

Novel carbon paste potentiometric sensor based on β -cyclodextrin for determination of levamisole hydrochloride

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Abbreviations: CPS, Carbon paste sensor; DBP, Dibutyl phthalate; LOD, Limit of detection; LR, Linear range; LVM, Levamisole hydrochloride

Abstract

A novel carbon paste sensor (CPS) based on β -cyclodextrin ionophore and NaTPB as an anionic additive was constructed. The sensor exhibited a Nernstian response for levamisole hydrochloride (LVM) over a wide concentration range of 8.1×10^{-6} to 1.0×10^{-2} mole L^{-1} , with a detection limit of 7.2×10^{-7} mol L^{-1} and with a slope value of 55.2 mV/decade. The potentiometric response is not affected by pH in the wide pH range 2-8 and the sensor showed fast dynamic response time 10s. The constructed sensor exhibited adequate selectivity for LVM with respect to a large number of common foreign inorganic cations, sugars, and amino acids. The novel sensor is used successfully as an indicator electrode for performing the potentiometric titration of drug sample solutions against NaTPB as titrant.

Keywords: Potentiometric sensor; Levamisole hydrochloride; β -cyclodextrin; Lipophilic anionic additive; Potentiometric titration

Introduction

In fact, the development and application of potentiometric sensors for pharmaceutical analysis continue to be of interest because these sensors offer the advantage of simple design and operation, selectivity, fast response, applicability to colored and turbid solutions and possible interface with automated and computerized systems. [1, 2] Thus, potentiometric sensors found many applications: in clinical chemistry, environmental protection, water, soil and analytical chemistry in general. [3]

Over the past five decades, carbon paste, i.e., a mixture of carbon powder and pasting liquid has become one of the most popular sensor materials used for the laboratory preparation of various sensors. The sensors properties are ease of preparation and use, renewal of surface, chemical inertness, robustness, response stability, no need of internal solution and suitability for a variety of sensing and detection application.[4-7] A distinct advantage of CPS is their very low ohmic resistance (less than 10 Ω instead of up to M Ω values for polymeric membrane sensors). Thus, experimental work with CPS is more convenient and simpler potentiometers.

Levamisole (LVM) (2, 3, 5, 6-tetrahydro-6-Phenyl imidazole [2, 1-b] thiazole) (Fig. 1) [8] ($C_{11}H_{13}N_2SCL$) belongs to synthetic imidazothiazole derivatives. It is a white to almost white crystalline powder, which is almost odorless and is freely soluble in water. It is quite stable in acid aqueous media but hydrolyzes in alkaline or neutral solutions.

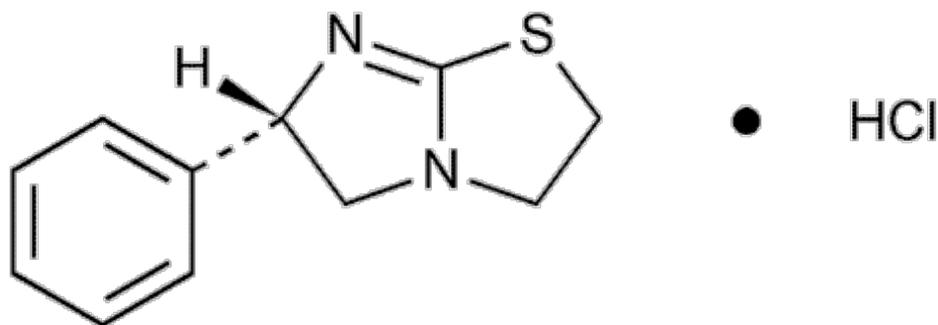


Figure 1: Chemical structure of levamisole hydrochloride

This drug is a broad spectrum anthelmintic drug widely used to control internal parasites in large livestock and occasionally in human medicine.[9] Because LVM acts as an inhibitor of lipid peroxidation, it is also a radio-protectant drug.[10] Also, levamisole is an immunomodulator in different cancer cells including colorectal, breast cancer, melanoma, and leukemia.[11] Besides, it has been shown that levamisole has anti-cancer activity in combination with fluorouracil (5-FU) as adjuvant therapy for colon carcinoma.[12]

Several analytical methods have been reported for the identification of LVM. These analytical techniques including HPLC [13-17], liquid chromatography-mass spectrometry(LC-MS) and LC-MS/MS.[18-21] Also, gas chromatography (GS), gas chromatography-mass spectrometry (GC-MS), thin - layer chromatography (TLC), capillary electrophoresis, atomic absorption, amperometric flow - injection methods and spectrophotometry were reported for LVM analysis.[22-29] However, these methods need expensive instruments as well as laborious and time - consuming extraction procedures.

Therefore, there is a critical need for the development of selective, inexpensive diagnostic tool for the determination of this analyte. Analytical methods based on potentiometric detection with potentiometric sensors can be considered a good alternative for determining levamisole ions.

Sensitivity and selectivity are the most important characteristics of potentiometric sensors. For improvement of these characteristics, functional materials and ligands play an important role in this issue; can act as anchor for the detected materials.[30-33]

β -cyclodextrin (β -CD) is a cyclic oligosaccharide having α -D-glucopyranose molecules. It is a bucket-shaped molecular host capable of forming inclusion complexes as its hydrophobic cavity can accommodate guest molecules of appropriate size. Cyclodextrins are environmentally friendly and allow a slow and sustained release of encapsulated drugs from their cavity. These properties have led to the use of cyclodextrins in pharmaceutical formulations. In addition, cyclodextrins enhance the solubility, stability, and bioavailability of drugs, reduce irritation, prevent incompatibility, and mask the odor of drugs.[30] Thus, CDs can be used as sensor modifiers.[31] Based on the formation of inclusion complexes between CD and LVM, CD can be tested as a sensing ionophore for potentiometric determination of LVM.

Beside electroactive materials, NaTPB is commonly used as a lipophilic anionic additive in potentiometric sensors selective for cations to reduce the membrane resistance, improve the behavior and selectivity and sensitivity sometimes, where the extraction capability is poor.

This has led to increasing interest by our research group in the development and applications of potentiometric sensors for determination of selected drugs. [32-40]

PVC membrane potentiometric sensors based on the ion-pairing agents phosphotungstic acid and phosphomolybdic acid, for determination of levamisole, were reported recently.[41] In line with the same approach, a novel sensor with characteristics that surpass those of these sensors was developed.

The results indicate adequate selectivity of the new sensor. In addition, the detection

limit of the present sensor is smaller ($7.2 \times 10^{-7} \text{ mol L}^{-1}$ vs. $1 \times 10^{-6} \text{ mol L}^{-1}$) and it spans a wider concentration range (8.1×10^{-6} to $1.0 \times 10^{-2} \text{ mol L}^{-1}$ vs 1.0×10^{-2} to $1 \times 10^{-6} \text{ mol L}^{-1}$) of measurements in a short response time (10 sec).

The present work reports the first time of construction, potentiometric characterization and analytical application of a novel levamisole modified carbon paste sensor based on β -cyclodextrin (β -CD) ionophore as electroactive material and dibutyl phthalate (DBP) as plasticizer, and focuses on the use of lipophilic anionic additive (NaTPB) for the development of a sensor used for determination of levamisole hydrochloride.

Experimental

Reagents and materials

All the chemicals used were of analytical grade. Bidi distilled water was used throughout all experiments. Dibutyl phthalate (DBP) was purchased from Merck (Germany). Stock solutions of the metal salts were prepared in bidi distilled water and standardized whenever necessary. Pure-grade levamisole hydrochloride (LVM, Mwt = $240.75 \text{ g.mol}^{-1}$) was supplied by KAHIRA Pharm. & Chem. Ind. Co., Egypt. Standard solution of $10^{-2} \text{ mol L}^{-1}$ levamisole hydrochloride was freshly prepared by dissolving the accurately weighed amount in bidi distilled water. Working solutions of the drug (1.0×10^{-8} – $1.0 \times 10^{-2} \text{ mol L}^{-1}$) were prepared by suitable dilution from the standard solution with bidi distilled water. Solutions of sodium hydroxide and hydrochloric acid of concentrations within the range (0.1–1.0) mol L^{-1} were used for adjusting the pH of the medium.

Apparatus

The electrochemical system of potentiometric sensors may be represented as follows: membrane/test solution/Ag/AgCl double-junction reference electrode. An Ag/AgCl double-junction reference electrode (Metrohm 6.0222.100) was used as the external reference. Potentiometric and pH-measurements were carried out using 702 titroprocessor equipped with a 665 dosimat by (Metrohm, Switzerland). An mLw W20 circulator thermostat was used to control the temperature of the test solutions.

Sensor Construction

The CPS sensor was prepared by mixing the required amount of the ionophore with graphite powder and plasticizer in a mortar until it was uniformly wetted. The ready-prepared paste is then packed into the hole of the sensor body. A fresh surface was obtained by gently pushing the stainless steel screw forward and polishing the new carbon paste surface with a weighing paper to obtain a shiny new surface. The sensor was preconditioned before use by soaking in $1.0 \times 10^{-3} \text{ mol L}^{-1}$ LVM solution for 1 h. When not in use, the sensor was stored in air.

Construction of calibration curves

The conditioned sensors were immersed in conjunction with the Ag/AgCl double-junction reference electrode in solutions of levamisole hydrochloride in the range of 1.0×10^{-8} - $1.0 \times 10^{-2} \text{ mol L}^{-1}$. They were allowed to equilibrate whilst stirring and recording the e.m.f. readings within $\pm 1 \text{ mV}$. The mV concentration profiles were plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown concentrations of levamisole hydrochloride.

Effect of pH

The effect of pH on the response of the investigated sensor was studied using $10^{-3} \text{ mol L}^{-1}$ LVM solutions over the pH range of 1.0–11.0. This is done by immersing the sensor in the drug solution. The pH was gradually increased or decreased by the addition of very small volumes of dilute NaOH or HCl solutions, respectively. The potential obtained at each pH was recorded.

Potentiometric titration of levamisole hydrochloride

Aliquots of $1.0 \times 10^{-2} \text{ mol L}^{-1}$ drug solution (pure) were transferred into 50-mL volumetric flasks and made up to the mark with bidi distilled water. Different concentrations of

LVM hydrochloride were prepared, then titrated potentiometrically with a standard solution of $1.0 \times 10^{-2} \text{ mol L}^{-1} \text{ NaTPB}$. The volume of the titrant at equivalence point was obtained using the conventional S-shaped curves.

Results and Discussion

Carbon paste sensors have several advantages of very low ohmic resistance, low cost, very short response time, reproducibility of the preparation process, simplicity, cheap and quick preparation process which provide the possibility of the measurements on small volumes as well as the ability for construction of a portable titration system. Therefore, the goal of this work is the fabrication of a novel modified carbon paste sensor for the determination of LVM in pure form.

Optimizing the composition of the sensor

It is well known that the sensitivity, linear dynamic range, and selectivity obtained for a given sensor depend significantly on the composition of the sensor. Several compositions for the investigated sensor were tested along with their other characteristics.

Sensitivity and selectivity of potentiometric sensors obtained for a given paste depend significantly on ingredients of paste, additives of the lipophilic anion (NaTPB) in addition to the nature and amount of the plasticizer used.

In this work, several sensors were constructed with different compositions. The ionophore (β -CD) is the most important sensing component in the sensor; as it selectively binds the target ion while discriminating against interfering ions. Different NaTPB contents, as shown in Table 1, were studied. The NaTPB in the composition of the carbon paste reduces ohmic resistance and improves response behavior and selectivity in cation-selective electrodes. Furthermore, the lipophilic additive may catalyze the exchange kinetics at the sample-electrode interface.[42,43]

The results showed that sensor 4 with the composition of 0.5 % β -CD, 0.3% NaTPB, 49.45% graphite and 49.75% plasticizer exhibited the best performance over linear concentration ranging from 8.1×10^{-6} to $1.0 \times 10^{-2} \text{ mol L}^{-1}$ with lower detection limit $7.2 \times 10^{-7} \text{ mol L}^{-1}$ and slope of $55.2 \text{ mV decade}^{-1}$.

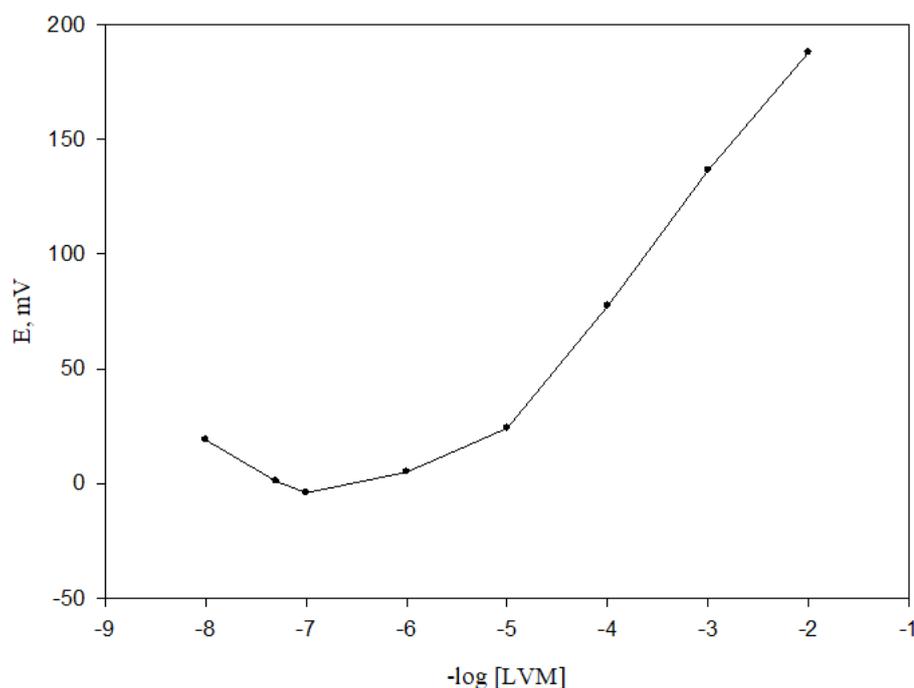


Figure 2: Calibration curve of LVM sensor

Sensor	Composition % w/w				Slope mV/decade	LR mol L ⁻¹	LOD mol L ⁻¹	r ²
	B-CD	Graphite	DBP	NaTPB				
1	0.3	49.85	49.85	-	38.8	1.0x10 ⁻⁵ -1.0x10 ⁻²	1.4x10 ⁻⁶	0.997
2	0.5	49.75	49.75	-	47.4	9.1x10 ⁻⁶ -1.0x10 ⁻²	5.5x10 ⁻⁶	0.998
3	0.7	49.65	49.65	-	35.2	1.0x10 ⁻⁵ -1.0x10 ⁻²	1.9x10 ⁻⁶	0.996
4*	0.5	49.45	49.75	0.3	55.2	8.1x10 ⁻⁶ -1.0x10 ⁻²	7.2x10 ⁻⁷	0.999
5	0.5	49.25	49.25	0.4	49.2	1.0x10 ⁻⁵ -1.0x10 ⁻²	2.9x10 ⁻⁶	0.998
6	0.5	9.05	49.75	0.5	50.6	1.0x10 ⁻⁵ -1.0x10 ⁻²	4.0x10 ⁻⁶	0.998

Sensor Performance

Table 1: Optimization of membrane composition (w/w %) for levamisole hydrochloride sensor.

LOD: Limit of detection; LR: Linear range

The performance characteristics of the selected sensor were studied as a function of the response time, for any sensor, this parameter is evaluated by measuring the average time required to achieve a potential within ± 0.1 mV of the final steady-state potential upon successive immersion of a series of interested ions, each having a 10-fold difference in concentration. The average static response time 10 s for the sensor was obtained when contacting different LVM+ solutions from 1.0×10^{-6} to 1.0×10^{-2} mol L⁻¹ (Fig. 3).

The effect of pH of the LVM test solutions on the sensor potential is graphically represented in Fig. 4. The pH has a negligible effect within the pH range of 2.0-8.0 for the investigated sensor.

The selectivity behavior of the investigated sensor was examined applying Bakker protocol. [44-46] The influence of some interfering species on the sensor response was studied graphically by plotting the potential responses for all species examined against log [concentration] of the added species. As shown from the calibration curves (Fig. 5), except for LVM there is no significant response of the sensor for interfering species tested.

Analytical applications

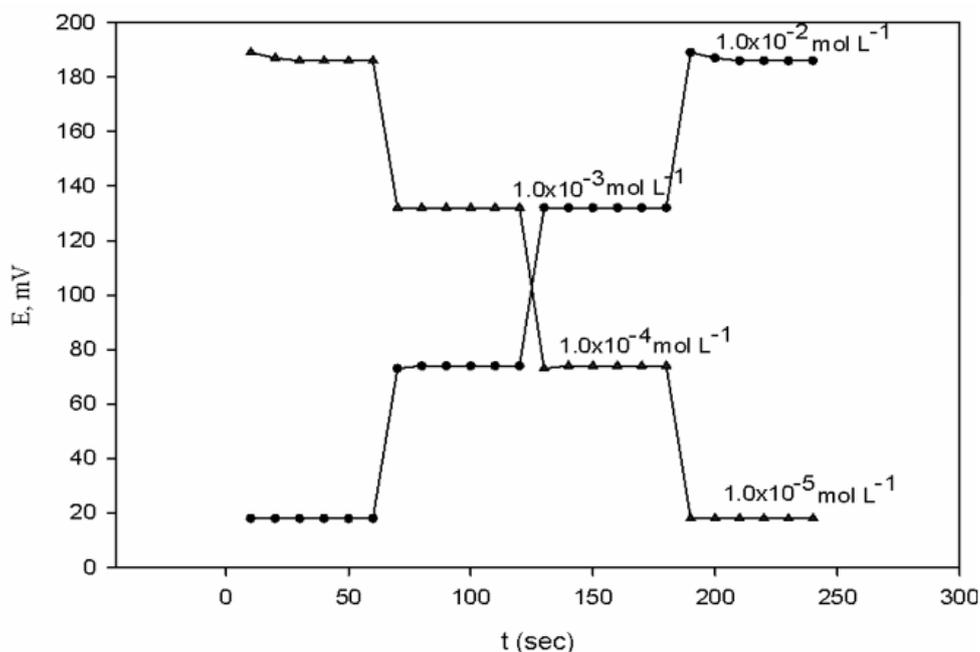


Figure 3: The dynamic response time of CPS for step changes in concentrations of LVM from low to high and vice versa

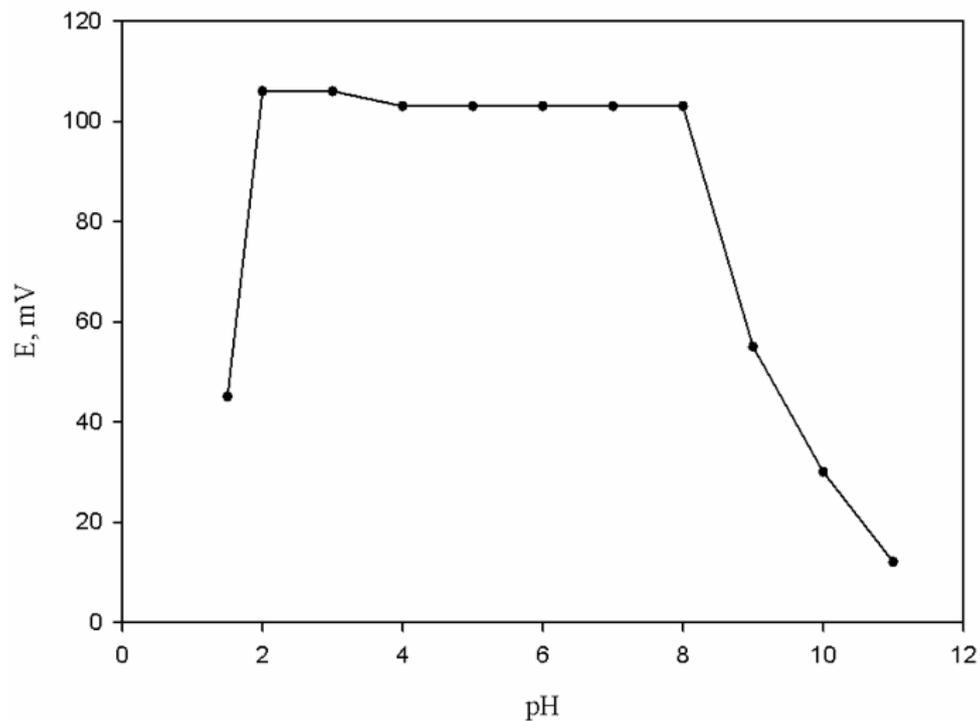


Figure 4: Effect of pH of the test solutions on the potential response of CPS sensor: $1.0 \times 10^{-3} \text{ mol L}^{-1}$ LVM solution

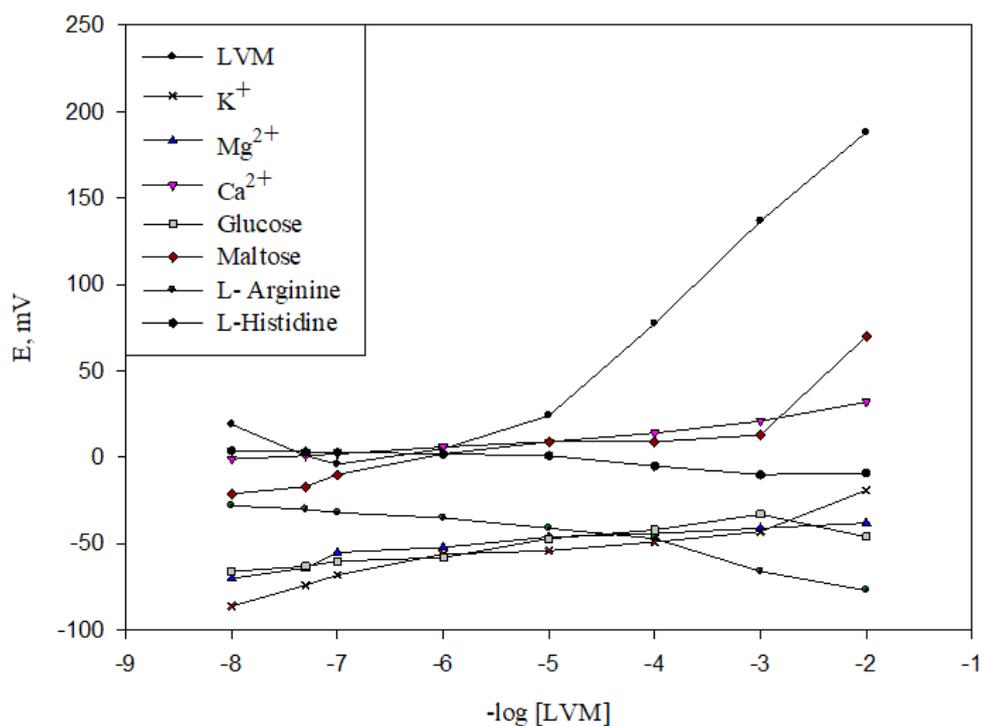


Figure 5: Calibration graphs of some inorganic cations, sugars and amino acids using CPS

The analytical usefulness of the investigated sensor was examined by determining LVM in pure form using potentiometric titration method. The proposed sensor can be applied successfully as an indicator sensor for titrating LVM pure samples against NaTPB titrant as shown in Fig. 6.

Conclusion

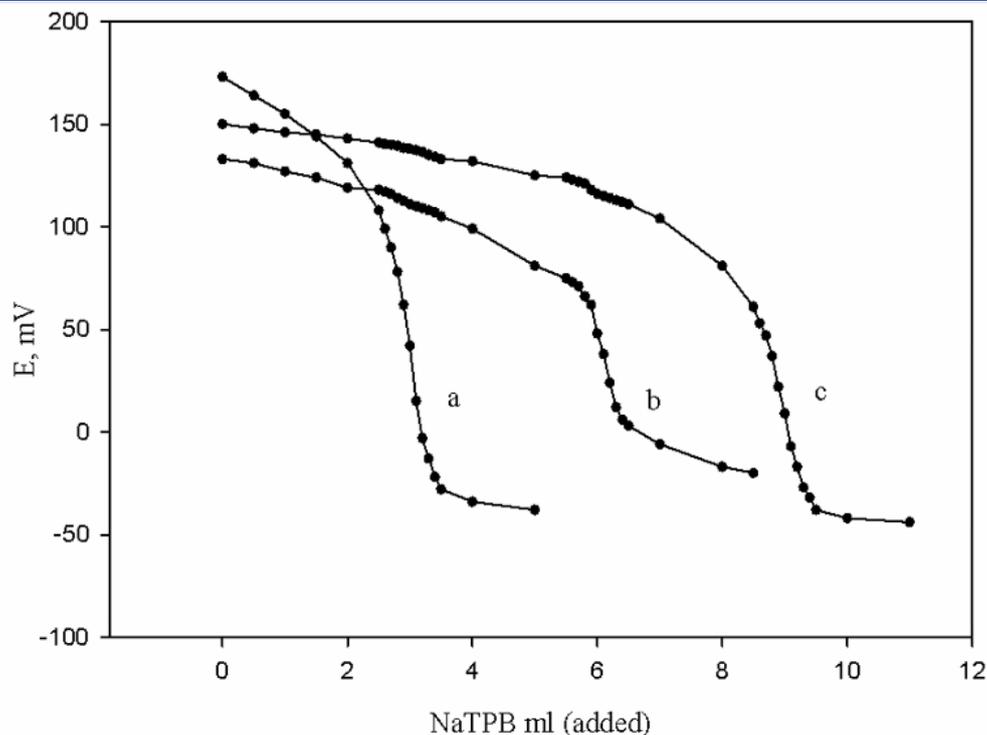


Figure 6: Potentiometric titration curves of (a) 3, (b) 6 and (c) 9 mL of 10^{-2} mol L^{-1} levamisole hydrochloride and 10^{-2} mol L^{-1} NaTPB as titrant

The present work demonstrates the fabrication of novel carbon paste sensor based on β -cyclodextrin ionophore and NaTPB as the anionic additive for potentiometric determination of LVM. The sensor has notable features as it provides measurements of the potential with a near-Nernstian slope of 55.2 mV/decade within the concentration range from 8.1×10^{-6} to 1.0×10^{-2} mole L^{-1} over the pH range 2-8 in a short response time (10 s). Attractively, it has a low detection limit of 7.2×10^{-7} mol L^{-1} . The investigated sensor was simple, sensitive and highly selective for LVM determination since the interferences of the excipients and impurities were nullified. In future, the present method will be considered as an excellent tool for the routine determination of LVM in quality control laboratories as a fast assay in its pharmaceutical preparations and biological fluids.

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Declaration

Authors, states that this research work is original and has not been published in whole or in part elsewhere.

Authorship (contribution or attribution)

All the authors have contributed equally.

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