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Polymer thin films embedded with metal nanoparticles for electrochemical biosensors applications

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ABSTRACT

Currently, polymer thin films embedded with metal nanoparticles provided the suitable microenvironment for biomolecules immobilization retaining their biological activity with desired orientation, to facilitate electron transfer between the immobilized enzymes and electrode surfaces, better conformation and high biological activity, resultant in enhanced sensing performance. This article reviews focus on various methods for brief discussion of fabrication of metal nanoparticles-polymer hybrid materials and their applications in different electrochemical biosensors. The performance of hybrid materials based electrochemical biosensor can be improved by synergic properties of the metal nanoparticles and polymer network with biomolecules interface via engineering of morphology, particle size, effective surface area, functionality, adsorption capability and electron-transfer properties. These attractive features to hybrid materials are expected to find applications in a new generation of miniaturized, smart biochip devices.

Contents

Abbreviations: MNPPF, Metal nanoparticles-polymers frameworks; MNPs, Metal nanoparticles; AuNPs, Gold nanoparticles; AgNPs, Silver rnanoparticles; PtNPs, Platinum nanoparticles; CuNPs, Copper nanoparticles; CuNFs, Copper nanoflowers; CoNPs, Cobalt nanoparticles; CdSNPs, Cadmium sulfide nanoparticles; FeONPs, Iron oxide nanoparticles; CNTs, Carbon nanotubes; MWCNT, Multi-walled carbon nanotubes; SPEEK, Sulfonated poly(ether-ether ketone); PSf, Poly(sulfone); PANI, Poly(aniline); PPy, Poly(pyrrole); PDDMAC, Poly(diallyldimethylammonium chloride); PVP, Poly(vinylpyrrolidone); PODS, Poly(octadecylsiloxane); PS-*b*-P4VP, Poly styrene block- poly-4-vinylpyridine; PMMA, Poly(methyl methacrylate); PVA, Polyvinyl alcohol; PEDOT, Poly(3,4- ethylenedioxythiophene); PDMA, Poly(*N*,*N*'- dimethyl aniline); PMPy, Poly(*N*-methylpyrrole); PGA, poly glutamic acid; PPAA, poly(trans-3-(3-pyridyl)acrylicacid); PHM, Poly(hexyl methacrylate); MIP, Molecular imprinted polymer; CT, Chitosan; IPN, Inter-penetrating network; MPTMS, 3-Mercaptopropyltrimethoxysilane; ThPh, Theophylline; AChE, Acetyl cholinesterase; CA, Creatinine amidohydrolase; CI, Creatine amidinohydrolase; SO, Sarcosine oxidase; β-CD, β-cyclodextrin; HAS, Human serum albumin; GO_x, Glucose oxidase; CRP, C-reactive protein; ODN, Oligonucleotide; Cys, Cysteamine; SNPs, Single-nucleotide polymorphisms; GMO, Genetically modified organisms; HRP, Horseradish peroxidise; EP, Epinephrine; DA, Dopamine; ATP, Adenosine triphosphate; AA, Ascorbic acid; UA, Uric acid; SPHINER, Solid-phase-incorporated-reagents; GCE, Glassy carbon electrode; CILE, Carbon ionic liquid electrode; ITO, Indium tin oxide; ISE, Ion selective electrode; SPE, Screen printed electrode; HPLC, High-performance liquid chromatography; AAS, Atomic absorption spectroscopy; CVD, Chemical vapor deposition; RDA, Recommended Dietary Allowances; AI, Adequate Intake; LOD, Limit of detection

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1. Introduction

Metal nanoparticles and polymers frameworks (MNPPFs) have attracted tremendous research interest, as emerging porous materials, in both academia and industry due to their structural diversity, flexibility and tenability as well as high porosity and thus a wide spectrum of applications such as gas storage and separation, selective heterogeneous catalysis, carbon dioxide capture, and guest dependent luminescence, etc (Long and Yaghi, 2009; Ferey, 2008; Liu, 2012; Heilmann, 2002; Ramesh et al., 2009). Interest in metal nanoparticles (MNPs) was motivated by their potential applications of electrochemical sensor (Guo and Dong, 2011), due to their small size (1–100 nm), unique chemical, physical and electronic properties (different from bulk material), flexibility to construct novel and improved sensing devices. Different kinds of nanoparticles are playing diversified roles in different electrochemical sensing systems (Katz et al., 2004). In general, excellent conductivity and catalytic properties of MNPs, make them suitable as "electronic wires" (to enhance the electron transfer between redox centers in target molecules and electrode surfaces), and electrochemical catalysts (due to their nanometer size and structure) (Wei et al., 2012). Metal oxide NPs, may be the semi-conductor NPs, are often used to immobilize target molecules due to compatibility, while other semiconductor nanoparticles based on metal chalcogenides (CdS, CdSe, CdTe) are generally used as labels or tracers for electrochemical analysis (Luo et al., 2006). Now, MNPs based electrochemical sensors and biosensors are playing important role in diagnostic devices (Pingarron et al., 2008; Wang, 2005).

Recently, Bobacka et al. (2003) and Adhikari and Majumdar (2004), reviewed polymers based electrochemical sensor, because of their unique properties of polymers (compatibility, conductive nature, electron promoter and low cost), which are helpful during fabrication of electrochemical sensors and biosensors (Yuan et al., 2012; Revin and John, 2012; Prakash and Shahi, 2011). Till time, single material modified electrodes were not commercialized because of their low sensitivity, poor selectivity, surface poisoning due to adsorbed intermediates and the interference from other species. MNPPFs modified electrodes avoid these problems, which are their attractive features as electrochemical sensors or electrochemical biosensors. Selectivity of electrochemical biosensor depends on the recognizing element (biomolecule, such as antibody) as well as host matrix and interaction between them. MNPPFs are very suitable to achieve the adequate sensitivity and stability, because MNPs act as redox mediator of biomolecules, and polymer acts as selective adsorbate for biomolecules (Ragupathy et al., 2009; Prakash and Shahi, 2011; Gopalan et al., 2009). Contamination of edible items, environment pollution (i.e., heavy metals, explosives, and toxins) and alteration in molecular or ionic concentration (i.e., metabolites, metal ions, hormones, and proteins) in human body are serious health problems. Thus, we need fast/reliable diagnostic tools for biological and chemical species in cost effective manner. Over past three decades electrochemical biosensors has great attendance to medical diagnosis and treatment, such devices easy way to produce the commercialization because of its simple, inexpensive, yet accurate, and sensitive platform for environmental monitoring, industrial quality control, patient diagnosis and treatment. Sensitivity, selectivity, response time, reproducibility, and long life time are highly desirable for electrochemical biosensor performance. Nobel metals, semiconductor (ITO) and carbons (glassy carbon, graphite, and diamond) are potential electrodes for electrochemical biosensors application. Output of electrochemical biosensor must be satisfied in human real samples with cost effective manner (Gubala et al., 2012).

Different electrochemical biosensors have been explored as sensor for diagnosis of genetic disorders like SNPs (Abbaspour and Noori, 2012), pathogens detection (Afonso et al., 2012), forensic applications (Riskin et al., 2008), drug response (Trouillon et al., 2012). Electrochemical biosensor were also applied in food and beverages, (Perez and Fabregas, 2012), GMO content detection in food (Zhao et al., 2011), measuring freshness of food (Ahmed et al., 2008), DNA sensor (Peng et al., 2006), triclosan sensor (Amiri et al., 2007), and other sensors (Kimmel et al., 2012).

In general, MNPPFs based biosensor processes are classified as signal transduction and bio-recognition element methods. Signal transductions are based on electrochemical, optical, thermal, piezo-electric, cantilever and mass sensitive analysis, while bio-recognition element method reveals antibodies (immunosensors), protein receptors, whole cells, nucleic acids and enzymes (Monosik et al., 2012). The electrochemical biosensors are of four types: (i) amperometric- potential is applied between working and reference electrode and the output current is measured continuously; (ii) potentiometric-measurement of charge potential accumulation at the working electrode in compared to the reference electrode in an electrochemical cell during no current flows between them; (iii) conductometric-measurement of variation in conductance/resistance due to the charges produced during enzymatic conversion; and (iv) Impedimetric-monitoring of variation in electrical properties arising from biorecognition events at the surfaces of modified electrodes.

This review focuses on recent advanced on MNPPFs as electrochemical biosensors, their challenge, design and desirable properties as a sensing device employing thin-film growth techniques. Different methods for fabrication MNPPFs, recent innovations and breakthroughs in electrochemical biosensor devices and the need for further frontier research to reach important objectives are also discussed.

1.1. Background

Sensors are devices to convert biological, chemical, or physical changes, into quantifiable and processable electrical signal, by recognizing selective and specific response to target analytes without any interference (Fig. 1). Transducer and detector devices are main component of a sensor. A signal processor collects, amplifies, and displays the signal. A biosensor is an analytical device for the detection of an analyte that combines a biological

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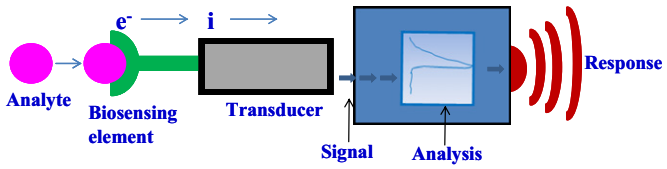

Fig. 1. A schematic of a electrochemical biosensor with electrochemical transducer.

component with a physicochemical detector. A common example of a commercial biosensor is the blood glucose biosensor, which uses the enzyme GO_x to break blood glucose down. A chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal. The chemical information, mentioned above, may originate from a chemical reaction of the analyte or from a physical property of the system investigated. Electrochemical biosensor is subclass of chemical sensor consisting electrochemical transducers with the high specificity of biological recognition processes (enzymes, proteins, antibodies, nucleic acids, cells, and tissues or receptors). These sensors selectively react with the target analyte and produce electrical signal, related to analyte concentration and show high sensitivity, and low detection limits. Biocatalytic and affinity biosensors are two categories of electrochemical biosensors. Electrochemical biosensors are currently one of the most active areas of research in analytical chemistry. Biosensor's performance is experimentally evaluated based on its sensitivity, LOD, linear and dynamic ranges, reproducibility or response precision, selectivity and interferences. Also, other parameters are often compared such as response time, ease of use, portability, operational and storage stability parameters have considered. Ideally, the sensing surface should be regenerable in order for several consecutive measurements to be made. Ubiquitously hanging the world by electrochemical biosensors because of applied to human beings in head to legs of biological fluids (Ronkainen et al., 2010).

1.2. Enzymatic and non-enzymatic electrochemical biosensors

Enzymatic electrochemical biosensors are advancing the development of self-testing and continuous monitoring of biological fluids. For viable electrochemical biosensor, immobilization of biological component with maintained enzyme activity (enzyme immobilization) has been described in the literature (Malhotra et al., 2006). General method for immobilization includes covalent, entrapment, cross-linking, precipitation, diffusion, electrochemical, drop coating, grafting, coupling, adsorption, solution phase, and template etc. Wilson Turner and (1992) proposed 'ideal enzyme' for biological fluids oxidation. Enzyme modification and immobilization were utilized to generate biocatalysts with improved stability and selectivity (Ronkainen et al., 2010). Improved enzyme selectivity affords novel biocatalysts, and finds sensing application in enzyme-related biotechnology. High specific interactions between enzymes and substrates, genetic mutation or chemical modification of enzymes represent the primary method for alteration of substrate selectivity.

Different enzymes (glycollate oxidase, lactate oxidase, glucose oxidase, xanthme oxidase, oxalate oxidase, L-amino acid oxidase, nitro–ethane oxidase, urate oxidase, sulfite oxidase, malate oxidase, cholesterol oxidase and ascorbate oxidase) were utilized for enzymatic electrochemical biosensors (Mulchandani and Rogers, 1998). Due to rapid progress in innovative efforts of efficient enzymatic electrochemical biosensors, specific electrochemical technologies were developed for fast response because of short diffusion paths (no cell walls) (Bartlett, 2008).

In-spite of dominating the electrochemical biosensor industry, enzymatic systems showed number of critical flaws. Stability of enzymatic systems is serious problem for enzymatic electrochemical biosensors. Despite numerous efforts, enzyme is still constrained to pH range (2–8) and below 44 °C, in addition with sterilization, and ambient humidity levels. Extremely high and low humidity significantly hampered the storage of sensors. Also, mediator electrodes immobilized with enzyme requires considerable attention for fabrication, electro-polymerisation, and covalent cross-linking. Thermal and chemical instability of enzyme prohibits enzymatic electrochemical biosensors for continuous monitoring of fermentation processes or human body, which requires sterilization. Numerous simple and reproducible enzyme immobilization methods (direct adsorption, sol–gel entrapment, cross-linking, etc.) have been reported for mass production and commercialization. Because of costly fabrication processes and short shelf life, enzymatic electrochemical biosensors are less viable. But, due to high selectivity of the enzyme towards biomolecules, enzymatic electrochemical biosensors remain commercially unchallenged. Recent advances indicate that electrochemical biosensors without using enzyme are just a dream. Non-enzymatic electrochemical biosensor persuaded as competitive area of research. Development and fabrication of cost effective, simple, accurate, portable and rapid electrochemical biosensors are socially important aiding patients (10% of the world population).

Noble metals and metal oxides are currently used for non-enzymatic electrochemical biosensor because of its suitability for oxidation of biological species, but sensitivity, selectivity and halide ion poisoning, are still serious problem (Wang et al., 2008). The interest in practical non-enzymatic electrochemical biosensor has been centred on the breakthrough in electro-catalysis, and to avoid the above-mentioned problems, versatile efforts were rendered for MNPPFs (Prakash and Shahi, 2011; Zhang et al., 2012).

2. Fabrication methodologies

Formation of MNPs in a polymer matrix is a popular tool for design of new MNPPF. Properties of polymer can be greatly altered by incorporating MNPs (Ferey, 2008). This impart magnetic, semiconductor, catalytic, or sensing properties, depending on the kind of nanoparticles, polymer, and their characteristics. To obtain MNPPFs with well-defined and reproducible properties, one should achieve suitable control over MNPs growth, particle size distribution, and particle–interface interactions. These are key issues for desired properties and targeted applications of MNPPFs.

The basic routes of preparation of MNPPFs are in situ synthesis of MNPs, polymers or both components simultaneously (Fig. 2). Final or precursor mixed components can proceed, for instance, in solution or in a polymer melt, in which processes, inorganic or organo metallic precursor molecules can also be bound to polymer molecules. The precursor's conversion to the final MNPs can take place in solutions, in polymer melts or in polymeric solids. Chemical procedure for the generation of MNPs is simple. Precursor's hydroxylation is also a common method for synthesis of MNPs. In contrast to powders, MNPs are surrounded by an organic shell (solids or viscous substances) and may be dispersing in water, organic solvents or even directly in melt polymer. Numerous, surface-modified MNPs are available, which was linked with a shell of organic thiols, where the thiol groups were attached to the particle surfaces. The surfaces of MNPs can also be modified with reactive organic groups that allow the attachment of polymer matrix to the MNPs surfaces, thus leading to a firm MNPPF interface. MNPs were also produced by evaporation of bulk

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materials (e.g., Ag). MNPPFs may be obtained basically not only as powders or coherent bodies without particular shape but also as films or fibers by suitable polymer processing. Thin films also can be manufactured from a liquid mixture of the composite components by casting followed by evaporation of the volatile parts or by insertion of a solid nanocomposite in a hot press, and fibers by conventional spinning processes including electrospinning.

2.1. Solid-phase-incorporated-reagents (SPHINER)

SPHINER method for synthesis of MNPPFs results of hybrid films from metal-selective extractants, which permit immobilization of metal-extractant complexes inside the non-functionalized polymeric matrices followed by metal reduction. Many approaches utilize various types of the MNPs, including Pt/graphite-epoxy; this is an important in biosensing applications (Macanas et al., 2006). The synthesized MNPs was used in the construction of new composite electrodes and offered advantages, such as a high electrical conductivity (Macanas et al., 2006).

2.2. Novel ex-situ and in-situ approaches

Morphological control over MNPs is an important aspect because it affects material performance. Thus, controllable particle size, shapes, and composition are important to alter the material properties. Two methods, ex-situ and in-situ, are well known for the synthesis of MNPPFs. In the ex-situ approach, NPs are first produced by soft-chemistry routes and then dispersed into polymeric matrices, while in in-situ approach, MNPs are generated inside a polymer matrix by decomposition (e.g., thermolysis, photolysis, radiolysis, etc.) or chemical reduction of a metallic precursor dissolved into the polymer. These types of polymer implanted with MNPs were extensively studied for photonic, optical, or electrical sensor devices (Ramesh et al., 2009). AuNPs/PANI hollow spheres, with controlled PANI shell thickness, showed improved conductivity and electrochemical activity for DA detection in biological fluids (Feng et al., 2006). Au/PPy nanocomposites were synthesized by polymerization of pyrrole in the presence of $AuCl_4^-$ onto the electrode, giving PPy and Au(0) followed by the enzyme immobilization, which showed the high performance for glucose and detection (Njagi and Andreescu, 2007).

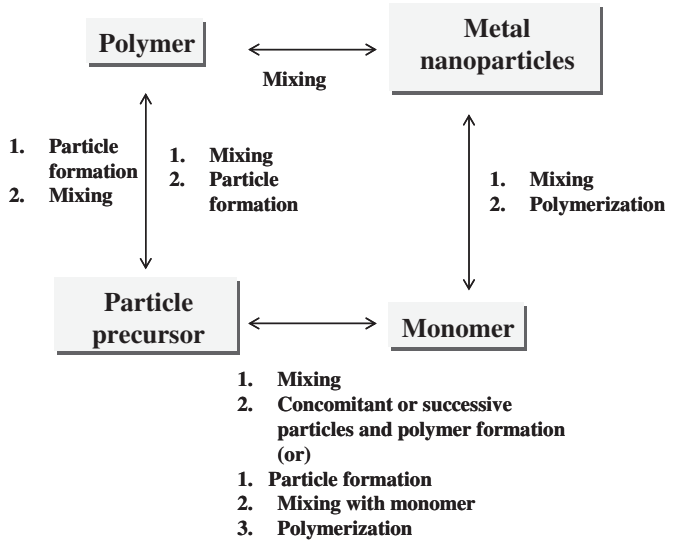

Fig. 2. The basic routes of preparation of MNPPF.

2.3. Controlled pyrolysis method

For the MNPPF synthesis, control pyrolysis is carried out in a gaseous or liquids phase at isothermal conditions. This method is interesting, because of uniqueness, chemically self-regulating and provide best solution for given problem (i.e., the nanoparticles formation and stabilization in polymer systems). A nanoscale of PHM-COOH was applied by spin-coating at 4000 rpm with various dilutions of the polymer on metal film; HRP was attached covalently onto surfaces activated with carbodiimide. Ag or Au colloids coated on the HRP surface by CVD with nanoscale range, showed the bioaffinity interactions in applications such as allergen, drug screening, glucose and proteins (CRP) (Fig. 3) (Bauer et al., 1999). Also, sonochemical method assists to form the high stable Au–FeO NPs/PEI composite, exhibited selective adsorbent for sulfur-containing amino acids by an external magnetic field (Seino et al., 2009).

2.4. Nanostructured polymer with MNPs

Functional groups interact with metal compounds, while subsequent reduction or thermal (or other) treatment results in NPs formation within the functional nanophase. During formation of MNPs, capping, reducing, stabilising or protective agents (polymers, surfactants) play important. Rao (2012) explored the use of PDDMAC as reducing agent and stabiliser, leads to the 6–15 nm of AuNPs formed on the carbon, showed the detection of dopamine and methanol. Au, Pd, and Pt, NPs formed in the PS-b-P4VP micelles (Antonietti et al., 1995; Spatz et al., 1996; Seregina et al., 1997) the MNPs morphology strongly depends on the type of reducing agent. "Cherry-like" morphology was observed used the sluggish reducing agent, while "raspberry-like"

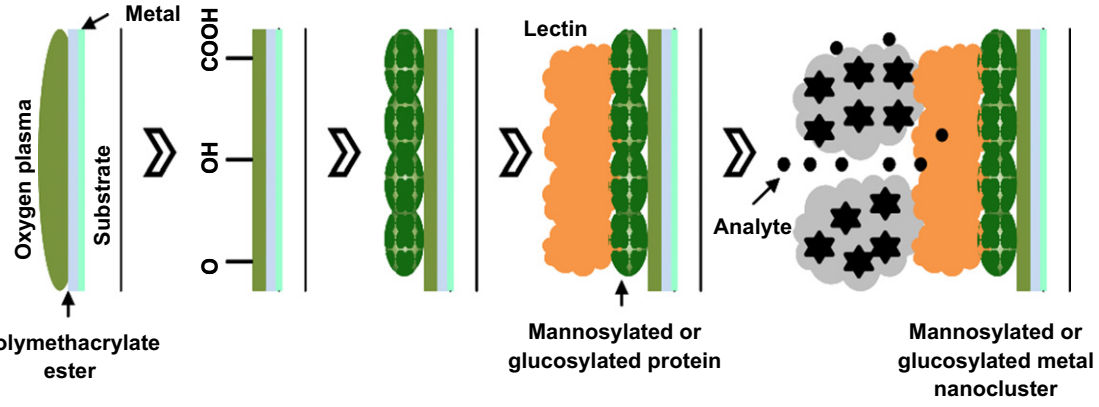

Fig. 3. Step by step schematic diagram of glucose-sensor construction.

morphology by fast reducing agent. By varying the metal compound type or the way of metal particle formation and treatment, we were able to influence the metal particle size and particle distribution. It is believed that any amphiphilic block copolymers, forming dense, functionalized micelles in water, can be used for templating of mesoporous metal oxides with MNPs. MNPPF with tunable properties are promising for future development of sophisticated applications. One can expect vigorous development of this field for years to come so that new polymeric systems yielding better control over MNPs formation and properties will be designed.

2.5. Ion implantation

Researchers interest on designing the polymer-based composite materials containing MNPs, mainly in fabrication of magneto-optic data storages, pico second optical switches, and directional connectors, because of MNPs effects, which exhibit a high non-linear susceptibility of the third order when exposed to ultra short (pico/femto second) laser pulses (Flytzanis et al., 1991). Now, one of the promising methods is ion implantation, which offers controllable MNPs synthesis at various depths under the surface and unlimitedly high-impurity doses (Townsend et al., 1994). One can produce almost any insulator by this method with tuning the MNP shape and implantation conditions (Khaibullin et al., 2002). MNPPF were fabricated by Ag implantation into epoxy resins (Stepanov et al., 1995) and PMMA (Stepanov et al., 2000) for optical properties. Ion implantation is useful tool for single impurities introduced into surface layer (less than micron range). Researcher interest in carbon-based composites with MNPs goes back a long way, because their exhaustive uses in magnetic properties, electric and optical properties.

2.6. Sol–gel

Development of the sol–gel science and technology is impressing and instructive, at present they show an intense development accompanied by important practical applications. It provides significant advantages described elsewhere (Tseng et al., 2010). Highly dispersed AuNPs in a sol–gel film for H_2O_2 sensing without immobilizing a mediator or enzyme was reported (Maduraiveeran and Ramaraj, 2007). Sols are dispersions of colloidal particles in a liquid. Depending on the precursor gels nature may be classified as: (a) well-ordered lamellar structures of inorganics with organics such as organopoly silsesquioxanes, covalent disordered polymeric networks, and polymer networks formed through physical aggregation and (b) disordered structures of inorganic and organic networks. The sol–gel process steps were earlier reported by Tripathi and Shahi (2011). Hydrolysis and condensation reactions were two steps involved in sol–gel reaction. Aerogel, xerogel, monoliths, films, fibers, powders and monosized of the shapes were produced by tuning the conditions (Fig. 4). Synthetic techniques used in the sol–gel process to generate metal–polymer hybrid materials include in situ formation of an inorganic network in the presence of a preformed organic polymer, and the simultaneous formation of organic polymer and metal oxide, forming IPN networks (Zou and Shen, 2008; Hajji et al., 1999). To date, the commercial application of sol–gel hybrid products is comparatively small, but promising of new technological development.

2.7. Miscellaneous methods

Self-assembled nanocomposite comprises discrete nanoscale metal and polymer components spontaneously organized with non-covalent interactions. These nanocomposites often demonstrate interesting properties because of the nanoscale of constituent phases, high interfacial area, and synergetic properties (McCaughey et al., 2004). Also, the layer-by-layer self-assembly technique has been applied to produce hybrid systems, based on electrostatic association between alternately deposited, oppositely charged components. MNPPFs can be prepared by non-hydrolytic sol–gel methods (Haas, 2002), involves the reaction of a "metal" halide with an oxygen donor, such as an alkoxide, ether, alcohol, and so forth, under non-aqueous conditions to form an inorganic oxide and alkyl halide by-products. The electrochemical method has been demonstrated with a polymer film fabricated on ITO-coated substrates through a layer-by-layer deposition of PDDMAC and an Ag^+ ion-DNA complex, followed by constant potential electrochemical reduction of the ions to AgNPs (Jayaraman et al., 2011).

Overall the fabrication of MNPPF was desired requirement to meet electrochemical applications based on the suitable their synthesis method. Nanoscopic properties of nanocomposite at the surface, interfaces, in bulk and under gas and supercritical fluid

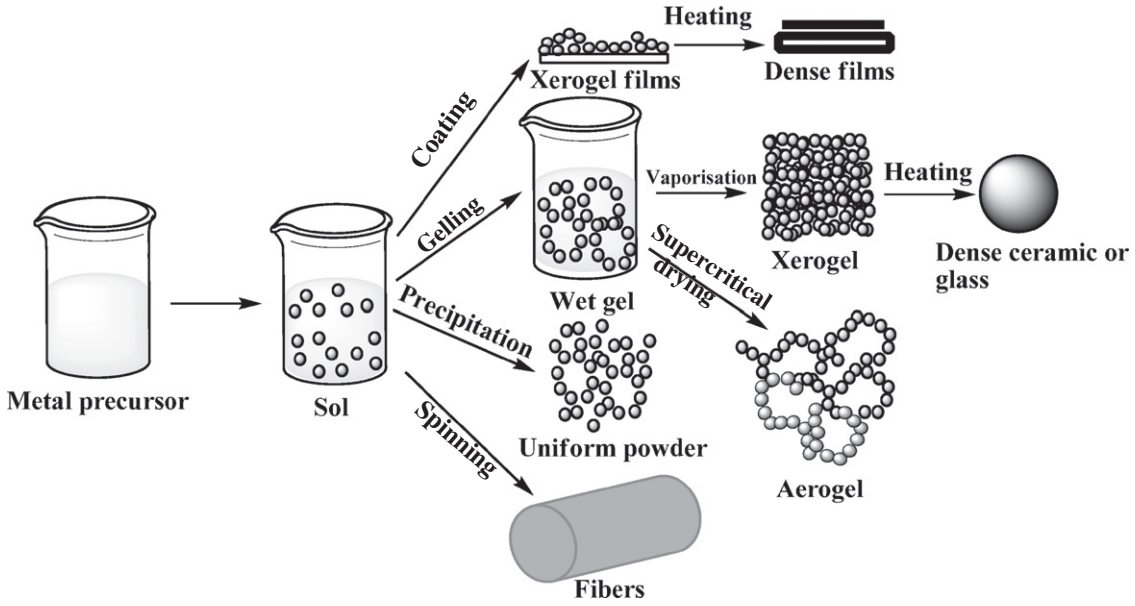

Fig. 4. Various steps in the sol–gel process to control the final morphology of the product.

treatments have attracted increasing interest in recent years for their industrial applications. Morphology, structure and electrochemical properties of metal–polymer hybrids depend on their synergic effect between composition, particles size, interfacial interactions, etc (Gao and Choudhury, 2003). Interaction between polymer and MNPs has significant impact on properties in comparison with that for microcomposites (Roy et al., 2005). The interfacial interactions strongly affect its thermal, mechanical, and other properties due to the high surface area-to-volume ratio. Molecular level tailoring of the polymer matrix improves interfacial area, leading to a significant volume fraction of polymer in the interaction zone surrounding the MNPs.

3. Electrochemical biosensing based on MNPPFs

Extremely increasing number of researchers has been exploring the production of novel nano-scale metal oxides, noble metal-doped metal oxides, and metal oxide-CNTs integrated into polymer nanocomposites. New analytical devices based on MNPPFs are cost-effective, highly sensitive due to the large surface-to-volume ratio of the nanostructure, and additionally show excellent selectivity when coupled to bio-recognition molecules with simple design (Liu, 2008). Because MNPs acts like electron connector, while polymer as selective adsorptive on electrode for target analyte, akin to beauty nature of MNPPF working as efficient device for electrochemical biosensor electrode (Ozcan et al., 2008). Table 1 summarises some different methods for the fabrication of MNPPF and their applications in sensing.

3.1. Selections of MNPPF for electrochemical biosensor and transducers

Sensitivity and selectivity are key elements in the electrochemical biosensors. MNPPF should be inherently sensitive for biological fluids detection because they effectively concentrate the target analyte in the presence of other analytes. Indeed, several portable devices and instruments based hybrid materials have been used to detect the biochemical/pathogens threats by direct method. While sensitivity depends in part on the method of signal transduction, it also depends on the strength of analyte binding to the MNPPF and on the dynamics the electrons of MNPPF (redox) within the analyte. Unusually slow redox behaviour caused to poor responses and sensitivity. Thus, maximum observable electric signal should depend in part on the MNPPF capacity.

The selectivity of electrochemical biosensor is major issue because of MNPPF suited for target analytes. Yet at present is not well developed (Yan et al., 2008). MNPPF selectivity of electrochemical biosensor, their mechanism has been proposed as: in the presence of enzyme, target analytes and oxygen undergo a reaction in which by-product are formed and electro-oxidation current of by-product is detected after use of MNPPF modified electrode (Ahmad et al., 2010), and other way, MNPPF modified electrode as better electron-acceptor from oxidation of enzyme by enzymatic reaction, thus causing an increase in the oxidation current of material during the analysis (Hou et al., 2012). Also, the interferences caused to overestimate of the responses current, it is critical problem. To overcome, recently many reported available in MNPPF modified electrodes for improved sensitivity and decrease the over potential, applied to the electrochemical biosensors (Solanki et al., 2011; Doong and Shih, 2010).

MNPPF contains numerous properties that suggest them as attractive sensory materials, but their implementation has been largely limited by transduction. Although sensing devices employ a variety of recognition elements, electrochemical detection techniques use predominantly some polymer. This is mostly due to their specific binding capabilities and catalytic activity (Grieshaber et al., 2008). Transducers must be low cost, ease of use, portability, and simplicity of construction in electrochemical biosensor. Electrochemical technique offers certain advantages for detection in electrochemical biosensors, does not depend on the reaction volume, and very small sample volumes can be used for measurement (Ronkainen-Matsuno et al., 2002). For example, without or little sample preparation used to get low LODs in immunoassays, and atto/zeptomole detecting electrochemical immunoassays was constructed (Jenkins et al., 1988).

Electrochemical transducer depends on the MNPPF property that's selectively reacts with the target analyte and produces an electrical signal at short interval. Many reported was available for enzymatic electrochemical biosensor using the different electrochemical transducers that not exploited in commercialisation due to problem in transducers/MNPPF development. To avoid the enzymatic electrochemical biosensor, upcoming generation interested on non-enzymatic sensor. Thus, here review hints for the development of non-enzymatic electrochemical biosensing was the specific intent based on MNPPF materials.

3.2. MNPPF for glucose sensor

Diagnosis and monitoring of diabetes was more highlighted by a recent report in which it was stated that 20% of the total world population affected by chronic disease. One of the proactive measures needed to control diabetes mellitus is monitoring and control of blood glucose levels with the help of home monitoring kits or reliable sensor. Electrochemical biosensors for this application must be easy to use, reliable, and cheap (Eggins, 2002). In a typical sensor, a drop of blood is placed on a disposable electrode sample strip on which the dry reagents have been deposited using a method similar to ink-jet printing technology. Test strip contain a mediator for the amperometric glucose detection. The current produced at constant potential gives readout to a liquid crystal display on the glucose meter. The redox centres of MNPPF can be bound with GO_x, the catalyses the direct glucose electro-oxidation (Choi et al., 2005). The most extensively studied direct glucose electro-oxidation catalyzing

Table 1
Methods for the fabrication of MNPPF and their sensing applications.

Modified electrode	Fabrication methods	Target anaytes	References
AgNPs/PEDOT-PSS/Au	Ex-situ	Ganoderma boninense	Dutse et al. (2012)
AuNPs-PDDA/PANI/GCE	In-situ	Dopamine	Prakash et al. (2009)
Ag-PANI-silica/ITO	γ-radiolysis	H_2O_2	Kim et al. (2010)
Pt-CNT-CHIT/PSS/Au	Self assembled	Cholesterol	Yang et al. (2006)
ChOx/CT-SnO_2/ITO	Sol–gel	Cholesterol	Ansari et al. (2008)
Cu-SPEEK/GCE	SPHINER	H_2O_2	Muraviev et al. (2006)
CuNPs-PANI/GCE	Electrochemical	Ascorbic acid	Xi et al. (2010)
PAMAM-AuNP/GO_x/ITO	Layer by layer	Glucose	Crespilho et al. (2006)
Nafion/PAMAM-Au//GO_x MWCNT	Ultrasound-radiated	Glucose	Wei et al. (2010)

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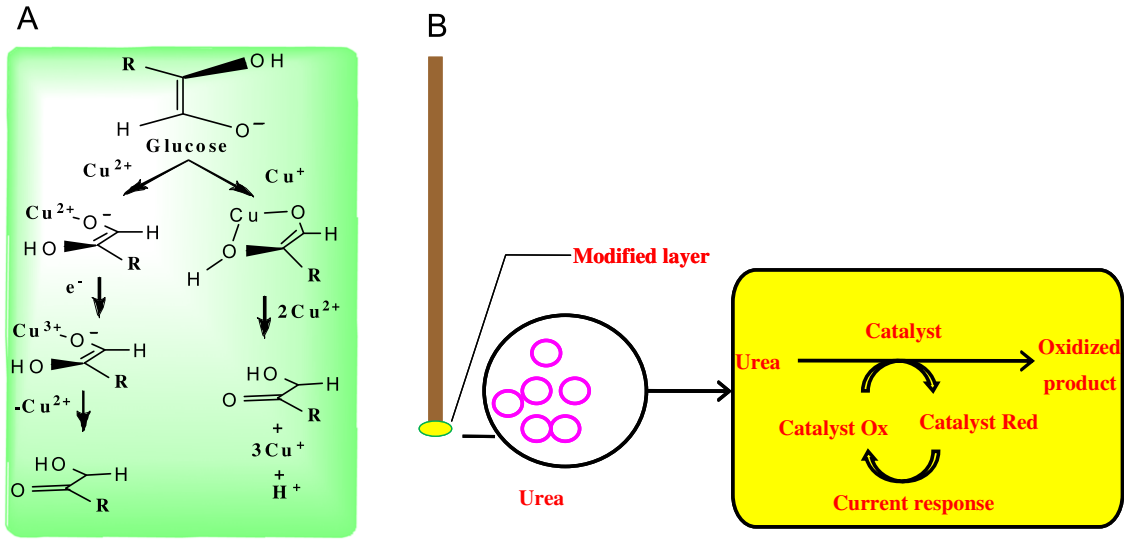

Fig. 5. (A) The mechanism of the CuPc: His non-enzymatic electrochemical biosensor response and (B) Catalytic process on the sensor/solution boundary.

redox matrix is made. Non-enzymatic electrochemical biosensor of glucose oxidation on copper electrode was presented in alkaline medium (Fig. 5A). The most accepted mechanism was that suggested earlier by Marioli and Kuwana (1992). Here the metal–polymer species were proposed to act as an electron-transfer mediator, while polymer as selective adsorbs (Guo and Li, 2010; Kang et al., 2007). Interestingly, it was suggested that the oxidation might not simply produce gluconic or glucuronic acid but might instead entail C–C bond cleavage generating lower molecular-weight products (formates and carbonates) (Luo and Baldwin, 1995) which involve in the transfer of 12 electrons. The current response for a definite glucose concentration has to be high selective MNPPF modified electrodes.

Electrochemical glucose oxidation involves complex processes of adsorption, electron transfer, and subsequent chemical rearrangement, which are combined with the surface reactions on the electrode surfaces. The information about the direct glucose oxidation on solid-state surfaces and new electrode materials will lead us to possible breakthroughs in designing the glucose sensing devices that realize innovative and powerful detection. Prakash and Shahi, 2011 reported that CuNFs grafted in PDMA and sulfonated ionomer modified GCE, for glucose detection and Guo and Li, 2010 suggested carbon/NiO hollow spheres embedded in PEDOT matrix modified electrode to detect glucose with high sensitivity.

Invasive implantable glucose sensors that have an intimate contact between the biological fluids or tissues and the biocatalytic sensor have been developed (Eggins, 2002; Klonoff, 2005). The minimally invasive glucose sensors are inserted subcutaneously into the arm or belly of a patient. More invasive, intravascular sensors that measure glucose levels in hospitalized diabetes patients are also being developed. Some problems such as pain, skin irritation, limited lifetime of the sensor, and accuracy of the data continue to slow down their wider use.

3.3. MNPPF for creatinine sensor

Chronic end-stage kidney failure affects many patients in the world. Creatinine is vital role in kidney dialysis process. Since the creatinine concentration in serum and urinary excretion relative to that of urea is less affected by sepsis, trauma, fever, or dietary changes factors. It levels give a more sensitive and specific index for evaluating glomerular filtration rate and, in general, for assessing renal, thyroid, and muscular functions. Homemade creatinine will be developing in cost effective and sensitive manner. Urine or blood drop are coating in smart chip to monitoring the creatinine concentration by current signal. Simple, fast, and accurate StatSensor™ electrochemical creatinine biosensors was first marketing test strip by "Nova Biomedical" in 2008. All of the electrochemical creatinine biosensors are based on a multienzyme sequence proposed by Tsuchida and Yoda (1983), consisting of CA, CI, and SO. The enzyme sequence catalyzes the conversion of creatinine via creatine and sarcosine to glycine, formaldehyde, and hydrogen peroxide as reaction sequence.

Yadav et al. (2011) demonstrated that FeONPs/CT graft-PANI composite film electrodeposited on surface of Pt electrode through glutaraldehyde coupling to develop the creatinine sensor with the sensitivity of the electrochemical biosensor was 3.9 $\mu A\ \mu M^{-1}\ cm^{-2}$ sensitivity, 1 μM LOD, and linearity (1–800 μM). Further, new ZnONPs/CT/MWCNT-COOH/PANI composite film has been synthesized on Pt electrode by electrochemical techniques and CA, CI, and SO enzymes immobilized on it to construct the electrochemical creatinine biosensor. It showed 0.5 μM LOD within 10 s at pH 7.5, linearity (10–650 μM) and sensitivity of 0.030 $\mu A\ \mu M^{-1}\ cm^{-2}$ (Yadav et al., 2012).

First mechanism for non-enzymatic creatinine sensor was developed in SPE (Chen et al., 2006). Creatinine was specific binding with β-CD to complex formation (Tsai and Syu, 2005), based on this interaction. Kumar et al. (2011) reported PEDOT incorporated with β-CD to develop the enzyme less creatinine sensor by potentiometry method, which was exhibited a fast response time, low LOD and good stability, retaining nearly 95% of the initial response after 1 month of shelf life in the presence of interferences.

3.4. MNPPF for cholesterol sensor

Public concerns about the risks of high cholesterol levels in blood began to rise in the 1980s.Cholesterol concentration is in blood rises from the normal value of 0.2–0.1 $g\ dl^{-1}$, if increased or decreased in blood leads to heart disease, arteriosclerosis, and other clinical (lipid) disorders and in the assessment of the risks of thrombosis and myocardial infarction (Ikonen, 2008). Small handheld electrochemical cholesterol meters for use in sports medicine capable of intermittent "spot" cholesterol monitoring are being manufactured by Biomedical Diagnostics Institute (Ireland). High levels of cholesterol concentration in the blood have been linked to damage to arteries and are potentially linked to diseases such as those associated with the cardiovascular system, which can lead to life-threatening shock, and its measurement has therefore become a vital component in medical

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monitoring. Recently, MNPPF is high desirable material for cholesterol sensor because of their biocompatibility and more surface area (nanosize materials) can effectively improve to the loading enzyme per unit to volume ratio of support and the excellent catalytic efficiency of the immobilized enzyme. Numerous patents and papers on MNPPF for cholesterol sensor were published (Khan et al., 2008; Ansari et al., 2008). The general mechanism is evidence that cholesterol in a membrane environment may be attacked more readily than the polyunsaturated fatty acids by reactive oxygen species, leads to main types of product (Iuliano, 2011).

Non-enzymatic cholesterol sensors were fabricated on silicon substrates for U-health and point of care system applications by using a non-ionic surfactant and electroplating technique, followed by nanoporous Pt deposition, showed linearity (10 μM–8 mM) and good temperature tolerance up to 50 °C (Lee et al., 2009). Further, macroporous Au-/nPts electrode was fabricated by electroplating PtNPs onto a coral-like shaped macroporous Au electrode structure using polymer and surfactant template for cholesterol detection (Lee and Park, 2010).

Up to now, conventional cholesterol sensor is not available in literature. A drop of blood from your finger is all that is needed to use kits and this test in a few minutes with accurate and inexpensive way to test your cholesterol level at home. OrSense Ltd., based in Rehovot, Israel, was devoted to the pioneering and development of non-invasive monitors of cholesterol in blood based on electro-optical technology performs non-invasive blood measurements by means of a finger probe, eliminating the need to draw blood by needle-stick.

3.5. MNPPF for urea sensor

Urea is very significant parameter as excess in blood serum from its permissible range causes dysfunction of the kidney in clinical analysis and dairy industry urea. Typically, its physiological levels range between 2.5 mM and 8.6 mM in serum depending on the daily protein ingestion (Beers and Berkow, 1999) and its analysis carried out frequently in various laboratories (Luo and Do, 2004). Small handheld electrochemical urea meters for use in medicine capable of intermittent "spot" urea monitoring are being manufactured by Urea assay Kit (ab83362) (Abcam plc UK). Small drop of urea is placed on the disposable electrode to determine the concentration of urea with high sensitivity and less cost are desirable. Generally, the urea sensor utilizes modified electrode and Urease as a transducer and selective enzyme, respectively. The mechanism of urea sensor at modified electrode was:

$$NH_2CONH_2 + 3H_2O \rightarrow 2NH_4^+ + OH^- + HCO_3^-$$

Urea monitoring procedure usually sets out from a urea hydrolysis reaction by urease/metals. When the sensing electrode is immersed in a test solution, there will be a selective response to urea. The resulting ions can be detected with an ion-sensitive membrane, or a gas-sensing electrode (Fig. 5B). Under this condition, the current on account of the water dissociation flows, which is proportional to the urea concentration and measured by voltammetry. Non-enzymatic urea sensor was initiating by Kozitsina et al. (2009), based systems based on the organic nickel(ii) complexes. Non-enzymatic urea sensor is ongoing research and it will be reach to all (sensor) in one hand.

3.6. MNPPF for amino acids and proteins detection

Identification and quantification of specific amino acid and proteins is an important issue in medical and clinical research. MNPPF used for amino acid and protein sensing due to their response in the presence of different analytes. Development in MNPPF based amino acid and protein sensors are current field. The first label-free electrochemistry of proteins came from mercury electrodes. Peptides and proteins containing cysteine/cystine showed specific electrochemical signals on mercury electrodes with the help of Hg–S bond formation (Havran et al., 2004; Palecek and Ostatna, 2007), reduction of disulfide groups (Tomschik et al., 1998), and the catalytic evolution of hydrogen in cobalt containing solutions (Brdicka reaction) (Brdicka, 1933; Heyrovsky, 2004). Fan et al. (2011), who reported Nafion/TiO_2/graphene/GCE electrode for response to the amino acids L-tryptophane and L-tyrosine with 0.7 and 2.3 μM LODs, and a sensitivity of 75.9 and 22.8 μA mM^{-1}, respectively. Further, Sharifi et al. (2012), simultaneously detection of cysteine and homocysteine at DNA/NiOxNPs/Os(III)-complex modified GCE without any separation or pretreatment process.

As for developing electrochemical protein sensor there are basically five different pathways summarized (Vestergaard et al., 2007): a change in the electrochemical signal of (i) a label, which selectively binds with the target protein (thyrombin,lysozyme, human IgE and insulin, etc.) (ii) electro-active amino acids (tyrosine, alanine tryptophan, etc.) of antibody or target protein, (Herzog and Arrigan, 2007), (iii) a secondary antibody-tagged probe, (iv) aptamers- and (v) an enzyme tagged probe can be monitored (Bini et al., 2007; Centi et al., 2007). Protein sensor based on transducer (MNPPF), fast, simple, and sensitive are desirable. Recently, using glycopolymer-modified AuNPs for electrochemical studies of saccharide–protein interactions new electric approach were proposed (Fig. 6) (Ishii et al., 2011). PVP-capped CdS particles were used

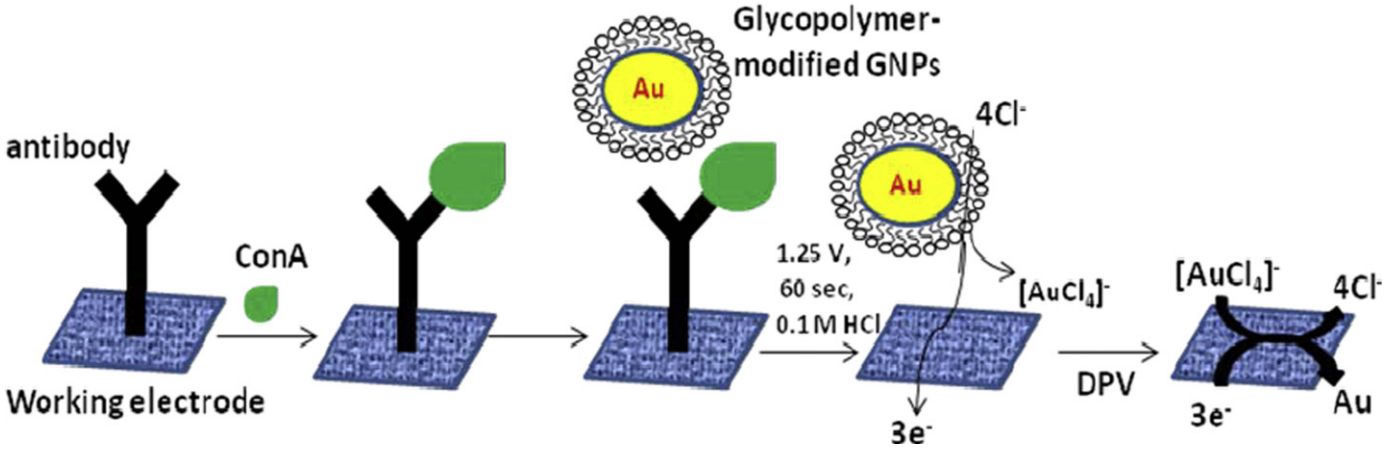
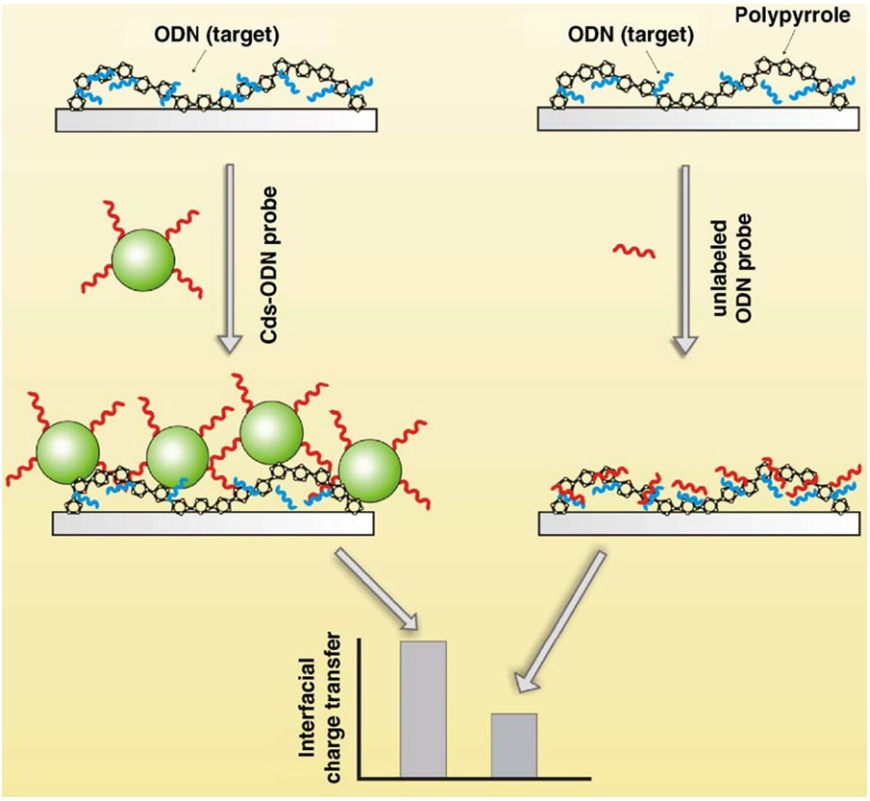


Fig. 6. Schematic diagram of glycopolymer-modified AuNPs for electrochemical studies of saccharide–protein interactions.



Scheme 1. Mechanism underlying the sensor response. (Top) Formation of a layer of CdS–ODN nanoparticles on the PPY-ODN film after hybridization. (Bottom) Binding of unlabeled ODN probes to the PPY-ODN film.

for haemoglobin electroanalysis, allowed the achievement of a 5 nM LOD (Liu et al., 2006). Omidfar et al. (2012), developed the high sensitivity electrochemical HSA sensor based on HSA/AuNPs (electrochemical label), MCM-41/PVA (immobilised platform) was exhibited with 1 μM LOD and excellent stability. So far, protein and amino acids sensors have been intensively developed, although many improvements are required in reproducibility and sensitivity. More, there is no doubt that a growing number of proteins and, it is to be hoped, MNPPF based label-free electrochemical biosensors will soon be used for the diagnosis and therapeutic follow-up of diseases.

3.7. MNPPF for DNA and neurotransmitters sensor

Electrochemical DNA sensors are applied to problems in transcriptional profiling and SNP detection. Osmetech has commercialized an electrochemical DNA sensor (eSensor®) based on the selective interaction between self assembled thiol with gold electrode surface and target DNA in the sample (Ronkainen et al., 2010). MNPPF based electrochemical DNA and neurotransmitters sensors are very attractive features such as good selectivity, sensitivity, stability, reusability and easy preparation. Better sensitivity and low LOD (42 ρM) of DNA detection preformed at AuNPs/Cys/PGA/GCE electrode (Zhang et al., 2009). Same authors, AgNPs/PPAA/MWCNTs-COOH/GCE reported for 3.2 ρM LOD complementary oligo nucleotides (ODN) detection (Zhang et al., 2009a). Specific ssDNA sequence was detected at V_2O_5/MWCNTs/CT/ CILE with 1.76 ρM LOD (Sun et al., 2010). Lee et al. (2003) also improved electrochemical DNA hybridisation detection at Au and ITO electrode modified with 11-mercaptoundecanoic acid and the polyelectrolytes PSS and PAH on Au electrodes by avidin–biotin interaction. Bonanni et al. (2008) applied the streptavidin-coated AuNPs/graphite epoxy composite electrode to improved charge transfer resistance signal for DNA hybridization. Further, enhancement in resistance value was achieved by using CdS NPs tagged-probe ODN for the hybridization of target ODN physically entrapped in the PPy film (Peng et al., 2006).The Scheme 1 shows a schematic mechanism of the sensory response by CdS NPs tagged-probe ODN on the PPY- target DNA.

Recent times, subject of neurotransmitters detection has been considerable interest in electro-analytical chemistry due to its play a crucial role in the functioning of the central nervous, cardiovascular, renal, and hormonal systems. AuNPs, PDDMAC, and PANI nanocomposites were formulated for DA detection with 50 μM low concentration (Prakash et al., 2009). Au/MPTMS/ITO electrode was used for selective detection of EP (Zhang et al., 2005). PdNCs/PMPy/Pt electrode was applied for routine analysis of AA (7 μM LOD), DA (12 nM LOD), and UA (27 nM LOD) in clinical tests (Atta et al., 2010).

3.8. MNPPF for detection of minerals in bio-fluids

Na^+, K^+, Ca^{2+} and Mg^{2+} etc., are essential minerals for dietary physiology. In normal physiological condition, the level of Na^+, K^+, Ca^{2+} and Mg^{2+} are 1.5 g, 4.7 g, 1.3 g and 0.42 g of RDA/AI, respectively (Nelson and Cox, 2000). Na^+ and K^+ are essential in co-regulating ATP. Ca^{2+} are needed for muscle, heart and digestive system health, builds bone, supports synthesis and function of blood cells. Mg^{2+} is required for processing ATP and bones. Thus, quantification of minerals needs to be monitored. Simple method, potentiomteric detection continues to be developed to monitor the minerals (Nelson and Cox, 2000) using ISE and it's prepared by polymeric membrane coated metal electrode (Buhlmann and Chen, 2012). MNPPFs was of great significance in development of ISE, because their versatility nature. Ferrocene modified electrode having high affinity with Ca^{2+} ion through co-ordination bond, showed feasible detection of Ca^{2+} ion (Maynadie et al., 2004). Numerous ISE have been commercial

product present by Orion ISE Series, Omega technology and Forston technology. However, need to improve the sensitivity and selectivity towards minerals detection.

4. Concluding remarks: Future prospects and challenges

MNPPF have become vibrant area of chemical research, particularly within the past five years. Dozens of different chemical reactions have been reported on MNPPF that include both organic transformations and inorganic reactions (ligand or metal addition/exchange). The resulting materials have been shown to provoke MNPPF with new electrochemical properties relevant to sensor, catalysis, and biomedical applications. The surge in interest and improved success no doubt coincides with the development MNPPF, allowing for higher surface areas, improved oxidation kinetics, and better selectivity. MNPPF catalytic efficiency continues to play an important role in many clinical environmental, industrial, pharmaceutical, defense, and security applications due to their superior sensitivity and selectivity. MNPPF based electrochemical biosensor electrodes offer high sensitivity, the possibility of long term stability, a resistance to thermal implications, and a low cost, simple and reproducible fabrication method, and as such they require a renewed approach to their design and development. Further, it will further push the development of useful and reliable electrochemical biosensor devices. However, certain limitation in uncertainty of its working mechanism, time-consuming characterization, shelf life and stability are biggest difficulty in electrochemical biosensor. Close to look the enzymatic electrochemical biosensor were obstruct their enzyme cost, whilst enzymatic free from it based on the MNPPF. To overcome before they supersede enzyme technology, though it would seem the goal of non-enzymatic sensing is close to being realized.

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