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Potentiometric Determination of Mebeverine Hydrochloride Using Imprinted Molecular Polymer in PVC Matrix Membrane

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Abstract

Four molecular imprinted polymer (MIP) membranes for Mebeverine.HCl (MBV.HCl) were prepared based on PVC matrix. The imprinted polymers were prepared by polymerization of 2-acrylamido-2-methyl-1-propane sulphonic acid (AMPS) as monomer, pentaerythritoltriacrylate (PETRA) as a cross linker ,benzoyl peroxide (BPO) as an initiator and mebeverine as a template. Four different types of plasticizers of different viscosities were used and the electrodes were fully characterized in terms of plasticizer type, response time, lifetime, pH and detection limit.

The MBV-MIP electrodes exhibited Nernstian response in concentration range from 1.0×10^{-6} to1.0×10^{-1} M with slopes of 13.98, 19.60, -20.43 and 19.01 mV/ decade. The detection limit and quantification are found to be 4×10^{-6}, 3×10^{-6}, $2\times 10^{-5}$and 1.2×10^{-6} M ,respectively. Interference study for inorganic cations and amino acids was also studied. The best electrode based tris (2-ethyl hexyl) phosphate plasticizer was applied successfully for potentiometric determination of mebeverine in commercial tablets. Excellent average recovery obtained by potentiometric methods was about 102.26% which is in good agreements with British Pharmacopoeia.

Keywords: molecularly imprinted electrodes, Mebeverine hydrochloride, potentiometric method, 2-Acrylamido-2-methyl-1-propane sulphonic acid monomer.

التقدير المجهادي لدواء المبفرين هيدروكلورايد باستعمال تقنية الطبعة الجزيئية في قالب بولي فاينيل كلورايد

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الخلاصة

تم تحضير عدد من بوليمرات الطبعة الجزيئية لدواء Mebeverine.HCl .على اساس استخدام بولي فاينيل كلورايد PVC كساند من خلال عملية البلمرة باستعمال 2–اكريل اميدو–2–مثيل–1–بروبان حامض السلفونيك(AMPS)(كمونيمر وبنتا اريثريتول تراي اكريليت(PETRA) كمادة تشابك و بنزويل بيروكسايد(BPO) كبادئ، و دواء Mebeverine.HCl كمادة اساس . بعد الحصول على المادة على القالب للدواء تم تحضير اربعة اقطاب باستخدام ملدنات مختلفة اللزوجة وتم دراسة عدة خصائص منها الاستجابة عمر القطب،الدالة الحامضية وحد التحسس.

أظهرت الاقطاب المحضرة استجابة نرنستية بتراكيز تتراوح بين (1.0×10^{-6} – 1.0×10^{-1}) مولاري وميل 19.60,13.98، 20.43– و19.01 ملي فو لت/ حقبة وحد التحسس ($3،4\times 10^{-6}$ ×10^{-6} ،

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2×10^{-6} ، 1.2×10^{-6}) مولاري على التوالي. كما تمت دراسة الانتقائية للاقطاب المحضرة مع الكاتايونات اللاعضوية والاحماض الامينية وكانت افضل النتائج المستحصلة هي للقطب الحاوي على الملدن ثلاثي (2- اثيل هكسيل) فوسفيت والذي تم تطبيقه بصورة ناجحة في المستحضرات الصيدلانية وكانت نسبة الاسترادادية مساوية الى 102.26% وهي نتيجة مقبولة بالمقارنة مع دستور الادوية البريطانية.

1. Introduction

Mebeverine hydrochloride(MBV.HCl), 3,4-dimethoxybenzoicacid4-[ethyl-2-(4-methoxyphenyl)-1-aminobutylveratrate hydrochloride, is a nonspecific antispasmodic agent which acts directly on the smooth muscle of the gastrointestinal tract. Mebeverine hydrochloride is widely used as a relaxant agent for the treatment of gastrointestinal spasmodic disorders such as irritable bowel syndrome also used in a variety of conditions affecting the vascular system and the gastro-intestinal and genito-urinary tracts [1]. The most common method used in determination of MBV. HCl is the chromatographic method which is high sensitive method but very expensive, time consuming and need special technical training. They include high performance liquid chromatography [2-4], online micelle electrokinetic chromatography [5,6], high performance thin layer chromatography[7], supercritical-fluid chromatography–mass spectrometry, and online reversed-phase liquid chromatography–gas chromatography[8]. Other alternatives include spectrophotometry[9,10] and first-derivative UV-spectrophotometry[11,12].

Synthesis of molecular imprinted polymers by functional monomer and cross-linker polymerization in the presence of template and developed in the wide fields, such as solid phase extraction[13], chromatographic separation[14]and biosensors[15]. Several papers were published in imprinted polymers using drugs as templates. Al-Bayati[16] prepared ibuprofen molecularly imprinted polymer using ibuprofen as a template and methacrylic acid as monomer with different plasticizers in PVC matrix and used for determination of ibuprofen in pharmaceutical samples. The molecularly imprinted and non-imprinted polymers were constructed by Al-Mustafa et al.[17]using dextromethorphan(DM) as a template, acrylic acid and 2-vinyl pyridine as monomers. The most effective electrodes were used in determination of DM in cough syrups. Abu-Dalo *et al*.[18] prepared a new electrochemical sensor using copper-carboxylbenzotrizole complex based on copper ion imprinted polymer in which the carboxylbenzotrizol is a new ligand used for MIP, the electrodes used for determination of copper ions in waste water samples. Several molecular imprinted polymer membranes of azithromycin constructed by Abu-Dalo et.al[19] using graphite electrode, the Azin-MIP was prepared by polymerization and the electrodes were used for determination of azithromycin in commercial tablets and capsules. Omidi *etal*.[20] described a molecular imprinted polymer nanoparticles for selective pre-concentration of herbicide, 2,4-dichlorophenoxy acetic (2,4-D) and the method was used for determination of 2,4-D in the urine and different water samples.

In the present study, four electrodes were constructed and characterized based on membranes containing mebeverine MIP in PVC matrix. Electrode parameters were determined including; working concentration range, Nernstian slope, detection limit, selectivity over a wide variety of some cations and pH range. The fabricated potentiometric sensors were applied for the determination of mebeverine in pure and in commercial tablets.

2. Experimental

2-1. Chemicals

Mebeverine hydrochloride was obtained from the State Company of Drug Industries and Medical Appliances (IRAQ-Medial East- Baghdad).Commercial mebeverine tablets obtained from local stores are; Asia-duspataline 135 mg, Eipico-colospasmin 135 mg and Abbott-duspataline 135 mg. Tri-butylphthalate (TBP), Nitrobenzene (NB),Tris(2-ethylhexyl)phosphate(TEPH) and Di-Butylsebacate (DBS) as well as metal salts were purchased from Sigma-Aldrich and used as received. Pentaerythritoltriacrylate (PETRA)(99%), 2-Acrylamido2-methyl-1-propane sulphonic acid(AMPS)(99%), benzoyl peroxide (BPO)(78%) was purchased from Sigma-Aldrich. Other chemicals used were of reagent grade with highest purity and used as received without further purification.

2-2. Apparatus

Potentiometric measurements were carried out with a digital voltmeter (HANA pH 211 instrument Microprocessor pH meter). pH measurements were made with a digital pH meter (wissenschaftlich-

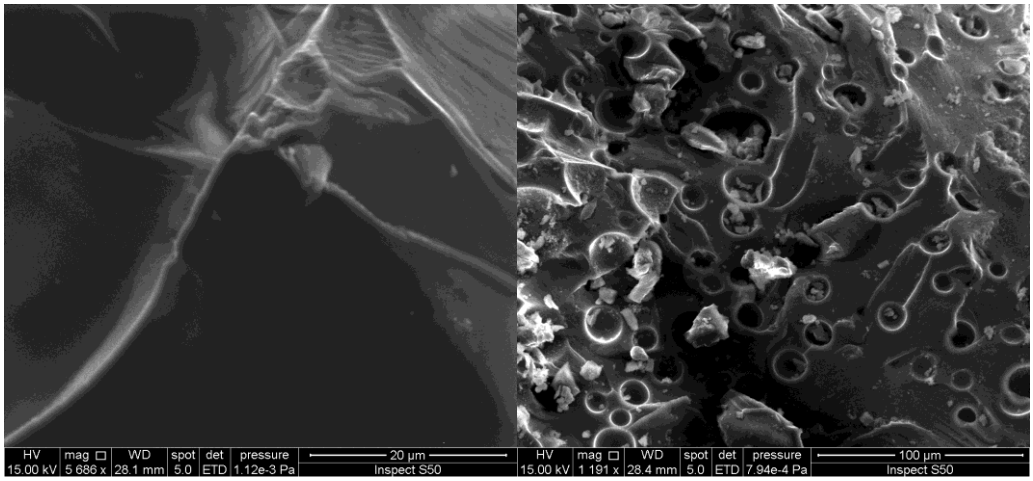
Technische Werkstätten GmbH WTW/pH meter in lab pH720-Germany). Scanning Electron Microscopy (SEM)[JSM-6390 A] (Tokyo, japan) was used to know the design of imprinted polymer and morphology of the particles ,the performance of the electrode was investigated by measuring the potential of MBV.HCl solutions at room temperature with a concentrations range from10^{-6} to 10^{-1}M. Each solution was stirred and the potential reading was recorded at equilibrium. The calibration curves obtained by plotting the response against logarithmic function of mebeverine concentration.

2-3. Synthesis of the imprinted polymer(MIP)

In a 50 mL screw cap glass test tube, 0.5 mmol (0.2330 g) of Mebeverine.HCl, 3.0 mmol (0.6217g) of the monomer (2-acrylamido-2-methyl-1-propane sulphonic acid(AMPS), 15 mmol (3.791 mL) of the cross-linker pentaerithritoltriacrylate (PETRA), 0.32mmol (0.0775g) of the initiator BPO and 5 mL of chloroform were added. The solution was degassed for 45 min[16]. with high purity nitrogen and cured at 75^0C for 3 hrs. The template (MBV-MIP) was removed by repeated washing with 30% acetic acid in methanol. The polymer was dried at 60^0C for 24 hrs. , grind and sieved to collect particle size of 125µm used for the preparation of the sensing membrane.

The sensing PVC membrane was prepared by mixing (0.17) g of high molecular weight PVC, (0.4) g of the plasticizer 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 30 mm 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 mebeverine.

The morphology of MIP and non- imprinted polymer NIP membranes before and after washing showed by electron microscope in Figure-1. A porous on the surface Figure-1(a) about 20 µm may indicate the binding sides to the polymer. Figure-1(b) shows clear holes about of 100 µm in sizes which may indicate a complete removal of the template from the membrane.



a b

Figure 1- SEM photograph of the surface of MIP**, a)** before washing **b)** after washing.

2-4. Potential Measurements

All measurements were carried out in a 50 mL double walled glass cell, with constant magnetic stirring of the test solution at room temperature. The performance of the electrodes was investigated by measuring the potential of mebeverine hydrochloride solutions prepared with a concentration range of 10^{-6} to 10^{-1} M by serial dilution. The slope, response time, detection limit and operative life were calculated from the calibration curve. The electrochemical performance of the two proposed sensors was evaluated according to the IUPAC recommendations data.

2-5.Sample preparation for analysis

Ten tablets of the drug formulations were weighed accurately (3.6172 g) and finely powdered in a small dish. An amount of powder equivalent to (0.1248 g) was accurately transferred to 100 mL volumetric flasks and diluted to the mark with distilled water to prepare 10^{-3} M solution of

mebeverine. Another amount of powder equivalent to (0.01248 g) transferred to 100 mL volumetric flask and diluted to the mark with deionized distilled water to prepare 10^{-4} M solution of mebeverine. The potential readings produced by immersing the prepared electrodes in the prepared solutions were recorded.

3. Results and Discussion

3.1.Characterization

(FTIR) spectra of leached and unleached mebeverine hydrochloride imprinted polymers MIP and NIP were recorded in the range of 400–4000 cm^{-1} as KBr disk Table-1. The FTIR spectrum of mebeverine showed sharp absorption band at1716 cm^{-1} for carbonyl stretching of ester group when comparing with the FTIR spectrum of MIP which showed broad bands at 1733 cm^{-1} of ester groups and crosslinker . The FTIR spectrum of NIP shows shoulder bands at 1739 cm^{-1} and 1731 cm^{-1} for the monomer and crosslinker str. ester carbonyl groups with disappearance of the band at 1716 cm^{-1} for str. carbonyl ester group of mebeverine.

Table 1- The most identified peaks of FTIR spectra for MBV-MIP and NIP using (AMPS) as a functional monomer

No.	Functional Group	MBV-MIP(AMPS) before template removal	MBV-MIP(AMPS)after template removal	MBV-NIP(AMPS)
1.	OH str.	3448	3473	3386
2.	N-H str.	3510	3500	3420
3.	C-H aliphatic str.	2945,2887	2981	2931
4.	C=O str.ester	1733	1731	1739
5.	C=O str.amide	1656	1716	1637
6.	C=C str.	1542	1645	1552
7.	C-O str. asymm.	1261	1269	1263
8.	C-O str. symm.	1163	1159	1176
9.	Out-of plane-para-sub	815	-	

3.2.Influence of membrane composition

Four membranes of different compositions were prepared using four different plasticizers with very different viscosities, tri-butylphosphate (TBP) (ν_e =3.114 cSt), nitro benzene (NB) (ν =2.030 cSt) and dibutylsebacate(DBS) (ν=11.0042cSt) and tris(-2-ethyl hexyl)phosphate(ν =8.015 cSt). The results of electrode specification were obtained from the calibration curves are listed in Table-1.

The calibration graphs obtained for the corresponding membranes, IB, IIB, IIIB and IVB were shown in Figure 2. Electrodes based on membrane containing NB and TEHP plasticizers gave good slopes of 19.60 and 19.01 mV/ decade except for electrode IIIB gave a negative slope of -20.43 mV/ decade. This behavior may be attributed to the high viscosity 11.0042cSt of DBS which increased the ion-exchange process between the MIP and the external solution of mebeverine, or may be attributed to the steric factor of the plasticizers (DBS) which increased the bond strength with the MIP. Excellent concentration range $10^{-6} – 10^{-1}$ M was obtained for electrode IVB comparing with the other electrodes which have life time of 40 days. Avery short life time 3 and 4 days for membrane based on NB and TPB may be attributed to the low viscosities of the plasticizers and leaching of the plasticizers from the membrane to the external solution and no chance for the electrodes IB and IIB to response to the mebeverine solution. The electrode IVB was used for determination of mebeverine in pharmaceutical tablets. Abnormal and constant response potentials were obtained during calibration of NIP.

Table 2- Parameter of MBV-MIP electrodes based on different plasticizers

Electrode No.	Membrane composition	Parameter				
		Slope mV/decade	Correlation coefficient/ M	Linearity range/ M	Detection limit/ M	Life time / day
IB	MBV-MIP +TBP	13.98	0.9806	$1\times(10^{-5}\text{-}10^{-2})$	4×10^{-6}	4
IIB	MBV-MIP + NB	19.60	0.9922	$1\times(10^{-5}\text{-}10^{-1})$	3×10^{-6}	3
IIIB	MBV-MIP + DBS	-20.43	0.9949	$1\times(10^{-4}\text{-}10^{-2})$	2×10^{-5}	50
IVB	MBV-MIP+ TEHP	19.01	0.9969	$1\times(10^{-6}\text{-}10^{-1})$	$1.2\text{x}10^{-6}$	40

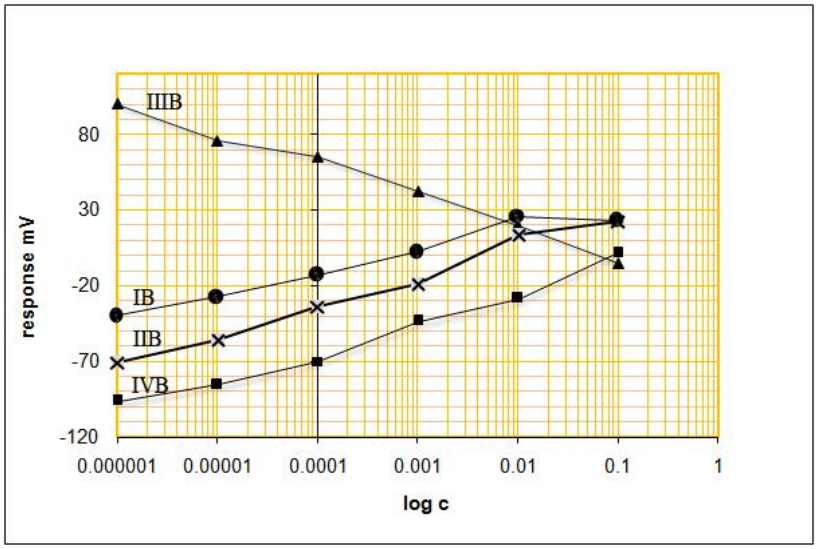


Figure 2- Calibration curves of MBV-MIPelectrodes; IB, IIB,IIIB and IVB.

3.3.Influence of pH

The effect of pH on the potential values of the four electrodes was studied over pH range from 2 to 11 and adjusting the pH by adding drops of 0.1 N HCl and 0.1 M NaOH to the aqueous solutions of the drugs and the potentials obtained at each value were recorded.

The effect of pH on the electrode potential was recorded for concentrations range from 1×10^{-4} to 1×10^{-2} M of mebeverine. The results obtained were listed in Table-3 and the typical plot of electrode potential versus pH for electrode IVB was shown in Figure-3.

Table 3-Working pH ranges for MBV-MIP electrodes

Electrode No.	Membrane composition	pH range		
		$1\text{x}10^{-2}$	$1\text{x}10^{-3}$	$1\text{x}10^{-4}$
IB	MBV-MIP +TBP	1.5 - 8.0	2.0 - 8.5	1.0 - 8.5
IIB	MBV-MIP + NB	2.0 – 6.5	1.0 – 11.3	2.0 – 9.9
IIIB	MBV-MIP + DBS	3.5 – 6.0	2.0 – 9.0	4.0 – 9.5
IVB	MBV-MIP + TEHP	1.5 – 7.5	1.5 - 8.5	1.5 - 8.0

At pH values less than 1.5 or in very high acidity, the electrode response has been increased rather irregularly. This may be due to the electrode response toMBV H^+ activities as well as MBV ions and in an alkaline solution (pH greater than 9) the electrode response has been decreased, may attributed to the decreasing in the solubility of MBV**.**

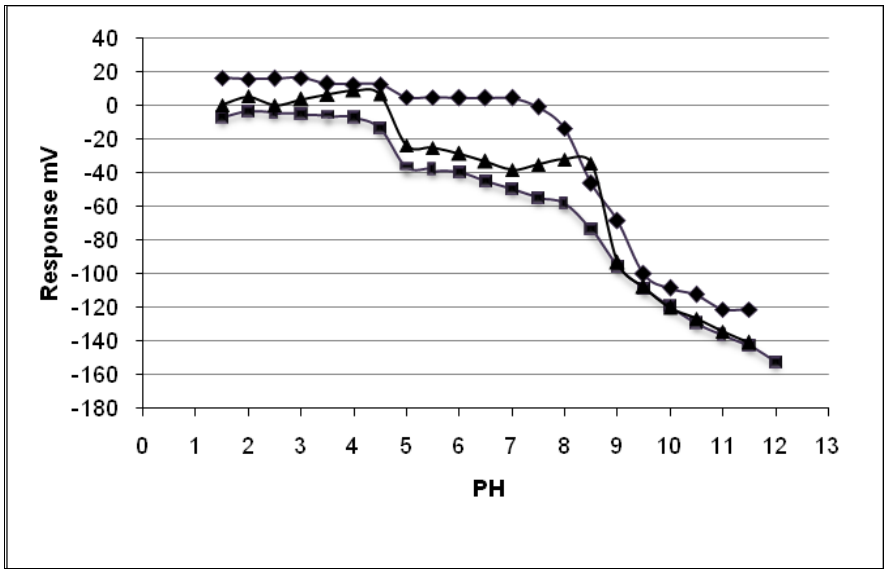


Figure 3- Typical plot of electrode response versus pH of electrode IVB at different concentrations(♦10^{-2}, ▲10^{-3} and ■10^{-4}) M.

3.4.Response time and life time

The response time for all MBV.MIP electrodes was obtained from the dynamic potential response at concentration range between 1×10^{-6} – 1×10^{-1} M by measuring the time required to reach 95 % equilibrium potential. The results indicate that the response time of the electrodes was approximately 15seconds for the solution of mebeverine at high concentration 10^{-1} M and about 46 seconds at low concentration10^{-6} M.

The electrode lifetime was obtained by measuring the slope periodically from calibration curves for MBV.MIP. Very short life time was noticed for electrodes IB and IIB (Table-2) and long life time was noticed for electrode about 40 days.

3.5.Selectivity coefficient

Separate solution method (SSM) [21] was used to determine the selectivity coefficients of the potentiometric sensor towards different species. In the SSM, the potential of a cell comprising a working electrode and a reference electrode is measured in two separate solutions; one containing the drug ions, E1, and the other containing the potential of interfering ions (E2), and S is the slope of the calibration graph. Selectivity coefficient was calculated using the following equation:

Log $K^{pot}=(E_2-E_1)Z_1F/2.303RT + (1-Z_1/Z_2)\log a_1$.

E_1, E_2, z_1 and z_2, a_1 and a_2 are the potentials, charge numbers and activities for the primary and interfering ions, respectively, at $a_1 = a_2$.

Selectivity coefficient of the electrodes IIB and IVB were studied toward several different substances; inorganic ions and amino acids (K^+,Na^+,Ca^{2+}, Mg^{2+},Fe^{+3},Al^{+3},proline,alanine,serine,glycine). Plotting of selectivity coefficient versus log concentration of mebeverine was measured at concentrations range from 10^{-1} to 10^{-6}M using electrode IVB as shown in Figure 4. As we noticed that all species, cations and amino acids at various concentrations showed no interference on electrode response. The values of selectivity coefficients at two mebeverine concentrations 10^{-3} M and 10^{-4} M using electrodes IIB and IVB were listed in Table-4. The results in Table-4 showed that all interfering species have no effect on electrode response, for example the selectivity coefficient range from $1.250\text{x}10^{-6}$at low concentration of mebeverine to $9.654\text{x}10^{-7}$at high concentration of mebeverine and for electrode IVB the selectivity coefficients range from $4.273\times10^{-7}$to 3.950×10^{-7}.

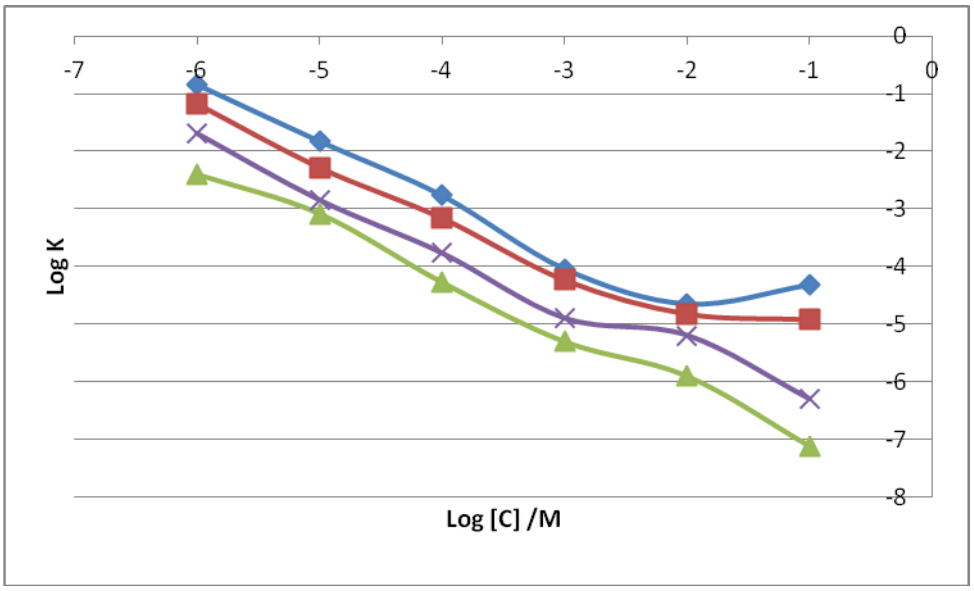


Figure 4-Variation of selectivity coefficient Log $K^{pot}_{A,B}$ with concentration at ($a_A = a_B$) using electrode IVB.(◊ - alanine, □ – glycine, X – serine, Δ – proline)

Table 4-Results of selectivity coefficients using separate solution method for some interfering species cations and amino acids)

Electrode No.	Concentration	Selectivity coefficient of interfering species at $a_A = a_B$			
		Na^+	Li^+		K^+
IIB	10^{-3} M	7.999×10^{-4}	4.143×10^{-4}		7.632×10^{-4}
	10^{-4} M	6.475×10^{-3}	5.241×10^{-3}		2.223×10^{-2}
		Ca^{2+}	Mg^{2+}	Al^{3+}	Fe^{3+}
	10^{-3} M	9.654×10^{-7}	1.012×10^{-5}	2.249×10^{-6}	1.176×10^{-2}
	10^{-4} M	1.250×10^{-6}	3.017×10^{-5}	1.587×10^{-6}	3.446×10^{-2}
		Alanine	Glycine	Proline	Serine
	10^{-3} M	2.121×10^{-4}	1.748×10^{-6}	1.737×10^{-5}	4.047×10^{-4}
	10^{-4} M	7.368×10^{-4}	1.078×10^{-5}	4.095×10^{-4}	1.677×10^{-3}
IVB		Na^+	Ca^{2+}		Fe^{3+}
	10^{-3} M	5.451×10^{-3}	3.950×10^{-7}		1.750×10^{-5}
	10^{-4} M	3.233×10^{-2}	4.273×10^{-7}		2.109×10^{-5}
		Alanine	Glycine	Proline	Serine
	10^{-3} M	9.148×10^{-5}	5.794×10^{-5}	4.563×10^{-6}	1.264×10^{-5}
	10^{-4} M	1.710×10^{-3}	6.848×10^{-4}	5.338×10^{-5}	1.702×10^{-4}

Quantitative analysis

The accuracy of electrodes IIB and IVB were measured by determining mebeverine in synthetic solutions of 10^{-3} and 10^{-4} M using standard additions method. Excellent results of %recovery were obtained in the range 97.95 to 102.73. A typical plot for membrane IIB at concentration of synthetic solution 10^{-3} M was shown in Figure 5 and the standard solution added was 0.1 M.

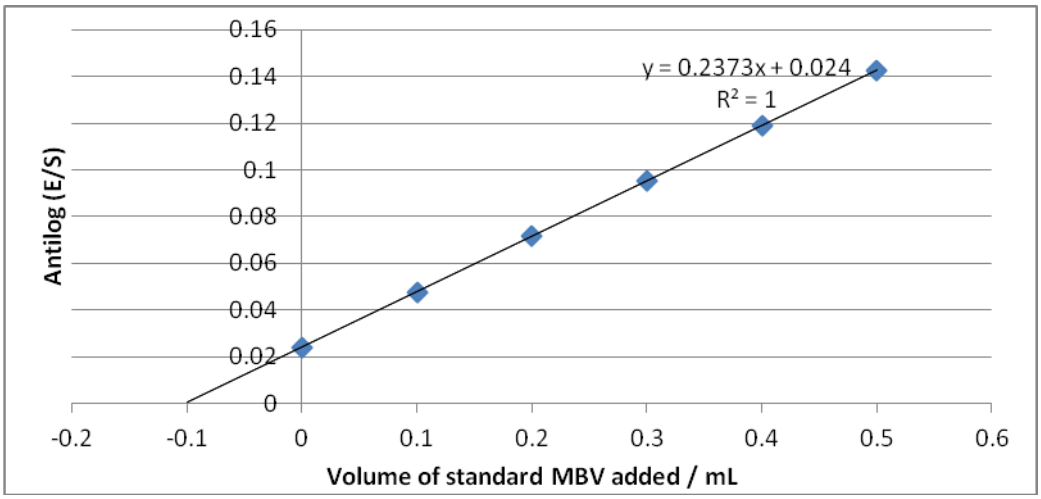


Figure 5- Variation of antilog (E/S) of synthetic solution of 10^{-3} M versus mL of standard MBV added using electrode IIB.

Direct method and standard additions method (SAM) were applied for determination of mebeverine in commercial pharmaceutical tablets (Asia-duspataline 135 mg, Epico-colospasmia135 mg and Abbott-duspataline 135 mg) obtained from local stores using membrane IVB based on TEHP plasticizer. The values of the % recovery Table-5 were in a good agreement with the value given in British Pharmacopoeia[22]. There is no interference of all species on electrode response, therefore, the values of recovery obtained by standard additions method were in good agreement with the results of direct method.

Table 5- Results of recovery and standard deviation of commercial drugs obtained by using membrane IVB.

Pharmaceutical Drug	Potentiometric methods	Concentration Prepared/ M	Concentration Found/ M	%Rec.	%RE	%RSD
Asia-duspataline 135 mg	Direct method	$1.0x10^{-3}$	$1.0570x10^{-3}$	105.65	5.65	-2.09
	SAM		$1.0112x10^{-3}$	101.12	1.12	1.88
	Direct method	$1.0x10^{-4}$	$1.0430x10^{-4}$	104.33	4.33	-0.15
	SAM		$9.8840x10^{-5}$	99.23	-0.75	-0.10
Epico-colospasmia 135 mg	Direct method	$1.0x10^{-3}$	$1.0210x10^{-3}$	102.06	2.06	-0.66
	SAM		$1.0083x10^{-3}$	100.83	0.83	0.008
	Direct method	$1.0x10^{-4}$	$0.9840x10^{-5}$	98.40	-1.59	-0.15
	SAM		$1.0178x10^{-4}$	101.78	1.78	1.43
Abbott-duspataline 135 mg	Direct method	$1.0x10^{-3}$	$1.0407x10^{-3}$	104.07	4.07	-0.58
	SAM		$1.0349x10^{-3}$	103.49	3.49	0.005
	Direct method	$1.0x10^{-4}$	$1.0110x10^{-4}$	101.13	1.13	-0.24
	SAM		$1.0154x10^{-4}$	101.34	1.54	-2.60

Conclusion

The constructed of molecularly imprinted electrodes sensors (MIP) using mebeverine as a template and 2-acrylamido2-methyl-1-propane sulphonic acid(AMPS) as monomer in different plasticizers. Excellent results of MIP which show high sensitivity, reasonable selectivity, fast static response, long-term stability and applicability over a wide pH range were obtained by using electrode based on TEHP plasticizer. Good recoveries were obtained for the determination of mebeverine in commercial tablets comparing with the British Pharmacopoeia.

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