Detection of Pathogens using Polythiophenes

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ABSTRACT

The utility of polythiophenes as chemical and electrochemical sensors is assessed across the literature for the last decade. Polythiophenes can be used as an alternative method to traditional surface modifications for the detection of biomolecules. Moreover, polythiophenes amplify the optical and electrochemical signals allowing the facile recognition of target molecules. Their high conductivity and stability facilitate the design of polythiophene-based sensors for the detection of pathogens. The analytes observed in particular are Escherichia coli (*E. coli*) and Salmonella enterica. The optical and electrochemical property changes of polythiophenes resulting from the interactions with pathogens will be investigated.

Keywords: Polythiophenes; Pathogens; Fluorescence; Electrochemical sensors

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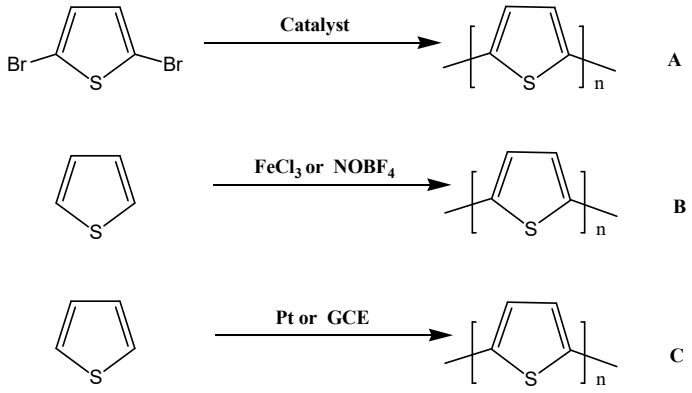
INTRODUCTION

Due to their high conductivity, excellent stability and reversible electrochemical properties, polymer-based conducting materials have attracted much attention [1-3]. They can be used in tissue engineering [4], energy storage [5,6], and medical applications [7]. The electrochemical sensors developed from conducting materials help with the minimization of organic contaminants on the surface, which affect the detection of biomolecules. Moreover, it was reported that polymer-based sensors demonstrate antimicrobial activity, which is required for biomedical applications [8]. Electrodes modified by redox conducting films, in combination with nanoparticles, can be used for the detection of enzymes, and other biological molecules [9]. Further studies show promise in polymer electrodes carrying conductors such as carbon nanotubes to efficiently improve the detection of molecules [10,11]. It was also reported that the incorporation of carbon nanotubes within the resulting electropolymerized polymers enhances the electrical/thermal conductivities, and the stability of the films on the surfaces of electrodes [12]. Sensors based on conducting materials and nanomaterials present several advantages such as lower limit of detection (LOD) of target molecules, a rapid response, and a better signal to noise ratio [13]. Polythiophenes are excellent conducting materials and have been used for the detection of several biomolecules such as oligonucleotides and amino acids. They are highly conducting, stable at both states on electrode surface, and their chemistry is well-established [14].

In this review, we describe the utilization of polythiophene-based sensors over the last decade for the detection of pathogens such as E. coli [15] and Salmonella enterica [16]. Changes in optical and electrochemical properties of polythiophenes surfaces will be discussed.

POLYTHIOPHENES

Different methods have been reported for the preparation of polythiophenes. They can be obtained via cross-coupling reaction (Scheme 1A) using a catalyst [17,18], chemical oxidation using $FeCl_3$ or $NOBF_4$ as oxidizing **agents (Scheme** 1B) [19,20], and electrochemical polymerization beyond the oxidation potential of the monomers on platinum (Pt) or glassy carbon electrodes (GCE) (Scheme 1C) [21,22].



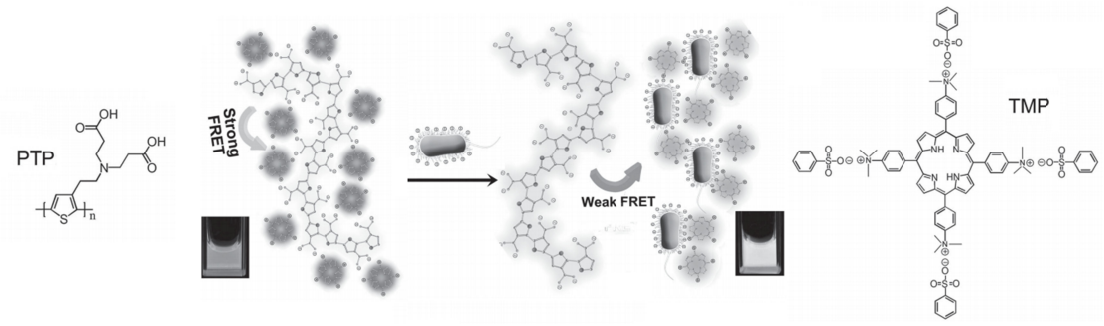
Scheme 1: Synthesis pathway of polythiophenes

The electrochemical oxidation using Pt or GCE electrode is the method commonly used for the deposition of polythiophenes on electrodes surfaces. This method is easy to use, gives rapid results and allows direct deposition of doped polythiophenes on the surface of the electrode, which facilitates the characterization of the electrochemical and optical properties.

DETECTION OF *E. COLI*

Food contaminated with bacterial pathogens is a leading cause of death worldwide [23]. E. coli is an important bacterial pathogen to be considered when developing a rapid and efficient method of detection due to their potential for outbreaks [24,25,26]. The detection of bacteria is deemed excessively time consuming, and thus the use of polythiophene derivatives based sensors permit a fast response.

Yan *et al.* described sensor based-polythiophenes for the detection of microorganisms and bacterium [27] in sources of drinking water using fluorescence resonance energy transfer (FRET), where polythiophene derivatives (PTP) and the [5,10,15,20-tetrakis(4-(trimethylammonio)-phenyl)-21H,23H-porphine tetratosylate] moiety (TMP) act as an anionic donor and a cationic receptor, respectively (Scheme 1). PTP and TMP were characterized by UV-vis and fluorescence emission spectra. The absorption maximum was found to be 438 nm for PTP and 412 nm (Soret band) for TMP. The emission maxima were found to be 560 and 655 nm for PTP and TMP, respectively. The excitation at 440 nm of the complex PTP/TMP shows a decrease of the florescence intensity of PTP and an increase of the one of TMP. At a concentration of 0.2 10^{-6} M of TMP, PTP was completely quenched. The FRET ratio ($I_{655\ nm}/I_{560\ nm}$) of the PTP/TMP was also increased. In the absence of E. coli bacteria, the optical signal of TMP has been amplified 5 times by PTP, which is due to the strong electrostatic interactions between anionic and cationic motifs. Figure 1a displays the fluorescence spectra of PTP/TPM complex in aqueous solution in the absence and presence of E. coli. The emission spectra of the PTP/TPM complex have also been tested in double distilled water (ddH_2O) and in tap-drinking water with an excitation wavelength of 440 nm as shown in figures 1c and 1e. In the presence of E. coli, the fluorescence intensity of TPM decreases whereas the fluorescence intensity of PTP increases. This behaviour is due to the electrostatic and hydrophobic interactions between the bacteria and TPM creating a gap between PTP and TPM, which leads also to a decrease of the FRET ratio ($I_{655\ nm}/I_{560\ nm}$) of the PTP/TPM complex. The FRET ratio reaches a plateau after CFU goes beyond 1.75×10^6 mL^{-1} for ddH_2O (Figure 1d) and 20×10^6 mL^{-1} for tap-drinking water (Figure 1f). Moreover, the emission color changed from red to yellow after addition of E. coli (Figure 1b).



Scheme 1: Diagram representing the strategic approach to using FRET to detect bacteria in drinking water, Reproduced with permission from [27].

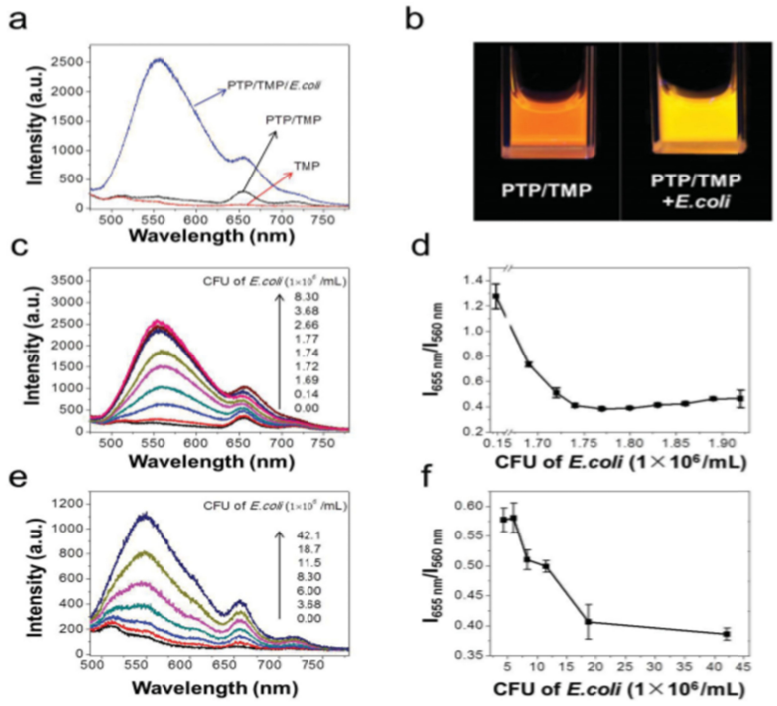


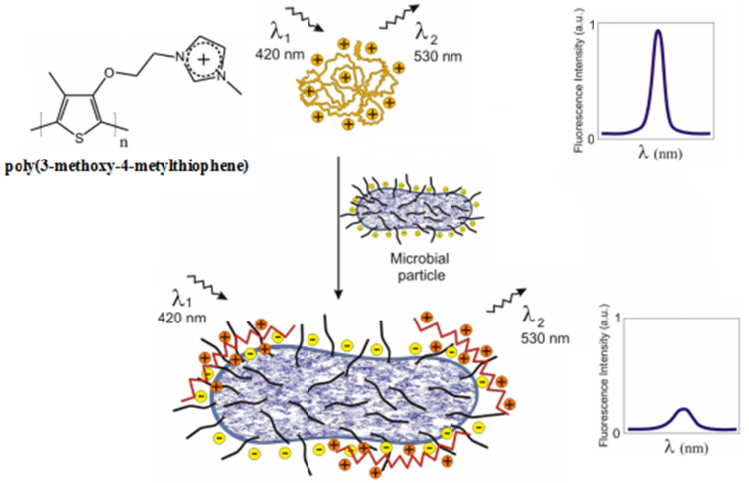
Figure 1: (a) Fluorescence intensity of the PTP/TMP complex in the presence and absence of E. coli. (b) UV vis spectra. (c) Fluorescence emission spectra obtained during the process of successive addition of E. coli in ddH_2O. (d) FRET ratio (e) Fluorescence emission spectra in the presence of E. coli in tap water. (f) FRET ratio. Reproduced with permission from [27].

Additionally, the adsorption of E. coli on TMP has been confirmed by phase-contrast and fluorescence microscope images. Using poly[3-(3′-N,N,N-triethylamino-1′-propyloxy)-4-methyl-2,5-thiophene hydrochloride] (PMNT) E. coli has been detected in ethanol aqueous solution. After gradual addition of E. coli, the fluorescence emission intensity of PMNT decreased as depicted in figure 2a. The fluorescence quenching efficiencies ($1 - I/I_0$) of PMNT enhanced by the presence of E. coli and reached a maximum value of 3.0×10^5 CFU/mL [28].

The observed fluorescence quenching is due to the electrostatic interactions between the negatively charged E. coli and the cationic PMNT, which was validated by phase-contrast and fluorescence microscope images (Figures 2c, d). Moreover, PMNT/polyisocyanide hybrid hydrogels have been found to have efficient antimicrobial activity toward a variety of pathogens including E. coli [29].

Similar results have been reported using a water-soluble sensor based on cationic poly(3-methoxy-4-metylthiophene). The formation of aggregates between

the E. coli and the polythiophenes yield to the fluorescence quenching (Scheme 2). In this study, it was found that the fluorescence quenching is influenced by the temperature, the presence of salts, and other contaminants in drinking water [30].



Scheme 2: Interactions of E. coli/polythiophenes. Reproduced with permission from [30].

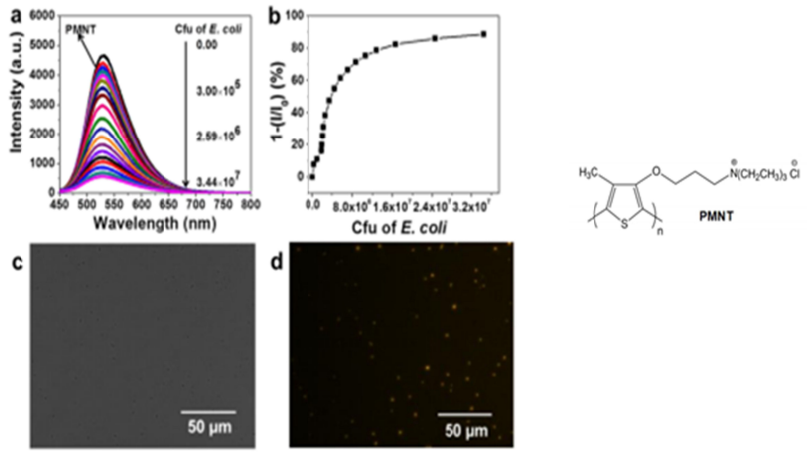


Figure 2: (a) Fluorescence emission spectra of PMNT in a 40% ethanol aqueous solution with the successive addition of an E. coli suspension. (b) Fluorescence quenching efficiencies of PMNT with different amounts of E. coli (c) Phase-contrast image and (d) fluorescence microscopy image of the PMNT/E. coli complex. Reproduced with permission from [28].

Other cationic polythiophenes such as imidazolium/ammonium functionalized poly(hexylthiophene) demonstrated excellent inhibition of E. coli bacteria by 97.5% [31,32]. Ammonium functionalized polythiophenes have been utilized to detect a variety of bacteria including S. aureus, S. epidermidis and P. aeruginosa [33].

Another study performed by Sinsinbar *et al.* showed the use of an unlabelled peptide with a polythiophene acetic acid (PTAA) for rapid detection of E. coli in drinking water. It was noted that the incorporation of an unlabelled peptide, which corresponds to the outer-membrane protease (OmpT) of E. coli improves the selectivity of previous sensors [34]. These proteases are noted to be present at the surface of all wild-type strains of the bacterial pathogen. Screening libraries have been exploited to determine the ideal peptide sequence for the detection of E. coli. CLLGDFFRRVKEKIG peptide ($LL37_{FRRV}$) was the preferred fragment for this study because it offered an ideal catalytic efficiency.

PTAA has an absorption maximum at 450 nm and displays a fluorescence emission maximum at 550 nm after excitation at 420 nm. After addition of peptide $LL37_{FRRV}$, a blue shift accompanied with an increase of the fluorescence intensity has been observed. These changes in the optical properties of PTAA in the

presence of $LL37_{FRRV}$ can be explained by the change of the geometry adopted by the PTAA backbone. PTAA is a π-conjugated system in which its backbone has a planar conformation, which was lost after addition of $LL37_{FRRV}$. The peptide $LL37_{FRRV}$ transmits its chirality to PTAA, resulting in a change of the conformation geometry of polymer backbone (non-planar) and causing a blue shift of the PTAA absorption, and an increase of the fluorescence emission intensity by 200%. It was reported that cleaved $LL37_{FRRV}$ has no effect on the optical properties of PTAA. The sensor PTAA/ $LL37_{FRRV}$ has been used to recognize different E. coli stains as presented in Figure 3. In figures 3B, Black, E. coli BL21 was used as a negative control and did not show any change in the fluorescence intensity of PTAA. The change of PTAA/$LL37_{FRRV}$ solution color can be perceived with the naked eye (Figure 3A). Moreover, all E. coli strains cause a significant reduction in the fluorescence intensity of PTAA by cleaving the peptide $LL37_{FRRV}$. Using this method, 1 CFU/mL of E. coli has been rapidly detected in water.

Two electrochemical/Quartz Crystal Microbalance (QCM) sensors for the detection of E.coli bacteria based on quinone functionalized polythiophenes and carbohydrates are outlined in scheme 4 [35]. Similar sensors have been developed using self-assembled monolayers (SAM) on Au electrodes [36]. The bacteria were detected via two transducers pili-mannose (A) as well as Concanavalin A (Con A) mediated lipopolysaccharides (LPS)-mannose (B). Quinone functionalized polythiophene was deposited on gold (Au) electrode by electrochemical oxidation of the corresponding monomer quinone-thiophene (QT) via cyclic voltammetry scans in acetonitrile. After ensuring stability of the film on the surface of the electrode, the transducers thiol mannose (SM) was deposited on the sensing layer by cyclic voltammetry scans. Both SM/QT/Au (Scheme 3A) and Con A/LPS/SM/QT/Au (Scheme 3B) surfaces were characterized by cyclic voltammetry. The binding process and the efficiency of both sensors (SM/QT and Con A/LPS/SM/QT) toward the detection of E. coli bacteria have been examined by square wave voltammetry (SWV) and QCM. SWV is more sensitive than cyclic voltammetry for the characterization of the phenomena occurring at the biointerfaces.

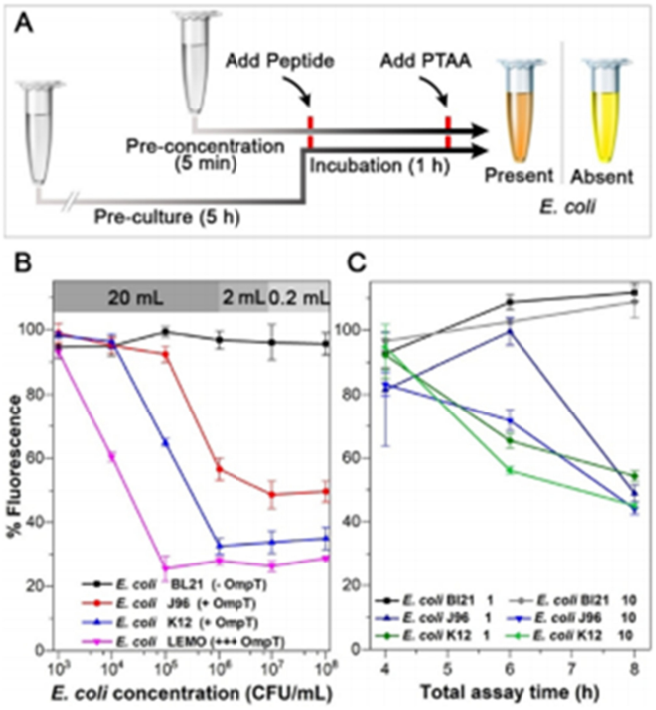
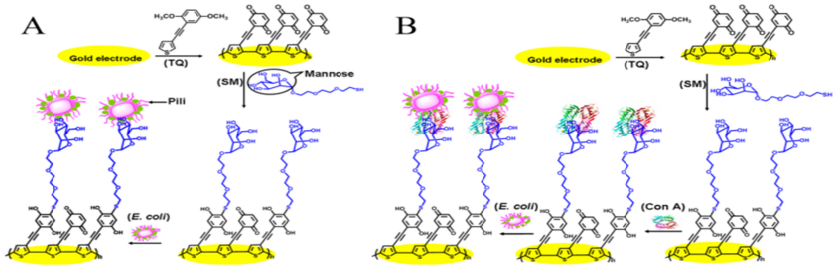


Figure 3. A) E. coli sensing using PTAA-$LL37_{FRRV}$ B). Fluorescence intensity of PTAA when mixed with $LL37_{FRRV}$ with different E. coli strains C) Fluorescence intensity of PTAA when mixed with $LL37_{FRRV}$ with E. coli K12 or J96 wildtype strains. Reproduced with permission from [34].



Scheme 3: (A) a direct E. coli detection using pili-mannose binding and (B) a Con A-mediated E. coli detection using LPS-mannose binding. Reproduced with permission from ref [35].

Figure 4A describes the SWV of the SM/QT/Au sensor after incubation with different concentrations of E. coli. It is worth noting that current of the SM/QT/Au sensor decreases by increasing the concentration of E. coli. This behaviour can be explained by the formation of an E. coli layer at the biointerface hindering the electron transfer of the electroactive species quinone/thiophene in the SM/QT/Au. Similar behaviour has been observed on chiral electrodes for the detection of amino acids. The limit of detection was found to be 8.0×10^2 cells/mL.

Figure 4B exhibits the electrochemical QCM (EQCM) measurements, which were performed with a single QCM electrode. The limit of detection was found to be 1.7×10^4 cells/mL, which is higher than the one found by SWV detection. Similar trends have been observed for Con A/LPS/SM/QT/Au sensor for the detection E. coli (Figure 5). The limits of detection were found to be 25 cells/mL and 50 cells/mL using SWV and EQCM techniques, respectively. E. coli strongly binds to the Con A/LPS/SM/QT/Au sensor.

Another electrochemical impedimetric biosensor based on mannose-functionalized poly(3-hexylthiophene)-b-poly(3-triethylene-glycol-thiophene) (P3HT-b-P3TEGT) nanoparticle for the detection of E. coli has been developed [37]. The sensor was fabricated by drop-casting of a solution mannose/P3HT-b-P3TEGT/ on GCE. Its performance toward detection of E. coli bacteria was evaluated by electrochemical impedance spectroscopy method (EIS). The modified mannose/P3HT-b-P3TEGT/GCE was incubated in a solution of E. coli. After 1 hour, the sensor was washed with deionized water to remove all free E. coli bacteria. Figure 5 describes the Nyquist plots recorded for the sensor. The width of the semicircle depends on the incubation concentration of the bacteria (Figure 6A, b-f). The E. coli bacteria attached to the surface of the sensor affects the electrical properties of the sensing layer at the interface. The limit of detection (LOD) was found to be 500 CFU/ml. Additionally, it was reported that the sensor presents outstanding selectivity toward E. coli recognition (Figure 5D). Furthermore, mannose plays an important role for bacteria detection. SEM images confirm that there is no adsorption of E-coli on P3HT-b-P3TEGT alone (Figure 7a), whereas the bacteria adhered with P3HT-b-P3TEGT/mannose (Figure 7b).

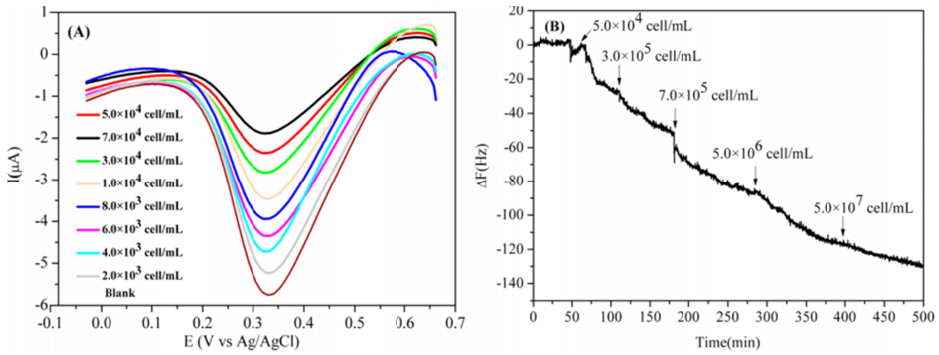


Figure 4. (A) SWV responses of an SM/TQ modified gold electrode after incubation with different concentrations of E. coli. (B) QCM frequency change vs time curve when SM/TQ was exposed to different concentrations of E. coli. Reproduced with permission from [35].

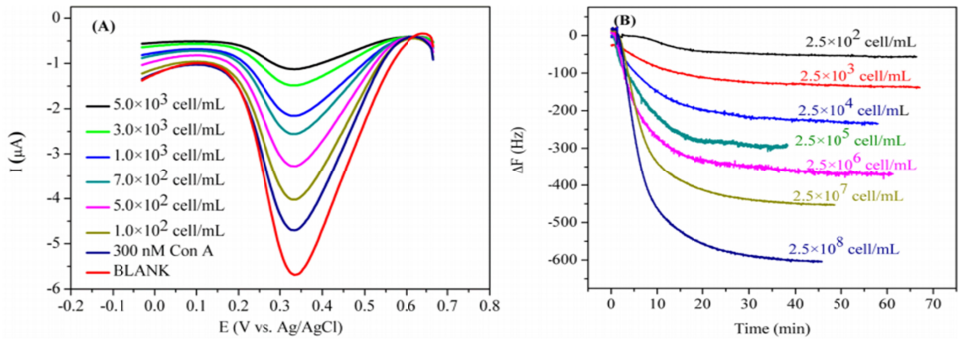


Figure 5. (A) SWV- responses of an SM/TQ gold electrode after incubation with 300 nM Con A and different concentrations of E. coli. (B) QCM frequency change vs time curve when Con A/SM/TQ electrodes were exposed to different concentrations of E. coli. Reproduced with permission from [35].

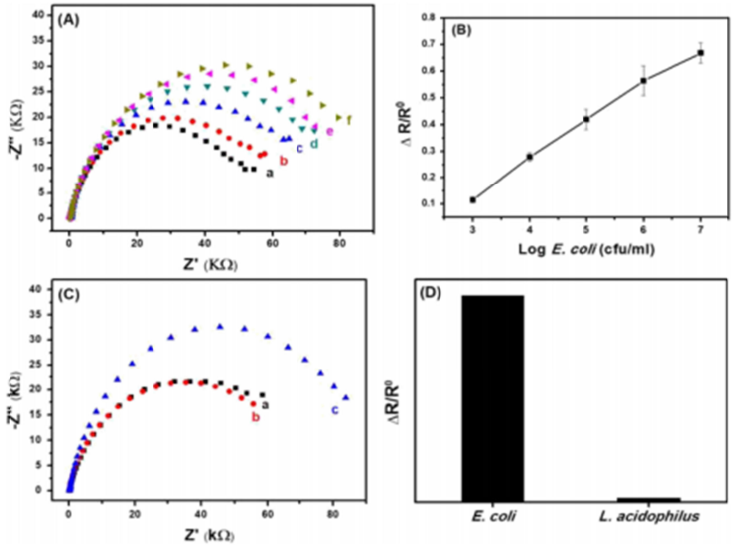


Figure 6: (A) Nyquist diagrams of a P3HT-b-P3TEGT/mannose-modified GCE obtained with increasing concentrations of E. coli in PBS: (a) Biosensors in PBS free of bacteria, (b) 103 cfu/mL, (c) 104 cfu/mL, (d) 105 cfu/mL, (e) 106 cfu/mL, (f)107 cfu/mL; (B) calibration curve; (C) Nyquist plot for selectivity test of P3HT-b-P3TEGT/mannose-modified GCE; (c) E. coli detection compared to (b) L. acidophilus and (a) free of bacteria; (D) histogram of average variation between the two bacteria. Reproduced with permission from [37].

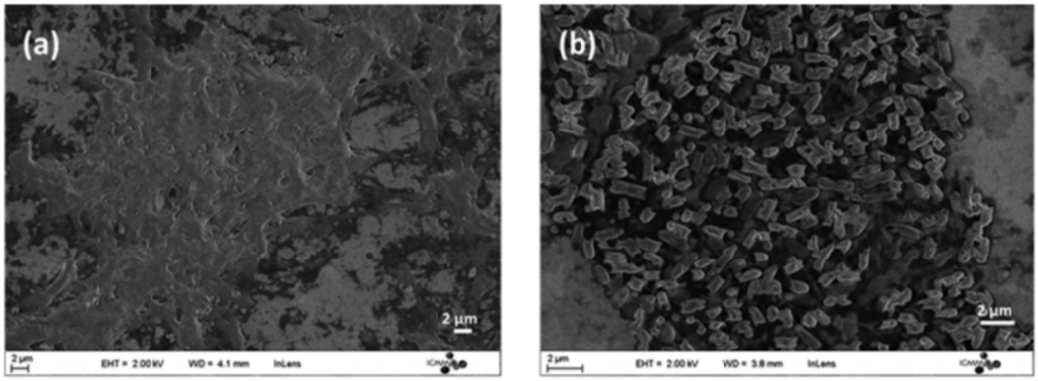


Figure 7: SEM images after incubation with E. coli (1.0 × 107 cfu/mL): (a) P3HT-b-P3TEGT film and (b) P3HT-b-P3TEGT/mannose film. . Reproduced with permission from [37].

DETECTION OF SALMONELLA

Salmonella is among foodborne pathogens that pose a threat to the health and wellness of humans [38,39]. Its presence in food may cause severe damage that requires painful and costly medical treatments, forcing further strain on the healthcare systems. Consequently, the fast detection of Salmonella in food is a necessity in order to

minimize the risk of infections to the general public. Biochemical [40] and PCR [41] techniques are the methods used to detect salmonella. However, these sensitive techniques require a multi-step process, which increases the time necessary for a diagnosis, enhancing the possibility of contamination. Electrochemical methods are a powerful tool that can be used to rapidly detect Salmonella and avoid subsequent deaths from caused by foodborne illnesses. Moreover, they present several advantages such as low cost, rapid screening data and ease in operation. An effective electrochemical DNA multiwall carbon nanotube (MWCNT) functionalized ITO sensor using cyclic voltammetry and EIS for the detection of Salmonella in food samples has been developed [42]. Other electrochemical sensors based on nanoparticles [43,44] and polypyrroles [45] have been utilized to detect salmonella. Nanoparticles and polypyrroles amplify the electrochemical signals and thus facilitate the sensing process.

Several approaches using polythiophenes modified electrode sensors examined either the detection of the Salmonella bacteria or biofilm components resulting from bacterial growth. Salmonella bacteria was detected by electrochemical QCM sensor through immobilizations of a protein A (PrA) and an anti-body S-IgG on the surface of polythiophenes modified electrode [46]. The presence of PrA and S-IgG on the surface of polythiophene modified electrode sensor was confirmed by fluorescence and Raman spectroscopies. Figure 8 describes the QCM responses of Salmonella on polythiophene as opposed to gold electrode sensor. For both surfaces Salmonella was recognized by S-IgG antibody.

For gold surfaces, two stages of Salmonella detection have been observed. The first stage between 0-500 s corresponds to the S-IgG/Salmonella interaction. The second stage after 500 s may correspond to the non-specific bacterial interactions. For polythiophene modified electrode surface, only S-IgG/Salmonella interaction has been observed.

Recently, it has been reported that the growth of Salmonella biofilms depends on the redox properties of the contact surfaces. A highly conducting polythiophene polymer PEDOT (poly(3,4-ethylenedioxythiophene)) was employed as a prototype for this study. PEDOT doped with different counter ions were prepared via electrochemical oxidation of the corresponding monomers [47]. The doped PEDOT (oxidized state) promotes the formation of biofilms whereas the undoped PEDOT (reduced state) inhibits their growth. This behavior can be explained by the electron density present on PEDOT at both states. At oxidized states, there is an electron sink allowing the respiration of bacteria and thus supporting biofouling process. Nevertheless, in the reduced state, the presence of high electron density prevents the bacteria from respiring, which reduce the bacterial growth (less fouling). In another study, luminescent oligothiophenes have the ability to probe Salmonella biofilm components such as curli protein and cellulose [48].

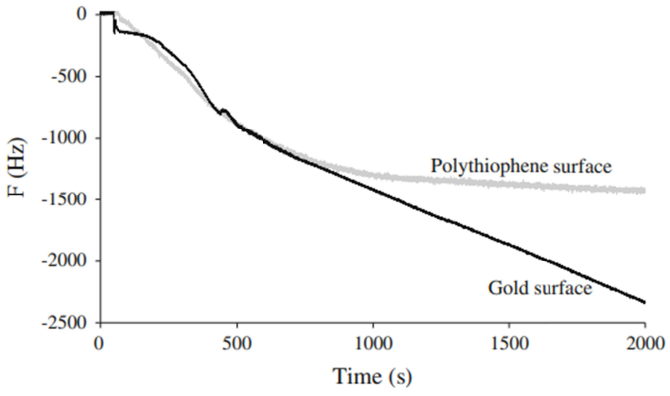


Figure 8: Quartz crystal microbalance responses to Salmonella immobilization on both polythiophene and modified gold surfaces (afterPrA and S-IgG successive immobilizations). Reproduced with permission from ref [46].

CONCLUSIONS

Polythiophene-based sensors have demonstrated their utility for the detection of pathogens such as E. coli and Salmonella. The ability to modify their optical and electrochemical properties enables tuning for bacteria detection. Additionally, the antimicrobial properties of polythiophenes offer significant opportunities for the development of rapid, cost-effective portable devices for the detection of these harmful pathogens.

Optical detection of pathogens may have some drawbacks such as biomolecule interferences, which limit their application in sensing. On the other hand, doped polythiophene combined with the appropriate electrochemical detection method can be advantageous for sensor design. Polythiophenes also have outstanding adhesion properties on platinum electrodes allowing the sensing layer to carry unambiguous transducers for the detection of pathogens in food, to avoid diseases.

CONFLICTS OF INTEREST STATEMENT

There are no conflicts to declare.

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