

## Memantine Potentiometric Membrane Sensor for Memantine Pharmaceutical Analysis; Computational Investigation

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Memantine (MEM) is one of the first novel class medications for treatment of Alzheimer's disease. In this study a potentiometric liquid membrane sensor is used for simple and fast determination of Memantine in pharmaceutical formulation and urine. Computational studies were done electronically and geometrically on Memantine and tetraphenylborate before and after complex formation. These studies demonstrated tetraphenylborate fits better with memantine than potassium tetrakis. Thus, for the membrane preparation Memantine-tetraphenylborate complexes were employed as electroactive materials in the membrane. The wide linear range ( $10^{-5}$ - $10^{-2}$  mol L<sup>-1</sup>), low detection limit ( $9.0 \times 10^{-6}$  mol L<sup>-1</sup>), and fast response time (~25s) are characterizations of the proposed sensors. Validation of the method shows suitability of the sensors for application in quality control analysis of Memantine in pharmaceutical formulation and urine.

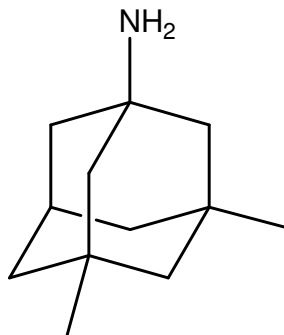
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**Keywords:** Potentiometric sensor; PVC membrane; Memantine; Computational Chemistry; Chemometrics; Density functional based tight binding (DFTB)

### 1. INTRODUCTION

Memantine (1-amino-3,5-dimethyladamantane) (Fig.1.) is a tricyclic amine structurally and pharmacologically related to the antiviral amantadine. The drug is used to treat Parkinson's disease, movement disorders and dementia syndrome. Memantine (MEM) acts as a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor complex. MEM was first synthesized in the 1960s and

was found in the 1970s to affect the CNS. In 1989 MEM was found to inhibit NMDARs with an  $IC_{50}$  of approximately 1  $\mu M$  (which corresponds well with its therapeutic concentration range). The principal mechanism of action of Memantine is believed to be the blockade of current through channels of N-methyl-D- aspartate (NMDA) receptors-a glutamate receptor subfamily broadly involved in brain function.



**Figure 1.** Chemical structure of Memantine

Memantine works by blocking the channel of NMDARs. MEM is classified as an ‘open channel blocker’ because it can enter the channel and block the current (only after the channel has ben opened). There can be overlap of the sites where MEM and  $Mg^{2+}$  bind [1]. MEM is well absorbed with peak plasma concentrations ( $C_{max}$ ) ranging from 22 to 46 ng/mL following a single dose of 20 mg; the time to achieve maximum plasma concentration ( $T_{max}$ ) following single doses of 10–40 mg ranges from 3 to 8 h.

Other techniques have been previously used to determine Memantine in a variety of matrices. These methods include high performance liquid chromatography (HPLC) [2,3] and gas chromatography coupled to mass spectrometry [4] (GC–MS) and LC–MS [5,6].

Potentiometric membrane sensors are playing an important role in pharmaceutical analysis [7–10] because of their simplicity, rapidity and accuracy over other analytical methods such as spectrophotometry and HPLC. Also, the other mentioned methods are elaborate, time-consuming and involve sophisticated equipment that might not be available in most analytical laboratories.

In this paper the interaction of Memantine with ion-pair reagents was studied by theoretical and calculative methods. According to the obtained results a Memantine ion-selective potentiometric membrane electrode can be developed based on the ion-pair compound of Memantine-tetraphenylbroate (Memantine-TPB) as the electroactive substance. The proposed electrode was successfully applied for the determination of Memantine in pharmaceutical formulations and urine samples.

Computational chemistry and molecular modeling play an important role in modern drug discovery and electrochemical science [11–17]. Computational work is also valuable in drug development where medium-sized organic pharmaceuticals are selected as candidates and are then made in larger quantities. Instead of modeling interactions with macromolecules the prediction of molecular properties for small molecules is more essential in the development stage.

The strength of binding usually correlates with the target molecules tendency to the ionophore and several energy contributions may be responsible for the binding. It is believed that amongst these energies, electrostatic interactions play a dominant role in the process - at least in sequence preference and target molecule positioning [18,19].

There are no studies to date in recent literature that have used computational methods to evaluate drug selective ligands by electronic properties. The lack of work in this area is probably due to the inherent difficulties associated with doing calculations on a Drug-Ligand complex. One of these problems includes the lack of parameters for semi-empirical or empirical methods (even though the numbers of atoms in typical drug complexes indicate the use of lower level calculations being appropriate).

In this study the Density Functional Theory (DFT) atomic population analysis was used to measure the Ligand-Drug complex. This was achieved by looking at the ability of the ligand to change in atomic charges and bond length.

## 2. EXPERIMENTAL PART

### 2.1. Materials and Reagents

The chemical reagents (analytical grade) were: Sodium tetraphenyl borate (NaTPB), high-molecular weight polyvinylchloride (PVC), dibutyl phthalate (DBP), benzyl acetate (BA), nitrobenzene (NB), tetrahydrofuran (THF), and the chloride and nitrate salts of the used cations (Merck Co.). Memantine and its tablet were obtained from different local pharmaceutical factories. All solutions were prepared using triply distilled water.

### 2.2. Reagents

The glass cell, where the Memantine-selective electrode was placed consisted of a R684 model Analion Ag/AgCl reference electrode as the internal reference electrode, and a calomel electrode (SCE, Philips). Both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with  $\pm 0.1$  mV precision.

### 2.3. Preparation of ion-pair compound

The ion-pair compound of Memantine-tetraphenylborate (MEM-TPB) was prepared by: 20 mL of  $0.01 \text{ mol L}^{-1}$  solution of memantine hydrochloride mixed with 20 mL of tetraphenyl borate solution ( $0.01 \text{ mol L}^{-1}$ ) under stirring. The resulting precipitate was filtered off, washed with water and dried [9,10].

### 2.4. Preparation of the electrodes

The general procedure to prepare the PVC membrane was as follows: Different amounts of the ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in

tetrahydrofuran (THF), and the solution was mixed well. The resulting mixture was transferred into a glass dish of 2 cm diameter. The solvent was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube (3-5 mm o.d.) was dipped into the mixture for about 10 s so that a transparent membrane of about 0.3 mm thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 10 h. The tube was then filled with an internal filling solution ( $1.0 \times 10^{-3}$  mol L<sup>-1</sup> Memantine hydrochloride). The electrode was finally conditioned for 24 h by soaking in a  $1.0 \times 10^{-3}$  mol L<sup>-1</sup> Memantine hydrochloride solution [20-23].

### 2.5. Standard Memantine hydrochloride solutions

A stock solution of  $10^{-1}$  mol L<sup>-1</sup> Memantine hydrochloride was prepared by dissolving the calculated weight of pure drug in 25 mL water. The working solutions ( $10^{-6}$  to  $10^{-1}$  mol L<sup>-1</sup>) were prepared by serial appropriate dilution of the stock solution.

### 2.6. Emf measurements

The following cell was assembled for the conduction of the emf (electromotive force) measurements:

Ag–AgCl | internal solution,  $10^{-3}$  mol L<sup>-1</sup> Memantine hydrochloride | PVC membrane | sample solution | Hg–Hg<sub>2</sub>Cl<sub>2</sub>, KCl (satd.)

These measurements were preceded by the calibration of the electrode with several Memantine hydrochloride solutions (working solutions).

### 2.7. Computational methods

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package [24]. Each species was initially optimized with PM3 method and then the optimized structures were again optimized with density functional theory, using the 6-31G\* basis set. Full geometry optimizations and frequency calculations were performed. Each species was found to be of minima by having no negative values in the frequency calculation. The calculations gave internal energies at 0 K. In order to obtain gas phase free energies at 298.15 K it was necessary to calculate the zero-point energies, and thermal corrections together with entropies to convert the internal energies to Gibbs energies at 298.15 K [25, 26].

Frequency calculations on these structures verified that they were of true minima and provided the necessary thermal corrections to calculate H (Enthalpy) and G (Gibbs free energy). Finally, full optimizations and frequency calculations for each species were performed with the DFT/6-31G\* [27,28].

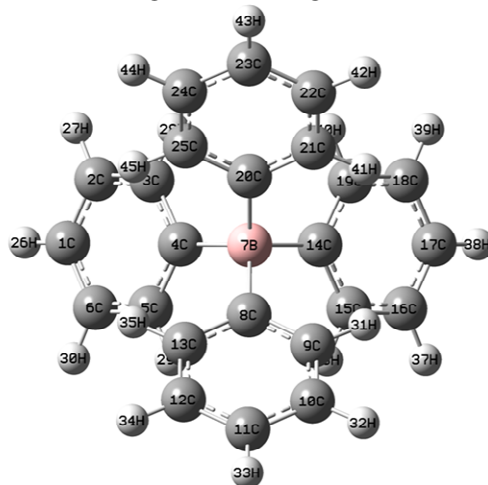
The other one-electron properties (dipole moment, polarizability, energies of the frontier molecular orbital) were also determined at the B3LYP/6-31G\* level. For the charged species the dipole moment was derived with respect to their mass center because for the non-neutral molecules, the calculated dipole moment depended on the origin of the coordinate system.

The stabilization energies of the selected complexes were determined with the help of the DFT calculations and calculated with a recently introduced method based on the combination of the approximate tight-binding DFTB with the empirical dispersion energy. The DFT methods are known to be inherently deficient for stacking interactions as they basically ignore the dispersion attraction [28-30]. As a consequence, their enlargement by an empirical dispersion term currently appears to be a very reasonable way to improve the major deficiency of the DFT method for the evaluation of the molecular complexes. It should also be mentioned that the interaction energies were obtained as the difference between the complex energy and the combined energies of the molecules in isolation [31].

### 3. RESULTS AND DISCUSSION

#### 3.1. Theoretical Study

Molecular parameters are controlled by the molecular geometry. Optimization of geometry is the most important step for the calculation of interaction energy. The optimized geometries and numeration of the atoms of the studied molecules; L1 for NaTPB (Fig. 2), L2 for KTpClPB, MEM for Drug (Fig. 3) and Drug-L1 for MEM-TPB (Fig. 4) and Drug-L2 for MEM-TpClPB are presented.

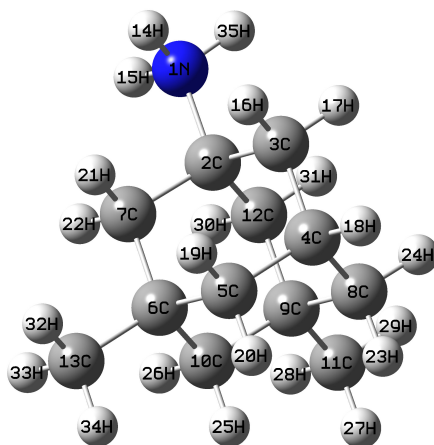


**Figure 2.** The full optimized structure of L1

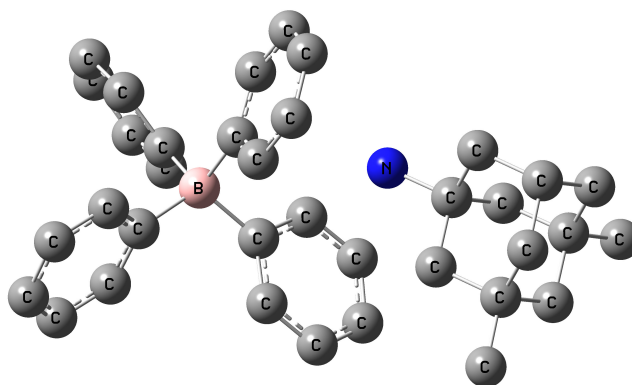
To obtain insight on MEM tendencies for L1 and L2 as potential ionophors, DFTB calculations (B3LYP/6-31G\*) were carried out. The interaction energy of the pair  $\Delta E_{A-B}$  between molecules A (L1 or L2) and B (the drug) was estimated as the difference between the formed complex energy and the energies of the isolated partners. Interaction energies were corrected for the basis set superposition error using the counterpoise method [32,33]:

$$\Delta E_{A-B} = E_{A-B} - E_A - E_B$$

It was obtained to be -77.945 and -63.459 Kcal/mol for  $\Delta E_{L1}$  and  $\Delta E_{L2}$ , respectively. It indicates L1 is a more appropriate ionophore for Memantine sensor in comparison to L2 as it contributes to its higher interaction energy. The main discussions further on shall be on L1-Memantine interactions.



**Figure 3.** The full optimized structure of Memantine



**Figure 4.** The full optimized structure of L1-Memantine complex

Results presented in Table 1 show that interactions existing between the drug and L1 are mostly electrostatic. The most noticeable atomic charge changes are shown in Table 1. Charge changes in the ion pairs are localized on specific atoms that interact together in each molecule [34-37]. According to Table 1 interactions between the drug and the studied ligands correspond to the N1 results in the occurrence of the most significant changes in the atomic charges and also bond lengths for the drug H14, H15, and H35, atomic charges changed from 0.303 to 0.318, 0.304 to 0.327 and 0.303 to 0.319, respectively, along with its bond lengths (N1-H14), (N1-H15), (N1-H35), which shifted from 1.040 to 1.054, 1.040 to 1.057 and 1.040 to 1.056, respectively.

**Table 1.** Significant computed atomic charges and bond length for Memantine before and after complex formation

Charges				Bonds		
	NO.	Memantine	Drug-complex B		Memantine	Drug-complex B
1	N	-0.349	-0.375	R(1,2)	1.564	1.533
13	C	0.142	0.137	R(1,14)	1.040	1.054
14	H	0.303	0.318	R(1,15)	1.040	1.057
15	H	0.304	0.329	R(1,35)	1.040	1.056
21	H	0.078	0.065	R(2,7)	1.546	1.547
22	H	0.067	0.077	R(13,6)	1.549	1.547
23	H	0.074	0.062	R(6,7)	1.556	1.553
25	H	0.072	0.059	R(7,22)	1.088	1.080
32	H	0.076	0.065	R(7,21)	1.088	1.082
33	H	0.076	0.064	R(13,32)	1.088	1.080
35	H	0.303	0.319			
	NO.	Tetraphenylborate	MEM-Complex	NO.	Tetraphenylborate	MEM-Complex
				R(2,3)	1.386	1.392
2	C	-0.078	-0.088	R(3,4)	1.401	1.407
3	C	-0.086	-0.125	R(4,7)	1.643	1.652
5	C	-0.086	-0.102	R(7,8)	1.643	1.637
8	C	-0.068	-0.079	R(7,14)	1.643	1.653
15	C	-0.086	-0.133	R(7,20)	1.643	1.636
26	H	0.030	0.053	R(8,9)	1.400	1.396
27	H	0.033	0.053	R(9,10)	1.386	1.388
28	H	0.042	0.058	R(14,15)	1.401	1.406
29	H	0.042	0.063	R(15,16)	1.386	1.393
30	H	0.033	0.056	R(17,18)	1.385	1.388
38	H	0.030	0.051	R(20,25)	1.400	1.396
39	H	0.033	0.056	R(24,25)	1.386	1.388
40	H	0.042	0.064			
					HOMO for L1	2.77
		HOMO for Drug	-13.50		LUMO for L1	10.9
		LUMO for Drug	3.73			

High values of polarizability (148.545 and 69.334 for L1 and drug, respectively) prove its role on interactions amongst L1 and the drug. The low values of dipole-dipole interactions (especially for that of L1=0.0) show it does not play a significant role between L1 and the studied drug. Moreover, since the studied molecules are in form of ions electrostatic interactions should also be considered.

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) for L1 and the drug calculated at B3LYP/6-31G(d) level are displayed in Table 1. The eigen values of LUMO and HOMO and their energy gap reflect the chemical activity of the molecule. LUMO as an electron acceptor represents the ability to obtain an electron, while HOMO as an electron donor represents the ability to donate an electron. From Table 1 the results illustrate that charge transfer interactions occur between L1 and the drug because the HOMO energy of L1 is close to the LUMO energy of the drug.

### 3.2. Membrane composition effect on the potential response of the sensor

The potential response of a sensor is greatly related to the membrane constituents so the influence of membrane composition on the potential response of the Memantine sensor was studied. For this purpose different membrane compositions (shown in Table 2) were tested. As can be seen, the membrane with the composition of 30% PVC, 7% Memantine-TPB, and 63% DBP (no. 3) was the optimum one in the development of this sensor. This membrane composition was selected after many considerations.

The high Memantine extraction into the liquid membrane was a result of the elevated ion-pair tendency to exchange with the Memantine cations. From Table 2, the 7 mg ion-pair (Memantine-TPB) is the best amount for the optimum response. The second factor that allows Memantine ions to be extracted from an aqueous solution into the membrane as an organic phase is a plasticizer. After the evaluation of three solvent mediators (NB, BA and DBP), it was observed that they do not have the same results if the optimum composition is used. DBP, which is a low-polar solvent mediator shows better response than BA and NB. NB and BA have higher dielectric constant values than DBP leading to the extraction of polar ions, which have negative effects on the extraction of Memantine ions as a hydrophobic ion.

The presence of lipophilic anions in a cation-selective membrane was also considered. As seen from Table 2 the presence of such anions in a cation-selective membrane (which is based on an ion-pair) decreases the response behavior of the sensor.

**Table 2.** Optimization of membrane ingredients

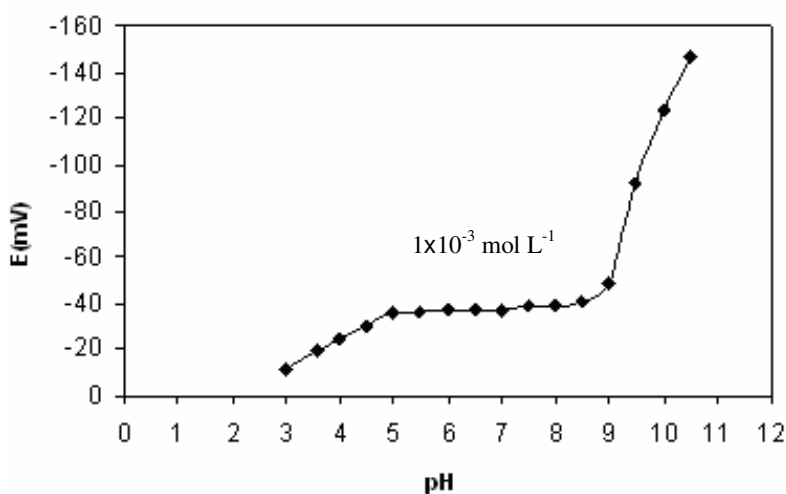
Membrane no.	Ion-pair (% wt.)	Plasticizer (% wt.)	PVC (% wt.)	Linear range (mol L <sup>-1</sup> )	Slope (mV decade <sup>-1</sup> )
1	5	DBP, 65	30	1.0×10 <sup>-5</sup> -1.0×10 <sup>-2</sup>	51.4
2	6	DBP, 64	30	1.0×10 <sup>-5</sup> -1.0×10 <sup>-2</sup>	55.1
3	7	DBP, 63	30	1.0×10 <sup>-5</sup> -1.0×10 <sup>-2</sup>	59.7
4	8	DBP, 62	30	5.0×10 <sup>-4</sup> -1.0×10 <sup>-2</sup>	47.5
5	7	NB, 63	30	5.0×10 <sup>-5</sup> -1.0×10 <sup>-3</sup>	16.3
6	7	BA, 63	30	5.0×10 <sup>-3</sup> -1.0×10 <sup>-2</sup>	11.6



### 3.3. pH effect on the electrode response

To understand the impact of pH on electrode response the potential was measured at two particular concentrations of the Memantine solution ( $1.0 \times 10^{-3} \text{ mol L}^{-1}$ ), from the pH value of 3.0 up to 10.5 (concentrated NaOH or HCl solutions were employed for the pH adjustment). Fig. 5 shows the potential remained constant despite the pH change in the range 5.0 to 8.5 indicating the applicability of this electrode in this specific pH range.

On the contrary, relatively noteworthy fluctuations in the potential vs. pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 8.5 can be justified by removing the positive charge on the drug molecule. The fluctuations below pH 5.0 were attributed to removing the ion-pair in the membrane.



**Figure 5.** The pH effect of the test solutions ( $1.0 \times 10^{-3} \text{ mol L}^{-1}$ ) on the potential response of the

### 3.4. Study of sensor properties

The properties of a potentiometric membrane sensor are characterized by parameters such as: measuring range, detection limit, response time, selectivity, lifetime and accuracy [37-40].

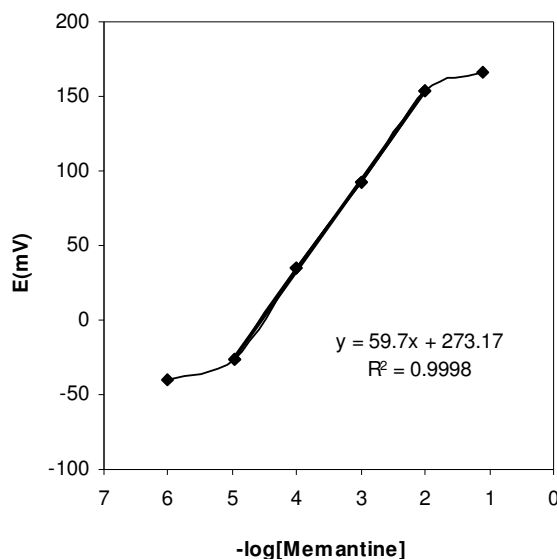
#### 3.4.1. Measuring range

The measuring range of an ion-selective electrode includes the linear part of the calibration graph (Fig. 6). Measurements can be performed in this lower range but it must be noted that more closely spaced calibration points are required for more precise determinations. According to another definition, the measuring range of an ion-selective electrode is defined as the activity range between the upper and lower detection limits. The applicable measuring range of the proposed sensor is between  $1 \times 10^{-5}$  and  $1 \times 10^{-2} \text{ mol L}^{-1}$ .

### 3.4.2. Detection limit

By extrapolating the linear parts of the ion-selective calibration curve the detection limit of the ion-selective electrode can be calculated. In practice, detection limits for the most selective electrodes are in the range of  $10^{-5}$ – $10^{-6}$  mol L<sup>-1</sup>.

In this work the detection limit of the proposed membrane sensor was  $9.0 \times 10^{-6}$  mol L<sup>-1</sup> and was calculated by extrapolating the two segments of the calibration curve (Fig. 6).



**Figure 6.** Calibration curve of the Memantine membrane sensor with the composition of membrane no. 3. The results are based on 8 measurements.

### 3.4.3. Response time

The response time of an electrode is evaluated by measuring the average time required to achieve a potential within  $\pm 0.1$  mV of the final steady-state potential, upon successive immersion of a series of interested ions, each having a ten-fold difference in concentration. It is notable that the experimental conditions such as; stirring, flow rate, ionic concentration, composition of test solution, concentration and composition of solution to which the electrode was exposed before experimental measurements were performed, any previous use or preconditioning of the electrode and the testing temperature, have an effect on the experimental response time of a sensor [41-44].

In this work less than a 10 s response time was obtained for the proposed electrode when contacting different Memantine solutions from  $1.0 \times 10^{-5}$  to  $1.0 \times 10^{-2}$  mol L<sup>-1</sup>.

### 3.4.4. Memantine electrode selectivity

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane. For example, sample solution interface,

mobility of the respective ions in the membrane and on the hydrophobic interactions between the primary ion and the organic membrane [45].

The selectivity of the Memantine membrane electrode is related to the free energy of transfer of the Memantine cation between aqueous and organic phases. The response of the electrode towards different substances was checked and the selectivity coefficient values  $K_{AB}^{Pot}$  were used to evaluate the interference degree. The selectivity coefficient values were obtained using the Matched Potential Method (MPM) [46-49].

The steps that need to be followed for the MPM method are: addition of a specified concentration of the primary ions (A,  $10^{-2}$  mol L<sup>-1</sup> of Memantine solution) to a reference solution ( $10^{-5}$  mol L<sup>-1</sup> of Memantine solution), and the potential measurement. Then, the interfering ions (B,  $10^{-2}$  mol L<sup>-1</sup>) are consecutively added to the same reference solution until the measured potential matches the one obtained before addition of the primary ions. The selectivity coefficient defined by the matched potential method,  $K_{MPM}$ , is equal to the ratio of the resulting primary ion activity (concentration) to the interfering ion activity,  $K_{MPM} = \Delta a_A/a_B$ .

The respective results are summarized in Table 3 depicting that the selectivity coefficient values of the electrode for all tested substances were in the order of  $10^{-3}$  or smaller. Given the low coefficient values it was considered that the function of the Memantine-selective membrane sensor would not be greatly disturbed.

**Table 3.** Selectivity coefficients of various interfering compound for Memantine sensor

Interference	Log $K_{MPM}$
Na <sup>+</sup>	-3.93
K <sup>+</sup>	-4.88
Li <sup>+</sup>	-3.21
NH <sub>4</sub> <sup>+</sup>	-4.33
Mg <sup>2+</sup>	-4.82
Ca <sup>2+</sup>	-4.90
Br <sup>-</sup>	-4.25
NO <sub>3</sub> <sup>-</sup>	-4.15

#### 3.4.5. Lifetime

The average lifetime for most of the reported ion-selective sensors is in the range of 4–10 weeks. After this time the slope of the sensor will decrease, and the detection limit will increase. The sensors were tested for 8 weeks during which time the electrodes were extensively used (one hour per day). The proposed sensors can be used for six weeks. Firstly, there is a slight gradual decrease in the slopes (from 59.7 to 54.3 mV decade<sup>-1</sup>) and then an increase in the detection limit (from  $9.0 \times 10^{-6}$  mol L<sup>-1</sup> to  $2.0 \times 10^{-5}$  mol L<sup>-1</sup>). It is well established that the loss of plasticizer (ionic site) from the polymeric film is due to leaching into the sample. This is the primary reason for limited lifetimes of the sensors.

### 3.5. Analytical application

#### 3.5.1. Determination of Memantine in formulations

The proposed sensor was evaluated by measuring the drug concentration in pharmaceutical formulations. The recovery results are shown in Table 4. The drug concentration was determined with the calibration method. The results are in satisfactory agreement with the labeled amounts. The RSD was equivalent to 1.95%.

**Table 4.** Results of Memantine assay in formulation by the Memantine membrane sensor

Samples	Stated content tablet	Found *
Alzantin-10 (sample 1)	10 mg	10.2±0.2 mg
Alzantin-10 (sample 2)	10 mg	10.3±0.3 mg
Alzantin-10 (sample 3)	10 mg	10.1±0.2 mg

#### 3.5.2. Recovery of Memantine from urine samples

In order to investigate the applicability of the new sensor for determination of the drug in biological fluids it was applied to the recovery of Memantine from urine samples. A 2.5 mL of  $10^{-3}$  mol L<sup>-1</sup> Memantine solution was transferred into a 10-mL volumetric flask. After addition of 2.5 mL of urine samples, the solution was diluted to the mark with water. The determination of Memantine solution content was done using the calibration method by the proposed sensor. The recovery of three replicate measurements was found to be 102.5%, 102.4% and 104.3%, respectively.

#### 3.6. Recovery of Memantine from urine samples

The linearity, detection limit, precision, accuracy, and ruggedness/robustness were the parameters which were used for the method validation [50-52].

As mentioned before, the measuring range of the Memantine sensor is between  $1 \times 10^{-5}$  and  $1 \times 10^{-2}$  mol L<sup>-1</sup>. The detection limit of the sensor was calculated as  $9.0 \times 10^{-6}$  mol L<sup>-1</sup> (2.7 µg/mL).

##### 3.6.1. Precision

The parameters of the repeatability and reproducibility were investigated in order to assess the precision of the technique. For the repeatability monitoring, 8 replicate standards samples 2, 20, 2000 µg/mL were measured. Then, the mean concentrations were found to be 2.03, 20.5, 204.2 µg/mL with associated RSD values of 1.4, 1.06, and 0.43%, respectively. Regarding the inter-day precision, the

same three concentrations were measured for 3 consecutive days providing mean Memantine concentrations of 2.03, 20.5, 204.2  $\mu\text{g/mL}$  and associated RSD values of 1.83, 1.04, and 0.25%, respectively.

### 3.6.2. Accuracy

The relevant error percentage and accuracy were calculated for each case. The resultant concentrations were  $2.03 \pm 0.04$ ,  $20.5 \pm 0.4$ , and  $204.2 \pm 1.3$   $\mu\text{g/mL}$  with relevant error percentages of 3.80, 1.26, and 0.35 %, respectively.

### 3.6.3. Ruggedness/Robustness

For ruggedness of the method a comparison was performed between the intra- and inter-day assay results for Memantine obtained by two analysts. The RSD values for the intra- and inter- day assays of Memantine in the cited formulations performed in the same laboratory did not exceed 2.7%. On the other hand, the robustness was examined while the parameter values (pH of eluent and laboratory temperature) were slightly changed. Memantine recovery percentages were good under most conditions and did not show any significant change when the critical parameters were modified.

## 4. CONCLUSIONS

In this study it is observed that types of interactions exist between drugs and ligands. The DFTB method was employed in this case as the molecules considered were in the form of ions that resulted in ion pair formation. This technique was used as it considers dispersion energies in addition to those calculated by DFT for further investigations. These theoretical calculations help select appropriate ionophores and also predict their selectivity for different drugs.

After a series of experiments involving the use of Memantine-TPB ion-pair complexes along with several plasticizers in the membrane design, it was concluded that the Memantine sensor exhibited excellent analytical performance characteristics. It demonstrated an advanced performance with a fast response time ( $\sim 25$  s), lower detection limit of  $9.0 \times 10^{-6}$  mol  $\text{L}^{-1}$  and pH independent potential responses across the range of 5.0–8.5.

The high sensitivity of this sensor allowed for the determination of Memantine in pharmaceutical analysis. The theoretical calculations are accurate and suitable methods to obtain interaction energies and therefore helped choose better ion pairs. Additionally, employing these methods finds the center of interactions in the target molecule and ionophore.

## ACKNOWLEDGEMENTS

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## References

1. J. W. Johnson and S. E. Kotermanski, *Curr. Opin. Pharmacol.* 6 (2006) 61
2. R. F. Suckow, M. F. Zhang, E. D. Collins, M. W. Fischman and T. B. Cooper, *J. Chromatogr. B* 729 (1999) 217
3. T. H. Duh, H. L. Wu, C. W. Pan and H. S. Kou, *J. Chromatogr. A* 1088 (2005) 171
4. H. J. Leis and G. Fauler, *J. Mass Spectrom.* 37 (2002) 477
5. M. J. Koeberle, P. M. Hughes, C. G. Wilson and G. G. Skellern, *J. Chromatogr. B* 787 (2003) 313
6. A. Periclou, D. Ventura, N. Rao and W. Abramowitz, *Ann. Pharmacother.* 38 (2004) 1389
7. M. R. Ganjali, T. Razavi, R. Dinarvand, S. Riahi and P. Norouzi, *Int. J. Electrochem. Sci.* 3 (2008) 1543
8. S. Riahi, M. F. Mousavi, S. Z. Bathaie and M. Shamsipur, *Anal. Chim. Acta* 548 (2005) 192
9. M. R. Ganjali, M. Hariri, S. Riahi, P. Norouzi and M. Javaheri, *Int. J. Electrochem. Sci.* 4 (2009) 295
10. M. R. Ganjali, T. Razavi, F. Faridbod, S. Riahi and P. Norouzi, *Current Pharm. Anal.* 5 (2009) 28
11. S. Riahi, M. R. Ganjali, P. Norouzi and F. Jafari, *Sens. Actuators B* 132 (2008) 13
12. W. C. Ripka and G. P. Vlasuk, *Annu. Rep. Med. Chem.* 32 (1997) 71
13. S. Riahi, A. B. Moghaddam, M. R. Ganjali and P. Norouzi, *Spectrochim. Acta Part A* 71 (2008) 1390
14. S. Riahi, M. R. Ganjali, A. B. Moghaddam, P. Norouzi and S. S. Hosseiny Davarani, *Spectrochim. Acta Part A* 70 (2008) 94
15. S. Riahi, M. R. Ganjali, A. B. Moghaddam and P. Norouzi, *J. Theor. Comput. Chem. (JTCC)* 6 (2007) 331
16. F. Faridbod, M. R. Ganjali, B. Larijani, P. Norouzi, S. Riahi and F. S. Mirnaghi, *Sensors*, 7 (2007) 3119
17. H. Karami, M. F. Mousavi, M. Shamsipur and S. Riahi, *J. Power Sources*, 154 (2006) 298
18. S. Riahi, M. R. Ganjali and P. Norouzi, *J. Theor. Comput. Chem. (JTCC)* 7 (2008) 317
19. S. Riahi, M. R. Ganjali, A. B. Moghaddam and P. Norouzi, *J. Theor. Comput. Chem. (JTCC)* 6 (2007) 255
20. M. R. Ganjali, Z. Memari, F. Faridbod, R. Dinarvand and P. Norouzi, *Electroanalysis* 20 (2008) 2663.
21. M. R. Ganjali, F. Faridbod, P. Norouzi and M. Adib, *Sens. Actuator B* 120 (2006) 119
22. M. R. Ganjali, P. Norouzi, R. Dinarvand, F. Faridbod, M. Moghlimi, *J. Anal. Chem.* 63 (2008) 684.
23. M. R. Ganjali, P. Norouzi, A. Daftari, F. Faridbod and M. Salavati-Niasari, *Sens. Actuator B* 120 (2007) 673
24. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, et al., Gaussian Inc. Pittsburgh, PA, 1998.
25. J. J. P. Stewart, *J. Comp. Chem.* 10 (1989) 221
26. W. Yang, Q. Wu, Direct Method for Optimized Effective Potentials in Density-Functional Theory, *Physical Review Letters*, 2002.
27. R. G. Parr and W. Yang, *Annu Rev. Phys. Chem.* 46 (1995) 701
28. F. B. Duijneveldt, R. J. G. C. M. Duijneveldt-van de and J. H. Lenthe, *Chem. Rev.* 94 (1994) 1873
29. T. A. Nieaus, M. Elstner, T. Frauenheim and S. Suhai, *J. Mol. Struct. (THEOCHEM)* 541 (2001) 185
30. H. Y. Zhou, E. Tajkhorshid, T. Frauenheim, S. Suhai and M. Elstner, *Chem. Phys.* 277 (2002) 91
31. P. Hobza and R. Zahradnik, *Intermolecular Complexes*, Elsevier, Amsterdam, 1988.
32. M. J. Frisch, J. E. Del Bene, J. S. Binkley and H. F. Schaefer, *J. Chem. Phys.* 84 (1986) 2279
33. D. W. Schwenke and D. G. Truhlar, *J. Chem. Phys.* 82 (1985) 2418
34. M. R. Ganjali, P. Norouzi, F. Faridbod, S. Riahi, J. Ravanshad, J. Tashkhourian, M. Salavati-Niasari and M. Javaheri, *IEEE Sens. J.* 7 (2007) 1138

35. M. R. Ganjali, P. Norouzi, F. S. Mirnaghi, S. Riahi and F. Faridbod, *IEEE Sens. J.* 7 (2007) 544
36. F. Faridbod, M. R. Ganjali, R. Dinarvand, P. Norouzi and S. Riahi, *Sensors*, 8 (2008) 1645
37. S. Riahi, F. Faridbod and M. R. Ganjali, *Sensor Lett.* 7 (2009) 42
38. M. R. Ganjali, P. Norouzi, M. Rezapour, F. Faridbod and M. R. Pourjavid, *Sensors*, 6 (2006) 1018
39. M. R. Ganjali, P. Norouzi, F. Faridbod, M. Yousefi, L. Naji and M. Salavati-Niasari, *Sens. Actuators B*, 120 (2007) 494
40. F. Faridbod, M. R. Ganjali, R. Dinarvand and P. Norouzi, *Sensors*, 8 (2008) 2331
41. M. R. Ganjali, P. Norouzi, F. Faridbod, A. Sepehrifard, M. Ghandi and A. Moghimi, *Can. J. Anal. Sci. Spec.* 52 (2007) 46
42. V. K. Gupta, A. K. Jain and G. Maheshwari, *Int. J. Electrochem. Sci.* 2 (2007) 102
43. M. R. Ganjali, R. Nemati, F. Faridbod P. Norouzi and F. Darviche, *Int. J. Electrochem. Sci.* 3 (2008) 1288
44. V. K. Gupta, R. N. Goyal and R. A. Sharma, *Int. J. Electrochem. Sci.* 4 (2009) 156
45. M. R. Ganjali, M. Tavakoli, F. Faridbod, S. Riahi, P. Norouzi and M. Salavati-Niasari, *Int. J. Electrochem. Sci.* 3 (2008) 1169
46. V. K. Gupta, M. Al Hayat, A. K. Singh and M. K. Pal, *Anal. Chim. Acta*, 634 (2009) 36
47. R. K. Mahajan, and P. Sood, *Int. J. Electrochem. Sci.* 2 (2007) 832
48. V. K. Gupta, S. Chandra, S. Agarwal and H. Lang, *Sens. Actuators B*, 107 (2005) 762
49. P. R. Buck and E. Lindner, *Pure Appl. Chem.* 66 (1994) 2527
50. M. R. Ganjali, M. Hariri, S. Riahi, P. Norouzi, and M. Javaheri, *Int. J. Electrochem. Sci.* 4 (2009) 295
51. M. R. Ganjali, B. Vesimohammadi, S. Riahi, and Parviz Norouzi, *Int. J. Electrochem. Sci.* 4 (2009) 740
52. F. Faridbod, M. R. Ganjali, S. Labbafi, R. Dinarvand, S. Riahi, and Parviz Norouzi, *Int. J. Electrochem. Sci.* 4 (2009) 772