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Short Communication

SPECTROSCOPIC AND VOLUMETRIC TECHNIQUES FOR THE ESTIMATION OF IVABRADINE IMPURITY 3,3'-(PROPANE-1,3-DIYL)BIS(7,8-DIMETHOXY-1,3,4,5-TETRAHYDRO-2H-BENZO[D]AZEPIN-2-ONE)

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ABSTRACT

Objective: Two simple and sensitive techniques-one spectrophotometric and one titrimetric-have been developed for the determination of 3,3'-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) commonly known as ivabradine impurity-9 (IVA-9).

Methods: The spectrophotometric method is based on the oxidation of drug impurity by excess cerium (IV) sulphate in acidic medium and the subsequent reaction of the remaining Ce(IV) with a known amount of ferrous ammonium sulphate. The resultant ferric ion is then made to react with thiocyanate in acid medium to form a brown coloured complex which is analyzed spectrophotometrically against the reagent blank. In the volumetric method, the un-reacted Ce(IV) is titrated against standard ferrous ammonium sulphate to estimate the quantity of IVA-9.

Results: The colored complex showed an absorption maximum at 479 nm when measured spectrophotometrically. The stated methods are validated statistically using the International Council for Harmonization guidelines-ICH Q2(R1) for precision and accuracy. The method showed a linear response from 0.5 to 100µg/ml with a correlation coefficient of 0.9985.

Conclusion: No estimation techniques have been reported to date for the determination of this molecule. The proposed techniques may be used for the routine quantification in its pure form and also in the presence of its parent drug molecule Ivabradine.

Keywords: Ivabradine impurity-7, Ce(IV), UV-Visible spectrophotometry, Drug impurity

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INTRODUCTION

3,3'-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) (IVA-9) is a pharmaceutical impurity formed en route the synthesis of anti-ischaemic drug ivabradine. Ivabradine is a cardiotonic agent used to treat suggestive chronic heart failures which are not managed by beta blockers. It's efficiency in treating angina pectoris and myocardial ischemia, without any negative hemodynamic effects, has been described [1]. Estimation of ivabradine has been achieved in the past by high-performance liquid chromatography [2-4], thin layer chromatography [5-8], liquid chromatography with spectrometry [9-11] and spectrophotometry [12, 13]. The polymorphism, co-crystallization [14], crystal chemistry [15] and sustained release studies [16] of ivabradine were reported. X-ray analysis and conformational studies [17] showed the chlorine salt of ivabradine as a horseshoe-shaped diastereomer with two asymmetric bicyclic moieties. The first part is made up of a seven-membered lactam structure and the second part contains a four-membered ring. The structure and properties of IVA-9 are expected to be significantly different from that of ivabradine as it is made up of two symmetric benzazepine units connected via aliphatic acyclic linkage and lacking tertiary amino nitrogen as seen in fig. 1(a) and 1(b).

The structural and chemical properties of drug molecules and their intermediates play a big role in pharmacokinetics and drug action. As IVA-9 is an intermediate impurity of drug ivabradine, we tried to explore the molecule. However, the perusal of literature revealed a dearth of details regarding the structure and property of this molecule. Though the spectrophotometric estimation of ivabradine in the presence of its degradation products has been described by Mostafa *et al.* [18], the structural properties of the title molecule were unexplored. Further, no estimation techniques have been reported so far to determine IVA-9 in its pure form or as a pharmaceutical intermediate. The authors have performed similar studies in the past on 4-nitro 2-phenoxy aniline using 8-hydroxyquinoline which is an impurity associated with the drug nimesulide [19, 20]. As an extension study, we propose one spectrophotometric method and one volumetric method for the determination of IVA-9 in the pure form also in the presence of its parent drug molecule ivabradine.

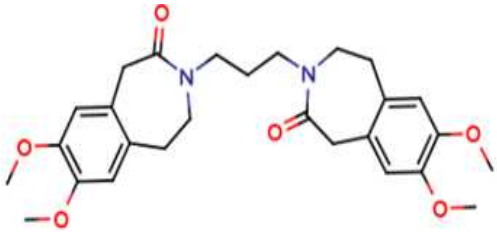

Fig. 1(a): Structure of IVA-9

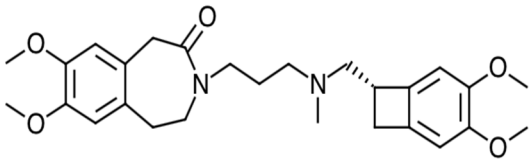

Fig. 1(b): Structure of ivabradine

The proposed methods involve the oxidation of IVA-9 by a surplus amount of Ce(IV) and the subsequent reaction of the remaining Ce(IV) with a known amount of ferrous ammonium sulphate. The resultant ferric ion is then made to react with thiocyanate in an acid medium to form a brown colour complex [21].

Reaction Scheme

Drug+Ce(IV) → Oxidized form of drug+Ce(III)

Excess Ce(IV)+Fe^{+2}→ Ce(III)+Fe^{+3}

Fe^{+3}+SCN^{-}→ Complex

Optimum reagent and reaction conditions were arrived at by fixing the concentration of one reagent while varying others. Ideal reagent concentrations and sequence of addition are listed below.

Different aliquots of reagent stock were mixed with 1 ml of 5 M hydrochloric acid and 3 ml of Ce(IV) sulpahate (400 µg/ml) and allowed to stand for 15 min. To this 2 ml of ferrous ammonium sulphate (300 µg/ml) was added and after 5 min, 1 ml of 30% potassium thiocyanate was added and mixed well. The solution was then made up using double distilled water and analyzed spectrophotometrically. The absorption maximum was recorded at 479 nm against the reagent blank (fig. 2).

The listed methods are validated statistically using ICH Q2(R1) guidelines[22]. The precision and accuracy of the method were ascertained by both intraday and interday recovery studies and given in table 1.

The sensitivity of the method is apparent from various regression parameters such as sandell sensitivity, molar absorptivity, limit of detection, limit of quantification etc. and demonstrated in table 2.

Under the listed optimum conditions, a linear response has been observed between absorbance and concentration of drug impurity over a wide range (fig. 3).

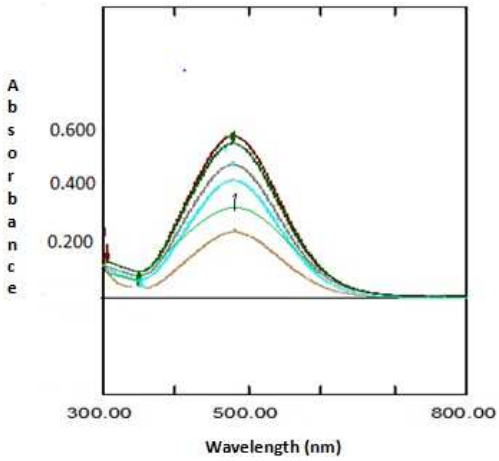

Fig. 2: Absorption maximum at 479 nm

Table 1: Recovery studies

Technique	Iva-9 added	Intra-day assessment			Inter-day assessment		
		Iva-9 obtained	% RE	% RSD	Iva-9 obtained	% RE	% RSD
Spectrophotometry	1.0	1.02	2.00	2.58	0.98	2.00	2.85
(µg/ml)	2.0	2.03	1.50	1.05	1.98	1.00	1.33
	3.0	3.03	1.00	0.87	2.95	1.67	1.80
Titration	2.0	2.02	1.00	0.98	1.95	2.50	2.80
(mg)	4.0	4.04	1.00	1.33	3.94	1.50	1.80
	6.0	6.03	0.50	0.55	5.92	1.33	2.20

Table 2: Regression parameters

Parameter	Range
$\lambda_{Max,}$ nm	479 nm
Beer's Law range, µg/ml	0.5–100 mg/l
Molar absorptivity, L mol^{-1} cm^{-1}	1.86062 $x10^5$
Limit of detection, µg/ml	0.14
Limit of quantification, µg/ml	0.42
Sandell sensitivity	0.0027
Regression Equation*	
Intercept	0.6136
Slope	-0.0512
S_a	0.0094
S_b	0.0014
Correlation Coefficient	-0.99848

*Y=a+bX, where Y is absorbance and X is concentration (µg/ml), S_a = Standard deviation of intercept and S_b = Standard deviation of the slope.

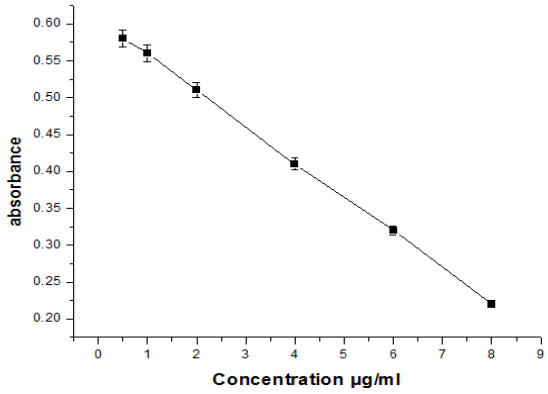

Fig. 3: Calibartion curve

For volumetric estimation, 10 ml of 50 µg/ml equivalent of stock solution is mixed with 1 ml of 1 M sodium acetate and 5 ml of 0.05M of Ce(IV) sulpahate. The contents were mixed throughly and made to stand for 15 min. To this 5 ml of 3 M sulphuric acid solution was added and titrated against 0.05 M ferrous ammonium sulphate using ferroin indicator. The experiment was repeated with a blank titration for comparison.

The reported methods are free from cumbersome extraction steps. Since no estimation techniques have been reported till date, the authors are hopeful that the proposed methods could be used for the determination of IVA-9 in the pure form and in pharmaceutical formulations. Further, there is scope to explore the said method as a marker test to find the presence 3,3'-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) as an impurity in the parent drug ivabradine.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

Declared none

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