APPENDIX A

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Molecularly imprinted polymer-modified electrode for on-line conductometric monitoring of haloacetic acids in chlorinated water

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conductometric sensor for on-line testing of haloacetic acids has been developed based on lab-on-chip device incorporated with an inte-d miniaturised liquid-handling system. The sensor utilises a molecularly imprinted polymer (MIP) synthesized by the interaction between roacetic acid (TCAA) template and a functional monomer, 4-vinylpyridine (VPD), together with cross-linking polymerisation of ethylene l dimethacrylate (EDMA). The ability of this MIP to change its conductivity in the presence of the target molecule into the imprint cavity has used to develop the sensor, which responds well to TCAA in a continuous flow system with relatively good linearity, although this depends on plied frequency. Thermal influences on the resistance of the sensor were in the order of 1.45% resistance signal variation per Kelvin at 3 kHz. sensor showed high specific sensitivity to the target analyte and a stable and reasonable signal response in a solution containing inorganic s. The sensitivity (range 0.5–5 $\mu g\,l^{-1}$) and selectivity achieved with standard TCAA and five other haloacetic acids (HAAs) (dichloro-, chloro-, tribromo-, dibromo-, and monobromoacetic acid) in water was good. Minimum sample volume required is 2.5 ml and the assay time in. The sensor has successfully been applied to haloacetic acid determination in domestic and commercial drinking water samples.

ords: Molecularly imprinted polymers; Disinfection by-products; Charge transfer complex; Haloacetic acids; Flow-through electrochemical system

troduction

aloacetic acids (HAAs) are disinfection by-products of the ination of drinking water that are known to cause serious h problems [1,2]. For example they are reported to cause creased risk of certain cancers, in particular of bladder nd rectal [4] cancers. Instrumental methods such as ion atography, GC–ECD, GC–MS and LC–MS, for determ-ng HAAs are time consuming, complicated and expensive utine analysis. Fast and sensitive screening methods could essential complement to these sophisticated instrumental ods. Importantly, a special electrode technique offers the bility of on-line testing for HAAs.

Electrochemical type of sensors (e.g. voltammetric, potentiometric, conductometric and capacitance) are becoming important tools in medical, biological and environmental sciences due to these simplicity, high sensitivity and relative cheapness [5,6]. The interest in conductometric sensors has been generated by their simplicity and easy fabrication. In particular, a conductometric transducer consisting of an interdigitated array electrode on a planar surface is suitable for miniaturization and mass production using photolithography or screen-printing technology [7]. Normally conductometric is the least selective of the electrochemical techniques, as it is difficult to distinguish between different ions. However, the sensitivity and specificity of this system can considerably be improved by incorporating it with highly selective recognition elements (either biological or synthetic substances).

Molecularly imprinted polymers (MIPs) are attractive as versatile and inexpensive materials capable of molecular recognition [8–10]. MIPs consist of highly cross-linked polymers that

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re synthesized in the presence of a template molecule [11,12]. bsequent removal of the template leaves a cavity that retains ffinity and selectivity for the template. The cavity is analogous the 'active site' of enzymes. Interest in the use of MIPs in ectrochemical sensors is increasing [13–16]. This is due to e advantage that the MIP gives to the electrochemical sensing vice, both in terms of the stability obtained from the abiotic operty of the MIP and the ease of operation and storage of the vice when fabricated with the MIP. Nevertheless, the transmation of MIP into a measurable electrochemical signal is nsidered to be an important factor, as this has been found to an obstacle in developing this type of material in electroemical sensor technology [16,17].

The aim of this work was to construct a conductomet c sensor for on-line detection of haloacetic acids in chloated water by using molecularly imprinted cross-linked ly(ethyleneglycoldimethacrylate-*co*-4-vinylpyridinium) salts ecific for trichloroacetic acid (TCAA) and structurally simar compounds as the recognition element. The sensor was signed as part of a lab-on-chip and has been successfully corporated into a miniaturised flow-through cell. An inteated sensor specific for the target analyte was fabricated ing gold screen-printing to deposit the interdigitated conducmetric electrodes at the glass plate, with measurement based detection of MIP-containing artificial recognition sites for CAA and its analogues. Additionally, the ability of molecularly printed cross-linked poly(ethyleneglycoldimethacrylate-*co*-vinylpyridinium) salts to change its conductivity due to e placement of the target molecule into the imprint cavy has been used to develop a detector for HAAs. The nylpyridinium entity fabricated into the MIP would form arge-transfer complexes with the target analyte HAAs, hich would produce the continuous conducting phase of e insulating poly(ethyleneglycoldimethacrylate) cross-link 8,19]. Electrically-conducting MIP thin-films from crossked poly(ethyleneglycoldimethacrylate-*co*-4-vinylpyridine) ve been produced at the interdigital transducer surface by freedical cross-linking copolymerisation of a functional monomer, vinylpyridine (VPD) and a cross-linker, ethylene glycol methacrylate (EDMA) in the presence of TCAA in acetonile.

In this paper, the sensor fabrication and the performance of the w-through haloacetic acid sensitive conductometric sensor presented. The new flow-through conductometric sensor was plied to haloacetic acid-determination of real-life samples.

Experimental

1. *Chemicals and materials*

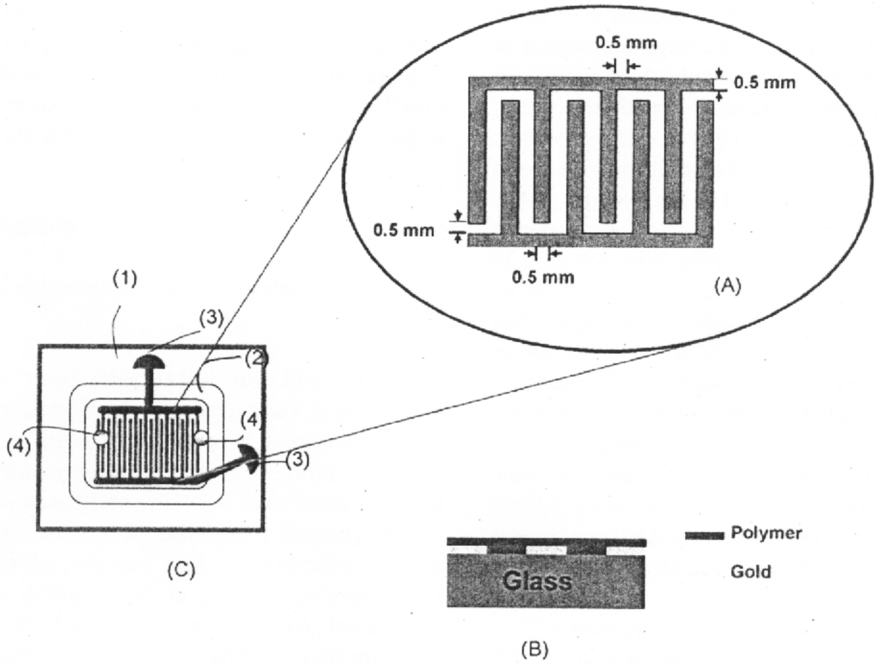
Ethylene glycol dimethacrylate (EDMA) and 4-vinylpyridine PD) were purchased from Aldrich Chemical Company (Milukee, WI, USA). 2,2′-Azobis-(isobutyronitrile) (AIBN) was tained from Janssen Chimica (Geel, Belgium). Polydimethyloxane and hardener (Sylgard 184) were obtained from w Corning Corporation (MI, USA). Trichloroacetic acid CAA) was purchased from Merck K.G. (Darmstadt, Germany). Dichloroacetic acid (DCAA), monochloroacetic acid (MCAA), dibromoacetic acid (DBAA), monobromoacetic acid (MBAA), tribromoacetic acid (TBAA) and malonic acid were obtained from Fluka Chemie AG (Buchs, Switzerland). VPD and EDMA were purified by distillation under reduced pressure. All solvents were analytical grades and dried with molecular sieves prior to use. Working standard solutions were prepared daily.

2.2. *Fabrication of the sensor device*

The sensor devices fabricated in this study were of thick-film type. The gold paste was screen-printed on a pre-cleaned borosilicate glass (1 mm thickness and 15 mm × 20 mm) with a pair of comb-type Au electrodes having interdigital distances of 0.5 mm and overall area 11 mm × 8 mm (Fig. 1A). This electrode unit was sintered at 550 °C for 3 h. The thickness after sintering was about 1 μm as measured by an atomic force microscopy (AFM) method. The procedure for immobilization of MIP on electrodes was as follows. TCAA (14 mg, 0.08 mmol) was dissolved in 1 ml of acetonitrile. Appropriate amounts of VPD and EDMA were admixed, followed by the addition of AIBN (9 mg, 0.05 mmol). These monomeric mixtures were purged with a stream of nitrogen gas for 1 min, and pre-polymerised at 65 °C for 1 min in a water-bath. The viscous polymer (6 μl) was spread evenly over the electrode pattern of the interdigitated conductometric gold electrode placed in a chamber. Subsequently, the chamber was flushed with nitrogen gas for 1 min to remove the radical scavenger oxygen before being closed and oven-heated at 70 °C for 18 h. After the immobilizing process, the electrode was washed with deionised water to remove the template molecules. A non-imprinted polymer (NIP) electrode, which was included as the control, was prepared in the same way as the MIP electrode, but in the absence of the TCAA template. Elemental analysis of the MIP thin-film coated on electrodes was performed on a JSM-5800 LV electron microscope (Jeol, MA, USA) equipped with an Oxford Instruments LINK-ISIS 300 X-ray detector and microanalysis system. The morphology of deposited film was inspected by an atomic force microscope (AFM) using a Nanoscope III Scanning tunnel microscope (Digital Instruments Inc., Santa Barbara, CA). The thickness of the films (see Fig. 1B) was determined by scratching with a needle and measuring depth of the scratches using an AFM (Digital Instruments, CA, USA) with a Nanotec Electrinica WSxM scanning probe microscopy software version 3.0 Beta 8.1 (Digital Instruments, CA, USA).

2.3. *Optimisation of polymer composition*

The optimal amount of functional monomer and cross-linking monomer required for the manufacture of the MIP film on interdigital electrode was verified. A set of molecularly imprinted polymer films and the corresponding non-imprinted polymer films were immobilized on interdigitated electrodes using the procedure described in Section 2.2, and their electrical conductivity and adhesive properties were determined. These polymeric films were synthesized with different initial amounts of cross-linking monomer and different mole ratios of functional



l. (A) Schematic top view, (B) schematic cross-section of the interdigitated conductometric sensor device. (C) Schematic diagram of the analytical microsystem. lass support; (2) silicone pad; (3) electrode contact; (4) drilled-through hole.

omer to template. The optimal amount of EDMA cross-er was examined by varying the amount of EDMA as 55, 65, 75 and 80 mol%, while the mole ratio of monomer to tem-e was kept constant at 2:1. Further, the functional monomer D) was applied at five different molar ratios with respect e template with a fixed amount of cross-linking monomer MA). These molar ratios were 1, 2, 4, 6 and 8 mol monomer mol of template. In the case of non-imprinted polymer film hich no template is added the amounts of VPD still relates to e stoichiometric ratios. The electrical resistance in air (R_a) e prepared thin-films on electrode was obtained by means of P 4254 Precision LCR. In a typical resistance measurement, lectrode was connected to HP 4254A Precision LCR meter lent Technologies, Palo Alto, CA) by soldering copper wires oppered gold electrode contacts. The AC frequency of 1 kHz used and the operating voltage was 100 mV.

Sensor fabrication

diagram of the flow-through conductometric sensor system own in Fig. 1C. The glass plate that constituted the integrated or array and wire connections with electrode-contacts, was led with a 16 mm × 13 mm, 3 mm thickness home-made sil-e pad (obtained from the commercial polydimethylsiloxane ardener). This silicone pad has a 11 mm × 9 mm × 1 mm cavity created by molding. Through holes of 1 mm diam-for sample inlet and outlet were drilled through the cav-Assembly of the thin-film sensor array with the silicone followed by incorporation into a Perspex housing-box of m × 3.0 cm × 0.4 cm gave the analytical microsystem with l internal volume of 90 μl. This integrated miniaturised device not only minimised the sample volume, but also considerably reduced the total assay time.

The sampling and conductometric analysis system of the sensor consists of a liquid port for delivery of water sample from a sample-reservoir, a peristaltic pump, a thermo set and the flow-through microcell/integrated MIP sensor incorporated with a conductometric apparatus controlled by a computer program developed in-house. The function of this system was on-line and the minimum sample volume required was 2.5 ml. The stand-alone sensor was operated at a continuous flow rate of 3 ml min^{-1} driven by Ismatec peristaltic pump (MCP-Process Series, Ismatec SA, Wertheim-Mondfeld, Germany). The sensor array output signals were monitored using a network analyser (HP 4254A Precision LCR, Hewlett Packard, Germany), which read the resistance signals from the sensor array with subsequent display on the Laptop screen. The resistance measurement of the sensor was performed by applying an alternating potential (100 mV) to the electrodes with a frequency between 100 Hz and 1 MHz. At the initial measurement, the electrical resistance of the sensors was measured in deionised water as a reference. The measurements were carried out at room temperature (24 ± 1 °C). The signal was allowed to reach a constant value before subsequent addition of the analyte. The sensitivity of the MIP-based sensor was measured as a function of the changes in the resistance of the polymer upon exposure to TCAA or other HAA analogs with concentrations from 0.0005 to 500 mg l^{-1}. A control experiment was carried out with the corresponding NIP-based sensor. In addition, technological parameters (operating frequency, temperature and electrolyte) for the sensor were identified with regard to the response to TCAA, using the electrode giving high resistance change with good adhesion of the deposited film as a model. For the sample measurement using the sensor, the signal response towards the analyte of sensor was reported as ΔR_s, where ΔR_s is the resistance shift response to the addition of known amounts of the analyte of interest. Every experiment was carried out in triplicate on any particular day of experimentation.

3. Results and discussion

3.1. *The MIP-based electrode-fabrication of the sensor device*

The electrically conducting MIP thin-film of poly(ethyleneglycoldimethacrylate-*co*-vinylpyridine) selective for haloacetic acids, was prepared at the gold electrode surface by thermal polymerisation using TCAA as the print molecule. Ethylene glycol dimethacrylate (EDMA) was chosen as the cross-linking monomer, due to its anticipated property of giving a high stability to the polymer, with corresponding rigidity of imprint structure. 4-Vinylpyridine (VPD) was adopted as functional monomer for the imprinting of TCAA, because its amine group is capable of interacting with the acid group of the template. Besides, VPD forms a charge-transfer complex with strong acidic molecules [18,19]: these can produce the continuous conducting phase of an insulating polymer (ethyleneglycoldimethacrylate) cross-link, enabling the signals of ligand binding to be detected.

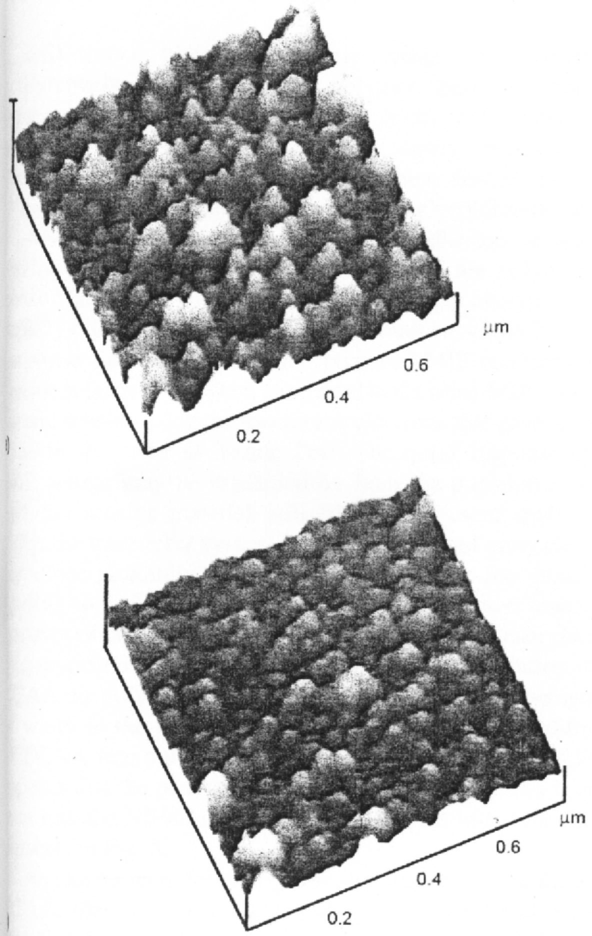
The immobilization of MIPs and the corresponding NIPs on the surface of gold interdigitated electrodes was successful using the method described here. A sketch of sensor-device showing film arrangement and electrode disposition over glass plates is given in Fig. 1. Both MIP and NIP gave a detectable signal on the conductometer when examined as dry layers on gold electrode. The cleaning profiles of both MIP and NIP were studied. For this, the deposited thin-film of both MIP and the corresponding NIP prepared with 2:1 monomer:template ratio and 5mol% EDMA was soaked in 100 ml-water, and resistance measurements were performed in open air after every hour of electrode soaking at ambient temperature. The polymers were washed with water until their resistance signal remained stable, which occurred after approximately 4 h of washing. The net change of resistance in air (ΔR_a) was calculated from the resistance obtained at the start and at the end of washing. The electrical resistances of the films on electrode were found to increase after the electrode was soaked in water. An increase from 2.7×10^8 to $7.6 \times 10^8\ \Omega$ occurred for the MIP film and from 6.9×10^8 to $8.5 \times 10^8\ \Omega$ for the corresponding NIP film both after soaking in water. The ΔR_a of MIP ($4.9 \times 10^8\ \Omega$) was almost three times higher than that of the corresponding NIP ($1.6 \times 10^8\ \Omega$). The changes in resistance of the corresponding NIP probably arise due to the removal of un-reacted monomers and some parts of the non-adhered polymer. The electrodes fabricated with either MIP or NIP, either before or after washing in water, gave a resistance signal higher than the plain electrode (R_a=$7.5 \times 10^3\ \Omega$).

The increase in the resistance signal of the MIP film (after polymerisation) when exposed to water can be explained in terms of a change in the surface conductivity of the polymer as template is gradually eluted by the water. This means that the electrical conductivity of MIP before template extraction is produced by the interactions of template at the imprint. The change in conductivity of MIP films corresponds to the charge transfer interactions of TCAA and polymer. Additional evidence supporting the formation of charge transfer complexes between the MIP and TCAA was an emerald-green coloring of only the MIP after polymerisation, which was eliminated by washing with water. This suggests that in the dry state, poly(ethyleneglycoldimethacrylate-*co*-vinylpyridinium) exists in the form of acid–base complexes of TCAA and VPD monomer. The increase in resistance of MIP after washing with water suggests dissociation of the template from the imprint sites. In the case of the NIP-based sensor, no TCAA molecules were involved in the polymerisation process. Therefore the vinylpyridine on the polymer backbone is unable to be quaternized and the imprint cavities are not produced in the polymer network due to the fact that TCAA was not used in NIP polymerisation.

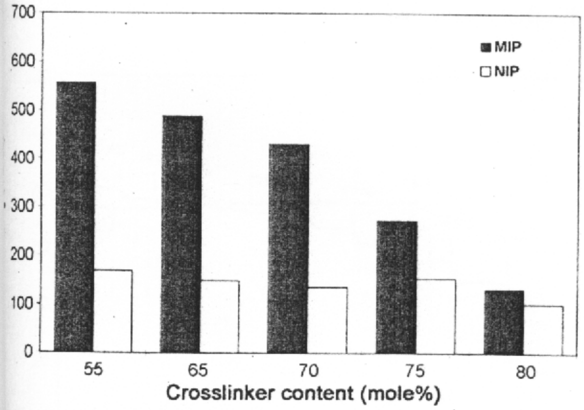
The interaction of template with MIP is apparently reversible. It is interesting that the incorporation of TCAA into the VPD-EDMA polymer not only enables the polymer to be conductive, but also improves the mechanical and adhesive properties of the film coating of the MIP. This may be because the charge-transfer complex between TCAA and VPD ions, which may swell and/or dissolve in water and can be crippled down by water flow from the surface of glass, as this is indicated by only HAA is released out from the MIP but not MIP during washing. After washing, the polymer morphology was examined using AFM. Fig. 2a and b show the AFM topographic images of MIP and non-imprinted polymers, respectively. AFM topographies of the MIP-film surface exhibit ridges and roughness, while smooth and uniform deposition is evident with the film of non-imprinted polymer. This result indicates the differences in the morphologies of polymer prepared in the presence and absence of the template molecule.

3.2. *The MIP-based electrode-optimisation of polymer composition*

The optimal composition of MIP film was examined in terms of resistance change as well as adhesive properties. The resistance change of the MIP due to the template extraction was examined in parallel experiments with non-imprinted polymers. Additionally, the imprint capacity, reflecting the efficiency of recognition of the MIPs was interpreted by comparing the resistance variation of MIP with the corresponding NIP. As seen in Fig. 3, there is a dependency in the degree of the ΔR_a as a function of the cross-linker amount for MIP, whereas this is not the case for NIP. Lower concentrations of EDMA (55, 65 and 70) give a higher resistance change than higher concentrations of EDMA (75 and 80). The imprinting factor, which represented the effect of the imprinting process, was the ratio of R_a of MIP-based electrode to R_a of the corresponding NIP-based electrode after washing with water for 4 h, was maximal with EDMA content between 55 and 65 mol%. However, the low amounts of EDMA



. Three-dimensional AFM images of: (a) MIP and (b) NIP thin-film pre- with 2:1 monomer:template ratio and 65 mol% EDMA (after washing with r for 4 h).



Effect of the amount of cross-linking monomer (EDMA) on the resistance ses of the MIP and NIP thin-film prepared with 2:1 monomer:template nd 65 mol% EDMA after 4 h exposure in water. Measurements were car- ut at 1 kHz and at room temperature. The functional monomer to template f 2:1 was used.

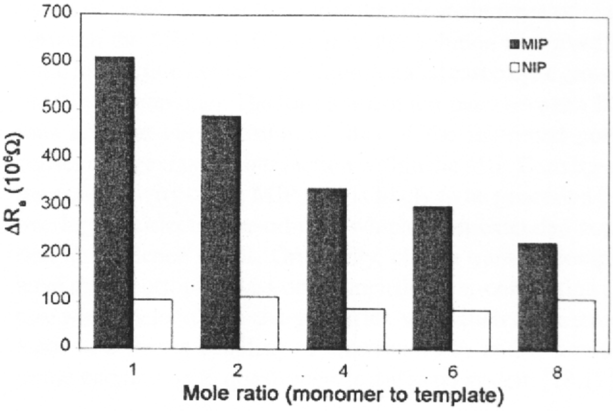


Fig. 4. Effect of the amount of functional monomer (VPD) on the resistance responses of the MIP and NIP thin-film prepared with 2:1 monomer:template ratio and 65 mol% EDMA after 4 h exposure in water. Measurements were carried out at 1 kHz and at room temperature. The cross-linker content of 65 mol% was used.

resulted in a poorer mechanical strength of the film. Therefore an EDMA content of 65 mol% was chosen to prepare the MIP for use in further investigations.

As shown in Fig. 4, further increase in the molar ratio of VPD to template shows a decrease in the resistance of MIP, but this is not evident with NIP. A maximum imprinting factor of 5.8 was obtained at a molar VPD to template ratio of 1:1, suggesting that the MIP forms 1:1 complexes with the TCAA molecules. Although a 1:1 monomer:template ratio is preferred, the 2:1 monomer:template ratio gave higher mechanical strength with good stability of film than the 1:1 monomer:template ratio. The results of this study suggest that the physical property of the film varies with the functional monomer:cross-linker ratio, and that the 2:1 monomer:template ratio may be suitable for combining with 65 mol% content of EDMA to produce a MIP film with good physical properties. Also, the 2:1 monomer:template ratio gave a relatively large value of imprinting factor (4.4). The low relative standard deviation (2.6%, $n = 3$) indicates good and reproducible coating. Since the MIP thin-film prepared with 2:1 monomer:template ratio and 65 mol% EDMA gives a high recognition selectivity to the template with good stability of film coated, this film type has been chosen as the recognition material for the development of a HAA sensitive conductometric sensor for on-line HAA analysis. Subsequent elemental analyses of MIP thin-film of this film type, which is layered on gold electrode, revealed an elemental composition of the film (and the gold paste) as C 45.9%, O 3.6%, Na 8.7%, Mg 3.0%, Al 1.3%, Au 0.10%, Ca 22.3% and Ag 15.1%. The thickness of MIP thin-film layered in place on the gold surface and on the glass surface was determined to be about 1 and 2 μm, respectively. The recorded resistance (R_0) of the film on electrode was found to be about 80 kΩ in deionised water at 3 kHz at room temperature (24 ± 1 °C). The percentage coefficient of variation for the R_0 values of the MIP electrode obtained for three different batches of the interdigitated conductometric gold electrode was found to be 0.1%.

3.3. *Conductometric sensor response*

MIP-based films, particularly made of hydrophobic (ethyleneglycoldimethacrylate) polymer, perform poorly in aqueous medium. For instance, the hydrophobic MIP based film is hardly wet and can be easily removed from the surface of metal and glass when soaked in water. While TCAA-imprinted poly(ethyleneglycoldimethacrylate-*co*-4-vinylpyridinium) offered a good adhesion in aqueous medium due to polyelectrolytic nature of the polymer. The sensor fabricated with this MIP responded to analyte in water rapidly (30 s) with a steady response obtained within 2 min. The response time shown with the prepared MIP conductometric sensor is fairly rapid when compared to the other MIP conductometric sensors using the membrane electrode that gave response time in the order of 30 min [14]. The quick response of this MIP sensor may be explained by both the transducer system and the sensing material utilised in the present study. Basically, the transducer system using interdigitated array electrode has close proximity of the sensing element to the transducer, leading to rapid measurement due to low diffusion times. The polarity of cross-linked poly(ethyleneglycoldimethacrylate-*co*-vinylpyridinium) material may promote the penetration of the TCAA to polymer, and it may also enhance the permeation of water in the polymer matrix leading to an easier diffusion of TCAA into polymer. Hence the sensor responds quickly. It appears that the penetration of water into the MIP film is easier than into the NIP film, as is evident from the initial baseline of sensors, in Fig. 5.

As can be seen, following repeated incremental additions of TCAA, there is a decrease in the resistance of the MIP sensor (see Fig. 5). The effect of various concentrations of TCAA on the resistance signal of NIP-based sensor is negligible. This suggests that the interaction of TCAA with the MIP fabricated in sensor could be measured in an aqueous solution. Also non-specific binding does not seem to affect conductivity of the sensor to a great extent. Apart from this, the rebinding of TCAA at the imprinted sites is taken into account to explain the increase of sensor conductivity. In an aqueous medium, hydrogen bond interaction of MIP and ligand is weak. This is due to the disturbance of water, so that it is clear that the main force of binding between the MIP and TCAA in water solution is derived from ionic interaction between the deprotonated carboxylic group and functional monomer. The formation of ion-pairs between TCAA ions and the vinylpyridinium ions of the imprinted polymer causes charge transfer interaction within the MIP. Consequently, the conductivity of the MIP film is likely to be generated by the overlapping electron π-orbitals which form extended conduction and valence bands. Ordinarily, charge transfer complexes have an anisotropic quasi-one-dimensional π-conducting structure with a delocolized charge carrier, while their chain structure leads to a strong coupling of electron states and to conformational excitations to quasi-one-dimensional system [18,19].

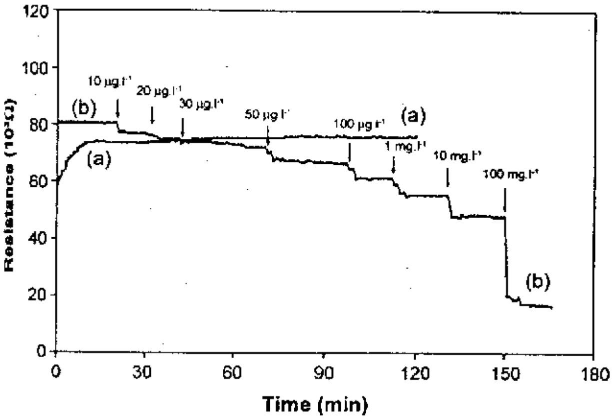


Fig. 5. Signal response of: (a) reference sensor and (b) MIP sensor to subsequent additions of TCAA at 1 kHz.

3.4. *Effect of experimental parameters on the sensor signal*

Since the sensing element of MIP-based sensor demonstrates a semiconducting polymer property and factors such as applied frequency, temperature and electrolytes are expected to have an effect on the conductivity of the semiconducting polymers [18,19]. Therefore variation in these factor may affect the signal response of the sensor.

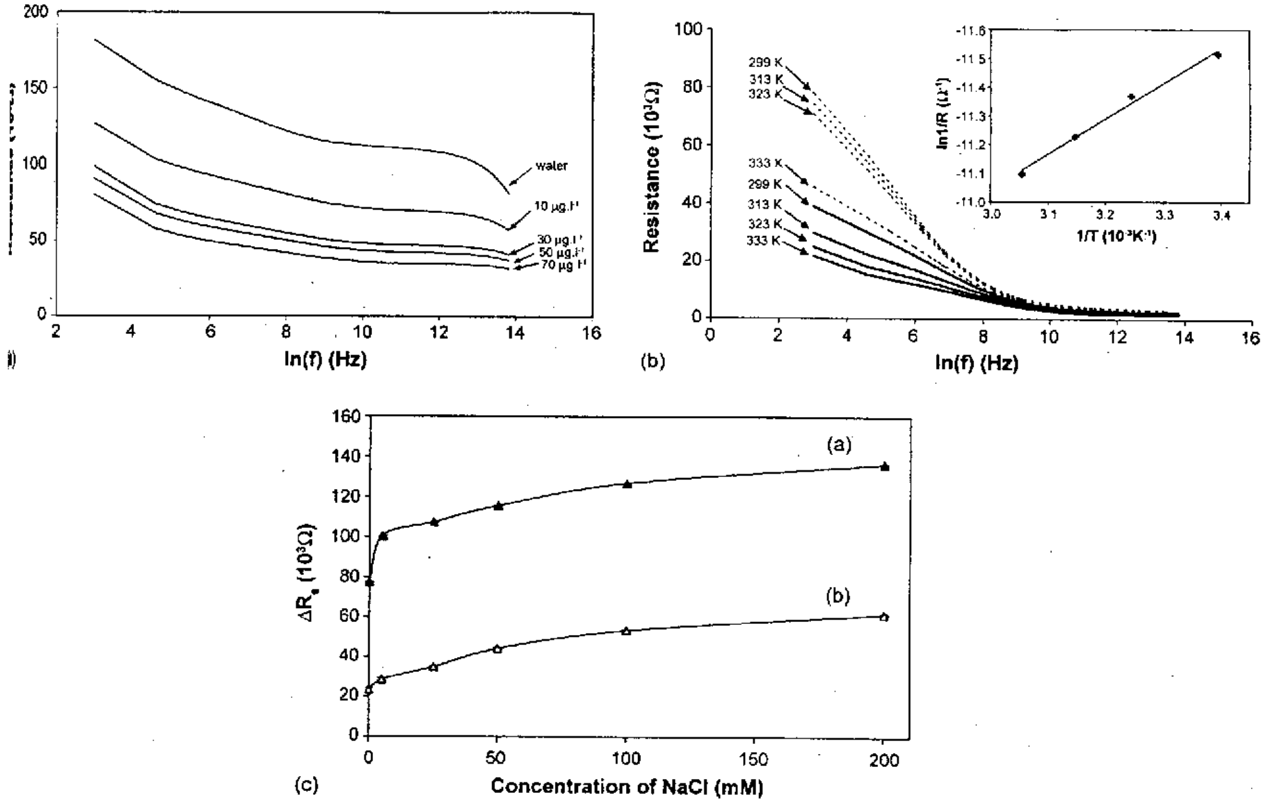
3.4.1. *Effect of applied frequency*

The effect of the applied frequency on the resistance response of MIP-based sensors was studied over an ac frequency range 0.1–1000 kHz using TCAA concentrations up to $70\,\mu\mathrm{g\,l^{-1}}$ (Fig. 6a). The results show that increasing the applied frequency decreases the electrical resistance of the sensor at all concentrations of TCAA used ($0–70\,\mu\mathrm{g\,l^{-1}}$). The resistance at lower frequencies represents the electron diffusion process in the poly(VPD-*co*-EDMA) film. As shown in Fig. 6a, the resistance of the sensor is sensitive to the presence of TCAA molecules in the solution, and on the applied frequency. The resistance variation on the addition of TCAA at the high frequency region was shown to be lower than that at the low frequency region. A reasonable signal response of sensor was obtained in the ac frequencies ranging 1–10 kHz. A frequency of 3 kHz was therefore chosen for operating the sensor in all remaining experiments.

3.4.2. *Effect of experimental temperature*

The influence of variation of the experimental temperature on the resistance response of the sensor upon exposure to TCAA ($200\,\mu\mathrm{g\,l^{-1}}$) was investigated over the temperature range of 299–333 K. As seen in Fig. 6b, the resistance of MIP sensor gradually decreases with increasing temperatures from 299 to 333 K. In contrast, the NIP-based sensor shows only a slight effect of temperature on the resistance at temperatures between 299 and 323 K, although the resistance of the sensor at the elevated temperature 333 K is much lower. As MIP and NIP films were prepared with the same monomer composition, differences in the conductivity behaviour are thus due to the imprinting effect. The electrical conductivity of MIP sensor obeys the Arrhenius equation:

$$\frac{1}{\Omega} = A \exp\left(\frac{-E_a}{RT}\right) \tag{1}$$



(a) Effect of the ac frequency on the resistance responses of the MIP sensor at various concentrations of TCAA. Measurements were carried out at room ature. (b) Effect of temperature on the resistance response upon 200 μg l^{-1} of TCAA for: reference sensor (dashed lines) and MIP sensor (thick lines), at s frequencies. Top right is Arrhenius plot for the electrical conductivity of MIP electrode. (c) Effect of NaCl on the resistance shift response of (a) MIP sensor) reference sensor at 3 kHz and at room temperature. Responses were initiated by the addition of 200 μg l^{-1} TCAA.

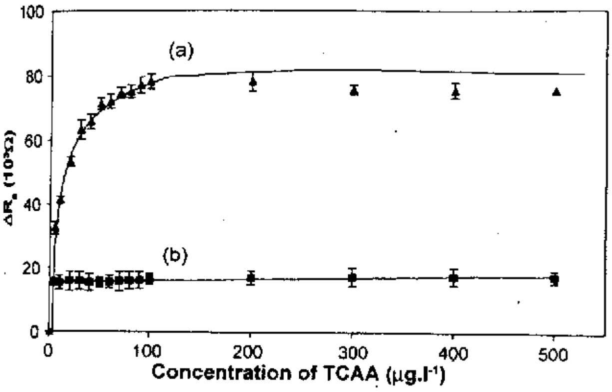
re A is the pre-exponential factor, E_a the activation energy, e gas constant and T is the temperature (see Fig. 6b, top t). A 35 K increase in temperature above room temperature, esistance of the MIP-based sensor decreased from 10^5 to Ω. The results obtained confirms that the MIP has semicon- ive like behaviour of π-type conjugative polymers [19–21]. rdingly, the main effect of temperature variations on the uctivity of the MIP sensor may be explained by a change arge-transfer as temperature varies. The activation energy ed from the Arrhenius type of temperature dependence of uctivity in the case of the MIP sensor may be associated the excitation energy for thermal generation of binding site e polymer. The resistance change obtained at different tem- tures also allows us to calculate the activation energy of inding site for MIP; the activation energy of 10.2 kcal/mol calculated from the data. The result obtained in this study onstrated that temperature changes could have strong influ- s on the sensitivity of the sensor. Thus, measurement using sensor should be carried out under controlled steady tem- ture.

Effect of electrolytes

e effect of the electrolyte on the resistance shift response e developed sensors was investigated. The data show that asing concentration of NaCl in sample solutions contain- 200 μg l^{-1} TCAA increases the magnitude of the sensor responses in both MIP- or NIP-based sensors (Fig. 6c). The increased conductivity observed with both MIP and NIP sensors when exposed to the analyte and electrolytes (NaCl) can be explained by the enrichment of the analyte and counter ions in the polymer particles, which gives a high local concentration of charged species close to the gold electrode surface in the sensing device. It can be seen (Fig. 6c) that there is a difference in the 200 μg l^{-1} TCAA-signal response of MIP and NIP sensors at every concentration of electrolyte studied. This difference seems to be constant independent of further addition of the electrolyte. Where the difference occurred, which is apparent in the NaCl concentration range between 0.2 and 3.4 mg l^{-1} (0.01–200 mM), the conductivity response of MIP sensor was always higher than that of NIP sensor, indicating the greater affinity with the target analyte of the former sensor.

3.5. Concentration dependence on signal response of sensor

As can be seen from Fig. 7, the MIP sensor gives a signal response primarily rising with an increase in the concentration of TCAA, while reference sensor shows a negligible shift of resistance response to the added TCAA. At higher concentrations of TCAA (>100 μg l^{-1}) the response of MIP sensor seems to be constant which is probably explained by the saturation of the recognition sites in the imprinted polymer. This suggests



ig. 7. Concentration dependence of the sensor response to TCAA for: (a) MIP sor and (b) reference sensor. Each point represents the average of three independent measurements. Measurements were carried out in distilled water at kHz and at room temperature.

hat the adsorbed analyte produces appropriate binding of analyte molecule at binding sites on the MIP film. The adsorption behaviour of the MIP film fabricated in sensor can be fitted to the Langmuir isotherm expressed as

$$\Omega = \frac{\Omega_{\max} K c}{1 + K c} \qquad (2)$$

where $\Omega_{\max}$ is the maximum value of the resistance response (Ω), K the modified adsorption equilibrium constant and c is the concentration of the analyte. Plot of $1/c$ versus $1/\Delta R_s$ yielded a straight line with a single apparent binding constant of 13 µM^{-1}. The affinity of the TCAA-imprinted polymer for its original template molecule is similar to those of the other MIPs reported in literatures [13,22].

3.6. Analytical characteristics

The calibration curves constructed from the resistance shift parameter dependency provided reasonable results. There was a linear relationship between the shift resistance of the MIP sensor and the logarithm of the concentrations ($\log c$) ($R^2 > 0.97$) of TCAA in the range of 0–100 µg l^{-1}, and the other five HAAs (DCAA, MCAA, TBAA, DBAA and MBAA) in the range of 1–500 µg l^{-1}, depending on the compound, and the mixture of total six HAAs in the range of 10–400 µg l^{-1}. The calibration data are shown in Table 1. The limits of detection as obtained according to $3S_b/m$ criterion, where m is the linear calibration and S_b were estimated as the standard deviation ($n = 3$) of the signal response for HAAs, were in the range 0.5–5 µg l^{-1} for the various HAAs. The US Environmental Protection Agency (USEPA) [23] has set a maximum contaminant level of 60 µg l^{-1} for the five commonly occurring acids namely TCAA, DCAA, MCAA, DBAA and MBAA in the stage 1 of the disinfection by-product regulation. Again, this is to be lowered in the coming years to 30 µg l^{-1}. Within this regulation, DCAA should never be present, and TCAA concentrations should not be more than 0 µg l^{-1} [24]. The MIP electrode can thus detect HAAs at concentrations well below the maximum permitted concentrations.

Table 1
Calibration data obtained for the analysis of TCAA and five other HAAs by the MIP sensor

Compound	Slope	R^2	Working range (µg l^{-1})	LOD (µg l^{-1})
TCAA	38.89	0.992	0–100	0.5
DCAA	27.17	0.993	1–500	1.2
MCAA	24.17	0.986	5–500	5.0
TBAA	5.81	0.972	10–500	5.3
DBAA	5.63	0.985	40–400	1.7
MBAA	11.20	0.987	30–400	1.2
Six HAAs[a]	117.23	0.980	10–400	5.0

[a] Refers to TCAA, DCAA, MCAA, TBAA, DBAA and MBAA altogether.

The stability of the MIP electrode has been investigated by repeating measurements of the sensor response to HAAs. The results revealed that a single MIP electrode was operated repeatedly more than 50 times with reliably reproducible detection signals and the electrode could be stored at room temperature more than 3 months without showing any loss of sensitivity.

3.7. Selectivity of the sensor

To assess the overall selectivity of the MIP electrode, the effects of structurally related haloacetic acid compounds such as DCAA, MCAA, TBAA, DBAA, MBAA and non-haloacetic acid compounds such as malonic acid and acetic acid, on sensor conductivity were examined. The results revealed that the NIP sensor exhibited relatively little response to both haloacetic acid and non-haloacetic acid compounds (data not shown). For the MIP sensor, non-haloacetic acid compounds, either acetic acid or malonic acid, in the 10–500 µg l^{-1} concentration range, generated negligible change in the electrical conductivity signal of the sensor (see Fig. 8). This indicates a definite imprint effect of the MIP coated on electrodes. On the other hand the concentrations of structurally related haloacetic acid compounds resulted in significant shift of the resistance of the sensor. The results indicate that the HAA analogues are capable of induc-

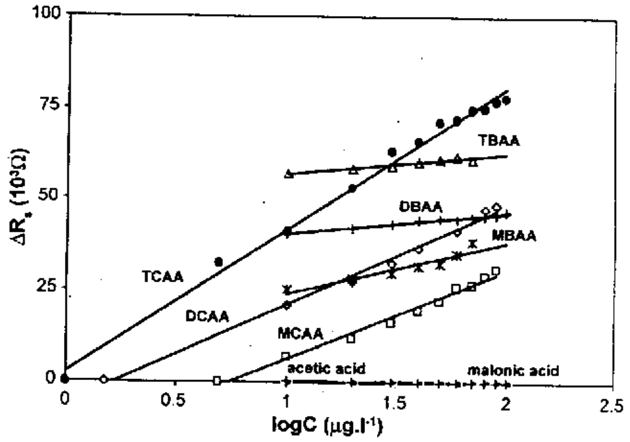


Fig. 8. Calibration curves for TCAA, DCAA, MCAA, TBAA, DBAA and MBAA obtained in the steady state on-line system using the developed MIP sensor.

changes in the conductivity of MIP due to their having a bility of locating in the TCAA-imprinted cavity, but at dif- nt degrees of fitting for each analogue. Calibration curves in 8 show that the chloro-HAAs all have about the same slope, the response to the bromo-HAAs of the sensor is much less itive. This is clearly due to the bromo-analogues not fitting the binding site very efficiently because bromide is much r than chloride. When the selectivity pattern of the sensor determined, by comparing the value of maximum resistance onse obtained for analogs to that for TCAA, it was found that ctivity of sensor decreases with weakening of the electroneg- ity of HAA and with an increase in the size of compounds. specificity shown with the MIP sensor could be explained he basis of ion-ion interaction combining to size and shape ory to the template. The selectivity value for DCAA was highest (94%), but also significant for MCAA (93%), MBAA %), TBAA (78%) and DBAA (66%) indicating that the assay group specific rather than analyte specific and thus suitable detection method for this group of HAAs. Since the selec- y values of HAAs (particularly MBAA, TBAA, DBAA) are ively low than those for DCAA, MCAA and TCAA, there be a possibility of inter-anionic competition for receptor in cavity, and TCAA could have preference over other five A analogs in terms of rebinding.

Sample analysis

he haloacetic acid conductometric sensor was used as an ytical tool for haloacetic acid determination in four water ples, including three brands of commercial bottled water d 25 l containers) and a municipal tap water (with home tion system). These water samples were assayed directly. libration curve of TCAA alone was prepared in range of ntration 0.5–10 μg l^{-1} and compared to that measured HAA in the samples. A method for analysis of HAAs ater, LLE–GC–ECD recommended by the USEPA [25] hod 552.2) was also used to verify the amounts of HAA e samples as obtained by the conductometric sensor. The lts obtained for analyses of each sample by the sensor and ethod 552.2 are displayed in Table 2. The measurement of As with the USEPA method revealed that only TCAA was ained in the samples. The results for HAAs analysis by the or method was in excellent agreement with that obtained the USEPA method.

r validation purposes a recovery study was performed by ng the above water samples with increasing amounts of

2
sis of haloacetic acid in water samples by the sensor method and the d 552.2 method [24]

le	HAA concentration measured (μg l^{-1})	
	The method 552.2	The sensor
d water A (1 l)	0.8 ± 0.10	0.7 ± 0.00
d water B (1 l)	0.9 ± 0.10	0.6 ± 0.01
d water C (25 l)	1.0 ± 0.01	0.8 ± 0.00
filtration system (home)	1.2 ± 0.07	1.2 ± 0.02

Table 3
Recovery data from analysis of haloacetic acids in water samples after spiking with either TCAA or a series of HAAs at various concentrations by the sensor method

Sample	Concentration of HAA in water sample[a] (μg l^{-1})	Measured[b] (μg l^{-1}) after adding HAAs (%Recovery)					
		μg l^{-1} added (TCAA)[c]			μg l^{-1} added (total six HAAs)[d]		
		30.04	60.56	90.39	Total 26.67	Total 55.33	Total 83.87
Bottled water A (1 l)	0.8 ± 0.10	31.1 ± 1.0 (101 ± 1)	61.4 ± 1.2 (100 ± 1)	95.1 ± 2.1 (104 ± 2)	27.3 ± 0.56 (100 ± 0.0)	58.8 ± 2.2 (105 ± 2)	87.8 ± 1.6 (104 ± 1)
Bottled water B (1 l)	0.9 ± 0.10	31.4 ± 0.72 (102 ± 0.0)	63.4 ± 1.7 (103 ± 1)	94.3 ± 1.5 (103 ± 1)	27.6 ± 0.62 (100 ± 0.0)	57.9 ± 1.2 (103 ± 2)	85.5 ± 0.69 (101 ± 1)
Bottled water C (25 l)	1.0 ± 0.01	31.0 ± 0.61 (100 ± 1)	62.2 ± 0.92 (101 ± 1)	94.0 ± 2.4 (103 ± 1)	27.6 ± 0.41 (100 ± 0.0)	57.9 ± 0.84 (103 ± 1)	88.9 ± 1.7 (105 ± 1)
Water filtration system (home)	1.2 ± 0.07	32.1 ± 0.92 (103 ± 0.0)	63.6 ± 0.91 (103 ± 1)	94.0 ± 1.4 (103 ± 1)	27.5 ± 0.25 (99 ± 0.0)	57.5 ± 0.83 (102 ± 1)	87.2 ± 1.4 (103 ± 1)

[a] HAA concentration measured by the USEPA method 552.2 (mean ± S.D., $n = 3$). Note that only TCAA was detected in all samples.
[b] Mean value ± R.S.D. ($n = 3$). The value in parenthesis is mean percent recovery of three independent measurements using only one electrode.
[c] Total six HAAs refers to TCAA, DCAA, MCAA, TBAA, DBAA and MBAA altogether.
[d] Expected concentrations are amounts added plus the amounts already present in the water sample.

either TCAA (30, 60 and 90 $\mu g\,l^{-1}$) or a mixture of six HAAs (4.5, 9 and 14 $\mu g\,l^{-1}$ each HAA, total 27, 54 and 84 $\mu g\,l^{-1}$). Recovery data for these analyses are summarized in Table 3. As it can be seen recoveries range between 99 and 105% and R.S.D. values less than 2% were achieved with bottled water A, B and C, and municipal tap water spiked with a standard solution of TCAA or total six HAAs at concentration level of 30, 60 or 90 $\mu g\,l^{-1}$, indicating that accuracy of assay with the sensor is good. It was shown that the haloacetic acid disinfection by-products in the real-life samples can be effectively measured with the sensor.

4. Conclusions

A flow-through haloacetic acid sensitive conductometric sensor based on the electrically-conducting imprinted polymer of cross-linked poly(ethyleneglycoldimethacrylate-*co*-4-vinylpyridinium) on screen-printed interdigitated electrode has been developed for on-line testing of haloacetic acids and shows a good response to trichloacetic acid template and structurally related compounds. The sensor has potential for use in detecting and measuring of HAAs, which are often presents in water as complex mixtures. The achieved sensitivity ranges and the detection limit show the suitability of this sensor for measuring HAAs in water. Moreover, the sensor exhibited the same recognition characteristics over 3 months when storage in dry conditions.

With its current sensitivity, the sensor can be operated as an early warning system for measuring these toxic compounds in water sources. The sensor would be complementary with the traditional analytical techniques used for measurement of HAAs as well as for fast environmental monitoring of the drinking water.

Compared to the traditional conductometric techniques for haloacetic acid assays this novel device offers considerable more advantages. Most important is on-line detection. This on-line potential is important because other methods for measuring HAA cannot be used on-line. The readout can be obtained within 2 or 3 min and sample volume requirement is low. Recently, Emmert et al. [26] proposed criteria for consideration of an ideal analyzer that could be used to monitor five regulated HAAs concentrations directly in drinking water distribution systems; namely it should operate in real or near real-time; provide method detection limits (MDLs) in the range of 0.5–5 $\mu g\,l^{-1}$ with mean percent recoveries of $100 \pm 5\%$ and percent relative standard deviations (%R.S.D.) of less than 10%; not suffer from total organic carbon interferences (i.e. acetic acid and malonic acid); be principally automated; require fairly low operator skill level; be compared directly with USEPA methods in real world situations; be inexpensive. Our proposed sensor practically meets all of these criteria. A patent for this developed sensor has been applied for in Thailand (ref No. 107046), and a worldwide patent application will follow.

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APPENDIX B

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The use of trichloroacetic acid imprinted polymer coated quartz crystal microbalance as a screening method for determination of haloacetic acids in drinking water

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stract

An alternative screening method for haloacetic acids (HAAs) disinfection by-products in drinking water is described. The method is based on use of piezoelectric quartz crystal microbalance (QCM) transducing system, where the electrode is coated with a trichloacctic acid-molecularly printed polymer (TCAA-MIP). This MIP comprises a crosslinked poly(ethyleneglycoldimethacrylate-*co*-4-vinylpyridine). The coated QCM is to specifically detect the analytes in water samples in terms of the mass change in relation to acid–base interactions of the analytes with the P. The TCAA-MIP coated QCM showed high specificity for the determination of TCAA in aqueous solutions containing inorganic anions, but ensitivity reduced in water samples containing hydrochloric acid due to a mass loss at the sensor surface. Cross-reactivity studies with HAA logs (dichloro-, monochloro-, tribromo-, dibromo-, and monobromo-acetic acids) and non-structurally related TCAA molecules (acetic acid malonic acid) indicated that recognition of the structurally related TCAA compounds by the TCAA-MIP-based QCM is due to a carboxylic functional group, and probably involves a combination of both size and shape selectivity. The total response time of sensor is in the order of min. The achieved limits of detection for HAAs (20–50 μg l^{-1}) are at present higher than the actual concentrations found in real-life samples, below the guidelines for the maximum permissible levels (60 μg l^{-1} for mixed HAAs). Recovery studies with drinking water samples spiked h TCAA or spiked with mixtures of HAAs revealed the reproducibility and precision of the method. The present work has demonstrated that proposed assay can be a fast, reliable and inexpensive screening method for HAA contaminants in water samples, but further refinement is quired to improve the limits of detection.

words: Haloacetic acids; Disinfection by-products; Molecularly imprinted polymer; Quartz crystal microbalance

Introduction

Chlorination, the most widely used disinfection process for inking water, produces two classes of disinfection by-products BPs); trihalomethanes and haloacetic acids [1,2]. After tri- lomethanes, haloacetic acids (HAAs) which include the llowing nine compounds: monochloroacetic acid (MCAA), hloroacetic acid (DCAA), trichloroacetic acid (TCAA), nobromoacetic acid (MBAA), dibromoacetic acid (DBAA), bromoacetic acid (TBAA), bromochloroacetic acid (BCAA), chlorobromoacetic acid (DCBAA), and dibromochloroacetic acid (DBCAA), represent the second most abundant DBP species in chlorinated drinking water. HAA disinfection by-products are usually present in water as a complex mixture, with a large proportion of DCAA and TCAA [3]. They are of great concern to public health, owing to their potential carcinogenic [4] and mutagenic effects [5]. Several previous DBP studies have focused mainly on the ingestion route of exposure to THMs, and todate THMs are monitored regularly in drinking water [6–8], whilst the presence of HAAs in water was rather disregarded. Evidence for the widespread occurrence of HAAs in environmental waters around the world is increasing [9–10]. Additionally, it is now clear that levels of THMs are not considered to be a good indicator of the levels of HAAs [11]. Recently, however, potential health risks to humans from long term exposure to particular HAAs has led to increased efforts to monitor

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and reduce their concentration in drinking waters [12]. Since determination of HAAs is quite a new environmental concern, few references are available dealing with development of liquid chromatographic methods for their analysis. The standard methods for determination of HAAs (such as ion chromatography, GC–ECD, GC–MS) are time consuming, complicated and costly for routine analysis of drinking water. A fast, simple and inexpensive analysis method is needed in order to complement these established sophisticated analytical techniques. The primary aim of the current study is to investigate the development of such a technique, with a view to eventually developing an on-line rapid screening method.

Electrochemical detection has been recognized as a useful method for organic acid analysis. However this technique cannot be used for monitoring HAA concentrations directly in water [13,14]. Although several non-crosslinked conducting polymers, such as poly(pyrrole) [15] or poly(vinyl chloride) incorporating the selective molecule such as polyoxyanion macrocyclics [16], have been used as a tool for the detection of organic ions in electrochemical analysis systems, none of these have shown sufficient specificity for the analytes. Recently, a conductometric sensor specific to the group of haloacetic acids (HAAs) has been developed by our research group [17]. The detection system of this sensor was based on molecular recognition of the analytes by a polymer prepared by a molecular-imprinting polymerization technique with a transduction of polyvinyl chloride membrane support. Molecularly imprinted polymers (MIPs), which recognize target molecules with size and shape-complementary cavities are becoming an important class of sensing materials due to their molecular recognition ability and good stability [18]. These artificial receptors have been incorporated in several transducing systems, such as electrochemical, piezoelectric and optical [19–22].

During the last decade, the introduction of polymer selectivity by the molecular imprinting technique has been made mostly with crosslinked polymers rather than non-crosslinked polymers. The reason is that the former polymers give greater stability and certainty of recognition. The most commonly used crosslinking monomer, ethylene glycol dimethacrylate (EDMA), has potential for molecular-imprinted polymer synthesis of organic compounds since it gives high molecular recognition to the polymer with good stability of the layer. However the EDMA polymer is hydrophobic and inert, and it is not therefore attractive to polar molecules of the analytes. Crosslinking polymerization of EDMA monomer with 4-vinyl pyridine (VPD) functional monomer is capable of generating an electrically conducting polymer [23] that would be advantageous, since the VPD monomer will not only form the reception site in MIP matrix but also make EDMA crosslink to be electrically active. This increases the attraction capability of the MIP produced, and perhaps improves the mechanical properties and processibility of the layer on electrode, due to the increased polarity of polymer. In addition to this, trichloroacetic acid (TCAA), which was chosen as the print molecule for this work, can be used as a doping agent.

By making use of the molecular-imprinting polymerisation technique, with appropriate modulation of the polymer composition, the recognition material engineered should be able to detect TCAA and structurally similar compounds directly in drinking water. The current study was designed to show that by using the TCAA-imprinted polymer coated quartz crystal microbalance (TCAA-MIP-QCM), it would be possible to specifically detect the group of HAAs in water, using mass-sensitive measurements. In this study, we have successfully synthesized TCAA-imprinted polymer of crosslinked poly(VPD-*co*-EDMA) as a spin-coated film at gold electrode surfaces, and evaluated its interaction with six commonly occurring HAAs, i.e., TCAA, DCAA, MCAA, TBAA, DBAA and MBAA, on QCM-based assay protocol. Since piezoelectric QCM, which is a well-known mass detection method, offers simplicity and low cost for chemical analysis, this assay method was chosen for the current study. Unspecific conductivity effects would be minimized by a dual QCM electrode comprising of multi-electrode structures on a single piezo-crystal with larger electrode diameters in contact with the liquid phase and two time smaller electrodes facing the gas-phase, according to techniques previously described in the literatures [24,25].

2. Experimental

2.1. Chemicals and materials

Ethylene glycol dimethacrylate (EDMA), 4-vinylpyridine (VPD) and malonic acid were obtained from Aldrich Chemical Company (Milwaukee, WI, USA). 2,2′-Azobis-(isobutyronitrile) (AIBN) was purchased from Janssen Chimica (Geel, Belgium). Trichloroacetic acid (TCAA) was purchased from Merck K.G. (Darmstadt, Germany). Dichloroacetic acid (DCAA), monochloroacetic acid (MCAA), dibromoacetic acid (DBAA), monobromoacetic acid (MBAA) and tribromoacetic acid (TBAA) were obtained from Fluka Chemie AG (Buchs, Switzerland). All chemicals for preparing buffer solution were analytical grade and were obtained from Merck (Darmstadt, Germany). All solvents were analytical grades and dried with molecular sieves prior to use.

2.2. Immobilisation of polymer on QCM electrode

To prepare the QCM electrode, a dual QCM-pattern designed as described in a previous study [24] was sequentially screen-printed on each side of 10 MHz AT-cut quartz disc (15 mm diameter), using the gold screen-printing technique. The electrode facing the aqueous phase had a diameter of 4.5 mm with 2.5 mm electrode on the gas-phase side. The thickness of the gold electrode layer on each side of the quartz crystal after sintering was determined by scratching with a needle and measuring depth of the scratches using an AFM (Digital Instruments Inc., Santa Barbara, CA) with a Nanotec Electrinica WSxM scanning probe microscopy software version 3.0 Beta 8.1, which this was found to be about 180 nm.

The procedure for immobilisation of MIP on electrodes was as follows: 14 mg of TCAA (0.08 mmol), 34 mg of VPD (0.32 mmol), 200 mg of EDMA (1.0 mmol) and 9 mg of AIBN (0.05 mmol) were dissolved in 1 ml of acetonitrile. Then, the olution was purged with a stream of nitrogen gas for 1 min nd pre-polymerisation was carried out at 65 °C for 1 min in a ater-bath. The non-imprinted polymer (NIP) was prepared in e same manner as the MIP, but in the absence of the TCAA mplate. A crystal was spin-coated with 10 μl of the MIP soluon onto the center of the surface of the analytical electrode with otation speed of 3000 rpm, following by spin-coating of 10 μl f the NIP solution at the reference electrode. Subsequently, the lank quartz was placed in a chamber flushed with nitrogen gas r 1 min. Polymerisation was carried out at 70 °C for 18 h in a ot-air oven. After the immobilizing process, the electrode was ashed with five portions of 100 ml de-ionised water to remove e template molecules. For removing the templates absorbed the recognition sites, a washing process in deionized water eded for at least 3 h. Finally, the electrode was dried in air for ernight. The thickness of the MIP coated films was inspected ing an AFM method that was similar to the method employed r measuring of the gold layer onto electrodes.

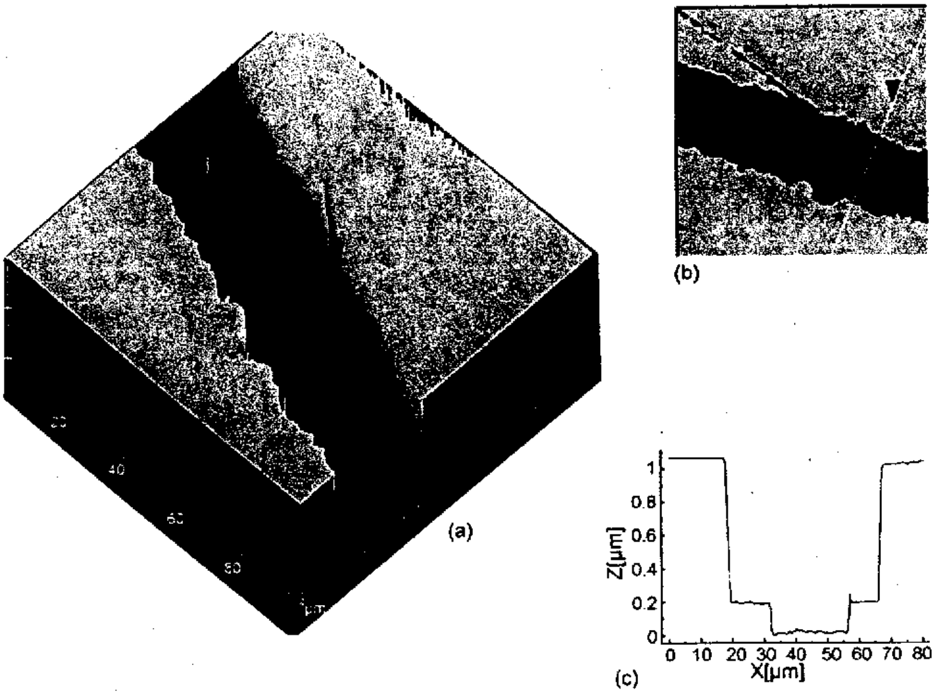
3. *Fabrication of the sensor device*

The QCM constructed with a coated TCAA-MIP and a coated rresponding NIP gold electrode was mounted in a flow-cell th a volume of 250 μl and placed in a thermostat at 25 °C. A me-built oscillator circuit and a self-programmed frequency ad-out were used with a processing software. The oscillator quency was measured by means of an HP 53131A frequency unter. The response of the oscillator circuit were checked by ans of a HP 8572C network analyser (Hewlett Packard, Gerany) to obtain data relating to acoustic damping and frequency shifts. The sensor experiments were performed using a flow system with a flow rate of 2 ml/min. Before making a measurement, the sensor was stabilized by running 200 ml de-ionised water through the cell for 3 h. One hundred milliliters of a series of standard solutions of TCAA and analogs were run through the cell separately. The frequency of both TCAA-MIP-QCM and the corresponding NIP-based QCM was recorded as parallel until a stable frequency was obtained. The water samples were analysed under the same condition as that used for the standard solutions. For the sample measurement using the sensor, the response of sensor exposed to a solution of the analyte was reported as frequency shift response ($-\Delta F$) which was the difference value of frequency shift of MIP electrode and frequency shift of NIP electrode. All measurements were performed in triplicate.

3. Results and discussion

3.1. *Performance of the TCAA-MIP-QCM*

Piezoelectric quartz crystal microbalance is well known as a remarkably sensitive mass detection method. Recently the use of MIPs coated onto piezoelectric QCM sensing system has attracted increase attention [19,20]. Normally, the integration of MIP into a piezoelectric QCM sensor requires thin or ultrathin MIP films (nanometres) on the transducer surface. This can be achieved in several ways; in situ electro-polymerisation; surface coating (direct or spin coating) [26]; physical entrapment of MIP particles into gel [27]; or chemical coupling of the MIP [28]. For this work the spin-coating method was used for immobilising MIP onto the QCM electrode.



1. (a) AFM 3D topography; (b) AFM of a cross-section of a scratch on a 20 kHz-MIP layer, and the measured depth of the polymer layer of 870 nm which is n on (c) the plot of depth (z) vs. width (x) generated using Nanotec Electrinica WSxM scanning probe microscopy software version 3.0 Beta 8.1. Scan rate of 0Hz is used.

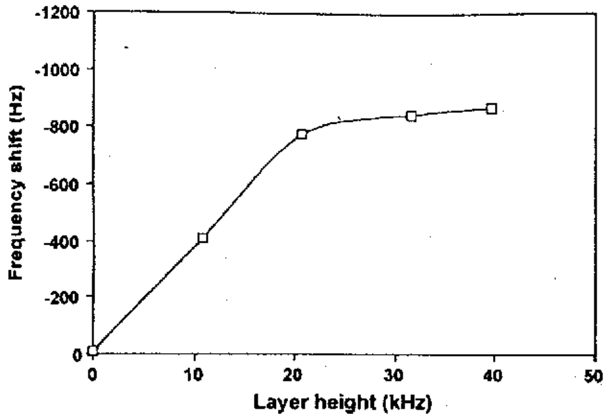


Fig. 2. The effect of imprinted layer height on frequency shift of the TCAA-imprinted coated QCM exposed to TCAA at concentration level of 100 μg l^{-1}.

The TCAA-imprinted polymer matrix from crosslinked poly(VPD-*co*-EDMA) have been produced by copolymerisation of VPD functional monomer and EDMA crosslinker in the presence of TCAA template in acetonitrile at the optimised TCAA/VPD/EDMA mole ratio (1:4:12). This polymer constitution did not only give high molecular recognition, i.e. the frequency shift response to 100 mg l^{-1} of TCAA was the highest comparing to that of the other TCAA/VPD/EDMA mole ratios; 1:2:12, 1:6:12, 1:8:12, 1:4:10, 1:4:15 and 1:4:18, but also provided a film on gold electrode surfaces with good stability in terms of adhesion. The low relative standard deviation (2.4%, $n = 4$) indicates good and reproducible coating. Viscosity, conductivity and pressure fluctuations were compensated for measurements with a coated NIP gold electrode as the reference electrode. The recorded Δf before and after MIP immobilization was found to be 0.0196 ± 0.0004 Hz, which corresponds to about 800 nm according to the Sauerbrey equation [29]:

$$\Delta f = \frac{f_0^2 \Delta m}{N \rho_q A}$$

where f_0 is the fundamental frequency of the crystal, N the modulus of quartz (167 kHz cm), ρ_q the quartz density (2.648 g cm^{-3}), and A is the piezoelectrically active. The film thickness obtained by the QCM was in good agreement with that measured by the AFM method (Fig. 1).

A preliminary evaluation of the various layer heights for bulk effects in TCAA-imprinted polymer of crosslinked poly(VPD-*co*-EDMA) prepared at 1:4:12 TCAA/VPD/EDMA molar ratio was performed by QCM measurement. The frequency shift of the different heights of imprinted layer in the range 0–40 kHz (or ~1580 nm as measured by an AFM method), showed a different frequency shift of the imprinted layer to 100 mg l^{-1} (ppm) TCAA solution, as seen in Fig. 2. The frequency shift of sensor greatly increased at initial layer-heights of the MIP and started to level off after 20 kHz layer-height. The compensated sensor response with a 800 nm-thickness (or 20 kHz-height) of the MIP layer for 100 mg l^{-1} TCAA solution is about 800 Hz. A measurement of noise of 6 Hz allows a detection limit for TCAA of about 54 μg l^{-1} (ppb), with a signal-to-noise ratio of 3:1. A steady response with the sensor was found within 20 min.

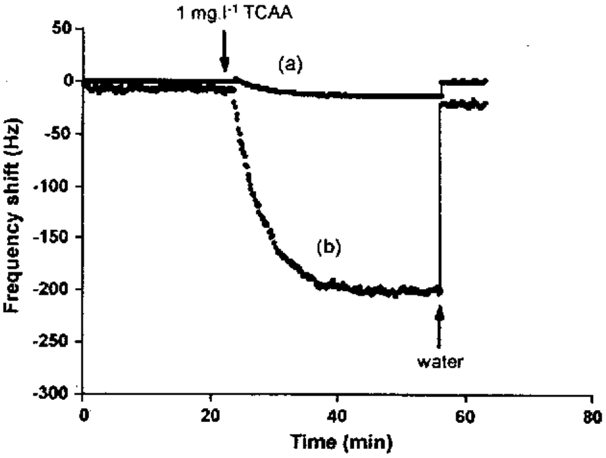


Fig. 3. Signal response of the QCM sensor with (a) NIP- and (b) MIP-coated electrode to TCAA at concentration level of 1 mg l^{-1}.

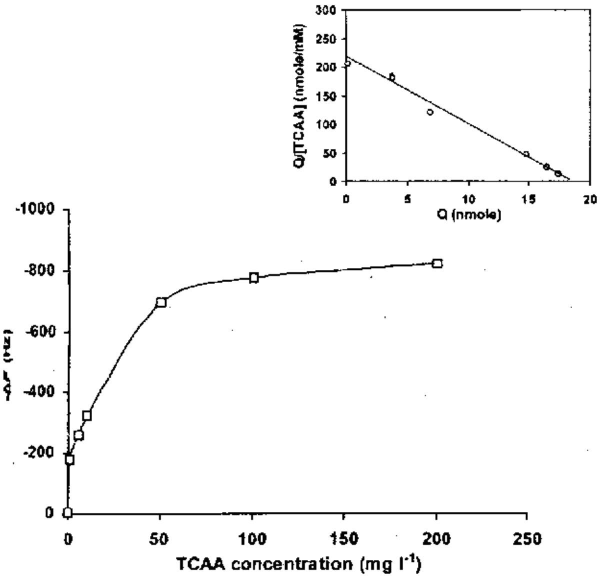
The effect of swelling of the MIP film on the sensor response was also investigated. The results revealed that the frequency response obtained using a 24 h-hydrated polymer (9.965 Hz) is similar to the frequency response using from the dry polymer (9.967 Hz) when measured in air after evaporation of water. In general, EDMA generates an imprinted polymer that is compact, inert and highly stable with respect to rigidity of polymer structure. The negligible change in signal response of the sensor after hydration of the MIP suggests that the imprinted structure produced by the EDMA-based polymer is very stable.

Several buffer solutions (pH 1, 4 and 7 buffers) were tested as background solutions for the QCM measurements. The frequency changes of the MIP-based QCM for 10 mg l^{-1} TCAA concentration were 482, 105, 210 and 374 Hz, respectively, when measured in de-ionised water, 0.2 M HCl–KCl buffer pH 1, 0.2 M phosphate buffer pH 4 and 0.2 M phosphate buffer pH 7 running solution. Hence, de-ionised water was employed as background solution for studying the interaction of TCAA-MIP-QCM with HAAs in water samples, since it afforded the highest sensor response.

3.2. The efficiency of TCAA-MIP coated QCM

3.2.1. Recognition of the template by the TCAA-MIP-QCM

The signal response of the QCM sensor with MIP and non-imprinted polymer-coatings when exposed to a solution of TCAA at a concentration of 1 mg l^{-1} is presented in Fig. 3. The TCAA solution causes a decrease in the frequency shift of the MIP sensor, and this effect is completely reversible after washing with pure water. In contrast, the effect of the TCAA solution on the frequency signal of the NIP-based sensor is very slight. These results indicate that TCAA-imprinted polymer coated onto QCM electrode affords a highly specific and significantly strong signal response to the template in water. The mass change of the MIP film when exposed to TCAA solution is presumably due to the change in the mass of the polymer as tem-



4. Effect of different concentration of TCAA (0–200 mg l^{-1}) on the fre-ncy shift response of the TCAA-MIP-QCM. Top right is Scatchard plot that lative to concentration dependence of the sensor.

te can insert itself into the imprint within the polymer matrix. e main force of binding between the MIP and TCAA in water lution might be expected to derive from acid–base interaction tween the carboxylate anion and vinylpyridinium cation of e MIP. In addition the results demonstrated that dissociation TCAA at the imprinted sites is possible in de-ionised water.

The effect of electrolytes (HCl, NaCl, KCl, K_2HPO_4 and H_2PO_4) on the signal response of the QCM sensor was stud-d. The signal responses of the MIP-coated QCM sensor for the ater solution containing inorganic substances (as individual) a concentration of 0.1 mM were measured under the opti-ized conditions. The polymer gave positive frequency shifts ith 0.1 mM HCl ($\Delta F = +40$). In contrast, frequency shifts of e MIP to 0.1 mM KCl, K_2HPO_4 or KH_2PO_4 in water solution ere negligible (<10 Hz). The positive frequency shift towards Cl of the MIP-based QCM electrode can be explained by a ass loss effect on the sensor surface due to the lighter ion otons [30]. These results demonstrated that TCAA-imprinted osslinked poly(VPD-*co*-EDMA) coated QCM is very sensitive wards the inorganic acid, hydrochloric acid, and this is likely limit the application of this sensor for the assay of HAAs in ater samples containing hydrochloric acid. However the sen-r is not affected by Na, K cation and Cl, HPO_4 and H_2PO_4 ions at concentrations below 0.1 mM.

As can be seen from Fig. 4, the TCAA-MIP-QCM gives quency shift responses correspondingly to the increasing ated concentrations of TCAA in water. The response of the AA-MIP-QCM reaches a plateau at the higher concentration 00 mg l^{-1}) of TCAA, suggesting a saturation of recognition s in the imprinted polymer with the template molecules. e adsorption behaviour of the MIP film fabricated in the sor can be fitted to the Langmuir isotherm. Accordingly, tchard analysis was used to estimate the binding param-rs of the polymers. The Scatchard equation is as follows:

$$Q/[\mathrm{TCAA}] = (Q_{\max} - Q)/K_D,$$

where Q is the amount of TCAA bound to the polymer, $Q_{\max}$ the apparent maximum number of binding sites, K_D the equilibrium dissociation constant, and [TCAA] represents the equilibrium concentration of TCAA. K_D and $Q_{\max}$ were determined from the slope of the straight line and the intercept of the Scatchard plot, and the binding constant (K_a) value was obtained from the reciprocal of the K_D value. Plot of Q/[TCAA] versus Q (see Fig. 4, top right) yielded a straight line with a dissociation constant value (K_d) of 0.094 mM ($K_a = 10.60\ \mathrm{mM}^{-1}$) and the $Q_{\max}$ value of 18.9 nmol.

Table 1
Binding constant (K_a), site population ($Q_{\max}$) and cross-reactivity related to TCAA (CR) of the TCAA-MIP-QCM responding to TCAA and analogs ($n = 3$)

Substrate	K_a (mM^{-1})	$Q_{\max}$ (nmol)	CR[a] (%)
TCAA	10.6	18.9	100
DCAA	7.0	14.1	80
MCAA	4.0	13.2	66
TBAA	6.4	13.8	84
DBAA	5.1	14.1	84
MBAA	4.3	13.2	83
Acetic acid	2.5	10.6	18
Malonic acid	2.2	12.6	20

[a] CR is the ratio of the frequency shift measured at EC_{50} for analog to that of TCAA. EC_{50} is the analyte concentration for which HAA binding to MIP is inhibited by 50%.

The recognition range of the TCAA-MIP-QCM was examined using five structurally related TCAA compounds such as DCAA, MCAA, TBAA, DBAA and MBAA and two non-related TCAA compounds (non-haloacetic acids) such as acetic acid and malonic acid as the substrates. For this purpose, the K_a and $Q_{\max}$ of TCAA-MIP-QCM responding for analogs were determined. The results are collected in Table 1. The results revealed that five HAA analogs have high capability of locating in the TCAA-imprinted cavity compare to both non-haloacetic acids (acetic acid and malonic acid), but their degree of fitting is lower than that of the TCAA template. The specificity of the TCAA-MIP-QCM for each analog was evaluated by measuring the cross-reactivity (CR) (i.e. is the ratio of the frequency shift measured at EC_{50} (see Section 3.2.2) for analog to that of TCAA). The results are shown in Table 1. As can be seen, CR value of the template was higher than that of other five HAA analogs. Also, there is some cross-reactivity of the TCAA-MIP-QCM with the non-haloacetic acids, malonic acid and acetic acid, but much lower degree than that obtained with HAA analogs. The selectivity profile of the TCAA-MIP-QCM for HAAs and non-haloacetic acids was in order as TCAA > DCAA > TBAA > DBAA > MBAA > MCAA > malonic acid > acetic acid. From the selectivity profile obtained, it seems that the tri- or di-substituted HAAs cross-react more than the mono-substituted HAAs, while the cross-reactivity of chloro-HAA and bromo-HAA analogs with the same degree of halogen substitution is not different. Thus, the recognition of the analogs of TCAA by the TCAA-MIP-QCM is due to a carboxylic group, and that this involves a combination of both size and shape selectivity. It appears that TCAA-MIP-QCM gives %CR value higher than 80% for four out of six HAAs (e.g.

Table 2
Analytical characteristics of the TCAA-MIP-QCM in the QCM-based assay when the QCM-based assay is conducted for a HAA(s) concentration ranging from 0.1 to 100 mg l^{-1} in de-ionised water ($n = 3$)

Compound	Equation	R^2	EC_{50} (mg l^{-1})
TCAA	$-\Delta F = -326.47\log(C) - 102.4$	0.984	4.5
DCAA	$-\Delta F = -318.72\log(C) + 109.8$	0.990	15
MCAA	$-\Delta F = -289.75\log(C) + 148.7$	0.997	19
TBAA	$-\Delta F = -312.83\log(C) + 119.6$	0.986	20
DBAA	$-\Delta F = -316.47\log(C) + 140.8$	0.992	23
MBAA	$-\Delta F = -292.7\log(C) + 144.5$	0.996	25
Six HAAs[a]	$-\Delta F = -559.40\log(C) + 321.7$	0.996	4.5

[a] Refers to TCAA, DCAA, MCAA, TBAA, DBAA and MBAA altogether.

DCAA, TBAA, DBAA and MBAA), and CR value between 70% and 60% for one out of six HAAs (e.g. MCAA) and CR value about 20% for non-haloacetic acids, malonic acid and acetic acid. This result suggests that there could be a possibility of inter-anionic competitions for recapture in TCAA binding sites. The mechanism for determination trace HAAs of the TCAA-MIP-QCM electrode may involve in the cooperation and competition of favorable structures of polymer–salt complexes formed between TCAA-MIP and six HAA anions [31]. It is possible that HAAs have similar capability of attaining charge balance in the polyion salts and/or similar supramolecular arrangement within the complex as TCAA, but that TCAA has preference over the HAAs in terms of re-binding.

3.2.2. *Analytical characteristics of the TCAA-MIP-QCM in the QCM-based assay of HAAs*

Analytical characteristics of the TCAA-MIP-QCM in the QCM-based assay of HAA were examined with a HAA concentration ranging from 0.1 to 100 mg l^{-1} in de-ionised water. The mathematic data are shown in Table 2. The calibration curves constructed from the frequency shift parameter ($-\Delta F$) dependency provided reasonable results for analysis of TCAA and other five HAA analogs (see Fig. 5). There was a linear relationship between frequency shift responses of the sensor against the logarithm of concentrations (log C) of TCAA and analogs (individually) and the mixture of total six HAAs, R^2 value > 0.98 with the equation shown for each analyte in Table 2. The measured EC_{50} value is 4.5 mg l^{-1} for TCAA and about 20 mg l^{-1} for the other five HAAs (see Table 2), calculated as the analyte concentration for which HAA binding to MIP is inhibited by 50%. The limits of detection (LOD) according to $3S_b/m$ criterion, where m is the linear calibration and S_b estimated as the standard deviation of the signal response for HAAs, were between 20 and 60 μg l^{-1} for the various HAAs (see the precise value for each compound in Table 3). Detection limits of TCAA and DCAA were in the mid to low μg l^{-1} range. The WHO has a guideline value for DCAA (50 μg l^{-1}) and TCAA (200 μg l^{-1}) [32], i.e. water samples must not contain these HAAs at concentration above these values. TCAA-MIP-QCM can therefore detect and measure DCAA or TCAA at concentrations below the maximum permitted concentrations. Moreover, the LOD values obtained for TCAA or DBAA analyses were lower than those in the literature using conductivity or amperometry methods (with incorporation of liquid chromatography analysis system) [16], see Table 3. The LOD values for MCAA or DBAA analyses were also lower than those in previous reports using HPLC–UV methods [16]. When compared with the membrane sensor, using a TCAA-imprinted polymer-deposited polyvinyl chloride membrane of a previous study [17], detection limits of HAAs with the QCM sensor were not improved (see Table 3).

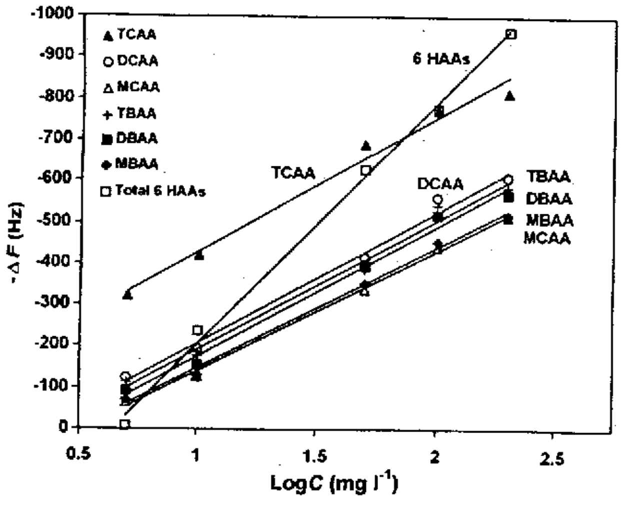


Fig. 5. The calibration plot of frequency shift parameter ($-\Delta F$) vs. added HAA(s) for the TCAA-MIP-QCM in the QCM-based assay of HAAs. Each point represents the average of three independent measurements.

For a mixture of HAAs in water samples, the proposed method can be used only for assay of total HAA. The US

Table 3
Comparison of μg l^{-1} detection limits obtained for the analysis of haloacetic acids by the QCM and several other published methods

Analyte	QCM[a]	Membrane sensor[b,a]	UV[c,d]	Conductivity[c,d]	Amperometry[c,d]
TCAA	50.0	1.0	5.10	80.0	100.0
DCAA	60.0	4.2	8.0	16.0	10.0
MCAA	35.0	4.2	70.0	8.0	1.00
TBAA	26.0	0.2	–	–	–
DBAA	20.0	0.5	90.0	30.0	100.0
MBAA	30.0	5.0	–	–	–

[a] An on-line method.
[b] Cited from Ref. [17].
[c] Cited from Ref. [16].
[d] Used in the conjunction with liquid chromatography.

able 4

nalysis data for HAAs spiked in two brands of commercial bottled water and a municipal tap water with home filtration system by the QCM-based assay

ompound/spiked concentration	Measured[a], $\mu g\,l^{-1}$ after adding HAAs (% recovery)		
	Bottled water from supermarket	Bottled water from local supplier	Municipal tap water[b]
TCAA 0.1 $mg\,l^{-1}$	103 ± 0.9	97 ± 5.3	104 ± 1.3
CAA 10 $mg\,l^{-1}$	102 ± 1.4	99 ± 1.5	102 ± 2.9
otal six HAAs[c] 0.12 $mg\,l^{-1}$ (0.02 $mg\,l^{-1}$ each)	102 ± 2.6	99 ± 1.9	103 ± 5.4
otal six HAAs[c] 12 $mg\,l^{-1}$ (2 $mg\,l^{-1}$ each)	101 ± 1.4	99 ± 1.3	97 ± 1.7

[a] Expected concentrations are amounts added plus the amounts already present in the water sample (mean ± R.S.D, $n = 3$).

[b] With home filtration system.

[c] Total six HAAs refers to TCAA, DCAA, MCAA, TBAA, DBAA and MBAA altogether.

nvironmental Protection Agency (USEPA) has set a maximum ontaminant level of 60 $g\,l^{-1}$ for the five commonly occurring cids namely TCAA, DCAA, MCAA, DBAA and MBAA in he Stage 1 of the disinfection by-product regulation [33]. The pecific sensitivity and selectivity apparent with the six HAAs ndicates the possibility of using the TCAA-MIP-QCM as an nalysis tool for measuring concentrations of HAA mixtures in rinking water samples. The stability of the TCAA-MIP-QCM s good, in that its analytical performance is unaffected after eing stored for more than 1 month at room temperature. The dvantages of the method developed in this work are the ease f the automation of the sensor system, the low cost per unit of ensor device as well as the potential to manufacturer the sensor n an industrial scale.

3. *Analysis of drinking water samples*

The QCM-based assay has been applied to the group analysis of HAAs in real-life samples. Two brands of commercial ottled water obtained either from a supermarket or local suplier and a municipal tap water with home filtration system were subjected to analysis by this method. Measurement of HAAs by the LLE-GC-ECD method is recommended by the USEPA [34], and assay of samples by this method revealed nly TCAA in the samples at concentration levels of 0.8, 1.0 nd 1.1 $\mu g\,l^{-1}$ contained in the bottled-water sample from a upermarket, the bottled-water sample from a local supplier nd municipal tap water with home filtration system, respectively. Hence the HAA contents in the water samples were elow the detection limit of the sensor described in this present udy.

Recovery studies of HAA analyses by the QCM sensor were arried out with the samples after spiking with two different mounts of TCAA standard solution (0.1 and 10 $mg\,l^{-1}$) or with e mixtures of six HAAs standard solution (0.02 and 2 $mg\,l^{-1}$ of ch, total 0.12 and 12 $mg\,l^{-1}$, respectively). A calibration curve s prepared by dissolving TCAA in de-ionised water to attain solutions having TCAA (or total six HAAs) concentration tween 0.01 and 50 $mg\,l^{-1}$ and compared to that measured for AA alone or the mixture of six HAAs in spiked samples. The alysis data for HAA in spiked water samples by the QCM ethod are summarized in Table 4. As can be seen, recoveries nge between 97% and 104% and %R.S.D. values less than 3% were achieved. The result demonstrates the reproducibility and precision of the assay with the sensor for the analysis of HAAs in drinking water samples.

4. Conclusions

It has been shown that TCAA-MIP-QCM can specially detect the group of HAAs in drinking water, using mass-sensitive measurements. The selectivity of the QCM to HAA analogs is satisfactory. Also, the analytical dynamic range for six HAAs (trichloro-, dichloro-, monochloro-, tribromo-, dibromo-, and monobromo-acetic acids) is large. The limits of detection of HAAs are at present higher than concentrations commonly found in actual drinking water samples, but are well below the maximum permissible levels of HAAs (60 $\mu g\,l^{-1}$) in water sample. However, further refinement will undoubtedly improve the limit of detection. It can therefore be concluded that the assay with TCAA-MIP-QCM can be used as a screening method of drinking waters contaminated with HAAs. The proposed method offers fast and cheap measurements.

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