with a content of GMOs >0.9% (for each ingredient) must be labelled. To enforce these regulations, reliable and fast methods for the detection and quantification of GMOs present in food products are needed.

An immunomagnetic electrochemical sensor (IMES) for detection of Bt-Cry 1Ab/Cry1Ac proteins in genetically modified corn samples has been recently developed (Volpe et al., 2006). The performances of the immunomagnetic electrochemical sensor, in terms of detection limit and total analysis time, are comparable to those of commercially available spectrophotometric kits and thus the proposed method represents a new approach for GMO analysis.

Conclusion

Nano biosensor research and development over the past decades have demonstrated that it is still a relatively young technology. The validation behind the slow and limited technology transfer could be attributed to cost considerations and some key technical barriers. Many of the more recent major advances had to await miniaturization technologies that are just becoming available through research. This technology has penetrated into non-medical applications including environment and food industry and given a renewed interest in biosensors. Microbial biosensors have been widely used in the environmental, food and diagnostics industry due to its advantages of low cost, stability and fast response .More and more companies are foraying into biosensor fabrication and marketing. The future would see more biological sensors, which could carry out multiple analyses in shorter time frames. The development of lab on chips and electronic noses at reasonable cost and short analysis times will help in increasing the safety and product quality of food. Application of biosensors in Food industry is extremely successful and has widened to agriculture and environmental. Enormous research studies are being undertaken by research and development companies and diagnostic centers to develop simple, sensitive and cost effective biosensor technologies

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