Research & Reviews: Journal of Pharmaceutical Analysis

e-ISSN:2320-0812

Analytical Method Development and Validation of Ticagrelor: Review

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Review Article

Received date: 04/9/2021
Accepted date: 20/9/2021
Published date: 27/9/2021

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Keywords: Ticagrelor, Literature Survey, HPLC, Validation, ICH Guidelines.

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ABSTRACT

Analytical method development and validation play important roles in the discovery and Manufacture of pharmaceuticals. Method development is the process of proving that an analytical method is acceptable for use to measure the concentration of a Ticagrelor in a compounded dosage form. The analytical method validation is essential for analytical method development and tested extensively for specificity, linearity, accuracy, precision, range, detection limit, and robustness. Literature survey reveals that the analytical methods based on UV spectroscopy, UPLC and RP-HPLC for the determination of Ticagrelor individually and in combination with other drugs. The methods were validated according to ICH guidelines. The developed methods are simple, sensitive, and reproducible and can be used for the routine analysis of Ticagrelor in bulk and Tablet dosage form.

INTRODUCTION

Ticagrelor is a platelet aggregation inhibitor reduces the rate of thrombotic cardiovascular events in patients with the acute coronary syndrome. Ticagrelor belongs to the class of triazolo pyrimidines which are polycyclic aromatic compounds containing triazole ring fused to a pyrimidine ring. Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation [1] (Figure 1).

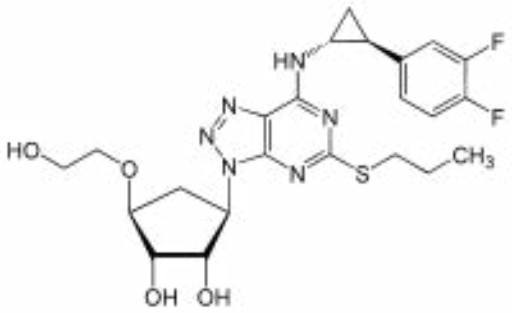

Figure 1: Ticagrelor

Ticagrelor is chemically known as (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol with a molecular formula of C23H28F2N6O4S and a molecular weight of 522.567 g/mol. It is freely soluble in Soluble in ethanol,dimethyl formamide sparingly soluble in water. Brilinta is the most available brand name in the market

The aim of the present study was A New Rp-Hplc Method for Simultaneous Estimation of Atorvastatin and Fenofibrate in Its Bulk and Tablet Dosage Form [3-10].

REVIEW OF LITERATURE:

1. Effat Souri et al., Have developed the simple and rapid UV spectrophotometric method for the determination of ticagrelor

in dosage forms. Two rapid and accurate spectrophotometric methods were described for the determination of Ticagrelor in pharmaceutical dosage forms. In the first method direct spectrophotometry was used for the quantification of ticagrelor at 255 nm. The second method was based on the ion pair complex formation of ticagrelor and bromocresol green extractable in chloroform. After optimization of the reaction, the resulting complex was measured at 416 nm. Linear calibration curves results were obtained at the range of 0.5-25 µg/ ml and 5-1000 µg/ml for the direct and ion-pair complex [11].

2. Darshana Pandya et al., Have developed the simple, precise, accurate, economical and reliable UV spectrophotometric method for the estimation of Ticagrelor in tablet dosage form. The λ max was found at the wavelength of 222 nm. Due to greater stability in methanol: water (1:1%v/v). It was selected for further study. Using the UV detector, the wavelength range was selected from 190 to 500 nm after the standard solution was scanned over the 190 to 800 nm range. It was thoroughly validated in accordance with ICH [12] after the development of the analytical process.

3. Harpal Narware et al., Have developed the accurate, precise, sensitive and reproducible UV spectrophotometric method for the quantitative determination of ticagrelor. The UV spectrophotometric determinations were performed at 282 nm using water as a solvent. The proposed method was validated according to International Conference on Harmonization ICH Q2 (R1) guidelines. The linearity range for ticagrelor was 5-25 µg/ml for UV method. The linearity of the calibration curves for each analyte in the desired concentration range was good (r2 >0.999) by UV method. Both the methods were accurate and precise with recoveries in the range of 98 and 99 % and relative standard deviation.

4. Anand Gupta et al., Have developed the simple, sensitive and accurate UV spectrophotometric method for the determination of Ticagrelor in pure state and in its pharmaceutical formulations. Accurate UV Method have been developed for the estimation of Ticagrelor in bulk drugs and its Tablet dosage form. The λ max was found to be 255nm.This drug was stable in the solvent composition of ACN:Methanol (85:15 v/v) as per the solution stability experiments and was also used as sample preparation diluent. In order to get reproducible results with the minimum run time, the established method was optimised. The Stationary Phase was C18 (250 x 4.6 mm i.e., 5µ) Mobile Phase was ACN: Methanol (85:15 v/v), Flow rate 1.0 ml/min, Injection volume 10 µl, PDA detection at λ max 255nm and Run time 7 min. It provides a linear response over the Conc. Range of 5-25 µg/ml with Correlation Co-efficient of 0.999 and LOD and LOQ was discovered to be 0.20 µg/ml and 0.61 µg/ml individually. % Recovery was found to be 99.06, 99.77, and 100.99% for the levels of 80, 100, and 120% individually. The method was discovered to be Robust with better accuracy and Precision having % RSD esteem under [2]. The limit of detection and limit of quantification was 0.05µg/ml and 0.20µg/ml individually [13].

5. Omaima et al., Have developed the simple, rapid, sensitive, precise, accurate and validated Ultra Performance Liquid Chromatographic (UPLC) method for the estimation of Ticagrelor in tablet dosage form. Chromatographic separation was achieved on an acuity UPLC BDS C8 (150 x 4.6 mm, 5m) column with a mobile phase composed of Buffer 0.1% OPA (2.2 pH) and Acetonitrile in the ratio of 60:40 at a flow rate of 1.0 ml/min and 1 µl injection volume. The effluents were detected at a wavelength of 240 nm using TUV detector. The retention time of Ticagrelor was found to be at 0.942 min. Percentage RSD of the Ticagrelor was found to be 0.7. The correlation coefficient for Ticagrelor was found to be 0.999. Recovery was found to be 99.51% in the formulation of Ticagrelor. LOQ, LO values obtained from regression equations of Ticagrelor were 1.35, 0.45 respectively.

6. Vegesna Swetha et al., The article reports on simple, precise and accurate RP-HPLC method for stability indicating assay and dissolution of Ticagrelor as per ICH guidelines. An isocratic separation was achieved using a Develosil ODS UG-5 C18 (150 X 4.6mm, 5µ particle size) columns with a flow rate of 1 ml/min and using a PDA detector to monitor the elute at 280 nm. The mobile phase consisted of potassium dihydrogen phosphate buffer: acetonitrile (60:40, v/v) with pH 3.0 adjusted with phosphoric acid [14]. The retention time 5.35, linearity concentration ranges of 20-80 µg/ml (r2 = 0.9992) with a limit of detection and quantitation of 0.05 and 0.15 µg/ml respectively. Intraday, inter day system and method precision were determined and accuracy was between 99.3-101.9%. Based on the results obtained from the analysis using proposed method, it can be concluded that the method has linear response in the range of 22.5-135 µg/ml for Ticagrelor respectively [15-20].

7. K. Tabassum et al., Have developed a new sensitive, specific and linear RP-HPLC was used for validation studies of Ticagrelor. The optimum chromatographic conditions comprised of C18 column (Kromasil, 250×4.6 mm, 5 µ) as the stationary phase and aqueous buffer containing 0.5 ml formic acid and trimethylamine each in acetonitrile and water in the ratio of 50:50 v/v as the mobile phase. The flow rate was 1.3 ml/min with discovery at 256 nm and a run time of 6 min. Ticagrelor's retention time was 3.372 min. The linearity studies indicated that 20-90 ppm with a correlation coefficient of 0.9956 was the range of the method established. The approach was precise, with a mean recovery of 99.93% being identified. In precision test, the % RSD was 0.069. In order to perform the assay of Ticagrelor in tablets and with a mean recovery of 99.82%, the validated method was applied.

8. P.R. Kulkarni et al., Have developed the accurate, Precise, Simple and Economical HPLC method for the estimation of Ticagrelor in bulk form. This method is also developed in RP-HPLC method using Primesil C18 column (Length: 250 nm, Diameter:4.6nm, Particle size:5µ) with a simple methanol and water (0.05% OPA) mixed in a proportion of 95:05 v/v as mobile phase. The retention time was found to be 4.5 min. The linearity was observed in a concentration range of 5-25 µg/ml with the correlation coefficient of 0.997. The results obtained were well within the acceptance criteria [21].

9. Delma D. Cruz et al., Have developed a simple, accurate and linear RP-HPLC method for the quantitative determination of Ticagrelor in tablet dosage forms. The separation was accomplished by the isocratic method by utilizing Phenomenex C18 column on a Shimadzu binary gradient liquid chromatography system furnished with LC-20AD solvent delivery system, SPD-20-A photo-

diode array detector, 20 µl loop volume in a rheodyne injector. The analyte was extracted by protein precipitation in the involvement of diethyl ether (protein precipitator). The mobile phase consists of acetonitrile and methanol in the ratio of 60:40% v/v. The separation was done with a flow rate of 1 ml/min at a detection wavelength of 254 nm. Retention time was found to be 4.503 min with a run time 10 min. Linearity shows in a range of 20-100 µg/ml, with a correlation coefficient of 0.9992 respectively. Stability studies of Ticagrelor in plasma were carried out by short term stability, long term stability and bench top stability studies. Short term stability, long term stability and bench top stability of Ticagrelor was carried out from 20 and 100 µg/ml concentration and %RSD was ascertained 0.12% and 0.08%, 0.18% and 0.15%, 1.19% and 1.30% respectively [22].

10. N L John Shane et al., Have developed a simple, reproducible and efficient Reverse Phase -High Performance Liquid Chromatography method for estimation of antiplatelet drug. This was separated using Shimadzu LC-20-AD with auto sampler and PDA/UV detector. The separation was achieved using a C18 Vydac Monomeric 120A (5.0-micron, 250 × 4.6 mm) column. Acetonitrile: Water Milli Q (60:40 v/v) was used as the mobile step at a flow rate of 1.0 ml/min. The method was linear with a line equation f(x)=1.90442e-005*×-0.302059 with correlation coefficient (R2) of 0.997. With RSD at 0.27% (intraday precision), the procedure was successful. The LOD & LOQ were 0.083µg/ml and 0.25µg/ml.

11. A. Ambasana et al., The article reports on simple, accurate, precise, reproducible and robust RP-HPLC method for the estimation of Ticagrelor Hydrochloride. The separation was achieved using Agilent Infinity 1220, Infinity Fast-LC (Pressure limit up to 600 bars) with auto sampler and PDA detector. The chromatographic analysis was done on ZORBAX Eclipse Plus 300SB C18 (250 x 4.6mm, 5.0 micron, PN 880995-902) column. Mobile phase consists of (A) Acetonitrile: (B) Potassium dihydrogen ortho phosphate buffer (40:60 v/v) at a flow rate of 1.0 ml/min. The method showed linear in the mentioned concentrations having line equation y = 22.848x + 1.3214 with correlation coefficient R2 of 0.9995. The recovery values for Ticagrelor ranged from 99.63% to 100.34%. The % RSD was 0.49% and 0.54%, respectively for intraday and interlay precision. The limit of detection and limit of quantification were 0.05µg/ml and 0.20µg/ml respectively. Newly developed method was statistically validated for accuracy, precision, linearity and solution stability hence it is directly applicable for the estimation of Ticagrelor in routine analysis [23-25].

12. N. Anil kumar et al., Have developed a stability indicating UV spectrophotometric method for the estimation of Ticagrelor in tablet dosage form. UV- Spectrophotometric technique UV/Vis double beam spectrophotometer with spectral band widths of 1 nm and 1.0 cm matched quartz cells and glass cells was used for UV regions respectively. Methanol and O-phosphoric acid were used as solvents at a ratio of 20:80 and the maximum absorbance of Ticagrelor was observed in methanol & O-phosphoric acid at 237nm in UV region. The linear calibration range was discovered to be 2µg/ml to 10µg/ml. The correlation coefficient (R2) is 0.9855 and the regression equation is y=0.0808x-0.0022 in UV region.

13. Kal. L. yani et al., Have developed a stability indicating HPLC method for determination of Ticagrelor in pharmaceutical dosage form. Separation of the drug was achieved on Hypersil BDS C18 column as stationary phase with mobile phase consisting of phosphate buffer pH 3.0 and acetonitrile in the ratio of 70: 30 V/V. The method showed a good linear response in the concentration range of 22.5-135µg/ml with correlation coefficient of 0.999. The flow rate was maintained at 1.0 ml/min and effluents were monitored at 254 nm. The retention time was 3.215 min. The percentage assay of Ticagrelor was 99.9%. The method was statistically validated for accuracy, precision, solution stability, selectivity, linearity, ruggedness, robustness and forced degradation studies.

14. Ayushi Mehta et al., Have developed a combination of Ticagrelor and Rivaroxaban a simple reversed phase (RP) HPLC & UV method to determine simultaneously in pure form and in different pharmaceutical formulations. Spectrophotometric estimation was done by derivative spectroscopic method and methanol as solvent. In this method λ max for Rivaroxaban and Ticagrelor were selected at 295 nm and 249nm. RP-HPLC analysis was carried out using Peerless C18 column and mobile phase composed of Acetonitrile: 10% Ortho-phosphoric acid in water pH 4.0 (60:40% v/v) at a flow rate of 1.0 ml/min and chromatogram was recorded at 249 nm. Linearity was evaluated over the concentration range of 2 -12 µg/ml and 9- 54 µg/ml for Rivaroxaban and Ticagrelor in UV and in RP-HPLC method. Linearity was evaluated over the concentration range of 2 - 4 µg/ml and 9-54 µg/ml for Rivaroxaban and Ticagrelor.

15. Gampa T. Rani et al., Have developed a sensitive, simple and accurate spectrophotometric method for the determination of Ticagrelor in bulk and pharmaceutical dosage form based on the formation of an ion-pair complex between the drug and bromothymol blue in a buffer solution at pH 1.2 (0.1N HCl). The optimum conditions for the analysis of drug is established and Ticagrelor was found to exhibit maximum absorbance at 414nm with chloroform as solvent. The Beer's law is found to be in concentration range of 50-400µg/ml and the regression line equation is Y= 0.0032× - 0.0012 with correlation coefficient of 0.999. The percentage recovery is found to be 100.1-100.8%. The precision is evaluated and relative standard deviation (RSD) is found to be less than 2%. The values of LOD & LOQ are 0.32 & 1.09 respectively.

16. T.P. Aneesh et al., Have developed a simple, precise and cost-effective method for the determination of Ticagrelor in pharmaceutical dosage forms. By using the Phenomenex C18 column on a Shimadzu binary gradient liquid chromatographic system equipped with LC-20AD solvent delivery system, SPD-20A photo diode array detector and rheodyne injector with 20 µl loop volume, the separation was achieved by isocratic method. The mobile phase developed for the estimation of the drug in dosage form and in human plasma contains 70:30% v/v ratio mixture of acetonitrile and methanol at a wavelength 254 nm at a flow rate of 1 ml/min. With a run time of 7 min, the retention time of Ticagrelor was found to be 3.793 min. The drug showed linearity in the range of 10-100 µg/ml with a correlation coefficient (r2) 0.9967. Within the acceptance of ICH, USP guidelines, the results were found. Each solution was injected three times, and %RSD was measured.

17. Livia M. Bueno et al., Have developed a simple, fast and sensitive analytical method by high-performance liquid chromatography (HPLC) for the simultaneous determination of ticagrelor and two synthesis impurities. The HPLC method was performed using an Agilent 1200 series equipment coupled to photodiode array detector (PDA) at 270 nm with a Zorbax Plus C8 column (150 × 4.6 mm, 5.0 µm), injection volume of 20 µl, at constant temperature of 25 °C. A mobile phase consists of acetonitrile: ammonium acetate 50 mm (57:43, v/v) and pH adjusted to 8.2 with ammonium hydroxide 6 M, at a flow rate of 0.7 mL/min. No interference peaks from excipients and diluent system indicated the specificity of the method. By calculating linear regression, the calibration curves showed determination coefficients (r^2) > 0.99. The limit of quantitation (LOQ) for impurities 1 and 2 were 2.0 and 0.2 µg/ml, separately. Intra and inter day relative standard deviations (RSDs) were < 2% for ticagrelor and < 6% for the impurities, proving the precision of the method. Besides, two major degradation products formed when sample solutions of ticagrelor were exposed to UVC radiation were elucidated and the mechanisms involved in the photolytic degradation of ticagrelor were proposed.

18. A.K.M. Pawar et al., Have described a simple, rapid, accurate and precise LC-MS Compatible RP-HPLC method for the determination of Ticagrelor in bulk. Separation of the drug was achieved on Unisol C18 column (100 mm × 4.6 mm, 5 µ) as stationary phase with mobile phase consisting of ammonium acetate buffer pH 4.5 and acetonitrile in the ratio of 40: 60 V/V. The method showed a good linear response in the concentration range of 10-50 µg/mL with correlation coefficient of 0.99. The flow rate was maintained at 1.0 mL/min and effluents were monitored at 250 nm. The retention time was 3.88 min. The method was validated for accuracy, precision, linearity, ruggedness, robustness, solution stability and selectivity. As per the ICH guidelines, the results were obtained within the limits and hence this method can be used for the determination of Ticagrelor in pharmaceutical dosage forms.

19. S.H. Rizwan et al., Have developed a simple, selective and reproducible Reversed-Phase High Performance Liquid Chromatographic (RP-HPLC) method for the estimation of Ticagrelor in Bulk and tablet dosage form, the proposed method was later extended to develop a dissolution method for the analysis of Ticagrelor in immediate release tablets. Analysis was performed on an Agilent 1220 HPLC system using a Qualisil BDS C18 column (250 mm × 4.6 mm, 5 μm particle size) with the mobile phase consisting of Acetonitrile and Water in the ratio (80: 20 v/v) at a flow rate of 1 ml/min. UV detection of the analyte was performed at 254nm. The retention time for Ticagrelor for routine analysis and in dissolution study was found to be 4.30 minutes. The developed method obeyed the basic system suitability parameters i.e. number of theoretical plates, tailing factor and repeatability. The calibration curve was linear showing a correlation coefficient of 0.991. Linearity was in the range of 20 µg/ml to 60 µg/ml. Accuracy of the method was in the range of 99.64 to 100.89%. Precision was found to be 1.74%.

20. Ashwini K. Parida et al., Have developed a reverse phase high performance liquid chromatographic (RP-HPLC) method for the estimation of Ticagrelor in pharmaceutical dosage forms. The chromatographic separation of Ticagrelor was achieved on a Symmetry C18 column (250 mm×4.6 mm, 5 µm particle size), Agilent LC1220 HPLC system with UV detection (VWD detector) at 256nm. The optimized mobile phase was consisted of Phosphate buffer: Methanol (pH adjusted to 4 with orthophosphoric acid) (25:75 v/v). The flow rate was 1 ml/min and effluents were monitored at 256nm. Chromatogram showed the main peak at a retention time of 2.750 min. The linearity was found in the concentration range of 5-50µg/ml. The Correlation coefficient was 0.999. The regression equation was found to be Y = 10290x+3252. The limit of detection and limit of quantitation for estimation of Ticagrelor was found to be 0.4 µg / ml and 1.28 µg / ml respectively. Recovery of Ticagrelor was found to be in the range of 99.57-99.97%.

21. Caren Gobetti et al., Have reported a stability-indicating HPLC method for the determination of ticagrelor in coated tablets. Chromatographic analysis was performed in a Shimadzu liquid chromatograph, equipped with Phenomenex® C18 column (250 x 4.6 mm, 5 µm), using the mobile phase consists of water: acetonitrile with 0.5% triethylamine (57:43 v/v) pH 7.0, at 0.7 ml/min stream rate and infusion volume of 20 µl. Under the given conditions, the method performed was specific, without interference from formulation excipients, stability- indicating, linear (r = 0.999) in the concentration range of 45.0 to 105.0 µg/ml, accurate (99.61% of mean recovery) and precise (%RSD=70%) and robust. It can be applied to ticagrelor tablets quality control, being adequate for routine analysis.

CONCLUSION

Literature survey suggested that various UV, UPLC and HPLC, and few simultaneous methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of the Ticagrelor in pure and pharmaceutical dosage form.

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