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Cyclodextrin-Based Potentiometric Sensors for *Metformin*

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Abstract: β-Cyclodextrins (β-CDs) based polyvinylchloride (PVC) electrodes were fabricated and applied for potentiometric determination of *Metformin* (Mf). Matrix composition optimization was done referring the effect of type and content of β-CDs, anionic sites and plasticizer. Electrodes incorporated with 2-hydroxypropyl-β-CD as sensing ionophore, sodium tetrakis (4-florophenyl) borate (NaTFPB) as anionic site and *o*-nitrophenyloctyl ether (*o*-NPOE) as electrode plasticizer showed the best electroanalytical performances. The fabricated electrodes worked satisfactorily in the concentration range from 10^{-6} to 10^{-2} mol L^{-1} with detection limit reaching 7×10^{-6} mol L^{-1} and fast response time of 8 s. The developed sensors possessed improved selectivity and have been successfully applied for the potentiometric determination of Mf in pharmaceutical formulation. Comparison of the obtained results with those provided by reference method revealed adequate accuracy for control assay.

Keywords: Potentiometric sensors; Cyclodextrins; *Metformin*; Pharmaceutical analysis.

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Introduction

GLUCOPHAGE, METFORMIN 0.5, CIDOPHAGE (500 mg *Metformin* hydrochloride tablets) and GLUCOPHAGE. XR, CIDOPHAGE RETARD (850 mg *Metformin* hydrochloride extended - release tablets) is used as the so-called anti-hyperglycemic drugs for the patient with the diabetes type 2 [1].

Several methods have been reported for the determination of *Metformin* (Mf) in pharmaceutical dosage forms and in biological fluids including HPLC [2,3], GLC [4], capillary electrophoresis [5], near infrared spectroscopy [6], UV spectrophotometry [7,8], conductometry [9], voltammetry [10], or by visual titration [11].

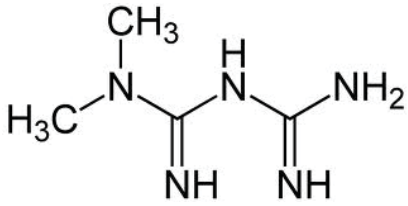

Fig. 1: *Structural formula of Metformin (Mf).*

Chemical sensors and biosensors are shown to offer alternative solutions, capable of satisfying the increasing demand for precise analytical information at lower cost through devices that require relatively simple instrumentation. Ideally, a sensor-based system needs only little, if any, pre-treatment of the sample and possible interfacing with FIA systems [12-16]. Concerning the potentiometric determination of Mf, PVC membrane electrodes were used for the potentiometric determination of Mf in the pharmaceutical preparations; the mentioned electrodes used ion pairs formed between Mf with tetraphenylborate, phosphomolybdate, reineckate or tungstosilicate as electroactive material [8,17,18]. Mf PVC and carbon paste electrode (CPEs) fabricated by formation of the ion pair in situ, soaking of the electrode in the ion pair aqueous solution, in addition to the classical modification of the electrode matrix with the ion pair, were also suggested [19]. Ion-pairs based electrodes are plagued by limited selectivity, thus their application are restricted to more challenging matrices and more selective molecular recognition component is clearly required.

The beauty of electrochemical techniques is to utilize a chemically modified electrode (CME) tailor made, for improved sensitivity and selectivity of the analytical applications [20-22]. Different types of ionophores such as crown ethers, calixarenes, cyclodextrins (CDs) or prophorines have been proposed; however, CDs were by far the most commonly used. CDs are naturally occurring macrocyclic oligosaccharides formed of 1,4-glucosidic bond linked D (+) glucopyranose oligomers of 6, 7, and 8 glucose units yielding α-, β-, and γ-CD, respectively, with toroidal three-dimensional cage configuration [23-25]. Due to the presence of primary and secondary hydroxyl group pointing outside the cavity, the exterior surface is hydrophilic whereas the interior surface, lined with C-H groups and ether-liked oxygen atoms, is hydrophobic. CDs can form inclusion complexes with different types of guests without the formation of chemical bonds or changing their structure [26] where the binding forces associated with the inclusion formation are attributed to number of factors, such as

hydrophobic forces, hydrogen bonding, size of the cavity, shape of the guest molecule and electrostatic interaction. Such unique properties introduced CDs as a sensing material in potentiometric sensors for many pharmaceutically important drugs [27,34].

In the present work, simple potentiometric PVC electrodes applying β-CDs as a sensing material, have been characterized and optimized for rapid, accurate, and low cost quantification of Mf. The fabricated sensors were subjected to a series of special tests in order to select the sensor possessing the most favorable electroanalytical characteristics for potentiometric determination of Mf.

Experimental

Reagents

All reagents were of the analytical grade, purchased form Sigma, Aldrich, or Fluka (if not stated otherwise) and doubly distilled water was used throughout the experiments. β-CDs derivatives including heptakis(2,6-di-*o*-methyl)-β-CD (I), 2-hydroxypropyl-β-CD (III), heptakis(2,3,6-tri-*o*-methyl)-β-CD (II), and native β-CD (IV) were used as sensing ionophores. Sodium tetraphenylborate (NaTPB), sodium tetrakis(4-fluorophenyl)borate (NaTFPB) or potassium tetrakis(4-chloro-phenyl)borate (KTCPB) were used as anionic sites. 2-Fluorophenyl 2-nitrophenyl ether (*f*-PNPE), *o*-nitrophenyloctylether (*o*-NPOE), dibutylphthalate (DBP), dioctylphthalate (DOP, BDH), dioctyl-sebacate (DOS, Avocado) and tricresylphosphate (TCP, Fluka) were used as membrane plasticizer.

Authentic Samples

Authentic metformin hydrochloride ($C_4H_{11}N_5$, HCl, M.W.165.6 g mol^{-1}) sample was supplied by the CID co. Egypt. Contents of Mf were assigned to be 98.23%. Stock drug solution (10^{-1} mol L^{-1}) was prepared by dissolving the appropriate amount of Mf in bidistilled water and kept at 4 ^{o}C.

Pharmaceutical Preparations

CIDOPHAGE, 500 and 850 mg, were purchased from local drug stores. Ten CIDOPHAGE (either 500 or 850 mg) tablets were weighed and grinded to finely divided powder. An accurate weight of the powder containing 500 mg Mf was mixed with 50 mL doubly distilled water, stirred well with a magnetic stirrer then filtered into 100 mL volumetric flask and analyzed according to the official methods with purity 95.71 and 94.68 % respectively [35].

Electrochemical Apparatus and Other Instrumentation

Potentiometric measurements were carried out using a 692-pH meter (Metrohm, Herisau, Switzerland, Art. no. 1.691.00100) with Ag/AgCl double-junction reference electrode (Metrohm, Art. no. 6.0726.100) and a combined pH glass electrode (Metrohm, Art. no. 6.0202.100).

Procedures

Sensor Construction

Electrode matrix cocktail composed of 2.5 mg β-CD (II), 2.75 mg NaTFPB, 360 mg *f*-NPOE, 240 mg PVC and 6 mL THF was poured in a Petri dish (5 cm diameter). After 24 h of slow evaporation of solvent, a master membrane with 0.11mm thickness was obtained. This master sheet was stored in a closed vessel at 4 ^{o}C. One end of a PVC tube (ID 1cm) was softened by immersion in THF for 1 min and a 2 cm diameter disk piece of the PVC membrane was mounted on the softened end of the PVC tubing with the help of adhesive solution prepared by dissolving PVC in THF. The PVC closed tube with the membrane was filled with 10^{-2} mol L^{-1} KCl and 10^{-2} mol L^{-1} Mf solution using Ag/AgCl as internal reference electrode and conditioned in 10^{-3} mol L^{-1} Mf for 24 h.

Sensor calibration

The electrodes were calibrated by transferring 25 ml aliquots of 10^{-6}-10^{-1} mol L^{-1} Mf solutions into a 50 mL double jacket thermostated glass cell at 25 ^{o}C followed by immersing the ISE for each drug in conjugation with Ag/AgCl double junction reference electrode in the solution. The potentials were recorded after stabilization and plotted against concentration in the logarithmic scale (-log [Mf]).

Electrode Response Time

The dynamic response time of the electrode was tested by measuring the time required to achieve a steady state potential (within ±1 mV) after successive immersion of the electrode in a series of drugs solutions, each having a 10-fold increase in concentration from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} [36].

Potentiometric Determination of Mf in Pharmaceutical Preparations

Mf was potentiometrically determined in pure solution and pharmaceutical preparations using the developed electrodes by potentiometric titration and standard addition method. For potentiometric titration, aliquots of the sample solutions containing 1.3 – 9.1 mg Mf were titrated against standardized NaTPB solution. The titration process was monitored using Mf sensor in conjugation with the conventional Ag/AgCl reference electrode and the potential values were plotted against the titrant volume to estimate the end point.

In the standard addition method, known increments of 10^{-2} mol L^{-1} standard Mf solution were added to 25mL aliquot of sample solution where the change in the potential readings was recorded for each increment and used to calculate the concentration of Mf in sample solution.

Results and Discussion

Cyclodextrins as Sensing Ionophores

The response of ionophore-based potentiometric sensors is usually governed by the molecular recognition ability between the analyte (guest) and the host molecule. The most important property of CDs is their ability to form supramolecular (inclusion) complexes with many appropriately sized organic ions and molecules, where the driving forces for the complexation are non-covalent, including van der Waals forces and directed hydrogen bonding. Inclusion complexes of Mf with β-CD were prepared and characterized [37,38] which devote the research team to apply CD as sensing material in Mf potentiometric sensor.

Optimal Sensor Matrices Compositions

Due to the critical role of the matrix composition on the electrode performance, the influence of the nature and amount of cyclodextrin, ionic additives and plasticizer, were tested in details to select the optimal electrode possessing the best sensitivity and selectivity towards Mf.

Effect of Sensing Material

Preliminary experiment declared that electrodes fabricated without incorporation of CD showed non-significant response towards Mf, while those modified with different CDs gave Nernstian responses with different slope values, demonstrating the crucial rule of the ionophore on the electrode response (Fig. 2a). Selection of the sensing ionophore was not restricted to higher response only, but also extends to the reproducibility of the potential readings through long time period. Sensors modified with β-CD (II) showed more stable Nernstian response during an operation period of 2 weeks (average slope was 64.2±4.2 mV decade^{-1}), while the slope values of sensors modified with ionophores III and IV decreased significantly after 5 days of operation (25.3±4.5 mV decade^{-1}).

On constructing an ISE, the amount of the sensing material in the electrode matrix should be sufficient to obtain reasonable complexation at the electrode surface that is responsible for the electrode potential. If such ionophore is present in excess, over-saturation occurs in the network hindering the complexation process leading to unsatisfactory measurements. β-CD (II) content in the fabricated electrode matrices was varied from 1 to 15 mg, incorporation of 2.5 mg of the aforementioned ionophore was sufficient to the proper performance of the sensor (slope values were 62.5±1.8 mV decade^{-1}).

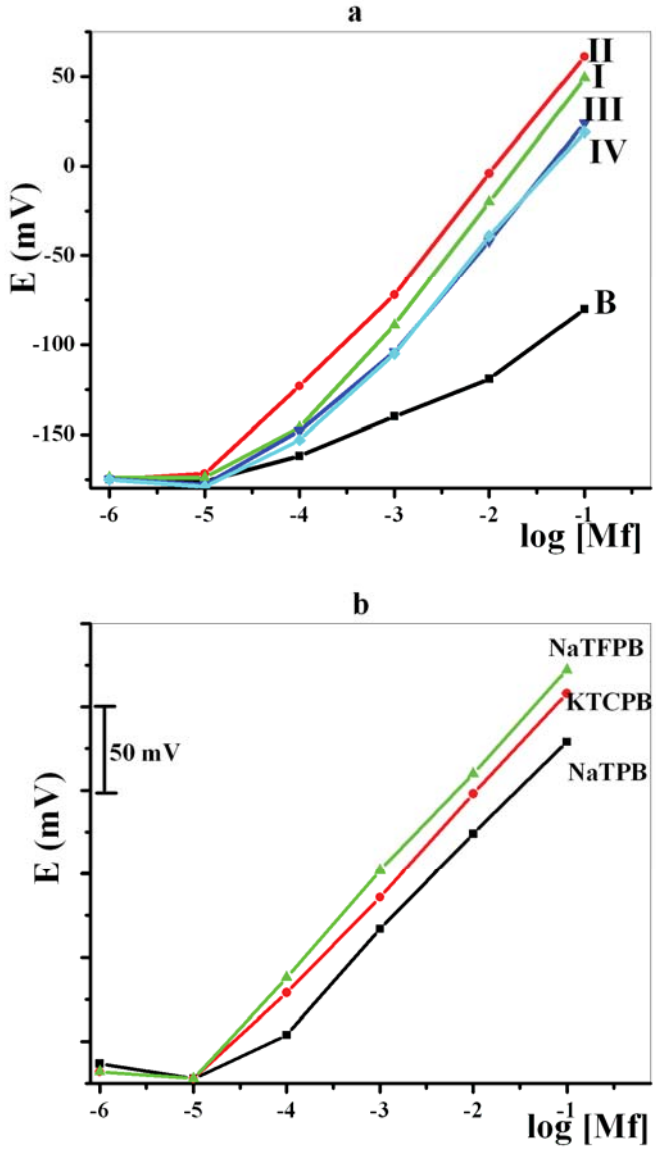

Fig. 2: *Effect of a) β -CD and b) anionic sites nature on Mf- sensor performance.*

Effect of Anionic Sites

It is well known that lipophilic ionic sites promote the interfacial ion-exchange kinetics and decrease the bulk resistance by providing mobile ionic sites in the electrode matrix [39,40]. β-CDs behave as neutral carrier ionophores and their ISEs functional only when anionic sites are incorporated. Different tetraphenylborate derivatives were tested and addition of NaTFPB

to the electrode matrix exhibited the highest slope value (Fig. 2b) compared with NaTPB or KTCPB salt. Furthermore, the content of NaTFPB was changed from 0 to 7 mg and addition 2.75 mg was selected.

Effect of Membrane Plasticizer

Sensitivity and selectivity obtained for a given ionophore based ion-selective electrode is greatly influenced by the polarity of the electrode matrix, which is defined by the dielectrical constant of the electrode plasticizer [41,42]. It should be noted that the nature of the plasticizer affects not only the polarity of the electrode phase but also the mobility of ionophore molecules and the state of the formed complexes. The influence of the plasticizer on the performance of Mf sensors modified with β-CD (II) and NaTFPB as ionic sites was studied using six plasticizers having different dielectric constant, namely; *f*-NPOE, *o*-NPOE, TCP, DOS, DBP and DOP (ε = 50, 24, 17.6, 5.2, 4.7 and 3.8, respectively). Plasticizer selection was crucial for appropriate sensor performance, as application of the less polar plasticizers decreased the sensitivity which might be attributed to less solvation of the ionophore and the formed Mf-β-CD complex. Higher sensitivity was observed for electrodes containing high polar, *f*-NPOE (Nernstian slope was 57.1±0.8 mV decade^{-1}), while other tested plasticizer gave less sensitive electrodes with lower Nernstian slopes (Fig. 3a). Moreover, the content of the selected plasticizer within the electrode matrices was varied; from different tested ratios, 1:1.5 PVC:*f*-NPOE was the best indicated by the highest Nernstian slope and lowest detection limit (Fig. 3b).

Sensor Performances

The potentiometric response characteristics of the developed sensors, at the optimal matrices compositions, were evaluated according to the IUPAC recommendation. The fabricated sensor displayed Nernstian cationic responses towards Mf (Fig. 4). Data obtained indicated that the developed sensors can be successfully applied for the potentiometric determination of Mf in the concentration range from 10^{-5} to 10^{-1} mol L^{-1} and the measured LOD was 7×10^{-6} mol L^{-1} with Nernstian slope 57.1±0.8 mV decade^{-1}.

For analytical applications, the sensor response time is of critical importance; therefore, the dynamic response times of the fabricated sensors were tested (Fig. 4). The response time was fast as about 8 s. In addition, the lifetimes of the fabricated electrodes were tested by performing day-to-day calibration.

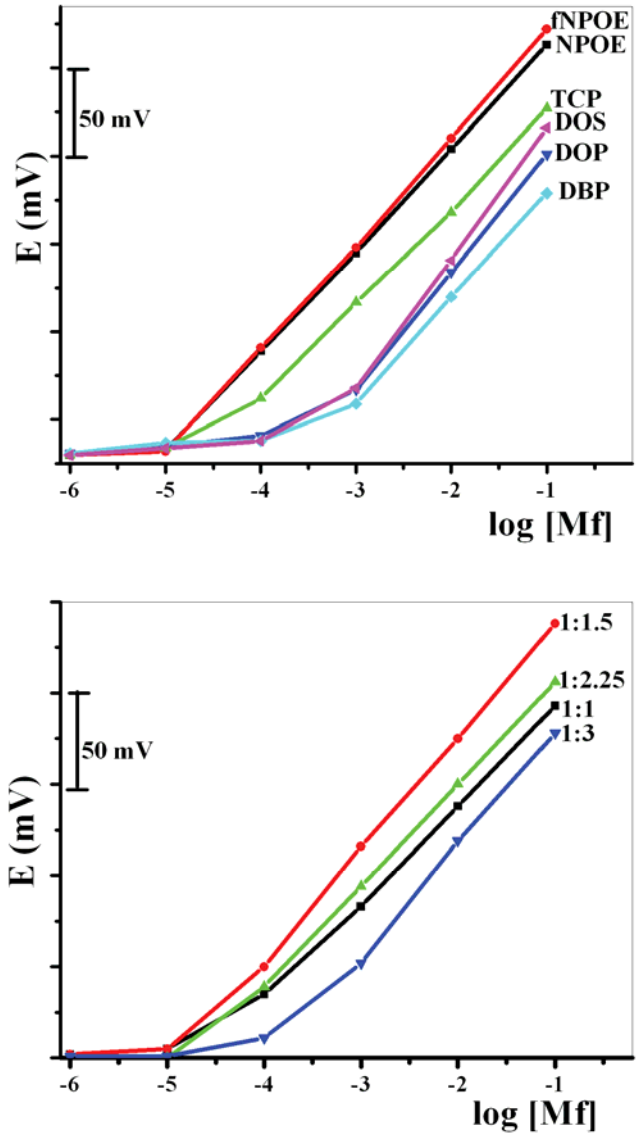

Fig. 3: *Effect of the plasticizer nature and content on Mf-β-CD-based sensor.*

PVC electrodes showed useful lifetime of 21 days during which the Nernstian slopes did not change significantly (±2 mV/decade), while the detection limit was shifted from 10^{-5} to 10^{-4} mol L^{-1} at the end of this period.

The selectivity of the prepared Mf sensors was tested towards different species using Matched Potential Method (MPM) as recommended by IUPAC [43].

The results (not shown) revealed a high selectivity toward Mf in the presence of other interferents, additives, and fillers commonly introduced in pharmaceutical formulations (such as glycine, caffeine, citrate, maltose, sucrose, and starch) as well as inorganic cations.

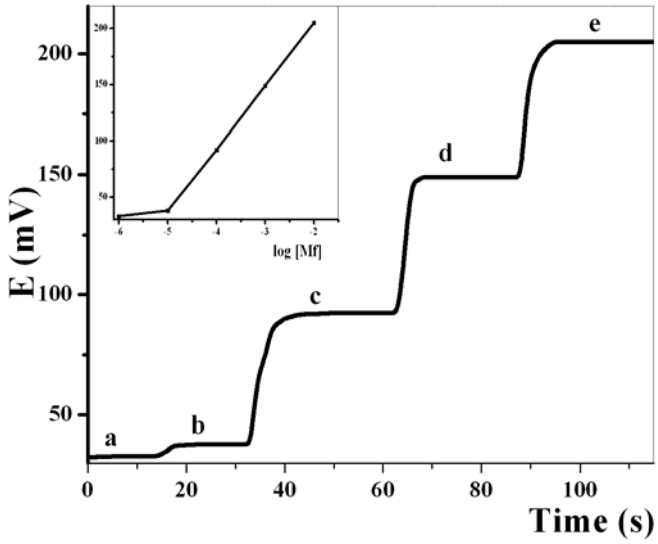

Fig. 4: *Dynamic response of DXM sensors:* a) 1×10^{-6}, b) 1×10^{-5}, c) 1×10^{-4}, d) 1×10^{-3}, and e) 1×10^{-2} mol L^{-1} Mf.

Potentiometric Titration

In addition to the direct potentiometric determination of Mf, the fabricated electrodes were used as indicator electrodes in potentiometric titration of Mf with NaTPB. Under the optimum conditions, titration curves were symmetrical (Fig. 5) with well-defined potential jumps (ΔE ranged from 100 to 170 mV) allowing the determination of 1.3 mg Mf.

Analytical Applications

The proposed electrodes were successfully employed for the assay of Mf in their authentic samples as well as pharmaceutical formulations applying standard addition and potentiometric titration methods. The results have clearly indicated satisfactory agreement between the contents of Mf in different samples determined by the sensor developed and with the aid of the official method (see Table I).

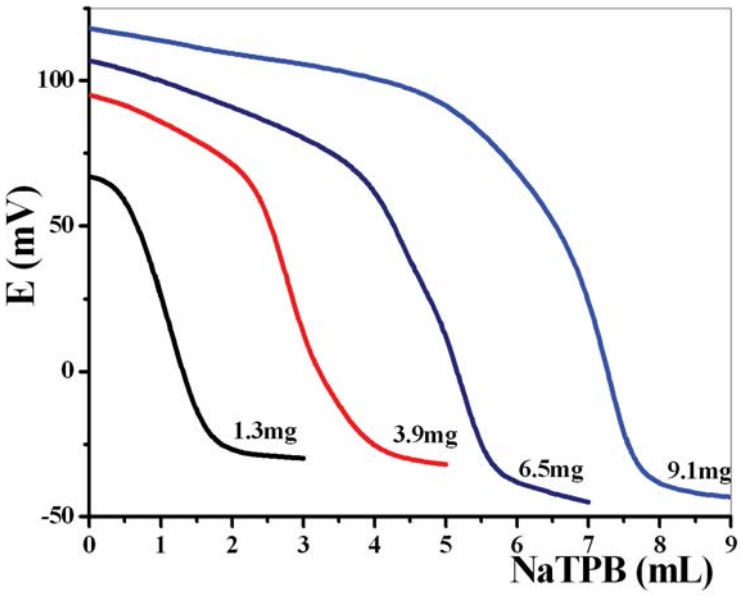

Fig. 5: *Potentiometric titration of Metformin with 10^{-2}M NaTPB using β-CD-modified PVC sensor.*

Table I: *Potentiometric determination of MF in pharmaceutical preparations*

	Taken (mg)	Found			
		Potentiometric Titration		***Standard Method***	
		Recovery*	RSD* (+/–)	Recovery	RSD (+/–)
Pure Solution	3.9	96.80	1.3	95.80	1.4
	6.5	98.50	0.8	97.50	1.8
	9.1	97.00	0.7	97.80	2.2
CIDOPHAGE	9.1	95.80	1.3	94.80	2.3
500 mg	18.2	97.20	1.1	96.20	2.1
	36.4	97.00	1.4	95.00	1.9
CIDOPHAGE	13.6	93.60	1.2	91.60	2.0
850 mg	39.0	94.30	1.2	92.30	2.8

* Average recoveries and the relative standard deviations (both in %) for five determinations

Conclusions

The present work demonstrates the fabrication of novel cyclodextrin-based metformin potentiometric sensors. The proposed electrodes showed Nernstian slopes in the concentration range 10^{-5} to 10^{-1} mol L^{-1} with fast response time (8 s) and long operational lifetime. The sensitivity was improved in almost one order of magnitudes compared with those based on Mf-ion pairs as sensing material.

As shown, the electrodes fabricated in laboratories were successfully applied to the potentiometric determination of Mf with high accuracy and precision and can be incorporated in routine analysis for drug quality control.

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