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Liquid Selective Electrodes for Dextromethorphan Hydrobromide Based on a Molecularly Imprinted Polymer in PVC Matrix Membrane

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Liquid and graphite coated electrodes of polymers imprinted with dextromethorphan hydrobromide (DM) were constructed using precipitation polymerization. The molecularly imprinted (MIP) and nonimprinted (NIP) polymers were synthesized using DM as a template, acrylic acid (AA) and 2-vinyl pyridine (VPY) as monomers, ethylene dimethacrylate (EDMA) as a cross-linker and benzoyl peroxide (BPO) as an initiator. The molecularly imprinted membranes and the non-imprinted membranes were prepared using dioctyl phthalate (DOP) and bis (2-ethylhexyl) sebacate (BEHS) as plasticizers in PVC matrix. The slopes and detection limits of the liquid electrodes ranged from 55.9 – 58.3 mV/decade and 3.0 x 10^{-6} – 6.0 x 10^{-5} M, respectively and their response time was about 1 minute. The Liquid electrodes were filled with 0.01 M DM solution and their response was stable in a pH range from 2.0 to 9.0 and with good selectivity for DM over several species. Graphite electrodes coated with MIP membrane of AA and DOP and AA and BEHS were prepared for DM determination. Graphite electrodes coated with MIP membrane of AA and DOP showed a near Nernstian response with slope of 52.4 mV/decade and a linear response for a concentration range of 5.0x 10^{-7} to 1.0 x 10^{-2} M and a response time of around 1 minute. The most effective electrodes were used to determine the concentration of DM in cough syrups.

Keywords: molecularly imprinted polymer; dextromethorphan-HBr; ion selective electrode plasticizers; drug electrodes.

1. INTRODUCTION

Dextromethorphan hydrobromide (DM) [(4bS,8aR,9S)-3-methoxy-11-methyl-6,7,8,8a,9,10-hexahydro-5H-9,4b-(epiminoethano)phenanthrene] is a popular non-opioid highly effective and safe antitussive agent. It is found in many of the over-the-counter cough and cold medicines either alone or in combination with other drugs such as antihistamines, analgesics, decongestants or expectorants [1,

2]. For cough treatment, DM is administered orally in solid or liquid doses containing 10-30 mg of DM three to seven times a day [3]. Several reports indicated that higher doses (60-120 mg) of DM can be used for the management of pain in post-surgical and cancer patients with little or no side effects [4]. Illicit very high doses of DM (100-1500 mg) are used for recreational purposes due to its hallucinogenic effects. Illicit high doses of DM can cause behavioral effect such as euphoria, hallucination, out-of-body experience depending on the size of dose taken [5].

Orally administered dextromethorphan is rapidly absorbed (2-2.5 hours) through the gastrointestinal track, enters the bloodstream and across the blood brain barrier (6). The antitussive activity of dextromethorphan lasts for approximately 5-6 hours, when it passes through the liver; the demethylation of dextromethorphan produces the metabolite dextrorphan, which is, at least, partly responsible for the medication neurological activity [7].

Several techniques have been used for the analysis of DM such as HPLC [8 - 10], GC [11 - 13], capillary electrophoresis [14, 15], UV-Vis spectroscopy [16, 17] derivative UV-Vis spectroscopy [18, 19]. These techniques are expensive, time consuming and destructive. Potentiometric ion selective electrodes (ISEs) can provide a cheaper, faster and nondestructive alternative for these methods. An attempt to design a PVC complex-based ISE for DM was reported by El-Naby [20]. The complex was based on phosphomolybdic acid as electro-active material in different plasticizers. Different DM–PVC, silver coated wires and coated graphite potentiometric sensors based on complexation of DM with cyclodextrin were described by Khaled et al. [21] and the developed electrodes used for determination of DM in pharmaceutical formulation.

Molecularly imprinted polymers (MIPs) are designed to possess selectivity for a certain molecule known as the template. MIPs and their applications in analytical chemistry has been the subject of several reviews [22, 23]. The design of MIPs is based on the formation of a complex between the analyte (template) and a functional monomer. In the presence of a large excess of a cross-linking agent, after polymerization, the template is removed from the polymer leaving specific recognition site with high affinity for the template molecule. MIP applications in the fields solid phase extraction were reviewed by Turiel et al. [23].

Several reports described the use MIPs as ionophores in ion selective electrodes for a variety of drugs and chemicals such as dopamine [24], diphenylamine [25], sertraline [26], ciprofloxacin [27], metoprolol [28], chlormequat [29], oxytetracycline [30] and nitrate ion [31]. Moein et al. [32] described a novel and sensitive method for the automated determination of dextromethorphan in biological fluids by coupling an online MIP-solid phase extraction cartridge to HPLC. They were able to attain a detection limit as low as 0.12 ng/ mL. However, no attempt was made to fabricate an MIP-based ion selective electrode for DM. A special review article was reviewed by Cheong el al. [33], the reviews in recent ca.10 years categorized into subgroups according to specified topics in separation science. In this work DM–MIP-based Liquid and graphite coated ion selective electrodes in PVC matrix membranes were prepared using 2-vinyl pyridine (VPY) and acrylic acid (AA) monomers, ethylene di-methacrylate (EDMA) cross-linker for polymerization with dioctyl phthalate (DOP) and diethyl hexyl sebacate (BEHS) plasticizers. The electrode parameters, pH, selectivity, sensitivity were determined and used for the determination of DM in antitussive syrups manufactured by Jordanian companies.

2. EXPERIMENTAL

2.1 Apparatus

All potentiometric measurements were made at room temperature with an Orion bench top pH/ISE model 525. The potentiometric measurements were recorded using the fabricated dextromethorphan HBr-MIP sensor in conjugation with secondary calomel electrode (SCE) as a reference electrode. The pH values were recorded using a Denver Instruments 420 pH meter. The potential measurements were made with a moderate stirring at sensitivity of 0.1 mV. Construction of the electrode body and immobilization of dextromethorphan HBr–MIP in the PVC matrix membrane were done using the method given by Craggs et al. [34].

2.2 Reagents

All of the chemical used were reagent grade with highest purity and used as received without further purification. Acrylic acid (AA) (99.5%), 2-vinyl pyridine (VPY) (97%), benzoyl peroxide (BPO) (75%), Ethylene di-methacrylate (EDMA) (98%), dioctyl phthalate (DOP) (99%), and bis(2-ethylhexyl) sebacate (BEHS) (97%) were purchased from Acros Organics. HPLC grade THF was obtained from TEDIA (USA). Dextromethorphan hydrobromide monohydrate (DM), ciprofloxacin and paracetamol were a gift from a Jordanian pharmaceutical company. All aqueous solutions were made in deionized water with electrical conductivity of 0.1 μS cm^{-1}. The antitussive syrups Coldex-D® and Colfed® were purchased locally from (Arab pharmaceutical Manufacturing Company, Jordan) and Nocuf® syrup from Jordan Sweden Medical and sterilization Co.

2.3 Synthesis of the Imprinted Polymer

In 50 mL screw cap glass test tube, 3 mmol of the monomer (AA or VPY), 15 mmol of the cross- linker EDMA, 0.5 mmol of the template drug DM, 0.3 mmol of the initiator (BPO) and 3 mL of chloroform were mixed. The solution was degased for 10 minutes with high purity nitrogen and cured at 75 ^{o}C for 2 hours. The polymer was dried and crushed and the template (DM) was removed by repeated washing with 30% acetic acid in water. The polymer was dried at 60 ^{o}C for 24 hours. The polymer was then ground and sieved and the particles with size less than 150 μm was collected and used for preparing the sensing membrane. The non-imprinted polymer (NIP) was made in the same way but without the template drug.

2.4 Synthesis of Membrane and Electrode Construction

The sensing PVC membrane was prepared by mixing 0.17 g of high molecular weight PVC, 0.4 g of the plasticizer (DOP or BEHS) and) 0.02 g of the MIP. After homogenization, 2-3 mL of THF was added and stirred. The mixture was poured in 5 cm in diameter glass ring and allowed to evaporate for 24 hours.

The electrode was made by attaching a circular disk (10 mm in diameter) of the PVC membrane to the end of Tygon tube using a concentrated PVC/THF solution as an adhesive. The other end of the Tygon tube was fixed to a glass tube into which silver wire coated with silver chloride was inserted and filled with 0.01 M solution of DM. The electrodes were preconditioned by soaking for two hours in 0.01 M solution prior to use.

The GCE was made by dipping a graphite rod (3 mm in diameter) in the above solution an allowing it to dry in air. The procedure was repeated until the coating thickness is about 0.5 mm. The GCE was also preconditioned in the way as the liquid electrode.

2.5 Determination of Dextromethorphan in Antitussive and Cold Syrups

The antitussive syrups used were Colfed® (10 mg DM/ 5 mL), Coldex® (10 mg DM/ 5 mL) and Nocuf® (5 mg DM/ 5 mL). The syrups were diluted 4 times with deionized water and the concentrations of the resulting solutions were measured using the method of standard addition. This was done by the addition of 1 mL of 0.1 M DM in 10% ethanol-water solution to 25 mL of the drug solution followed by measuring the potential of the solution. This procedure was repeated at least 5 times.

3. RESULTS AND DISCUSSION

3.1 Liquid Membranes and Graphite Coated Electrode (GCE)

MIP based liquid electrodes, their working ranges and Nernstian response slopes have been investigated. The electrodes are based on an MIP made of the monomers VPY and AA incorporated in a PVC matrix with the two plasticizers BEHS and DOP. The inner solution of all liquid electrodes was 0.01M aqueous DM solution. Two monomers, vinyl pyridine (VPY) and acrylic acid (AA), were used for the synthesis of molecularly imprinted (MIPs) and non-imprinted polymers (NIPs). Although the acid-base properties of the two monomers are different, the results obtained indicate that both monomers can be used for the preparation of effective MIPs for DM. The plasticizer is an important component of the sensing membrane that acts as a solvent for the various components and determines the mobility of the analyte in it. Both of the plasticizers used, DOP and BEHS, are suited for the fabrication of MIP-based DM electrodes. Table 1 summarizes the parameters of the fabricated and tested electrodes, four are liquid electrodes and four are graphite electrodes. It can be seen that all of the liquid electrodes have slopes between 52.4-58.3 mV/decade and linear dynamic ranges between $5x10^{-7}$- 0.01 M except for the electrode based on AA and BEHS which has a high slope and a narrow dynamic working range. All of the liquid electrodes prepared have a short response time (about 1 minute) especially at high concentrations of DM. The values listed in Table 1 also indicates that the liquid electrodes based on VPY and BEHS plasticizer gives the best results among the tested electrodes, therefore, the liquid electrode based on BEHS was used to determine dextromethorphan concentration in pharmaceutical samples.

The response and the linear dynamic range for two of the fabricated liquid electrodes using VPY as a functional monomer and BEHS or DOP as plasticizer are shown in Figure 1. Both electrodes have a near Nernstian response with slopes of 55.87 and 56.55 mV/ decade, respectively. It can be seen that the two electrodes have a wide working dynamic ranges and a low detection limits of 5.0 x 10^{-6} and 3.0 x 10^{-6} M.

Because of their rugged and maintenance free design, solid electrodes are considered superior to liquid electrodes. In this study, MIP-based graphite coated electrodes (GCE) were fabricated for the analysis of DM. The results indicate that response and the linear range of the GCEs are highly dependent on the thickness of the membrane. Excellent response and dynamic working range was attained when membrane thickness is about 0.5 mm. MIP-and NIP GCE based on AA as a monomer and DOP or BEHS as plasticizer were tested and their specifications are summarized in Table 1. The MIP electrode based on DOP has a slope of 52.4 mV/decade and detection limit of 2.0 x 10^{-7} M. After five days the slope decreased to 46.1mV/decade. The GCE has a fast dynamic response time (about 1 minute) similar to the liquid electrodes. This electrode was used for the determination of DM in pharmaceutical formulations. A similar GCE fabricated using an NIP exhibit very low slope (22.2 mV/ decade) which demonstrates the impact of molecular imprinting on selectivity and the response of electrode. NIP electrode based on BEHS plasticizer gives a nonlinear response with a slope of 19.9 mV/decade and R= 0.7850 indicating that molecular imprinting is essential in the fabrication of electrode with a sensitivity and selectivity. The electrode response for GCE fabricated using MIP was found to be higher than that of GCE fabricated using NIP as shown in Figure 2.

Table1. Electrode parameters of the MIP- and NIP based dextromethorphan hydrobromide (MD) sensors.

Electrode Number	Type of electrode	Slope mV/decade	Concentration range / M	Correlation coefficient	Detection limit / M
1	MIP:VPY+BEHS Liquid electrode	55.9	$10^{-2} – 10^{-5}$	0.9994	3.0 x 10^{-6}
2	MIP: VPY+DOP Liquid electrode	56.6	$10^{-2} – 10^{-5}$	0.9988	5.0 x 10^{-6}
3	MIP: AA+BEHS Liquid electrode	78.1	$10^{-3} – 4.0x10^{-5}$	0.9987	1.5 x 10^{-5}
4	MIP: AA+DOP Liquid electrode	58.3	$10^{-2} – 2.0x10^{-5}$	0.9975	6.0 x 10^{-5}
5	MIP: AA+DOP Graphite electrode	52.4	$10^{-2} – 5.0x10^{-7}$	0.9996	2.0 x 10^{-7}
6	NIP: AA+DOP Graphite electrode	22.5	$10^{-2} – 10^{-7}$	0.9789	1.0 x 10^{7}
7	MIP: AA+BEHS Graphite electrode	41.9	$10^{-2} – 10^{-5}$	0.9836	1.0 x 10^{-5}
8	NIP: AA+BEHS Graphite electrode	19.9	$10^{-2} – 10^{-5}$	0.7850	1.0 x 10^{-5}

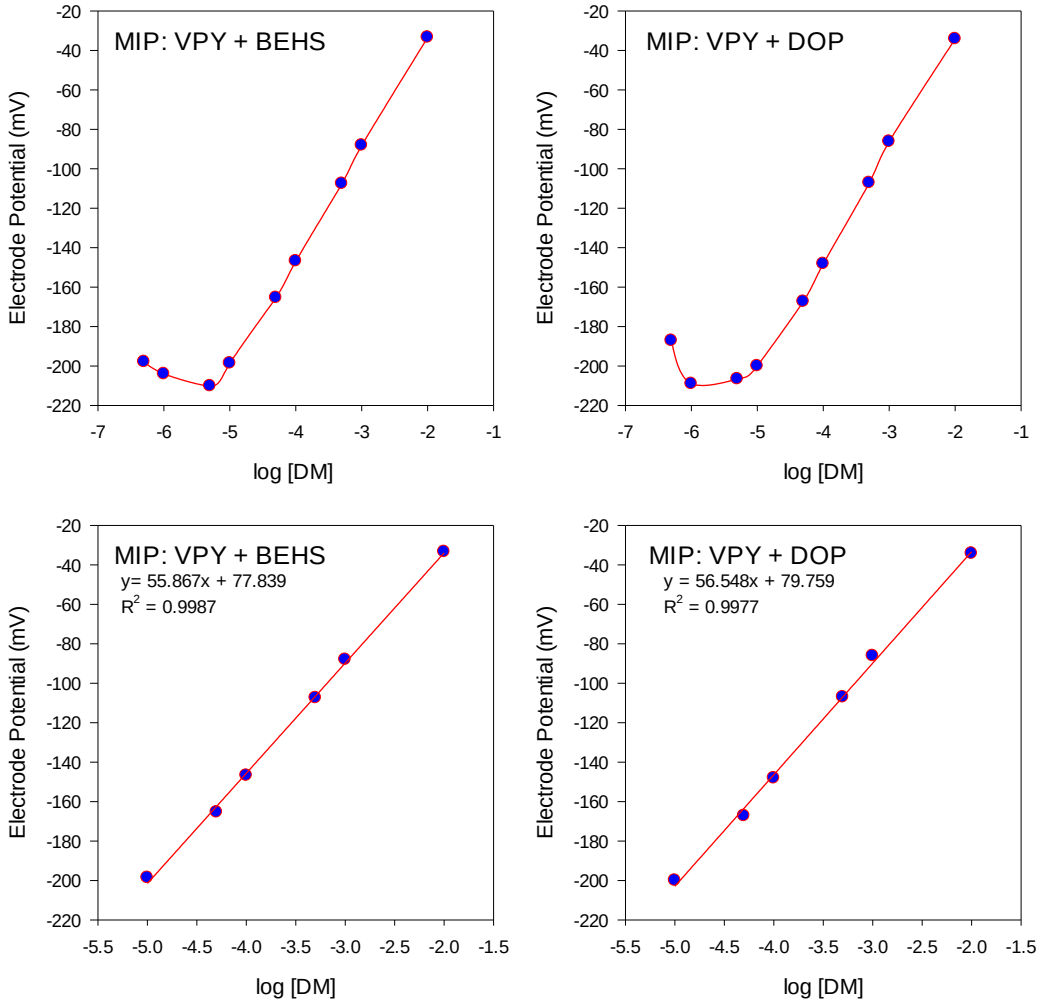

Figure 1. Calibration curves for MIP-based liquid DM-PVC sensors using DOP and BEHS plasticizers.

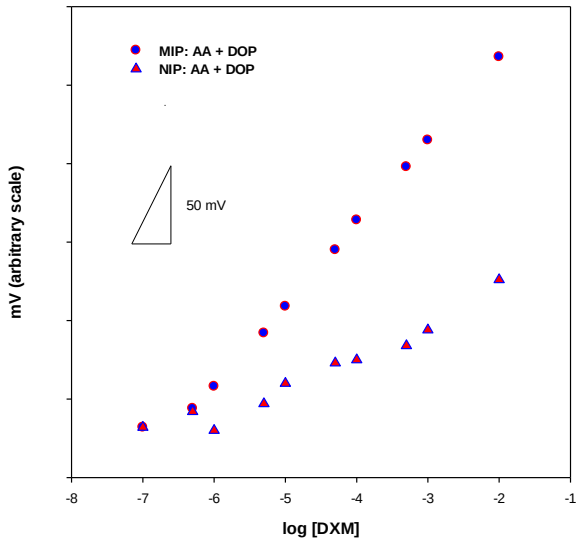

Figure 2. Electrode response of MIP-and NIP electrodes based on AA as a monomer and DOP as plasticizer without any additives.

3.2 Selectivity coefficient

Selectivity coefficients were determined by using separate solution method (SSM). The potential of the electrode is measured for each of two separate solutions, one containing dextromethorphan (A) of activity a_A and charge z_A (but not B), the other containing the interfering species (B) with charge z_B when ($a_A = a_B$). The selectivity coefficients were calculated using the equation [35]:

$$\text{Log. } K^{pot}_{A,B} = [\,(E_B - E_A)\, z_A F / 2.303\, RT\,] + (1 - z_A / z_B)\, \log a_A$$

Because DM is mainly found in pharmaceutical formulation in combination with other drugs, the interference of the antibiotic ciprofloxacin (CIPRO) with DM determination by the separate solution method over a wide range of concentrations was investigated. Figure 3 shows a comparison of a liquid electrode based on VPY and BEHS to separate solutions of DM and CIPRO of equal concentrations. It can be seen that the electrode response due to DM is significantly higher than that to CIPRO.

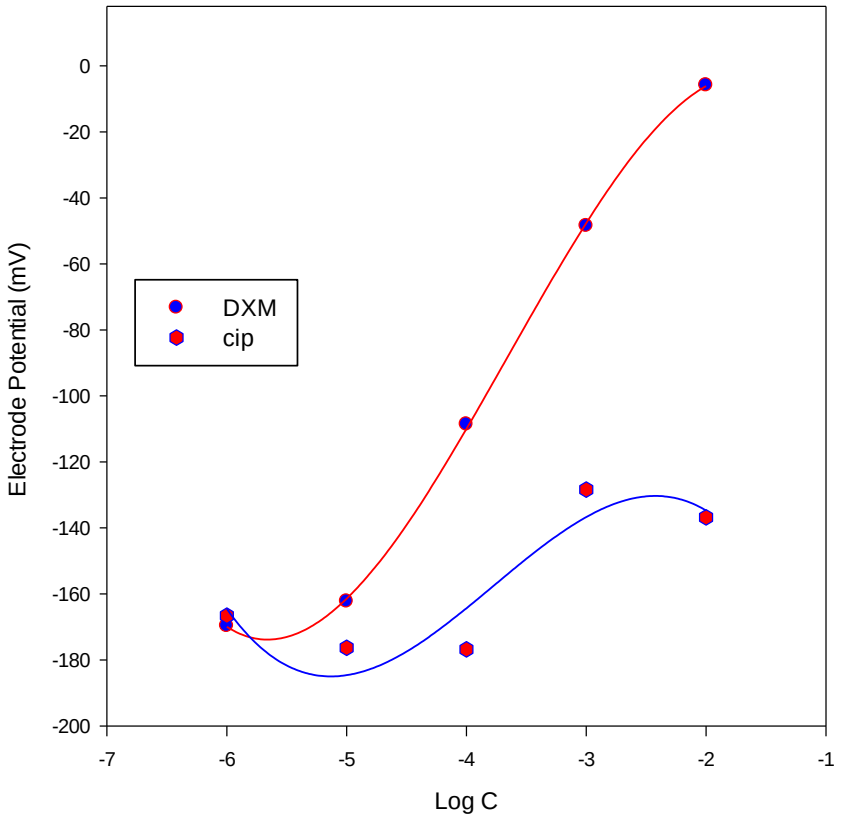

Figure 3. Comparison of the response of MIP-Based liquid electrode to separate solutions of DM and CIPRO of equal concentration, the electrode membrane is made of VPY as a monomer and BEHS as a plasticizer.

Plot of the selectivity coefficient $K^{pot}_{DM,Cipro}$ versus log [DM] for the same electrode is shown in Figure 4. The values of the selectivity coefficients $K^{pot}_{DM,Cipro}$ ranged from 0.544 to 0.0034 over dextromethorphan concentrations from 10^{-5} M to 10^{-2} M which indicates that small or no interference from CIPRO within this range. However, values of $K^{pot}_{DM,Cipro}$ greater than one were obtained at lower concentrations $(at\ a_A = a_B = 1 \times 10^{-6},\ K^{pot}_{DM,Cipro} = 1.144)$ which indicate that CIPRO interferes with determination of DM at low concentrations that are lower than the dynamic useful range of the electrode.

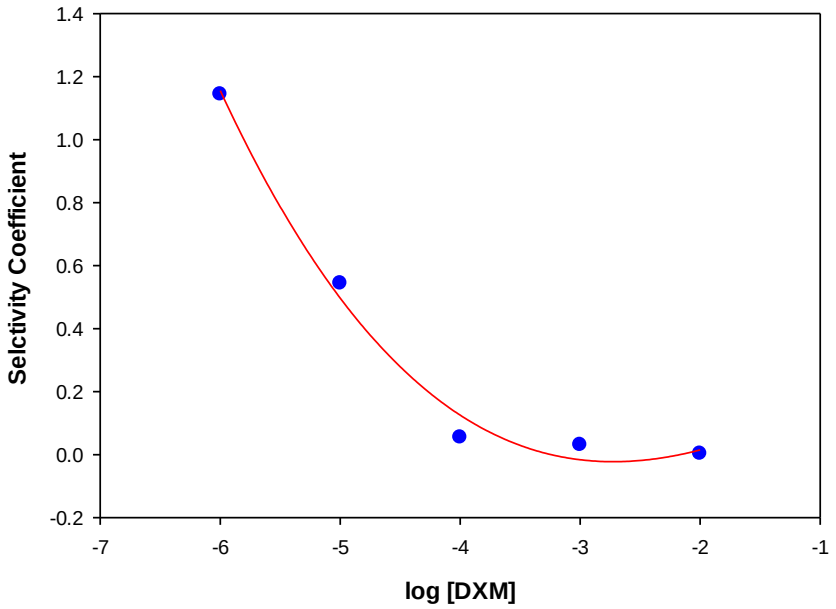

Figure 4. Variation of the selectivity coefficient $\log K^{pot}_{DM,Cipro}$ with concentration, the selectivity coefficient was calculated by the separate solution method.

The selectivity coefficients for the Interference of glucose, paracetamol, Ketorolac, amoxicillin, NaBr, KNO_3 and $Ba(NO_3)_2$ at $a_A = a_B = 1 \times 10^{-3}$ M are listed in Table 2. All species have selectivity coefficients well bellow of unity which indicates that these species do not interfere with dextromethorphan determination.

Table 2. Selectivity coefficient of some interfering specie calculated by separate solution method using dextromethorphan hydrobromide electrodes

Type of electrode	Selectivity coefficient of interfering species at $a_A = a_B = 0.001$ M						
	Glucose	Paracetamol	Ketorolac	Amoxicillin	NaBr	KNO_3	$Ba(NO_3)_2$
MIP: VPY+BEHS	1.7×10^{-2}	1.2×10^{-2}	8.6×10^{-3}	7.0×10^{-3}	5.4×10^{-3}	6.3×10^{-3}	1.4×10^{-4}
MIP: VPY+DOP	1.1×10^{-2}	9.6×10^{-3}	6.0×10^{-3}	3.9×10^{-3}	4.2×10^{-3}	3.6×10^{-3}	1.4×10^{-4}
MIP:AA+BEHS	1.6×10^{-2}	1.1×10^{-2}	1.4×10^{-2}	8.9×10^{-3}	8.0×10^{-3}	7.9×10^{-3}	2.5×10^{-4}
MIP: AA+DOP	1.7×10^{-2}	1.4×10^{-2}	5.2×10^{-3}	4.7×10^{-3}	4.2×10^{-3}	3.9×10^{-3}	2.5×10^{-4}

A plot of $\log K^{pot}_{DM,Cipro}$ with type of interfering species is shown in Figure 5. It can be seen that selectivity coefficients for all of the species are below one which indicates that these drugs, monovalent ions and divalent ions do not interfere with the dextromethorphan determination by these electrodes.

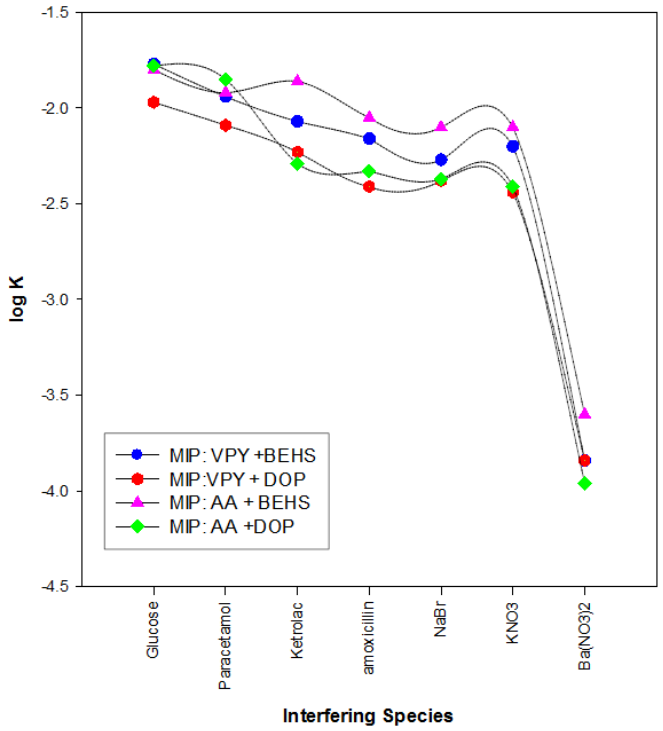

Figure 5. The selectivity coefficients of glucose, paracetamol, ketoroloc, amoxicillin, NaBr, KNO_3 and $Ba(NO_3)_2$. For the details of the electrodes see the graph legend.

3.3 pH effect

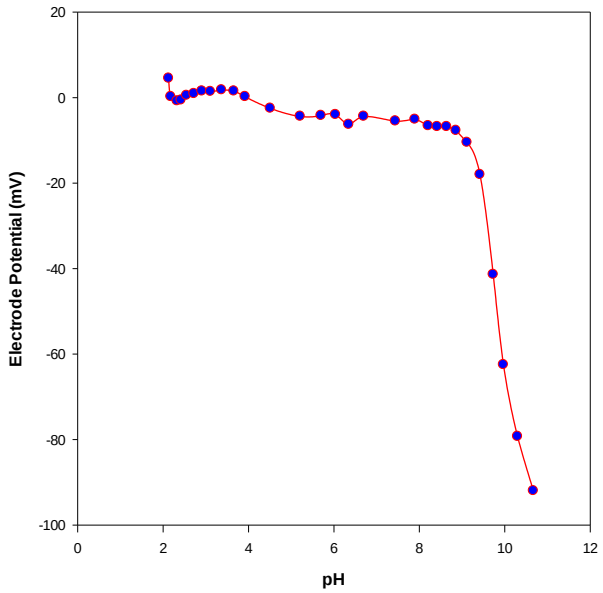

Figure 6. Effect of pH on the potential response of MIP-based liquid electrode made of VPY as a monomer and BEHS as a plasticizer. The test solution contains 1x10 $^{-3}$ M DM.

Figure 6 shows the effect of pH on the response of the MIP-based liquid electrode at a DM concentration of $1x10^{-3}$ M. The pH of the measured solution was adjusted with aqueous solutions HCl and NaOH. Based on figure 6 the electrode can be used in the pH range between 2 and 9. At higher pH values the response of the electrode started to decrease due the precipitation of DM in the test solution.

Two previous attempts were made to fabricate complex-based selective electrodes for DM. El-Naby [20] prepared DM selective electrodes based on association complexes with ammonium reinecakte and phosphomolybdic acid as electroactive material. The second attempt was by Khaled and coworkers [21] who prepared liquid electrodes, silver wire coated electrodes and graphite coated electrode for the determination of DM. The electrodes were based on cyclodextrins ionophores and were used for the determination of DM in pharmaceutical formulation in patch and flow injection analysis. When the performance of the MIP-based liquid and graphite coated electrodes of DM reported herein is compared with performance of the complex-based electrodes, it can be seen that MIP-based electrodes have better selectivity, can be used over a wider pH range and have longer shelf life. The useful pH range (2-9) observed for MIP-based electrode reported herein is wider than that observed for the complex-based selective electrodes (2.5-6.6) reported previously [20,21].

3.4 Quantitative analysis of DM

The method of standard addition [36] was applied for the determination of DM concentrations in antitussive and cold syrups manufactured by Jordanian pharmaceutical companies. The results were obtained using graphite coated electrode (MIP:AA+DOP) and a liquid electrode (MIP: VPY+BEHS) are listed in Table 3. The recoveries ranging from 91.6% to 112.7% were found for the three investigated syrups. The reported percent recoveries of the drugs in Table 3 were calculated using the values reported by the manufacturer which was obtained using the recommended assay by the British Pharmacopoeia [37].

Table 3. Percent recovery of commercial pharmaceutical formulations using standard addition method, the value of the recovery is the average of five measurements

Electrode	Drug	Calculated DM	Measured DM	% Recovery
Liquid MIP: VPY+PEHS	Colfed	1.419×10^{-3} M	1.60×10^{-3} M	112.6
	Coldex-D	1.419×10^{-3} M	1.30×10^{-3} M	91.6
	Nocuf	7.094×10^{-4} M	7.36×10^{-4} M	103.6
Graphite MIP: AA+DOP	Colfed	1.345×10^{-3} M	1.35×10^{-3} M	99.5
	Coldex-D	1.298×10^{-3} M	1.35×10^{-3} M	96.15
	Nocuf	7.094×10^{-4} M	7.99×10^{-4} M	112.7

4. CONCLUSION

Dextromethorphan hydrobromide (DM) selective electrodes based on molecularly imprinted polymer in PVC matrix membrane were successfully fabricated. The electrodes show a near Nernstian

response with slopes ranging from 52.4 to 58.3 mV/ decade and usable over the concentration range of 0.01 to 5.0×10^{-6} M. The new electrodes exhibited short response time, good stability, sensitivity and selectivity and life times of more than three months. The electrodes have a stable potential over a wide pH range (2.0-9.0). Finally, the fabricated MIP sensors can be used for the determination of DM in pharmaceutical formulations.

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