

Research Article

ELECTROCHEMICAL DETERMINATION OF AMLODIPINE BESILATE AND BENAZEPRIL HYDROCHLORIDE IN THEIR BINARY MIXTURE USING PVC AND COATED GRAPHITE SENSORS

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ABSTRACT

Objective: Design and prepare two ion selective electrodes, Amlodipine–PVC sensor and Benazepril–coated graphite sensor for determination of amlodipine besilate and benazepril hydrochloride in their binary mixture. **Methods:** The sensors design is based on the ion pair of amlodipine besilate or benazepril hydrochloride with sodium tetraphenylborate using dioctylphthalate as a plasticizer. **Results:** Under the optimum conditions, the proposed sensors shows the slopes of 28.400 and 58.500 mV per concentration decade in the concentration range of 10^{-5} – 10^{-2} for amlodipine besilate and benazepril hydrochloride, respectively. The sensors exhibit a very good selectivity for the studied drugs with respect to a large number of interfering ions. The sensor enables determining the studied drugs in their binary mixtures with good percent recovery of each drug which indicates the higher selectivity of the prepared sensors. **Conclusion:** The sensors were successfully used for potentiometric determination of amlodipine besilate and benazepril hydrochloride in pure solutions and in their combined dosage form.

Keywords: Amlodipine besilate; benazepril hydrochloride; ion selective electrode

INTRODUCTION

Amlodipine besilate (AML) is 3-ethyl-5-methyl (\pm)-2-[(2-aminoethoxy) methyl]-4- (2-chlorophenyl)-1, 4-dihydro-6-methyl-3,5-pyridine dicarboxylate, mono benz-ene sulphonate, Figure 1. It is a white to pale yellow crystalline powder. It's slightly soluble in water and in isopropyl alcohol, sparingly soluble in dehydrated alcohol and freely soluble in methyl alcohol. Benazepril hydrochloride (BNZ) is {3S-3-[1S-1-Ethoxycarbonyl-3-phenylpropylamino]-2, 3, 4, 5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl} acetic acid hydrochloride, Figure 2. It is a white to off-white crystalline powder, soluble (greater than 100 mg/mL) in water, in ethanol and in methanol [1].

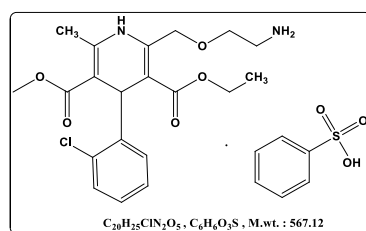


Figure 1: Structural formula of AML.

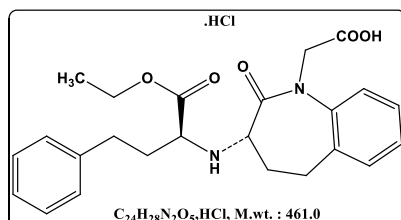


Figure 2: Structural formula of BNZ.

With respect to literature review, several methods have been reported for simultaneous determination of AML and BNZ in their binary mixture including, HPLC [2-5], HPTLC [6], LC MS/MS [7] and UV spectrophotometric methods [8-11].

The aim of this work is to design and prepare two ion selective electrodes, AML–PVC sensor and BNZ–coated graphite sensor for determination of AML and BNZ in bulk powder and in their combined dosage form.

Experimental

MATERIALS

- **Pure samples**—Pure AML (certified to contain 99.1%) and BNZ (certified to contain 99.2%) were kindly supplied by Marcyrl Pharmaceutical Industries, El-Obour city, Egypt.
- **Pharmaceutical formulation**— Norvapril® tablets 5/10 (Batch no. 1622677, manufactured by Marcyrl Pharmaceutical Industries, El-Obour city, Egypt), labeled to contain 5 mg of AML and 10 mg of BNZ, were purchased from local market.

Chemicals and solvents

All reagents used were of analytical grade and water used throughout the procedure was freshly distilled.

- Methanol, tetrahydrofuran, dioctyl phthalate (DOP), and poly (vinyl chloride) (PVC) of high relative molecular weight (Sigma-Aldrich, Germany).
- Sodium tetraphenylborate (Sigma-Aldrich, Germany), prepared as 10^{-2} M aqueous solution.
- Glucose, glycine, sucrose, urea, potassium chloride, calcium chloride, magnesium chloride, sodium chloride and nickel chloride (El-Nasr Company, Egypt), prepared as 10^{-3} M aqueous solution.
- Sodium hydroxide (El-Nasr Company, Egypt), prepared as 0.1 N aqueous solution.
- Hydrochloric acid (El-Nasr Company, Egypt), prepared as 0.1 N aqueous solution.
- Monobasic potassium phosphate, potassium chloride, boric acid, glacial acetic acid and sodium acetate tri-hydrate (El-Nasr Company, Egypt).
- Buffers of different pH values prepared as prescribed in US pharmacopeia [12]; Hydrochloric acid buffer, pH 2, Acetate buffer pH range from 4 to 5.5, Phosphate buffer pH range from 6 to 8 and Alkaline borate buffer pH range from 8 to 10.

Apparatus

- Jenway pH meter 3510 (USA) with Ag/AgCl reference electrode no 924017-LO3-Q11C.
- Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian).

Standard solutions

Standard solution of AML

A stock standard solution of AML (10^{-2} M) was prepared by dissolving 0.567 g of the drug powder in 50 mL of methanol and completed to 100 mL with the solvent. Different working solutions of varying strengths ranging from (10^{-6} to 10^{-3} M) were prepared by suitable dilution from the stock standard solution with water.

Standard solution of BNZ

A stock standard solution of BNZ (10^{-2} M) was prepared by dissolving 0.461 g of the drug powder in 50 mL of water and completed to 100 mL with the solvent. Different working solutions of varying strengths ranging from (10^{-6} to 10^{-3} M) were prepared by suitable dilution from the stock standard solution with water.

Procedures

Preparation of AML-PVC membrane sensor

(i). Preparation of the ion association complex

The ion association complex, AML tetraphenylborate (AML-TPB) was prepared by mixing of 50 mL of 10^{-2} M of both AML and sodium tetraphenylborate solutions. The resulting precipitate was left in contact with their mother liquor for 6 h, then the precipitate was filtered and washed thoroughly with distilled water and left to dry at room temperature for 24 h.

(ii). Preparation of the membrane

In a glass petri dish (5-cm diameter), 161 mg of DOP was thoroughly mixed with 161 mg of PVC and 28 mg of AML-TPB. The mixture was dissolved in 10 mL of tetrahydrofuran. The petri dish was then covered with a Whatman No. 3 filter paper and left to stand overnight to allow for solvent evaporation at room temperature. A master membrane with a thickness of 0.1 mm was obtained.

(iii). Electrode assembly

From the master membrane, an 8 mm diameter disk was cut out from the prepared membrane and glued using tetrahydrofuran to a transposable PVC tip that was clipped into the end of the electrode glass part. The resulting electrode body was filled with equal portions of 10^{-2} M KCl and 10^{-2} M AML. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 2 h. When not in use, the sensor was stored in air.

Preparation of BNZ-coated graphite sensor

(i). Preparation of the ion association complex

The ion association complex, BNZ-tetraphenylborate (BNZ-TPB) was prepared by mixing of 50 mL of 10^{-2} M of both BNZ and sodium tetraphenylborate solutions. The resulting precipitate was left in contact with their mother liquor for 6 h, then the precipitate was filtered and washed thoroughly with distilled water and left to dry at room temperature for 24 h.

(ii). Preparation of the membrane

In a glass petri dish (5-cm diameter), 157 mg of DOP was thoroughly mixed with 157 mg of PVC and 36 mg of BNZ-TPB. The mixture was dissolved in 10 mL of tetrahydrofuran and homogenized thoroughly. The solvent was slowly evaporated at room temperature until oily concentrated mixture was obtained.

(iii). Electrode assembly

It was prepared using commercial graphite bar (2.5 cm length an, 3 mm diameter). One end of the bar was used for connection, while the other was dipped in the electro active membrane mixture. The process was repeated several times until a layer of a proper

thickness were formed covering the terminal end of graphite bar. The electrode was left standing at room temperature to dry. The uncoated end of the graphite rod was sealed in a poly tetra ethylene tube; the tube was filled with metallic mercury into which a copper wire was dipped. The prepared sensor was preconditioned by soaking in 10^{-2} M drug solution for 4 h. When not in use, the sensor was stored in air.

Potential measurement conditions of the proposed sensors

- The electrochemical system can be represented as following:
 - (I) For AML-PVC membrane sensor: internal reference electrode/ internal filling solution/ PVC membrane/ test solution/ external reference electrode.
 - (II) For BNZ-coated graphite: reference electrode / test solution / graphite electrode.
- pH range: 3-7 for AML-PVC membrane sensor and 3-9 for BNZ-coated graphite sensor.
- Soaking time: 2 h for AML-PVC membrane sensor and 4 h for BNZ-coated graphite sensor.
- Response time: 40 s for AML-PVC membrane sensor and 60 s for BNZ-coated graphite sensor.
- Sensor stability: 5 weeks for AML-PVC membrane sensor and 3 weeks for BNZ-coated graphite sensor.

Sensors calibration

The conditioned sensors were immersed in conjunction with Ag/AgCl reference electrode in the solutions of AML or BNZ in the range of 10^{-6} to 10^{-2} M. They were allowed to equilibrate while stirring until achieving constant reading of the potentiometer. Then, the electromotive force values were recorded within ± 1 mV. Calibration graphs were plotted that related the recorded electrode potential values versus the negative logarithmic value of the drug concentration.

Procedure for pharmaceutical preparation

Ten Norvapril® tablets (each tablet labeled to contain 5 mg AML and 10 mg BNZ) were weighed and then finely powdered. Appropriate weight of powder equivalent to 46 mg was accurately weighed, transferred to 10 mL volumetric flask and the volume was made up to 5 mL with methanol. The solution was shaken vigorously for 20 min then sonicated for 30 min and filtered. The volume was completed to 10 mL with methanol to produce a stock solution labeled to contain (4×10^{-3}) M of AMP and (1×10^{-2}) M of BNZ. Necessary dilutions of the stock solution were made and analyzed using the general procedure of the described method.

RESULTS AND DISCUSSION

Electrochemical techniques are powerful and versatile analytical techniques that offer high sensitivity, accuracy, and precision as well as a large linear dynamic range, with relatively low-cost instrumentation [13,14].

In the present study, two types of ion selective membrane electrodes, PVC membrane and coated graphite sensors have been constructed for selective determination of AML and BNZ, respectively. The methods are based on the fact that, AML and BNZ behave as a cation with an anionic type of ion exchanger such as tetraphenylborate to prepare water insoluble association complex using precipitation-based technique. The resulting precipitates have low solubility product, suitable grain size and physically compatible with the matrix.

Performance characteristics of the developed sensors

The electrochemical performance of the investigated sensors was evaluated according to IUPAC recommendation data [15]. Calibrations were carried out by immersing the developed sensors in conjunction with Ag/AgCl reference electrode in solutions of AML and BNZ in the concentration range of 10^{-6} to 10^{-2} M. The potential displayed by the proposed sensors for constructive measurements of the standard drug solutions in the same day and from day to day did not vary by more than ± 1 mV. Calibration slopes did not change

by more than ±1 mV/decade concentration over a period of 5 weeks for AML-PVC membrane sensor and 3 weeks for BNZ-coated graphite sensor. The performance characteristics of the proposed sensors were summarized in Table 1. The profile of the potential in mV versus negative logarithmic molar concentration of AML or BNZ for the investigated sensors was plotted as shown in Figures 3, 4.

Table 1: The performance characteristics of the proposed described sensors.

Parameters	AML-PVC sensor	BNZ-Coated graphite sensor
Slope	-28.4000	-58.5000
Intercept	314.4000	287.0000
Coefficient of determination(r^2)	0.9997	0.9999
Range (M)	10^{-5} - 10^{-2}	10^{-5} - 10^{-2}
LOD (M)	8.5×10^{-6}	9.5×10^{-6}
Working pH range	3-7	3-9
Response time (s)	40	60
Stability (weeks)	5	3
Accuracy (mean %R) *	99.66	99.91
Repeatability (%RSD) *	0.446	0.519
Intermediate precision (%RSD) *	0.669	0.750

* Average of three determinations for three concentrations repeated three times.

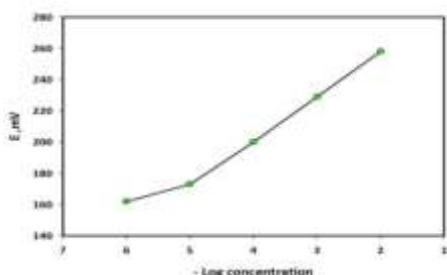


Figure 3: Profile of the potential in mV/- Log molar concentration of AML using PVC membrane sensor.

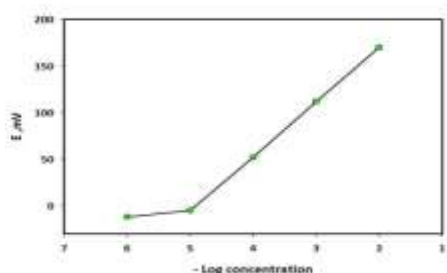


Figure 4: Profile of the potential in mV/- Log molar concentration of BNZ using coated graphite sensor.

Optimization of the sensors composition

(i). Effect of ion association complex percentage

The ion association complex is the most important part of an ion selective sensor. It is the electro active ingredient which is responsible for the selective recognition of the ion in the developed sensor.

AML-PVC mebrane sensor

The main components of a PVC membrane sensor are ion association complex, PVC and plasticizer. For the preparation of the membrane, the ion association complex, plasticizer and PVC should be taken in the appropriate percentage-weight ratios to improve the performance of the developed sensor. AML-TPB was prepared and tested as a modifier for the proposed sensor. It was studied by

varying the percentages of the ion association complex, while keeping the percentages of the PVC and the plasticizer equal 1:1 as shown in Table 2. The sensor made of 8% (w/w) of AML-TPB exhibited a near Nernstian slope of 28.40 mV/decade.

BNZ-coated graphite sensor

The ion association complex, BNZ-TPB, was prepared and tested as a modifier for the proposed sensor. It was studied by varying the percentages of the ion association complex, while keeping the percentages of the PVC and the plasticizer equal 1:1 as shown in Table 2. The sensor made of 10% (w/w) of BNZ-TPB exhibited a near Nernstian slope of 58.50 mV/decade. However, further addition of the modifier displays somewhat smaller slopes and sensitivity, most probably due to some in homogeneities.

Table 2: Optimization of the membrane composition % (w/w) of the AML-PVC membrane sensor and BNZ-coated graphite sensor.

	Composition (w/w) %			Linearity range (M)	Slope (mV/decade)	r^2
	AML-TPB	PVC	DOP			
AML-PVC membrane sensor	4	48	48	1×10^{-5} - 1×10^{-2}	-24.2000	0.9989
	8	46	46	1×10^{-5} - 1×10^{-2}	-28.4000	0.9997
	10	45	45	1×10^{-5} - 1×10^{-2}	-26.8000	0.9993
	12	44	44	1×10^{-5} - 1×10^{-2}	-25.6000	0.9991
	Composition (w/w) %			Linearity range (M)	Slope (mV/decade)	r^2
	BNZ-TPB	PVC	DOP			
BNZ-Coated graphite sensor	4	48	48	1×10^{-5} - 1×10^{-2}	-49.0000	0.9990
	8	46	46	1×10^{-5} - 1×10^{-2}	-54.1000	0.9992
	10	45	45	1×10^{-5} - 1×10^{-2}	-58.5000	0.9999
	12	44	44	1×10^{-5} - 1×10^{-2}	-56.3000	0.9993

(ii). Effect of soaking time

Freshly prepared sensors must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. The investigated sensors were soaked in 10^{-2} M solution of the corresponding drug. Calibration graphs were constructed for the sensor after different time intervals (0, 2, 4, 6 and 8 h) till the slope of the calibration graph deviated largely from the Nernstian value and the sensor. The results indicated that the optimum soaking time was 2 h for AML-PVC membrane sensor and 4 h for the BNZ-coated graphite sensor as shown in Table 3.

Table 3: Effect of soaking time on the described sensors

Soaking time/h	AML-PVC sensor	BNZ-Coated graphite sensor
0	-26.2000	-51.5000
2	-28.4000	-54.8000
4	-26.8000	-58.5000
6	-25.4000	-55.7000
8	-21.3000	-53.5000

(iii). Effect of pH

The stability of the potential readings was investigated over a wide pH range (2-12) to determine the working pH range of the proposed sensors. The investigations were performed in 10^{-2} and 10^{-3} M of the studied drug solutions. The potential obtained at each pH value was recorded. Representative curves for the effect of pH on the proposed sensors are shown in Figures 5, 6. For AML-PVC membrane sensor the potential remained constant in the pH range (3-7) whereas in

the case of BNZ-coated graphite sensor the potential remained unchanged in the range (3–9).

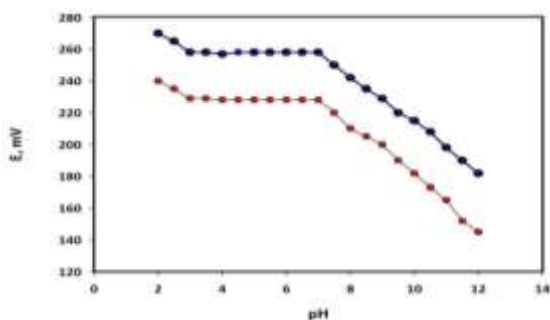


Figure 5: Effect of pH on the response of AML using PVC membrane sensor

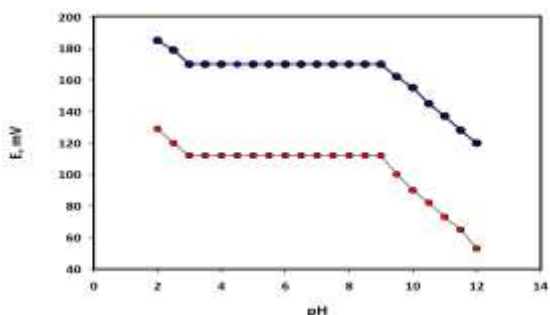


Figure 6: Effect of pH on the response of BNZ using coated graphite sensor.

(iv). Sensors selectivity

The influence of the related interfering compounds on the response of the investigated sensors towards the drug was investigated. The separate solution method (SSM) was applied based on measuring the potential of 10⁻³ M solution of each drug and the interfering ions separately. Then the selectivity coefficients $\log K_{Drug J^{+z}}^{pot}$ were calculated by applying the following equation [16]:

$$\log K_{Drug J^{+z}}^{pot} = \frac{E_2 - E_1}{S} + \log[drug] - \log[J^{+z}]^{\frac{1}{z}}$$

Where E1 and E2 are the electrode potential of 10⁻³ M solution of each of investigated drug and interferent ion [J^{+z}], respectively, and S is the slope of calibration curve. The interfering compounds were; potassium chloride, calcium chloride, magnesium chloride, sodium chloride, nickel chloride, glucose, urea, glycine and sucrose.

The results of the calculated selectivity coefficients indicated that the proposed sensors were highly selective towards the studied drugs as shown in Table 4.

(v). Response time of the proposed sensors

For analytical applications, the response time of the prepared sensor is of critical importance. The average time required for the electrode to reach a steady potential response within ±1 mV of the final equilibrium value after successive immersion of a series of the drug solutions, each having a 10-fold difference in concentration, was investigated. Stable responses were achieved within 40 s for AML-PVC membrane sensor and 60 s for BNZ-coated graphite sensor.

Table 4: Selectivity coefficients of the described sensors using separated solution method.

Interferant	-Log $K_{Drug, J^{+z}}^{pot}$ of AML-		Log $K_{Drug, J^{+z}}^{pot}$ of BNZ-	
	PVC sensor	membrane	Coated sensor	graphite
AML	-----		1.066	
BNZ	1.09		-----	
Calcium chloride	1.076		1.009	
Magnesium chloride	1.014		1.002	
Sodium chloride	1.083		1.005	
Nickel chloride	1.061		1.015	
Glucose	1.096		1.034	
Urea	1.077		1.093	
Glycine	1.056		1.07	
Sucrose	1.069		1.091	

Method validation

Validation of the described methods was performed in a compliance with International Conference of Harmonization (ICH) guidelines [17].

Linearity and range

Under the described experimental conditions, the calibration graph for each sensor was constructed by plotting the recorded sensor potential versus negative logarithmic value of the drug concentration. The regression plots were found to be linear over the range of 10⁻⁵–10⁻² M for the studied drugs, as shown in Figures 3, 4.

Limit of detection

Limit of detection was measured by interception of the extrapolated arms of Figures 3, 4. It was found to be 8.5x10⁻⁶ for AML-PVC membrane sensor and 9.5x10⁻⁶ M for BNZ-coated graphite sensor. The small values of LOD indicate good sensitivity of the described sensors.

Accuracy and precision:

Accuracy of the described methods, calculated as the mean percent recovery (%R), was assessed by applying the described procedure for triplicate determination of three concentration levels covering the linearity range of each drug (10⁻², 10⁻³ and 10⁻⁵ M). The results in Table 1, indicated the accuracy of the proposed method.

Precision of the methods, calculated as the percent of relative standard deviation (%RSD), was assessed by triplicate determination of three concentration levels covering the linearity range of each drug (10⁻², 10⁻³ and 10⁻⁵ M) within one day for repeatability and on three successive days for Inter mediate precision. The small values of %RSD indicated high precision of the method as shown in Table 1.

Specificity

The specificity of the described methods was assured by applying them to laboratory prepared mixtures of AML and BNZ at different ratios. The specific sensor of each drug was adopted for its selective determination with good percent recovery as shown in Table 5.

Table 5 : Determination of AML and BNZ in laboratory mixtures by the described sensors

AML taken (M)	BNZ taken (M)	AML-PVC sensor		BNZ-Coated graphite sensor	
		AML found	AML (%R)	BNZ found	BNZ (%R)
10 ⁻²	10 ⁻²	0.9946 x10 ⁻²	99.46	1.0006 x10 ⁻²	100.06
10 ⁻²	4x10 ⁻²	1.0123 x10 ⁻²	101.23	3.9928 x10 ⁻²	99.82
10 ⁻²	2x10 ⁻²	1.0013 x10 ⁻²	100.13	2.0116 x10 ⁻²	100.58
4x10 ⁻²	10 ⁻²	3.9864 x10 ⁻²	99.66	0.9894 x10 ⁻²	98.94
2x10 ⁻²	10 ⁻²	2.0170 x10 ⁻²	100.85	1.0024 x10 ⁻²	100.24
Mean ± %RSD			100.27±0.759		99.93±0.619

Pharmaceutical applications

The described electrochemical methods were applied for the determination of AML or BNZ in Norvapril® tablets. Satisfactory results were obtained in good agreement with the label claim, indicating no interference from excipients and additives. The obtained results were statistically compared to those obtained by the reported method [11]. No significant differences were found by applying t-test and F-test at 95% confidence level, indicating good accuracy and precision of the proposed method for the analysis of the studied drugs in their pharmaceutical dosage form, as shown in Table (6).

Table 6: Determination of AML and BNZ in Norvapril® tablets by the described sensors and reported methods [11]

Parameters	AML-PVC sensor	BNZ-Coated graphite sensor	Reported method*	
	AML	BNZ	AML	BNZ
N**	5	5	5	5
\bar{X} ***	99.72	100.52	100.03	100.14
SD	0.825	0.946	1.170	1.321
Variance	0.681	0.895	1.368	1.746
t-test (2.306) ****	0.483	0.531		
F-test (6.388) ****	2.010	1.950		

* Simultaneous equation method at 360 nm and 240 nm.

** Number of experiments.*** The mean of percent recovery of pharmaceutical preparation **** The values in parenthesis are tabulated values of "t" and "F" at (P = 0.05).

CONCLUSIONS

Two ion selective electrodes were designed for selective determination of AML and BNZ, namely; AML-PVC membrane sensor and BNZ-coated graphite sensor. The designed sensors seem to give better results of detection limit, dynamic range and higher selectivity. Also, BNZ-coated graphite sensor has simple design can be applied in small volume of sample.

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