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Review Article

An Overview on Various Analytical Methods for Estimation of Atenolol and Amiodarone from its Bulk and Pharmaceutical Dosage Forms

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ABSTRACT

The main objective of this review is to unify and interpret widely scattered information of reported studies on potential, reliable and efficient analytical methodologies which can estimate Atenolol and Amiodarone separately. The information and suggested outlined below may facilitate and guide further needed studies to optimize the use of analytical techniques like High Performance Liquid Chromatography (HPLC), Bioanalytical Methods, UV Spectroscopy, Stability indicating RP-HPLC methods etc. for determination of Atenolol and Amiodarone in formulation. From the reviewed literature it is obvious that HPLC is a commonly available method of testing in pharmaceutical laboratory so this method should be of choice for complete determination of Atenolol and Amiodarone. Selection of analytical methods is determined by several factors such as speed, convenience, specificity, accuracy, precision, sensitivity, selectivity, cost, availability of instruments, technical expertise and the number of samples to be analyzed.

Keywords: Atenolol, Amiodarone, Analytical estimation, HPLC, UV

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INTRODUCTION

Atenolol is a beta blocker medication primarily used to treat high blood pressure and heart-associated chest pain. Atenolol, however, does not seem to improve mortality in those with high blood pressure (AHFS, 2018; Tomiyama H and Yamashina A, 2014; DiNicolantonio JJ, *et al.*, 2015). Other uses include the prevention of migraines and treatment of certain irregular heartbeats. It is taken by mouth or by injection into a vein. It can also be used with other blood pressure medications (British National Formulary, 2018).

Common side effects include feeling tired, heart failure, dizziness, depression, and shortness of breath. Other serious side effects include bronchospasm. Use is not recommended during pregnancy and alternative drugs are preferred when breastfeeding. It works by blocking β1-adrenergic receptors in the heart, thus decreasing the heart rate and workload.

Atenolol was patented in 1969 and approved for medical use in 1975. It is available as a generic medication. In 2018, it was the 42nd most commonly prescribed medication in the United States, with more than 18 million prescriptions (Beard Jr EL, 2001; Ali MU, *et al.*, 2018; Florey K, 1981; Akiful HM, *et al.*, 2012; Godge RK, *et al.*, 2017) *(Figure 1)*.

Amiodarone is an antiarrhythmic medication used to treat and prevent a number of types of irregular heartbeats (Beard Jr EL, 2001). This includes Ventricular Tachycardia (VT), Ventricular Fibrillation (VF), and wide complex tachycardia, as well as atrial fibrillation and paroxysmal supraventricular tachycardia (Ali MU, *et al.*, 2018). Evidence in cardiac arrest, however, is poor. It can be given by mouth, intravenously, or intraosseously. When used by mouth, it can take a few weeks for effects to begin. Common side effects include feeling tired, tremor, nausea, and constipation (Florey K, 1981). As amiodarone can have serious side effects, it is mainly recommended only for significant ventricular arrhythmias. Serious side effects include lung toxicity such as interstitial pneumonitis, liver problems, heart arrhythmias, vision problems, thyroid problems, and death If taken during pregnancy or breastfeeding it can cause problems in the fetus. It is a class III antiarrhythmic medication. It works partly by increasing the time before a heart cell can contract again.

Amiodarone was first made in 1961 and came into medical use in 1962 for chest pain believed to be related to the heart. It was pulled from the market in 1967 due to side effects. In 1974 it was found to be useful for arrhythmias and reintroduced. It is on the World Health Organization's List of Essential Medi-

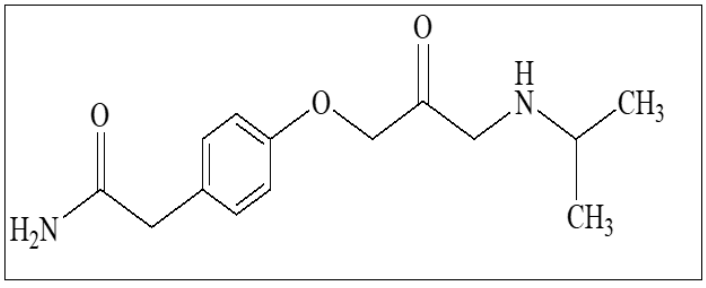

Figure 1: Structure of Atenolol

cines. It is available as a generic medication. In 2017, it was the 196th most commonly prescribed medication in the United States, with more than two million prescriptions *(Figure 2)*.

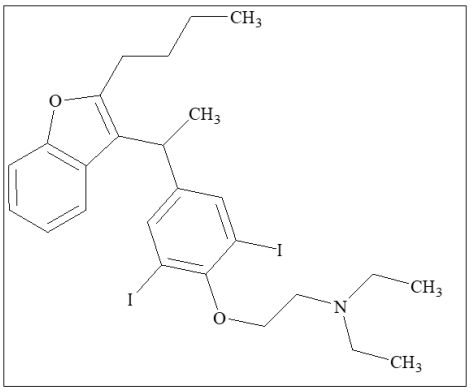

Figure 2: Structure of Amiodarone

ANALYTICAL METHODS

Analytical methods development and validation play important roles in the discovery, development, and manufacture of pharmaceuticals. Pharmaceutical products formulated with more than one drug, typically referred to as combination products, are intended to meet previously unmet patients need by combining the therapeutic effects of two or more drugs in one product. These combination products can present daunting challenges to the analytical chemist responsible for the development and validation of analytical methods. This review contains the various simultaneous estimation methods (spectrophotometric, High Performance Liquid Chromatography (HPLC) and High-Performance Thin Layer Chromatography (HPTLC) which are employed for the quantitative estimation of drug products containing antihypertensive analytes. The official test methods that result from these processes are used by quality control laboratories to ensure the identity, purity, potency, and performance of drug products.

Validation of RP-HPLC method

The developed method for estimating Atenolol and amiodarone was validated for the following parameters according to ICH guidelines (Nilesh S, *et al.*, 2021; Sabir AM, 2013; ICH I, 2005; Hausherr A, *et al.*, 2020; Pendbhaje NS, *et al.*, 2021; Sule S, *et al.*, 2014).

Filtration analysis: A filtration study of an analytical technique explores the filter's interference with extraneous materials, deposition on the filter bed, and filter compatibility with the sample.

Specificity: Specificity is the capacity to access the analyte unequivocally in the presence of potentially present components.

Linearity and range: The ability of an analytical method to elicit test results that are proportional to the concentration of an analyte in samples within a given range, either directly or through a well-defined mathematical transformation.

Decisiveness The statistical treatment of test results obtained by examination of samples with analyte concentrations around the claimed spectrum determines the analytical method's linearity.

As a function of analyte concentration, the region is graphically plotted. Curve fitting percentages are measured. Acceptance is a state of mind. Criteria include: The plot should be linear, with the origin at the middle. The correlation coefficient (r2) must be greater than 0.999.

Accuracy (%Recovery): The closeness of agreement between the value accepted as a standard true value or an accepted reference value and the value of the value found is expressed by the analytical procedure's accuracy.

Criteria for acceptance: The average recovery rate should be between 98.00 and 102.00 percent. The Relative Standard Deviation (RSD) does not exceed 2.0%.

Precision: When a technique is applied repeatedly to several Samplings of a homogeneous sample, the precision of an analytical method is the degree of agreement among individual test results. A Standard Deviation or Relative Standard Deviation is used to express the accuracy of an empirical system. There are two levels of precision: repeatability and intermediate precision. It is carried out on a sample API. From the same sample matrix, render six separate test solutions of the 100 percent test concentration. Every test solution should be injected twice.

Accuracy in the middle:

Precisely in the middle of the day: It is carried out by making another researcher analyse the data on a different day to ensure that the findings are repeatable. Samples prepared in the same way that the Repeatability parameter samples were (6 Samples prepared).

Criteria for acceptance: For test results, the percent RSD of 6 samples NMT 2.0% was used.

NMT 2.0% for test results, percent RSD of total 12 samples.

(6 of Repeatability and 6 of Intermediate precision)

Robustness: The robustness of an analytical technique is a measure of its ability to remain unaffected by minor yet deliberate changes in system parameters, and it indicates its efficiency during regular use.

Detection:

Limit Of Detection (LOD): Under the specified experimental conditions, the lowest concentration of the analyte in the sample that the system can detect but not necessarily quantify simply means that the sample is below or above a certain threshold. Limits are defined in percentages or parts per million. The detection limit will be calculated not only by the measurement technique, but also by the type of instrument used.

S/N= 2/1 or 3/1

Where, S=Signal, N=Noise

It may be calculated based on the Standard Deviation (SD) of the response and slope of the curve(S).

LOD=3.3 (SD)/S

Where, SD=Standard deviation, S=Slope

Limit Of Quantitation (LOQ): The lowest amount of analyte in a sample that can be calculated with reasonable precision and accuracy under the specified experimental conditions is known as the limit of quantitation (LOQ). It is expressed as the percentage of analyte in the sample (e.g., parts per billion). The S/N ratio should not be less than 10 and the RSD should be less than 3%.

S/N= 10/1

Where S=Signal N=Noise

It may be calculated based on the Standard Deviation (SD) of the response and slope of the curve(S).

LOQ=10 (SD)/S

Where, SD=Standard deviation, S=Slope

Experimental work

Literature survey revealed that was determined by UV-visible spectroscopy and HPLC. In the current work, the authors have proposed a simple, specific, valid and robust RP-HPLC method for the estimation of Atenolol and amiodarone in pharmaceutical active substance form *(Tables 1 and 2)*.

Table 1: Analytical methods used for the estimation of Atenolol from bulk and formulations

Sr. No.	Name of author	Name of journal	Title of article	Analytical conditions
UV Spectrophotometric				
1	Madhurai P, et al. (Madhurai P, et al., 2015)	International Journal of Pharmaceutical Chemical and Biological Science	Quantitative estimation of atenolol in pharmaceutical Dosage forms by using visible spectroscopy.	Solvent-Distilled water
				λ max-549 nm
				Beer-Lambert's limits (µg/mL)-
				2-10
				linear regression equation-
				Y=0.0572 C+0 .0033
				correlation coefficient-0.9990
				% RSD-0.319
				% Recovery-99.5%%
				LOD-5.88 µg/mL
				LOQ-17.83 µg/mL
Turbidimetric analysis				
1	Al-Awadie NS and Khudhair AF (Al-Awadie NS and Khudhair AF, 2014)	Iraqi Journal of Science	Determination of Atenolol in pharmaceutical formulations by continuous flow injection analysis via turbidimetric (T180o) and scattered light effect at two opposite position (2N90o) using Ayah 4SW-3D-T180-2N90-Solar-CFI Analyzer	Turbidimetric: T180º
				Scattered light effect at two opposite position (2N90º).
				Incident light in namely +90º and -90º
				Linearity of Atenolol is ranged from (0.1-11) mmol. L^{-1}
				Correlation coefficient-0.938
				LOD-0.05 mmol. L^{-1}
Kinetic method				
1	Fadnis AG and Agarwal R (Fadnis AG and Agarwal R, 2015)	J Chem Pharm Res	Kinetic method for estimation of Atenolol	Fixed Time Method:
				103 [Unknown-1] $moldm^{-3}$ = 3.75(calculated): 3.75(actual)
				103 [Unknown-2] $moldm^{-3}$ =6.26 ± 0.01(calculated): 6.25(actual)
Bioanalytical methods				
1	Yilmaz B, et al. (Yilmaz B, et al., 2012)	Journal of Chromatographic Science	HPLC Method for Determination of Atenolol in Human Plasma and Application to a Pharmacokinetic Study in Turkey.	Column-Ace C18 reverse-phase column
				M.P- methanol=water (50:50, v/v)
				λ max-549 nm
				Beer-Lambert's limits-
				5-150 ng/mL
				correlation coefficient-0.9990
				% RSD-0.319
				% Recovery-98.4%
				LOD-1.5 ng/mL
				LOQ-5 ng/mL
Stability-Indicating HPLC method				
1	Belal F, et al. (Belal F, et al., 2008)	Journal of Chromatography Separation Technique	Stability-indicating HPLC Method for the Determination of Atenolol in Pharmaceutical Preparations.	Column-C8 Column (250 mm × 4.6 mm i.d., 5 µm)
				M.P-acetonitrile: methanol:0.02 M phosphate buffer, pH 5 (20:20:60)
				Flow rate-1 ml/min
				λ max-226 nm
				Beer-Lambert's limits-
				0.05-10 µg/ml
				Correlation coefficient-1
				% Recovery-100.4%
				LOD-0.01 µg/mL
				LOQ-0.03 µg/mL
				stability-indicating capability-acid and base media

UV-HPLC				
1	Goebel K and Rolim CM (Goebel K and Rolim CM, 2007)	Latin American Journal of Pharmacy	Validation of UV Spectrophotometric and HPLC Methods for Quantitative Determination of Atenolol in Pharmaceutical Preparations.	Column-Purospher RP-18 (250 mm × 4.6 mm, 5 µm)
				Solvent-10 mM ammonium acetate buffer (pH 7.0) and acetonitrile (80:20 v/v)
				λ max-275 nm
				Beer-Lambert's limits (µg/mL)-
				2-10
				Correlation coefficient-0.9990
				% Recovery-98.5%
Reverse Phase High Performance Liquid Chromatography				
1	Kumar N, et al. (Kumar N, et al., 2010)	E-Journal of Chemistry	Estimation of Atenolol by Reverse Phase High Performance Liquid Chromatography	Column-ODS and dimensions of column was 25 mm × 4.6 mm
				M.P-phosphate buffer and acetonitrile (53:47 v/v)
				λ max-230 nm
				Flow rate-2.1. mL/min
				Beer-Lambert's limits-
				5-150 ng/mL
				correlation coefficient-0.9990
				% RSD-0.6
				% Recovery-99.6%
				LOD-510 ng/mL
				LOQ-120 ng/mL
2	Kori S, et al. (Kori S, et al., 2013)	International Journal of Science and Research	Method Development and Validation of Atenolol Drug by Spectrophotometric and HPLC Technique in Forensic Application	Column-RPC18 column
				λ max-226 nm
				Flow rate-2.1. mL/min
				Beer-Lambert's limits-
				25-50 µg/mL
				correlation coefficient-0.9990
				% RSD-0.5
				% Recovery-99.5%
				LOD-2.00 µg/mL
				LOQ-6.3 µg/mL
3	Baskara BL (Baskara BL, 2011)	Asian journal of applied science	Facile and Rapid RP-HPLC for method determination of Atenolol in pharmaceutical formulation.	Column-Atlantis dC18
				λmax-225 nm
				Flow rate-1.00 ml/min
				Beer-Lambert's limits-
				1-100 µg/mL
				correlation coefficient-0.999
				% Recovery-98.03-102.5%
				LOD-0.4 µg/mL
				LOQ-1.0 µg/mL

Table 2: Analytical methods used for the estimation of Amiodarone from bulk and formulations

Sr. No.	Name of author	Name of journal	Title of article	Analytical conditions
UV -HPLC				
1	Al-Rimawi F (Al-Rimawi F, 2010)	Pharmaceutica Analytica Acta	Validation of an HPLC-UV Method for the Determination of Amiodarone Impurities in Tablet Formulations	Column- C18 column
				λ max-240 nm
				Mob. Phase-buffer solution pH 5.0, methanol, and acetonitrile (30:30:40, v/v/v)
				Beer-Lambert's limits (µg/mL)-
				0.005-0.015
				Correlation coefficient-0.9990
				% Recovery-99.7%
				LOD-0.0005 µg/mL
				LOQ-0.0002 µg/mL

Bioanalytical methods				
1	Rodrigues M, et al, (Rodrigues M, et al., 2013)	Journal of Chromatographic Science	A Rapid HPLC Method for the Simultaneous Determination of Amiodarone and its Major Metabolite in Rat Plasma and Tissues: A Useful Tool for Pharmacokinetic Studies	Column-LiChroCART Purospher Star C18 column (55 3 4 mm, 3 mm)
				λ max-254 nm
				Mob. Phase- phosphate buffer (50 mM) with 0.1% formic acid (pH 3.1)-methanol-acetonitrile (45:5:50, v/v/v)
				Flow rate-1.3 mL/min
				Beer-Lambert's limits (µg/mL)-
				0.1-15
				correlation coefficient-0.995
				% Recovery-97.7 %
2	Jun AS and Brocks DR (Jun AS and Brocks DR, 2001)	Journal of pharmaceutical science	High performance liquid chromatographic assay of amiodarone in rate plasma.	Column-C8 analytical column
				λ max-242 nm
				Mob. Phase- buffer solution pH 5.0, methanol, and acetonitrile (30:30:40, v/v/v)
				Correlation coefficient-0.998
				% Recovery-75-82%
				LOD-0.035 µg/mL
				LOQ-0.035 µg/mL
RP-HPLC				
1	Babji P, et al. (Babji P, et al., 2013)	Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry	Development and validation of RP-HPLC method for amiodarone tablets in pharmaceutical dosage forms	Column-Hypersil BDS column
				λ max-240 nm
				Mob. Phase-Acetonitrile: 0.5%Triethylamine Buffer pH to 6.5 with orthophosphoric acid (75:25)
				Flow rate-2.0 mL/min
				Correlation coefficient-0.9990
				% Recovery-99.7-100.1%
2	Thyagarajapuram N and Alexander KS (Thyagarajapuram N and Alexander KS, 2003)	Journal of Liquid Chromatography and Related Technologies	A Simplified Method for the Estimation of Amiodarone Hydrochloride by Reverse-Phase High Performance Liquid Chromatography	Column-Novapak C8 column 3.9 150 mm-particle size of 4 mm
				λ max-240 nm
				Flow rate-1.5 mL/min
				Mob. Phase-methanol, water, and acetic acid in a 95:4:1
				Linear equation-y ¼ 27683 x þ 42192
				Correlation coefficient-0.94
				% Recovery-99.7%
				LOD-3.12 µg/mL
				LOQ-0.936 µg/mL
3	Amit G, et al. (Amit G, et al., 2018)	World Journal of Pharmaceutical Research	Development and validation of new RP-HPLC method for analysis of amiodarone hydrochloride and its related compounds	Column-Column-Novapak C8 column 3.9* 150 mm-particle size of 4 mm
				λ max-240 nm
				Flow rate-1.0 mL/min
				Mob. Phase- Acetonitrile: Water (80:20)
				Degradation Study-acid hydrolysis (1 M HCl at 60°C for 3 hrs),
				basic hydrolysis (1 M NaOH at 60°C for 3 hrs)
				oxidation (6% H_2O_2 at 60°C for 3 hrs)
Stability indicating RP-HPLC method				
1	Mallu UR, et al. (Mallu UR, et al., 2010)	Drug Invention Today	Method Development of stability indicating HPLC method for the determination of Amiodarone Hydrochloride in pharmaceutical dosage form	Column-Column-Novapak C8 column 3.9* 150 mm-particle size of 4 mm
				λ max-240 nm
				Flow rate-1.0 mL/min
				Mob. Phase-acetate buffer-Acetonitrile (15:85 v/v)
				Linearity range-12.5 to 75 µg/mL
				Correlation coefficient-0.999
				% Recovery-99.24 %

2	Ana Silva Coelho et.al (Coelho AS, et al., 2020)	Brazilian Journal of Pharmaceutical Sciences	Stability-indicating HPLC method for determination of amiodarone hydrochloride and its impurities in tablets: a detailed forced degradation study	Column-Agilent Zorbax Eclipse XDB-C18 column (100 × 3.0 mm, 3.5 µm).
				λ max-242 nm
				Flow rate-1.0 mL/min
				Mob. Phase- 50 mM acetate buffer pH 5.5 (A) and a mixture of methanol-acetonitrile (3:4, v/v) (B) in gradient elution
				Linear equation- y=151.12 x -877.23
				Correlation coefficient-0.999
				%RSD-1.29
				% Recovery-99.7%
				LOD-8.0 µg/mL
				LOQ-9.0 µg/mL

CONCLUSION

Presented work is focused on the use of different analytical methods like High Performance Liquid Chromatography (HPLC), Bioanalytical Methods, UV Spectroscopy, Stability indicating RP-HPLC methods etc. for determination of Atenolol and Amiodarone in formulation as well as in API. From the reviewed literature it is obvious that HPLC is a commonly available method of testing in pharmaceutical laboratory so this method should be of choice for complete determination of Atenolol and Amiodarone. No one analytical methods are available in market for the simultaneous estimation of the Atenolol and amiodarone in Pharmaceutical dosage form and bulk drugs.

REFERENCES

1. AHFS. Atenolol Monograph for Professionals". Drugs. 2018.
2. Tomiyama H, Yamashina A. Beta-blockers in the management of hypertension and/or chronic kidney disease. Int J Hypertens. 2014; 14.
3. DiNicolantonio JJ, Fares H, Niazi AK, Chatterjee S, D'Ascenzo F, Cerrato E, *et al.* β-Blockers in hypertension, diabetes, heart failure and acute myocardial infarction: a review of the literature. Open Heart. 2015; 2(1).
4. British National Formulary: BNF 76. Pharmaceutical Press. 2018; 151-153.
5. Beard Jr EL. The american society of health system pharmacists. JONA'S Healthcare Law, Ethics Regul. 2001; 3(3): 78-79.
6. Ali MU, Fitzpatrick-Lewis D, Kenny M, Raina P, Atkins DL, Soar J, *et al.* Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: a systematic review. Resuscitation. 2018; 132: 63-72.
7. Florey K. Analytical profiles of drug substances and excipients. Academic press. 1981.
8. Akiful HM, Nivedita G, Prashanth KK, Pradeep KT, Hasan AS, Prakash VD. Simultaneous estimation of atenolol and chlorthalidone as bulk and in tablet dosage form using UV-spectrophotometry. J Pharm Biol Sci. 2012; 1(4): 20-23.
9. Godge RK, Shinde GS, Dighe NS. Quantitative estimation and validation of atenolol and amlodipine besylate by absorbance ratio (Q) method. J Ejpmr. 2017; 4(7): 412-415.
10. Nilesh S, Pendhbaje R, Nirmal V, Ashwini A, Jamdhade S, Pathan M. Method Development and Validation by HPLC: A Brief Review. Research and Reviews: A Journal of Pharmaceutical Science. 2021; 12(1): 27-39.
11. Sabir AM. HPLC method development and validation -A review. Int Res J Pharm. 2013; 4(4): 39-46.
12. ICH I. Q2 (R1): Validation of analytical procedures: text and methodology. International Conference on Harmonization. 2005.
13. Hausherr A, Roessle C, Pinet E, Vasseur V, Abarou T, Benakouche S, *et al.* Development and validation of a new HPLC method for the analysis of a novel oral suspension formulation of 50 mg/ml ursodeoxycholic acid for newborns. Pharm Technol Hosp Pharm. 2020; 5(1).
14. Pendbhaje NS, Jamdhade AA, Pathan SM, Nirmal RV. A Review on Quantification of Brexpiprazole in Its Bulk and Pharmaceutical Dosage Form by Various Analytical Methods. International Journal of Pharmaceutical Research and Applications. 2021; 6(1): 1118-1132.
15. Sule S, Ambadekar S, Nikam D, Sule A, Bhure S. A practical approach to RP HPLC analytical method development. World J Pharm Sci. 2014; 3(9).
16. Madhurai P, Babu GR, Rao PS, Kiran BS, Kumari MV. Quantitative estimation of atenolol in pharmaceutical dosage forms by using visible spectroscopy. Int J Pharm Chem Biol Sci. 2015; 5(3).
17. Al-Awadie NS, Khudhair AF. Determination of Atenolol in pharmaceutical formulations by continuous flow injection analysis via turbidimetric (T180o) and scattered light effect at two opposite position (2N90o) using Ayah 4SW-3D-T180-2N90-Solar-CFI Analyser. Iraqi J Sci. 2014; 55(1): 12-26.
18. Fadnis AG, Agarwal R. Kinetic method for estimation of Atenolol. J Chem. 2011; 3(6): 899-904.
19. Yilmaz B, Arslan S, Asci A. HPLC method for determination of atenolol in human plasma and application to a pharmacokinetic study in Turkey. J Chromatogr Sci. 2012; 50(10): 914-919.
20. Belal F, Elbrashy A, Eid M, Nasr JJ. Stability-indicating HPLC method for the determination of quetiapine: application to tablets and human plasma. J Liq Chrom Relat Tech. 2008; 31(9): 1283-1298.
21. Goebel K, Rolim CM. Validation of UV spectrophotometric and HPLC methods for Quantitative determination of atenolol in pharmaceutical preparations. Lat Am J Pharm. 2007; 26(5): 765-760.
22. Kumar N, Verma N, Songh O, Joshi N, Singh KG. Estimation of atenolol by reverse phase high performance liquid chromatography. E J Chem. 2010; 7(3): 962-966.
23. Kori S, Goyal J, Sharma S, Pahade NK, Tandekar M. Method Development and Validation of Atenolol Drug by Spectrophotometric and HPLC Technique in Forensic Application. Int J Sci Res. 2013; 4: 438.

24. Baskara BL. Facile and Rapid RP-HPLC for method determination of Atenolol in pharmaceutical formulation. Asian J Pharm Sci. 2011; 4(3): 306-313.

25. Al-Rimawi F. Validation of an HPLC-UV method for the Determination of Amiodarone Impurities in Tablet Formulations. Pharm Anal Acta. 2010; 1(1): 1000105.

26. Rodrigues M, Alves G, Ferreira A, Queiroz J, Falcão A. A rapid HPLC method for the simultaneous determination of amiodarone and its major metabolite in rat plasma and tissues: a useful tool for pharmacokinetic studies. J Chromatogr Sci. 2013; 51(4): 361-370.

27. Jun AS, Brocks DR. High-performance liquid chromatographic assay of amiodarone in rat plasma. J Pharm Pharmaceut Sci. 2001; 4(3): 263-268.

28. Babji P, Prasadarao M, Narasimharao D, Shankar S, Beravalli R. Development and validation of RP-HPLC method for Amiodarone tablets in pharmaceutical dosage forms. Asian journal of pharmaceutical analysis and medicinal chemistry. 2013; 1(3): 155-161.

29. Thyagarajapuram N, Alexander KS. A simplified method for the estimation of amiodarone hydrochloride by reverse-phase high performance liquid chromatography. J Liq Chromatogr Relat. 2003; 26(8): 1315-1326.

30. Amit G, Deepesh P, Advait A. Development and validation of new RP-HPLC method for analysis of amiodarone hydrochloride and its related compounds. World J Pharm Res. 2018; 7(18).

31. Mallu UR, Reddy KH, Bobbarala V, Penumajji S. Method Development of stability indicating HPLC method for the determination of Amiodarone Hydrochloride in pharmaceutical dosage form. Drug Invent. 2010; 2(2).

32. Coelho AS, Ribeiro IF, Lages EB. Stability-indicating HPLC method for determination of amiodarone hydrochloride and its impurities in tablets: a detailed forced degradation study. Braz J Pharm Sci. 2020; 56.