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Preparation and analysis of PVC-Membrane Potentiometric diazepam-Selective Sensor Based on Molecular Imprinted Polymer

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Abstract

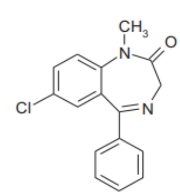
A molecularly imprinted polymer was used to make two electrodes (MIP). MIP was manufactured using Diazepam (DZP) as the template, Allyl chloride as the monomer, and Ethylene glycol di methacrylate(EGDMA) as the cross-linker. Non-imprinting polymers (NIP) were created using the identical composition, minus the template (Diazepam). Tritolyl phosphate (TTP) and dibutyl sebacate (DBS) are examples of plasticizers utilized in the PVC matrix to produce films. DIA-MIP electrode slope, detection limit, durability, and linearity range are evaluated. The outcomes of the selectivity measurements on the interfering cations (Al^{3+}, Ca^{2+}, and K^{+}) indicate that they do not inhibit Diazepam. The produced electrode exhibited a favorable response, including to conduct research on pharmaceuticals.

Keywords:

Molecularly imprinted electrode, diazepam, potential metering, (Allyl chloride) monomer, and different plasticizers(TTP) (DBS) .

Diazepam, 7chloro1, 3dihydro1methyl 5phenyl2H1, 4benzodiazepin2one, is the most often prescribed benzodiazepine hypnotic, tranquillizer, anticonvulsant, and muscle relaxant (Hosseini and Motaharian, 2015). Rapid and dependable screening procedures for drugs and poisons in highly intricate biological specimens (urine, serum)for use in forensic and clinical toxicology. Are in high demand (Liu et al., 2013).Diazepam is one of the most often prescribed 1,4-benzodiazepines and is commonly marketed under Valium(Honeychurch et al., 2013).

The effects of sleeping aids. DZP is a benzodiazepine that provides a positive allosteric regulation receptor for gamma-aminobutyric acid, increasing receptor-binding GABA molecules. This modification will induce repolarization of GABA receptors (channel ligand) and have a calming effect(Omar and Eesa, 2017) . The receptors are located in the central nervous system and the mechanism explanation by which DZP induces drowsiness and reduces stress . In Indonesia, DZP is considered a substance class of psychoactive medications, and its prescription is subject to government regulation. To obtain DZP, one must visit a physician and get a prescription (Hasanah et al., 2021).



Figuer:1 Chemical structure of Diazepam

(Casarrubea et al., 2012).

2. Experimental

2.1. Preparation of MIP and NIP

To prepare diazepam molecularly imprinted polymer (DZP -MIP1), one mmole (0.131g) of diazepam was combined with 1 ml of Allyl chloride as the monomer. Next, 3.77ml (g) of EGDMA ethylene glycol di methacrylate was included in the mix as the cross-linker, and mmole (0.3g) of benzoyl peroxide was added as the initiator. The amalgamation was agitated for 5 minutes to achieve a homogenous solution, and then oxygen was removed from the mixture by passing N2 over it for 20 minutes. The resulting tube was inserted. a container filled with water at 65 degrees Celsius. The molecularly imprinted polymer resulted as soon as the procedure ended completely solidified, and following the polymerisation process, it disintegrated into a tiny polymer particle. Sonication was used on this material. in a 9:1 mixture of CH_3OH and CH_3COOH, eliminating the MIP sample document. How big are dia-MIP1 particles (75-125 m)Non-molecularly imprinted polymers can be made in the same way components and under the same circumstances as molecularly imprinted polymers. DZP -MIP1, but without the diazepam (template)

2.2. Instruments

This study utilized a WTW model ion analyzer, a WTW model pH 720 pH meter, and a calomel electrode that has reached saturation (Gallenkamp, USA). The DZP-MIP was an electrode fabricated in a test tube, and every potentiometric experiment was performed at room temperature. In conjunction with the Ag-AgCl and the reference electrode, the diazepam-MIP electrode was a 0.1 M diazepam dissolved in the internal fluid. Placing the PVC tube (1-4 cm in length) in a clear dish and soaking it in THF caused it to become flattened and polished. A membrane was trimmed to match the outer diameter of the PVC tubing and adhered to the precise result. The opposite orientation of the PVC and, finally, the tubing was fastened towards the electrode device. The electrodes were enhanced by good soaking them in 0.1 M diazepam solution for a minimum of three hours prior to use.

2.3. Materials and chemicals

Diazepam was acquired to do with the state corporation for Pills industry and Healthcare Equipment (IRAQ- SID- Samara). Commercial diazepam pills bought from nearby pharmacies include VALIAPAM 10 tablets 500 mg from (SDI-Iraq), Valium 10 tablets 5 mg from (Australian), and. Plasticizers, Tritoly phosphate 90% was utilized as received and dibutyl sebacate (DBS) (purity of 97.0%), were acquired from Sigma-Aldrich. As a monomer, allyl chloride was used; ethylene glycol di methacrylate (EGDMA) and benzoyl peroxide (BPO)(78%) were acquired from Sigma-Aldrich. The chemicals utilized were of the purest concentration of reagents and were used without extra cleansing.

2.4. The creation of standard solutions

Producing a common fluid of 0.01 M Diazepam by breaking down 0.1423 g of legal Diazepam in methanol and then filling a 50 mL volumetric flask with the resulting solution. Using the same method, the additional solutions were produced in 50 mL at concentrations ranging from ($5x10^{-5}$ to 10^{-2}) M. all competing cations (Al^{3+}, Ca^{2+}, and K^{+}) were made as a 0.1 M stock solution at concentrations ranging from ($5x10^{-5}$ to 10^{-2}) M and then reduction of to 100 mL

2.5. Synthesis of Membrane Molecularly Imprinted Polymers Electrode

According to Thomas and Moody (Moody and Thomas, 1988) , the Diazepam membrane was immobilized within the PVC tube DZP-MIP (0.036g) was combined with other plasticizers (0.45g) employed in this study, including TTP(electrode M1), DBS, and others (electrode M2). Then, 0.2g of it was PVC powder. Added 7 mL of tetra hydro furan and mixed until a thick, viscous liquid was obtained. The fluids were then stirred until the combination was complete and homogenous. The whole combination was poured into a glass ring (30-35 mm in diameter) and set on a flat glass with a superimposed ribbon filter. At ambient temperature, the solvent was permitted to vaporize for at least (24-48) hours. The obtained membrane had a varied thickness than other membranes, ranging between (0.4) and (0.7) mm. This membrane size was appropriate for preparing electrodes.

Construction of Ion-Selective Electrodes

Electrode body structure and immobilization were accomplished as Mahajan et al (Mahajan and Sood, 2007) described. The glass tube had been filled with 0.1 M diazepam fluid as an internal fluid. Membrane electrode requirements include soaking the membrane in a standard (0.1) M diazepam solution for at the very least two to three hours prior actual metrics(Aljabari and Al-Bayati, 2023, Al-Bayati and Hadi, 2022).

2.7.Pharmaceutical Sample Preparation

Extract the active ingredients from pharmaceutical samples by grinding the crushing tablets using a mortar and pestle. Then, take an acceptable quantity required in advance for use in 50 mL of solutions. Utilized a correct methanol concentration (CH3OH) for dissolving pharmaceutical samples and filled the volumetric flask to 50 mL with methanol while stirring for more than 30 minutes. After filtering the fluid via 0.07m cellulose filter paper, amounts or proportions of 5 x10^{-3} M and 5 x10^{-4} M diazepam were achieved.

3. Results and Discussion

The polymer molecular imprint of diazepam was identified after it was determined using UV-Vis the drug's wavelength. As demonstrated in the figures, a preliminary diagnosis was made to confirm the presence of the drug in this imprint.

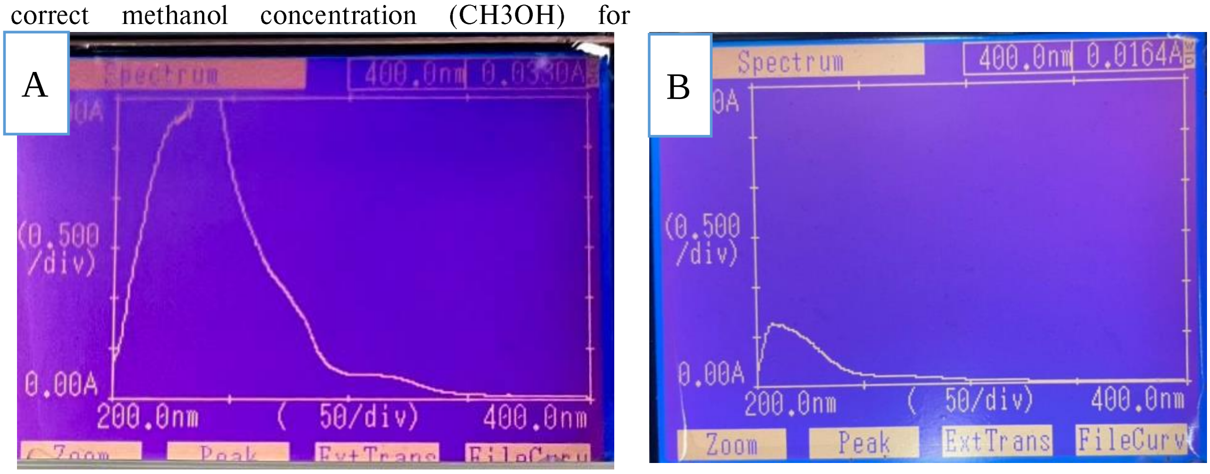
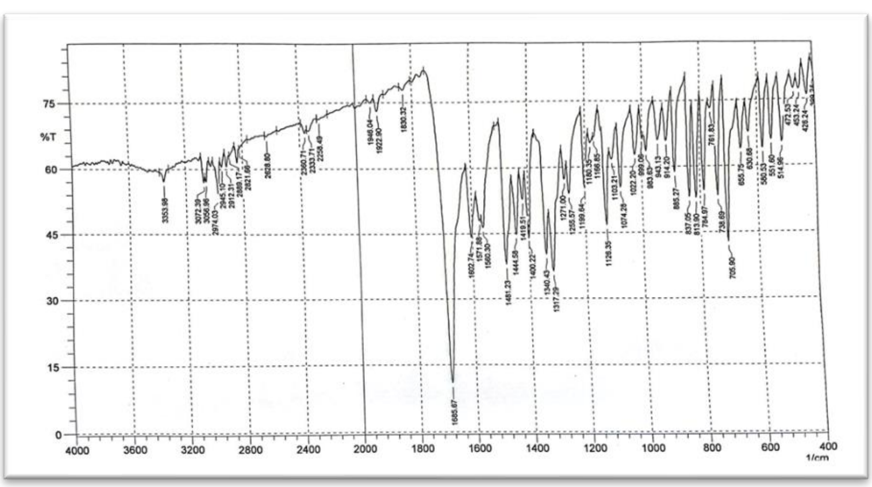


Figure 2- A and B the absorption of diazepam drug at 235 nm before and after extraction .

MIP of was synthesized using bulk polymerization (non-covalent). A functional monomer played a crucial role in researching interactions with the template. The MIP and NIP were made using ethylene glycol di methacrylate as the monomer. FTIR analysis FTIR is an essential chemical characterization technique for detecting functional groups in a molecule. The FTIR spectra of various MIP and NIP are presented in Table(1), Figure 3,4



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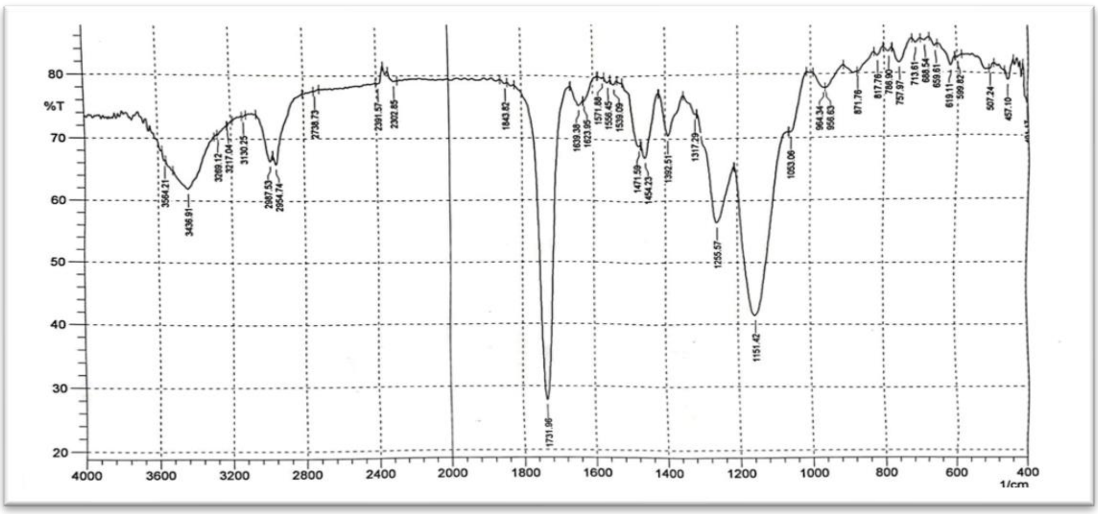


Figure 4A: FTIR spectrum of DZP-MIP prior to and following elimination (after removal of the template Diazepam).

B

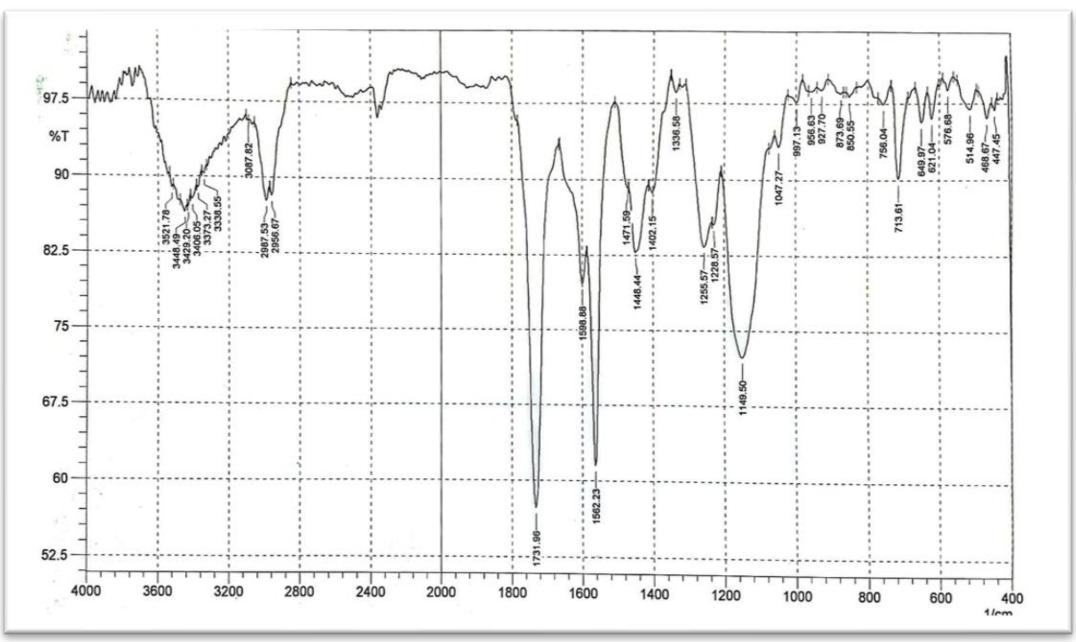


Figure 3: FTIR spectra of diazepam standard.

Figure 4B: FTIR spectrum of DZP-MIP prior to and following elimination (before removal of the template Diazepam).

Table 1: The structures of the main three compositions of DZP-MIP and the bands indicate MIP before &after the removal template

Template (Diazepam)	Monomer (Allyl chloride)	Cross linker (Ethylene glycol di methacrylat)	
Band	Drug(Template)	MIP before extraction	MIP after extraction
N C-H $_{\text{aliph. str.}}$	2945,2912	2983,2962	2987,2954

N C-H aromatic str.	3056	3180	-
N O=C-N str. amid	1685	1639	-
N C=C aromatic. str.	1602	1554	-
N C-Cl.	813	806	817
str. N N-C=O carbonyl	--	1730	1731

The KBr pellet method was used to record transmission infrared of the Fourier transform spectroscopy spectrum of what has been leached and unleashed Diazepam (DZP) imprinted polymer MIP and NIP in the range 400–4000 cm-1 (Table-1). The FTIR spectra of Ate displayed the following bands: (2945,2912, 3056,1685, 1602, 813) cm-1 for NC-H aliphatic stretching, NC-H aromatic stretching ,N O=C-N stretching. amid, NC=C aromatic stretching N-C-CL stretching and N N-C=O carbonyl. Before template removal, the FTIR spectra of the Diazepam MIP(DZP) displayed the following bands: 3180, 1639, and 1554 cm-1 for N C-H aromatic stretching, NO=C-N aromatic stretching , and N C=C aromatic stretching. The absence of N C-H aromatic stretching, NO=C-N aromatic stretching, and N C=C aromatic stretching in the FTIR spectrum of the MIP(DZP) following template removal indicates that the drug has been extracted from the template. Using allyl chloride as a monomer for synthesizing other MIPs for Diazepam (DZP), the FTIR spectra of the MIPs before and after removing the template and NIP are shown in Table. The values of the band (Abbas et al., 2020) Ion-selective electrodes (ISE) are among the most widely used types of band electrodes. commonplace sensors based on voltage analysis. Utilized in laboratory experiments, industrial applications, process control, physiological assessments, and ecological monitoring. Membranes of electrodes that respond to Reaction analysis of concentration that generate ions that may be detected using an ion-selective electrode (Aljabari and Al-Bayati, 2021) . Electrodes with a membrane are divided into two primary categories: ion-selective, which are sensitive to ions, and molecular-selective, which is sensitive to molecules which are utilized for measuring molecular analytes (Al-Nisani et al., 2021, Ameen et al., 2015) . Electronic current travels along electrons in metals but along ions in liquids. Ion-selective electrodes operate based on these two distinct forms of electrical conductivity(Ismaeel and Al-Bayati, 2021, Bichan et al., 2023) .It is possible to do electrical analysis using one of these galvanic cells, electrolysis, and used to assess the conductivity of each electrochemical reaction (Muhammad, 2013).

These cells must be in touch, having fluid across the membrane and inside the cell. There are further ISE configurations where wires are attached to the membrane on only one side. Conventional cell composition consists of:Outer ref. Test solution membrane internal ref.

Or

Outer ref. Test solution ion-selective electrode

a device's internal electric current An electrolytic cell is required equal zero. Based on this need, the cell is created based on the terms of the underlying principle behind the construction of electrolytic cells .

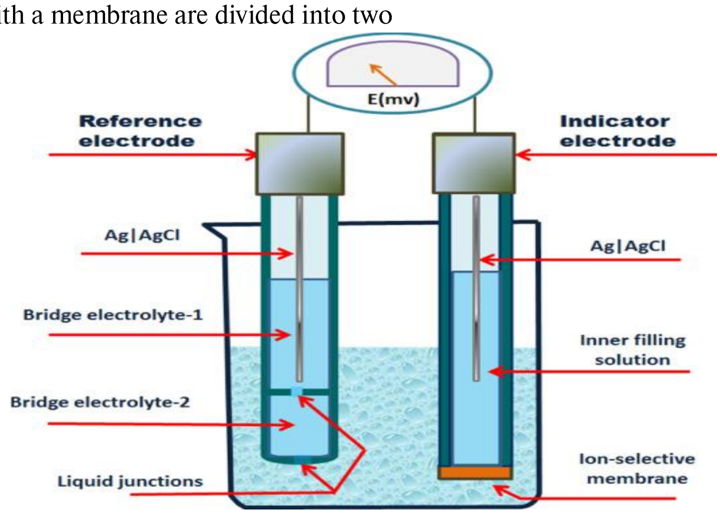
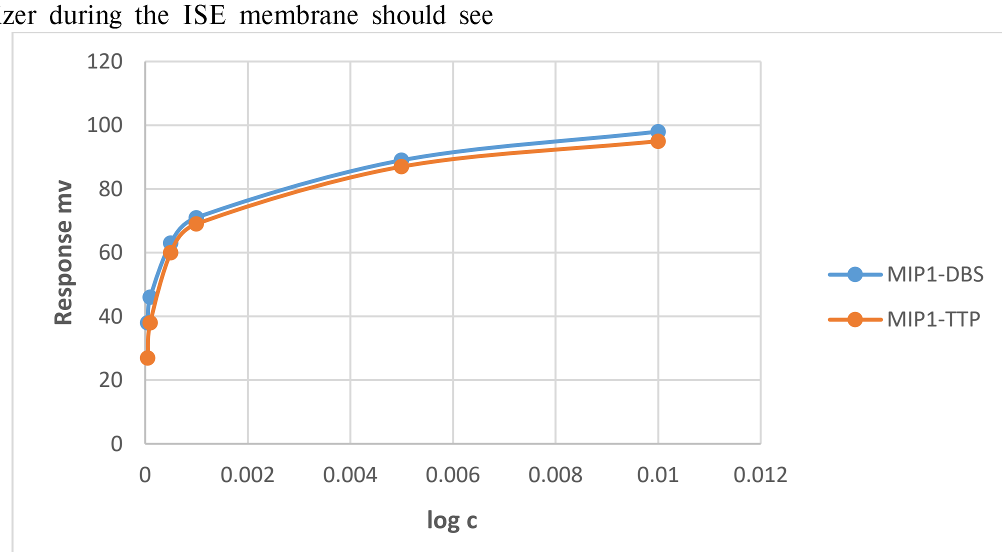


Fig. 5 Figure the typical potentiometric cell is depicted here using an ion-selective electrode in the accompanying(Abd El-Rahman and Salem, 2015)

Using diazepam as a template, allyl chloride and ethylene glycol di methacrylate (EGDMA) as monomers and cross-linkers, respectively, as well as the benzoyl peroxide as an initiator, two electrodes were produced. Plasticizers are indispensable to ISE membranes. Membranes, including polymer and other materials compatibility ingredients, offer a membrane-homogeneous environment when plasticizers are utilized as membrane solvents. However, leaching of the plasticizer during the ISE membrane should see some practical use. be prevented because it would harm the electrode's performance over time. Because of a PVC matrix, four electrodes have been manufactured. The plasticizers dibutyl sebacate(DBS) and Tritolyl phosphate(TTP) are examples. The linearity range, correlation coefficients, detection limit (M), and life duration of the DZP-MIP1 (M1, M2) membrane-based electrodes were evaluated (day). The gathered information is presented in table 1 and figure 5.



Fig(6): For DZP-MIP membrane electrodes, calibration curve.

Table 2: Characteristics of the diazepam-MIP electrode built with several functional plasticizers and monomers.

Membrane composition	DZP-MIP+TTP(M1)	DZP-MIP+DBS (M2)
Slop (mV/decade)	25.818933	29.31258
Linearity range (M)	5×10^{-5}-1×10^{-2}	5×10^{-5}-1×10^{-2}
Correlation coefficient	0.9994	0.9964
The detection limit (M)	5×10^{-6}	5.5×10^{-6}
Lifetime (day)	17	12

3.1.Effect of pH on electrodes response :

Two electrodes were fabricated using Diazepam as a template and allyl chloride as a precursor.

A pH investigation was conducted on DZP membrane electrodes with varying concentrations of DZP ($5\times\mathbf{10^{-3}}$ and $5\times\mathbf{10^{-4}}$). In pH investigations, pH testing(1-11) uses HCL acid(0.1M,1M) or NH4OH (0.1M,1M). As indicated in Table (2) and Figure 3, the end result achieved by including the proper amount of HCl/NH4OH are as follows: (6). The composition of electrodes is responsible for the difference in pH-value-related potential (Mahdi and Al-Bayati, 2020)

Table 3: Working pH range for Selective diazepam electrode

Number and design of MIPs	Membranes	Membrane design	pH range	
			5×10^{-3}	5×10^{-4}
MIP DZP+EGDMA+ALL	M1	DZP-MIP+TTP	5.5-8.5	6-8
	M2	DZP-MIP+DBS	3-5.5	4-7.5

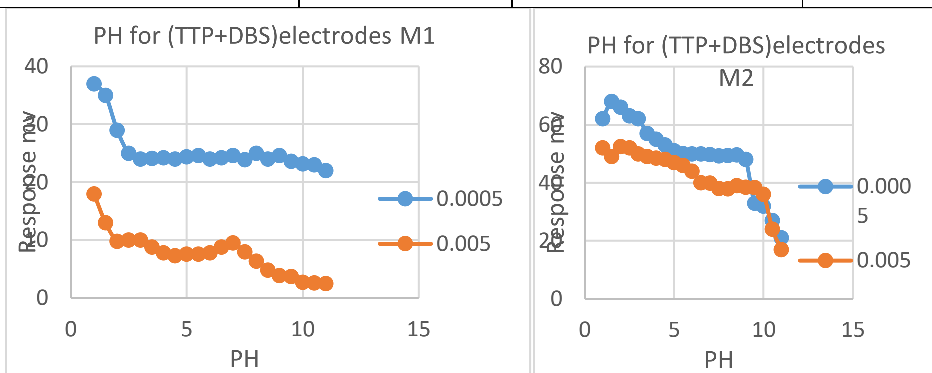


Fig. (7): Effect of pH on the Diazepam [DZP-MIP+ TTP(M1) and DZP-MIP +DBS (M2)] electrodes at concentrations 5×10-3 and 5×10-4.

Interference studies

Two electrodes were fabricated using Diazepam as a template and allyl chloride as a precursor. The pH For measuring the selectivity coefficient, a different solution approach was used. Utilize the unique equation required for these parameters, as shown in the following equation.

Log K pot= [(EB − EA)/(2.303RT/z F)] + (1 −zA/zB) log aA (Al-Safi and Al-Bayati, 2018)

EA, EB, zA, zB, and aA are, in order as well as the charges, potentials, and actions of the primary A ions and the interfering B ions when aA = aB.

The findings for principal ion selectivity coefficients and interference from other ions, such as (K^{+}, $Ca^{2+}$and Al^{3+}), have been obtained in this investigation. Primary ion charge and secondary ion interference charge, as well as the concentration and composition of the electrodes, all have a role in determining the selectivity coefficients. All selectivity coefficient values were presented in Tables 3, 4 and Figures.(7,8) Using several electrodes of the DZP membrane, a study was conducted

Table 4: Selectivity coefficients for (DZP-MIP+TTP) electrode at different concentrations of Diazepam.

Con.	Concentrations of Diazepam (M): concentrations of interference ions (M)					
	Interfering ions					
	Al3+		Ca2+		K+	
	EB (mv)	KA,B	EB (mv)	KA,B	EB (mv)	KA,B
10^{-2}	52	1.6533×10^{-2}	43	2.3430×10^{-3}	30	5.007×10^{-4}
5×10^{-3}	49	2.8232×10^{-2}	39	1.1573×10^{-3}	26	1.6847×10^{-4}
1×10^{-3}	45	9.8398×10^{-2}	31	8.9279×10^{-4}	20	1.0583×10^{-4}
5×10^{-4}	37	9.8398×10^{-2}	24	3.0866×10^{-4}	18	3.8931×10^{-5}
5×10^{-4}	25	3.1368×10^{-1}	20	3.4019×10^{-4}	14	2.9230×10^{-5}
5×10^{-5}	23	2.6244×10^{-1}	15	2.1780×10^{-4}	13	1.1756×10^{-5}

Table 5: Selectivity coefficients for (DZP-MIP+DBS) electrode at different concentrations of Diazepam.

Con.	Concentrations of Diazepam (M): concentrations of interference ions (M)
	Interfering ions

	Al3+		Ca2+		K+1	
	EB (mv)	KA,B	EB (mv)	KA,B	EB (mv)	KA,B
10^{-2}	47	2.3040E-02	40	4.2041E-03	35	1.9337E-03
5×10^{-3}	45	3.6912E-02	35	1.6827E-03	31	5.7037E-04
1×10^{-3}	40	1.0249E-01	31	1.5982E-03	27	3.6904E-04
5×10^{-4}	35	1.4032E-01	22	5.0539E-04	22	1.0885E-04
1×10^{-4}	23	7.3036E-01	15	2.9960E-04	20	6.5106E-05
5×10^{-5}	21	2.8442E-05	13	1.5172 E-05	16	1.5172E-05

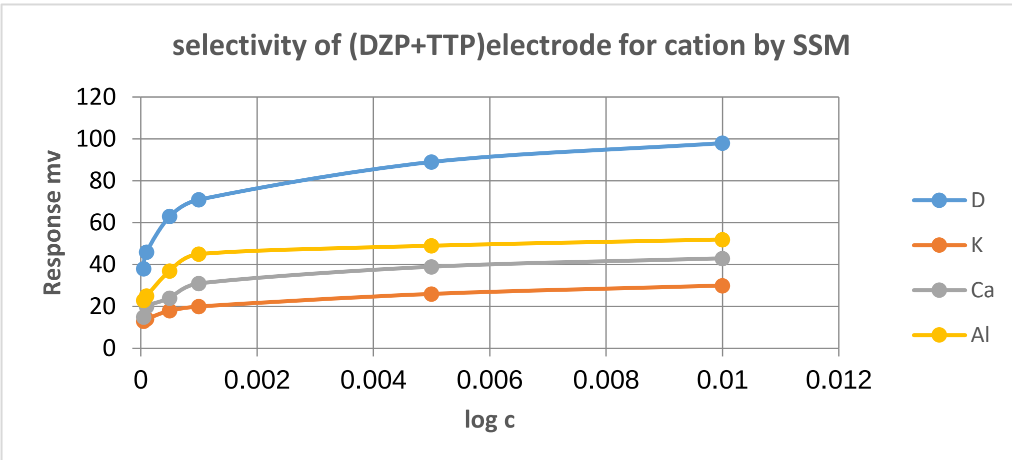


Fig .(8): Selectivity of (DZP+TTP) ions at the electrodes using the Separation Solution Method.

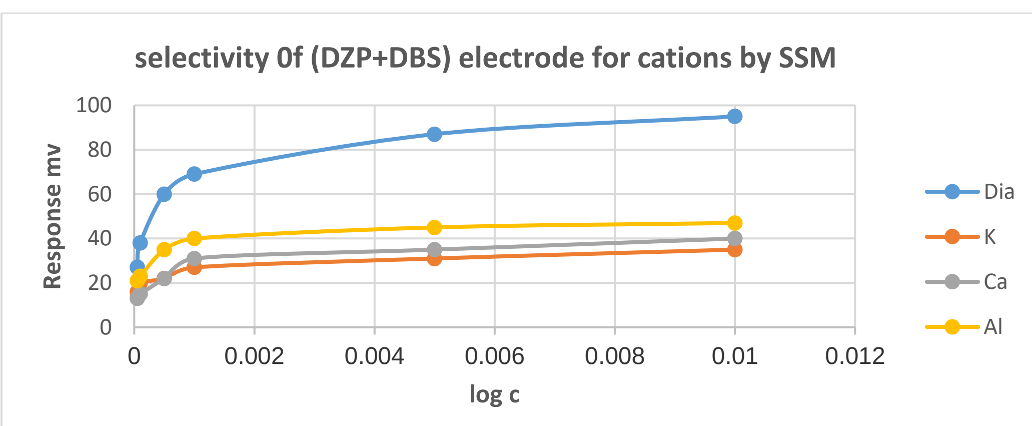


Fig. (9): Selectivity of (DZP-DBS) ions at the electrodes using the Separation Solution Method

Calculation by Multiple Standard Addition Method (MSA)

The concentrations employed in this method ($5x10^{-3}$ and $5x10^{-4}$) for graphing the antilog E/S (Y-axis) versus the normal level diazepam were investigated (X-axis). Figs. (9,10) depict what we found of diazepam ratios computed based on electrodes on DZP-MIP+ TTP, DZP-MIP+DBS.s performed on electrodes of DZP membrane utilizing various concentrations of DZP

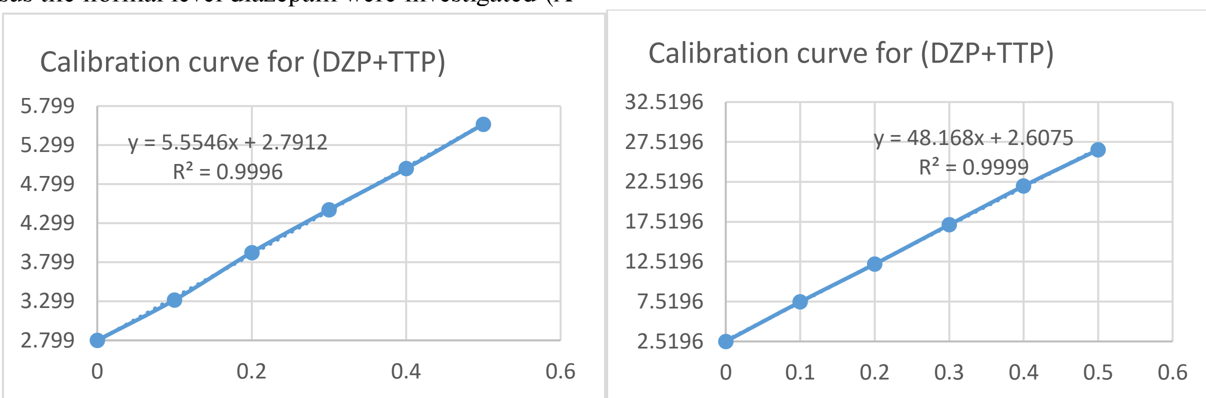


Fig.(10): Antilog (E / S) in comparison to the total volume of the increased standard for the purpose of determining diazepam solution (5×10-3 and 5×10-4) by MSA using (DZP–MIP + TTP) electrode.

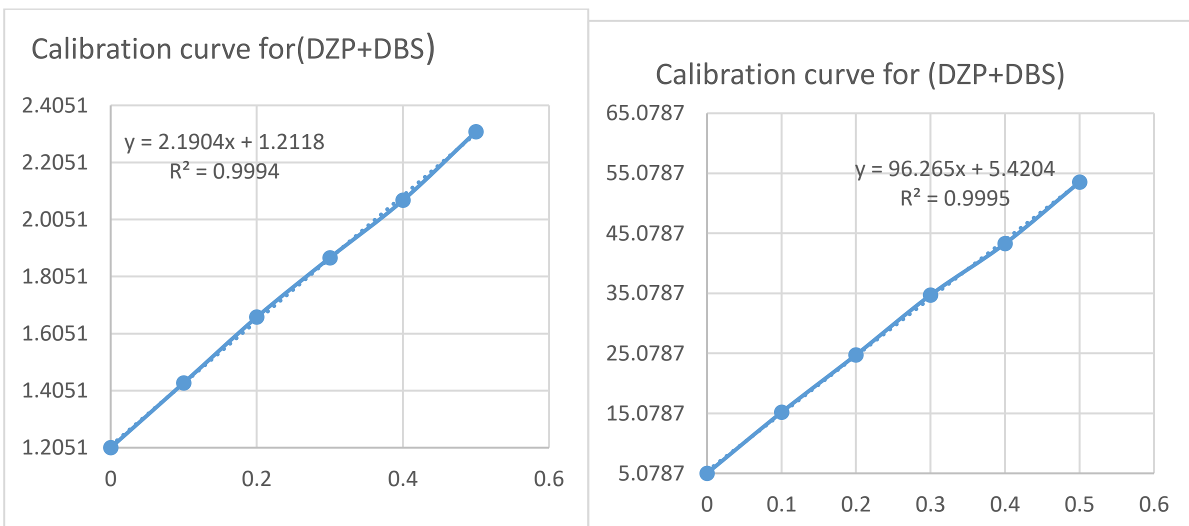


Fig.(11): Antilog (E / S) in comparison to the total volume of the increased standard for the purpose of determining Diazepam solution (5×10-3 and 5×10-4) by MSA using (DZP–MIP+ DBS) electrode.

3.4. Applications of pharmaceuticals.

Molecularly imprinted polymer-based ion selective electrodes were utilized to determine diazepam in medicines. This ISE includes standard addition, direct, Gran plot, and multiple standard addition measurements. They were preparing solutions of Diazepam at 510-3 and 510-4 M concentrations. The RE%, RC%, and RSD% of Diazepam in medicinal use were calculated. The outcomes achieved are shown in Table(6).

Table 6: Determination of Diazepam Samples by Ion Selective electrodes (ISEs) techniques based on PVC membranes.

Electrode No.	Concentration (M)

	Sample	Measurement using potentiometric methods		
		Direct	SAM	MSA
DZP-MIP+TPH	5×10^{-3}	5.0164×10^{-3}	5.0283×10^{-3}	4.9966×10^{-3}
	RSD%	1.36	1.79	....
	RC%	100.33	100.566	99.93
	RE%	0.33	0.566	-0.07
	5×10^{-4}	4.9345×10^{-4}	5.0512×10^{-4}	4.9977×10^{-4}
	RSD%	2.232	0.6435	....
	RC%	98.69	101.024	99.95
	RE%	-1.31	1.024	-0.05
Electrode No.	Concentration (M)			
	Sample	Measurement using potentiometric methods		
		Direct	SAM	MSA
DZP-MIP+DBS	5×10^{-3}	5.0542×10^{-3}	5.0449×10^{-3}	4.98×10^{-3}
	RSD%	0.78		1.02
	RC%	101.08	100.89	99.6
	RE%	1.08	0.898	-0.40
	5×10^{-4}	5.0178×10^{-4}	5.0618×10^{-4}	4.9848×10^{-4}
	RSD%	1.5744		0.51
	RC%	100.36	101.236	99.7
	RE%	0.36	1.236	-0.3

Table7: Sample analyses of pharmaceutical Diazepam using DZP-MIP+TTPelectrode.

pharmaceutical	(Iraq)		
Concentration prepared	Direct	SAM	MSA
	5×10^{-3}	5×10^{-3}	5×10^{-3}
found	4.9277×10^{-3}	4.9929×10^{-3}	4.9304×10^{-3}
RC%	98.55	99.85	98.61
RSD%	1.4089	1.02	....
RE%	-1.45	-0.14	-1.39
pharmaceutical	Direct method	SAM	MAS
Concentration prepared	5×10^{-4}	5×10^{-4}	5×10^{-4}
Found	4.8468×10^{-4}	5.0499×10^{-4}	4.9792×10^{-4}
RSD%	2.232	0.77	....
RC%	98.69	100.998	99.58
RE%	-1.31	0.998	-0.42

Table8: Sample analyses of pharmaceutical Diazepam using DZP-MIP+DBS electrode.

pharmaceutical	(Iraq)		
Concentration prepared	Direct	SAM	MSA
	5×10^{-3}	5×10^{-3}	5×10^{-3}
found	4.975×10^{-3}	4.9729×10^{-3}	4.9622×10^{-3}
RC%	99.51	99.458	99.24
RSD%	0.7966		1.02

RE%	-0.49	-0.542	-0.76
pharmaceutical	Direct method	SAM	MAS
Concentration prepared	5×10^{-4}	5×10^{-4}	5×10^{-4}
Found	4.9524×10^{-4}	5.01×10^{-4}	4.9838×10^{-4}
RSD%	1.1788		0.5086
RC%	99.05	100.2	99.32
RE%	-0.95	0.2	-0.68

*each measurement was carried out thrice.

5. Conclusion

By combining different plasticizer's with diazepam membranes, selective electrodes can be created. TTP and DBS plasticizer's were employed to manufacture PVC-based diazepam membrane electrodes. The results obtained for all electrodes applied to standard and medicinal solutions were excellent. The purpose of developing electrodes for use in pharmaceutical analytical determination is to .

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