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DEVELOPMENT AND VALIDATION OF NEW RP-HPLC METHOD FOR ANALYSIS OF AMIODARONE HYDROCHLORIDE AND ITS RELATED COMPOUNDS

Amit Gosar[1]*, Deepesh Patil[1], Advait Avalaskar[1], Narendra Aarkashi[1], Samadhan Aware[1], Srinivasan Kuduva[1] and Rajender[2]

Indoco Remedies LTD R&D Centre, R - 92/93, Ground Floor, TTC M.I.D.C, Industrial Area, Rabale, Navi Mumbai - 400 701, India.

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***Corresponding Author**
Dr. Amit Gosar
Indoco Remedies LTD
R&D Centre, R - 92/93,
Ground Floor, TTC
M.I.D.C, Industrial Area,
Rabale, Navi Mumbai -
400 701, India.

ABSTRACT

The purpose of this research study is to develop a novel, simple, precise, accurate and economical method for determination of related substances in Amiodarone Hydrochloride API. Efficient chromatographic method was developed to separate nine impurities using Zorbax Eclipse XDB C-18 (150 x 4.6 x 5µm) column with isocratic program. The detection of all impurities was observed at 240nm. Regression analysis showed R^2 value (correlation coefficient) > 0.999 for Amiodarone Hydrochloride and all its impurities. A solution of Amiodarone Hydrochloride in ACN:H_2O (8:2) was found stable for 48 hrs. The degradation study was done within the given guidelines prescribed by ICH. Degradation was found to occur under Basic Stress Condition but Amiodarone Hydrochloride was stable to acidic and oxidative stress condition. The method is validated for Linearity, Accuracy and Precision.

KEYWORDS: Amiodarone Hydrochloride, RP-HPLC, Isocratic, Validation.

1. INTRODUCTION

Amidarone Hydrochloride is chemically known as (2-butylbenzofuran-3-yl) (4-(2-diethylamino) ethoxy)-3,5-diiodophenyl)methanone hydrochloride is a class III anti-arrthythmic agent and prolongs phase 3 of cardiac action potencial, the repolarization phase where there is normally decreased calcium permeability and is also a non-competititive β-adrenergic inhibitor.[11] Even though it is official in IP(1), BP(2),USP(3), the method was not

found suitable to separate the known pharamacoepial impurities along with two newly discovered impurities i.e 2- hydroxy benzaldehyde and Methyl 2-(2-formylphenoxy) hexanoate.

Amiodarone can be used to treat tachyarrhythmia, including atrial fibrillation, ventricular tachycardia and patients at high risk of sudden cardiac death.[12] Although amiodarone is effective, it is not generally recommended for minor rhythm disturbances because of its toxicity. It is a difficult and challenging drug to use in clinical practice. This is because of its very prolonged half-life and because of its multiple adverse effects.[13] It has one active metabolite: desethylamiodarone. De-ethylating of amiodarone occurs via cytochrome P450 3A4 (CYP3A4) and by CYP2C8.[14]

2. OBJECTIVES OF THE STUDY

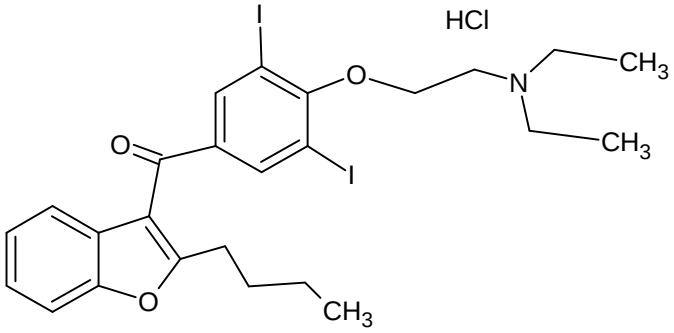
The literature survey reveals that few analytical methods have been reported for Amiodarone Hydrochloride and its related compounds including spectroscopic methods (5)(6), high performance liquid chromatography(HPLC) methods.[7,8,9] Our objective is to develop and validate new RP-HPLC method for determination of Amiodarone Hydrochloride and its related compounds. The proposed RP-HPLC method utilizes economical solvent system having advantage like better rentention time, sharp and symmetric peak shape. The method is validated according to ICH Guidelines.[4]

3. INSTRUMENTATION

Waters, Alliance 2695 series HPLC system comprising a quaternary pump, an autosampler, a thermostatted column compartment, a solvent cabinet with degasser along with photodiode array (PDA) 2998 and ultraviolet (UV) 2487 detectors were used for separation and detection. Data acquisition and calculations were carried out using Waters Empower3 software (Milford). Sartorius (Germany) analytical balance was used for weighing material.

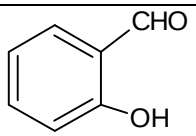
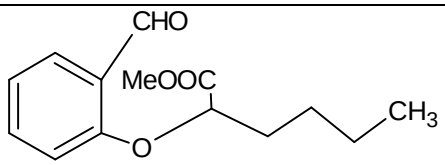
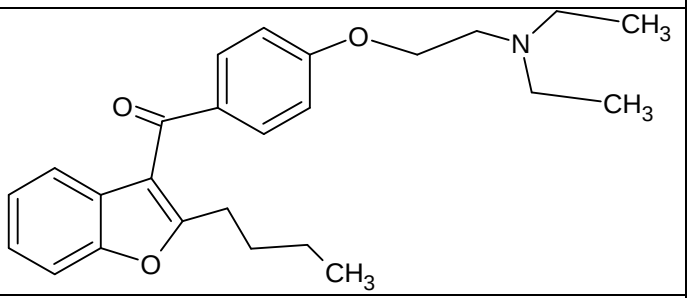
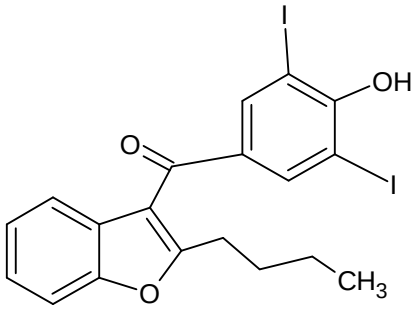
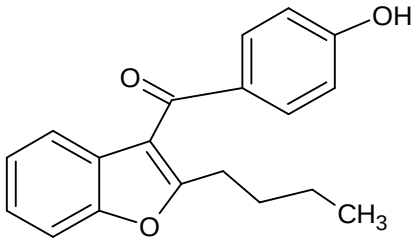
4. MATERIALS AND REAGENT

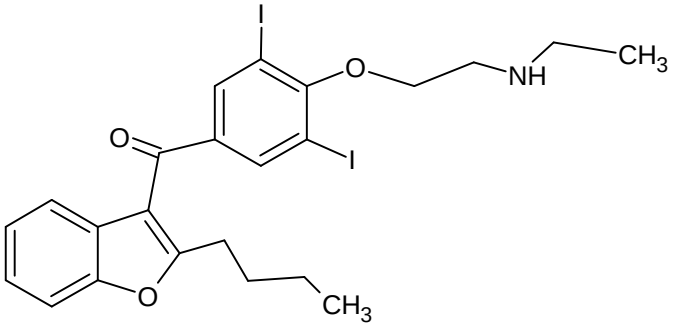
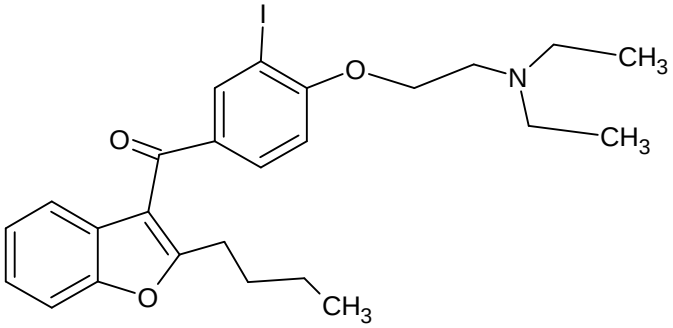
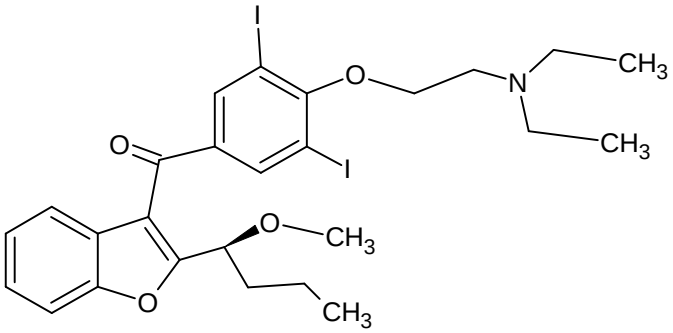
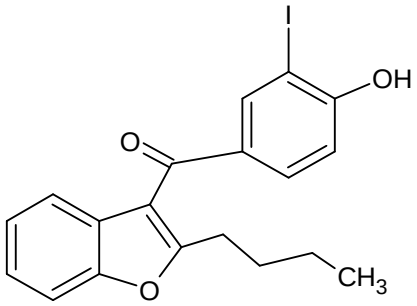
Amiodarone HCl sample, woking standard and its related substances working standard were received from Analytical Research and Development department of Indoco Research Centre (Navi Mumbai). HPLC grade Ammonium Acetate, Acetic acid, Acetonitrile, Methanol and HPLC grade water were purchased from Merck (India).



Chemical/IUPAC Name: (2-butylbenzofuran-3-yl) (4-(2-(diethylamino)ethoxy)-3, diiiodophenyl) methanone hydrochloride.

Table No. 1: Chemical name of Amiodarone Hydrochloride and its related substances.

Sr. No.	Component Name	Chemical Name	Structure
1	2-HBHD	2- hydroxy benzaldehyde	
2	MFPH	Methyl 2-(2-formylphenoxy) hexanoate	
3	IMP-A	(2-butylbenzofuran-3-yl) (4-(2-(diethylamino) ethoxy) phenyl) methanone	
4	IMP-D	(2-butylbenzofuran-3-yl) (4-hydroxy-3,5-diiodophenyl) methanone	
5	IMP-E	(2-butylbenzofuran-3-yl) (4-hydroxyphenyl) methanone	

6	IMP-B	(2-butylbenzofuran-3-yl) (4-(2-ethylamino)ethoxy)-3,5-diiodophenyl) methanone	
7	IMP-C	(2-butylbenzofuran-3-yl) (4-(2-diethylamino) ethoxy) -3-iodophenyl) methanone	
8	IMP-G	(S)-(4-(2-(diethylamino)ehtoxy) -3,5-diiodophenyl) (2-(1-methoxybutyl) benzofuran-3-yl) methanone	
9	IMP-F	(2-butylbenzofuran-3-yl) (4-hydroxy-3-iodophenyl) methanone.	

5. CHROMATOGRAPHIC CONDITION AND MEASUREMENT PROCEDURE

5.1 Preparation of Mobile Phase

5.1.1 Buffer preparation

Transfer 3.85 g of ammonium acetate into 1L bottle, containing 1000 mL of water, dissolve and shake well. Adjust to pH 4.9 ± 0.05 with acetic acid. Filter the solution through a 0.45µm membrane filter, and degas by sonication for 2 minutes.

5.1.1.1 Mobile phase

Mix 3 volume of buffer preparation, 3 volume of methanol and 4 volume of acetonitrile and degas by sonication for 2 mins.

5.2 Diluent

Mix 8 volumes of acetonitrile and 2 volumes of water and degas by sonication for 2 minutes.

5.3 Preparation of Blank

Use diluent as a blank

Table No. 2: Chromatographic Conditions.

Column	Zorbax Eclipse XDB, C18 (150mm x 4.6 mm, 5 µm)
Column Temperature	30°C ± 2°C
Flow Rate	1.0 mL/min
Injection Volume	10 µL
Detector Wavelength	240 nm
Run Time	50 minutes
Retention Time	Amiodarone about 25.3 minutes, RRT 1.0.
Needle wash	Acetonitrile: Water (80:20)

5.4 Preparation of solutions

5.4.1 Reference solution (a)

Transfer about 5 mg of Amiodarone HCL impurity D, impurity E and Amiodarone HCl working standard into 25 mL volumetric flask, dissolve in about 10 mL of diluent and make upto the mark with diluent.

Transfer 1.0 mL of above solution to 20 mL volumetric flask and make upto mark with diluent.

5.4.2 Reference solution (b)

Transfer about 10 mg of Amiodarone HCl working standard into 10 mL volumetric flask, dissolve in about 5 mL of diluent and make upto the mark with diluent.

Transfer 1 mL of above solution to 100 mL volumetric flask and make upto the mark with diluent. Further transfer 1 mL of above solution into 10 mL volumetric flask and make upto the mark with diluent.

5.4.3 Test solution

Transfer about 10 mg of Amiodarone HCL sample into 10 mL volumetric flask, dissolve in about 5 mL of diluent and make upto the mark with diluent.

Table No. 3: Injection sequence.

SI#	Description	No. of Injections
1	Blank	1
2	Reference solution (a)	1
3	Blank	1
4	Reference solution (b)	5
5	Test solution	2

5.5 Procedure

Equilibrate the HPLC system with the initial composition until a steady baseline is obtained. Inject Blank and reference solution (a). Ensure that all the system suitability parameters meet the requirements. Inject blank, reference solution (b) and test solution as per injection sequence and record the chromatograms. Make blank correction if necessary.

Table No. 4: Peak name with Retention Time and Relative Response Factor.

Sr. No.	Peak Name	Relative Retention Time	Relative Retention Factor
1	Amiodarone HCL	1.00	1.00
2	2 HBHD	0.09	0.73
3	MFPH	0.21	0.36
4	Impurity A	0.22	0.55
5	Impurity D	0.29	0.87
6	Impurity E	0.36	0.91
7	Impurity B	0.42	1.04
8	Impurity C	0.52	1.06
9	Impurity G	0.63	1.10
10	Impurity F	0.73	1.21

6. System suitability

6.1 Acceptance criteria

6.1.1 Resolution*:* The resolution between the peaks due to impurity D and impurity E in the chromatogram obtained with system suitability solution should not be less than 3.5.

6.1.2 %RSD*:* The percent relative standard deviation of five replicates for the peak due to Amiodarone in the chromatogram obtained with reference solution (b) should not be more than 5.0.

7. Calculation

Calculate impurity content by formula given below:

$$\% \text{ Known impurities} = \frac{AI \times WS \times 1 \times 1 \times 1}{AR \times WT \times 100 \times 10 \times RRF} \times P$$

$$\% \text{ Unknown impurity} = \frac{AU \times WS \times 1 \times 1}{AR \times WT \times 100 \times 10} \times P$$

Total impurities =[Sum of known impurities + sum of unknown impurities]

Where,

AI = Average peak area for respective impurity in test solution.

AR = Average peak area of Amiodarone in reference solution (b).

AU = Average peak area of unknown impurity in test solution.

WS = Weight in mg of Amiodarone HCl working standard taken for reference solution (b) preparation.

WT = Weight in mg of Amiodarone HCl sample taken for test solution preparation.

P = Potency of Amiodarone HCl working standard.

8. RESULT AND DISCUSSION

To develop a selective and sensitive method, the primary concern was to bring about resolution between all known impurities and Amiodarone Hydrochloride. To begin with method from USP was refered. It was observed that two of known impurities were co-eluting and retention time of Amiodarone was constantly changing. Hence method was deviated. Different types of buffer for example phosphate buffer of pH 3-6, citrate buffer of pH 3-5 and ammonium acetate buffer of pH 4-6 were studies in combination with acetonitrile and methanol. Buffer pH played a important role in separation of impurities. To improve separation, pH was reduced, at limit level all impurities were found to be separate but when spiked at test concentration, two impurities were found to be merging with principal peak. Hence buffer ammonium acetate with pH adjusted to 4.9 with Glacial Acetic Acid was selected. Study was done by changing the ratio of Acetonitrile and Methanol. It was observed that the polarity of Methanol played a major role in separation of impurities. Hence mobile phase was optimized to Buffer:Acetonitrile:Methanol (300:400:300).

Since most of the impurities are non-polar in nature, various C-18 columns were screened. The parameters like tailing factor and theoretical plates were recorded during the study. From obtained data Zorbax Eclipse XDB C-18 (150 x 4.6 x 5µm) was found suitable for analysis.

All impurities were prepared at 100 ppm and their UV-visible spectra was acquired. The Amiodarone and all its impurities has good and satisfactory response at 240nm. Hence detection at 240nm was selected for method-development.

Retention time were confirmed by injecting working standards of Impurity-D, Impuriy-E and Amiodarone Hydrochloride. For System Suitability, the resolution between Impurity D and Impurity E should be not less then 3.5. Relative Standard Deviation for five replicate injections should not be more then 5%.

9. Analytical Method Validation

The developed method is subjected to analytical method validation, which is conducted according to International Council for harmonisation (ICH) guidelines. The parameters with which analytical method is validated are specificity, limit of detection and limit of quantitation, linearity, accuracy, precision, robustness, solution stability and degradation study.

9.1 Specificity

Specificity is capability of the method to measure the analyte response in presence of impurities. The typical chromatograms of blank Solution, Reference Solution (a), Reference Solution (b), and Impurities Spike Solution are given from figure 1 to figure 4 respectively. The results indicate that all impurities are well separated under the current chromatographic conditions. There was no interference of peak from blank solution and samples solution within retention time of impurities obtained. Peak purity for Amiodaraone and its impurities were passing. For retention time of each impurity and its peak purity refer table no.5.

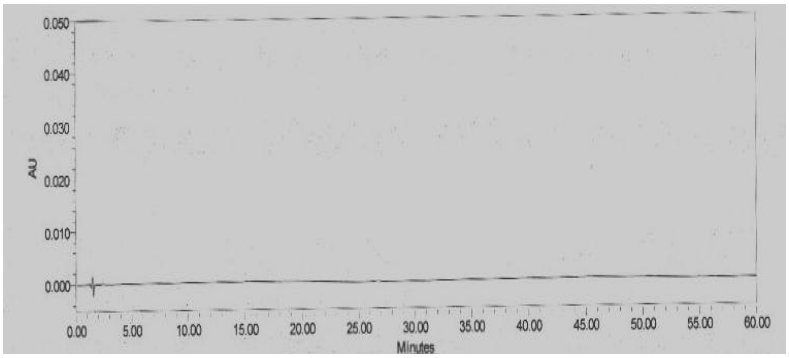


Figure No. 1: Blank.

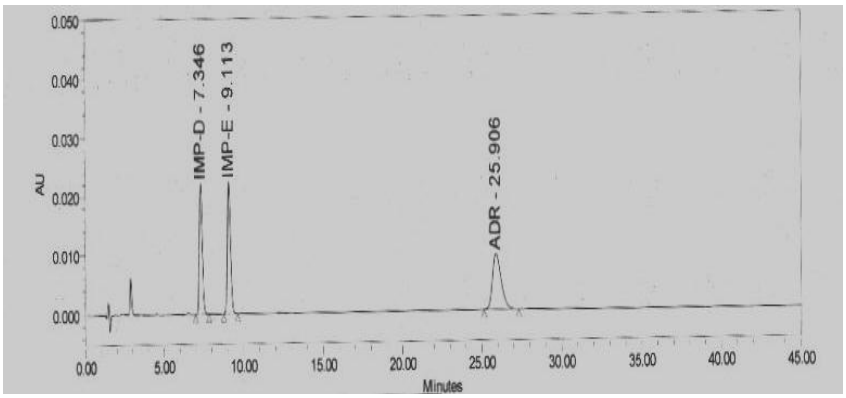


Figure No. 2: Reference Solution (a).

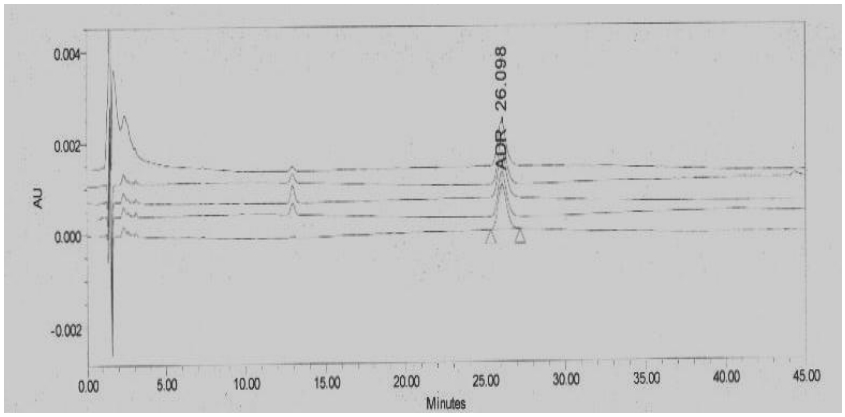
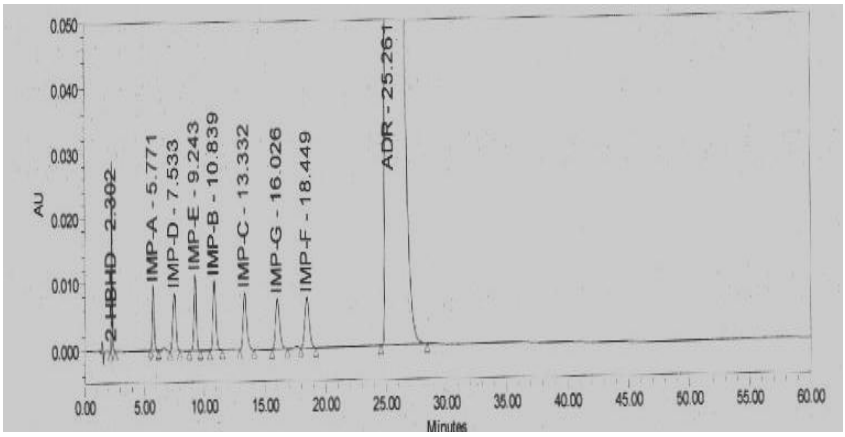
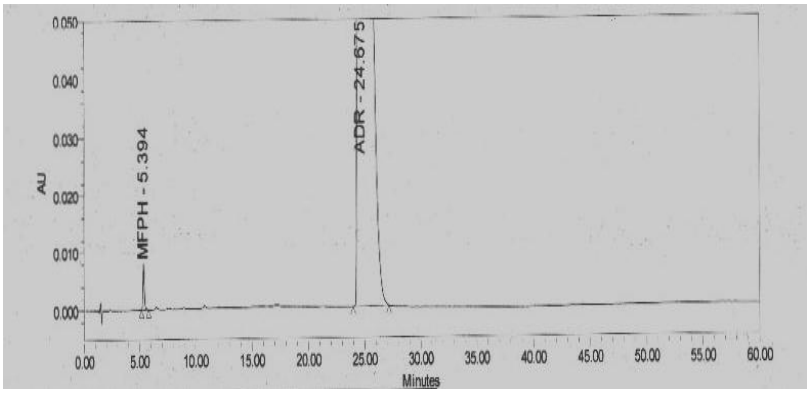


Figure No. 3: Reference Solution (b).



(A): Spike Soltuion containing impurities other than MFPH



(B) Spike Soltuion containing impurity MFPH

Figure No. 4: Impurities spiked in sample.

Table No. 5: Peak purity and RT Ratio for Amiodarone and its impurities.

Sr. No.	Peak name	RT	RT Ratio	Purity Angle	Purity Threshold
1	2-HBHD	2.30	0.09	8.33	47.34
2	MFPH	5.40	0.21	2.92	9.63
3	IMP-A	5.77	0.22	0.19	1.11
4	IMP-D	7.53	0.29	0.22	2.46
5	IMP-E	9.24	0.36	0.59	2.38
6	IMP-B	10.84	0.42	0.07	0.24
7	IMP-C	13.33	0.52	0.10	0.35
8	IMP-G	16.03	0.63	0.04	0.24
9	IMP-F	18.45	0.73	0.24	3.34
10	ADR	25.26	1.00	1.02	25.07

9.2 Limit of Detection and Limit of Quantification

Series of standard solution of Amiodarone and its impurities were prepared and injected in concentration ranging from 50% to 300%. Limit of detection (LOD) and Limit of Quantitation (LOQ) was calculated based on residual standard deviation of regression line and slope. Both calculated LOD and LOQ were well within limit. The LOQ is below 0.011% for all impurities and Amiodarone API. For complete details of LOQ and LOD refer Table.

Table No. 6: LOD and LOQ.

Sr. No.	Name of Impurity	LOD (%)	LOQ (%)
1	2-HBHD	0.001	0.003
2	MFPH	0.004	0.011
3	IMP-A	0.001	0.002
4	IMP-D	0.003	0.008
5	IMP-E	0.002	0.007
6	IMP-B	0.003	0.009
7	IMP-C	0.002	0.005
8	IMP-G	0.002	0.006

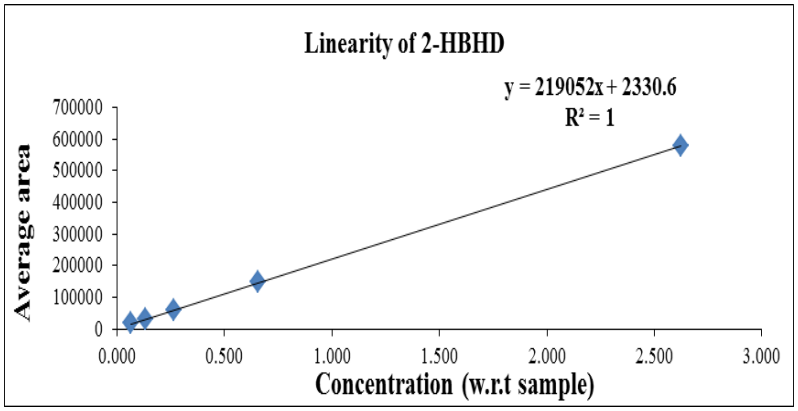
9	IMP-F	0.002	0.006
10	ADR	0.002	0.006

9.3 Linearity

Series of linearity solution of Amiodarone and its impurities were prepared from 50% to 300% of test concentration. Lineariy curves were drawn by plotting the peak areas of Amiodarone and its impurities against its corresponding concentration of linearity solution. Observed regression coefficient was greater than 0.998 and % y-intercept was less than 5.0%

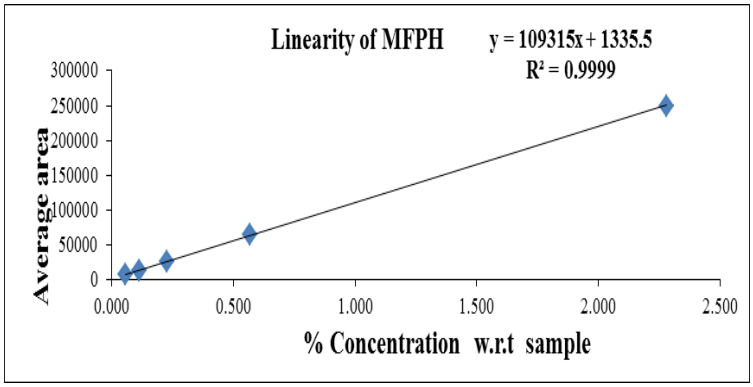
Table No. 7: Linearity table and its R^2 values.

2-HBHD



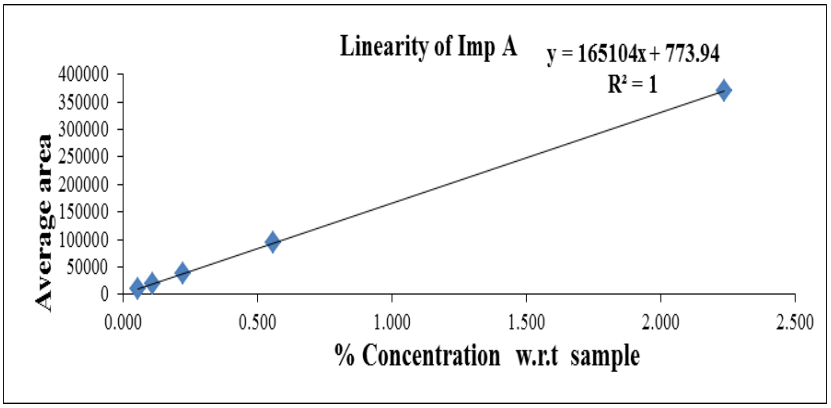
Slope	**219051.64**
Intercept	**2330.62**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**1.59**

MFPH



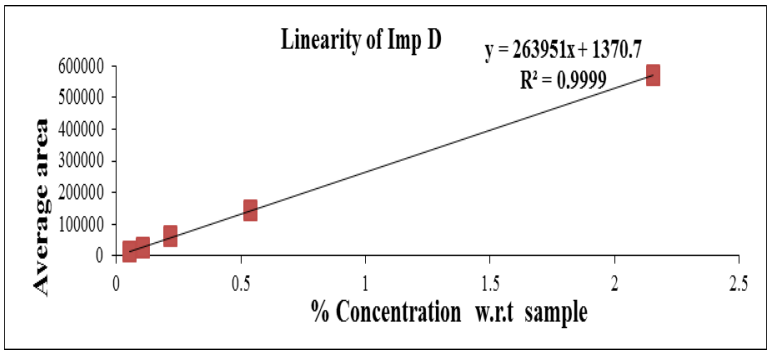
Slope	**109314.63**
Intercept	**1335.46**
Corelation Coefficent (R^2)	**0.9999**
% Y-Intercept	**2.05**

IMP-A



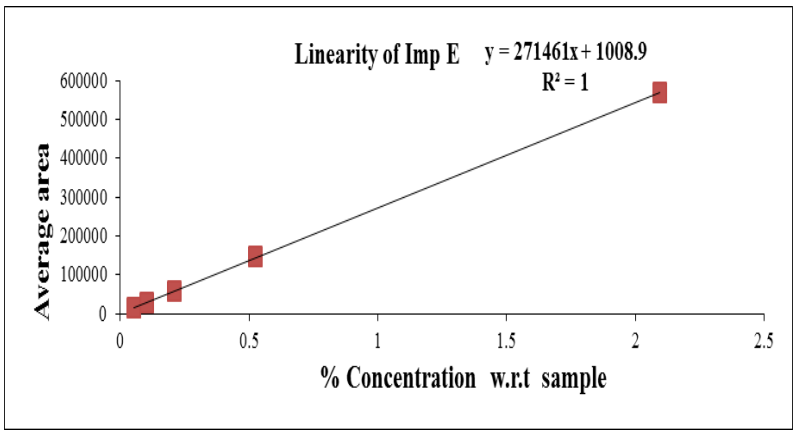
Slope	165103.51
Intercept	773.94
Corelation Coefficent (R^2)	1.0000
% Y-Intercept	0.83

IMP-D



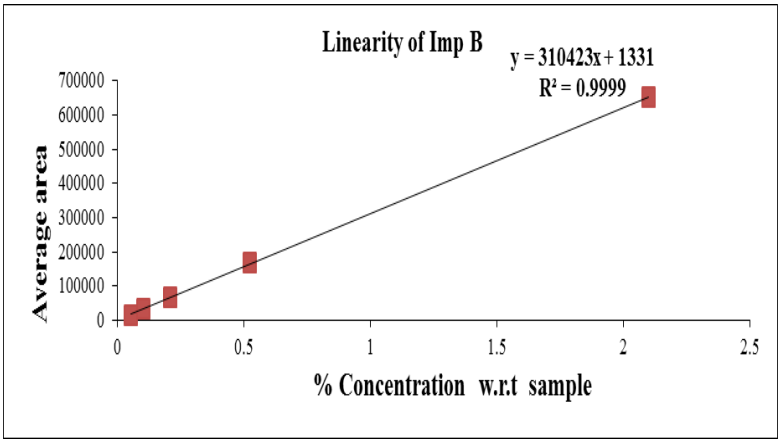
Slope	**263950.76**
Intercept	**1370.67**
Corelation Coefficent (R^2)	**0.9999**
% Y-Intercept	**0.94**

IMP-E



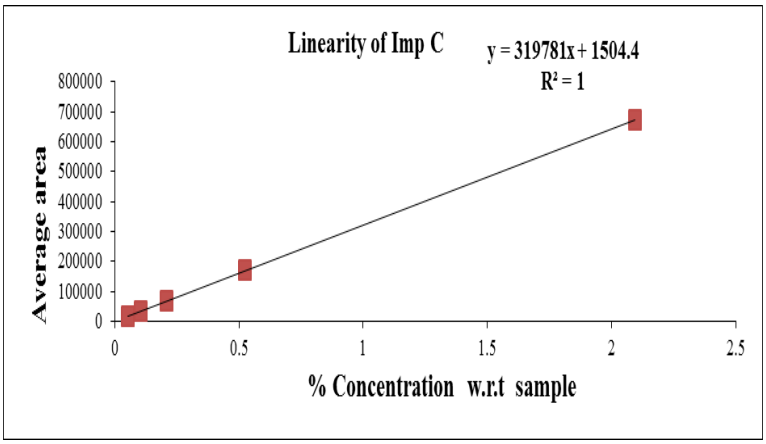
Slope	**271460.61**
Intercept	**1008.89**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**0.69**

IMP-B



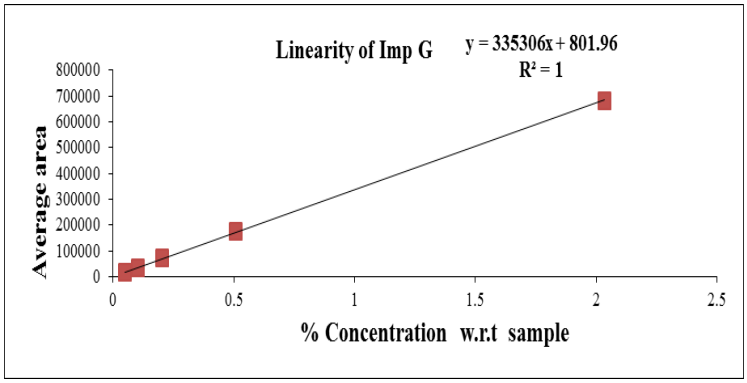
Slope	**310423.31**
Intercept	**1331.05**
Corelation Coefficent (R^2)	**0.9999**
% Y-Intercept	**0.80**

IMP-C



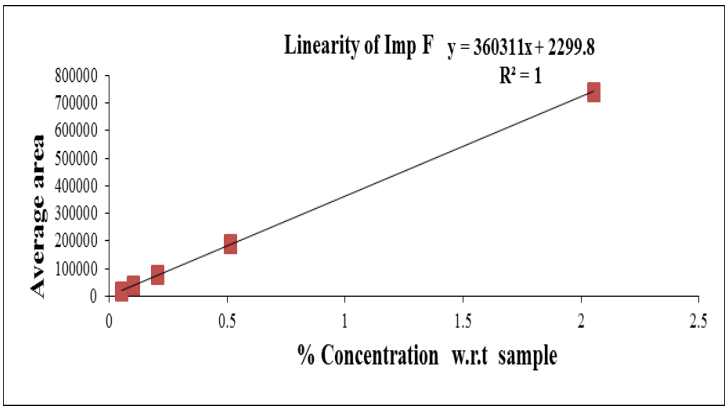
Slope	**319780.75**
Intercept	**1504.45**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**0.88**

IMP-G



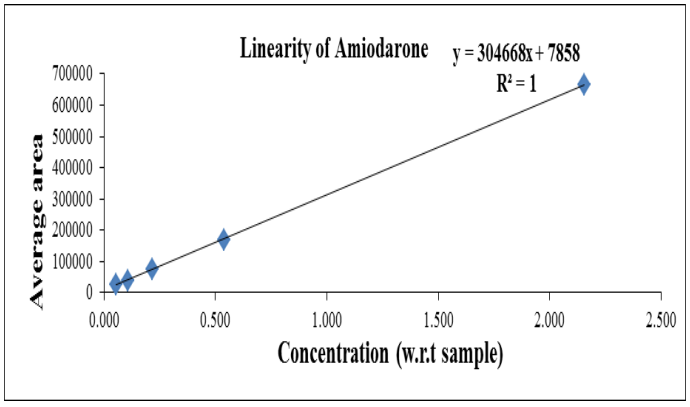
Slope	**335306.32**
Intercept	**801.96**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**0.46**

IMP-F



Slope	**360310.56**
Intercept	**2299.80**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**1.21**

Amiodarone



Slope	**304667.54**
Intercept	**7858.04**
Corelation Coefficent (R^2)	**1.0000**
% Y-Intercept	**4.62**

9.4 Accuracy

Accuracy of method is calculated and established by carrying out recovery studies of Impurities. The test solution was spiked with imputrities solution at specific limit level concentration 50%, 100%, 200%. Each spiked test solution was analyzed for recovery study of impurities. Recovery established is between 85% to 110%.

Table No. 8: Recovery of impurities at 50%.

Sr.No.	IMP Name	As Such Test Area	% CONTENT	Area of 0.05 % Level	RRF	Thereotical imp Added %	%ofIMP Observed	CORRECTED OBSERVED	%ofRecovery
1	2HBHD	0	0.00	14853	0.73	0.062	0.058	0.058	92.92
2	IMP-A	2274	0.01	11536	0.55	0.048	0.060	0.048	100.24
3	IMP-D	0	0.00	15856	0.87	0.052	0.052	0.052	100.42
4	IMP-E	0	0.00	16386	0.91	0.049	0.051	0.051	104.11
5	IMP-B	4600	0.01	21706	1.04	0.050	0.060	0.047	94.97
6	IMP-C	0	0.00	17391	1.06	0.050	0.047	0.047	94.21
7	IMP-G	0	0.00	17882	1.10	0.049	0.046	0.046	94.98
8	IMP-F	0	0.00	19786	1.21	0.048	0.047	0.047	96.50
9	MFPH	0	0.00	6532	0.36	0.053	0.052	0.052	98.50

Table No. 9: Recovery of impurities at 100%.

Sr.No.	IMP Name	As Such Test Area	% CONTENT	Area of 0.10 % Level	RRF	Thereotical imp Added %	%ofIMP Observed	CORRECTED OBSERVED	%ofRecovery
1	2HBHD	0	0.00	29142	0.73	0.125	0.114	0.114	91.15
2	IMP-A	2274	0.01	21438	0.55	0.096	0.111	0.100	103.50
3	IMP-D	0	0.00	32877	0.87	0.104	0.108	0.108	104.11
4	IMP-E	0	0.00	33377	0.91	0.099	0.105	0.105	106.04
5	IMP-B	4600	0.01	37645	1.04	0.099	0.103	0.091	91.54
6	IMP-C	0	0.00	33822	1.06	0.099	0.091	0.091	91.61
7	IMP-G	0	0.00	32451	1.10	0.098	0.084	0.084	86.18
8	IMP-F	0	0.00	36253	1.21	0.097	0.085	0.085	88.41
9	MFPH	0	0.00	11826	0.36	0.105	0.094	0.094	89.16

Table No. 10: Recovery of impurities at 200%.

Sr.No.	IMP Name	As Such Test Area	% CONTENT	Area of 0.20 % Level	RRF	Thereotical imp Added %	% of IMP Observed	CORRECTED OBSERVED	% of Recovery
1	2HBHD	0	0.00	60231	**0.73**	0.250	0.235	0.235	**94.20**
2	IMP-A	2274	0.01	42368	**0.55**	0.192	0.220	0.208	**108.16**
3	IMP-D	0	0.00	61686	**0.87**	0.207	0.202	0.202	**97.67**
4	IMP-E	0	0.00	60701	**0.91**	0.197	0.190	0.190	**96.42**
5	IMP-B	4600	0.01	72591	**1.04**	0.198	0.199	0.187	**94.07**
6	IMP-C	0	0.00	71721	**1.06**	0.199	0.193	0.193	**97.13**
7	IMP-G	0	0.00	69562	**1.10**	0.195	0.180	0.180	**92.37**
8	IMP-F	0	0.00	74033	**1.21**	0.193	0.174	0.174	**90.27**
9	MFPH	0	0.00	28033	**0.36**	0.210	0.222	0.222	**105.68**

9.5 Precision

System precision was carried out by analyzing five injections of reference solution (b) of Amiodarone API at limit level concentration. Relative standard deviation for peak area of Amiodarone was calculated and found to be 0.22%.

9.6 Robustness

Robustness was studied by making small but deliberate changes in optimized method conditions and evaluating the effect on resolution between IMP-D and IMP-E. The mobile phase flow rate was changed by 0.1 units from 1.0 to 0.9 and 1.1 ml/min. The pH was varied by 0.1 units to 4.8 and 5.0. When these changes were made all other conditions, including components of mobile phase were held constant.

9.7 Solution Stability

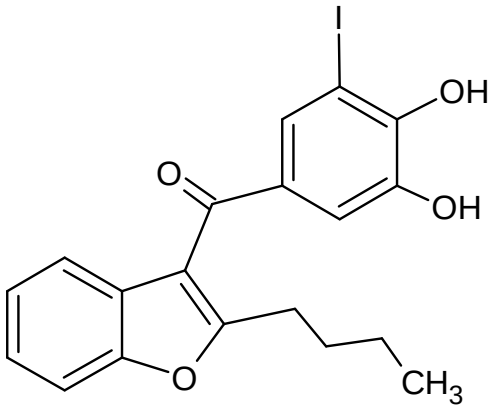
The solution stability of Amiodarone hydrochloride and its impurities in related substances method was evaluated by leaving a spiked solution in tightly capped volumetric flask at room temperature for 48 hrs and analysis of all its impurities content was done at interval of 12hrs.

9.8 Degradation Study

All degradation study was performed at initial drug concentration of 1.0mg/ml. The stress condition used for the study were acid hydrolysis (1 M HCl at 60˚C for 3 hrs), basic hydrolysis (1 M NaOH at 60˚C for 3 hrs) and oxidation (6% H_2O_2 at 60˚C for 3 hrs). It was observed that Amiodarone degraded extensively under basic condition but was quiet stable under acidic and oxidative condition.

Table No. 11: Degradation Under Basic Condition.

Sr.No.	IMP Name	Area	RRF	% of IMP
1	2HBHD	810766	0.73	2.93
2	MFPH	0	0.36	0.00
3	IMP A	0	0.55	0.00
4	IMP D	2372435	0.87	7.20
5	IMP E	84432	0.91	0.25
6	IMP B	31774	1.04	0.08
7	IMP C	0	1.06	0.00
8	IMP G	0	1.10	0.00
9	IMP F	56500	1.21	0.12
10	Individual Impurity	9853367	1.00	26.02
11	Unknown Impurity	11233819	1.00	29.67
12	Total Impurities			40.25



The degradation product formed used basic hydrolysis condition is 2-butyl-3-benzofurnayl-3,4-dihydroxy-5-iodophenylketone. The molecular mass of this product is observed to be 436.24 g/mol (10).

Table No. 12: Degradation Under Acidic Condition.

Sr.No.	IMP Name	Area	RRF	% of IMP
1	2HBHD	0	0.73	0.00
2	MFPH	1399	0.36	0.01
3	IMP A	2842	0.55	0.01
4	IMP D	45053	0.87	0.14
5	IMP E	3664	0.91	0.01
6	IMP B	5737	1.04	0.01
7	IMP C	1357	1.06	0.00
8	IMP G	1523	1.10	0.00
9	IMP F	0	1.21	0.00
10	Individual Impurity	6394	1.00	0.02
11	Unknown Impurity	19070	1.00	0.05
12	Total Impurities			0.24

Table No. 13: Degradation Under Oxidative Condition.

Sr.No.	IMP Name	Area	RRF	% of IMP
1	**2HBHD**	0	0.73	0.00
2	**MFPH**	1168	0.36	0.01
3	**IMP A**	3346	0.55	0.02
4	**IMP D**	32294	0.87	0.10
5	**IMP E**	736	0.91	0.00
6	**IMP B**	21017	1.04	0.05
7	**IMP C**	3719	1.06	0.01
8	**IMP G**	1237	1.10	0.00
9	**IMP F**	0	1.21	0.00
10	**Individual Impurity**	142221	1.00	0.38
11	**Unknown Impurity**	171964	1.00	0.45
12	**Total Impurities**			0.64

10. CONCLUSION

The analytical method validation for Amiodarone Hydrochloride by Reverse Phase HPLC was carried out by performing the parameters such as specificity, limit of detection and limit of quantitation, linearity, accuracy, precision, robustness, solution stability and degradation study. All the data has been compiled and found to be satisfactory. Hence, method developed for Reverse Phase HPLC can be suitably used for analysis of Amiodarone Hydrochloride active pharmaceutical ingredient.

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