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Area Under Curve Method Development And Validation For Estimation Of Dronedarone In Bulk And Tablet Dosage Form

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Abstract

A simple, precise and economical UV - spectrophotometric method has been developed for the estimation of Dronedarone in pharmaceutical dosage form. Method applied was area under curve (AUC) in which area was integrated in the wavelength range of 270.40 nm – 300.0 nm. Calibration curves were plotted for the method by using instrumental response at selected wavelengths and concentrations of analyte in the solution. Linearity for the detector response was observed in the concentration range of 4-24 µg/ml for the method. Tablet formulation was analyzed and the percentage of drug determined in the assays was 98.00% – 102.00%. Accuracy and precision studies were carried out and results were satisfactory. The results of the analysis were validated statistically. Limit of detection and limit of quantitation were determined for the method. The method was validated by following the analytical performance parameters suggested by the International Conference on Harmonization. All validation parameters were within the acceptable range. The developed method was successfully applied to estimate the amount of Dronedarone in pharmaceutical formulation.

Keywords: Dronedarone, UV-spectrophotometry, Area Under Curve, Validation.

INTRODUCTION

Dronedarone is chemically a benzofuran derivative related to amiodarone, a popular anti-arrhythmic drug. In Dronedarone, the iodine moieties are not present, thus reducing toxic effects on the thyroid and other organs [1-4]. A methyl sulfonamide group is added to reduce solubility in fats and hepatic impairment. Dronedarone displays amiodarone like class III anti-arrhythmic activity in vitro and in clinical trials. [5-8]. The drug also exhibits activity in each of the four Vaughan-Williams antiarrhythmic classes. Its synthetic name is N-{2-butyl – 3 – {p – {3-{dibutyl amino} propoxyl} benzoyl}-5-benzofuranyl} methane sulphonamide [1].

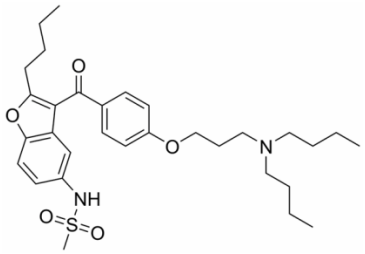

Figure 1: Chemical structure of Dronedarone

Literature survey reveals a few chromatographic methods for the determination of Dronedarone in its pure form and tablet dosage form [2-6] and few methods for its estimation have been reported [7]. So far, no derivative spectrophotometric method has been reported for the estimation of Dronedarone from pharmaceutical dosage forms. This paper deals with validation and development of a method by area under curve for the assay of Dronedarone from its bulk drug and in pharmaceutical dosage forms.

The method was validated according to ICH guidelines [9]. Thus the objective of present study was to develop a method that can be applied for the routine analysis of Dronedarone in tablet formulations.

MATERIALS AND METHODS

Dronedarone working standard was obtained as gift sample from Alkem Pharma Mumbai, India. A tablet formulation containing 50 mg of Dronedarone was purchased from local market Multaq from Sanofi Aventis. All chemicals and reagents used were of analytical grade.

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INSTRUMENTS USED

A double beam UV-VIS spectrophotometer (UV-2450, Shimadzu, Japan) connected to computer loaded with spectra manager software UV Probe 2.21 with 10 mm quartz cells was used. The spectra were obtained with the instrumental parameters as follows: wavelength range: 200-400 nm; scan speed: medium; sampling interval: 1.0 nm; band width (Δλ):10.0 nm; spectral slit width: 1 nm. All weights were taken on electronic balance (Model Shimadzu AUX 120).

PREPARATION OF STANDARD STOCK AND WORKING STANDARD SOLUTION

The standard stock solution of Dronedarone was prepared by dissolving accurately weighed 10 mg of the drug in methanol and diluted to 100 mL to obtain a final concentration of 100 µg/mL.

METHOD: AREA UNDER CURVE

The AUC (area under curve) method is applicable where there is no sharp peak or when broad spectra are obtained. It involves the calculation of integrated value of area with respect to the wavelength between the two selected wavelengths 270.40 and 300.0nm. Area calculation processing item calculates the area bound by the curve and the horizontal axis. The horizontal axis is selected by entering the wavelength range over which area has to be calculated. This wavelength range is selected on the basis of repeated observations so as to get the linearity between area under curve and concentration. The spectrum obtained from zero order derivative was used to calculate AUC. The calibration curve was constructed by plotting concentration (4-24 µg/mL) versus AUC.

PREPARATION OF SAMPLE SOLUTION

Ten Dronedarone tablets (50 mg each) were weighed, transferred to a clean dry mortar and ground into a fine powder using a pestle. Tablet powder equivalent to 10 mg of drug was transferred to a 100 mL volumetric flask and 50 mL methanol was added. After sonication for 10 min, the mixture was diluted to volume 100 ml with methanol and filtered through Whatman filter paper (No. 41). From the filtrate an appropriate aliquot was taken in such a way that the final concentration in 10 mL is 12 µg/mL. The responses were measured and concentration in the sample was determined by comparing the response of sample with that of the standard.

VALIDATION OF METHOD

The proposed method was validated as per ICH-Guidelines Q2 (R1) [9].

LINEARITY

For the method, linearity was repeated 3 times for validation. The calibration curve was constructed by plotting the response y-axis versus the theoretical concentrations of standards x-axis, by using linear regression analysis. Linearity was expressed as a correlation coefficient; r2 the value must be > 0.999.

PRECISION

The intraday and interday precision of the proposed spectrophotometric method was determined by estimating the corresponding response 3 times on the same day and on 3 different days over a period of one week for 3 different concentrations of Dronedarone for area under curve 8, 12, and 16 µg/mL and the results are reported in terms of percent relative standard deviation.

ACCURACY

The accuracy of the method was determined by calculating recoveries of Dronedarone by the method of standard additions. The study was performed by spiking known amounts of Dronedarone at three concentrations (viz. 3.2, 4.0, and 4.8 µg/mL; ranging from 80% to 120%) into a sample solution with known amount of the analyte (4 µg/mL). Three samples were prepared at each of these concentrations. The recovery of added drug was estimated by measuring the response and by fitting these values to the straight-line equation of calibration curve.

SPECIFICITY

Results of analysis for solutions prepared from tablet formulation showed that there is no interference of excipients when compared with the working standard solution. Thus, the method was said to be specific.

RUGGEDNESS

Ruggedness of the proposed method was determined by analyzing aliquots from homogenous slot (16 µg/mL) in different laboratories by different analysts using similar operational and environmental conditions. The results are reported in terms of percent relative standard deviation.

RESULTS AND DISCUSSION

The molecular structure of the Dronedarone is presented in Fig.1. Methanol was selected as the solvent for Dronedarone because provides good solubility and other characteristics for AUC measurements. The absorption spectrum of Dronedarone in methanol for the method is indicated in Fig. 2.

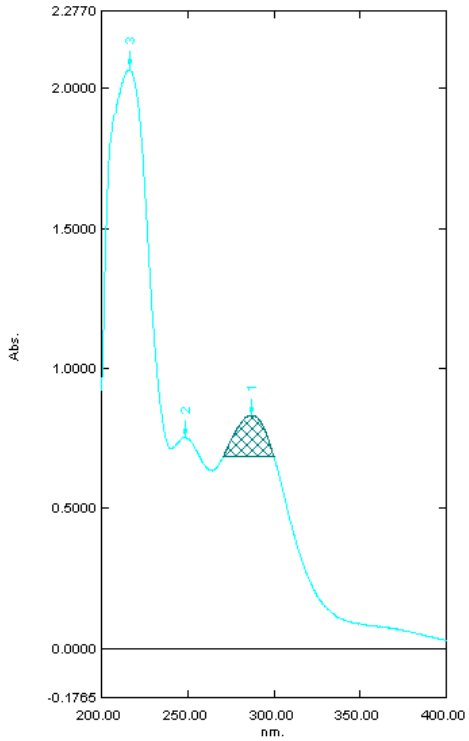

Figure 2: Area under curve spectrum of Dronedarone in methanol

Optical characteristics of Dronedarone were calculated by the proposed method and are presented in Table 1.

Table 1: Optical characteristics of Dronedarone

Parameters	Dronedarone
Beer-Lambert's range(µg/mL)	4-24
λ max(nm)/ wave length range (nm)	289
Slope	0.066
Intercept	0.120
Correlation coefficient	0.999
Limit of detection (µg/mL)	0.027
Limit of quantitation (µg/mL)	0.084

Table 2: Assay results of commercial Dronedarone tablet.

Dronedarone marketed formulation	Label claim/Tablet	%recovery	% RSD
Tablet	50 mg	100.03%	0.29

*Average of three determinations

Table 3: Results of Precision studies

Conc. µg/mL	Intra-day		Inter-day	
	% Recovery	% RSD	% Recovery	% RSD
8	99.99	0.03	100.02	0.03
12	100.49	0.18	100.38	0.58
16	99.97	0.04	99.99	0.02

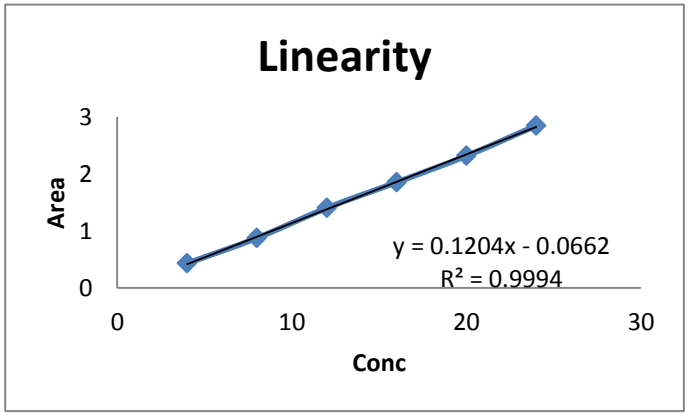

Figure 3: Calibration curve of Dronedarone at 289nm

The intra-day and inter-day precision values (%RSD) were calculated for Dronedarone (results shown in Table

3) and the values obtained (⩽2%) comply with the stated limits of the guidelines. The accuracy of Dronedarone was evaluated by the percent recovery studies at concentration levels of 80, 100, and 120% and the values obtained were found to be in the acceptable limits (⩽2%) (results presented in Table 4).

Table 4: Results of Accuracy studies

Nominal Value %	Initial amount	Added amount µg/ml	% Recovery	% RSD
80	4	3.2	99.88	0.34
100	4	4	99.98	0.20
120	4	4.8	99.95	0.28

This indicates that there was no interference from the excipients present in the dosage form. Ruggedness of proposed method was determined with the help of two different analysts. and results were evaluated by calculating the %RSD value and lying within the range (results shown in Table 5).

Table 5: Results of Ruggedness studies

Analyst	Amount found of Dronedarone [%]	%RSD [n=3]
I	100.01	0.02
II	99.99	0.04

CONCLUSION

The UV spectrophotometric AUC method developed for determination of Dronedarone was based on different analytical techniques, UV-Spectrophotometric, AUC method. The method was validated and found to be simple, sensitive, accurate, and precise in compliance to the limits stated in the ICH guidelines. Hence, we conclude that the method can be used successfully for routine analysis of pharmaceutical dosage forms containing Dronedarone. The proposed spectrophotometric method will not replace the presently known methods available for the analysis of Dronedarone. However, it can serve as an alternative where advanced instruments (e.g. HPLC) are not available for routine analysis.

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