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Original Article

A SIMPLE AND PORTABLE INSTRUMENT FOR DETERMINATION OF CAPTOPRIL IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Objective: This article describes the application and the performance of a cheap, simple and portable device that can be used for colorimetric quantitative determination of captopril (CPT) in pharmaceutical preparations.

Methods: The sensor is a light detector resistor (LDR) placed into a black PTFE cell and coupled to a low cost multimeter (Ohmmeter). The instrument has been tested and is easy and fast to use. The quantitative study is based mainly on reduction of ammonium molybdate by captopril, in the presence of sulphuric acid, producing a green-yellow compound (λ_{max} 407 nm). The calibration curves were obtained by plotting the electric resistance of the LDR against the CPT concentration on the range of 4.60 x 10^{-4} to 1.84 x 10^{-3} mol l^{-1} with a good coefficient of determination (R^2 = 0.9962).

Results: Statistical analysis of the obtained results showed no significant difference between the proposed methodology and the official reported method as evident from the *t*-test and variance ratio at 95% confidence level.

Conclusion: The results of this study demonstrate that the instrument can be used for simple, accurate, precise, fast, *in situ* and low-cost colorimetric analysis of captopril in pharmaceuticals products.

Keywords: Optical sensor, Resistance measurements, Captopril, Quality control, Pharmaceuticals formulations.

INTRODUCTION

Captopril, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline (Figure 1), (CPT) is an angiotensin-converting enzyme inhibitor, which reduces peripheral resistance and lowers blood pressure. It is extensively used for the treatment of hypertension [1] and congestive failure [2].

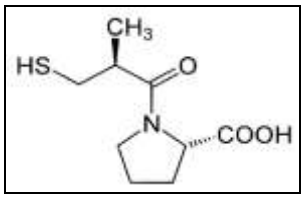

Fig. 1: Chemical structure of captopril.

In order to assure the quality of CPT containing pharmaceutical formulations, several analytical techniques have been used for its determination, including batch fluorimetry [3], chemiluminescence [4 – 7], atomic absorption spectrometry [8, 9], high-performance liquid chromatography [10 – 17], gas chromatography [18], differential pulse polarography [19], amperometry [20 – 22], volumetric titration [23], potentiometric titration [24 – 28], capillary electrophoresis [29], conductometry [30], coulometry [31], voltammetry [32], diffuse reflectance spectroscopy [33] and spectrophotometry [27, 34 – 45].

However, some of these methods are typically expensive, time consuming, laborious and are not well suited to field applications or process control monitoring. In addition, chromatographic methods are slow and require expensive and complicated instrumentation, features that make them unattractive to routine analysis. Titrimetric method has suffered from a lack of specificity and sensitivity, under certain circumstances, such as the presence of unsaturated organic compounds. The proposed approach is relatively reliable, low cost and compact to be handled even by unskilled personnel. Therefore, there is a considerable interest in the development of highly reliable, cost effective, sensitive, and selective detection devices for determination of CPT in marketed dosage formulations. Instrumentation has become integral with chemical measurements. The multimeter is an essential piece of equipment on the workbench of an electrician. It is a universal instrument, useful not only for measuring electrical quantities, such as voltage, current, and resistance, but also for testing electrical and electronic circuits.

Thus, the multimeter could also be a very useful instrument for the chemistry laboratory bench. Contemporary electronics and instrumentation have reached a level of application that allows the measurement, direct or indirect, of chemical quantities. These measurements involve the encoding of chemical information into electrical signals. This transduction can be carried out through a variety of physical and chemical principles, and for most cases, the resultant electrical quantity could be measured using a multimeter. Colorimetric [46 – 49], potentiometric [50 – 55] and conductimetric [55, 56] systems based on a multimeter have been described in the literature.

Coupled with optical sensors and transducers, the multimeter could provide a means for the measurement of chemical parameters. Optical sensors are of great interest because of their favorable characteristics when compared to other kind of sensors. Portable optical sensors, specially, are of value for enabling in situ chemical analysis [47, 57, 58].

Moreover, optical sensors-based instruments have a simple assembly and low cost, are versatile and can be employed in the determination of many chemical parameters with promising results. Thus, the objective of this work was the application of a portable instrument for determination of CPT in pharmaceutical formulations. The results agreed fairly well with those obtained by the USP standard procedure [23] at 95% confidence level.

MATERIALS AND METHODS

Apparatus

A prototype of the portable device (Figure 2) described for Rossi et al. [46] was used for all resistance measurements realized in this work. A desk 9 W lamp Startec was used as the light source, placed some 17 cm upon the cell. A digital multimeter Minipa® ET–1502 was used to collect the resistance measurements. An ordinary glass tube with internal diameter of 5.0 mm and length of 50.0 mm was used as the sample cell.

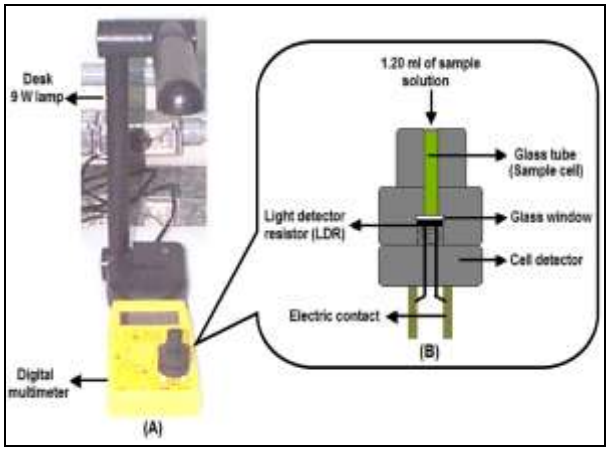

Fig. 2: (A) General view of the optical device assembled on a digital multimeter. (B) Schematic diagram of the optical device.

Volume measurements were made with plunger-operated pipetter (100–1000 mL) and Metrohm model 665 automatic burettes. All experiments were performed in a thermostated room (25±1) °C.

Reagents and solutions

All reagents and chemicals used were of analytical grade and the solvents were spectroscopic grade. For the preparation of the solutions and samples, deionized water was used.

Captopril (standard substance) was purchased from Purifarma, São Paulo, Brazil (purity grade > 99.9%, calculated on the dried basis). Its characteristic was consistent with the United States Pharmacopoeia (USP) [23]. A stock solution (CPTS – 1000 mg l-1) of CPT standard was prepared daily by dissolving 50.0 mg of the reference substance in deionized water and diluting to the mark in a 50.0 ml volumetric flask. Working standard solutions were obtained by appropriate dilution of this stock solution with the same solvent and were standardized by the standard procedure reported in official method of the USP [23].

The sulphuric acid (Mallinckrodt, Xalostoc, Mexico) solution 8.73 mol l^{-1} was prepared in the usual way, from the concentrated acid (96%).

The ammonium molybdate $[(NH_4)_6.Mo_7.O_{24}.4H_2O]$ (Mallinckrodt, Xalostoc, Mexico) aqueous solution 2% (m v^{-1}) was prepared daily.

Pharmaceutical formulations (tablets) of six commercial brands were analyzed. These tablets were purchased from local drugstores and all were tested prior to the listed expiration date. All studied pharmaceuticals were package labeled to contain 12.5 and 25.0 mg of CPT per tablet.

Procedure for the calibration curve

Aliquots (0.3 ml) of standard solution containing CPT the range of 4.60×10^{-4} – 1.84×10^{-3} mol l^{-1} were transferred quantitatively into reaction flasks followed by the addition of 3.0 ml H_2SO_4 (8.73 mol l^{-1}) and 1.0 ml of ammonium molybdate (2.0% m v^{-1}) solutions, under stirring. The solutions were stoppered to room temperature (25±1 °C) for 30 min. After the time, the solutions were diluted to 5.0 ml with deionized water. The blank solution is prepared in a similar way, but omitting CPT. The constant volume of 1200 µL of this solution was put into the sample cell with micropipette and the resistance measurements were obtained against corresponding reagent blank. Calibration graphs were prepared by plotting the electric resistance of the LDR against drug concentration. These graphs or the corresponding linear least squares equations were used to convert resistance measurement into CPT concentration, for any analyzed sample [44].

Procedure for the assay of CPT in selected marketed brands

Six market brands of CPT tablet from local drugstores were randomly selected and analyzed using the portable device. For the determination of CPT in pharmaceutical samples, the average tablet weight was calculated from the contents of twenty tablets that been finely powdered, homogenized and weighed. A portion of this powder, equivalent to ca. 41.7 mg of CPT was accurately weighed and dissolved in 7.0 ml of chloroform by shaking for 20 min in a mechanical shaker. The resulting mixture was filtered, transferred into a 10 mL volumetric flask and the volume completed with chloroform. Aliquots of 3.0 ml from this solution were transferred into 5.0 ml graduated flasks and were analyzed according to the recommended procedure for the calibration curve. The quantity per tablet was calculated from the standard calibration graph.

Repeatability study (precision)

To examine the repeatability of the measurement system, replicate (n = 10) determinations were made on the same solution containing equivalent to 1.15×10^{-3} mol l^{-1} of CPT. This solution was analyzed according to the recommended procedure for the assay of content of CPT in pharmaceutical formulations. The precision was calculated in terms of percentage relative standard deviation (% RSD).

Accuracy/recovery studies

To study the accuracy of the proposed device for the determination of CPT in the dosage forms, recovery experiments were carried out by the standard addition method. This study was performed by addition of known amounts (4.14×10^{-4}; 4.60×10^{-4}; 5.06×10^{-4} and 5.52×10^{-4} mol l^{-1}, corresponding to levels of 90; 100; 110 and 120%, respectively) of the standard substance (pure drug – CPT) to a known concentration of the previously analyzed commercial tablets (samples A, B, C and D). The resulting mixtures were analyzed according to the recommended procedure for the assay of content of CPT in pharmaceutical formulations. The recovery of drug was calculated by comparing the concentration obtained from the spiked mixtures with those of the pure drug

RESULTS AND DISCUSSION

Colorimetry involves the measurement of the concentration of the chemical species thought the amount of light absorbed at certain wavelengths. The extent of absorption of light is measured through the intensity of the radiation transmitted by the sample solution [59]. A multimeter can performed colorimetric measurements when coupled with a photodetector, such as a light-dependent resistor (LDR). The LDR is a semiconductor whose resistance depends on the intensity of the radiation striking its surface.

The value of the resistance of the sensor (LDR) decreases as the intensity of the incident light increases [46]. In this way, for quantitative purposes, calibration curves can be obtained by plotting the electric resistance of the LDR (R) against the analyte concentration (C) by a linear relationship. Thus, in this work a multimeter was used to measure the resistance of the LDR.

The captopril/ammonium molybdate/H_2SO_4 system

The tone of the color of a reduced solution of Mo (VI) changes as a function of the variation of the concentration of each absorbent particle, which derived from the reduction of the Mo (VI), the concentration and of the reducing strength of the used reducing agent. The CPT has been used as reducing agent due to reactivity of the thiol group of this compound. Thus, the formation of the green-yellow product ($\lambda_{max.}$ 407 nm) involves the reaction of CPT with molybdate ions, in acidic media.

The optimum experimental conditions and studies of the stability of this product were established in a work previously developed in our laboratory [44]. Thus, the experimental conditions used in this work were the same conditions utilized in that approach. The relationship between the electric resistance of the LDR and the concentration of CPT under optimal conditions was examined.

The analytical curve (Figure 3) was obtained by the method of least squares from eleven points, each of which was the average of three determinations.

This curve was obtained by plotting the electric resistance of the LDR against the CPT concentration on the range of 4.60 x 10^{-4} to 1.84 x 10^{-3} mol l^{-1} of CPT, in the final solution, with a good coefficient of determination (R^2 = 0.9962; slope = 12377.25 ± 487.14 l mol^{-1} cm^{-1} and intercept = -3.5968 ± 0.5148). The limit of detection – LOD ($3.SD_{blank}$) was 3.15 x 10^{-4} mol l^{-1}[60].

Coefficient of determination is not true indicator of linearity, therefore the Fischer variance ratio [61] (test of linearity) was used. The test of linearity was performed by using the Statistica v. 10.0 statistical software. Thus, the test for adequateness of the linearity model allows the validity of the regression model and the chosen working range to be verified. The ANOVA lack of fit model is based on the comparison of the tabulated F of Fisher values with the observed *F* of Fischer calculated on the basis on the experimental results, and on the sums of squares [62]. Thus, in the test of linearity of proposed method, i.e. Fischer variance ratio, calculated value of $F_{lack\ of\ fit}$ (F_{Cal} = 0.97) for the analyte was less than tabulated *F* value ($F_{Tab\ (5,\ 14)}$ = 2.96) which indicates linearity of response. device for the samples ranged from 0.4 to 2.4%, as shown in Table 1. According to Horwitz [64], the maximum RSD value acceptable for the working level of the analyte (1.15 x 10^{-3} mol l^{-1}) is 8.0%. The AOAC [65] set the maximum acceptable RSD value at 5.3% for the same analyte level. The repeatability of the measurement system was investigated. The relative standard deviation (RSD) at this concentration level was 0.7%. This is good evidence of repeatability of the measurement system.

Table 1: Determination of CPT in commercial pharmaceutical preparations

Sample	Label value [a]	Proposed device				Official method [23]	
		Found [b]	RSD (%) [c]	*t*-value (2.78)[d]	*F*-value (19.00) [d]	Found [b]	RSD (%) [c]
A	25.0	24.6±0.2	0.8	2.31	4.00	24.9±0.1	0.4
B	25.0	25.6±0.3	1.2	2.29	2.25	24.6±0.2	0.8
C	25.0	25.0±0.1	0.4	2.27	4.00	24.8±0.2	0.8
D	25.0	24.2±0.6	2.4	2.55	4.00	25.2±0.3	1.2
E	12.5	12.4±0.3	2.4	0.30	9.00	12.4±0.1	0.8
F	12.5	12.1±0.2	1.6	0.79	4.00	12.0±0.1	0.8

[a] Label to content for tablets: mg unit $^{-1}$, [b] Average value ± standard deviation (SD) of three determinations, [c] Relative standard deviation (RSD) of three determinations,[d] The figures between parentheses are the theoretical values of *t* and *F* at *P* = 0.05.

Table 2: Recovery/accuracy data for four different concentrations of CPT spiked to pharmaceuticals by the proposed device

Sample	Added (x 10^{-4} mol l^{-1})	Found (x 10^{-4} mol l^{-1})	Recovery (%) [a]
A	4.14	4.13	99.7
	4.60	4.62	100.4
	5.06	5.10	100.8
	5.52	5.45	98.7
			μ^{a} = 99.9 ± 0.9
B	4.14	4.17	100.7
	4.60	4.55	98.9
	5.06	5.11	101.0
	5.52	5.55	100.5
			μ^{a} = 100.3 ± 1.0
C	4.14	4.11	99.3
	4.60	4.65	101.1
	5.06	5.01	99.0
	5.52	5.49	99.5
			μ^{a} = 99.7 ± 0.9
D	4.14	4.20	101.4
	4.60	4.51	98.0
	5.06	5.00	98.8
	5.52	5.59	101.2
			μ^{a} = 99.8 ± 1.7

[a] Average ± relative standard deviation (RSD) of three determinations.

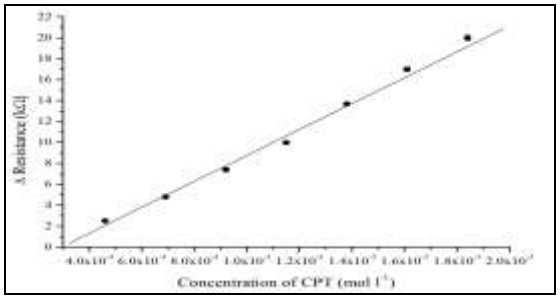

Fig. 3: Analytical curve for determination of CPT.

Analytical applications and repeatability studies

In order to assess the utility of the presently portable device it was applied to the estimation of CPT in several pharmaceutical forms. The samples were prepared using the developed method. Then, the measurement system was successfully applied for CPT determination in six tablet formulations. The results, presented in Table 1, compare favorably with the official method of the USP [23], which testifies to the applicability of the proposed device to the determination of CPT in pharmaceutical dosage. Comparing the results obtained with proposed device with those obtained by the official method, based on the Student's *t* values (accuracy) and on the *F* test (precision) is observed concordance for the 95% (α = 0.05) confidence level [63]. Thus, both Student's *t* and *F* test showed

that there is statistical equivalence between the results of the proposed device and the official method, indicating very good accuracy and precision.The RSD values obtained with proposed

Accuracy/recovery studies

In order to check the accuracy and precision of the portable device, we also carried out a recovery study. The results of the recovery tests were presented in Table 2. The recovery mean values for all samples within the range of 99.7 – 100.3% and RSDs were within 0.9 – 1.7% ensure an accurate and precise measurement system to be applied to pharmaceutical dosage forms.

CONCLUSION

From the above results and from general observations in the laboratory, it can be concluded that the very simple and portable device proposed for Rossi et al. [46] can be used for colorimetric quantitative determination of CPT in pharmaceutical preparations. Statistical comparison for the results of the portable device with the official reported method indicates that there is no significant difference, at 95% confidence level, with regard to accuracy and precision. Additionally, it fulfills all the main demands of routine analysis as it is robust, has low instrumentation and operational cost in comparison to chromatographic methods. Thus, the results obtained demonstrate clearly the possibility of an alternative use of this measurement system for the quality control of the drugs. Moreover, this instrument can be used for simple, accurate, precise, fast, in situ and low-cost colorimetric analysis of CPT in pharmaceuticals products.

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