

Synthesis, Characterization of Chlorpheniramine maleate–Molecularly Imprinted Polymers and Their Application as Sensors for the Determination of the Drug in Some Pharmaceutical Preparations

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Abstract

New chlorpheniramine maleate (CPM) selective electrochemical membranes were prepared by using chlorpheniramine maleate -molecularly imprinted polymers. MIP was prepared by bulk polymerization using 2-hydroxyethyl methacrylate (2-HEMA) as monomer, ethylene glycol dimethacrylate (EGDMA) as a cross-linker and a benzoyl peroxide (BPO) as an initiator at 60°C. Three CPM-MIP electrodes were constructed by using tri-tolyl Phosphate (ToCP), tris (2- ethyl hexyl) Phosphate (TEHP) and tributyl Phosphate (TBP) as plasticizers in PVC matrix. Electrode parameters including slopes, working concentrations ph. The interference effect in the presence of (Na⁺, Mg⁺², Al⁺³, Glycine, Alanine, Arginine and Phenylalanine) was studied using the separated and mixed methods to determine the selectivity coefficient determination. NIP prepared by using the same composition of MIP molecularly imprinted polymer electrodes except the template (CPM). The slopes of CMP-MIP are 21.00, 21.50 and 19.08 mV/ decade, linearity range for the electrodes around. (10⁻⁵ - 10⁻¹) M, the stable at a pH range from 4.0 to 8.5 and lifetime ranged from 30 to 10 days. The suggested electrodes were successfully applied for the determine of CPM in some pharmaceutical preparations, which were given acceptable accuracy.

Keywords: Molecularly Imprinted Polymers, Chlorpheniramine maleate, Different plasticizers, Pharmaceutical samples

Introduction

Chlorpheniramine maleate (CPM), 3-(p-chlorophenyl)- 3-(2-pyridyl)-N,N-dimethyl propyl amine ($C_{16}H_{19}ClN_2$, $C_4H_4O_4$), is a powerful first-generation alkylamine anti-histamine, H₁- receptor antagonist, widespread used for relieve symptoms of joint cold and allergies rhinitis, with weakness soothing property, the structure is shown in Figure(1).

Chlorpheniramine was used to relieve symptoms of allergies reactions, hay fever, rhinitis, urticarial, and asthma. Its done used in veterinary medicine. One of the most commonly used of the classical antihistaminic, it habit causes less drowsiness and anesthesia than promethazine. Chlorpheniramine is a histamine H₁ antagonist of the alkyl amine class. Competing with histamine for the normal H₁-receptor places on effector cells of the digestive system, vascular and respiratory system [1, 2]. Many analytical methods are described for determination of Chlorpheniramine maleate in pharmaceuticals such as spectrophotometric methods and derivative spectrophotometric [3- 6], gas chromatography and liquid chromatography with ion pair reagents [7- 10]. Chlorpheniramine maleate tablets made by Manfei et al. and used as samples for analysis using near infrared chemical imaging to acquire the concentration information of CPM coupled with partial least squares for quantitative analysis of CPM [11]. Molecular imprinted polymers (MIPs) exhibiting high selectivity to the template molecules and used for chemical analysis. MIP is formed by polymerization of the template and the functional monomers. Few papers were published of chlorpheniramine maleate molecularly imprinted polymers, such as chlorpheniramine-imprinted polymer which was prepared by Chen et al. [12] used for solid phase extraction and used for separation of chlorpheniramine from diphenhydramine. MIP for d-chlorpheniramine has been prepared by Jun and chino [13] and using methacrylic acid and ethylene glycol dimethacrylate as a functional monomer and cross-linker. MIP showed the highest recognition for chlorpheniramine and slight recognition for its structurally related compounds. Preparation of spherical MIP is described by Walsh et al. [14] with chlorpheniramine and other antihistamine drugs and studied the physical properties of the polymers. Recent MIP was reviewed by Jesika et al. [15] including the previous and current literature regarding the analytical tools employed for synthesized MIPs. The review was about bio-macro molecules such as antibodies and enzymes. Recently several papers were published in electrochemical by preparing electrodes based on MIP for drug determination. MIP and NIP were constructed by Al-Mustafa et al. [16] using dextromethorphan as a template and used for determination of CPM in cough syrups. Abu-Dalo et al. [17] prepared a new electrochemical sensor using copper-carboxyl benzotrizole complex based on copper ion imprinted polymer with carboxyl benzotrizol as a new ligand, the electrodes used for determination of copper ions in wastewater samples. Several molecular imprinted polymer membranes of azithromycin constructed by Abu-Dalo et al. [18] using graphite electrode, the Azin-MIP was prepared by thermal polymerization and the electrodes were used for the determination of azithromycin in commercial tablets and capsules. Al-Bayati [19] prepared ibuprofen MIP using methacrylic acid as monomer with different plasticizers and determined ibuprofen in pharmaceutical samples. Graphite electrodes coated with membranes based on risperidone imprinted polymer used for determination of risperidone in pharmaceutical formulations [20]. In this study the chlorpheniramine maleate imprinted polymer sensors were prepared using different plasticizers in PVC matrix by polymerization with 2-hydroxyethyl methacrylate as a monomer. The electrode parameters were studied and applied for the determination of CMP in pharmaceutical samples.

Experimental

Apparatus

Expansible ion analyst sample WTW from Germany, pH meter WTW model pH 720, Germany and a saturated calomel electrode type Gallenkamp, USA were used in this work. All potentiometric measurements were made at room temperature. The performance of the electrodes were investigated by measuring the potential of CPM solutions with concentrations ranged from 10^{-6} to 10^{-1} M. Each solution was stirred and the potential was recorded at equilibrium. The calibration curves were obtained by plotting the response against logarithmic function of Chlorpheniramine maleate concentration. Construction of the electrode body and immobilization of CPM-MIP in PVC matrix membrane it was conducted use the method given by Craggs et al [21].

Reagents and standard solutions

1. All chemical reagents used were with the highest purity, 2-hydroxy ethyl methacrylate (2-HEMA), benzoyl peroxide (98%), ethylene glycol dimethacrylate (EGDMA) (98%). Plasticizer, tri- tolyl phosphate (ToCP), tris (2-ethyl hexyl) phosphate (TEHP) and tri butyl phosphate (TBP) were obtained from Fluka AG. Other chemicals and reagents of analytical grade quality were obtained from Fluka, BDH and Aldrich. The values of viscosity and dielectric constant are listed in Table (2).
2. chlorpheniramine maleate standard was a gift from the State Company of Drug Industries and Medical Appliances (SDI- Iraq). Panadol tablets (Australia) and Tylohot tablet of 4 mg chlorpheniramine maleate (Turkey) were obtained from local pharmacies.
3. The stock Standard solution of 0.1 M chlorpheniramine maleate it has been prepare by dissolve 3.908g of standard Chlorpheniramine maleate in ethanol and diluted to 100 mL; standard solutions ranging of 10^{-6} - 10^{-1} M it has been freshly prepared from the stock solution.
4. 0.1M stock solution of each of interfering species; NaCl, MgCl₂, Al(NO₃)₃.9H₂O, glycine, alanine, arginine and phenylalanine were prepared.

Synthesis of Imprinted Polymer

In glass test tube 50 mL , 8.2449 mmol (1.0730 gm) of the monomer (2-HEMA), 14.00 mmol(2.7750 gm) of the cross-linker (EGDMA), 0.7258 mmol (0.2837gm) of drug as template, 0.1238 mmol (0.030gm) of initiator (BPO) and 5 mL of chloroform were mixed in a good way even dissolve all components. The solution was degased for 30 minutes with nitrogen gas and cured at 60⁰C for 30 minutes. The polymer was leave for 24 hours to dry and after that was crushed and washed with (1:9) (methanol: acetonitrile) to eject template and washed repeatedly to make sure every drug was ejected the polymer and dried at 60⁰C for 24 hours. The polymer was ground and sifted by mortar the particles with size less than 100 μm was collection and used in preparation sensing. The non-imprinted polymer (NIP) it has been prepared using the same method but without drug (Template).

Synthesis of Membrane and Electrode

The PVC membrane it has been prepared by mixing 0.1700 gm PVC, 0.4000 gmToCP, TEHP and TBP as plasticizers and 0.0200 gm of the MIP. This mixture it has been resolved in 4 mL of THF, and the mixture was poured into a (35) cm diameter glass ring and allowed to evaporate for 24 hours. Construction of the electrode was made depending to the reference [21].

Morphological Characterization

MIP according to the different types of interaction of template and functional monomer in polymerization process can be divided into covalent, non-covalent, metal ion and non-polar imprinting.[22] In this work, we will mainly focus on the one most common types, covalent imprinting, metal ion imprinting and non-covalent imprinting. Non-covalent imprinting refers to molecular imprinting strategies in which template and functional monomer form a complex in solution mainly driven by weak forces such as hydrogen bonding, electrostatic interactions, hydrophobic effects and pi-pi interaction. Non-covalent imprinting is the predominant method for imprinting due to the ease of preparation. Typically, this technique requires no or little synthetic chemistry. The imprinting process starts spontaneously when monomer and template are mixed together. The associated monomer/template complex is stable under polymerization conditions such as free radical polymerization. However, non-covalent imprinting has drawbacks Non-covalent imprinting process is a dynamic equilibration. That leads to low yield of imprinted sites. It also creates a lot of non-selective binding sites due to the heterogeneity of non-covalent imprinting process, which may largely affect the imprinting efficiency.

Scanning electron microscopy (SEM) was used for primary evaluation of the MIP particles. Fig3 (a and b) shows the morphology of MIP before and after washing showed by electron microscope in figure 1. A pore on the surface (figure 3a) about 10 μm may indicate the binding sites to the polymer. Figure 3b shows clear holes about of 20 μm in sizes which may indicate a complete removal of the template from the membrane.

Potential Measurements

All measurements conducted out in a 50 mL double walled glass cell, with fixed magnetic stirring of the test solution at room temperature. The performance of the electrodes was investigated by measuring the potential of Chlorpheniramine maleate solutions prepared with a concentration range of (10^{-6} - 10^{-1}) M by prepared serial dilution. The slope, response time, detection limit and life time were calculated from the calibration curve. The electrochemical performance of the two proposed sensors it was rated depending on the IUPAC recommendations data.

Sample preparation for analysis

Ten tablets of each drug formulation were weighed accurately 6.4163g and soft powdered in a small dish. An amount of powder equivalent to 0.0390g of the drug was accurately transferred to 100 mL volumetric flasks and diluted to the mark with distilled water to prepare 10^{-3} M solution of Chlorpheniramine maleate. Another amount of powder equivalent to 0.0039 g transferred to 100 ml volumetric flasks and diluted to the mark with deionized distilled water to prepare 10^{-4} M solution of Chlorpheniramine maleate. The probably readings production by immersing the prepared electrodes in the prepared solutions were recorded.

Results and discussion

Characterization

The Fourier transmission infrared spectrometry (FTIR) spectra of leached and unleached Chlorpheniramine maleate imprinted polymers MIP and CPM were recorded in the range of $(400-4000) \text{ cm}^{-1}$ by the KBr pellet method (table 1). The FTIR spectrum of Chlorpheniramine maleate shows a sharp peak at 1701 cm^{-1} for carbonyl stretching of ester group when comparing with the FTIR spectrum of MIP (before template removal) which show two peaks at $(1635, 1724) \text{ cm}^{-1}$ of ester groups and cross-linked. The FTIR spectrum of CPM and MIP (before template removal) shows sharp peak at 651 cm^{-1} for the substitution chloride, also appearance band Out-of plane-para- substitution at 864 cm^{-1} and show peaks at $(1558, 1585) \text{ cm}^{-1}$ for aromatic conjugation and when compared with the FTIR spectrum of MIP (after template removal) all these peaks were disappeared.

Influence of membrane composition

Electrodes based on membranes of CMP-MIP and CPM-NIP in PVC matrix were prepared using chlorpheniramine maleate as a template and 2-hydroxyethyl methacrylate as monomer and ToCP, TEHP and TBP as plasticizers. All CPM electrodes were calibrated at different concentrations of CMP solutions ranged from $(10^{-6} - 10^{-1}) \text{ M}$ and electrodes reach equilibrium very fast in all of these concentrations of CMP. Electrodes based on membranes (I, II and III) show good electrode parameters and the results of electrode specification are listed in Table 2. The conductivity of the PVC membrane depends on the value of dielectric constant and by increasing the dielectric constant the conductivity of PVC membrane increases. Also, the quantity and viscosity of the plasticizer influence the parameters of the electrode and the mobility of the species in the membrane. All the electrodes (I, II and III) show near-Nernstian slopes of 21.00, 21.51 and 19.08 mV/decade with excellent detection limits as shown in Table 2, the lifetime of electrode based on ToCP plasticizer was around 30 days higher than the other plasticizers due to the high viscosity of ToCP (58.0 cSt). The electrodes were calibrated two times a week over CMP concentration ranged from $10^{-1} - 10^{-6} \text{ M}$ and the slopes during this period gives response drift of $\pm 0.90 \text{ mv/decade}$. The ratio of template 0.7258 mmole: 8.2449 mmole monomer: 14.0000 mmole cross linker: 1.600 mmole (1: 34: 57.8: 6.6) used in this study gave good results for CPM-MIP electrodes. This ratio shows non-covalent bonding and can easily remove the template from the polymer. The calibration curves of CMP electrodes were plotted on Orion 7 cycle semi log paper and their results are listed in Figure 4. The values of detection limit were calculated using equation $\Delta E = 59/z$ [22].

Effect of pH

Effect of pH on the electrochemical of CMP-MIP sensor was studied. The electrode response was measured at a fixed concentration of chlorpheniramine solution (10^{-2} , 10^{-3} and 10^{-4}) M at different pH values. The pH of CMP solution was adjusted by adding hydrochloric acid or sodium hydroxide solution and the response of CMP-MIP sensor is independent on pH range from 4.0 to 8.5. At pH values lower than 4.0 the CMP becomes unstable may be due to the interaction of nitrogen species of CMP with hydrogen ion forming a bond or the electrode sensor response to hydrogen ion, while at $\text{pH} > 8.0$ the basicity of CMP solution leads to the

formation of non-ionic of CMP. The results of pH study are listed in Table 3 and a plot of electrode based on ToCP plasticizer at three concentrations of CMP is shown in Fig. 5.

Interference studies

The selectivity coefficients of some inorganic cations and species (Na^+ , Mg^{+2} , Al^{+3} , glycine, alanine, arginine and phenylalanine) were determined by using separate solution method (SSM). The potential was measured for two solutions, one containing chlorpheniramine maleate and the other contains the interfering species and using the equation 1 [23] for calculating the selectivity coefficient.

$$\text{Log } K_{\text{pot}} = \frac{(\text{EB} - \text{EA})}{(2.303RT/zF)} + (1 - z_A/z_B) \log a_A \dots \dots \dots (1)$$

EA, EB; z_A , z_B ; and a_A , are the potentials, charge numbers, and activities for the primary A and interfering B ions, respectively at $a_A = a_B$.

The selectivity coefficients were also calculated by the using mixed solution method according to the equation 2 [24].

$$K_{\text{pot}A,B} = a_A / (a_B)^{z_A/z_B} \dots \dots \dots (2)$$

The selectivity coefficients of electrodes (I, II and III) were calculated for CMP concentrations ranged from (10^{-6} - 10^{-1}) M. Selectivity coefficients for the electrode based on ToCP plasticizer were listed in Table 4. The values of selectivity coefficients presented in Table 5 indicate that the interference of all species increase by decreasing the concentration of CMP solutions. The order of interference effect for cations is monovalent > divalent > trivalent. None of the species glycine, alanine, arginine and phenylalanine interferes seriously with electrode response. Fig. 6 shows the plot of log concentration with log K.

Mixed solution method was also used at two fixed of concentrations of interfering species at (10^{-2} and 10^{-3}) M using the equation 2. The results of selectivity coefficients of the species using mixed solution method are listed in Table 7. The same behavior of selectivity coefficient was obtained by the two methods.

Sample analysis

Standard addition and direct methods were used for determination of chlorpheniramine maleate in commercial tablets using CMP-MIP (I) electrode. Two types of pharmaceutical formulations, (Panadol) from Australia and Tylolhot from (Turkey) were used for analysis. The values of recoveries and relative standard deviations using electrodes I, II and III are listed in Table 8, 9 and 10. Good recoveries were obtained ranged from (101 – 105) % which is in good agreements with British Pharmacopoeia (BP) [25]. The relative standard deviation was ranged (0.6300 to 1.8700)

Conclusion

In this work chlorpheniramine maleate, imprinted polymers were prepared by using 2-hydroxy ethyl methacrylate as a monomer with different plasticizers. The good sensor was based on ToCP plasticizer and used for determination of CMP in commercial tablets, and the specification of the electrodes was studied.

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Table (1): The most identified peaks of FTIR spectra for CPM and CPM-MIP using (HEMA) as a functional monomer

No.	Functional Group	CPM	CPM-MIP(HEMA)before template removal	CPM - MIP(HEMA)after template removal
1.	OH str.(cm^{-1})	3444	3498	3522
2.	N-H str. (cm^{-1})	----	3432	----
3.	Sp ³ -CH str. (cm^{-1})	2966	2954	2985
4.	C=O str.ester (cm^{-1})	1701	1635,1724	1635,1728
5.	C=C str. (cm^{-1})	1558	1585	-----
6.	C-O str. Asymm (cm^{-1}).	1234	1261	1261
7.	C-O str. symm. (cm^{-1})	1061	1165	1168
8.	Out-of plane-para-sub(cm^{-1})	864	864	---
9.	C-Cl str. (cm^{-1})	651	651	---

Table (2): Electrode parameters of the CPM-MIP and CMP-NIP based on CPM sensor

Membrane composition	Electrode parameters						
	Slope mV/decade	Linearity range / M	Correlation coefficient	Detection limit / M	Life time / days	Dielectric constant	Viscosity cSt
CPM-MIP + ToCP (I)	21.00	$1 \times 10^{-1} - 1 \times 10^{-5}$	0.9949	7.0×10^{-6}	~ 30	6.90	58.0
CPM-MIP + TEHP (II)	21.51	$1 \times 10^{-1} - 1 \times 10^{-5}$	0.9859	1.0×10^{-5}	~ 22	4.80	12.0
CPM-MIP + TBP (III)	19.08	$1 \times 10^{-1} - 2 \times 10^{-5}$	0.9993	4.0×10^{-6}	~ 10	7.95	3.3
CPM-NIP + ToCP (IV)	12.06	$1 \times 10^{-1} - 4 \times 10^{-3}$	0.9671	7×10^{-3}	~ 2	6.90	58.0
CPM-NIP + TEHP (V)	9.01	$1 \times 10^{-2} - 1 \times 10^{-4}$	0.8861	3×10^{-3}	3	4.80	12.0
CPM-NIP + TBP (VI)	11.14	$1 \times 10^{-2} - 1 \times 10^{-5}$	0.9668	4×10^{-4}	3	7.95	3.3

Table (3): Results of pH range for the electrodes at three different concentrations of MP

Number	Membrane Composition	pH range		
		1×10^{-2} M	1×10^{-3} M	1×10^{-4} M
I	CPM- 2HEMA+ToCP	4-8	5.5-8.5	3.5-8
II	CPM -2HEMA + TEHP	4-7.5	5-7	3-7.5
III	CPM -2HEMA + TBPH	5-8	3.5-6	3-7.5

Table (4): Selectivity coefficients of some interfering species measured by separate using separate solution method with electrode based on ToCP plasticizer

Selectivity coefficients of interfering species							
Conc. of CPM M	Na ⁺	Mg ²⁺	Al ³⁺	Alanine	Glycine	Arginine	Phenyl alanine
10 ⁻¹	0.11200	0.19400	0.735X10 ⁻³	0.695X10 ⁻³	0.143X10 ⁻²	0.885X10 ⁻²	0.615X10 ⁻²
10 ⁻²	0.12700	0.04200	0.181X10 ⁻³	0.695X10 ⁻²	0.483X10 ⁻²	0.112X10 ⁻²	0.335X10 ⁻²
10 ⁻³	0.16200	0.280X10 ⁻²	0.027X10 ⁻³	0.02000	0.428X10 ⁻²	0.297X10 ⁻²	0.379X10 ⁻²
10 ⁻⁴	0.42800	0.233X10 ⁻²	0.110X10 ⁻³	0.01100	0.18300	0.10000	0.02300
10 ⁻⁵	0.54500	0.280X10 ⁻³	0.021X10 ⁻³	0.01400	0.08800	0.06100	0.02000
10 ⁻⁶	0.88500	0.162X10 ⁻³	0.971X10 ⁻⁵	0.03300	0.06100	0.20600	0.02600

Table (5): Selectivity coefficients of some interfering species measured by separate using separate solution method with electrode based on TEHP plasticizer

Selectivity coefficients of interfering species							
Conc. of CPM M	Na ⁺	Mg ²⁺	Al ³⁺	Alanine	Glycine	Arginine	Phenyl alanine
10 ⁻¹	0.0370	0.693X10 ⁻³	0.317X10 ⁻²	0.0180	0.820X10 ⁻⁴	0.0300	0.257X10 ⁻³
10 ⁻²	0.0260	0.505X10 ⁻³	0.124X10 ⁻²	0.0160	0.179X10 ⁻³	0.0360	0.801X10 ⁻³
10 ⁻³	0.0420	0.460X10 ⁻³	0.600X10 ⁻³	0.0490	0.459X10 ⁻³	0.0420	0.171X10 ⁻²
10 ⁻⁴	0.4570	0.263X10 ⁻²	0.108X10 ⁻²	0.8070	0.164X10 ⁻²	0.3690	0.667X10 ⁻²
10 ⁻⁵	0.6940	0.465X10 ⁻³	0.255X10 ⁻³	0.4150	0.336X10 ⁻²	0.2330	0.991X10 ⁻²
10 ⁻⁶	0.3390	0.561X10 ⁻⁴	0.670X10 ⁻⁴	0.05730	0.260X10 ⁻²	0.0580	0.468X10 ⁻²

Table (6): Selectivity coefficients of some interfering species measured by separate using separate solution method with electrode based on TBP plasticizer

Conc. of CPM M	Selectivity coefficients of interfering species						
	Na ⁺	Mg ⁺²	Al ⁺³	Alanine	Glycine	Arginine	Phenyl alanine
10 ⁻¹	0.636X10 ⁻²	0.111X10 ⁻²	0.368X10 ⁻³	0.268X10 ⁻²	0.701X10 ⁻³	0.123X10 ⁻²	0.407X10 ⁻³
10 ⁻²	0.0160	0.109X10 ⁻²	0.261X10 ⁻³	0.0110	0.724X10 ⁻²	0.467X10 ⁻³	0.128X10 ⁻²
10 ⁻³	0.0860	0.265X10 ⁻²	0.375X10 ⁻³	0.0610	0.0640	0.0400	0.636X10 ⁻²
10 ⁻⁴	0.2750	0.191X10 ⁻²	0.339X10 ⁻³	0.2290	0.0570	0.1440	0.0360
10 ⁻⁵	0.3470	0.138X10 ⁻²	0.145X10 ⁻³	0.3010	0.1960	0.2640	0.1250
10 ⁻⁶	0.3840	0.762X10 ⁻³	0.582X10 ⁻⁴	0.2710	0.2180	0.1840	0.2450

Table (7): Results of selectivity coefficients measured by mixed solution method of interfering species using membrane I,II and III

Electrode No.	Conc. of CPM M	Na ⁺	Mg ⁺²	Al ⁺³	Alanine	Glycine	Arginine	Phenyl alanine
I	10 ⁻²	0.100	0.011	0.117X10 ⁻²	0.060	0.180	0.080	0.12
	10 ⁻³	0.800	0.022	0.189X10 ⁻²	0.300	0.600	0.400	0.31
II	10 ⁻²	0.070	0.311x10 ⁻²	0.175x10 ⁻²	0.040	0.058	0.120	0.038
	10 ⁻³	0.340	0.807x10 ⁻²	0.189x10 ⁻²	0.260	0.300	0.400	0.200
III	10 ⁻²	0.180	0.070	0.588X10 ⁻²	2	0.2	0.2	0.2
	10 ⁻³	0.020	0.089	0.379X10 ⁻²	10	1.6	1	0.6

Table (8): CMP determination in commercial samples by direct and standard addition methods using electrode I

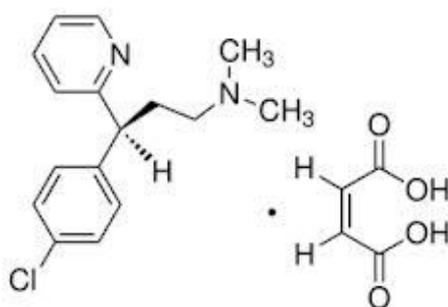
Pharmaceutical drug	Potentiometric methods	Prepared Concentration /M	Concentration Found/M	%Rec.	%RE	%RSD
Tylohol	Direct method	1.0x10 ⁻³	1.016x10 ⁻³	101.6000	1.6000	1.5000
	SAM		1.013x10 ⁻³	101.3000	1.3000	1.8700
	Direct method	1.0x10 ⁻⁴	1.019x10 ⁻⁴	101.9000	1.9000	0.8600
	SAM		1.014x10 ⁻⁴	101.4000	1.4000	1.0520
Panadol	Direct method	1.0x10 ⁻³	1.021x10 ⁻³	102.1000	2.1000	1.7800
	SAM		1.018x10 ⁻³	101.8000	1.8000	0.8070
	Direct method	1.0x10 ⁻⁴	1.02x10 ⁻⁴	102	2	0.6300
	SAM		1.015x10 ⁻⁴	105	1.5000	1.4000

Table(9): CMP determination in commercial samples by direct and standard addition methods using electrode II

Pharmaceutical drug	Potentiometric methods	Concentration Prepared/M	Concentration Found/M	%Rec.	%RE	%RSD
Tylohol	Direct method	1.0×10^{-3}	1.021×10^{-3}	102.1000	2	1.3000
	SAM		1.018×10^{-3}	101.8000	1.8000	1.4000
	Direct method	1.0×10^{-4}	1.013×10^{-4}	101.3000	1.3000	1.0600
	SAM		1.011×10^{-4}	101.1000	1.1000	1.7000
Panadol	Direct method	1.0×10^{-3}	1.017×10^{-3}	101.7000	1.7000	1.0100
	SAM		1.015×10^{-3}	101.5000	1.5000	0.8700
	Direct method	1.0×10^{-4}	1.015×10^{-4}	101.5000	1.5000	1.5000
	SAM		1.013×10^{-4}	101.3000	1.3000	1.2100

Table (10): CMP determination in commercial samples by direct and standard addition methods using electrode III

Pharmaceutical drug	Potentiometric methods	Concentration Prepared/M	Concentration Found/M	%Rec.	%RE	%RSD
Tylohol	Direct method	1.0×10^{-3}	1.03×10^{-3}	103	3	1.2000
	SAM		1.025×10^{-3}	102.5000	2.500	0.9700
	Direct method	1.0×10^{-4}	1.026×10^{-4}	102.6000	2.6000	1.3000
	SAM		1.02×10^{-4}	102	2	1.1000
Panadol	Direct method	1.0×10^{-3}	1.023×10^{-3}	102.3000	2.3000	1.3700
	SAM		1.016×10^{-3}	101.6000	1.6000	1.5000
	Direct method	1.0×10^{-4}	1.021×10^{-4}	102.1000	2.1000	1.4000
	SAM		1.019×10^{-4}	101.9000	1.9000	1.2000

**Figure (1): Structure of chlorpheniramine maleate**

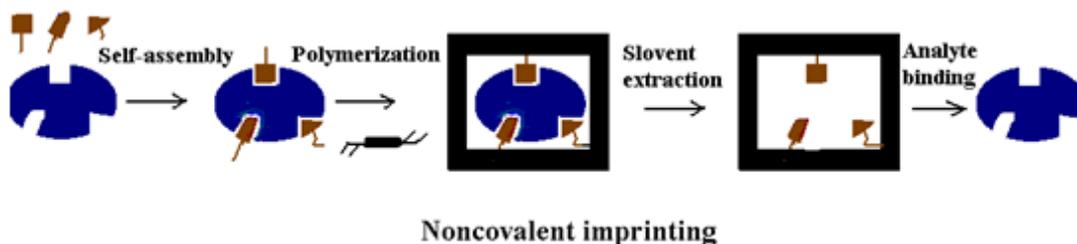


Figure (2): Schematic representation of the non-covalent and covalent molecular imprinting procedures

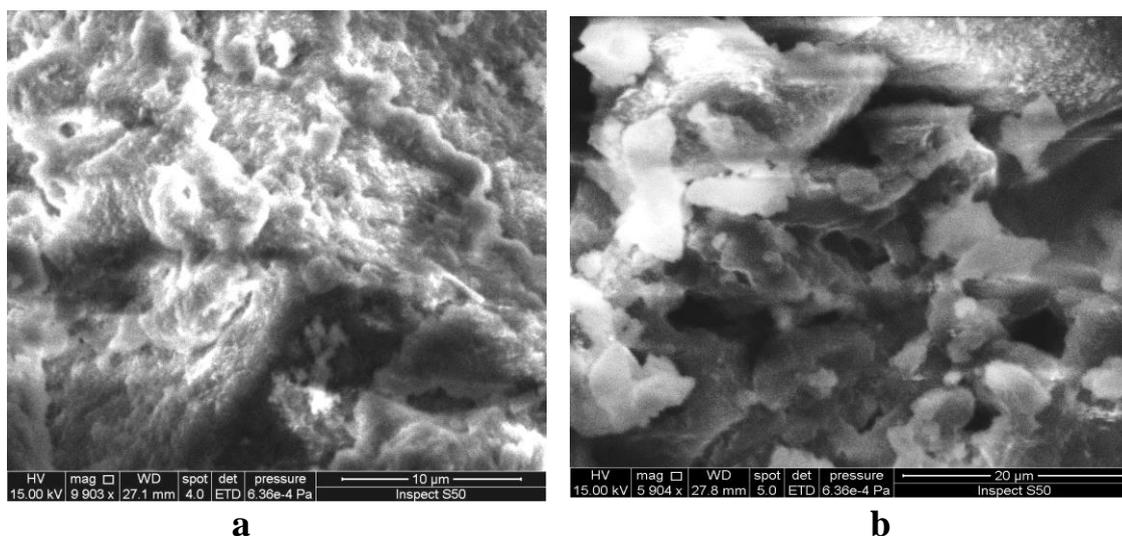


Figure (3): SEM photographs of the surface of MIP, a) before washing b) after washing.

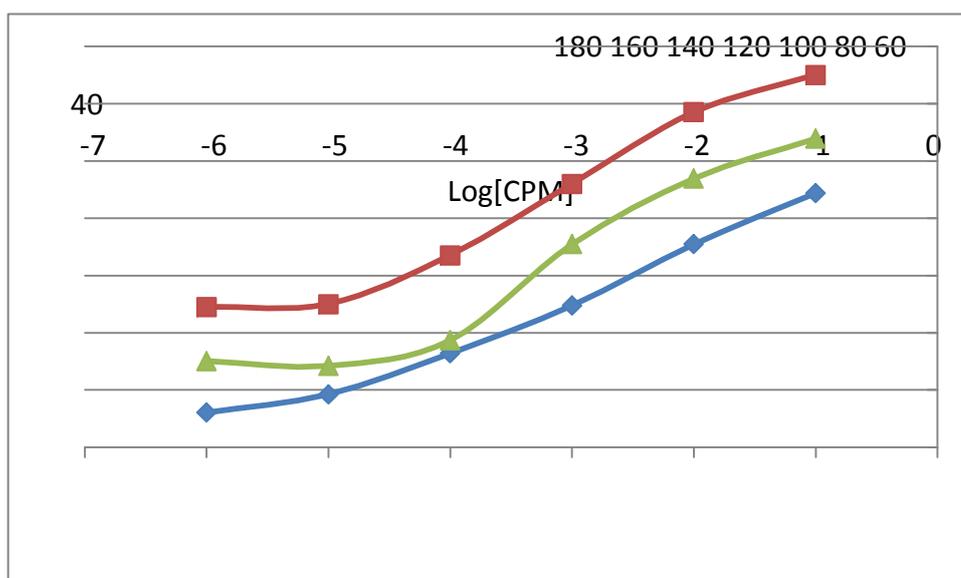


Figure (4): Calibration curves of CMP-MIP electrodes using; \diamond -TBP, Δ -TEHP and \square -ToCP as Plasticizer

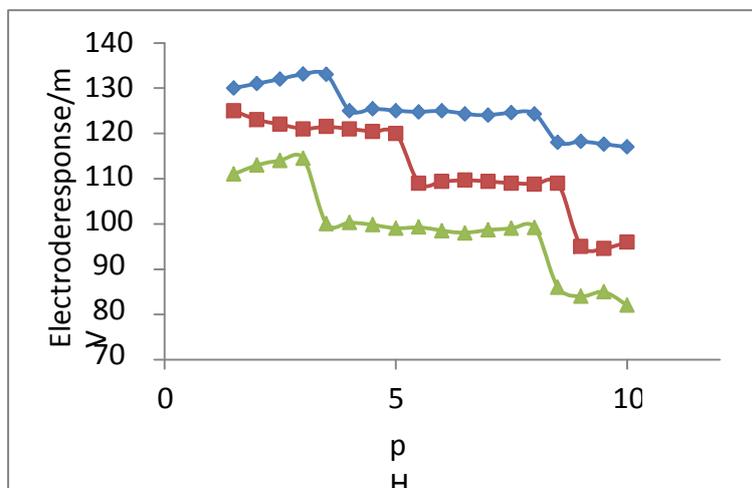


Figure (5): Plot of electrode response with pH of electrode based on ToCP plasticizer at three different of CMP concentrations; Δ - 10^{-4} M, \square - 10^{-3} M and \diamond - 10^{-2} M

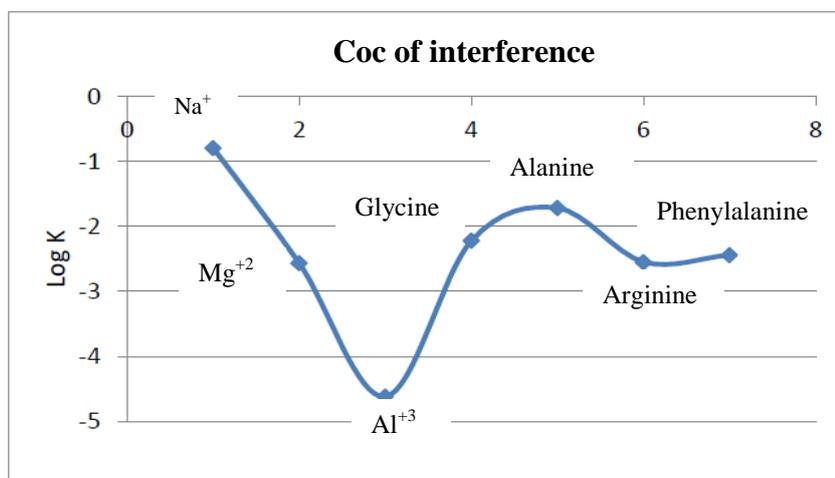


Figure (6): Plot of log K of interfering species at concentration 10^{-3} M of CMP; 1- Na^+ , 2- Mg^{+2} , 3- Al^{+3} , 4-glycine, 5-alanine, 6-arginine and 7-phenyl alanine.