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Argentimetric Assay of Captopril in Bulk Drug and in Tablets

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Three simple, selective and cost-effective procedures for the determination of captopril in bulk drug and in tablets are described. All the procedures make use of silver nitrate as a reagent and involve titrimetry and spectrophotometry as measurement techniques. In titrimetry (Method A), the aqueous solution of the drug is titrated directly with the standard silver nitrate solution to a potassium chromate end-point. In one spectrophotometric method (Method B), the sample solution is treated with excess of silver nitrate and a known amount of methyl orange and the increase in absorbance at 520 nm, caused by a decrease in pH due to release of nitric acid, is measured and related to drug concentration. The other spectrophotometric method (Method C) involves the addition of a measured excess of silver nitrate to the sample solution followed by the determination of residual silver ion by an ion-associate complex formation reaction involving eosin and 1,10-phenanthroline. The decrease in absorbance at 550 nm, which corresponds to Ag^+ reacted with the drug, is measured and is found to be linearly related to drug concentration. All experimental variables involved in the methods were investigated and optimized. Stoichiometry of the reaction that forms the basis for titrimetry is found. Method A is applicable in the range of 1.0-20.0 mg of drug while methods B and C can be conveniently used in the concentration ranges of 2.5-50.0 and 0.25-4.0 μg ml^{-1}, respectively. Several optical characteristics such as molar absorptivity, Sandell sensitivity, limits of detection and quantification, and correlation coefficient were calculated. The methods were applied to the analysis of tablets containing captopril. Statistical treatment of the results indicates that the procedures are precise and accurate. The excipients used as additives in tablets did not interfere in the proposed procedures as revealed by the recovery studies.

Keywords: Captopril, Silver nitrate, Titrimetry, Methyl orange, Eosin-1,10-Phenanthroline, Spectrophotometry

INTRODUCTION

Captopril (CPT), 1-(3-mercapto-2-D-methyl-1-oxopropyl)-1-proline, is a lysine analogue of enalaprilate. It is an orally active antihypertensive drug [1], acting primarily by inhibiting the angiotension-converting enzyme. It is also used in treating chronic congestive heart failure. It is permitted by USP [2], IP [3] and BP [4]. All pharmacopoeias describe an iodometric titration procedure for its estimation. Several methods are available for determining CPT in its dosage forms. Presently, the most widely used technique for its determination is high-performance liquid-chromatography [5-14]. Though the technique is rapid and sensitive, quite often it involves precolumn derivatization [6-10] and multiple extraction steps. A couple of gas chromatographic methods [15,16] reported for determining CPT in dosage forms also involve derivatization besides being poorly sensitive [15]. Methods based on derivative and difference ultraviolet spectrophotometry [17,18] have been employed but the techniques are of great utility for resolving mixtures than

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individual ingredients. Several other methods proposed for the determination of CPT include fluroimetry [19,20], coulometry [21], amperometry [22] and polarography [23,24], atomic absorption spectrometry [25], capillary isotachophoresis [26] and capillary electrophoresis [27,28].

Very few titrimetric procedures are found in the literature for the assay of CPT in dosage forms. Potentiometric and visual titrimetric methods [29] were first reported by Mohamed et al. Titration of nitric acid released, on reacting the drug with silver nitrate, against sodium hydroxide with potentiometric [30] and conductometric [31] end-point detection has served as the basis of micro determination of the drug in dosage forms. Direct potentiometric titration of the -SH group of the drug with silver nitrate using sulfide-selective indicator electrode was accomplished by Buzlanova and Karandi [32].

Many spectrophotometric methods involve the use of reagents that react with this compound to form species that absorb in the visible region. One of the sensitive methods uses Folin-Ciocalteu reagent [33], which is reduced to a blue species and measured at 760 nm. Recently [34], the same procedure has been automated by adapting to flow-injection device using online solid phase extraction, but the sensitivity has been far less than the manual procedure. Emmanuel and Haluankar [35] have proposed a method, which involves the treatment of CPT with citric acid and boiling for 30 min at 98 °C followed by addition of acetic anhydride and measurement at 570 nm. Methods [36] using phenylfurone or dichlorophenol indophenol also involves heating for 60 min besides lacking sensitivity. The drug has also been estimated in tablets by three procedures [37] involving iron(III), iodine and iodine-starch reagents. The methods reported by Ashry and Ibrahim [38] either lack sensitivity (using N-bromophthalimide-promethazine) or involves boiling for 30 min (using molybdophosphoric acid), and hence unsuitable for routine analysis. A few indirect spectrophotometric methods involving the use of bromate-celestine blue [39], 2,2′-diphenyl-1-picryl hydrazyl [40], chromium(VI)-metol-primary arylamine [41], iron(III)-1,10-phenanthroline [42] and metavanadate-H_2O_2 [43] combinations are also found in literature, but suffer from one or the other disadvantage.

Therefore, it was considered desirable to develop additional assay methods suitable for the rapid and reliable quality control of CPT in pharmaceutical formulations. The versatility of titrimetry is well known and spectrophotometry offers the advantages of sensitivity, selectivity and rapidity. In this study, both titrimetric and spectrophotometric approaches were followed to develop rapid and selective alternative procedures for the determination of CPT in commercial dosage forms. The methods are based on the reaction of silver(I) ion with sulphydril group of CPT, which is followed by either titrimetry or spectrophotometry.

EXPERIMENTAL

Apparatus

A Systronics model 106 digital spectrophotometer with 1-cm matched quartz cells was used for the absorbance measurements.

Reagents

All chemicals used were of analytical reagent grade and double distilled water was used throughout the study.

A 0.01 mol l^{-1} solution of silver nitrate was prepared by dissolving about 0.42 g of silver nitrate in water and diluting to 250 ml in a volumetric flask and stored in a dark bottle. It was standardized by Mohr's titration [44] and used for the titrimetric work (Method A). The solution was diluted to obtain a 15 μg ml^{-1} of Ag^+ ion solution to be used in spectrophotometric method C. A 2 mg ml^{-1} $AgNO_3$ solution was prepared by dissolving 100 mg silver nitrate in 50 ml of water.

A 0.05% solution of methyl orange was prepared by dissolving 59 mg of the dye (85% dye content) in water and diluting to 100 ml. This was diluted to a 0.005% solution and used in Method B. A 10 mg amount of eosin (2,4,5,7-tetrabromofluorescein) was dissolved in 100 ml of water to obtain a 0.01% solution and stored in an amber colored bottle. A 0.02% solution of 1,10-phenanthroline was prepared by dissolving 20 mg of reagent in 100 ml water. Aqueous solutions of sodium acetate trihydrate (2.5 mol l^{-1}) and potassium chromate indicator (5%) were prepared in the usual way.

Pharmaceutical grade CPT was provided by Cipla India Ltd. (Mumbai, India) and was used as received. A stock standard solution containing 2 mg ml^{-1} of CPT was prepared

by dissolving a weighed amount of pure drug in water and used in titrimetry (Method A). The stock solution was diluted appropriately to get 100 μg ml^{-1} and 10 μg ml^{-1} solutions for use in Methods B and C, respectively.

Sample Solutions

An accurately weighed amount of the finely powdered tablets equivalent to 200 mg of CPT was transferred into a 100 ml calibrated flask, shaken for about 20 min with 60 ml water and diluted to volume with water, mixed well and filtered using a Whatman No. 41 filter paper. The first 10 ml portion of the filtrate was discarded and the filtrate was used for assay by titrimetry. The filtrate was diluted to working concentrations, as indicated in the preparation of standard solutions, for use in the spectrophotometric methods B (100 μg ml^{-1}) and C (10 μg ml^{-1}).

Determination of Pure Drug

Titrimetry (Method A). A 10 ml aliquot of the drug solution containing 1.0-20.0 mg CPT was transferred into a 100 ml titration flask, a pinch of borax and 0.5 ml of potassium chromate indicator were added and titrated to a brick-red end point with 0.01 mol l^{-1} silver nitrate solution. An indicator blank titration was run and correction applied. The drug content was calculated from:

$$\text{mg of drug} = VM_wS/n$$

where V is the volume of silver nitrate solution added (ml), Mw is the relative molecular weight of the drug, S is the concentration of silver nitrate solution (mol l^{-1}) and n is the number of moles of silver nitrate solution reacting with one mole of drug.

Spectrophotometry (Method B). In each of a series of 10 ml calibrated flasks were placed 0.25-5.0 ml of 100 μg ml^{-1} CPT solution by means of a micro burette followed by the addition of 1 ml of 2 mg ml^{-1} silver nitrate solution, mixed well and allowed to stand for 10 min. Then, 1 ml of 0.005% methyl orange dye solution was added to each flask, diluted to volume with water and the absorbance was measured at 520 nm against the reagent as a blank.

Spectrophotometry (Method C). Different aliquots 0.25-4.0 ml) of 10 μg ml^{-1} CPT solution were placed in a series of 10 ml calibrated flasks and the total volume was adjusted to 5.0 ml by adding requisite volume of water. A 1.5 ml volume of 15 μg ml^{-1} silver (I) solution was added to each flask, mixed well and, after 5 min., 1ml of 2.5 mol l^{-1} sodium acetate was added to each flask. Finally, 1 ml each of 0.02% 1,10-phenanthroline and 0.01% eosin solutions were added and diluted to the mark with water and mixed well. The absorbance of the solutions was measured at 550 nm against a water blank.

The increase (Method B) or decrease (Method C) in absorbance were plotted as a function of concentration of the drug to obtain the calibration graphs. The concentration of unknown was read from the calibration graph or deduced from the linear regression equation derived using the Beer's law data. A convenient aliquot of the tablet solution of proper concentration was treated in a manner described under procedures.

Recovery Experiment

Known amounts of pure drug in three different levels were added to a fixed amount of the drug in the formulation (pre-analyzed), and the total amount of the drug was determined by using the proposed procedures. Percent recovery of the added pure drug was calculated from:

$$\%\text{Recovery} = [(A_v - A_u)/A_a)] \times 100$$

where A_v is the total amount of the analyte found, A_u is the amount of the analyte present in the formulation and A_a is the amount of the pure analyte added to formulation.

RESULTS AND DISCUSSION

Captopril contains a -SH group, which can be oxidized to a dimer or converted to a mercaptide by treatment with a suitable metal ion [45-47].

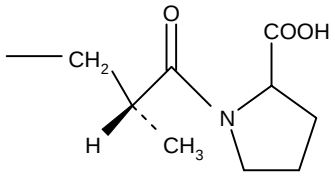
Method A

In this method, captopril was titrated directly with silver nitrate using chromate as an indicator. Since the working of the indicator is pH dependent [48], the effect of pH was examined. The pH of the solution at the end-point was 8-9 and a sharp color change was observed when 1.0-20.0 mg of the

drug was titrated with 0.5 ml of the indicator. A blank titration was found necessary. The reaction stoichiometry was found to be 1: 1 (CPT: $AgNO_3$), according to the following scheme:

$$RSH + AgNO_3 \rightarrow RSAg + HNO_3$$

where R is:



The relation between the drug content and the titration end-point was evaluated by calculating the correlation coefficient using the method of linear treatment of least-squares, and the value was found to be 0.9986 (n = 7), suggesting a definite stoichiometric reaction between the titrant and the analyte in the concentration range studied.

Method B

The spectrophotometric method using methyl orange is based on the facts that the color of the dye is controlled by the pH of the solution and the color change is not abrupt but occurs in a continuous manner when the pH changes continuously. Since the reaction between CPT and $AgNO_3$ follows a definite stoichiometry forming nitric acid, the addition of a fixed amount of $AgNO_3$ to increasing concentrations of CPT results in a proportional decrease in the pH of the solution. This causes a concomitant increase in the concentration of the acid form of methyl orange when a fixed amount of the dye is present in a series of solutions containing increasing concentrations of CPT and a large excess of $AgNO_3$. This was revealed by a proportional increase in the absorbance of the solution at 520 nm, which was corroborated by a correlation coefficient of 0.9998.

A preliminary investigation revealed that 1 ml of 0.005% methyl orange acidic solution produced a convenient maximum absorbance in a total volume of 10 ml. Hence, different amounts of CPT were added to 1 ml of a 0.005% dye solution in the presence of 1 ml of 2 mg ml^{-1} $AgNO_3$ solution and the absorbance was measured at 520 nm. The

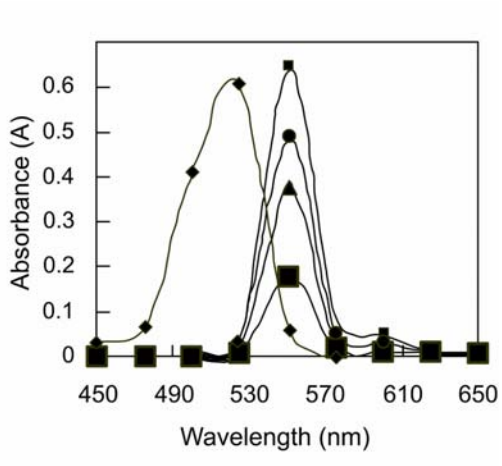


Fig. 1. Absorption spectra of system blank (♦), reagent blank (■) and solution after adding 10 (●), 20 (▲) and 30 (■) μg CPT.

absorbance increased linearly and became constant for the drug concentration of 50 μg ml^{-1} indicating a complete conversion of the basic form of the dye (yellow) to its acidic form (red).

Method C

Trace amounts of silver ion have been determined by the formation of an intensely colored ternary ion-pair complex with 1,10-phenanthroline (Phen) and 2,4,5,7-tetra bromofluorescein (TBF) as $[Ag(Phen)_2]^{2+}$. $[TBF]^{2-}$ [49]. In the presence of increasing amounts of CPT, proportionally increasing amounts of the added silver ion are fixed as silver mercaptide by the -SH group of CPT. As a result, there is a decrease in the silver ion concentration for the formation of the ternary complex (Fig. 1). This causes a concomitant decrease in the absorbance of the solutions, which is proportional to the captopril concentration.

The various parameters involved in the formation of the mercaptide and the ion-pair complex were optimized. It was found that 1.5 ml of a 15 μg ml^{-1} solution of silver ion was required to obtain a desirable maximum absorbance. A fraction of silver ions was fixed by the thiol group of captopril. Although 5 min standing time was found to be adequate for the formation of the mercaptide, 10 min were allowed for the reaction. One ml of each of 0.02% 1,10-phenanthroline and

0.01% eosin was found to be optimum for the formation of the ternary ion-pair complex with 22.5 μg of silver ions. In the presence of excess of 1,10-phenanthroline, the mercaptide dissociates and silver ions are released, causing a slow increase in the absorbance values. An excess of eosin causes the slow precipitation of the ion-pair complex. The ion-pair complex is reported to be stable for nearly 15 days in the pH range of 6-8. Since the pH of the solution decreases due to the release of nitric acid during the mercaptide formation, 1 ml of 2.5 mol l^{-1} sodium acetate was found necessary to maintain the required pH. The effective pH was found to be 6-8. It was observed that silver mercaptide is not formed quantitatively from the ternary ion-pair complex of silver. Hence, 1,10-phenanthroline and eosin must be added to the unreacted silver ions after the formation of silver mercaptide. Two blanks were prepared for this system. The reagent blank, which contained optimum concentrations of the reagents except CPT, gave the maximum absorbance (Fig. 1). The other blank was prepared in the absence of CPT and silver ions to determine the contribution of the other reagents to the absorbance of the system. As the absorbance of this second blank was comparable to that of water, the absorbance of the complex was measured against water. The decrease in absorbance values at 550 nm was plotted against the increasing concentration of captopril to obtain the calibration graph.

Analytical Data

The linearity of the calibration graphs is apparent from the correlation coefficient, r, obtained by determining the best-fit line via linear least-squares treatment. The linearity based on the Beer's law is obeyed up to 50 μg ml^{-1} in Method B and, in and inverse way, up to 4 μg ml^{-1} in Method C. The correlation coefficient r, the slope m and the intercept Z of the equation of the regression equation A = Z + mC (A = absorbance, C = CPT concentration in mol l^{-1}) are summarized in Table 1. The apparent molar absorptivity (ε) Sandell sensitivity, limit of detection (LOD) and limit of quantification (LOQ) are also given in Table 1.

Table 1. Analytical Parameters

Parameter	Method B	Method C
λ_{max} (nm)	520	550
Linear range (μg ml^{-1})	2.50-50.0	0.25-4.0
ε (l mol^{-1} cm^{-1})	1.40×10^3	3.27×10^4
Sandell sensitivity (ng cm^{-2})	166.70	6.6400
LOD (μg ml^{-1})	1.0600	0.3200
LOQ (μg ml^{-1})	3.5200	1.0500
m	6.00×10^{-3}	-7.60×10^{-2}
Z	0.0000	0.3800
r	0.9998	-0.9804

Accuracy and Precision of the Methods

Under the optimum conditions, the accuracy and precision of the methods were determined by performing seven replicate analyses on pure drug in three different levels (amounts). The results of the study are compiled in Table 2 and indicate that the methods are fairly accurate (%relative error, %RE <2) and precise (%relative standard deviation, %RSD <3).

Applications

The proposed methods were applied to the assay of different brands of tablets containing captopril. The results are confidence level, the evaluated student's t- and F-values are less than the tabulated values, as shown in Table 3, indicating that the proposed methods are as accurate and precise as the official method.

Table 2. Accuracy and Precision of the Proposed Methods Based on Seven Replicate Determinations

Method A				Method B				Method C			
Amount taken (mg)	Amount found (mg)	RE (%)	RSD (%)	Amount taken (μg)	Amount found (μg)	RE (%)	RSD (%)	Amount taken (μg)	Amount found (μg)	RE (%)	RSD (%)
3.00	3.05	1.67	2.36	100.00	100.22	0.23	1.30	10.00	9.82	1.80	1.22
10.00	10.08	0.80	0.53	200.00	200.27	0.14	0.34	20.00	20.26	1.30	1.71
17.00	16.73	1.58	1.41	300.00	300.94	0.31	0.29	30.00	30.44	1.47	2.14

The accuracy and reliability of the methods were further given in Table 3. The validity of the methods was tested by analyzing the same batch tablets by the official methods [3]. Statistical analysis of the results revealed that at a 95% ascertained through recovery studies. To a fixed and known amount of the drug in the pre analyzed tablet solutions, pure CPT was added in three different levels and the total amount was determined by the proposed methods. The percent recoveries of the pure drug added (Table 4) indicated that neither the end-point detection in the titrimetric method nor the absorbance in the spectrophotometric methods were affected by the commonly encountered excipients such as talc, starch, lactose, gum acacia, sodium alginate and magnesium stearate. Metal ions such as mercury(II), cadmium(II) and zinc(II), and iodide and cyanide ions, which interfere in the thiol group determination through metal mercaptide formation [50], are seldom present in the tablet preparations, and hence the methods can be considered specific for captopril.

CONCLUSIONS

In conclusion, the methods based on silver mercaptide formation are found to be very simple, relatively specific, accurate and precise for the determination of CPT in tablets. Method A is the first direct titrimetric procedure with visual end-point detection ever reported for CPT and is characterised by the absence of any critical working conditions, sharp end-point, and long and dynamic linear range of determination. This is in contrast to narrow range of applicability (0.5-5.0 mg) in potentiometric [30] and large amount (100 mg) required in conductometric [31] titration methods. The spectrophotometric methods employ very mild working conditions without heating or extraction steps and are fairly sensitive compared to many methods reported earlier [36,41,43]. In fact, method C, based on ion-pair complex formation, is one of the most sensitive ever developed for CPT. Both methods are highly reliable owing to the stability of the dye and ion-pair complex which are ultimately measured. This is amply demonstrated by the high reproducibility of the results. These merits, in addition to the use of simple and inexpensive reagents and instrument, suggest the use of the methods in drug control laboratories.

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Table 3. Results of Analyses of Tablets Containing Captopril

Brand name of tablet (Company)	Label claim (mg)	Found (% Recovery ± SD)[a]			
		Method A	Method B	Method C	Reference method
Acetin (Wockhardt)	25.00	97.96 ± 0.85 (t = 1.72, F = 1.88)	98.64 ± 0.26 (t = 0.43, F = 5.68)	99.14 ± 0.38 (t = 1.20, F = 2.66)	98.76 ± 0.62
Angiopril (Torrent)	50.00	98.26 ± 0.67 (t = 2.11, F = 3.11)	97.74 ± 0.42 (t = 0.67, F = 1.22)	98.10 ± 0.36 (t = 2.17, F = 1.11)	97.56 ± 0.38
	25.00	101.23 ± 1.02 (t = 1.30, F = 4.92)	101.36 ± 0.24 (t = 2.38, F = 3.67)	100.78 ± 0.64 (t = 1.07, F = 1.940	100.62 ± 0.46
Captopril (Lupin Lab Ltd.)	25.00	101.66 ± 0.96 (t = 1.61, F =2.94)	100.96 ± 0.62 (t = 0.30, F = 1.23)	101.28 ± 0.53 (t = 1.20, F = 1.12)	100.84 ± 0.56
	12.50	99.35 ± 0.74 (t = 0.58, F = 1.74)	98.16 ± 0.38 (t = 2.08, F = 2.17)	98.63 ± 0.66 (t = 0.40, F = 1.39)	98.78 ± 0.56

[a]Average value of five determinations; Tabulated t value at 95 % confidence level = 2.77 and Tabulated F value at 95% confidence level = 6.39.

Table 4. Results of Recovery Study Using Standard-Addition Method[a]

Brand name of tablet	Method A					Method B					Method C				
	Amount of drug in extract (mg)	Amount of pure drug added (mg)	Total amount found (mg)	%Recovery of pure drug added	SD	Amount of drug in extract (μg)	Amount of pure drug added (μg)	Total amount found (mg)	%Recovery of pure drug added	SD	Amount of drug in extract (μg)	Amount of pure drug added (μg)	Total amount found (μg)	%Recovery of pure drug Added	SD
	0.99	5.00	6.07	101.60	0.55	49.60	100.00	152.47	102.87	0.35	9.98	10.00	19.23	98.50	0.80
Acetin	0.99	10.00	11.02	100.31	0.96	49.60	200.00	250.05	100.23	1.01	9.98	20.00	30.63	103.25	0.44
	0.99	15.00	15.89	99.33	0.66	49.60	300.00	345.44	98.61	0.31	9.98	30.00	39.27	97.63	0.48
Anpgiocril	2.03	5.00	7.16	102.59	0.61	5.01	100.00	107.98	102.97	0.96	5.11	10.00	15.41	103.00	0.62
	2.03	10.00	12.07	100.40	0.72	5.01	200.00	204.25	99.62	0.68	5.11	20.00	24.68	99.41	0.41
	2.03	15.00	16.66	97.53	1.00	5.01	300.00	301.84	98.94	0.28	5.11	30.00	34.41	99.46	0.57
Captopril	2.95	5.00	8.17	104.41	0.46	4.93	100.00	105.98	101.05	0.43	4.96	10.00	15.36	102.00	0.87
	2.95	10.00	12.96	100.10	0.02	4.93	200.00	205.59	100.33	0.99	4.96	20.00	24.59	98.15	0.64
	2.95	15.00	17.58	97.53	0.44	4.93	300.00	299.01	98.02	1.41	4.96	30.00	34.17	97.37	0.29

[a]Mean value of three determinations, SD = Standard deviation.

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