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RP-HPLC method development and validation for the analyisis of dronedarone hydrochloride in tablet dosage form

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ABSTRACT

A simple RP-HPLC method was developed and validated for assay of Dronedarone hydrochloride in tablet dosage form. Dronedarone hydrochloride is an antiarrythmic drug used to treat atrial fibrillation or atrial flutter. Isocratic elution was employed on a HIBAR- 5µ C18 column (250×4.6mm) as a stationary phase. The mobile phase consisted of 0.01M Disodium hydrogen orthophosphate (pH adjusted to 3.0 with orthophosphoric acid): Acetonitrile in the ratio of 40:60 % v/v and the flow rate was 1ml/min. The detection was carried in the room temperature at 292 nm. Linearity was observed in concentration range of 1-5µg/ml. The retention time for Dronedarone hydrochloride was 5.6 min. The method was validated as per the ICH guidelines. The proposed method was successfully applied for the estimation of Dronedarone hydrochloride in tablet dosage form.

Key words: Dronedarone hydrochloride, RP-HPLC method, Validation

INTRODUCTION

Dronedarone hydrochloride is approved by CDSCO in 2010 to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors[1]. Dronedarone hydrochloride is an antiarrythmic drug invented and manufactured by Sanofi. Dronedarone hydrochloride is available in India in the brand name of Multaq® as a 400 mg tablet[2]. Its primary activity is to block the outward potassium currents involved in cardiac repolarization. The chemical name of dronedarone hydrochloride is N-{2-butyl-3-[4-(3-dibutylaminopropoxy) benzoyl] benzofuran-5-yl} methanesulfonamide, hydrochloride[3]. The literature review revealed few methods of estimation of Dronedarone hydrochloride by UV spectroscopy[4-6], HPLC[7-9] and LCMS[10]. The objective of the present study is to develop a simple, sensitive and economical RP-HPLC method for the estimation of Dronedarone hydrochloride in its tablet form.

EXPERIMENTAL METHOD

Chemicals and reagents

All the chemicals used were of analytical grade and the solvents were of HPLC grade which has procured from SDFCL, Mumbai. Dronedarone hydrochloride was purchased from Sigma Aldrich, India. Tablet Maltaq® was procured from local market.

Instruments and analytical conditions

Shimadzu Prominence UFLC (Shimadzu Corporation, Kyoto, Japan) equipped with LC-20 AD pump, SPD-M20A diode array detector, DGU-20A3

degasar, SK-20 AC auto sampler and CTO- 10 ASVP column oven. Chromatograms were recorded and integrated on PC installed with LC solutions chromatographic software. The Chromatographic separation was performed using HIBAR- 5µ [C18] column (250×4.6mm) as a stationary phase. Isocratic elution with 0.01M Disodium hydrogen orthophosphate (pH adjusted to 3.0 with orthophosphoric acid): Acetonitrile in the ratio of 40:60 % v/v used as a mobile phase with a flow rate of 1.0 ml/min. The mobile phase was prepared freshly and it was degassed by sonicating for 5 min before use. The column was equilibrated for at least 30min before the injection. The detection was carried in the room temperature using λ max of 292 nm.

Preparation of stock, working standard solutions and sample solutions

Stock solution was prepared by transferring10mg of Dronedarone hydrochloride in 10ml standard flask and it was dissolved in methanol and made up to the mark. Further dilution was done by serial dilution method for obtaining respective concentration with methanol.

A total number of 20 tablets were weighed and the average weight was calculated. From the powdered tablets quantity equivalent to 10mg was taken and it was dissolved in methanol, sonicated, volume made up with methanol and filtered through whatmann filter paper. The resulting solution was diluted to required concentration with appropriate dilutions.

Method Validation Procedure

The objective of the method validation is to demonstrate that the method is suitable for its intended purpose as prescribed in ICH guidelines. The developed method has been validated as per ICH guidelines for system suitability, linearity, precision, accuracy, limit of detection, limit of quantification and robustness.

RESULTS AND DISCUSSION

System Suitability Parameter

System suitability tests were carried out on freshly prepared standard stock solutions of Dronedarone hydrochloride. Parameters such as tailing factor, number of theoretical plates (N) and retention time (RT) were determined by injecting standards in six replicates. The results of system suitability indicate better performance of system Table (1) (Fig.1).

Linearity

Working standard solutions of Dronedarone hydrochloride was injected into the chromatographic system. The linearity range of Dronedarone hydrochloride is 1-5µg/ml as showed in Table (2). The peak area was determined for each concentration of the drug solution. Calibration curve was obtained by plotting the peak area versus the applied concentrations Dronedarone hydrochloride (Fig.2). The linear correlation coefficient was found to be 0.9979.

Accuracy

The accuracy of the method was determined by calculating recovery of Dronedarone hydrochloride by the method of standard addition. Known amount of Dronedarone hydrochloride (50%, 100%, and 150%) was added to a pre quantified sample solution. The recovery studies were carried out three times over the specified concentration range and the amount of Dronedarone hydrochloride was estimated by measuring the peak area ratios. From the above determination, percentage recovery and standard deviation of percentage recovery were calculated. The results of the recovery analysis are enclosed under Table (3).

Precision

Repeatability of the method was checked by injecting six replicates injections of 3 µg/ml of the solution and % RSD was calculated Table (4). To analyze the intraday precision solutions of Dronedarone hydrochloride containing 2, 3 and 4 µg/mL series were analyzed six times on the same day and % RSD was calculated. To analyze the interday precision solutions of Dronedarone hydrochloride containing 2, 3 and 4 µg/mL series were analyzed on three different days and % RSD were calculated. The results of intraday and interday precision are given in Table (5).

Robustness

To determine the robustness of the method, three parameters from the optimized chromatographic conditions were varied. The typical variations includes variation in flow rate by ± 0.1ml/min, variation in mobile phase ratio by ± 0.1% and variation in pH of buffer ± 0.5.

Limit of Detection (LOD) and Limit of Quantification (LOQ)

Estimation of LOD and LOQ were done based on the standard deviation of the response and the slope of the calibration curve. The results obtained are presented in Table (6).

Method Application for the assay of Dronedarone hydrochloride in tablets

The validated high performance liquid chromatography method was applied for determination Dronedarone hydrochloride in tablet dosage form. Marketed tablet dosage form available contains 400mg of Dronedarone hydrochloride. 20 tablets were weighed and the average weight was calculated. From the powdered tablets quantity equivalent to 10mg was taken and it was dissolved in Methanol. It was sonicated and volume made upto 10ml with Methanol and it was filtered through Whatmann filter paper. This solution was further diluted to get a solution having concentration of 4µg/ml Dronedarone hydrochloride. 20µl of this solution was injected into the HPLC system under the specified chromatographic conditions. The analyte peaks were identified by comparisons with those of respective standard for their retention time. The peak areas were used to calculate the concentration. The assay results, expressed as % of the label claim in Table (7).

Table 1: System Performance for Dronedarone hydrochloride

Drug substance	Retention time	Tailing factor	No of Theoretical plates
Dronedarone hydrochloride	5.6 min	1.091	4058

Table 2: Linearity data for Dronedarone hydrochloride

SL No	Concentration (µg/ml)	Peak area
1	1	47126
2	2	90676
3	3	135436
4	4	209493
5	5	272574
Correlation coefficient (r^2)		0.9979
Slope		40243.1
Intercept		6474.5

Table 3: Accuracy-%Recovery of Dronedarone hydrochloride

Sample ID	Concentration (µg/ml)		%Recovery of Pure drug	Statistical Analysis
	Pure drug	Formulation		
S1:50%	1.5	3	100.27	Mean= 99.95%
S2:50%	1.5	3	99.69	S.D. = 0.2946
S3:50%	1.5	3	99.89	% R.S.D.= 0.29
S4:100%	3	3	100.26	Mean= 100.19%
S5:100%	3	3	100.45	S.D. = 0.2957
S6:100%	3	3	99.87	% R.S.D.= 0.30
S7:150%	4.5	3	99.78	Mean= 99.75%
S8:150%	4.5	3	99.34	S.D. = 0.3958
S9:150%	4.5	3	100.13	% R.S.D.= 0.40

Table 4: Repeatability data of Dronedarone hydrochloride

S.No	Sample ID (3 µg/ml)	Peak Area
1.	S1	135786
2.	S2	134598
3.	S3	132856
4.	S4	133296
5.	S5	134362

6.	S6	135023 Mean= 134320.17 S.D. = 1087.59 % R.S.D.= 0.81%

Table 5: Inter-day & Intra-day Precision of Dronedarone hydrochloride

S.No	Concentration (µg/ml)	Intra Day (n=6)	Inter Day (n=6)
1.	2	Mean = 92346.78 S.D. = 708.96 % R.S.D.= 0.77	Mean = 91234.54 S.D. = 689.78 % R.S.D.= 0.75
2.	3	Mean = 135458 S.D. = 876.56 % R.S.D.= 0.65	Mean = 136848.64 S.D. = 997.74 % R.S.D.= 0.73
3.	4	Mean = 201949.45 S.D. = 1778.23 % R.S.D.= 0.88	Mean = 200867.36 S.D. = 1567.78 % R.S.D.= 0.78

Table 6: LOD and LOQ of Dronedarone hydrochloride

1.	Limit of Detection concentration in µg/ml	0.089
2.	Limit of Quantitation concentration in µg/ml	0.27

Table 7: Assay of Dronedarone hydrochloride Tablets

Brand name of tablets	Labelled amount of Drug (mg)	Mean (±SD) Assay (n = 6)	% Label Claim
Maltaq®	400	400.89 (±0.978)	100.22%

Fig. 1: Chromatogram of Dronedarone hydrochloride

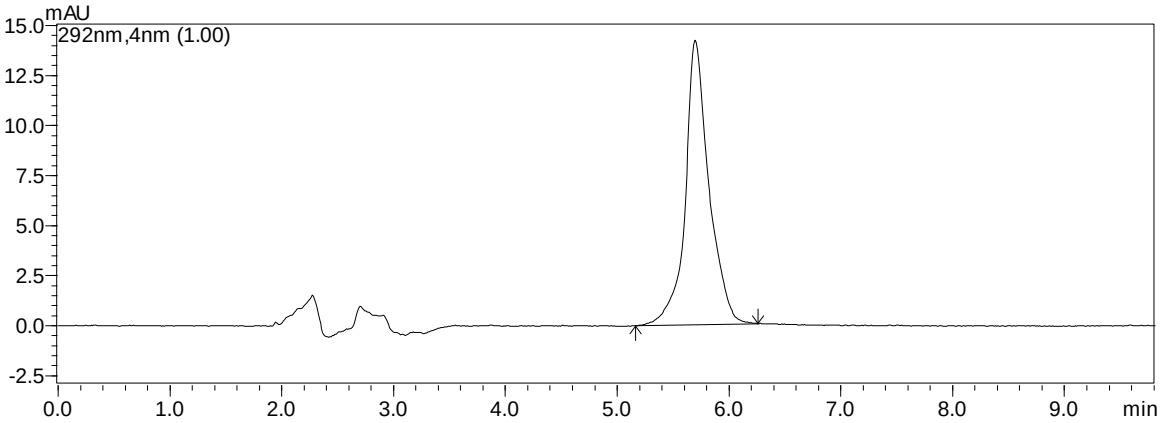
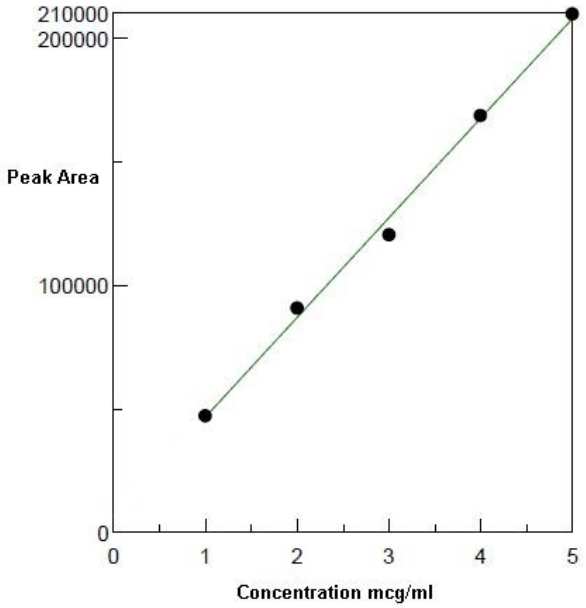


Fig. 2: Calibration graph of Dronedarone hydrochloride



CONCLUSION

A validated RP-HPLC method has been developed for the determination of Dronedarone hydrochloride tablet dosage form. The proposed method is simple, sensitive, rapid, accurate, precise and specific. Its chromatographic run time of 5.6 min allows the analysis of a large number of samples in short period of time. The method it is suitable for the routine analysis of Dronedarone hydrochloride pharmaceutical dosage form.

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