ORIGINAL ARTICLE

# Development and Validation of a New Stability Indicating RP-UFLC Method for the Estimation of Ranolazine Tablets

**Sai Gnaneswari Aluri, Mukthinuthalapati Mathrusri Annapurna**

*Department of Pharmaceutical Analysis, Gandhi Institute of Technology and Management (Deemed to be University), GITAM Institute of Pharmacy, Visakhapatnam, Andhra pradesh-530045, India*

## Abstract

**Introduction:** Ranolazine is a piperazine derivative used for the treatment of chronic angina (chest pain). It is a new anti-ischemic drug and can be used alone or with other medications to treat chronic angina (ongoing chest pain or pressure that is felt when the heart does not get enough oxygen). A new stability indicating RP-UFLC method has been proposed for the quanification of Ranolazine in pharmaceutical formulations. Shimadzu Model CBM-20A/20 Alite high performance liquid chromatography system with PDA detector and Agilent $C_{18}$ column were used for the chromatographic study. **Materials and Methods:** Mobile phase mixture consisting of tetra butyl ammonium hydrogen sulfate and methanol (47:53, v/v) with flow rate 0.8 mL/min was selected for the chromatographic study of Ranolazine with detection wavelength 215 nm. **Results and Discussion:** Ranolazine has shown linearity over the concentration range of 0.1–50 µg/ml with linear regression equation, y = 71784x + 4994.2 ($R^2$ = 0.9999). The LOD and LOQ were found to be 0.0319 µg/ml and 0.0981 µg/ml, respectively. Stress degradation studies were performed by exposing Ranolazine to various stress conditions and the method was validated as per ICH guidelines.

**Key words:** ICH guidelines, Ranolazine, RP-UFLC, stability indicating, stress degradation studies, validation

## INTRODUCTION

Ranolazine is used to treat chronic angina and works by improving the blood flow and helps the heart to work more efficiently. Ranolazine is a new anti-ischemic drug.[1,2] Ranolazine is a selective late-sodium current inhibitor. Ranolazine works by a different mechanism than traditional anti-angina drugs. Instead of acting on the oxygen supply-demand balance, the mechanism of action of beta-blockers, calcium channel blockers and nitrates. By reducing the flow of calcium into the cells, Ranolazine helps the heart to relax by improving the blood flow to the heart muscle and relieves the symptoms of angina pectoris.[3] There are three types of angina: Stable angina which is the most common type and happens when the heart is working harder than usual. Unstable angina is the most dangerous which does not follow a pattern and happens without physical exertion where as Variant angina is rare, and it happens only during resting. Ranolazine was approved as an anti-anginal agent by FDA in 2006. Ranolazine is a well-tolerated medication that selectively inhibits the late sodium current.[4,5] Ranolazine has a molecular formula $C_{24}H_{33}N_3O_4$ and molecular weight 427.5 g/mol. It is chemically N-(2, 6-dimethyl phenyl)-2-(4-(2-hydroxy-3-(2-methoxy phenoxy) propyl) piperazin-1-yl) acetamide.[6] [Figure 1] with pKa value 7.2.

Literature survey reveals that analytical techniques such as spectrophotometry, High-performance thin-layer chromatography (HPTLC), liquid chromatography (LC) with tandem mass spectrometry (MS), and high performance liquid chromatography (HPLC) were developed earlier for the quantification of Ranolazine in pharmaceutical formulations and also in biological fluids. Patil *et al*.

**Address for correspondence:**
Sai Gnaneswari Aluri, Department of Pharmaceutical Analysis, Gandhi Institute of Technology and Management (Deemed to be University), GITAM Institute of Pharmacy, Visakhapatnam, Andhra Pradesh - 530 045, India.
E-mail: gnaneswari.aluri@gmail.com

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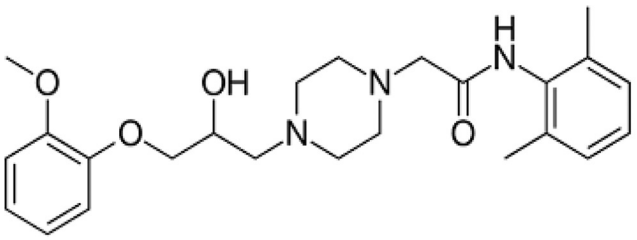

**Figure 1:** Structure of Ranolazine

developed a spectrophotometric[7] method in methanol where the λmax was detected at 235 nm, and the linearity was observed as 2–12 µg/mL. Khedkar *et al*. developed a stability indicating HPTLC[8] method using a mobile phase mixture chloroform: methanol:toluene (5:1:1 v/v/v) with detection wavelength at 273 nm and found that Ranolazine undergoes degradation in acid, base and oxidation conditions.

Lakshmi *et al*.,[9] have developed a RP-HPLC method for the estimation of Ranolazine in tablet dosage forms using C 8 column. A mixture of phosphate buffer and acetonitrile (30:70, v/v) was used as the mobile phase a flow rate of 0.5 mL/min (Detection wavelength at 273 nm) and the linearity range was reported as 10–125 µg/mL. Pratik *et al*.,[10] have developed an analytical method, that is, liquid chromatographic method for the estimation of Ranolazine in tablet dosage forms using Kromasil ODS C18 column. A mixture of Potassium di-hydrogen phosphate buffer (pH adjusted to 3.0 with diluted orthophosphoric acid): Methanol (40:60, v/v) was used as the mobile phase a flow rate of 1.0 mL/min (Detection wavelength at 225 nm) and the linearity range was reported as 2–10 µg/mL. Sharma *et al*.,[11] have developed a new isocratic validated stability indicating liquid chromatographic method using HiQ Sil C-18 HS column and mobile phase methanol: Water (99:1) with detection wave length 273 nm and the linearity was observed as 10–400 µg/mL.

Luo *et al*.,[12] have developed an analytical and semi-preparative resolution of the enantiomers of Ranolazine using cellulose tris (3, 5 dimethyl phenyl carbamate chiral stationary phases. The retention times of the enantiomers were <7.5 min with flow rate 1.0 ml/min on the analytical scale with resolution greater than 2. (2.95), whereas on semi-preparative scale both the enantiomers was separated at less than 13 min when flow rate remains as 2 ml/min. The authors have also isolated and investigated the two enantiomers using optical rotation and circular dichroism.

Nalawade *et al*.,[13] have developed a LLE-HPLC method for the estimation of Ranolazine in human plasma in presence of an internal standard, Resperidone using Hypersil BDS C18 column and analytical column HiQSil C18 column. A mixture of acetonitrile: 20 mM phosphate buffer (pH 2.0) (40:60, v/v) was used as the mobile phase a flow rate of 1.0 mL/min (Detection wavelength at 225 nm). During the study a diluent consisting of methanol: water (50:50, v/v) was used and Ranolazine was eluted at 3.728 min and that of the Resperidone, internal standard at 4.390 min. LC-MS methods were also developed for the estimation of Ranolazine in human plasma[14-17] and rat plasma.[18] Penman *et al*.[19] characterized the metabolites in man and Xie *et al*. studied the pharmacokinetics of Ranolazine in dog.[20] In the present study the authors have developed a new stability indicating RP-UFLC method for the estimation of Ranolazine and the method was validated as per ICH guidelines.

## MATERIALS AND METHODS

Ranolazine pure drug sample (API) was obtained from Cipla Limited (India) as gift sample. HPLC grade water (Merck), HPLC grade methanol (Merck) and other chemicals such as tetra butyl ammonium hydrogen sulfate (TBHS), sodium hydroxide, hydrochloric acid, and hydrogen peroxide (30% w/v) were of AR grade and procured from S. D. Fine Chemicals.

### Preparation of 10 mM TBHS solution

TBHS ($C_{16}H_{37}NO_4S$) is an ion pairing agent. The molecular weight of TBHS is 339.54 grams/mole. About 3.3954 g TBHS was accurately weighed and transferred to a 1000 ml volumetric flask and dissolved in HPLC grade water to prepare 10 mM solution and the pH of the resulting solution is 3.4. This buffer solution was filtered through 0.42 µm membrane filter and used for the preparation of mobile phase.

### Preparation of mobile phase and diluent

The mobile phase was prepared using TBHS buffer and methanol in 47:53, v/v ratio. Both organic and aqueous phase were sonicated and filtered prior to use. The diluent was prepared by mixing TBHS buffer and methanol in 60:40, v/v ratio.

### Preparation of stock solution of Ranolazine

About 25 mg of Ranolazine was accurately weighed and dissolved in 25 mL volumetric flask in methanol and the volume was made up volume. This solution is known as stock solution (1000 µg/mL), and this was further diluted with mobile phase to produce a concentration of 100 µg/mL which is known as working standard solution and these solutions were stored in refrigerator at 2–8°C.

### Instrumentation and chromatographic conditions

Shimadzu Model CBM-20A/20 Alite HPLC system with PDA detector and Agilent C18 column were used for the chromatographic study. Mobile phase mixture consisting of

TBHS and Methanol in the ratio 47:53, v/v with a flow rate 0.8 mL/min was chosen for the chromatographic elution of Ranolazine (Detection wavelength 215 nm). The injection volume was 20 µl and the total run time was 10 min.

### Method validation[21]

#### *Linearity study*

A series of 0.1–50 µg/mL of Ranolazine solutions were prepared from the stock solution on dilution with the diluent and each of these solutions were injected ($n$ = 3) into the UFLC system and the chromatograms were recorded. The peak area for each of these solutions ($n$ = 3) was noted at its retention time, and the mean peak area was calculated. Calibration curve was drawn by plotting the concentration of Ranolazine solutions on the x-axis and the corresponding mean peak area on the y-axis. The LOD and LOQ were calculated from the signal to noise ratio (S/N). The LOD is 3.3 times the signal to noise ratio and that of LOQ is 10 times the signal to noise ratio.

#### *Precision study*

Precision of the method was evaluated intra-day and inter-day precision studies. Three different concentration solutions (5, 10 and 20 µg/mL) of Ranolazine were prepared within the linearity range on the same day (intra-day precision) and on three consecutive days (inter-day precision) and the chromatographic study was performed. The mean peak area ($n$ = 3) and thereby the % RSD was calculated.

#### *Accuracy study*

Accuracy of the method was measured by spiking the Ranolazine formulation (10 µg/mL) solution (50, 100, 150%) with a known concentration of standard drug ($n$ = 3) where the final concentrations were found to be 15, 20 and 25 µg/mL. The mean peak area was calculated from the chromatograms obtained and finally the % RSD was calculated from the linear regression equation.

#### *Robustness study*

The robustness of the method was proved by incorporating a very small changes in the optimized chromatographic conditions such as pH (±0.1; 3.3 and 3.5), mobile phase composition (±2%; 45:55 and 49:51), flow rate (±0.1 mL; 0.7 and 0.9 mL/min), and detection wavelength (±2 nm; 213 and 217 nm).

### Assay of Ranolazine tablets

Ranolazine is available with different brand names such as Corvela (Cipla Ltd.), Ranogard (Abbott India Ltd.), Ranz (Intas Biopharmaceuticals), Rolazin (Macleods Pharmaceuticals Ltd.) etc as tablets (Label claim: 500 mg). 20 tablets of Ranolazine were weighed accurately and powdered. Powder equivalent to 25 mg of Ranolazine of two different brands was accurately weighed and transferred in to two different 25 ml volumetric flasks and dissolved in HPLC grade methanol followed by sonication and filtered. The filtrate was then diluted with the diluent (TBHS: Methanol 50: 50, v/v) and 20 µL of each of these two different branded solutions were injected in to the UFLC system ($n$ = 3), and the average peak area was calculated from the resultant chromatograms. The amount of Ranolazine was calculated from the calibration curve.

### Stress degradation studies[22]

Stress degradation studies were performed to determine the stability of Ranolazine toward stress conditions such as acidic hydrolysis, basic hydrolysis, oxidation, and thermal degradation. The specificity of the method can be known from the stability studies, and therefore, Ranolazine was exposed to the following stress conditions and the stability was studied.

Acidic degradation was performed by heating Ranolazine solution with 1 mL of 0.1 N HCl solution at 75°C for 1 h on a water bath. The stressed sample was then cooled, neutralized with 1.0 mL 0.1 N sodium hydroxide solution, diluted with mobile phase and then 20 µl of the solution was injected in to the UFLC system.

Alkaline degradation was performed by heating Ranolazine solution with 1.0 mL 0.1 N sodium hydroxide solution at 75°C for 1 h on a water bath. The stressed sample was then cooled, neutralized with 1.0 mL of 0.1 N HCl solution, diluted with mobile phase and then 20 µl of the resulting solution was injected in to the UFLC system.

Oxidative degradation was performed by heating Ranolazine solution with 1.0 mL 30% hydrogen peroxide solution at 75°C for 1 h on a water bath. The stressed sample was then cooled, diluted with mobile phase, and then, 20 µl of the resulting solution was injected in to the UFLC system.

Thermal degradation was performed by heating the Ranolazine solution at 75°C for 1 h on a water bath and then cooled, diluted with mobile phase and 20 µl of the resulting solution was injected in to the UFLC system.

## RESULTS AND DISCUSSION

The authors have developed a new stability indicating RP-UFLC method for the determination of Ranolazine in API and tablets. Ion pair chromatography is a widely used analytical technique especially for performing reverse phase chromatography. In general, an ion pairing agent contains both an ionic functional group as well as a hydrophobic part which is a hydrocarbon chain. These ion pairing agents

**Table 1:** Literature survey of Ranolazine

| Mobile phase (v/v)/Flow rate (ml/min) | λ (nm) | Linearity (µg/ml) | Method | Ref |
|---|---|---|---|---|
| Phosphate buffer: Acetonitrile (30:70)/0.5 | 273 | 10–125 | HPLC | 9 |
| Potassium dihydrogen phosphate buffer (pH adjusted to 3.0 with diluted orthophosphoric acid):Methanol (40:60)/1.0 | 225 | 2–10 | HPLC | 10 |
| Methanol: Water (99:1) | 273 | 10–400 | HPLC<br>Stability indicating | 11 |
| 10 mM Tetra butyl ammonium hydrogen sulfate: Methanol (47:53) | 215 | 0.1–50 | HPLC<br>Ion pairing agent<br>Stability indicating | Present method |

**Table 2:** Method optimization of Ranolazine

| Trial | Column | Mobile phase (v/v) | Flow rate (mL/min) | Rt (min) | Theoretical plates | Tailing factor | Observations |
|---|---|---|---|---|---|---|---|
| 1 | Agilent $C_{18}$ | 55:45 | 1.0 | 2.215 | 4404 | 2.091 | Peak tailing |
| 2 | Agilent $C_{18}$ | 50:50 | 1.0 | 2.228 | 4047 | 2.159 | Peak tailing |
| 3 | Agilent $C_{18}$ | 50:50 | 0.8 | 3.896 | 4665 | 1.991 | Peak tailing |
| 3 | Agilent $C_{18}$ | 47:53 | 0.8 | 3.517 | 4599 | 1.145 | Method optimized |

**Table 3:** Linearity study of Ranolazine

| Conc. (µg/mL) | *Mean peak area | % RSD |
|---|---|---|
| 0 | 0 | - |
| 0.1 | 7216 | 0.31 |
| 0.2 | 14937 | 0.26 |
| 0.5 | 35872 | 0.42 |
| 1 | 71252 | 0.71 |
| 2 | 144267 | 0.58 |
| 5 | 375924 | 0.61 |
| 10 | 745682 | 0.23 |
| 20 | 1426959 | 0.33 |
| 30 | 2178824 | 0.29 |
| 40 | 2875624 | 0.18 |
| 50 | 3582657 | 0.43 |

*Mean of three replicates

**Table 4:** Intraday precision study of Ranolazine

| Conc. (µg/mL) | *Mean peak area | Statistical analysis |
|---|---|---|
| | | *Mean±SD (%RSD) |
| 5 | 375924 | 375893.00±1954.64 (0.52) |
| 5 | 375891 | |
| 5 | 375864 | |
| 10 | 745682 | 745636.67±4548.38 (0.61) |
| 10 | 745597 | |
| 10 | 745631 | |
| 20 | 1426827 | 1426928±6849.25 (0.48) |
| 20 | 1426998 | |
| 20 | 1426959 | |

*Mean of three replicates

allow the separation of ionic and highly polar substances in columns used for RP-HPLC. The ion pair reagents are usually an alkyl sulfate an alkyl sulfonate or an alkyl ammonium salt. In the present study ion pairing reagent, TBHS was chosen for the aqueous phase of the mobile phase. Earlier different authors have proposed various analytical methods for Ranolazine and the present proposed method was compared with the previously published methods in Table 1.

## Method optimization

Ranolazine (10 µg/mL) was initially injected in to the UFLC system fitted with Agilent C18 column in which the mobile composition was 10 mM TBHS: Methanol (55:45) and flow rate was 1.0 ml/min where Ranolazine was eluted at 2.215 min with theoretical plates 4404 and tailing factor 2.091 (Trial 1). As the tailing factor is greater than 2.0 which is not within the acceptable system suitability parameters, another trial (Trial 2) was made in which the mobile phase ratio was slightly altered as 50:50 with the same flow rate where the retention time was reported as 2.228 min but the tailing factor was again greater than 2.0. Therefore, keeping the mobile phase composition same the flow rate was altered as 0.8 ml/min (Trial 3) and somehow the tailing factor was decreased and the retention was reported as 3.896 min. Finally, a small change was made in the mobile phase composition i.e. 47:53 keeping the flow rate as 0.8 ml/min by which Ranolazine was eluted at 3.517 min (Trial 4) with theoretical plates 4599 (More than 2000) and tailing factor was 1.145 and the method was optimized [Table 2]. The chromatograms obtained during the method optimization process were shown in Figure 2.

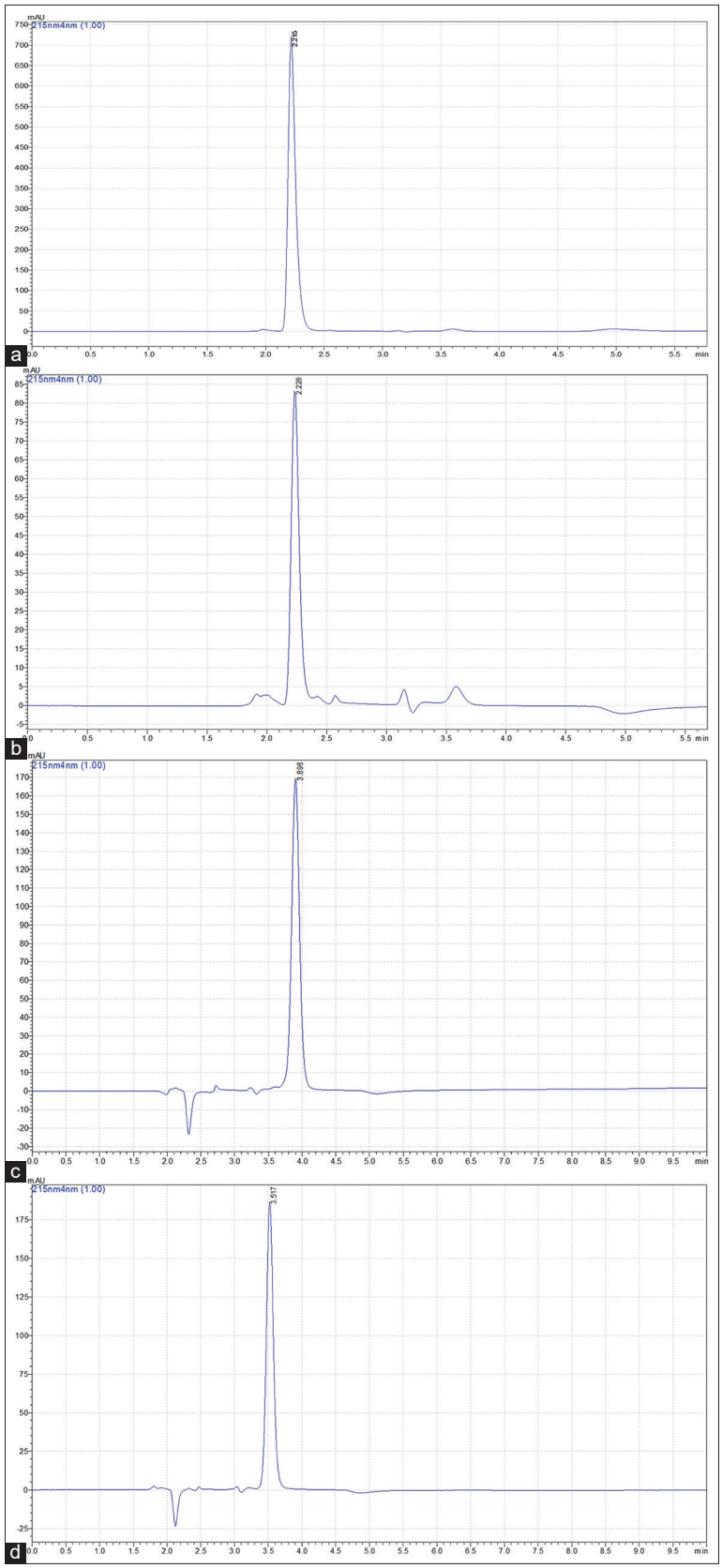


**Figure 2:** Representative chromatograms of Ranolazine during method optimization. (a) Trial 1: Mobile phase: TBHS: Methanol (55:45); Flow rate: 1.0 ml/min; Rt 2.215 min Theoretical plates: 4404; Tailing factor: 2.091 (>2) (b) Trial 2: Mobile phase: TBHS: Methanol (50:50); Flow rate: 1.0 ml/min; Rt 2.228 min Theoretical plates: 4047; Tailing factor: 2.159 (>2) (c) Trial 3: Mobile phase: TBHS: Methanol (50:50); Flow rate: 0.8 ml/min; Rt 3.896 min Theoretical plates: 4665; Tailing factor: 1.991 (>2) (d) Trial 4: Mobile phase: TBHS: Methanol (47:53); Flow rate: 0.8 ml/min; Rt 3.517 min Theoretical plates: 4599; Tailing factor: 1.145 (Method optimized)

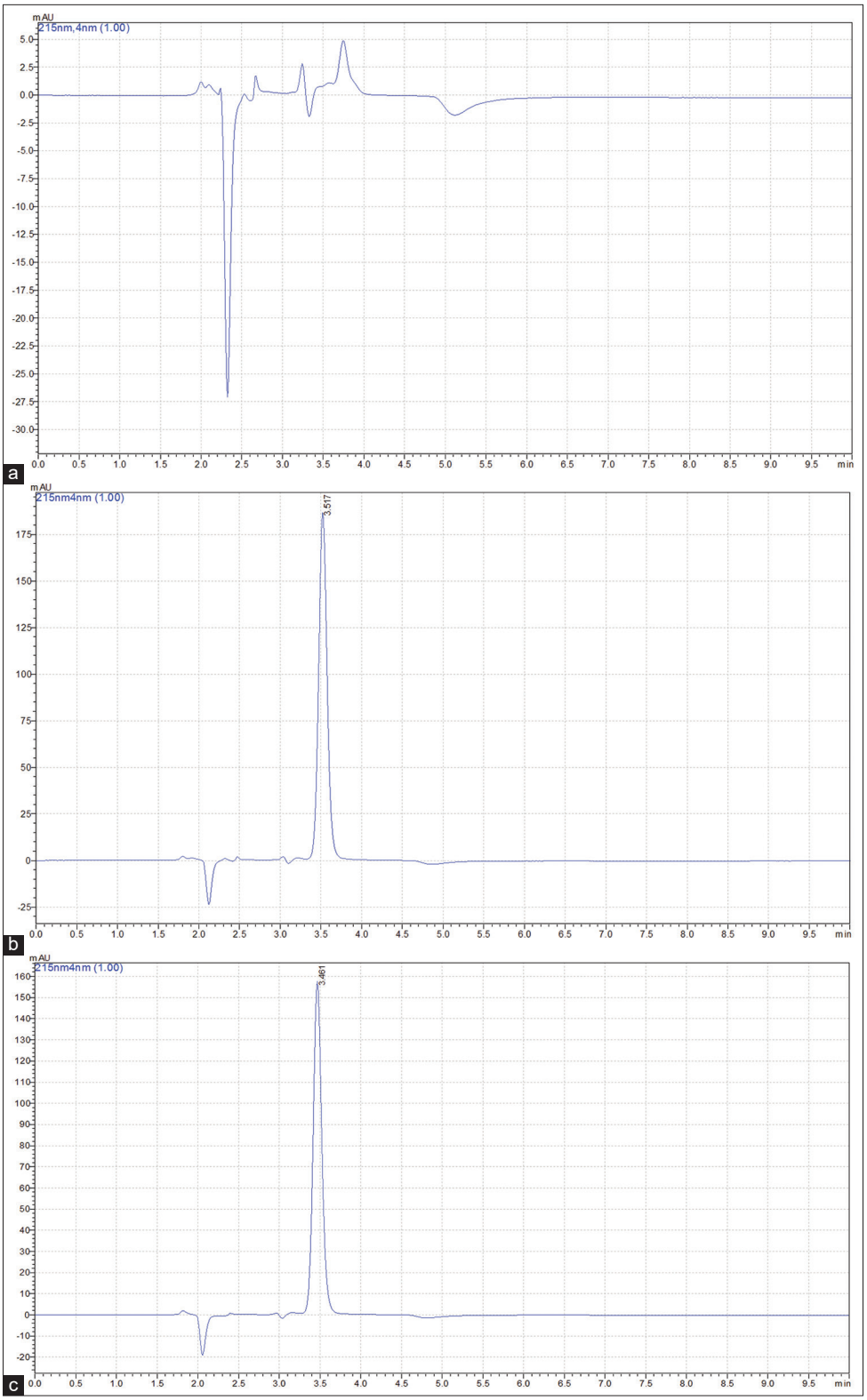


**Figure 3:** (a) Placebo (b) Representative chromatogram of Ranolazine standard (API) (20 µg/mL) (Rt 3.517 min). (c) Representative chromatogram of Ranolazine formulation (20 µg/mL) (Rt 3.461 min)

## Method validation

Ranolazine obeys Beer-Lambert's law over the concentration range of 0.1–50 µg/mL (% RSD 0.18–0.71) [Table 3] and representative chromatograms of the placebo and Ranolazine API were shown in Figure 3a and b. The LOD and LOQ were found to be 0.0319 µg/ml and 0.0981 µg/ml, respectively. The linear regression equation

was found to be y = 71784x + 4994.2 ($R^2$ = 0.9999) and the calibration curve was shown in Figure 4. The %RSD was found to be 0.48–0.61 (Intraday) [Table 4] and 0.82–0.91 (Inter-day) [Table 5] in precision studies which is less than 2.0 indicating that the method is precise. The % recovery in accuracy studies was found to be 99.15–99.80% [Table 6] and % RSD was (0.43–0.84) less than 2% indicating that the method is accurate. The % RSD in robustness study was found to be 0.23–1.03 which was <2% indicating that the method is robust [Table 7].

### Assay of Ranolazine tablets

The assay of Ranolazine was found to be 99.728–99.862 [Table 8] in tablets. The chromatogram observed for one of the brands of Ranolazine tablet formulation and that of the placebo were shown in Figure 3c. The excipients of the formulation have not interfered with the pure drug peak.

### Stress degradation studies of Ranolazine

Ranolazine (API) was eluted as a sharp peak at 3.517 min with accepted system suitability parameters, that is, theoretical plates 4599.815 (>2000) and tailing factor 1.145 (<1.5). During the acidic degradation studies Ranolazine has undergone 21.92% degradation with theoretical plates 4803.294 (>2000) and tailing factor 1.142 respectively. During the alkaline degradation studies, Ranolazine was eluted at 3.593 min and is found to be highly resistant as there is very negligible amount of degradation (0.48%) of the drug (Theoretical plates: 4944.832 (>2000) and Tailing factor: 1.131). Ranolazine was eluted at 3.584 min with an extra peak 2.197 min during the oxidative degradation and has shown 25.92% degradation. Ranolazine is found to be more sensitive towards oxidation and this may be due to the presence of hydroxyl group present in the molecular structure of the drug. The theoretical plates were found to be 4831.328 (>2000) and tailing factor 1.155 respectively with resolution 6.377 which is greater than 2. Ranolazine has shown negligible amount of degradation during thermal degradation (0.53%) with theoretical plates 4570.918 (>2000) and tailing factor 1.177, respectively. The method is selective and specific as the drug peak does not

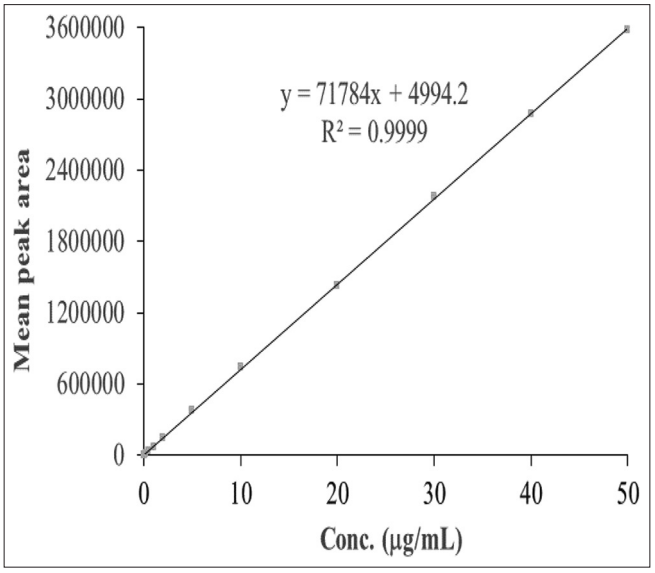


**Figure 4:** Calibration curve of Ranolazine

**Table 5:** Inter day precision study of Ranolazine

| Conc. (µg/mL) | *Mean peak area | | | *Mean±SD (% RSD) |
|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | |
| 5 | 375924 | 375726 | 375895 | 375810.5±3081.65 (0.82) |
| 10 | 745682 | 745726 | 745598 | 745668.67±6561.88 (0.88) |
| 20 | 1426827 | 1425983 | 1426952 | 1426587.33±12981.95 (0.91) |

*Mean of three replicates

**Table 6:** Accuracy study of Ranolazine

| Spiked Conc. (µg/mL) | Formulation (µg/mL) | Total Conc. (µg/mL) | *Conc. Obtained (µg/mL) ± SD (%RSD) | % Recovery |
|---|---|---|---|---|
| 5 (50%) | 10 | 15 | 14.97±0.0644 (0.43) | 99.80 |
| | 10 | 15 | | |
| | 10 | 15 | | |
| 10 (100%) | 10 | 20 | 19.83±0.1031 (0.52) | 99.15 |
| | 10 | 20 | | |
| | 10 | 20 | | |
| 15 (150%) | 10 | 25 | 24.91±0.2092 (0.84) | 99.64 |
| | 10 | 25 | | |
| | 10 | 25 | | |

*Mean of three replicates

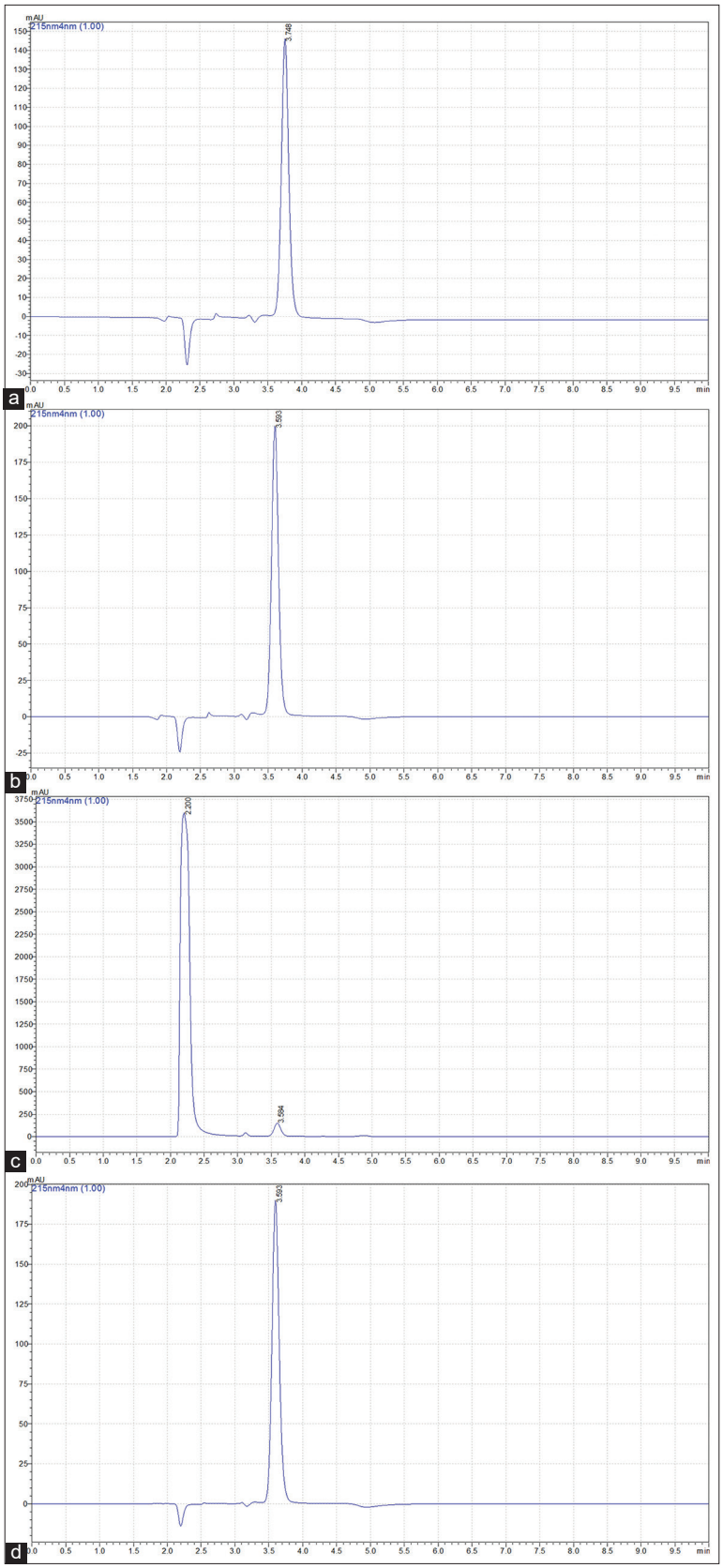


**Figure 5:** Chromatograms of Ranolazine during stress degradation studies (a) Acid degradation (b) Alkaline degradation (c) Oxidative degradation (d) Thermal degradation

interfere with any other degradant peaks. The details of the degradation studies including the % recovery were given in Table 9 and the corresponding chromatograms were shown in Figure 5.

**Table 7:** Robustness study of Ranolazine (10 µg/mL)

| Parameter | Condition | *Mean peak area±SD (%RSD) |
|---|---|---|
| Flow rate (±0.1 ml/min) | 0.7 | 759221±7364.44 (0.97) |
| | 0.8 | |
| | 0.9 | |
| Detection wavelength (±2 nm) | 213 | 759124±1745.99 (0.23) |
| | 215 | |
| | 217 | |
| Mobile phase composition tetra butyl ammonium hydrogen sulfate: Methanol (±2%, v/v) | 49:51 | 759193±3947.80 (0.52) |
| | 47:53 | |
| | 45:55 | |
| pH | 3.5 | 759298±7820.77 (1.03) |
| | 3.4 | |
| | 3.3 | |

*Mean of three replicates

**Table 8:** Assay of Ranolazine tablets

| S. No. | Brand name | Label claim (mg) | *Observed amount (%w/w) | % Recovery* |
|---|---|---|---|---|
| 1 | Brand I | 500 | 498.64 | 99.728 |
| 2 | Brand II | 500 | 499.31 | 99.862 |

*Mean of three replicates

**Table 9:** Stress degradation studies of Ranolazine

| Stress condition (Temp°C/Time min) | Rt (min) | Mean peak area | % Recovery | % Drug degradation | Theoretical plates | Tailing factor |
|---|---|---|---|---|---|---|
| Standard drug | 3.517 | 1426959 | 100 | ----- | 4599.815 | 1.145 |
| Acidic degradation 0.1N HCl/75°C/1 h | 3.748 | 1114173 | 78.08 | 21.92 | 4803.294 | 1.142 |
| Alkaline degradation 0.1N NaOH/75°C/1 h | 3.593 | 1420212 | 99.52 | 0.48 | 4944.832 | 1.131 |
| Oxidative degradation 30% $H_2O_2$/75°C/1 h | 3.584<br>2.197 | 1057138 | 74.08 | 25.92<br>Resolution = 6.377 | 4831.328 | 1.155 |
| Thermal degradation 75°C/1 h | 3.593 | 1419412 | 99.47 | 0.53 | 4570.918 | 1.177 |

*Mean of three replicates

## CONCLUSIONS

A new reverse phase stability indicating RP-UFLC has been developed for the quantification of Ranolazine using an ion pairing reagent, TBHS and validated as per ICH guidelines. The method is simple, selective, specific, precise, accurate, and robust and can be used for the estimation of Ranolazine in pharmaceutical formulations and at the same time this method is very much useful for the pharmacokinetic studies.

## ACKNOWLEDGMENT

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