*Scientific paper*

# Ion Selective Phosphotungestate and β-cyclodextrin Based Membrane Electrodes for Stability-Indicating Determination of Midodrine Hydrochloride

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## Abstract

This paper reports the construction and evaluation of two ion selective electrodes for the determination midodrine hydrochloride (MD) by direct potentiometry in pure drug substance and in tablet formulations. Precipitation based technique was used for fabrication of the first membrane sensor (sensor 1) using phosphotungestate (PT) and dioctylphthalate (DOP) as cation exchanger and solvent mediator, respectively. β-cyclodextrin (β-CD)-based technique with PT as a fixed anionic site in PVC matrix was used for fabrication of the second membrane sensor (sensor 2). The proposed sensors showed fast, stable Nernstian responses of 54 and 56 mV/decade for sensors 1 and 2, respectively, across a relatively wide MD concentration range ($1 \times 10^{-4}$ to $1 \times 10^{-1}$ mol/L and $5 \times 10^{-5}$ to $1 \times 10^{-1}$ mol/L for sensor 1 and 2, respectively) in the pH range of 5–7. Sensor 1 and sensor 2 can be used for three and two weeks, respectively without any measurable change in sensitivity. The suggested electrodes succeeded to determine intact MD in the presence of up to 10% of its degradation product and displayed good selectivity in presence of common inorganic and organic species.

**Keywords:** Ion-selective electrodes, phosphotungestate, β-cyclodextrin, midodrine hydro-chloride, deglymidodrine, determination, tablets.

## 1. Introduction

Midodrine, 2-amino-*N*-[2-(2,5-dimethoxy-phenyl)-2-hydroxyethyl] acetamide, is an α- adrenergic agonist.[1] It is capable of inducing venous and arterial vasoconstriction causing elevation of systemic blood pressure accompanied by a reduction in the heart rate. It is used for treatment of orthostatic hypotension.[2,3]

Literature survey revealed a colorimetric method for determination of MD in pharmaceutical formulations.[4] MD was also determined in plasma by several methods based on HPLC (with native fluorescence detection[5,6] or UV detection[7]), capillary electrophoresis[8] and gas chromatography.[9]

Recently, there has been a growing need for construction of chemical sensors for fast and economical monitoring of pharmaceutical compounds. Ion selective electrodes (ISEs) based on material transport across a specific membrane are now widely used in the determination of drugs in pure and pharmaceutical dosage forms. Selective membranes in ISEs have shown both ion exchange and perm-selectivity of the sensor ions and the signal is generated by charge separation at the interface between the ion selective membrane and the solution due to selective partitioning of ionic species between these two phases.[10, 11] The high selectivity of these electrodes imparts a great advantage over other techniques.[12] Analytes in colored, turbid and viscous samples can be determined accurately without separation. Furthermore, they show rapid response to changes in concentration and can be used through a wide range of concentration and they are tolerant to small changes in pH. They are also simple and cheap to develop, setup and run.[13] Various reports have been published which highlight the important contribution of ion selective sensors for quantification of drugs.[14–16]

Cyclodextrins are optically active oligosaccharides that form inclusion compounds in the aqueous and in solid state with organic molecules. By alkylation of the hydroxyl groups in the 2-, 3- and 6- positions, cyclodextrins become lipophilic. This enables their incorporation in plasticized PVC membranes and use as ionophores in ion-selective electrodes.[17] They were previously applied as sen-

sor ionophores to potentiometric ISEs for the determination of drugs.[18–21]

Midodrine HCl is a prodrug for deglymidodrine (2-Amino-1-(2,5-dimethoxy-phenyl)-ethanol), it is formulated as such to increase the bioavailability of the drug from 50% to 93%.[22] Being an amide, MD was found to easily undergo acid or alkaline hydrolysis to produce deglymidodrine. None of the reported methods was concerned with either the degradation of MD or its determination in presence of its degradation product.

The aim of the present work was to develop a method for the determination of midodrine HCl in the presence of its alkaline degradation product by using ion selective electrodes.

# 2. Experimental

## 2. 1. Apparatus

Jenway digital ion analyzer Model 3330 (Spectronic Camspec Ltd, Garforth, UK) with Ag/AgCl double junction reference electrode No. Z113107-1EAPW (Aldrich Chemical Co., St. Louis, MO) was used. The influence of pH on the response of the electrodes was studied using a glass pH electrode (Jenway No. 924005-BO3-Q11C).

## 2. 2. Reference Samples and Pharmaceutical Formulations

Pure standard of midodrine hydrochloride, was kindly supplied by Glaxo SmithKline pharmaceutical company. Purity was reported to be 100.1 ± 0.8 according to the reported method.[4] Midodrine tablets labeled to contain 2.5 mg manufactured by Nile Company for Pharmaceuticals and Chemical Industries (Cairo, Egypt) was purchased from local market.

## 2. 3. Chemicals and Standard Solutions

Water used was bi-distilled. All chemicals and solvents used were of analytical grade. Nitrophenyl octyl ether (NPOE), dioctyl phthalate (DOP), sodium phosphotungestate tribasic (PT) were purchased from Aldrich (Steinhein, Germany). Ammonium reineckate (RN), sodium tetraphenylborate (TPB), tetrahydrofuran (THF), poly(vinyl chloride) (PVC) of high molecular weight were purchased from BDH (Poole, England). (2-Hydroxypropyl)-β-cyclodextrin from Fluka (Steinhein, Germany). Sodium hydroxide, HCl and potassium chloride were purchased from Prolabo (Pennsylvania, USA).

MD stock solution ($1.0 \times 10^{-1}$ mol/L) was prepared using water as a solvent. MD working solutions ($1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ mol/L) were prepared by serial dilutions from MD stock solution using water as a solvent.

## 2. 4. Procedures

### 2. 4. 1. Preparation and Identification of the Degradation Products

Accelerated alkaline-degradation was performed by dissolving 50 mg of pure MD powder in 50 mL of 1N sodium hydroxide. The solution was refluxed for 30 minutes. Complete degradation was checked by TLC using toluene-methanol-acetic acid (10 : 2 : 0.1 v/v/v) as a developing system. After complete degradation the solution was extracted three times with chloroform (3 × 10 mL). The chloroform extract was evaporated to dryness. The structure of the obtained degradation product was elucidated and confirmed by mass spectrometry (Figure 1).

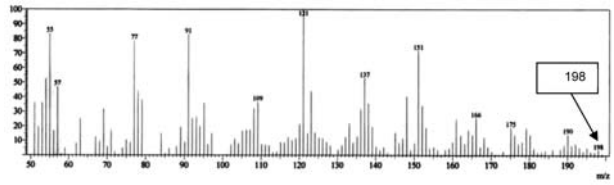



**Figure 1.** Mass spectrum of deglymidodrine

### 2. 4. 2. Preparation of the Membrane Sensors

MD ion pair complex was prepared by mixing 10 mL of $1.0 \times 10^{-2}$ mol/L solution of MD with 10 mL saturated solution of the ion exchanger solution. The resultant precipitate was filtered using Whatman filter paper no. 42, washed with cold water, dried at room temperature (about 20 °C) and ground to fine powder.

For the preparation of sensor 1, a portion (10 mg) of drug-ion exchanger was thoroughly mixed with 0.19 g PVC and 0.35 mL DOP in a glass petri dish (5 cm diameter) then dissolved in 5 mL THF.[23,24] Sensor 2 was prepared by mixing 0.04 g β-CD with 0.4 mL DOP and 0.01 g PT in a glass petri dish (5 cm diameter). PVC (0.18 g), previously dissolved in 6 mL THF was added and the contents were mixed thoroughly. The petri dishes were covered with a filter paper and left to stand overnight to allow solvent evaporation at room temperature. A master membrane with thickness of 0.1 mm was obtained and used for the construction of the electrodes.

### 2. 6. 3 Preparation of the Electrode Assembly

From the prepared master membranes (sensors), a disk (≈ 5 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the glassy electrode body. Equal volumes of $1 \times 10^{-2}$ mol/L MD and $1 \times 10^{-2}$ mol/L KCl were mixed and this solution was used as internal solution for both electrodes. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The cell, Ag–AgCl / internal solution,

$10^{-2}$ mol/L MD, $10^{-2}$ M KCl / PVC membrane sensor / test solution / Ag–AgCl, KC1 (saturated), was assembled for measuring the electromotive force. The electrodes were conditioned by soaking in $1 \times 10^{-2}$ mol/L MD solution for one day and were stored in distilled water when not in use.

### 2. 6. 4. Direct Potentiometric Determination of MD in its Pure Samples

The conditioned electrodes were calibrated separately by transferring 50 mL aliquots of solutions covering the concentration range of ($1.0 \times 10^{-6}$ to $1.0 \times 10^{-1}$ mol/L) MD, into a series of 100 mL beakers. The electrode system was immersed in each solution, in conjunction with a double junction Ag/AgCl reference electrode.

The electrodes were washed with distilled water between measurements. For each electrode, the electrode potential was plotted versus each negative logarithmic concentration of MD standard solutions. The regression equations of the obtained calibration plots were used for subsequent measurements of unknown samples.

### 2. 6. 5. Direct Potentiometric Determination of MD in its Pharmaceutical Formulation

Ten tablets of the drug formulations were weighted and finely powdered in a small dish. An accurately weighed portion of the powder (14.535 mg) was transferred to a 50 mL volumetric flask (to prepare $1.0 \times 10^{-3}$ mol/L MD) and filled up to the mark with water. The potential readings produced by immersing the prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode in the prepared solution were recorded. The concentration of MD was calculated from the corresponding regression equation.

### 2. 6. 6 Determination of Midodrine HCl in the Presence of its Alkaline Degradation Product

Ten milliliters of MD solution ($1.0 \times 10^{-2}$ mol/L) were quantitatively transferred to a series of 100 mL volumetric flasks. Aliquots from the corresponding degradation product solution ($1.0 \times 10^{-2}$ mol/L) were added, and the volume was completed with water to prepare mixtures containing 10 : 0.1, 10 : 0.3, 10 : 0.5, 10 : 1.0, 10 : 3.0 and 10 : 5.0 MD: degradation product ratios.

## 3. Results and Discussion

Selective membranes in ion selective electrodes have shown both ion exchange and perm-selectivity for the sensor ion.[10] In this work two ion selective membrane sensors were proposed.

### 3. 1. Membrane composition and Response Characteristics

Preparation of sensor 1 originates from the fact that MD behaves as a cation in acid medium due to the protonation of the free amino group (Figure 2), this fact suggests the use of a cationic exchanger. The type of the ion exchanger affects the response of the sensor,[10] therefore, three cationic exchangers, namely TPB, PT and RN, were tried for the preparation of the membrane sensor. Insoluble ion association complexes with suitable grain size with MD were formed with the three cationic exchangers. The ratio of MD to the ion exchanger in the formed complexes was found to be 1:1 as proven by elemental analysis and the obtained Nernstian slopes (about 60 mV/ decade) so MD acts as a monoionic species due to the presence of the free amino group (Figure 2). The complexes were prepared, characterized, and incorporated with a suitable solvent mediator in poly (vinyl chloride) matrix membranes which were used for constructing the electrodes.

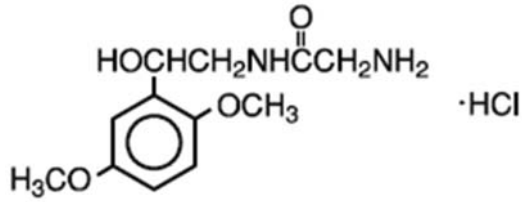



**Figure 2.** Chemical structure of midodrine hydrochloride

The MD extraction into membrane sensor 1 was a result of the ion-pair tendency to exchange with the MD cations. From Table 1, MD- PT appears to have the highest tendency to exchange with MD (best Nernestian response). β-CD based technique was used in the preparation of sensor 2 where MD is extracted into the membrane via inclusion into the β-CD cavities through inclusion-complex formation.[25]

The second factor that allows MD ions to be extracted from an aqueous solution into the membrane, as an organic phase, is the plasticizer. After the evaluation of two plasticizers, namely NPOE and DOP, (as examples for plasticizers from diesters of dicarboxylic acids and nitroaromatic compounds respectively), Table 1 shows that DOP, which is a low-polar solvent mediator shows a slightly better response than NPOE that has a higher dielectric constant value leading to the extraction of polar ions, which have negative effects on the extraction of MD ion as a hydrophobic ion.

Based on the IUPAC recommendations,[26] the response characteristics of the designed electrodes were assessed. Table 2 displays the slopes, linear ranges and validation parameters for the MD ion-selective electrodes. The suggested electrodes exhibited a Nernstian slope of 54.1 and 56.0 mV/ decade for sensor 1 and 2, respectively in a wide MD concentration range, from 1 ×

$10^{-4}$ M to $1 \times 10^{-1}$ M for sensor 1 and from $5 \times 10^{-5}$ to $1 \times 10^{-1}$ for sensor 2 (Figure 3). The deviation from the ideal Nernestian slope (60 mV/ decade), is due to the fact that the electrode responds to activities of the drug rather than the concentration. The suggested electrodes exhibited a fast response time (10–15 s). The lifetime of the PVC membrane electrode was studied by periodically recalibrating the potentiometric MD response in the standard MD solutions. After the conditioning step, the electrode was repeatedly calibrated every week. No significant change in the electrode performance for sensors 1 and 2 was observed during 3 and 2 weeks, respectively.

**Table 1.** Effect of the type of electro-active species and plasticizer on the slope and concentration range for potentiometric determination of MD.

| Electro-active species | Plasticizer | Slope | Concentration range (Molar) |
|---|---|---|---|
| TPB | DOP | 53.0 ± 0.8 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| TPB | NPOE | 51.0 ± 2.1 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| PT | DOP | 54.1± 1.0 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| PT | NPOE | 53.0 ± 1.8 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| RN | DOP | 47.5 ± 3.0 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| RN | NPOE | 44.5 ± 2.4 | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ |
| β-CD | DOP | 56.0 ± 1.0 | $5.0 \times 10^{-5}$ –$1.0 \times 10^{-1}$ |
| β-CD | NPOE | 55.7 ± 2.6 | $5.0 \times 10^{-5}$ –$1.0 \times 10^{-1}$ |

The optimum equilibration time for the electrode after soaking in $1 \times 10^{-2}$ M MD was 24 hours. After this time the electrodes generated stable potentials in contact with the MD solution. On soaking for a longer time the slope decreased gradually and this may be attributed to the gradual leaching of the electroactive species into the bathing solution[27]. Therefore, the electrode should be kept dry when not in use for a long time.

To evaluate the precision of measurements, three concentrations within the linear concentration range ($1 \times 10^{-3}$, $1 \times 10^{-2}$ and $1 \times 10^{-1}$ mol/L solutions) of MD were chosen. Three solutions of each concentration were prepared and analyzed in triplicate (repeatability assay). This reproducibility assay was repeated on three different days (Table 2).

**Table 2.** Response characteristics of the two investigated electrodes.

| Parameter | Sensor 1 | Sensor 2 |
|---|---|---|
| Slope (mV/decade) $n = 3$ | 54.1 ± 1.0 | 56.0 ± 1.0 |
| Intercept (mV) $n = 3$ | 190.9 ± 2.0 | 173.5 ± 1.2 |
| Correlation coefficient ($r^2$) | 0.999 | 0.998 |
| Concentration range (M) | $1.0 \times 10^{-4}$ –$1.0 \times 10^{-1}$ | $5.0 \times 10^{-5}$ –$1.0 \times 10^{-1}$ |
| Response time (s) | 15 | 10 |
| Working pH range | 5–7 | 5–7 |
| Stability (weeks) | 3 | 2 |
| Average accuracy [a] (% ± SD) | 99.8 ± 1.3 | 100.0 ± 1.2 |
| Precision [b] | | |
| *Repeatability* | ± 0.6 | ± 1.2 |
| *Reproducibility* | ± 1.0 | ± 2.4 |
| Robustness [c] | ± 0.5 | ± 0.7 |
| Robustness [d] | ± 1.3 | ± 0.9 |
| Ruggedness [e] | ± 0.6 | ± 0.4 |

[a] Average recovery (%) of five concentration levels (from $10^{-4}$ to $10^{-1}$) each repeated three times. [b] Three concentration levels each repeated three times. [c] Relative standard deviation (RSD, %) of determining $10^{-2}$ and $10^{-3}$ M solutions at pH 4.5 instead of pH 6 (in water), [d] using DBS as plasticizer instead of DOP. [e] RSD (%) of determining $10^{-2}$ and $10^{-3}$ M solutions using Jenway 3505 digital ion analyzer instead of 3330.

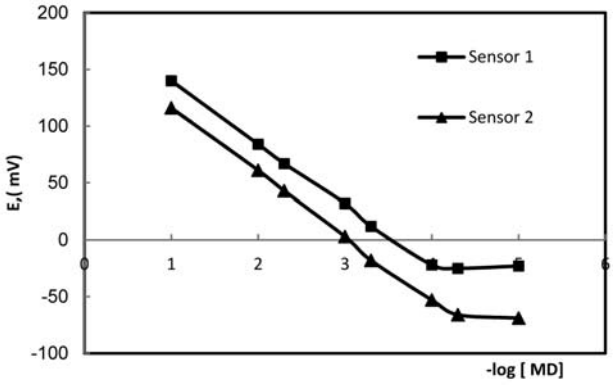



**Figure 3.** Potentiometric profile of sensor 1 and sensor 2.

As for the robustness, calibration of the standard solutions was carried out by the same method but using dibutyl sebasate instead of DOP as plasticizer. The method demonstrated efficient stability. Also the pH range 5–7 makes the method robust. To study the method's ruggedness, $10^{-3}$ and $10^{-2}$ mol/L solutions of MD were analyzed by the suggested electrode using Jenway 3505 digital ion analyzer instead of 3330 Model. Results proved the stability of the method upon changing the instrument (Table 2).

## 3. 2. The Effect of pH on the Electrode Response

The potentiometric response of the suggested electrodes was found sensitive to pH changes. Figure 4 shows a typical pH response curve for the prepared electrodes, over a pH range of 2.5–10.0, where the pH was adjusted with hydrochloric acid and sodium hydroxide solutions. The electrode response was hardly affected by the pH change from 5 up to 7 (pKa 7.9), i.e., in this pH range is MD completely ionized, dissociated and sensed and this allowed working in water without using a buffer solution. Below pH 5, the electrode response increased with the increase in solution acidity as the membrane may extract $H^+$ leading to a noisy response.[28] The decrease in potential at pH > 7.5 was due to the gradual decrease in the concentration of the MD mono cation due to the formation of the non-protonated amino group.

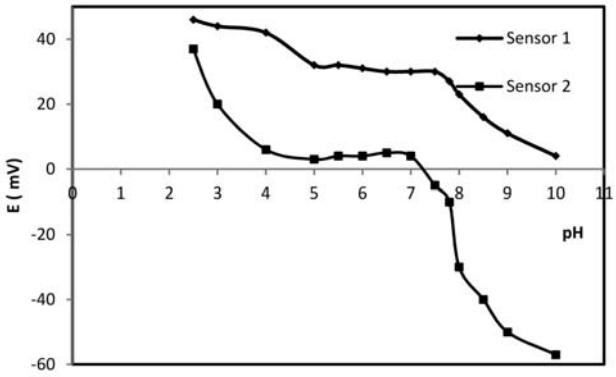



**Figure 4.** Effect of pH on the response of sensor 1 and sensor 2 in $10^{-3}$ M MD.

## 3. 3. Sensor 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.[29] A number of pharmaceutical additives and diluents commonly used in drug formulation were examined for their effect on the assay method. The selectivity coefficients were determined by the separate solution method and calculated from the following equation.[26]

$$-\log(K^{pot}{}_{primary\ ion\ interferent}) = \left[\frac{(E_M - E_{MD})}{2.303RT / Z_{MD}F}\right] + \left[1 + \frac{Z_{MD}}{Z_M}\right]\log[MD]$$

Where $E_{MD}$ and $E_M$ are the potential readings recorded after exposing the electrode to the same concentration of the studied drug and the interferent, respectively, $Z_{MD}$ and $Z_M$ are the charges on MD and the interfering ion, respectively and 2.303RT / $Z_{MD}$F represents the slope of the investigated sensor (mV / decade).

**Table 3.** Potentiometric selectivity coefficients (K pot MD) of MD for the proposed sensors by separate solution method ($n$ = 3).

| Interferent | Selectivity Coefficient | |
|---|---|---|
| $10^{-3}$ M | Sensor 1 | Sensor 2 |
| Urea | $3.1 \times 10^{-5}$ | $9.8 \times 10^{-5}$ |
| Starch | $1.3 \times 10^{-5}$ | $5.3 \times 10^{-5}$ |
| Sucrose | $2.1 \times 10^{-5}$ | $5.4 \times 10^{-5}$ |
| Lactose | $8.9 \times 10^{-6}$ | $4.1 \times 10^{-6}$ |
| Talc | $2.0 \times 10^{-5}$ | $7.1 \times 10^{-5}$ |
| MgO | $6.6 \times 10^{-6}$ | $2.4 \times 10^{-6}$ |
| NaCl | $2.2 \times 10^{-4}$ | $3.9 \times 10^{-4}$ |
| KCl | $1.1 \times 10^{-3}$ | $1.7 \times 10^{-4}$ |
| $CaCl_2$ | $2.3 \times 10^{-4}$ | $1.6 \times 10^{-4}$ |
| Glycine | $1.8 \times 10^{-5}$ | $8.4 \times 10^{-5}$ |
| Deglymidodrine | $1.4 \times 10^{-4}$ | $4.4 \times 10^{-4}$ |

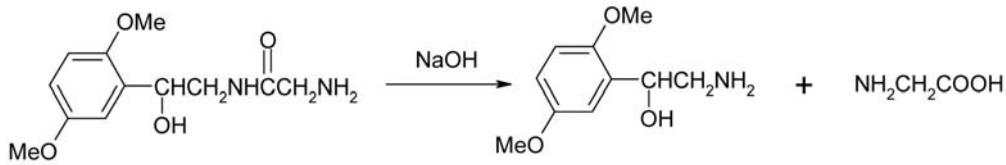
It is obvious from Table 3 that none of the tested interfering species have a significant influence on the potentiometric response of the electrode towards MD.

Having an amide linkage, MD was found to undergo both acid and alkaline hydrolysis. Degradation of MD was induced by boiling with 1 M NaOH or 2N HCl. Scheme 1 shows the suggested alkaline degradation pathway of the drug. The degradation process was followed using TLC silica gel 60 $F_{254}$ plates and toluene: methanol: acetic acid (10 : 2 : 0.1 v/v/v) as the developing solvent. The intact drug was entirely degraded after boiling with 1 M NaOH for 30 minutes or with 2M HCl for 2 hours. The degradation product deglymidodrine was confirmed by mass spectra (m/z = 198) (Figure 1). The presence of degylmidodrine is undesirable in pharmaceutical formulation as it reduces the pharmacokinetic of the drug by 43%.[22]

The selectivity of the suggested electrode was also examined in the presence of the possible degradation products of MD. Table 4 shows the results obtained upon analysis of synthetic mixtures containing different ratios of intact drug to degraded sample, varying from 10 : 0.1 to 10:5.0. The results showed that both sensors can be successfully used for selective determination of intact drug in the presence of up to 10% of it degradation products.

## 3. 4. Analytical Application

As none of the commonly used tablet additives show significant interference with the determination of MD, the new proposed electrodes were successfully applied for MD determination in tablets without prior extraction as shown in Table 5. Results obtained prove the applicability of the method as demonstrated by the non significant difference between the results obtained by the suggested method and the reported one, (Table 5).




Midodrine Deglymidodrine Glycine

**Table 4.** Determination of MD in laboratory prepared mixtures containing different ratios of MD and its induced alkaline degradation product by the proposed sensors.

| Drug : degradate ratio | Drug % recovery ± SD (*n* = 3) Sensor 1 | Sensor 2 |
|---|---|---|
| 10 : 0.1 | 99.1 ± 0.7 | 100.2 ± 0.9 |
| 10 : 0.3 | 102.1 ± 1.9 | 100.2 ± 1.2 |
| 10 : 0.5 | 100.6 ± 1.7 | 99.9 ± 0.9 |
| 10 : 1.0 | 101.1 ± 1.4 | 102.2 ± 0.7 |
| 10 : 3.0 | 120.8 ± 2.0 | 120.9 ± 1.7 |
| 10 : 5.0 | 150.2 ± 1.7 | 140.0 ± 2.3 |

**Table 5.** Determination of MD in Midodrine tablets by the suggested potentiometric and the reported [4] methods.

| Product | Found % ± SD (*n* = 3) Sensor 1 | Sensor 2 | Reported method |
|---|---|---|---|
| Midodrine tablets 2.5 mg | 102.1 | 101.4 | 102.0 |
| SD | 1.0 | 0.9 | 0.6 |
| Variance | 1.0 | 0.8 | 0.4 |
| F test | 2.5 (19.0) | 2.0 (19.0) | |
| Student t test | 0.146 (2.776) | 0.949 (2.776) | |

Figures between parenthesis are the corresponding tabulated values (P = 0.05)

## 4. Conclusion

Two new sensors were described for the determination of midodrine hydrochloride. The described sensors are sufficiently simple and selective for the quantitative determination of MD in pure form and pharmaceutical formulation. The use of 2-hydroxy propyl-β-cyclodextrin as ionophore increased the membrane sensitivity and selectivity as in sensor 2 in comparison with sensor 1. The proposed sensors offer advantages of fast response and elimination of drug pre-treatment or separation steps and can therefore be used for routine analysis of MD in quality-control laboratories.

## 5. References

1. The Merck Index, in: M. J. O'Neil (Ed.), An Encyclopedia of Chemicals, drugs, and Biologicals., Merck & Co., Inc., Whitehouse Station, NJ, USA, 2006, p. 1066.
2. D. McTavish, *Drugs* **1989**, *38*, 757–777.
3. H. Pittner, *Gen. Pharmacol*. **1983**, *14*, 107–109.
4. A. El-Gindy, S. Sallam, R. A. Abdel-Salam, *Anal. Chem. An Indian J.* **2008**, *7*, 1–16.
5. W. Posch, W. Lindner, *Biomed. Chromatog.* **1989**, *3*, 153–156.
6. H. Yoshida, Y. Ohno, K. Yoshikuni, K. Todoroki, H. Nohta, M. Yamaguchi, *Anal. Sci.* **2003**, *19*, 317–319.
7. M. G. Quagla, A. Farina, E. Bossu, C. V*, J. Pharm. Biomed. Anal.* **1998**, *18*, 171–177.
8. T. Barth, M. Pupo, K. Borges, L. Okano, P. Bonato, *Electrophor*. **2010**, *31*, 1521–1528.
9. S. Tsutsumi, T. Suwa, N. Masuda, T. Minagawa, M. Sano, T. Tamatani, K. Tsuchida, Clin.Rep. **1987**, *21*, 1895–1899.
10. G. Moody, J. Thomas, Selective Ion Sensitive Electrodes, Merrow Technical Library, **1971**.
11. B. Singhal, *World J. Chem.* **2011**, *6*, 59–74.
12. B. A. Conway, Ion Selective Electrodes, Ottawa Press, **1995**.
13. S. Hassan, W. H. Mahmoud, A. M. Othman, *Anal. Chimica Acta* **1996**, *322*, 39–48.
14. V. V. Cosofret, *Trends Anal. Chem*. **1991**, *10*, 298–301.
15. V. K. Gupta, A. Nayak, S. Agarwal, B. Singhal, *Chem. & High Throughput Screen* **2007**, *14*, 284–302.
16. R. I. Stefan, G. E. Baiuleseu, H. Y. Aboul-enien, *Anal. Chem*. **1997**, *27*, 307–321.
17. A. Ferancová, J. Labuda, *Fresenius J. Anal. Chem.* **2001**, *370*, 1–10.
18. A. M. El-Kosasy, M. A. Shehataa, N. Y. Hassana, A. S. Fayeda, B. A. El-Zeany, *Talanta* **2005**, *66*, 746–754.
19. J. Lima, M. Montenegro, *Mikrochim. Acta* **1999**, *131* 187–190.
20. Nashwa M. H. Rizk, Samah S. Abbas, F. A. EL-Sayed, A. Abo-Bakr, *Int. J. Electrochem.* **2009**, *4*, 396–406.
21. A. M. Pimenta, A. N. Araújo, M. C. B. S. M. Montenegro, *Anal. Chimica Acta* **2002**, *470*, 185–194.

22. J. Rautio (Ed.), Prodrug and targeted delivery, *47*, Wiely-VCH, Verlag GmbH & Co. **2002**.
23. S. M. Hassan, S. A. Marzouk, *Talanta* **1994**, *41*, 891–899.
24. T. S. Ma, S. M. Hassan, Organic Analysis Using Ion Selective Electrodes, Academic Press, London, **1982**.
25. G. N. Valsami, M. A. Koupparis, P. E. Macheras, *Pharm. Res.* **1992**, *9*, 94–100.
26. IUPAC Analytical Chemistry Division Commission on Analytical Nomenclature, *Pure Applied Chemistry* **2000**, *72*, 1851–2082.
27. A. F. Shoukry, Y. M. Issa, R. El-Shiekh, M. Zareh, *Anal. Lett.***1991**, *24*, 1581–1590.
28. A. M. El-Kosasy, A. E.-R. S. A, *J. Pharm. Biomed. Anal.* **2002**, *29*, 585–592.
29. M. R. Ganjali, M. Tavakoli, F. Faridbod, S. Riahi, N. P, M. Salavati-Niassari, *Int. J. Electrochem. Sci.* **2008**, *3*, 1169–1175.

## Povzetek

Članek poroča o konstrukciji in vrednotenju dveh ionsko selektivnih elektrod za določanje midodrin hidroklorida (MD) v farmacevtskih pripravkih. Za izdelavo prvega membranskega senzorja (senzor 1) smo uporabili tehniko precipitacije z uporabo fosfovolframata oz. dioktilftalata kot kationskega izmenjevalca oz. mediatorskega topila. β-ciklodekstrinska tehnika z uporabo fosfovolframata kot fiksnega anionskega mesta v PVC matriksu je bila uporabljena za izdelavo drugega membranskega senzorja (senzor 2). Predlagana senzorja s hitrimi, stabilnimi Nernstovimi odzivi, 54 oz. 56 mV/dekado za senzor 1 oz. senzor 2, v relativno širokem koncentracijskem območju MD ($1 \times 10^{-4}$ do $1 \times 10^{-1}$ mol/L oz. $5 \times 10^{-5}$ do $1 \times 10^{-1}$ mol/L za senzor 1 oz. 2) in pH območju 5–7 in sta uporabna tri oz. dva tedna brez merljivih sprememb v občutljivosti. Z njima lahko uspešno določimo čist MD v prisotnosti do 10 % razpadnega produkta, poleg tega pa elektrodi kažeta dobro selektivnost v prisotnosti običajnih anorganskih in organskih primesi.