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DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD FOR ESTIMATION OF DRUG RANOLAZINE IN TABLET DOSAGE FORM BY USING RP-HPLC TECHNIQUE

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ABSTRACT

A simple, accurate, precise, and robust Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative estimation of Ranolazine in tablet dosage form. The chromatographic separation was achieved using a C18 column with a mobile phase consisting of [specify solvents, e.g., acetonitrile and phosphate buffer] in a suitable ratio, delivered at a flow rate of [e.g., 1.0 mL/min], and detection was carried out at a wavelength of [e.g., 272 nm]. The method exhibited good linearity over a concentration range of [e.g., 10–100 µg/mL] with a correlation coefficient (R^2) greater than 0.999. The retention time of Ranolazine was found to be [e.g., 5.8 minutes], indicating a sharp and well-resolved peak. Validation of the method was performed in accordance with ICH guidelines(ICH Q2), assessing parameters such as specificity, linearity, accuracy, precision, robustness, LOD, and LOQ. The method demonstrated excellent recovery (98–102%) and low %RSD (<2%) for intra-day and inter-day precision studies. The proposed RP-HPLC method is suitable for routine quality control analysis of Ranolazine in tablet formulations.

KEYWORDS: Ranolazine, RP-HPLC, Method Development, Validation, Tablet Dosage Form, ICH Guidelines, Estimation, Pharmaceutical Analysis.

1. INTRODUCTION

1.1 Analytical Chemistry

Analytical chemistry deals with methods for determining the chemical composition of samples of matter. A qualitative method yields information about the identity of atomic or molecular species or the functional groups in the sample; a

quantitative method, in contrast, provides numerical information as to the relative amount of one or more of these components.[1]

1.1.1. Factors Affecting the Choice of Analytical Method

- An important task for the analyst is to select best procedure for a given determination this will require careful consideration of the following criteria:
- The type of analysis required: elemental or molecular, routine or occasional.
- Problem arising from the nature of the material to be investigated, e.g. radio- active substance, corrosive substance, substances affected by water.
- Possible interference from components of the material other than those of interest.
- The concentration range to be investigated.
- The accuracy required.
- The facilities available, particularly the instrument.
- The time required to complete the analysis.[2]

1.1.2 Classification of Analytical Methods

- The various methods of analysis can be broadly classified into two categories; Classical methods and Instrumental methods:[3,4]

A) Classical Methods

a. Volumetric Methods

In volumetric, procedures the volume or mass of a standard reagent required to react completely with the analyte were measured.

b. Gravimetric Methods

In gravimetric measurements, the mass of the analyte or some compound produced from the analyte was determined. The extent of their general application is, however, decreasing with the passage of time and with the advent of instrumental methods to supplant them.

B. Instrumental Methods

These methods are based upon the measurement of some physical properties as conductivity, electrode potential, light absorption or emission, mass-to-charge ratio and fluorescence of substance. There are many techniques available for the analysis of analytes:

a) Spectroscopic Analysis

1. Ultraviolet and visible spectrophotometry
2. Fluorescence and phosphorescence spectrophotometry
3. Atomic spectrophotometry (emission and absorption)
4. Infra-red spectrophotometry
5. Raman spectroscopy
6. X-ray spectroscopy
7. Radio chemical techniques including activation analysis
8. NMR spectroscopy
9. ESR spectroscopy

b) Electrochemical Techniques

1. Potentiometry
2. Voltametry
3. Stripping techniques
4. Amperometric techniques
5. Coulometry
6. Electrogravimetry
7. Conductance techniques

c) Chromatographic Methods

1. Gas chromatography (GC)
2. High performance liquid chromatography (HPLC)
3. High-performance thin layer chromatography (HPTLC)

d) Miscellaneous Techniques

1. Thermal analysis
2. Mass spectrometry
3. Kinetic techniques

Amongst all the techniques mentioned above UV-Visible spectrophotometry, High performance liquid chromatography (HPLC) and High performance thin layer chromatography (HPTLC) are the most widely used techniques for quantitative analysis of pharmaceutical substances.[5, 6]

1.2 Chromatography

Definition and History

Chromatography is a non-destructive procedure for resolving a multi-component mixture of trace, minor, or major constituents into its individual fractions. Different variations may be applied to solids, liquids, and gases. While chromatography may be applied both qualitatively and quantitatively, it is primarily a separation tool. Quantitative analysis can be carried out by measuring the area of the chromatographic peak.[7,8]

Chromatography is relatively a new technique, which was first invented by M.Tswett, a botanist in 1906 in Warsaw. In that year, he was successful in doing the separation of chlorophyll, xanthophylls and several other colored substances by percolating vegetable extracts through a column of calcium carbonate. The calcium carbonate column acted as an adsorbent and the different substances got adsorbed to different extent and this gives rise to colored bands at different positions, on the column. Tswett termed this system of colored bands as the chromatogram and the method as chromatography after the Greek words Chroma and graphs meaning "color" and "writing" respectively. However, in the majority of chromatographic procedures no colored products are formed and the term is a misomer.[9]

In a classical manner it can be defined as "a separation process that is achieved by distribution of Considerable advances has since been made and the method is used to separate colored as well as colorless substances. The column of calcium carbonate, used in Tswett's method, remains stationary and is therefore termed as the stationary phase. The solution of vegetable extracts moves or flows down the column and is therefore termed as the mobile phase.

Chromatography may be regarded as a method of separation in which separation of solutes occur between a stationary phase and a mobile phase.[10]

1.3 High Performance Liquid Chromatography (HPLC)

High performance liquid Chromatography HPLC is the most versatile and widely used analytical technique. It utilizes a liquid mobile phase to separate the components of mixture. These components (or analytes) are first dissolved in a solvent, and then forced to flow through a chromatographic column under high pressure. In the column, the mixture is resolved into its components. As a result, HPLC acquires a high degree of versatility not found in other chromatographic systems and it has the ability to separate a wide variety of chemical mixtures.

HPLC uses high pressure to force solvent through closed columns containing very fine particles that give high resolution separations. The technique is used to separate and determine species in a variety of organic, inorganic, and biological materials.

The basic components of an HPLC system include a solvent reservoir, pump, injector, analytical column, detector, recorder and waste reservoir. HPLC is used either in the liquid-solid adsorption chromatography mode or the liquid-liquid partition chromatography mode, either normal or reversed phase. Both partition and adsorption chromatography operates on differences in solute polarity since polarity is important in determining both adsorption and solubility.[11]

1.3.1 Principle of Separation in HPLC: Partition Chromatography

Stationary phase adsorbed solvent held on the Surface, or within the grains or fibers of an inert solid supporting matrix. Sample molecules equilibrate (partition) between liquid stationary phase and mobile phase.(Mobile phase is liquid in LC and HPLC systems and gaseous in GLC systems).Retention depend on a sample molecule's escaping tendency into the mobile phase versus its solubility in stationary phase. Quantitatively given by the partition coefficient, KD, the ratio of solubilities in the two phase.[12,13]

KD = Solute in stationary phase / Solute in stationary phase

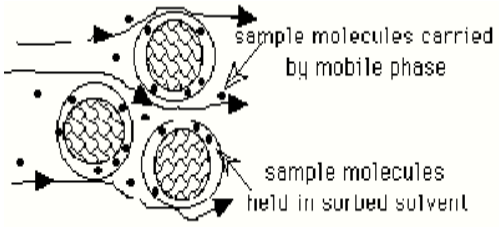


Fig. 1: Partition of analytes.

1.3.2 Types of HPLC Techniques

A. Based on modes of separation

1. **Normal phase chromatography**

- Mechanism: Retention by interaction of the stationary phase's polar surface with
- Polar parts of the sample molecules.
- Stationary phase: It is bonded siloxane with polar functional group like SiO2.
- Mobile phase: Non -polar solvents like heptanes, hexane, cyclohexane, chloroform etc.
- Application: Separation of non-ionic, nonpolar to medium polar substances.[12]

2. Reverse phase chromatography

- Mechanism: Retention by inter action of the stationary phase's nonpolar hydrocarbon ChainWith non -polar parts of sample molecules.
- Stationary phase: It is bonded siloxane with nonpolar functional groups like n-Octadecyl (C18) or n- octyl (C8), ethyl, phenyl, - (CH2)n -diol, -(CH2)n-CN.
- Mobile phase: Polar solvents like methanol, Acetonitrile, water or buffer.
- Application: Separation of non-ionic and ion forming nonpolar to medium polar sub.[12]

B. Based on principle of separation

1. Adsorption chromatography
2. Ion exchange chromatography
3. Ion pair chromatography
4. Size exclusion or Gel permeation chromatography
5. Affinity chromatography
6. Chiral phase chromatography.[13,14]

C. Based on Elution Technique

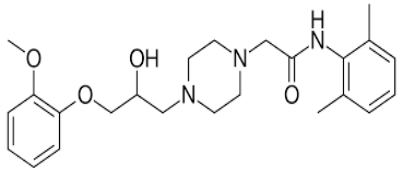
1. Isocratic Separation: In this technique, the same mobile combination is used throughout the process of separation. The same polarity or elution strength is maintained throughout the process.
2. Gradient Separation: In this technique, a mobile phase combination of lower polarity or strength is used followed by gradually increasing the polarity or elution strength.[13,14]

D. Based on the Scale of Operation

1. Analytical HPLC: Where only analysis of the samples is done. Recovery of the Samples for reusing is normally not done, since the samples used in very low.
2. Preparative HPLC: where the individual fractions of pure Compounds can be collected using fraction collector. The collected samples are reused.[15,16]

DRUG PROFILE [31]

Table-1: Ranolazine

Sr. No	Parameter	Description
1	IUPAC NAME	(*RS*)-*N*-(2,6-Dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]piperazin-1-yl]acetamide
2	Chemical Structure	
3	Drug category	Anti-anginal
4	Chemical formula	$C_{24}H_{33}N_3O_4$
5	Molecular weight	427.537
6	pKa value	7.2
7	State	White Solid
8	Solubility in solvent	Methanol
9	Route	Oral

10	BCS Classification	Class II
11	Bioavailability	35% to 50%

Mechanism of action

Ranolazine inhibits persistent or late inward sodium current (INa) in cardiac muscle during a sort of voltage-gated sodium channels. Inhibiting the current that leads to reduction of intracellular calcium levels. This successively results in reduced tension within the heart wall, resulting in reduced oxygen requirements for the muscle. The QT prolongation effect of ranolazine on the surface electrocardiogram is that the results of inhibition of IKr, which prolongs the ventricular nerve impulse. Ranolazine also exhibits its effects on the delayed rectifier current (hERG/IKr potassium channels), it readily stimulates myogenesis, and it reduces a pro-oxidant inflammation /oxidative condition, and activates the calcium signaling pathway, Ranolazine prolongs the nerve impulse duration, with corresponding QT interval prolongation on electrocardiography, blocks the INa current, and prevents calcium overload caused by the hyperactive INa current, thus it stabilizes the membrane and reducing excitability.

- **Adverse Reactions**

1. Dizziness
2. Nausea
3. Stomach pain
4. Constipation
5. Headache
6. Dry mouth.

MATERIALS & EQUIPMENTS

Table No. 2: List of Materials.

Sr.No.	Name of Materials	Supplier
1	Ranolazine API	Pharmchem, Rohtak
2	Renulaz-500 SR Tablets	Torrent Pharmaceuticals Ltd.
3	Water-HPLC Grade	S d Fine-Chem Limited
4	Acetonitrile- HPLC Grade	Thermofisher Scientific Ltd.
5	Tetrahydrofuran- HPLC Grade	Thermofisher Scientific Ltd.
6	Methanol- HPLC Grade	Merck Life Science Pvt. Ltd

Table No.3: List of Equipments.

Sr. No.	Name	Specification
1	HPLC System	Shimadzu LC 2010 PLUS Autosampler
2	Software	LabSolution, Shimadzu
3	Column	Inertsil ODS C18, 250 X 4.6 X 5 µm
4	UV Spectrophotometer	Shimadzu
5	Analytical balance	Shimadzu UniBloCAP
6	pH meter	Digital Contech
7	Ultra-sonicator	Wenser Ultra Sonicator
8	Filter	Nylon 0.45µm

METHOD DEVELOPMENT

A) Selection of wavelength

a) Determination of λ max: Standard stock solution of Ranolazine was diluted separately with diluents to obtain final concentration of 20 µg/ml, solution was scanned using UV-Visible Spectrophotometer in the spectrum mode between the wavelength ranges of 400 nm to 200nm**.** The wavelength selected was 269 nm. UV Spectra shown in figure.

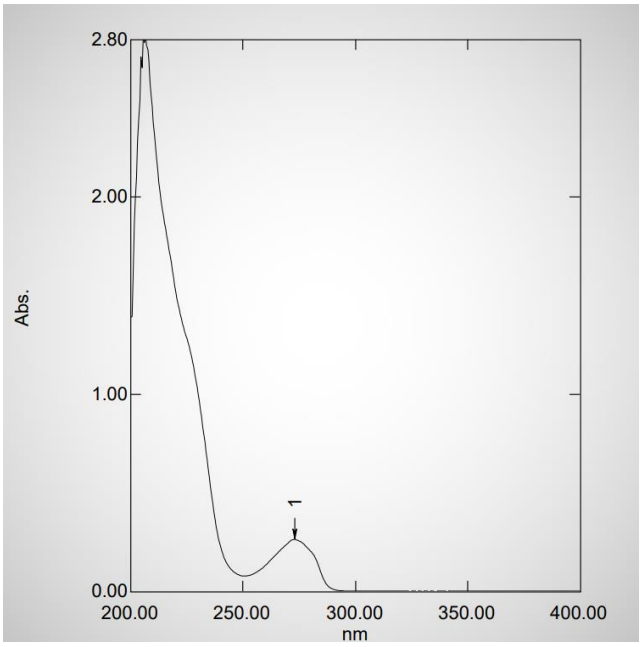


Fig. 11:- UV Spectra of Ranolazine.

B) Selection of mobile phase : There are various factors to be related with the selection of MP such as best separation, peak index, peak summary, theoretical plates etc. MP gives symmetrical and well separate peak in less time, after trying various mobile phase the mobile phase selected as Acetonitrile, Methanol and Tetrahydrofuran in the proportion 45:50:5 respectively.

C) Preparation of Mobile phase: Prepare mixture of Acetonitrile, Methanol and Tetrahydrofuran in the proportion 45:50:5 respectively, Filter through 0.45 µ Nylon membrane filter paper and degas prior to use and degassed it by sonication.

D) Preparation of Ranolazine Standard Solution: Weigh accurately about 50 mg of Ranolazine working standard and transfer to a 50 ml volumetric flask. Add 20 ml of diluent and sonicate to dissolve. Dilute to volume with diluent and mix. Transfer 1.0 ml of solution into a 10 ml of volumetric flask and dilute to volume with the diluent and mix. (Dilution scheme: 50mg → 50.0 ml → 1 ml /10.0 ml)

E) Preparation of Test Solution: Weigh and transfer 63mg of sample powder and transfer to a 50 ml volumetric flask. Add 20 ml of diluent and sonicate to dissolve. Dilute to volume with diluent and mix. Transfer 1.0 ml of solution into a 10 ml of volumetric flask and dilute to volume with the diluent and mix.

(Dilution scheme: 63mg → 50 ml → 1 ml →10.0 ml)

F) Selection of flow rate: Different MP flow rates are investigated for optimum flow rate for which the column plate number was maximum. Flow rate of 1. ml/min was selected.

G) Baseline Stabilization: The detector was turned on for an hour before the actual run in order to obtain the stable UV light. The mobile phase run was started at desired flow rate and the run was continued until the stable baseline was obtained.

RESULT & DISCUSSION

1) System Suitability:

The system suitability test is a pharmacopeia requirement and is used to verify, whether the resolution and reproducibility of the chromatographic system are adequate for analysis. The tests were performed by collecting data from Single injection of blank (Diluent) and five replicate injections of standard solution were injected into the chromatographic system. The chromatogram of system suitability studies are shown in figure 16 to 21 and results are shown in table 4.

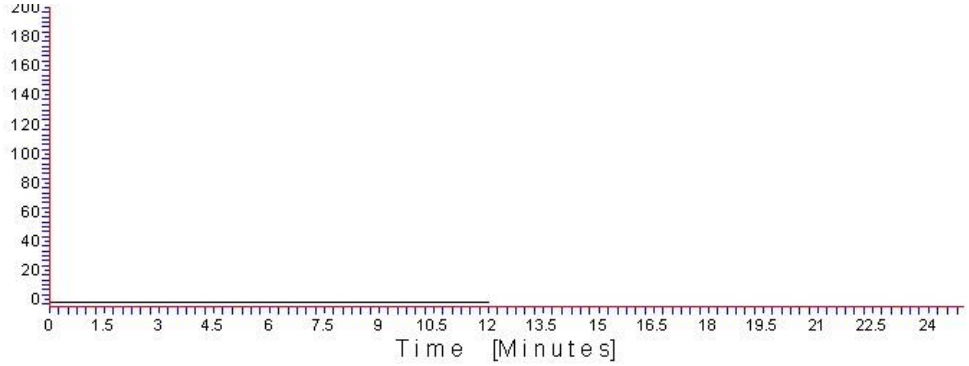


Figure 16: Chromatogram of Blank for System Suitability.

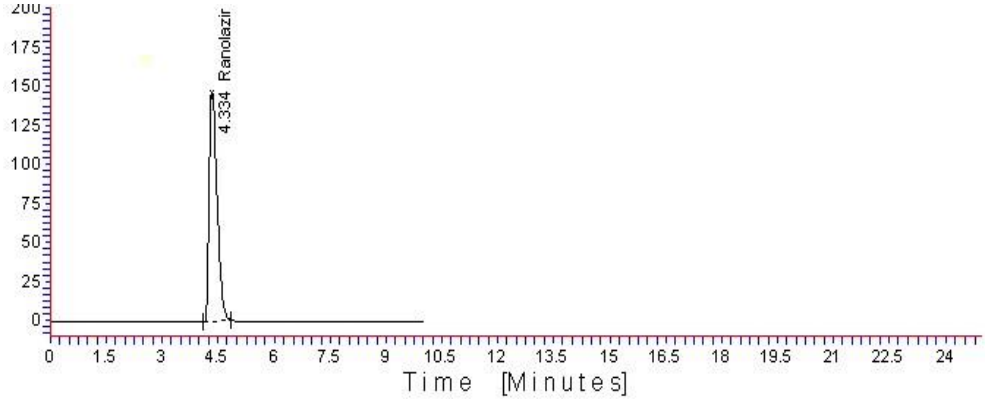


Figure 17: Chromatogram of STD 1 for System Suitability.

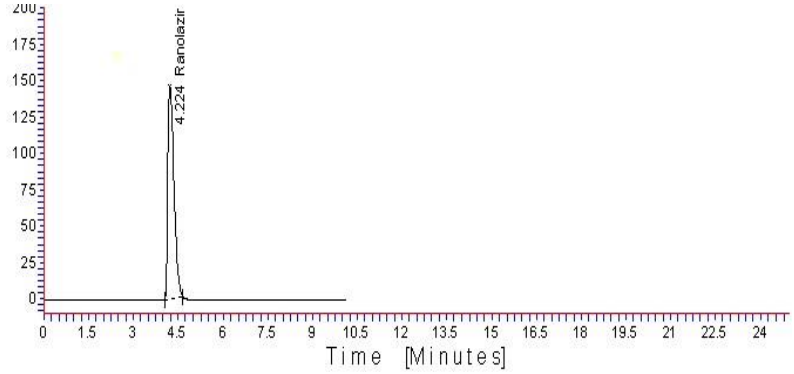


Figure 18: Chromatogram of STD 2 for System Suitability.

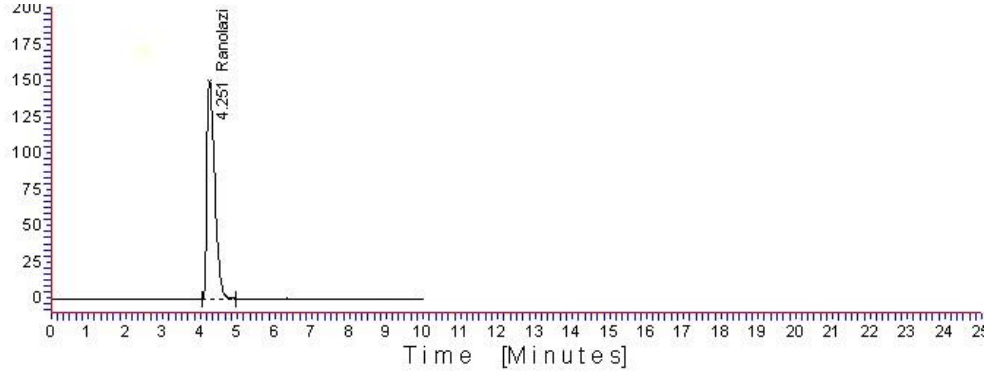


Figure 19: Chromatogram of STD 3 for System Suitability.

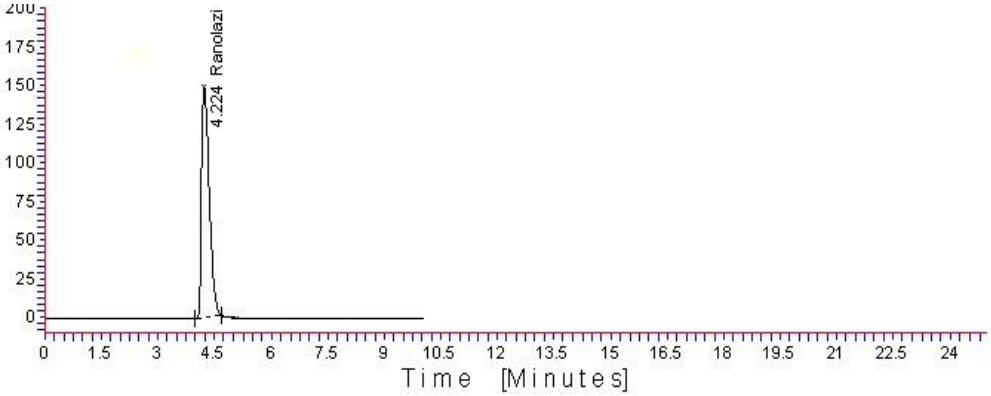


Figure 20: Chromatogram of STD 4 for System Suitability.

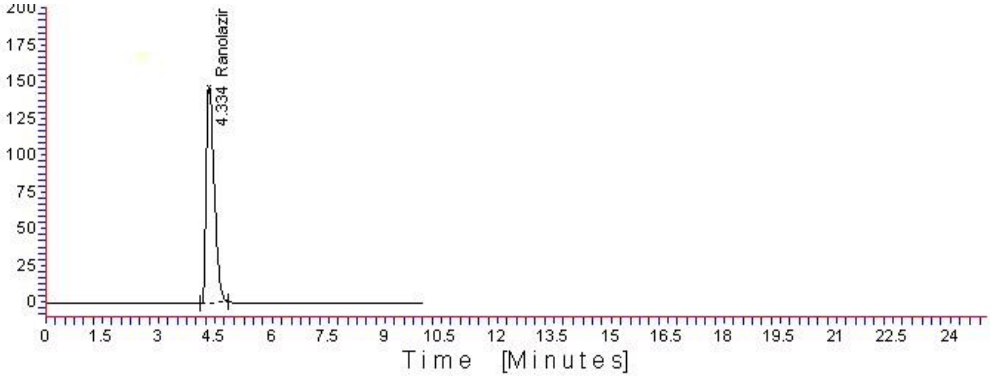


Figure 21: Chromatogram of STD 5 for System Suitability.

Table-4: System suitability.

Sr. No.	Area of Ranolazine
1	2189.70
2	2169.56
3	2139.32
4	2198.09
5	2189.70
Mean	**2177.27**
Standard Deviation (±)	**23.68**
(%) Relative Standard Deviation	**1.09**
Theoretical plates number(N)	**12448.2**

Acceptance criteria

1. The relative standard deviation of five replicate injections of standard solution for peak area response of Ranolazine should not be more than 2.0%.
2. The Tailing factor for Ranolazine peak in standard solution should not be more than 2.0.
3. The theoretical plates number(N) for Ranolazine peak in standard solution should not be less than 2000.

Observation

The data demonstrated that the system suitability is within the acceptance criteria, thus the system is suitable.

2) Linearity & Range

Prepared a series of standard preparations (five preparations) of Ranolazine over a range starting from 50% to at least 150% of the specified limits of assay.

Preparation of linearity stock solutions

Weigh accurately about 50mg of Ranolazine working standard to a 50 ml volumetric flask. Add 20 ml of diluent & sonicate for 15 minutes to dissolve. Dilute to volume with diluent and mix. The preparation of linearity solutions is given in Table 5.

Table –5: Dilutions for linearity of standard.

Linearity level	Standard concentration	Amount of stock solution preparation of Ranolazine to be transferred (ml)	Volume made up to (ml) with Diluent	Concentration of Ranolazine (ppm)
Level – 1	50%	2.5 ml	50	50
Level – 2	75%	3.7 ml	50	75
Level – 3	100%	5.0 ml	50	100
Level – 4	125%	6.7 ml	50	125
Level – 5	150%	7.5 ml	50	150

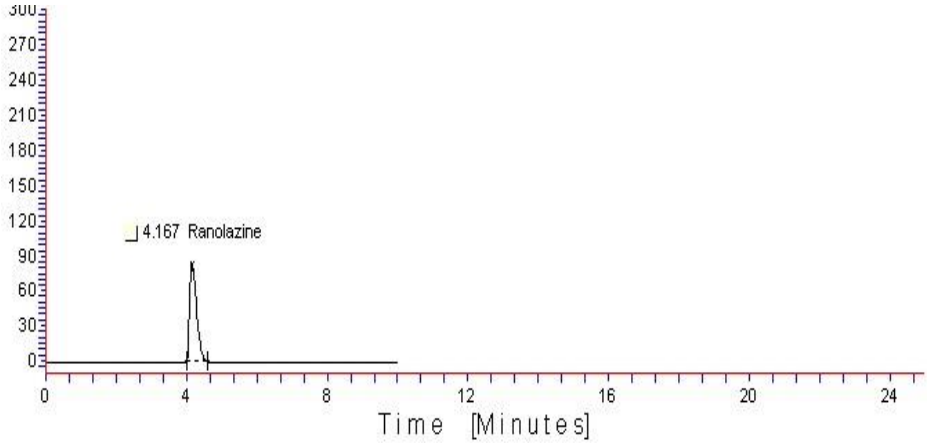


Figure 22: Chromatogram of Linearity 50%.

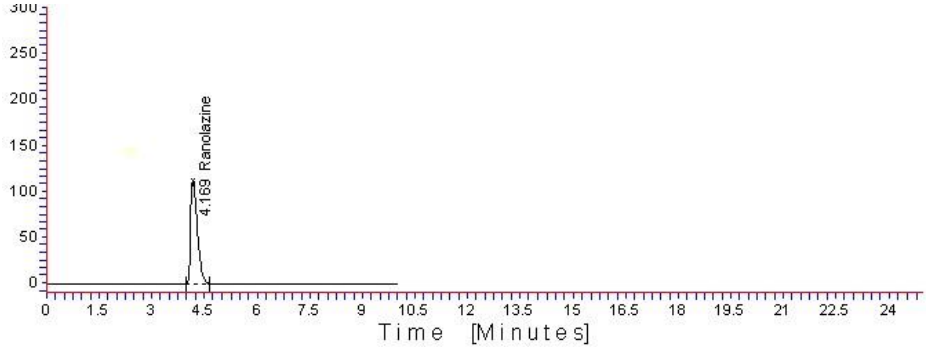


Figure 23: Chromatogram of Linearity 75%.

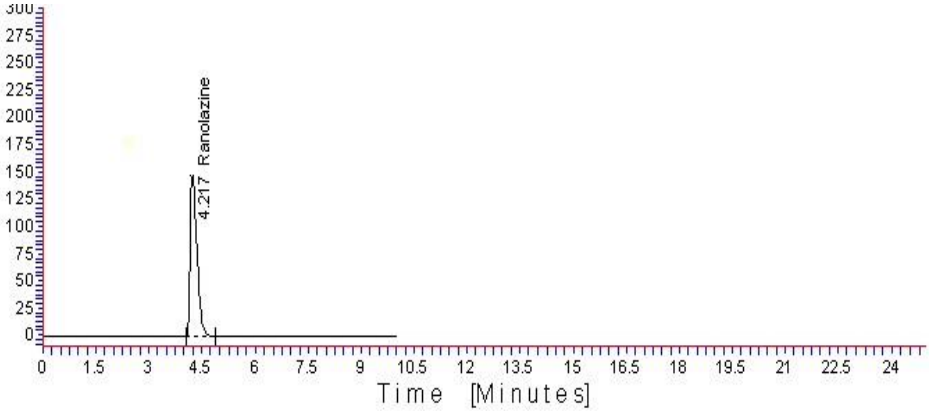


Figure 24: Chromatogram of Linearity 100%.

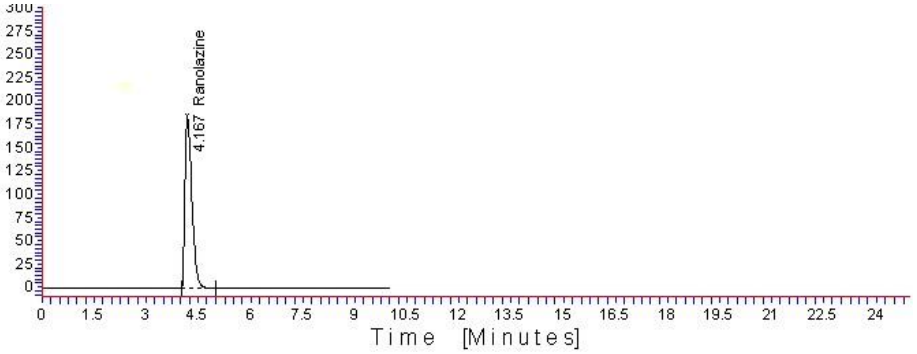


Figure 25: Chromatogram of Linearity 125%.

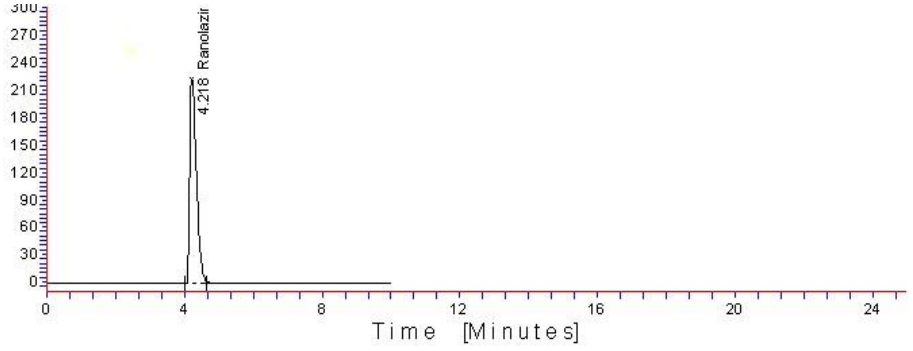
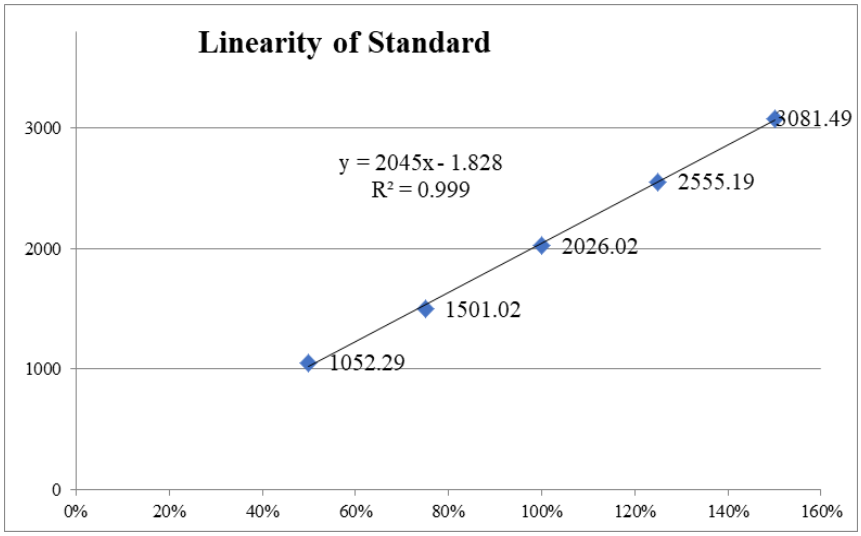


Figure 26: Chromatogram of Linearity 150%.

Table -6: Results of linearity of standard.

Linearity Level	Standard concentration (in %)	Standard Concentration (in ppm)	Area	Correlation Coefficient
Level – 1	50	50	1052.29	**0.999**
Level – 2	75	75	1501.02	
Level – 3	100	100	2026.02	
Level – 4	125	125	2555.19	
Level – 5	150	150	3081.49	



Observation

A. A linearity graph of the average area at each level against the concentration (%) is plotted and is found to be a straight line graph.

B. The correlation coefficient is found to be more than 0.999.

C. Hence it is concluded that, the method is found to be linear in the range of 50% to 150% of the working concentration.

D. The range for the analytical method is 50 ppm to 150 ppm.

3) Accuracy (% Recovery)

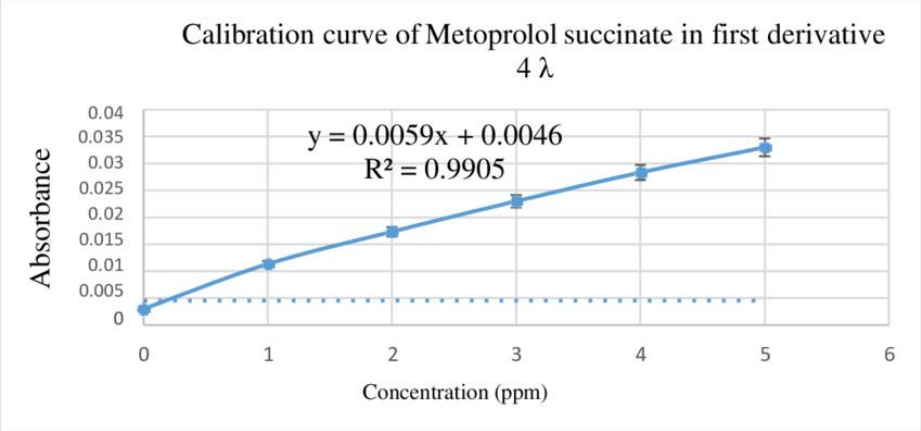
Procedure: Weigh and transfer accurately, Ranolazine API at 50%, 75%, 100%, 125% and 150% of the working concentration. Working (assay) concentration of Ranolazine is 100 ppm. The preparation of accuracy solutions is given in Table-6.

Table -7: Dilutions for Accuracy.

Level	Sample Name	Amount of Ranolazine to be weighed (mg)	Make up volume in ml
First level	Rec-50%	25.0	50
Second level	Rec-75%	37.5	50
Third level	Rec-100%	50.0	50
Fourth level	Rec-125%	62.5	50
Fifth level	Rec-150%	75.0	50

Further transfer 10 ml of each of the above solution to 50 ml and dilute with diluent and mix.

CALIBRATION CURVE



Calibration Curve for Ranolazine Estimation by RP-HPLC

Chromatographic Conditions

- **Column**: X-terra C8 (150 mm × 4.6 mm I.D., 5 µm particle size)
- **Mobile Phase**: Sodium dihydrogen phosphate buffer (pH 5.0) and Acetonitrile in a 600:400 v/v ratio
- **Flow Rate**: 1.0 mL/min
- **Detection Wavelength**: 210 nm
- **Injection Volume**: 20 µL
- **Retention Time**: Approximately 5.08 minutes

Linearity Range

- **Concentration Range**: 50–150 µg/mL
- **Correlation Coefficient (r^2)**: 0.999, indicating excellent linearity
- **Regression Equation**: y = 0.006x – 0.0048

System Suitability Parameters

- **Theoretical Plates**: 2000
- **Tailing Factor**: <2.0
- **Resolution**: >2.0
- **Relative Standard Deviation (RSD)**: <2.0% for precision

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

- **LOD**: 0.807 µg/mL
- **LOQ**: 2.446 µg/mL

Calibration Curve Data

Concentration (µg/mL)	Absorbance
50	0.300
100	0.600
150	0.900

Validation Parameters

- **Accuracy**: 98%–101% recovery from tablet formulations
- **Precision**:

- **Intra-day**: <1.0% RSD
- **Inter-day**: <1.5% RSD
- **Robustness**: Method remains unaffected by small variations in chromatographic conditions
- **Specificity**: No interference from excipients or degradation products

CONCLUSION

The developed RP-HPLC method for estimation of Ranolazine is accurate, precise, robust, and specific. The method has been found to be better than previously reported method, because of its less retention time, use of readily available mobile phase, UV detection and better resolution of peaks. In addition, the main features of the developed method are short run time and retention time around 4.22±0.25 min. The run time is relatively short, which will enable rapid quantification of many samples in routine and quality-control analysis of various formulations containing Ranolazine. All these factors make this method suitable for quantification of Ranolazine in bulk drugs and in pharmaceutical dosage forms without any interference. The Results undertaken according International Conference on Harmonization (ICH) guidelines reveal that the method is selective and specific.

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