

## DEVELOPMENT AND VALIDATION OF A SPECTROPHOTOMETRIC METHOD FOR DETERMINATION OF DRONEDARONE IN BULK DRUG AND PHARMACEUTICAL FORMULATION

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### ABSTRACT

A simple, sensitive and accurate spectrophotometric method has been developed for the determination of Dronedarone in bulk formulation. The  $\lambda$  max of the Dronedarone was found to be 290nm in Acetonitrile: Buffer (pH 6.5). The method shows high sensitivity with linearity 5 to 30 $\mu$ g/ml (regression equation:  $Y=0.038x-0.059$ ;  $r^2=0.999$ ). The apparent molar absorptivity was found to be  $1.89 \times 10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$  in Acetonitrile: phosphate Buffer (pH 6.5). This method was tested and validated for various parameters according to ICH guidelines and USP. The Detection limit and quantitation limit were found to be 0.4  $\mu$ g ml<sup>-1</sup> and 1.25  $\mu$ g ml<sup>-1</sup> in Acetonitrile: Buffer (pH 6.5) respectively. The results demonstrated that the procedure is accurate, precise and reproducible (relative standard deviation < 2%), while being simple, cheap and less time consuming and can be suitably applied for the estimation of Dronedarone in bulk and pharmaceutical formulation.

### KEY WORDS

Dronedarone, Acetonitrile: Buffer (pH 6.5). Spectrophotometry.

### 1. INTRODUCTION

Dronedarone is a drug discovered by Sanofi-Aventis, mainly for the indication of cardiac arrhythmias. Chemically, Dronedarone is a benzofuran derivative with IUPAC name N-(2-Butyl-3-(p-(3 (dibutylamino) propoxyl) benzoyl) -5- benzofuranyl) methane sulfonamide. Dronedarone is related to amiodarone, a popular antiarrhythmic. The use of amiodarone is limited by toxicity due its high iodine content (pulmonary fibrosis, thyroid disease) as well as by liver disease. In dronedarone, the iodine moieties are not present, reducing toxic effects on the thyroid and other organs. Dronedarone displays amiodarone –

like class III antiarrhythmic activity in vitro and in clinical trials. The drug also appears to exhibit activity in each of the 4 Vaughan-Williams antiarrhythmic disease. Therefore in the present study, a spectroscopic method has been developed for the estimation of Dronedarone in the bulk and tablet dosage form using Acetonitrile: phosphate Buffer (pH 6.5)[70:30v/v]. The method developed is specific, precise, accurate and well validated. This method is economical. The developed method was validated as per ICH guidelines and USP requirements .suitable statistical tests were performed on validation data [1-6].

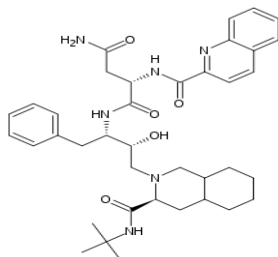


Figure-1: Structure of Dronedarone

## 2. MATERIALS AND METHOD

### 2.1 Instrument

UV-Visible Spectrophotometer, LABINDIA Analytical Instruments Pvt. Ltd, model UV3092 connected to computer loaded with UVWin5 software ver.5.2.0.1104, have a wavelength accuracy of 0.1nm and matched quartz cells of 10mm path length was used for all spectral measurements.

**2.2 Reagents and materials:** Dronedarone pure drug was obtained from MSN Laboratories Limited (Hyderabad) as a gift sample with 99.25% (w/w) assay value and was used without further purification. All chemicals and reagents used were of analytical grade (Rankem, India). Dronedarone tablets were

purchased from local market and used with in self-life period. Each tablet was labeled contain 400 mg of Dronedarone.

### 2.3 Selection of wavelength

In order to ascertain the wavelength of maximum absorption ( $\lambda_{max}$ ) of the drug, different solutions of the drugs ( $5\mu\text{g/ml}$  -  $30\mu\text{g/ml}$ ) in Acetonitrile: phosphate Buffer (pH 6.5) was scanned using spectrophotometer within the wavelength region of 200 – 400 nm against Acetonitrile: Buffer (pH 6.5) [70:30 v/v] as blank. The resulting spectra were shown in **Fig 2** and the absorption curve showed characteristic absorption maxima at 290 nm for Dronedarone.

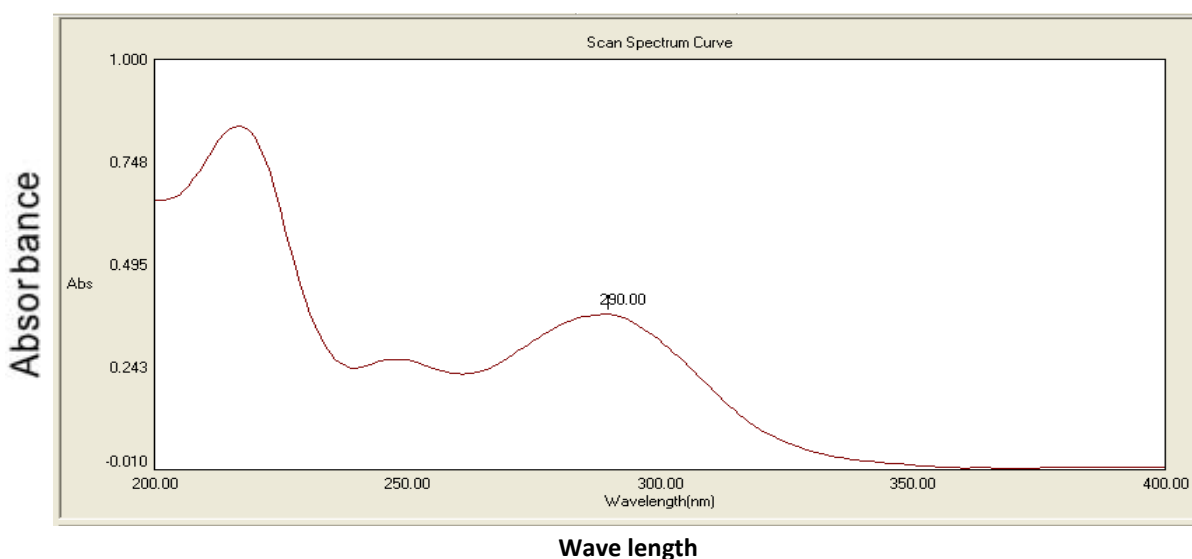


Figure-2: Absorption spectrum of Dronedarone

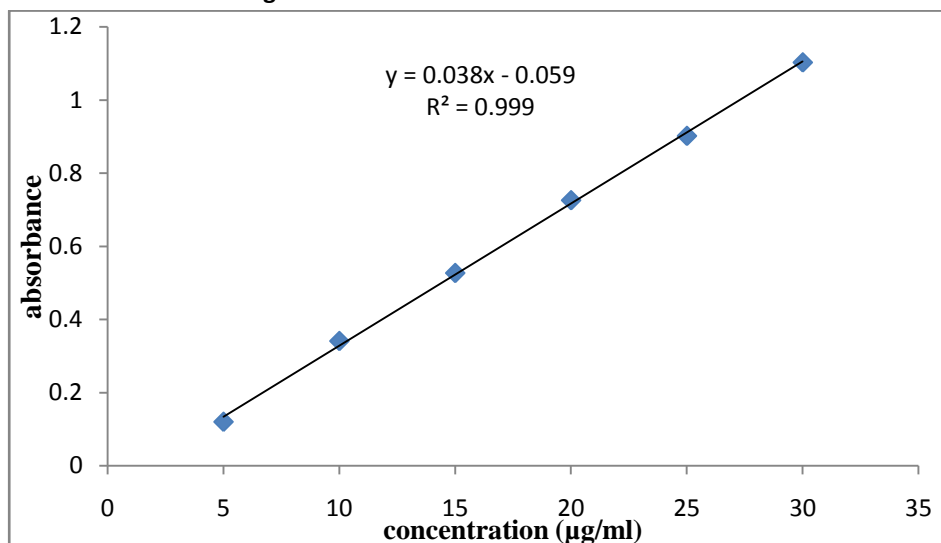
### 2.4 Preparation of stock solution

10 mg of Dronedarone was accurately weighed and dissolved in 100 ml of Acetonitrile: phosphate Buffer (pH 6.5) [70:30] in 100ml volumetric flask to get the concentration about  $100\mu\text{g ml}^{-1}$  stock solution.

### 2.5 Preparation of calibration curve

A series of concentrations were prepared in the range of  $5\text{--}30\mu\text{g/ml}$  of Dronedarone in a 10 ml standard flask in ACN: Buffer (pH 6.5) [70:30, v/v] medium and absorbance were found at 290 nm with an overlaid spectrum (**Fig 3**).

Figure 3: Calibration curve of Dronedarone



### 3. METHOD VALIDATION

#### 3.1 Specificity

Dronedarone solutions ( $5 \mu\text{g ml}^{-1}$ ) were prepared in both the selected media along with and without common excipients (starch, talc, ethyl cellulose, magnesium stearate) separately. All the solutions were scanned from 200 to 400 nm and checked for change in the absorbance at respective wavelengths. (Table 1)

#### 3.2 Accuracy

As a part of determining accuracy of the proposed method, drug concentrations were prepared from independent stock solution and analyzed ( $N = 9$ ). Accuracy was assessed as mean percentage recovery. (Table 2)

#### 3.3 Precision

Repeatability was determined by using different levels of drug concentrations (same concentration levels taken in accuracy study), prepared from independent stock solution and analyzed ( $N = 9$ ) (Table 3). Inter-day and intra-day variation and instrument variations were taken to determine intermediate precision of the proposed methods. Different levels of drug concentrations in triplicates were prepared three different times in a day and studied for intra-day variation. Same protocol was

followed for three different days to study inter-day variation ( $N = 27$ ).

#### 3.4 Linearity

The linearity is established for the proposed method, nine separate series of solutions of the drug ( $5\text{--}30 \mu\text{g ml}^{-1}$  in ACN: Buffer (pH 6.5) [70:30, v/v] medium) were prepared from the stock solutions and analyzed.

#### 3.5 Robustness

Robustness of the proposed method is determined by (a) changing strength of the media by  $\pm 2\%$  and (b) stability of the Dronedarone in the both selected medium at room temperature for 8 hrs. Three different concentrations (LQC, MQC and HQC) were prepared in both media with different strength. Mean percentage recovery was determined (Table 4).

#### 3.6 Estimation from formulations

Twenty tablets were weighed and pulverized. Amount of the powder equivalent to 10 mg of Dronedarone was taken and extracted with solvent for 30 min. This solution was diluted to prepare a  $100 \mu\text{g ml}^{-1}$  concentration in respective media. Finally solution was filtered through Whatman filter paper number 40 and the filtrate was diluted to prepare a  $10 \mu\text{g ml}^{-1}$  concentration and the sample was analysed using proposed methods (Table 5).

**Table 1: Optical Characteristics and Regression Equation of Dronedarone**

Parameters	Values
$\lambda_{\max}$	290 nm
Beer's law limit ( $\mu\text{g}/\text{ml}$ )	5-30
Molar absorptivity ( $\text{lit}/\text{mol}\cdot\text{cm}$ )	
Regression equation( $y=mx+c$ )	$y = 0.038x-0.059$
Slope (m)	0.038
Intercept(c) 0.0233	0.059
Correlation coefficient( $r^2$ )	0.999
Limit of detection(LOD) ( $\mu\text{g}/\text{ml}$ )	
Limit of quantification (LOQ)( $\mu\text{g}/\text{ml}$ )	1.25

$Y^* = ax+b$ , where 'x' is concentration in  $\mu\text{g}/\text{ml}$  and Y is absorbance $10^{-3}$

**Table 2: Accuracy data of the developed method**

Sno	Concentration (mcg/ml)	Mean Absorbance	S.D	%RSD	%Recovery
1	10	0.87	0.086	0.125	99.99
2	15	0.22	0.080	0.170	100.23
3	20	0.72	0.11	0.223	100.11

S.D-Standard Deviation, %RSD-Relative Standard Deviation

**Table 3: Precision data of the developed method**

Sno	Concentration (mcg/ml)	Intra-day repeatability % R.S.D(N = 27)			Inter-day repeatability % R.S.D (N = 9)
		Day 1	Day 2	Day 3	
1	10	1.23	0.79	0.87	1.69
2	15	0.66	0.56	0.22	0.42
3	20	0.57	0.33	0.72	0.82

**Table 4: Robustness data for the developed method**

Sno	Concentration (mcg/ml)	Mean Absorbance (N=9)	S.D	%Recovery	%Recovery of SD
1	10	0.273	0.080	100.5	0.079
2	10	0.744	0.01	99.5	0.1

**Table 5: Assay of Dronedarone**

Sample	Labeled amount (mg)	Amount found (mg)	%Purity
Dronedarone (Trade name : MULTAQ)	400mg	400mg	99.98

## 4. RESULTS AND DISCUSSIONS

The UV spectrophotometric method was used to quantify the dronedarone in tablet dosage forms. The UV spectrum (**Fig 2**) shows absorption maxima at 290 nm. The calibration curve showed linearity over a concentration range from 5-30 µg/mL, which follows the Beer and Lambert's law. The slope and intercept of the calibration line was determined by linear regression. The UV spectrophotometric method was developed and validated as per designed protocol, based on ICH Q2B guidelines.

The calibration curve was developed for absorbance Vs concentration (µg/ml) and it was linear over concentration range of 5-30 µg/ml. The regression line equation for the analysis was  $y = 0.038x - 0.059$  with regression coefficient of 0.999. The LOD and LOQ values were shown in **Table 1**. And the calibration curve was shown in **Fig 3**.

### 4.1. ANALYTICAL VALIDATION

#### 4.2. Specificity and selectivity

The specificity of the method was determined by checking for interference with the drug from placebo components. This method was proven by the no change in absorbance of the drug with and without excipients at respective wavelength. Therefore proposed method was specific and selective for the drug.

#### 4.3. Accuracy

The accuracy of the method was evaluated by the recovery studies. Recovery studies were carried out at three levels of concentrations i.e. 10, 15, 20 µg/ml by the addition of known amounts of the standard to the placebo preparation within the analytical concentration range of the proposed method. The percentage recovery values were found to be 99.99-100.23 with %RSD of <2% (**Table 2**) which indicates that the proposed method was accurate.

#### 4.4 Precision

Precision determined by studying repeatability and intermediate precision. Repeatability (% R.S.D.) In ACN: Buffer (pH 6.5) [70:30, v/v], at all three levels of concentrations (**Table 3**). Repeatability results indicate the precision under the same operating conditions over a short interval of time and inter-assay precision. Intermediate precision expresses

within-laboratory variations in different days and in different instruments. In intermediate precision study, % R.S.D. values were not more than 2.5% in all the cases (**Table 3**). R.S.D. values were within the acceptable range indicating that these methods have excellent repeatability and intermediate precision.

#### 4.5 Linearity

In ACN: Buffer (pH 6.5) [70:30, v/v] medium the linearity range was found to be 5–30 µg ml<sup>-1</sup> at 290 nm. Lower values of parameters like standard error of slope and intercept (**Table 2**) indicated high precision of the proposed methods. (**Table 2**)

#### 4.6 Robustness

Variation of strength in the selected media by ± 2% did not have any significant effect on absorbance. The mean % recoveries (± S.D.) were found to be 100.5±0.080 and 99.9±0.01 in ACN: Buffer (pH 6.5) [70:30, v/v] respectively (**Table 4**).

#### 4.7 Estimation of formulations

In ACN: Buffer (pH 6.5) [70:30, v/v] the assay values of Dronedarone for tablet ranged from 99.98±0.001 % with Relative standard deviation not more than 0.1 %. Assay values of formulations were same as mentioned in the label claim; this indicated that the interference of excipient matrix is insignificant in estimation of Dronedarone by proposed methods. The estimated drug content with low values of standard deviation established the precision of the proposed methods. (**Table 5**)

## 5. CONCLUSION

The proposed spectrophotometric method for quantification of dronedarone in pharmaceutical dosage forms has been developed and validated. The method was selective, precise, accurate, reproducible and linear over the concentration range. The method is simple and suitable for the determination of dronedarone in formulations without interference of excipients or other common degradation products.

## 6. ACKNOWLEDGEMENTS

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