Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
PubMed (National Library of Medicine): ID: (101671502)
Research Article
Volume 8, Issue 5: September-October: 2019, 71-74
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

ION CHROMATOGRAPHY METHOD FOR DETERMINATION OF ISOPROPYLAMINE CONTENT IN METOPROLOL SUCCINATE

Rohan More*, Dr. Amit Gosar, Dr. Tabrez Shaikh and Amit Joglekar
Indoco Remedies Limited, Analytical Research & Development Department, Navi Mumbai, 400701, Maharashtra, India.

Article Info: Received 07 September 2019; Accepted 30 September. 2019
DOI: https://doi.org/10.32553/jbpr.v8i5.657
Corresponding author: Rohan More
Conflict of interest statement: No conflict of interest

ABSTRACT:
A simple, sensitive, specific, linear and effective Ion chromatography method has been developed and validated for the determination of Isopropylamine content in Metoprolol Succinate. Isopropylamine is possible impurity that may be present in Metoprolol succinate samples. The method was validated as per International Council for Harmonisation (ICH) guidelines, for which limit of detection and limit of quantitation obtained were 29 ppm and 87 ppm respectively. % RSD for System precision observed was 1.38. The regression coefficient found for the linearity study was 0.9997. The % recovery of the spiked Isopropylamine in drug substance obtained was in the range of 83.2 to 100.7 from 50 % to 150 % level ensured the accuracy of the method. The method can be adapted to determine Isopropylamine content in Metoprolol Succinate drug substance (API).
Keywords: Ion chromatography (IC), Metoprolol Succinate, Isopropylamine, development, validation.

INTRODUCTION

Metoprolol succinate is chemically (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) salt (Fig 1). It is a white crystalline powder with formula $C_{34}H_{56}N_2O_{10}$ and molecular mass 652.8 g/mol [1]. It is used as a selective β1 receptor blocker used as an antihypertensive i.e., used in high blood pressure. It can also be used in the treatment of congestive heart failure (CHF) Post myocardial infarction [2].

In the manufacturing process of Metoprolol succinate, Isopropylamine is used as a starting material. As amines are derivatives of ammonia in which one or more hydrogen atoms have been replaced by an alkyl or aryl group. In Isopropylamine, it is replaced with the isopropyl group (Fig 1). Several amines and their acetylated derivatives are involved in normal and neoplastic cell growth, in transcription and translation of RNA and in protein synthesis, therefore they need to be controlled in drug substances [3]. Hence the method is developed and validated by Ion chromatography for the determination of Isopropyl amine.

Literature survey reveals many analytical methods are reported by various techniques such as UV Spectrophotometer, Gas chromatography (GC), High performance liquid chromatography (HPLC) and other derivatization techniques for the determination of amines in food and pharmaceutical drug samples [4-6]. The present developed method by Ion chromatography (IC) was validated according to ICH guidelines to prove its suitability and reliability of the method for the determination of Isopropylamine in pharmaceutical drug substances during routine analysis.

STRUCTURE

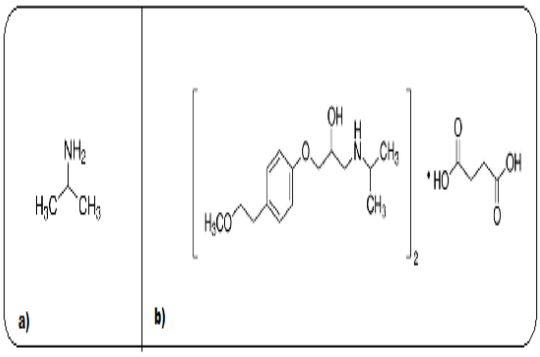


Figure 1: Structure of a) Isopropylamine and b) Metoprolol Succinate

EXPERIMENTAL

Material

Metoprolol Succinate drug substance sample and Isopropylamine standard were obtained from Analytical Research and Development (ARD) Department of Indoco Remedies Limited, Rabale.

Chemicals and Reagents

AR grade Methanesulfonic acid was purchased from Merck. Water used for the preparation of the solution was from Milli-Q water purification system (Merck).

Instrumentation

Ion chromatograph Model-ICS-5000+ Make: Thermo Fisher Scientific (Dionex) is equipped with a quaternary gradient pump, degasser, AS-AP automated sampler and a column oven. This IC system is hyphenated with conductivity detector along with Chromeleon software version 6.80. Analytical balance used was of Sartorius make with model ME 235 P.

Chromatographic conditions

IC column used for the analysis was IonPac CG 17 (Guard column) having a 50mm length, 4.0 mm internal diameter and 5 µm particle size (Thermo make) and IonPac CS 17 (Analytical column) having 250mm length, 4.0 mm internal diameter and 5 µm particle size (Thermo make). The mobile phase used for elution was Methanesulfonic acid of 2 mM concentration using the isocratic mode of elution. The flow rate, column oven temperature cell temperature was set to 1.0 mL/min, 40°C and 35°C respectively. The Cation Suppressor CERS 500 (4mm) was used in recycle mode applying current as 50 mA. The injection volume was optimized to 20 µL.

Preparation of Solutions

2 mM Methanesulfonic acid was used as a diluent for all the preparations and also taken as blank. The test sample solution was prepared of concentration 50.0 mg/mL filtered through 0.45 µm nylon filter paper using a syringe filter. The standard solution of Isopropylamine was prepared of 1000 ppm with respect to the test solution concentration.

RESULTS

Method Optimization

The Dionex IonPac CS17 cation-exchange column, which has been designed specifically for the analysis of polyvalent amines was chosen to set the method [7]. Isopropylamine gets retained on the stationary phase by forming cation in the mobile phase. The retention time for Isopropylamine obtained was about 14.0 minutes. The mobile phase was optimized to Methanesulfonic acid of concentration 2mM with an isocratic run. The Suppressor current was set to 50 mA and recycle mode used for suppression to maintain a stable baseline. Chromatographic run time kept was 50 minutes.

Method Validation

The analytical method validation work was conducted according to the ICH (International Conference on Harmonization) guidelines [8-11]. The parameter with which analytical method is validated is Specificity, Precision, Limit of detection, Limit of quantitation, Linearity and Accuracy.

Specificity:

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

The specificity of the method was established by observing the interference from Blank at the retention time of Isopropylamine analyte peak observed in Standard solution. The method was found to be highly specific for detection of Isopropylamine as there is no interference in the blank. The retention time of Isopropylamine is about 14.0 minutes (Fig. 3). Hence, the method has been demonstrated for specificity.

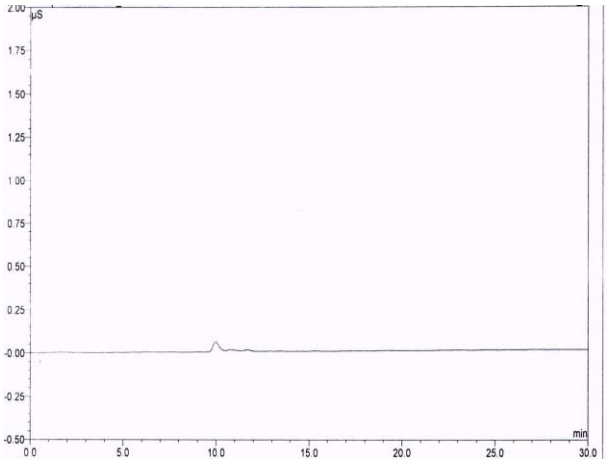


Figure 2: Typical IC chromatogram for Blank

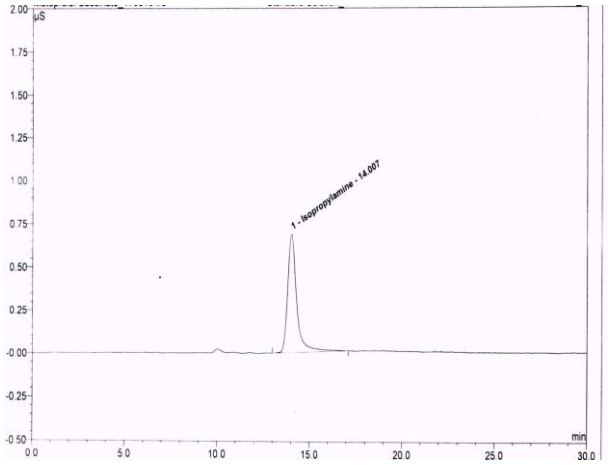


Figure 3: Typical IC chromatogram for Standard

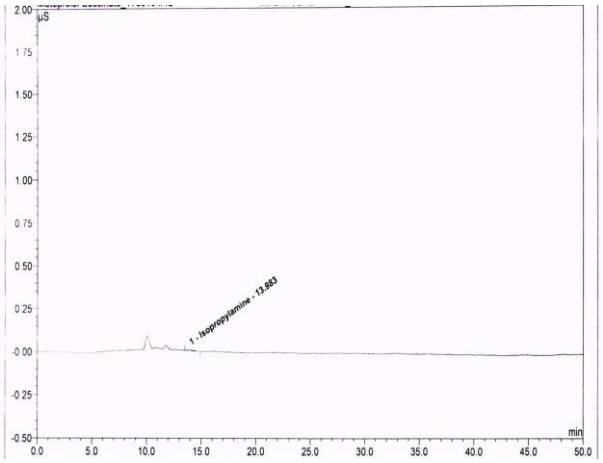


Figure 4: Typical IC chromatogram for Test sample

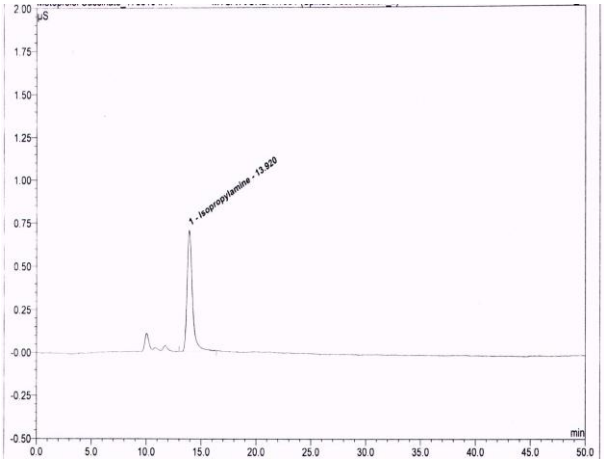


Figure 5: Typical IC chromatogram for Spiked Test sample

Precision:

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous the sample under the prescribed conditions.

System precision was established by injecting six replicated injections of standard solution where percent Relative standard deviation (%RSD) for Isopropylamine peak area was 1.38.

Limit of detection and Limit of quantitation:

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

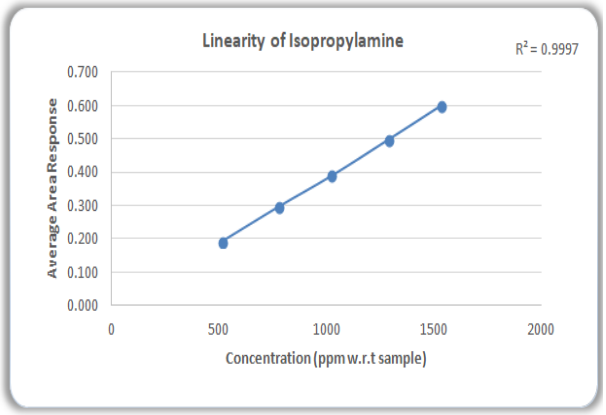
The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

Series of standard solutions of Isopropylamine was prepared in a concentration ranging from 50% to 150% of target concentration (1000 ppm w.r.t. sample). Limit of detection (LOD) and Limit of quantitation (LOQ) was calculated based on a residual standard deviation of the regression line and slope method. Limit of detection obtained for Isopropylamine was 29 ppm and Limit of quantitation 87 ppm.

Linearity:

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

Series of linearity solution of Isopropylamine were prepared from 50 to 150% of target concentration (1000 ppm w.r.t sample). Linearity curves were drawn by plotting the peak area of Isopropylamine against its corresponding concentration of linearity solution (Graph-1). The observed regression coefficient for linearity curve was 0.9997.



Graph-1: Linearity of Isopropylamine

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

The accuracy of the method was determined in terms of recovery by spiking of known amounts of Isopropylamine in drug substances at levels 50%, 100% and 150% of the specified limit. The method was highly accurate for which recovery of Isopropylamine in the drug substances with the range of 83.2 to 100.7 % at all level.

CONCLUSION

A simple, rapid, highly sensitive, selective and reproducible IC method for the determination of Isopropylamine content in Metoprolol Succinate is developed and validated. The method proved to be Specific, Precise, Linear and Accurate. From the results of all the data produced, we can conclude that the present method can be useful for determination of Isopropylamine content with desired precision and accuracy along with high throughput. Ion chromatography is the most suitable technique for the determination of ionic component like Isopropylamine. Hence, this method can be used in the quality control department for routine Isopropylamine analysis for pharmaceutical substances.

ACKNOWLEDGEMENT

The author wishes to thank to the management of Indoco Remedies Limited for supporting this work by providing the samples of Metoprolol Succinate API and Isopropylamine standard required for this research.

REFERENCES

1. Baldania, Sunil L., Ankit B. Parmar, Kashyap K. Bhatt, Dimal A. Shah, and Usmangani K. Chhalotiya. "Simultaneous Estimation of Metoprolol Succinate and Olmesartan Medoxomil in Pharmaceutical Formulation by Thin-Layer Chromatographic-Densitometric Method." *ISRN Analytical Chemistry* 2012 (2012).

2. Givertz, Michael M., and Jay N. Cohn. "Pharmacologic management of heart failure in the ambulatory setting." In Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease: Fourth Edition, pp. 241-269. Elsevier Inc., 2012.

3. Casella, Innocenzo G., Giacomo A. Palladino, and Michela Contursi. "Determination of aliphatic amines by cation-exchange chromatography with suppressed conductivity detection after solid phase extraction." Journal of separation science 31, no. 21 (2008): 3718-3726.

4. Nagaraju, Cherukuru, Raja Gorla, Uttam Kumar Ray, Nagasrinivas Kanteti, Sharma Hemant Kumar, and Siddaiah Vidavalur. "A simple and sensitive spectrophotometric method for the determination of trace level mono isopropylamine in pharmaceutical drug substances." International Journal of Pharmaceutical Sciences and Research 7, no. 2 (2016): 834.

5. Golovnja, R. V., N. G. Enikeeva, I-L. Zuravleva, and A. S. Zjuzko. "A gas chromatographic analysis of monocarbonyl compounds and amines in the volatile components of wheaten bread." Food/Nahrung 18, no. 2 (1974): 143-156.

6. Verma, KrishnaáK. "Determination of ammonia and aliphatic amines in environmental aqueous samples utilizing pre-column derivatization to their phenylthioureas and high performance liquid chromatography." Analyst 124, no. 7 (1999): 1017-1021.

7. Product Manual for Thermo Scientific Dionex IonPac™ CS17 Column

8. Swartz ME, Krull IS. Handbook of analytical validation. CRC Press; 2012 Apr 24.

9. Chan CC, Lee YC, Lam H, Zhang XM, editors. Analytical method validation and instrument performance verification. John Wiley & Sons; 2004 Apr.

10. ICH Guidance, Validation of Analytical Methods, Definition and Terminology. International Conference on Harmonization, Q2B: Geneva; Nov, 2005: 1-10.

11. ICH Guidance, Validation of Analytical Procedures Methodology. International Conference on Harmonization, Q3A (R2): Geneva; Oct, 2006: 1-15.