

A REVIEW ON ANALYTICAL TECHNIQUES FOR ESTIMATION OF ARRHYTHMIAS DRUG - DRONEDARONE HYDROCHLORIDE

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ABSTRACT

Dronedarone Hydrochloride is a drug used to treat arrhythmias, i.e., to treat improper rhythmicity of heart. It works by controlling heart's rhythm i.e., it alters the continuous progression of electrical signal in the heart. Normal heart rhythm can be restored by this process of Dronedarone HCl. For the determination of Dronedarone HCl in pharmaceutical dosage form and bulk form, several analytical methods including HPTLC, UV and HPLC has been developed. Methods indicating human plasma stability and impurity profiling are also described for

Dronedarone HCl. For qualitative and quantitative estimation of Dronedarone HCl these analytical methods can be used and it can also be used for its related degradants in bulk formulations and biological fluids. The following study depicts the review on analytical methods which includes to estimate the anti-arrhythmic drug, Dronedarone HCl.

Key words: Anti arrhythmias, Biological fluid Dronedarone Hydrochloride, HPLC.

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INTRODUCTION

Cardiac dysrhythmia also called as irregular heart beat or cardiac arrhythmias is a problem with either too fast or too slow heart beat i.e., irregular beat. Arrhythmias serves to be a common disorder in almost all parts of the world. Almost 2% to 3% population of Europe and North America, as of 2014 is affected by atrial fibrillation. Statistics shows that from 29,000 deaths in 1990 has been increased to 112,000 deaths which occurred in 2013, due to atrial fibrillation and atrial flutter. Almost 15% of all the deaths which occurred globally is due to sudden cardiac death, it is the reason for about half of the death which occurred due to cardiovascular diseases. Ventricular arrhythmias is the reason for about 80% of sudden cardiac death. Dysrhythmias is very common among elderly people but can occur at any age.¹

For the management of paroxysmal or persistent atrial fibrillation, a non-iodinated benzofuron derivative, Dronedarone HCl is made in use. Amiodarone, a famous anti-arrhythmic drug, whose use is restricted to toxicity because of its high content of iodine, leading to liver diseases, to which Dronedarone is chemically related. In clinical trials and in vitro Dronedarone HCl displays amiodarone-like class III anti-arrhythmic activity though it differs by lacking iodine and it is expected to be less toxic. Shorter elimination of half-life and much smaller volume of distribution has been found in Dronedarone HCl.²

The white fine powder Dronedarone HCl is freely soluble in methylene chloride and methanol and is

practically insoluble in water. According to the Vaughan-Williams classification scheme the class III antiarrhythmic compounds are contained by potassium channel blockers. The potassium channels that are responsible for phase 3 repolarization are bind to and blocked by these drugs. Hence, delayed repolarization due to blockage of these channels results in increase in effective refractive period (ERP) and increase in action potential duration.³

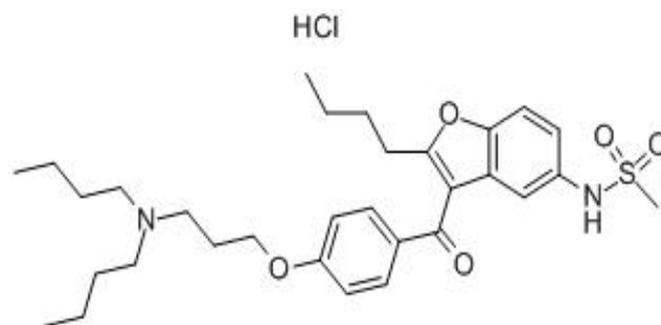


Fig 1: Structure of Dronedarone Hcl

IUPAC: N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-methanesulfonamide monohydrochloride.

Molecular Formula: C₃₁H₄₄N₂O₅S•HCl

Available brand: Multaq (Sanofi Aventis) available as 400mg tablet.

Molecular weight: 593.224g

ANALYTICAL METHODS

CHROMATOGRAPHIC METHODS

HPTLC method:

For the quantitative detection of Dronedarone HCl a stability indicating High Performance Thin Layer Chromatography (HPTLC) method has been developed. Using pre coated silica gel and suitable mobile phase the process was carried out. The drug showed considerable

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absorbance at 288 nm. According to the ICH guidelines stress testing was performed. The subjected drug was then hydrolysed under different pH conditions, oxidation, thermal degradation and photolysis. The peak homogeneity data is obtained by observing the peak purity parameter. According to ICH guidelines the method was successfully certified. The concentration range of 40-200 mg/band was found for the linearity of the suggested method. The correlation coefficient value was shown greater than 0.997 by regression analysis. Based on the recovery studies the accuracy of the method was established.⁴

RP-HPLC method

For the estimation analysis of Dronedarone HCl a Reverse phase High-Performance Liquid Chromatography (RP-HPLC) method has been established. All the parameters were fixed and the analysis was performed. At 289nm the effluents were monitored and at 1 ml/min the flow rate of mobile phase was maintained. Ten minutes was the total run time when the sample was injected. Column saturation time, selection of wavelength, pH of mobile phase etc., are the experimental conditions which were critically studied and the optimum conditions were selected. In RP-HPLC linear range was 5-15 µg/mL, mean recovery was found to be 99.99-100.03% and 4.7 min is the Retention time found for Dronedarone HCl. Degradation in acid, base, thermal and peroxide was found in the range 8-20%.⁵

Stability indicating HPLC method

For Dronedarone HCl in its bulk form the authentication and development of stability showing HPLC methods are described in this study. As suggested by International Conference on Harmonization, Dronedarone was put to stress degradation under different condition. The produced sample was then used for Dronedarone HCl in developing a stability showing high performance liquid chromatography. From the peak of degradation products, the peak of Dronedarone hydrochloride was explained well and was analysed with the suitable column and the mobile phase at a flow rate of 1 ml/min by using gradient method. Using a UV detector at 291 nm the findings were executed. From the drug peak the degradation product peak was explained well. To this drug and its degradation products this method is proved to be specific.⁶

In another study, Dronedarone HCl in presence of its degradants which are formed due to stress condition are quantitatively estimated and values were evaluated. For Dronedarone HCl and its degradants a chromatographic separation using Zorbax XDB C8 was achieved, 1.0mL/min is the flow rate set for 3.5µm column and an aqueous solution of 0.05M ammonium acetate and acetonitrile (40:60 v/v) as the mobile phase. The detector's wavelength was 220nm and 30oC was the temperature at which the column was maintained. The stressed samples which were obtained by exposure of the drug Dronedarone

HCl to photolytic, oxidation, thermal, hydrolytic stress condition were analysed by the given process. Over a range of 10 - 300 µg/mL the described method shows excellent linearity for Dronedarone HCl. The correlation coefficient is 0.999. The specificity of the method for the estimation of Dronedarone HCl in presence of its degradants was demonstrated by stressed sample chromatograms. 2% or less is always the relative standard deviation found for six measurements of peak area.⁷

RP-HPLC Method for Dronedarone HCl in Tablet formulation:

Using RP-HPLC method, the tablet form of Dronedarone HCl was quantitatively analysed. Using Waters Symmetry C8, an isocratic separation was obtained, at 290 nm (UV detector) the particle size of the column (flow rate of 1mL/min) was 5µm. For its precision, linearity, specificity, robustness, accuracy and solution stability this method was certified. Stress testing of drug (forced degradation) and assessing of interference from the placebo determines the specificity of the drug. With LOD and LOQ of 0.1 and 0.3 µg/ml respectively the method was found to be proportional over the concentration range of 20-80µg/mL ($r^2=0.999$). The method was 99.2-100.5% accurate. The assay is stability-indicating because the resulting degradation products from stress studies did not involve the findings of Dronedarone HCl. For the quantitative analysis of tablet form of Dronedarone Hydrochloride, this was the appropriate and booming method found.⁸

SPECTROPHOTOMETRIC METHOD

Estimation of Dronedarone Hydrochloride in tablet by developing stability indicating UV method is the objective of this study and also 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.⁹

MULTIVARIATE TECHNIQUE

For the determination of Dronedarone HCl in pharmaceutical dosage forms, an accurate and precise UV spectrophotometric method with multivariate calibration technique has been defined. The process of constructing a mathematical model that relates a property such as content or identity to the absorbance of a set of known reference samples at more than one wavelength is termed as multivariate calibration. At 288nm Dronedarone showed maximum wavelength using methanol as a solvent and in the linear range of 10-35µg/ml, it obeyed Beer's law. Quantitative estimation of Dronedarone HCl in tablet and drug form can be successfully performed as this

method was found to be accurate and precise. 10

IMPURITY PROFILING OF DRONEDARONE HCL

By making use of RP-HPLC technique the impurity profiling of Dronedarone HCl has been certified and developed. To show the nature of the drug, the drug substance was subjected to the different conditions such as oxidation, hydrolysis (acid and base), thermal degradation and photolysis, as per ICH guidelines of stress conditions. During the acid base hydrolysis and thermal degradation a significant alteration was observed. By using NMR, FTIR and LC-MS spectral analysis the major degradants were known. For chromatographic conditions the samples generated from forced degradation studies and impurity-spiked solution were efficient. For the samples obtained from the forced degradation studies the resolution was found to be 1.5 times greater. The detected wavelength was 220nm for LC method and linear gradient elution was observed. Using chromatography under variable compositions of different temperatures, solvents and pH values the behaviour of all the impurities were observed and the values were interpreted.11

ESTIMATION OF DRUGS IN BIOLOGICAL FLUIDS

To overcome the restricted iodine related toxicities of amiodarone, Dronedarone was developed. Dronedarone taken once circulates as active metabolite in humans. To investigate the pharmacokinetics of Dronedarone a liquid chromatography-mass spectrometry (LC -MS/MS) method was certified and developed for Dronedarone HCl and de-butyl Dronedarone simultaneously in human plasma. Amiodarone was used as internal standard (IS). At the flow rate of 0.7 ml/min effective separation was performed. Within 5.5 min time the observation of total separation was successfully carried out. The values were observed when the detection was carried out. All the values were found to be within the limits when intra and inter day values were examined.12

RP-HPLC METHOD IN PLASMA:

For the quantification of Dronedarone HCl in plasma, a reverse phase high performance liquid chromatography combined with UV-detection has been developed and certified. By simple protein precipitation sample preparation was done. Chrom atographic conditions were optimised and the procedure was run using the standard and the sample. Retention time was found to be 5.8 minutes. Specificity and selectivity, system suitability, recovery, linearity range, limit of detection (LOD) and limit of quantification (LOQ) and precision are different analytical performance parameters which were figured out. The concentration range was fixed as 300-700ng for the drug in plasma and all the values were found to be in range. 87.69% was the average recovery percentage found and 42.17 ng/ml and 127.78 ng/ml are the LOD and LOC values respectively. For the reliable quantification of Dronedarone HCl in plasma the proposed methods were

successfully applied because of its high sensitivity, precision and accuracy.13

DISCUSSION

In pharmaceutical formulations and biological matters, several methods has been described for the estimation of Dronedarone hydrochloride. It can be concluded that HPLC, UV spectrophotometry and HPTLC are the most simple and easy methods for Dronedarone HCl estimation in pharmaceutical formulations while HPLC-UV and LC-MS/MS can be widely used for Dronedarone HCl estimation in biological fluids like plasma, urine and serum. It was also found that the impurity profiling of the drug was done using RP-HPLC method. Stability indicating methods done by HPTLC and HPLC-UV has also been reported. Thus, the current review helps researchers to widen their ideas on different improved aspects for further studies on the evaluation of the drug.

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