Comparative Study of Different Ionophores in Ion Selective Electrodes for Stability indicating Determination of Moxifloxacin

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Received: 6 May 2014 / Accepted after minor revision: 5 August 2014 /
Published online: 31 August 2014

Abstract- Three novel moxifloxacin (MO) selective electrodes were investigated with 2-nitrophenyl octyl ether as a plasticizer in a polymeric matrix of polyvinyl chloride (PVC). Sensor 1 was fabricated using tetrakis(4-chlorophenyl)borate (TpClPB) as an anionic exchanger without incorporation of an ionophore. Sensor 2 used 2-hydroxyl β-cyclodextrin as an ionophore while sensor 3 was constructed using 4-tertiary butyl sulfocalix-8-arene as an ionophore. Linear responses of MO within the concentration ranges of $10^{-5}$ to $10^{-2}$ mol L$^{-1}$ were obtained using sensors 1, 2 and 3, respectively. Near Nernstian slopes of 49.79, 51.50 and 52.10 mV/decade over the pH range of 2–5 were observed. The selectivity coefficients of the developed sensors indicated excellent selectivity for MO. The proposed sensors displayed useful analytical characteristics for the determination of MO in bulk powder, pharmaceutical formulation, and biological fluids (plasma) and in the presence of its alkaline degradation product and thus could be used for stability-indicating studies.

Keywords- Moxifloxacin, β-cyclodextrin, Calixarene, Potentiometry, Stability-indicating method
1. INTRODUCTION

Moxifloxacin hydrochloride (MO), is \((1\text{-Cyclopropyl-6-fluoro-8-methoxy-7-}\{(4aS,7aS)\text{-octahydro-6H-pyrrolo[3,4-}\text{-b}]\text{pyridin-6-yl}\}4\text{-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride}\), Fig. 1. It is a fluoroquinolone antibacterial agent [1]. Many analytical methods including RP-HPLC [2-4] and UV-spectroscopic [5-7] and HPTLC [8] were reported for the estimation of MO in bulk, pharmaceutical formulation and in biological samples.

![Chemical structure of moxifloxacin](image)

Fig. 1. Chemical structure of moxifloxacin

There is no stability-indicating electrochemical method reported for the estimation of MO in its pharmaceutical formulations. Therefore, attempts were made in this study to develop a fast, sensitive, selective and stability-indicating method for its determination.

Cyclodextrins are known to accommodate a wide variety of organic, inorganic and biologic guest molecules to form stable host-guest inclusion complexes or nanostructure supramolecular assemblies in their hydrophobic cavity while exhibiting high molecular selectivity and enantioselectivity [9,10]. They have been previously applied as sensor ionophores in potentiometric ion selective electrodes for the determination of fluorinated surfactants [11], chiral molecules incorporating aryl rings [12], protonated amines [13] and quaternary ammonium drugs [14].

Calixarenes are cavity-shaped cyclic oligomers made up of phenol units linked via alkylidene groups. Their configuration includes a number of selective factors, such as cavity-size, conformation and substituents, which leads to the formation of typical host-guest complexes with numerous compounds and allow for a variety of applications in ion-selective membranes and electrodes [15–21].

The present work describes the use of functionalized cyclodextrin derivatives and sulphonated calix[8]arene as neutral ionophores for the development of novel sensors for the determination of MO. These sensors are able to selectively, determine MO from its impurities, degradation products and placebo components. The developed method was
validated with respect to specificity, linearity, limit of detection and quantification, precision, accuracy and robustness. Force degradation studies were performed on the placebo and drug product.

2. EXPERIMENTAL

2.1. Instrument

Potentiometric measurements were made at 25°C±1 with a Hanna (Model 211) pH/mV meter. A single junction calomel reference electrode (Model HI 5412) was used in conjunction with the drug sensor. AWPA pH combined glass electrode Model CD740 was used for pH measurements. Bandelin sonorex, RK 510S, magnetic stirrer and a silver wire (1mm diameter) immersed in the internal solutions were also applied.

2.2. Reagents

All chemicals and reagents used were of analytical reagent grade, and water was bi-distilled. Polyvinyl chloride (PVC), 2-hydroxy β-cyclodextrin and 4-tertary butyl sulfocalix-8-arene were obtained from Fluka (Steinheim, Germany). 2-Nitrophenyl octyl ether (NPOE) and tetrakis(4-chlorophenyl)borate (TpClPB) were purchased from Aldrich (Steinheim, Germany). Tetrahydrofuran (THF) was obtained from BDH (Poole, England). Potassium chloride was obtained from Prolabo (Pennsylvania, USA). Phosphate buffer pH 4 was prepared [1]. Plasma was supplied by VACSERA (Giza, Egypt) and used within 24 h.

2.3. Samples

2.3.1. Pure sample

Moxifloxacin hydrochloride (MO) was kindly supplied by Bayer Schering Pharma AG, Leverkusen, Germany. Its purity was found to be 100.45±0.84 according to the BP HPLC method [1].

2.3.2. Pharmaceutical dosage form

Avalox® film coated tablets (Bayer Schering Pharma AG, Leverkusen, Germany) batch no. BXG0DH1. Each film coated tablet claimed to contain 436.8 mg of moxifloxacin hydrochloride equivalent to 400 mg of free moxifloxacin.

2.4. Prepared solutions

All calculations were done regarding moxifloxacin free base.

2.4.1. Stock standard solutions
MO stock solution \((10^{-2} \text{ mol L}^{-1})\) in either water or phosphate buffer pH 4 was prepared by transferring 0.4379 g of moxifloxacin hydrochloride (equivalent to 0.4014 g of MO free base) into two separate 100 mL measuring flasks. Fifty milliliters of either water or phosphate buffer pH 4 were added and shaking was done for few minutes and the volume was completed with the same solvent.

2.4.2. Working standard solutions

MO working solutions \((10^{-6}-10^{-3} \text{ mol L}^{-1})\) were prepared by suitable dilution from its stock solution using either water or phosphate buffer pH 4.

2.4.3. Laboratory-prepared mixtures

A volume of 2.5 mL of MO stock solution \((10^{-2} \text{ mol L}^{-1})\) was transferred accurately into a series of 25 mL measuring flasks. Aliquots from its alkaline degradation product \((10^{-2} \text{ mol L}^{-1})\) solution were added to prepare mixtures containing 10-80% degradation product.

2.5. Procedures

2.5.1. Fabrication of membrane sensors

For the preparation of sensor 1, 400 mg NPOE was mixed with 50 mg TpClPB and 190 mg PVC in a 5 cm Petri dish. The mixture was dissolved in 6 mL THF. Fifty milligrams of 2-hydroxy β-cyclodextrin or 50 mg 4-tertarybutylsulfocalix-8-arene were added to the previous components for the preparation of sensors 2 and 3, respectively. The Petri dishes were covered with filter paper and left to stand overnight at room temperature to allow solvent evaporation.

Master membranes 0.1 mm in thickness were obtained. From each master membrane, a disk (about 8 mm in diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of an electrode glass body. The electrodes were then filled with an internal solution of equal volumes of \(10^{-2} \text{ mol L}^{-1}\) MO and \(10^{-2} \text{ mol L}^{-1}\) KCl. Ag/AgCl wire (1 mm diameter) was used as an internal reference electrode. The sensors were conditioned by soaking in \(10^{-2} \text{ mol L}^{-1}\) aqueous MO solution for 24 h, and they were stored in the same solution when not in use.

2.5.2. Sensors calibration

The conditioned sensors were calibrated by separately transferring 50 mL aliquots of solutions \((10^{-6} \text{ to } 10^{-2} \text{ mol L}^{-1})\) of MO into a series of 100 mL beakers. The membrane sensors, in conjunction with single junction calomel reference electrode, were immersed in the above test solutions and allowed to equilibrate while stirring. The potential was recorded
after stabilizing to ±1 mV, and the electromotive force was plotted as a function of the negative logarithm of MO concentration.

2.5.3. Effect of pH

The effect of pH on the potential values of the three electrode systems was studied over a pH range of 1–12 at 1-pH interval by immersing the electrodes in \(10^{-3}\) and \(10^{-4}\) mol L\(^{-1}\) MO solutions. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

2.5.4. Sensors selectivity

The potentiometric selectivity coefficients \(K_{\text{pot MO,I}}\) of the proposed sensors towards different substances were determined by a separate solution method using the following equation (Eq. 1) [22]:

\[
-log(K_{A,B}^{\text{pot}}) = \frac{E_1 - E_2}{2.303 \frac{RT}{Z_A F}} + \left(1 - \frac{Z_A}{Z_B}\right) \log a_A
\]  

(1)

where \(K_{A,B}^{\text{pot}}\) is the potentiometric selectivity coefficient, \(E_1\) is the potential measured in \(10^{-3}\) mol L\(^{-1}\) MO solution, \(E_2\) is the potential measured in \(10^{-3}\) mol L\(^{-1}\) interferent solution, \(Z_A\) and \(Z_B\) are the charges of MO and interfering ion, respectively, \(a_A\) is the activity of the drug and \(2.303RT/Z_A F\) represents the slope of the investigated sensors (mV/concentration decade).

2.5.5. Determination of MO in its pharmaceutical formulation

A portion of Avalox\textsuperscript{®} powdered tablets equivalent to 20.07 mg MO free base was transferred into 50-mL volumetric flasks and extracted with phosphate buffer solution pH 4 then the volume was completed with the same solvent. The concentration of the prepared samples was \(10^{-3}\) mol L\(^{-1}\). The potentiometric measurements were performed using the proposed sensors in conjunction with single junction calomel reference electrode, and the potential readings were compared to the calibration plots.

2.5.6. Determination of MO in the presence of its alkaline degradate

A degraded sample of MO was prepared by adding 25 mL NaOH (2 mol L\(^{-1}\)) to 10 mL drug solution (\(10^{-2}\) mol L\(^{-1}\)) and refluxing for 1 hr. The resulting solution was tested for complete degradation by the thin layer chromatography technique using butanol: methanol: \(\text{NH}_3\) (6:1:2 by volume) as a mobile phase and detecting the spots at 254 nm. The degraded
solution was neutralized, transferred quantitatively into a 100-mL volumetric flask and brought to volume with water. Aliquots of standard drug solution ($10^{-3}$ mol L$^{-1}$) were mixed with its degraded sample ($10^{-3}$ mol L$^{-1}$) in different ratios. The emf values of these laboratory-prepared mixtures were recorded and results were compared with the calibration plot.

2.5.7. Determination of MO in plasma

One millilitre of each of $10^{-2}$ and $10^{-3}$ mol L$^{-1}$ standard drug solution were added separately into two 20-mL stoppered shaking tubes each containing 9 mL of plasma and the tubes were shaken for 1 min. The membrane sensors were immersed in conjunction with the reference electrode in these solutions and then washed with water between measurements. The emf produced for each solution was measured by the proposed sensors, and the concentration of MO was determined from the corresponding regression equation.

3. RESULTS AND DISCUSSION

The development and application of ion-selective electrodes (ISEs) continue to be of interest for pharmaceutical analysis because these sensors offer the advantages of simple design and operation, fast response, reasonable selectivity, low detection limit, high accuracy, wide concentration range applicability to colored and turbid solutions, and possible interfacing with automated and computerized systems [23].

The molecular recognition and inclusion complexation are of current interest in host-guest and supramolecular chemistry and offer a promising approach to chemical sensing [24, 25]. The use of selective inclusion complexation and complementary ionic or hydrogen bonding are two main strategies for preparing synthetic host molecules that recognize the structure of guest molecules [26].

Modified cyclodextrins (CDs), either natural or synthetic, are viewed as molecular receptors, as is shown in Fig. 2. In the case of natural CD, cooperative binding with certain guest molecules was mostly attributed to intermolecular hydrogen bonding between the CD molecules, while intermolecular interactions between the host and guest molecules (hydrogen bonds, hydrophobic interactions and Van der Waals forces) contributed to cooperative binding processes when synthetic CDs were used [27]. Although the size and geometry of the guest mainly govern the binding strength, it is possible to influence the host-guest interactions by modifying the three hydroxyl groups on each glucose unit. Indeed, the use of 2-hydroxy propyl β-cyclodextrin enhanced the interaction properties between host and guest molecules [28].

Calixarenes are well-known as selective ligands for various ions through dipole-dipole interactions, as shown in Fig. 2. They can complex with a large variety of cation substrates to
form stable host–guest inclusion complexes. This property of calixarenes has been largely exploited for the development of a number of cation-selective electrodes [29–31].

The present work evaluates the possibility of using 2-hydroxy propyl β-cyclodextrin and 4-tertary butyl sulfo-calix-8-arene as sensor ionophores in the preparation of MO-selective electrodes 2 and 3, respectively, using PVC as a polymeric matrix to immobilize the sensors and to attain the formation of highly stable complexes.

Fig. 2. Toroidal shape of (A) 2-hydroxy propyl β-cyclodextrin molecule and (B) 4-sulfo-calix[8]arene molecule

3.1. Performance characteristics of MO sensors

The positive MO ion prefers the high donation sites (OH-groups and sulphonate acid) of 2-hydroxy propyl β-cyclodextrin and calixarene structures rather than the methyl groups. Thus, in the absence of ionophores in sensor 1, the lowest slope value is found accompanied by the highest selectivity coefficient values. A higher selectivity coefficient value corresponds with more attack by interfering cations on the electrode membrane. The presence of OH-groups only in sensor 2 was not enough to perform the proper chelation, which was demonstrated by a slope of 51.50 mV/decade and the high selectivity coefficient values compared to sensor 3. The sulphonated calix[8]arene-based sensor 3 shows the best near nernstian slope (52.10 mV/decade) and selectivity coefficient values. The host-guest complex is stabilized via an electrostatic interaction between the cationic MO and anionic sulphonated calix[8]arene. Moreover, calix[8]arene has a larger internal cavity size (9.5 Å) [32] than 2-hydroxy propyl β-cyclodextrin (6 Å) [33]. This allows the drug to fit well in the calixarene cavity and strongly bond to the calixarene donation sites. The results reveal that, as ionophores, 2-hydroxy propyl β-cyclodextrin and calix-8-arene provide high stability to the complexes formed with cationic drug present in solution; thus, the membrane selectivity and sensitivity are substantially enhanced. The electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards [22].
Fig. 3. Profile of the potential in mV versus –log concentrations of MO in mol L\(^{-1}\) obtained with sensors 1, 2 and 3

Table 1. Electrochemical response characteristics of the three investigated M sensor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensor 1</th>
<th>Sensor 2</th>
<th>Sensor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope (mV/decade)(^a)</td>
<td>49.79</td>
<td>51.50</td>
<td>52.10</td>
</tr>
<tr>
<td>Intercept (mV)</td>
<td>299.74</td>
<td>315.35</td>
<td>328.6</td>
</tr>
<tr>
<td>LOD (mol L(^{-1}))(^b)</td>
<td>3.1\times10(^{-6})</td>
<td>6.8\times10(^{-6})</td>
<td>8.4\times10(^{-6})</td>
</tr>
<tr>
<td>Response time (s)</td>
<td>30</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Working pH range</td>
<td>2–5</td>
<td>2–5</td>
<td>2–5</td>
</tr>
<tr>
<td>Concentration Range (mol L(^{-1}))</td>
<td>10(^{-5}) to 10(^{-2})</td>
<td>10(^{-5}) to 10(^{-2})</td>
<td>10(^{-5}) to 10(^{-2})</td>
</tr>
<tr>
<td>Stability (days)</td>
<td>25</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Average recovery (%)</td>
<td>100.05±0.67</td>
<td>99.97±0.42</td>
<td>100.02±0.35</td>
</tr>
<tr>
<td>± S.D.(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.9998</td>
<td>0.9999</td>
<td>0.9999</td>
</tr>
</tbody>
</table>

\(^a\) Average of five determinations
\(^b\) Limit of detection (measured by interception of the extrapolated arms of Fig. 3)

Table 1 shows the results obtained over a period of two months for two different assemblies of each sensor. Typical calibration plots are shown in Fig. 3. The slopes of the calibration plots are 49.79, 51.50 and 52.10 mV/concentration decade for sensors 1, 2 and 3, respectively. Deviation from the ideal near nernstian slope (60 mV) is due to the electrodes responding to the activity of the drug cation rather than its concentration. The sensors displayed constant potential readings for day to day measurements, and the calibration slopes
did not change by more than ±2 mV/decade over a period of 25, 45 and 50 days for sensors 1, 2 and 3, respectively. The detection limits of the three sensors were estimated according to the IUPAC definition [22].

3.2. Dynamic response time

Dynamic response time is an important factor for analytical applications of ion-selective electrodes. In this study, practical response time was recorded by increasing MO concentration by up to 10-fold. The required time for the sensors to reach values within ±1 mV of the final equilibrium potential was 30, 15 and 10 s for sensors 1, 2 and 3, respectively.

3.3. Effect of pH and temperature

For quantitative measurements with ion selective electrodes, studies were carried out to reach the optimum experimental conditions. The potential pH profile obtained indicates that the responses of the three sensors are fairly constant over the pH range 2-5, Fig. 4. Therefore, the pH range from 2 to 5 was assumed to be the working pH range of the three sensors.

The results suggest that the electrodes exhibit a slight increase in their potential as the temperature rises in the range of 20-35°C. However, the calibration plots obtained at different temperatures are parallel, and the limit of detection, slope and response time do not significantly vary with temperature indicating reasonable thermal stability of PVC membranes up to 35°C.

![Fig. 4. Effect of pH on the response of sensors 1, 2 and 3](image-url)
3.4. Sensors selectivity

Table 2 shows the potentiometric selectivity coefficients of the proposed sensors in the presence of degradates and some other inorganic cations (K\(^+\), Na\(^+\), NH\(_4\)^+, Mg\(^{2+}\), and Ca\(^{2+}\)) that are usually found in biological fluids. The results reveal that the proposed membrane sensors display high selectivity and that sensors 2 and 3 are at least 10-100 times more selective than sensor 1. Sensor 3 displays higher selectivity and lower response for the potentially interfering species than sensor 2. This can be attributed to the preferential interaction between the MO cation and very polar sulphonylic acid groups present in the calix[8]arene structure.

Table 2. Potentiometric selectivity coefficients (K\text{pot}_{\text{MO},i}) of the three proposed sensors using the separate solutions method (SSM) [22]

<table>
<thead>
<tr>
<th>Interfering substance</th>
<th>Selectivity coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensor 1</td>
</tr>
<tr>
<td>Degradate</td>
<td>1.82×10(^{-2})</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>3.86×10(^{-2})</td>
</tr>
<tr>
<td>K(^+)</td>
<td>3.71×10(^{-2})</td>
</tr>
<tr>
<td>NH(_4)^+</td>
<td>3.54×10(^{-2})</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>3.70×10(^{-2})</td>
</tr>
<tr>
<td>Mg(^{2+})</td>
<td>2.16×10(^{-2})</td>
</tr>
<tr>
<td>Ca(^{2+})</td>
<td>3.50×10(^{-2})</td>
</tr>
<tr>
<td>Fe(^{3+})</td>
<td>4.63×10(^{-2})</td>
</tr>
<tr>
<td>Glycine</td>
<td>4.09×10(^{-2})</td>
</tr>
<tr>
<td>glucose</td>
<td>3.67×10(^{-2})</td>
</tr>
<tr>
<td>Lactose</td>
<td>3.52×10(^{-2})</td>
</tr>
<tr>
<td>Starch</td>
<td>3.33×10(^{-2})</td>
</tr>
<tr>
<td>Urea</td>
<td>2.24×10(^{-2})</td>
</tr>
</tbody>
</table>

3.5. Potentiometric determination of MO in pharmaceutical formulation

The proposed sensors were applied for the analysis of MO pharmaceutical formulation. The results prove the applicability of the three sensors for the determination of pharmaceutical formulation containing MO, Table 3. To examine the validity of the proposed sensors, the obtained results were compared to those of the BP HPLC method [1] and no significant difference was observed. Moreover, the proposed sensors do not require preliminary drug extraction as described in the official method.
Table 3. Determination of MO in Avalox® tablet by the proposed electrodes and the official method [1]

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Recovery (%) ± S.D.° of MO</th>
<th>Sensor 1</th>
<th>Sensor 2</th>
<th>Sensor 3</th>
<th>Official methodb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avalox® tablet (batch no. BXG0DH1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>101.18±0.68</td>
<td>100.21±0.42</td>
<td>100.60±0.31</td>
<td>100.85±0.55</td>
<td></td>
</tr>
</tbody>
</table>

° Average of five determinations.

b BP HPLC method.

The values in parentheses are the corresponding theoretical values for t and F at P = 0.05

3.6. Potentiometric determination of MO in the presence of its alkaline degradate

Complete degradation of MO was induced by boiling with 2 mol L⁻¹ NaOH for 1 hr. Fig. 5 shows the suggested alkaline degradation of the drug. The induced alkaline degradation was tested by TLC, and complete separation, with Rf values of 0.45 for MO and 0.35 for its degradation product, was obtained. Table 4 shows the results obtained upon analysis of synthetic mixtures containing different ratios of intact drug and degraded sample varying from 100:0 to 30:70, intact MO: degradant, respectively. The results show that the sensors can be successfully used for selective determination of intact drug in the presence of >70% of its degradate. Thus, these sensors are recommended for use in stability-indicating methods.

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

<table>
<thead>
<tr>
<th>Ratio (%) drug:degradate</th>
<th>Drug recovery (%) ± S.D.°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensor 1</td>
</tr>
<tr>
<td>100:0</td>
<td>100.07±0.62</td>
</tr>
<tr>
<td>90:10</td>
<td>97.54±0.52</td>
</tr>
<tr>
<td>70:30</td>
<td>96.02±0.83</td>
</tr>
<tr>
<td>50:50</td>
<td>95.89±0.24</td>
</tr>
<tr>
<td>30:70</td>
<td>99.92±0.98</td>
</tr>
</tbody>
</table>

° Average of three determinations
Fig. 5. Suggested degradation pathway for moxifloxacin by sodium hydroxide

3.7. Potentiometric determination of MO in plasma

The results obtained for the determination of MO in spiked human plasma show that a wide concentration range of the drug can be determined by the investigated sensors with high precision and accuracy. The results presented in Table 5 show that sensors 2 and 3 are more sensitive than sensor 1 in plasma samples.

The response times of the proposed sensors are instant (within 15 s), so the sensors are rapidly transferred back and forth between the biological samples and the deionized bi-distilled water between measurements to protect the sensing component from adhering to the surface of some matrix components. It is concluded that the proposed sensors can be successfully applied to in vitro studies and for clinical use.
Table 5. Determination of MO in spiked human plasma by the proposed sensors

<table>
<thead>
<tr>
<th>Concentration [mol L(^{-1})]</th>
<th>Recovery (%) ± S.D.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensor 1</td>
</tr>
<tr>
<td>1×10(^{-3})</td>
<td>103.75±2.13</td>
</tr>
<tr>
<td>1×10(^{-4})</td>
<td>104.14±2.42</td>
</tr>
</tbody>
</table>

\(^a\) Average of three determinations

4. CONCLUSION

The described sensors are sufficiently simple and selective for the quantitative determination of MO in pure form, pharmaceutical formulation, in the presence of its degradate and in plasma. The use of 2-hydroxy propyl β-cyclodextrin and sulphonated calix-8-arene as ionophores increased the membrane sensitivity and selectivity of sensors 2 and 3 in comparison with sensor 1. The proposed sensors offer advantages of fast response and elimination of drug pre-treatment or separation steps. They can therefore be used for routine analysis of MO in quality-control laboratories.

REFERENCES