Available online at www.ijpsdr.com

International Journal of Pharmaceutical Sciences and Drug Research 2015; 7(1): 116-119

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Stability Indicating UV Spectrophotometric Method for Determination of Dronedarone Hydrochloride

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ABSTRACT

The objective of this study was to develop stability UV method for estimation of Dronedarone Hydrochloride in tablet to compare % degradation of this drug determined by this UV method to HPTLC method reported by us earlier. Analysis of bulk as well as marketed tablet formulation by exposure to same degradative conditions was done and % degradation obtained by spectroscopy was determined. Method development and validation was done as per ICH guidelines. % degradation observed by both methods was comparable. The variation in the results of this drug estimated by HPTLC and spectrophotometric method was statistically insignificant. This suggests that the spectrophotometric method is suitable to determine stability profile. Hence a simple UV spectrophotometry can be used to monitor stability of Dronedarone Hydrochloride.

Keywords: Dronedarone Hydrochloride, spectrophotometry, stability, Statistical study, HPTLC.

INTRODUCTION

DronedaroneHydrochloride (N-(2-Butyl-3-{4-[3-(dibutylamino) propoxy] benzoyl}-1-benzofuran-5-yl) methane sulfonamide hydrochloride; (Figure 1) is a widely used for the paroxysmal or persistent atrial fibrillation or atrial flutter. [1-2]

The most common method used for determination of stability of drug is by HPLC/HPTLC. However, many laboratories in resource-constrained settings may not afford to have HPTLC equipment, which also requires skilled personnel to operate it. An alternative is to carry out drug estimations by spectrophotometry which is relatively cheap and simple.

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Received: 05 August, 2014; **Accepted:** 07 November, 2014

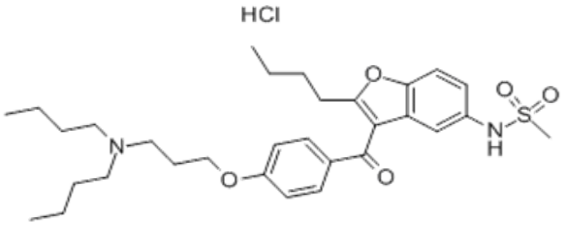

Fig. 1: Dronedarone hydrochloride

Literature survey revealed that various analytical methods like spectrophotometric [3], Simple HPLC [4-5], bio-analytical RPHPLC [6], SIM RPHPLC [7-10] and UPLC [11], Simple HPTLC [12], LC-MS [13] and few more [14-17] have been reported for the determination of Dronedarone hydrochloride and either individually or combination with some other drugs, but none of these studies have developed and validated stability indicating method by spectroscopy and compared it by different methods.

Development of SIM is based on systematic exposure of API to various stress conditions. Systematic

optimization trials are required to arrive at combination of concentration of stress reagent and duration of exposure, to obtain degradation preferably in the 10-30% range. Typical degradative conditions involve hydrolysis under different pH conditions, photolysis and thermal. Achieving 100% degradation could possibly cause secondary degradation. Secondary degradation products are the degradation products, which are not likely to be formed under normal storage conditions. The review of literature prompted us to develop spectrophotometric method for determination of stability of Dronedarone Hydrochloride and validation of the method.

MATERIALS AND METHODS

Dronedarone Hydrochloride was procured from Lupin Pharmaceuticals. INC, Mumbai. Methanol (AR grade), acetone (AR grade), Hydrochloric acid (AR grade), Sodium Hydroxide (AR grade), Hydrogen peroxide (AR grade) were used. Dronedarone tablets were procured from local market.

Instrumentation

For Spectrophotometric method, Jasco V 550 double beam UV-VIS Spectrophotometer was used.

Standard preparation

Standard stock solution of Dronedarone Hydrochloride was prepared by dissolving 10 mg of drug in 10 ml of MeOH to get concentration of 1000µg/ml. from the standard stock solution; working standard solution was prepared to contain 100 µg/ml of Dronedarone Hydrochloride by taking 1ml from standard stock solution in 10 ml volumetric flask and volume was made up to the mark by MeOH.

Selection of detection wavelength

From the standard stock solution in MeOH further dilutions were done using MeOH and scanned over the range of 200-400nm and spectrum was obtained. It was observed that the drug showed considerable absorbance at 288nm, shown in Fig 2.

Stress degradation studies

Stress degradation studies using optimized stress conditions [18] and sample was tested using spectrophotometry. For each condition, two samples were prepared, the blank subjected to stress in the similar manner as the drug solution. Dry heat and photolytic degradation were carried out in solid state.

Degradation under alkali catalyzed hydrolytic condition: To 10 mg of drug in 10 ml volumetric flask, 2Nmethanolic NaOH was added and volume was made up to the mark. The above solution was kept for 24 hours at room temperature.

Degradation under acid catalyzed hydrolytic condition: To 10 mg Dronedarone hydrochloride in a volumetric flask, 10 ml 2N methanolic HCl was added (1000ppm).The above solution was kept for 24 hours at room temperature.

Degradation under neutral hydrolytic condition: To 10 ml of MeOH, 50 mg Dronedarone hydrochloride was added to obtain 5000µg/ml solution. To this solution, water was added& volume was made up to 50 ml with water (1000ppm). The above solution was heated at 80°C for 5 hours.

Degradation under oxidative condition: To 50 mg Dronedarone hydrochloride, 10 ml of MeOH was added to obtain 5000µg.mL^{-1} solution. To this solution, 10 ml of 6%H_2O_2 was added& volume was made up to 50 ml with MeOH (1000ppm). The above solution was heated at 80°C for 2 hours.

Degradation under dry heat: Dry heat studies were performed by keeping drug sample in oven overnight at 60°C. 10 mg was weighed &dissolved in 10ml MeOH (1000ppm).

Photo-degradation studies

The photolytic stability study of the drug was studied by exposing the drug to UV light providing illumination of NLT 200 watt hr/m^2 followed by cool white fluorescence light of NLT1.2 million Lux-Hr. After each exposure, 10 mg of drug was accurately weighed and transferred to 10 ml of volumetric flask; the volume was made up with methanol to obtain 1000 µg.mL^{-1} solution.

Also the developed method was validated as per ICH guidelines, for the parameters specificity, linearity, precision, LOD, LOQ and robustness.

Statistical analysis [19]

Comparison between % degradation obtained by HPTLC and UV methodis done by paired t test using formula, t = [đ/(s/√n)] shown in Table 1.

Null hypothesis (H_0) i.e there is no significant difference between mean increased in results by two methods.

$$\mathbf{S^2 = (1/n\text{-}1) \sum (d\text{-} đ)^2}$$

$$S^2 = \sqrt{[(1/7\text{-}1)* 126.4327]}$$

$$S = 4.6387$$

$$t = [đ/(s/\sqrt{n})]$$

$$\mathbf{t = 0.1694}$$

Calculated | t | is less than tabulated t (2.18), H_0 may be accepted at 5% level of significance and conclude that results by two methods do not differ significantly.

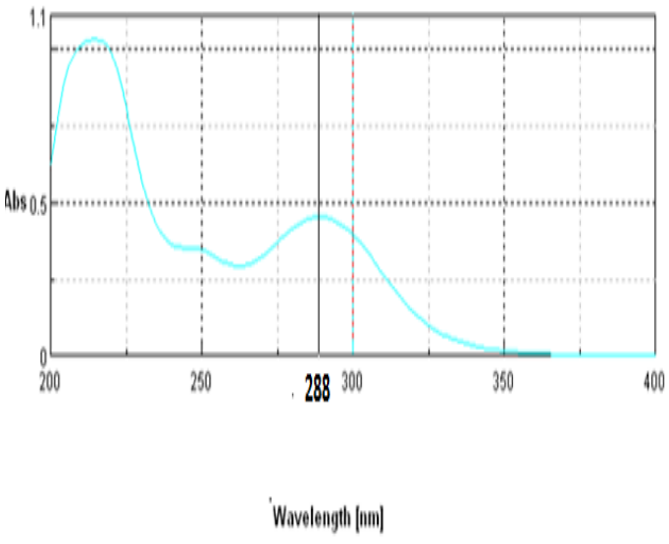

Fig. 2: UV spectrum of Dronedarone Hydrochloride (10µg/ml)

Table 1: Statistical analysis

Conditions	HPTLC (x)	UV (y)	d=(x - y)	(d- đ)	(d- đ) ²
Acid	20.39	23.70	-3.31	-3.60714	13.0114
Alkali	15.26	16.43	-1.17	-1.46714	2.1525
Neutral	16.92	20.53	-3.61	-3.90714	15.2657
Oxidation	17.27	11.50	5.77	5.472857	29.9521
Thermal	24.25	28.63	-4.38	-4.67714	21.8756
UV	18.9	12.20	6.7	6.402857	40.9965
Fluorescence	23.08	21.00	2.08	1.782857	3.1785
			đ=0.297143		**∑ (d- đ) ² = 126.4327**

Table 2: Comparison study by HPTLC and spectrophotometric method

Parameter	Optimized Condition	% Deg (HPTLC)	% Deg (UV)
Acid	2N HCl overnight	20.39	23.70
Alkali	2N NaOH overnight	15.26	16.43
Neutral	Heating 5 hours at 80°C	16.92	20.53
Oxidation	Heating with 6% H_2O_2 for 2 hours at 80°C	17.27	11.50
Thermal	60°C overnight	24.25	28.63
UV	200 Watt Hrs/Square Meter	18.9	12.20
Fluorescence	1.2 Million Lux. Hrs	23.08	21.00

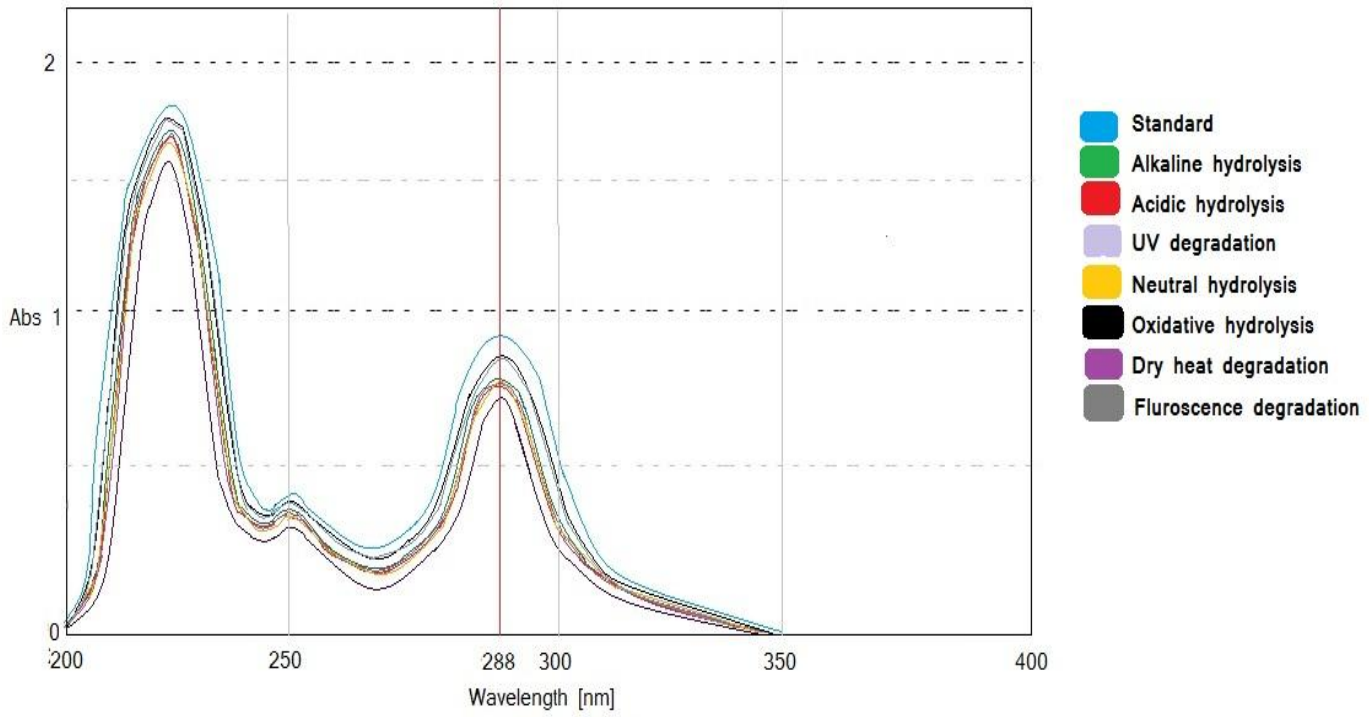

Fig. 3: Overlay spectrum degradation conditions of Dronedarone Hydrochloride (20µg/ml)

Table 3: Comparison of validation study by HPTLC and spectrophotometric method

Validation parameters	HPTLC	UV
Linearity Equation	Y=20.98x+710	Y=0.0426x+0.076
(R^2)	R^2 = 0.995	R^2 = 0.997
Range	40-200 ng/band	10-50µg/ml
Precision	% RSD < 2	% RSD < 2
Assay	100.47%	99.36%
Accuracy	% Recovery	% Recovery
80	99.14	98.76
100	100.83	97.77
120	94.72	99.49
Limit of Detection	3.85ng/band	0.488µg/ml
Limit of Quantitation	11.66ng/band	1.478µg/ml
Specificity	Specific	Specific
Robustness	Robust	Robust

RESULT AND DISCUSSION

Working standard solution of Dronedarone Hydrochloride (100µg/ml) was exposed to various optimized stress degradation conditions and upon subsequent dilution spectrum of 20µg/ml was taken in each condition is shown in Fig. 3.

The bulk Dronedarone Hydrochloride was exposed to optimized stress conditions and % degradation was determined. The results obtained by this method, and the results obtained by HPTLC reported by us earlier are shown in Table 2

The developed methods were validated as per ICH Q2A (R1) and their comparison study is shown in Table 3.

The developed spectrophotometric method was found to be simple, sensitive, accurate and repeatable for

analysis of Dronedarone Hydrochloride in the tablet without any interference from excipients. The results indicated the stability of the method to study stability of the Dronedarone Hydrochloride under various force degradation conditions like hydrolysis under different pH conditions, dry heat and photolytic degradation. The % degradation upon exposure of bulk to degradative conditions by HPTLC and Spectrophotometric method was similar and the difference in the results of % degradation estimated by HPTLC and Spectrophotometric method were statistically insignificant. This suggests that the spectrophotometric method is as accurate as the HPTLC method to determine stability profile. Hence laboratories that do not have HPTLC equipment can also undertake this drug estimations using spectrophotometer.

ACKNOWLEDGMENT

Authors are thankful to INC., Lupin pharmaceuticals INC., Mumbai for providing working standard of Dronedarone hydrochloride. Authors are also thankful to the principal and Management, AISSMS College of Pharmacy, Pune for providing required facilities for research work.

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Source of Support: Nil, Conflict of Interest: None declared.