DEVELOPMENT AND VALIDATION OF A SHORT RUNTIME STABILITY INDICATING METHOD FOR DETERMINATION OF MEXILETINE HYDROCHLORIDE BY USING HPLC SYSTEM

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Abstract

In a short runtime process (about 10 minutes), with the isocratic method, a mixture of some degradation molecules and Mexiletine.HCl was separated and detected by means of an UV-Vis/HPLC system. A good chromatography separation was performed on Bonda pack C18 300 x 3.9 mm 10µm with mobile phase consisted Methanol: Anhydrous sodium acetate buffer in the ratio of 60:40(v/v), respectively. The Mexiletine.HCl assay shows a linear (r^2 = 0.999) calibration range over the concentration range of 1000 - 3200µg/mL of analyte concentration. The method was precise (%RSD < 1)) and accurate, with recovery in the range 99.63% - 100.22%. LOD was found to be 18µg/mL and the LOQ value was found to be 59.4µg/mL. Moreover, the method was successfully used for the separation of Mexiletine.HCl from its degradation product. The method was validated as per ICH guidelines, and the investigated results of the validation processes showed that the method was trustworthy enough to be routinely used in laboratories.

Keywords: Mexiletine.HCl, HPLC method, validation, Impurities.

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1. INTRODUCTION

Mexiletine HCl, often referred to as 1-(2,6-Dimethylphenoxy) propan-2-amine; hydrochloride (Fig. 1), is an orally active class I antiarrhythmic medication used to prevent and cure ventricular arrhythmias, particularly following myocardial infarction. structurally similar to lidocaine, but active when taken orally. Mexiletine HCl has been shown to be effective in reducing induced ventricular arrhythmias, including those brought on by coronary artery ligation and glycoside poisoning, in studies on animals. Upper gastrointestinal unease, fainting, tremor, and trouble in coordination were the most frequently reported adverse drugs replies.

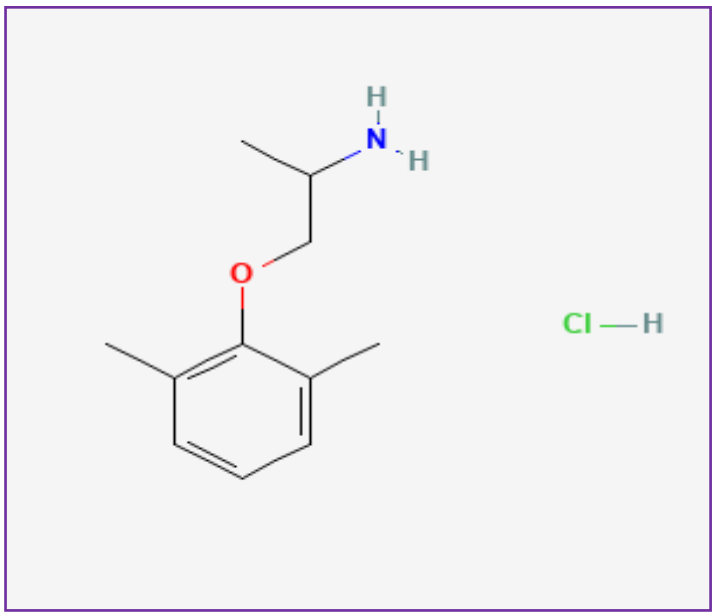

Fig. 1: Structure of Mexiletine.HCl

APIs as Mexiletine are viewed analytical. As quality control causes, HCl is primarily evaluated in biological samples and pharmaceutical formulations. Based on the complexity of the matrices and the anticipated conc. levels of the analytes, the analytical needs differ significantly in every case. In an effort for higher purity and low detection limits, APIs in biological samples are often determined by methods of separation combined to extremely sensitive detection devices (such as mass spectroscopy and fluorescence).

The quality control of pharmaceutical formulations, on the other hand, requires quick analysis, cost effectiveness, and a force degradation study method without, of course, compromising quality. In order to extend the retention period of the Mexiletine hydrochloride, this was attempted. Based on the extensive survey on Mexiletine.HCl, which has been quantified till to date in plasma, drug substance and drug product using different analytical techniques. Very few of stability-indicating methods by utilizing RP-HPLC are available and their drawbacks are mentioned below.

The methods used for the simultaneous detection of mexiletine hydrochloride and/or its related compound, 2,6-dimethylphenol, were stated by Belal to be selective and stability-indicating. the author Not mention the forced degradation (acid, alkaline, oxidative, thermal,

photolytic, & ultra violet) and 3 stability-indicating methods.

Very a few of research reports are available literature on Mexiletine Hydrochloride along with the forced degradation study. The above-mentioned facts from the literature review convey that, there is a need to develop the stability indicating method in order to achieve the short run time and complete force degradation by using RP-HPLC.

2. MATERIAL AND METHODS

The Indian company Srini Pharmaceuticals Private Limited provided mexiletine hydrochloride as a gift, and it was utilized as a reference standard without additional purification. Water (H_2O), anhydrous sodium acetate buffer, HPLC grade methanol (CH_3OH), and acetic acid were acquired from Merck Specialties, Pvt. Ltd. in Mumbai, India. Before use, all solvents and solutions are by ultrasound degassed (PCI, Mumbai, India, and Ultra Sonicator).

Instrumentation:
An analytical column Bonda pack C18 300 x 3.9mm 10m, an electronic balance built by DENVER (model number SI234), a Rheodyne manual sample injector with switch (77251), a PEAK LC 7000 isocratic HPLC, and a PEAK 7000 delivery system were used for chromatography. The sample was injected through a 20-L loop Rheodyne injector. The PEAK LC programme was used. The wave length of max. absorbance was determined by a UV2301 Spectrophotometer.

SOLUTIONS PREPARATION
Standard stock solution preparation
Place a standard weight of 50.0 mg of mexiletine hydrochloride into a 25 ml volumetric flask, sonicate 15 ml of mobile phase to dissolve it, then add more mobile phase to make up the disparity. 2000 g/mL in concentration.
Making a sample stock solution
Place a precise weight of 50.0 mg of mexiletine hydrochloride sample into a 25 ml volumetric flask. Then, sonicate 15 ml of mobile phase to dissolve it, and add enough mobile phase to make up the difference. 2000 g/ml of concentration.
Mobile phase preparation:
Buffer: Mix 500 ml of milli 'Q' water with 11.5 g of anhydrous sodium acetate. Glacial acetic acid, 3.2 mL, added, combined, and allowed to cool pH can be altered with hydrochloric acid to 4.8 0.1, then milli 'Q' water can be used to form 1000 ml. Degas after filter over a 0.45 m membrane.
Mobile Phase: Mix 600 ml of methanol and 400 ml of buffer for the mobile phase. The diluent was the mobile phase.

METHOD VALIDATION:
Specificity:
The ability to evaluate the Mexiletine Hydrochloride analytic of interest precisely and specifically in the presence of other substances that could be anticipated to be present in the sample solution is known as specificity. Peak purity and interference from unidentified peaks were looked at for the active peak.
Limit of Quantitation and Detection Limits:
The minimum amount of mexiletine hydrochloride in a sample that can be identified but not necessarily quantitated is known as the detection limit. The lowest level of mexiletine hydrochloride in a sample that can be identified with reasonable accuracy and precision is known as the quantitation limit.
Precision:
Precision, when an analytical method is used repeatedly to evaluate the same Mexiletine Hydrochloride homogeneous sample. The determination of intra-and inter-day precision was done by analyzing six sample solutions at 100% concentration (2000μg/mL) (n=6) by two different chemists.
Linearity:

The method's ability to produce test results that are appropriate to analytic conc. within a certain range, directly or by an exact mathematical transformation.16 The test solutions were created at concentrations between 0.02-0.2 mg/mL (or around 200%--200% of the test concentration). Injections of the solutions were made in triplicate. Calculations were made for the slope and coefficient of determination.

Accuracy:

The extent that the experimental value matches the real value is known as accuracy. Three different concentrations, ranging from 80% to 120% of the sample concentration, were used to test it. Mexiletine Hydrochloride amount as had been spiked were recovered.

Stress Analysis:

Mexiletine Hydrochloride's stability is a crucial factor that might impact purity, potency, and safety. The method used must be stability-indicating in order to monitor possible shifts in a product over time. This section covers the experimental stress conditions.

Acidic Stress:

After being dissolved in 10.0 ml of 0.1N HCl, the drug material was left to stand at room temperature for 24 hours. The sample was then diluted to 50 ml with diluent and combined after the sample solution had been neutralised with 10.0 ml of 0.1N NaOH. A further dilution was carried out by mixing thoroughly 5.0ml of the solution with 50ml of the sample solvent.

Alkaline Stress:

After being dissolved in 10.0 mL of 0.1N NaOH, the drug material was left to sit at room temperature for 24 hours. Following the neutralisation of the sample solution with 10.0 ml of 0.1N HCl, the sample was diluted to 50 ml with the diluent and mixed. A further dilution was carried out by mixing thoroughly 5.0ml of the solution with 50ml of the sample solvent.

Oxidative Stress:

The sample was dissolved in 2.0 ml of 30% hydrogen peroxide and allowed to sit on the work surface for 5 hours before being diluted to 50 ml with sample solvent and being combined. By mixing 5.0ml of sample solvent with 50ml of the original sample, the sample was further diluted. This sample solution was injected right away to prevent excessive deterioration.

Thermal Stress:

Thermal Stress: A part of the sample was baked at 80 °C for five hours. The sample solution of mexiletine hydrochloride was produced with a 2000 g/ml concentration in diluent after it had warmed to room temperature.

UV Photolytic Stress:

After some mexiletine hydrochloride was strained under UV light, a sample solution was made with a 2000 g/ml concentration in diluent.

3. RESULTS AND DISCUSSION

Method Development:

In the development of the HPLC method, different mobile phases have been evaluated for the evaluation of Mexiletine Hydrochloride drug content in API. In selecting the mobile phase, sensitivity, pKa, and eluting efficiency were taken into account. Different mobile phase compositions (such as methanol with 1% phosphoric acid, acetonitrile with potassium phosphate, methanol with sodium phosphate, and others) have been evaluated in order to find an efficient stability-indicating approach. The mobile phase was composed of a mixture of Methanol: Anhydrous Sodium Acetate Buffer in the ratio of 60:40(v/v), which was chosen because it produced nice symmetrical peaks after doing numerous chromatographic runs with an array of solvent forms.

Buffer:

Mix 500 ml of milli'Q'water with 11.5 g of anhydrous sodium acetate to dissolve it. Glacial acetic acid, 3.2 mL, added,

combined, and allowed to cool pH should be adjusted with hydrochloric acid to 4.8 0.1, then milli'Q'water can be used to form 1000 ml. Degas before filter over a 0.45 m membrane.

Mobile Phase:

Mix 600 ml of Methanol and 400 ml of Buffer.

Sonication was used to filter and degas the mobile phase. A Bonda pack C18 300 x 3.9 mm 10 m was used to obtain the chromatographic separation. The column temperature was set at 30°C, and the flow rate was set at 1.0 ml/min. The 254nm UV detector wavelength was chosen. The overall run time was 10.0 minutes, and the injection volume was 20 L. The sample solvent was the mobile phase. These final optimised chromatographic conditions results are outlined in Table 1 and reveal that based on these optimised chromatographic circumstances, a crisp, obvious, and well-defined symmetrical peak at Rt = 4.87min was generated.

Fig.2: The Blank Chromatogram of Mexiletine. HCl.

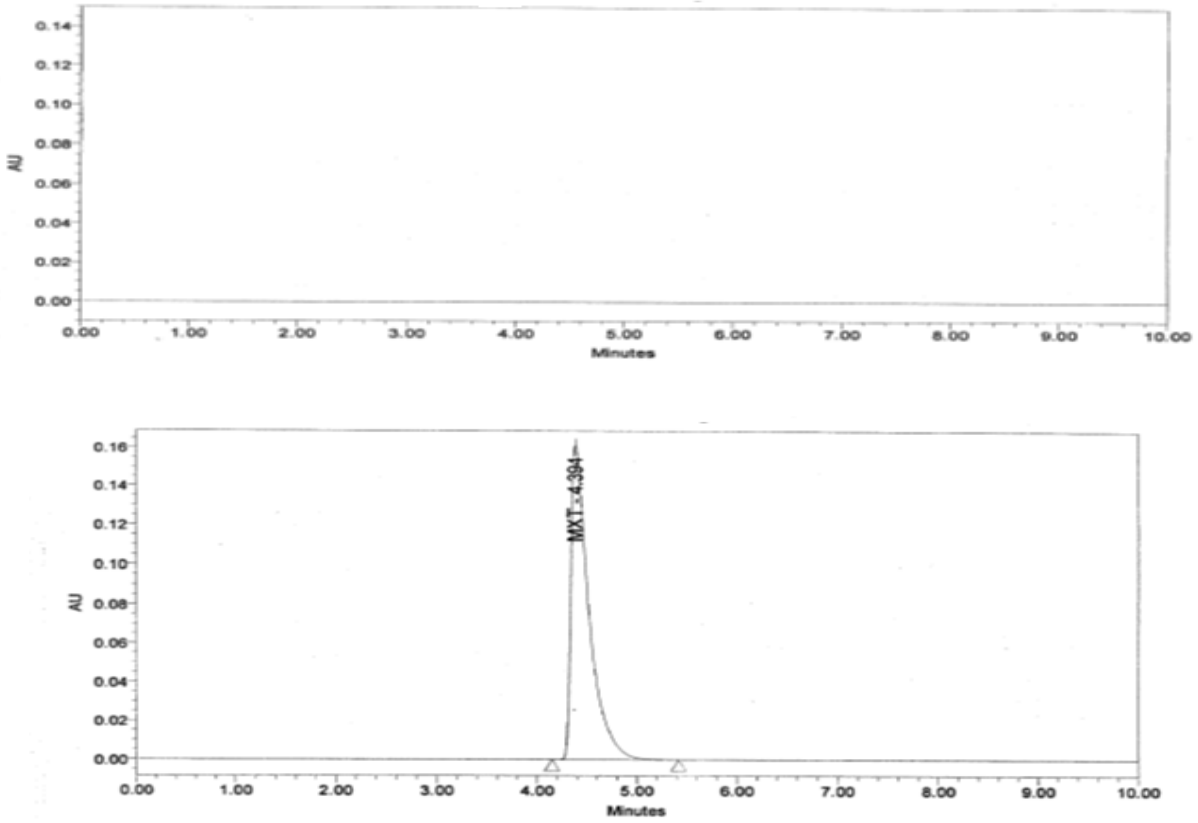

Fig.3: The Standard Chromatogram of Mexiletine. HCl.

Table 1: Final optimized chromatographic conditions

S. No.	Condition	Results
1	Mobile phase	Methanol: Anhydrous sodium acetate buffer in the ratio of 60:40(v/v).
2	Pump mode	Isocratic
3	pH	4.8
4	Diluents	Mobile phase
5	Column	Bonda pack C18 300 x 3.9 mm 10µm
6	Column Temperature	Ambient
7	Wavelength	254 nm.
8	Injection Volume	20µl.
9	Flow rate	1.0mL/min.
10	Run time	10min.

Validation of the proposed method:
The method received approval in line with ICH and FDA criteria. The system appropriateness, specificity, precision, linearity, accuracy, and stress study were the variables utilized to verify this approach.

System Suitability:
During the approach validation, the ensuing system appropriateness metrics were tracked and documented. Mexiletine Hydrochloride had a retention period of 4.8 minutes. From five following injections of the working standard solution, the RSD of the mexiletine hydrochloride peak region was less than 2.0%. During the method's validation, the results for system the suitability fulfilled the required standards. Table2 shows the results of the system suitability study.

Table 2. System suitability results

S. No.	Peak Name	Retention time (Minutes)	Area	USP Plate Count (Limit: NLT 2000)	USP Tailing (Limit: NMT2.0)
1	Mexiletine Hydrochloride	4.608	1950175	16012	1.26
2		4.601	1947131	18521	1.20
3		4.604	1952914	15558	1.29
4		4.606	1957366	16825	1.22
5		4.603	1947391	18952	1.25
6		4.605	1956104	17915	1.23
Mean			1951846.83		
STDEV			4349.99		
%RSD			0.22		

Specificity:
The sample solvent and standard solution were injected to guarantee process specificity. The detector of the photodiode array determined the peak purity. The approach is specific for determining the chromatographic purity of the drug substance mexiletine hydrochloride since no interference or impact of the analyses' UV spectrum was found.

Limit of Detection and Limit of Quantitation:
The LOQ and LOQ for mexiletine hydrochloride were computed based on the standard deviation of the response and the slope in order to assess the analytical method's sensitivity.
The results of LOD=18µg/ml and LOQ=59.4µg/ml

Precision:
By injecting six duplicates of a sample solution containing 100 g/mL, method precision (intraday) and intermediate precision (inter-day) tests took place. Method precision and Intermediate precision have %RSD values of 0.4% and 0.3%, respectively. The procedure is suitably exact as shown by the % assay for method precision being 100.0% and intermediate precision being 100.3%. In Table 3, the results of the test and RSD are shown.

Table 3: Results of precision study and ruggedness study.

Sample Preparation.	**Assay (% w/w on anhydrous basis)**	**% Assay (% w/w on anhydrous basis)**
	Intra-day precision	**Inter-day precision**
1	100.6685	100.3433
2	100.5245	100.9583
3	100.5518	100.3726
4	100.7599	100.4887
5	100.9218	100.4286
6	100.8212	100.1397
Mean	**100.7080**	**100.4552**
SD	**0.1555**	**0.2734**
%RSD	**0.15**	**0.27**

Linearity:
The calibration curves of mexiletine hydrochloride at 254 nm (n = 3) using the suggested method's linear regression data (Table 4) explain a good linear connection across the concentration range of 1000-3200 g/mL with regard to the peak area. The slopes of standard curves showed no significant difference. The straight line's observed equation was determined to be 984.98x -15693, with an R2-value of more than 0.9993 (Figure 4). Mexiletine Hydrochloride demonstrated linearity findings across the concentration range, which indicated that the strength of the detector response is appropriate to the concentration of the examined material.

Table 4: Linearity results for Mexiletine Hydrochloride

Range (%)	Concentration w.r.t std. (µg/mL)	MXT Peak area
50	1000	967071
80	1600	1564859
100	2000	1961386
120	2400	2334540
160	3200	3140505
Slope:		984.98
Intercept:		-15693
r^2:		0.9999

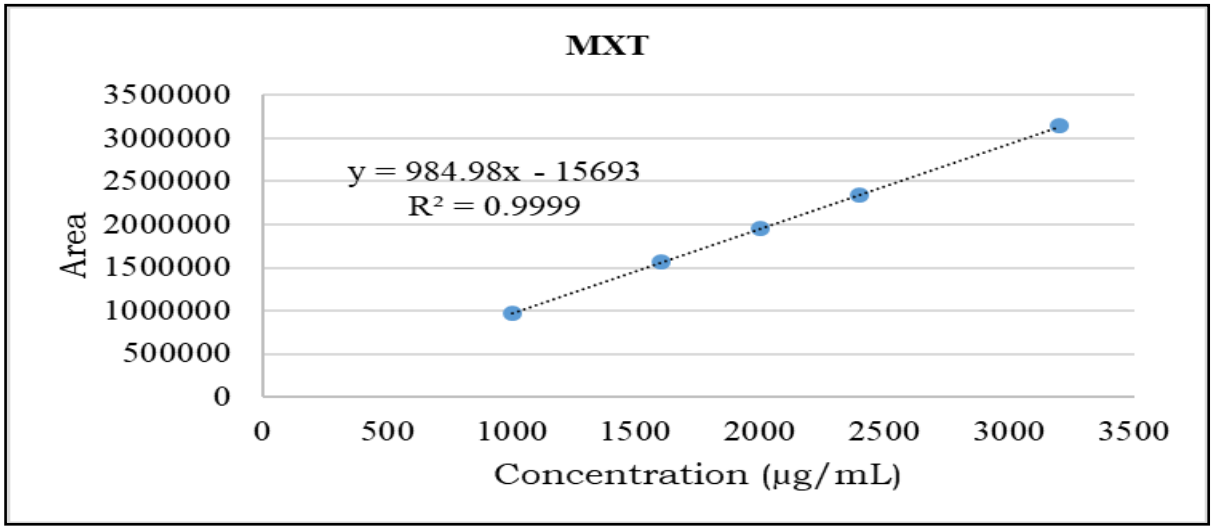

Figure 4: Linear calibration curve for Mexiletine Hydrochloride

Accuracy:
Mexiletine Hydrochloride Drug material was injected in triplicate at concentrations corresponding to 80%, 100%, and 120% of the target concentration in order to assess the method's accuracy. Table 5's findings for the percent recovery show that the approach meets all the requirements for approval. As a result, the technique is reliable for determining mexiletine hydrochloride.

The suggested HPLC test method's accuracy was evaluated in triplicate at three concentration levels, or (80, 100, and 120%), namely 1600, 2000, and 2400 g/mL. The slope and y-intercept of the resulting calibration curve were used to compute the percentage of RSD and recoveries. The recovery % got varied from 99.63% to 100.22% (Table 3).

Table 5: Recovery results.

Concentration Level	Preparation	% Recovery	Average
80 % Concentration	1	99.6389	99.7393
	2	99.7455	
	3	99.8336	
100 % Concentration	1	99.7050	99.8286
	2	99.7688	
	3	100.0122	
120 % Concentration	1	100.0453	100.1257
	2	100.1047	

Stress Study:
In the next factors, stress tests on Mexiletine Hydrochloride pharmacological substances occurred. In Table 6, a summary of the findings from the stress research is shown. A UV detector was used to record the chromatograms in order to assess the peak's spectral purity.

Table 6: Forced Degradation results.

Name of the study	Condition	Specification	%Assay	Purity1 Angle	Purity1 Threshold
Acid hydrolysis	0.1 N HCl	A purity 1 Angle less than purity 1 threshold	102.9	3.789	10.062
Base hydrolysis	0.1 N NaOH		100.5	3.612	10.064
Oxidative	3% H_2O_2		97.5	2.237	11.075
Heat	80°c for 8 hrs		100.0	4.338	10.039
photolytic	Sunlight		100.30	2.344	11.050
photolytic	UV light		100.31	2.311	11.008

4. CONCLUSION

The stated method for HPLC that had been developed had specificity, sensitivity, accuracy, and precision confirmed. Mexiletine Hydrochloride was shown to have a good linear relationship in the concentration range of 1000-3200 g/ml. It was found that the correlation coefficient (R2) was 0.9999. The results of the intra-day precision (0.15) and inter-day precision (0.27) tests were adequate to show the accuracy and repeatability of the created HPLC technique. Sample preparation was quick and effective. It was found that UV detection at 254 nm was suitable. This showed that the proposed HPLC near was straightforward, quick—as evidenced by a brief retention time—sensitive, accurate, precise, and efficient—and that it would be suitable for the regular routine quality control (Q.C.) examination of Mexiletine Hydrochloride from its bulk medication. The findings of the studies on forced decline indicate that the developed HPLC method is stability indicating.

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