RESEARCH ARTICLE

# A Rapid, Selective and Sensitive Electrospray Ionization Assisted LC-MS Method for Ranolazine and Identification of Its Two Potential Genotoxic Impurities

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**ABSTRACT**

A rapid, sensitive and selective electrospray ionization liquid chromatography-mass spectrometry (LC-MS) approach was developed to find and quantify the two genotoxic RANO contaminants (A and G) and forced degradation products of RANO in formulations of pharmaceutical drugs. X Select CSH C18 (100 x 3.0 mm, 2.5 µm) instrument was utilized for the separation with mobile phase containing of ammonia solution (A) and methanol (B) in gradient elution. About 254 nm as detection wavelength and 0.3 mL/min as flow rate were maintained. RANO has been degraded under stress conditions like thermal, oxidative, hydrolytic, peroxide, photolytic, acid and base, conditions. The resultant RANO products of degradation were well separated from RANO and its contaminants. Based on ICH rules the validation process was complying with the acceptance of precision, linearity, robustness and accuracy. To quantify the constituent contaminants (A and G), a positive electrospray ionization was connected to a triple quadrupole mass detector. The contaminants were determined in terms of LoD and LoQ values of 0.075 and 0.25 ppm, respectively, using the multiple reaction monitoring (MRM) mode.

**Keywords:** Ranolazine, Genotoxic impurities, Impurity A and G, PDA, LC-MS.

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**Conflict of interest:** None

## INTRODUCTION

An orally used RAN is a derivative of piperazine that inhibits the channel current of sodium ion and the channel current of potassium ion.[1] Additionally, RANO has advantageous metabolic characteristics and has no impact on heart rate. Chemically it is known as N- (2, 6- dimethyl phenyl) -2- [4- [2-hydroxy-3- (2-methoxyphenoxy) propyl] piperazin-1-yl] acetamide with molecular formula is $C_{24}H_{33}N_3O_4$ and molecular weight is 427.54 g/mol was approved by US Food and Drug Administration (FDA) in 2006. RANO was used to the medication as a second-line treatment for chronic stable angina pectoris (CSAP).[2] The increasing demand for the medication undoubtedly demonstrates the need to identify and characterize contaminants and/or degradation products to ensure the pharmaceutical formulations' safety profile and adhere to regulatory bodies' recommendations.[3-6] The pharmaceutical company's primary responsibility is to identify and measure any possible genotoxic contaminants (GTIs). So, it was necessary to establish an highly selective analytical approach that was sensitive to the low-level quantification of these GTIs. Identifying and quantifying contaminants during the drug manufacturing process is extremely difficult. The existence of GTIs in pharmaceutical products causes genetic mutations, and they may result in cancer in humans.[4] From a regulatory viewpoint, the quality of API and pharmaceutical products depends on detecting the contaminant threshold limit value of GTIs in pharmaceutical products. The majority of contaminants arise from the synthetic process of the API or deposit or products transported or via chemical degradation of API at any given condition.[7-8]

Numerous spectrophotometric approaches are available to the determination of RANO in tablets and bulk medicines.[9,10] Chromatographic analysis of RANO in bulk and tablets,[11] high-performance thin layer chromatography (HPTLC),[12,13] stability-indicating analytical methods,[14-19] Enantiomeric separation,[20] identification of RANO and its contaminants related to the process[21] and several quantification approaches were developed for Ranolazine identification and metabolites of

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ranolazine in biological samples using liquid chromatography-mass spectrometry (LC-MS).[22-26]

However, until now, the LC-MS method has not been documented for the two RANO probable genotoxic contaminants. This study demonstrates the creation and verification of a targeted, quick, accurate, and straightforward LC-MS method for the detection of two putative process-related genotoxic contaminants.

## MATERIAL AND METHODS[27-30]

### Chemicals and Reagents

About 99% purity RANO; Impurity A (99% purity) and G (99% purity) were supplied by SynZeal Research Pvt. Ltd, Ahmadabad, India. Merck solution Private Limited, Mumbai, India, provided LC-MS standard solvents, acetonitrile and methanol. S.D Fine Chem. Ltd, Mumbai, India provided reagents of formic acid and ammonium solution. Millipore Milli-Q- plus instrument, Milford, USA was utilised to get high standard purity water.

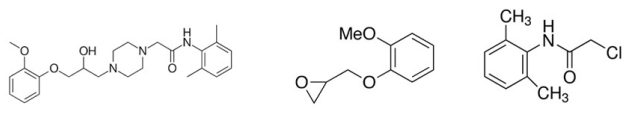
### Instrumentation

*Chromatography and mass spectrometric conditions*[27]

The study was conducted using an ESI source operating in positive-ion detection mode, an Agilent 1200 (Agilent Technologies Inc., Santa Clara, CA, USA), an API 4000 (AB Sciex, Foster City, CA, USA), and a tandem mass spectrometer. Chromatographic isolation was optimized by using X Select CSH C18 (100 x 3.0 mm, 2.5 µm) column with mobile phase consisting 0.1% ammonia solution (A) and methanol and acetonitrile (B) using a gradient program. Contaminants A and G were quantified in positive MRM mode by utilizing ESI with transition ion pairs with m/z values 181.1 > 151.1 and m/z 198.2 > 107.1, respectively. RANO was observed through the m/z value of transition ion pair 382.2→214.1. Analyst 1.6.2 software, Applied Bio Systems, USA was utilized for both data gathering and assessment. The structure of RANO and its impurities (A and G) were shown in Figure 1. Mass spectrometer conditions were incorporated in Table 1.

*Stock and standard solutions preparation*[29,30]

Ten milligrams of ranolazine contaminant A and ten mg of ranolazine contaminant G were added to a 100 mL standard flask and dissolved in 100 parts per milliliter of methanol to create the ranolazine contaminants stock solution. The impurities were validated at 0.075, 0.25, 0.5, 0.75, 1.5 and 2.25 ppm concentration and filtered before the analysis through 0.45-µm nylon membrane filters. In order to prepare test sample spiked with standard at the LoQ, 50, 100, and 150% level by 10 mg of trail sample dissolving in a 10 mL standard flask with a standard solution.




**Ranolazine** | **Impurity-A** 2-[(2-Methoxyphenoxy) methyl] oxirane | **Impurity-G** 2-Chloro-N-(2,6-dimethyl phenyl) acetamide

**Figure 1:** Ranolazine and impurities[27]

**Table 1:** Mass spectrometer conditions[28]

| *Condition* | *Positive* |
|---|---|
| Capillary Voltage (V) | 4000 |
| Corona Current (µA) | 10.0 |
| Charging voltage (V) | 2000 |
| Dry gas flow (l/min) | 12.0 |
| Nebulizer pressure (psig) | 35.0 |
| Drying gas temperature (°C) | 249.0 |
| Vaporizer temperature (°C) | 200.0 |

*Forced degradation studies*[31,32]

To prepare the degradation sample, each sample takes 10 mg of RANO, which 10 mg RANO dissolved in 100 mL of diluent (Mixture water and acetonitrile in 30:70% v/v proportion)[33]. A 1-mg/mL concentration solution is prepared by taking 0.1 mL from this solution and diluting it to 10 mL. The sample was exposed to acid (0.1 N concentration HCl, 4 hours at 70ºC), base (0.1 N concentration NaOH, 4 hours at room temperature), severe oxidation (30% $H_2O_2$ for 4 hours at room temperature), thermal (80ºC, 6 hours), and photolytic (1.2 million lux h, 200 wh/$m^2$, 48 hours) degradation conditions.

*Method validation*

The approach has been validated through accuracy, specificity, precision, linearity and robustness.[34-39]

## RESULTS AND DISCUSSIONS

### Optimization Conditions of Chromatography

Preliminary research experiments have been conducted for the optimization of liquid chromatographic conditions to get high resolution between RANO and impurities of RANO, which is of prime importance for the selectivity and sensitivity of the method. Initial experiments were conducted by utilizing various kinds of columns with different chemistries along with Fortis C8, C18, and XSelect CSH C18 (100 x 3.0 mm, 2.5 µm). Volatile buffers include ammonia solutions, 10 mM concentrated ammonium acetate, methanol, 10 mM concentrated ammonium formate, and acetonitrile, which are compatible with LC-MS. Trials on XSelect CSH C18 columns with mobile phase used an ammonia solution, and methanol was identified to be good in comparison with other buffers. Gradient elution was used to reach the final LC separation using a mobile phase that included methanol (B) and ammonia solution (A). ($T_{min}$/% ammonia solution): 0–7/55, 7–10/90 and 10–15/55, should maintain 254 nm detection wavelength, 0.3 mL/min as flow rate, column T at 45ºC and 10 µL was injection volume. The same approach was used to LC-MS research and to get excellent signal and sensitivity for RANO and its contaminants (A and G) by optimizing the mass spectrometric parameters. The chromatogram of RANO and

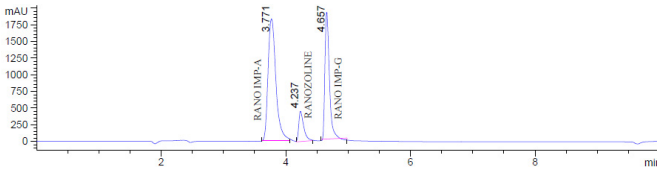



**Figure 2:** Chromatogram of RANO and its impurities (A and G)

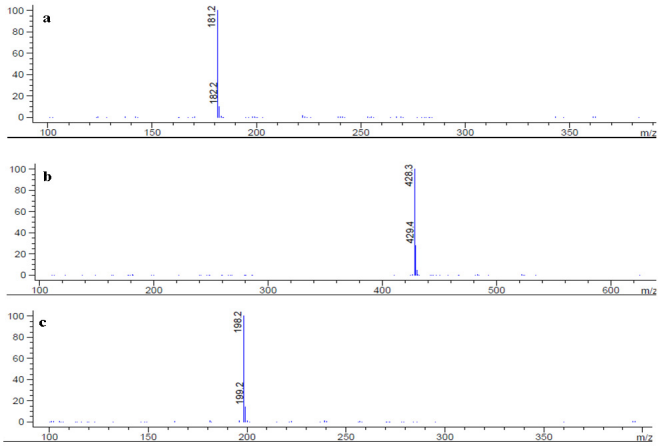



**Figure 3:** LC-MS spectra (a) impurity A (*m/z* 181.2), (b) RANO (*m/z 428.3*), (c) impurity G (*m/z* 198.2)

its impurities (A and G) are represented in Figure 2. LC-MS spectra (a) impurity A (m/z 181.2), (b) RANO (m/z 428.3), (c) impurity G (m/z 198.2) has been shown in Figure 3.

### Forced Degradation Behavior

The degradation study revealed that RANO was unstable to acidic, basic and peroxide conditions. The study results of degradation are presented in Table 2 and Figure 4.

### Specificity

Specificity was determined by injecting 1.0 ppm of RANO, impurity A and impurity G. Assessment of peak purity of RANO, impurity A and impurity G was performed by utilizing PDA detector. The purity threshold value was greater than the purity angle, showing that the peak was pure, so the technique has been identified as specific. The retention time of the API and contaminants A and G were 3.77 (impurity A), 4.23 (RANO) and 4.65 (impurity G), respectively.

### Linearity

The working standard solutions of impurity A (Figure 5) and impurity G (Figure 6) at five various kinds of concentrations

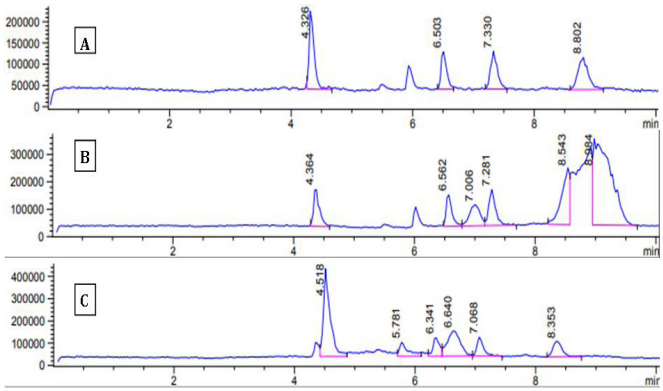



**Figure 4:** Typical chromatograms of samples (A) acid degradation, (B) hydrolytic degradation and (C) oxidative degradation

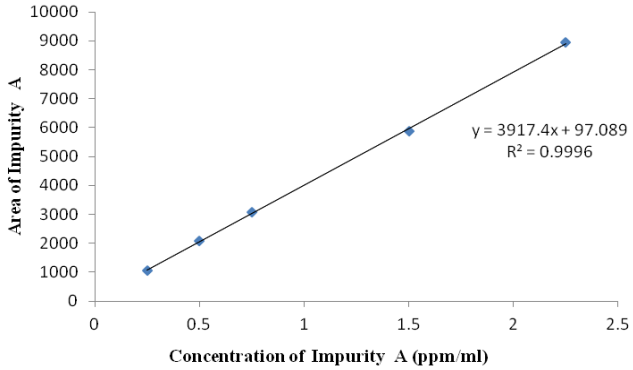



**Figure 5:** Linearity curve of impurity A

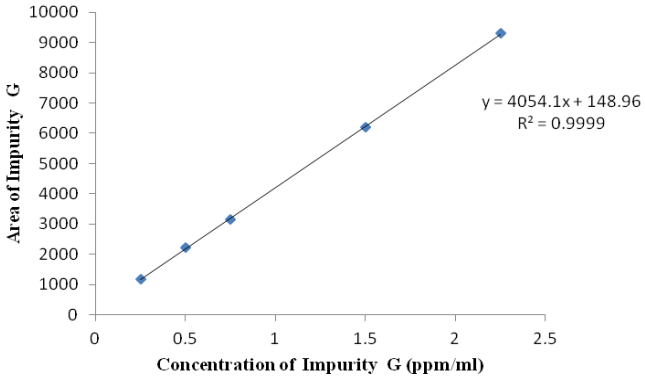



**Figure 6:** Linearity curve of impurity G

**Table 2:** Optimized conditions for forced degradation of RANO

| *Stress condition* | *Stressor concentration* | *Exposed condition* | *Duration (hours)* | *Degradation products (DPs) obtained* |
|---|---|---|---|---|
| Hydrolysis of acid | HCl (0.1N) | Reflux at 70°C | 4 | DP-1 (6.5), DP-2 (7.3), DP-3 (8.8) |
| Hydrolysis of base | NaOH (0.1N) | At room temperature | 4 | DP-1 (6.5), DP-4 (7.0), DP-2 (7.2), DP-5 (8.5) and DP-3 (8.9) |
| Oxidation | 30% (v/v) $H_2O_2$ | At room temperature | 4 | DP-6 (5.7), DP-7 (6.3), DP-1 (6.6), DP-4 (7.0) and DP-8 (8.3) |
| Photolysis | Solution | 1.2 million lux h, 200 wh/$m^2$ | 48 | No-degradation |
| Thermal | Solid state | 80°C | 6 | No-degradation |

**Table 3:** Parameters for linear regression equation

| *Parameter* | *Impurity A* | *Impurity G* |
|---|---|---|
| Calibration range | 0.25–2.25 ppm | 0.25–2.25 ppm |
| Linearity equation | y = 3917.4x + 97.089 | y = 4054.1x + 148.96 |
| Determination coefficient ($r^2$) | 0.9996 | 0.9999 |
| Detection limit (ppm) | 0.075 | 0.075 |
| Quantitation limit (ppm) | 0.25 | 0.25 |

**Table 4:** Accuracy data of impurities (A and G)

| *Parameter* | *A -Impurity* | *G -Impurity* |
|---|---|---|
| Accuracy at LoQ level (n = 3) | | |
| Added amount in ppm | 0.25 | 0.25 |
| Recovered amount in ppm | 0.24 | 0.23 |
| %recovery | 96.1 | 92 |
| %RSD | 0.56 | 1.31 |
| Accuracy at 100% level (n = 3) | | |
| Added amount in ppm | 1.5 | 1.5 |
| Recovered amount in ppm | 1.482 | 1.51 |
| %recovery | 98.8 | 100.8 |
| %RSD | 1.41 | 0.87 |
| Accuracy at 150% level (n = 3) | | |
| Added amount in ppm | 2.25 | 2.25 |
| Recovered amount in ppm | 2.14 | 2.29 |
| %recovery | 95.11 | 101.7 |
| %RSD | 1.33 | 0.95 |

**Table 5:** Impurities (A and G) precision data

| *Actual concentration (ppm) Impurity A* | *Intraday precision* | *Interday precision* |
|---|---|---|
| | *Measured concentrated (ppm); RSD (%)* | *Measured concentrated (ppm); RSD (%)* |
| 1.5 | 1.479; 1.62 | 1.493; 1.38 |
| Impurity G | | |
| 1.5 | 1.520; 1.11 | 1.481; 0.78 |

(n = 3) ranging from 0.25 to 2.25 ppm were analysed in order to evaluate linearity. Plotted the calibration curve between impurity A and impurity G's peak regions (Y-axis) and concentration in parts per million (X-axis). After fitting to a linear regression model with a weighting scheme of 1/x, the data from a linear regression were examined to estimate the slope, intercept, and correlation coefficient (Table 3).

### Accuracy

The proposed technique accuracy has been assessed by injecting impurities (A and G) in three distinct concentrations, i.e., 0.25, 1.5 and 2.25 ppm (LoQ, 100 and 150%) in triplicate. The recovery obtained for both impurities was within 90 to 110% (Table 4).

### Precision

The precision of the proposed approach has been evaluated by assessing six replicate injections of 100% standard stock solution (1.5 ppm). The %RSD for intermediate precision and repeatability are shown in Table 5.

### Robustness

By changing the chromatographic parameters, such as the flow rate, buffer pH, and mobile phase ratio, by ± 0.1, ± 2%, and ± 0.1, respectively, the resilience of this approach was verified. The strategy was deemed reliable within the confines of its functioning limitations.

## CONCLUSION

The present developed approach was verified in view of ICH guidelines. The LC-MS approach is highly sensitive, specific, and reproducible; hence, it has been utilized to quantify RANO and contaminants of RANO (A and G) in drugs. In this technique, MRM mode was utilized to quantification, gives better sensitivity. The LoD and LoQ of the approach have been identified very less, as 0.075 and 0.25 ppm for impurity A and impurity G. This approach can be used in the quantitation of these impurities in the quality control department for routine low-level impurity analysis for pharmaceutical substances.

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