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DEVELOPMENT AND VALIDATION OF NEW SIMPLE, SENSITIVE AND VALIDATED RP-HPLC METHOD FOR THE ESTIMATION OF TICAGRELOR IN BULK FORM AND MARKETED FORMULATION

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Abstract:

Objective: The current investigation was pointed at developing and progressively validating novel, simple, responsive and stable RP-HPLC method for the Quantitative Determination of Ticagrelor in active pharmaceutical ingredient and Marketed Pharmaceutical Dosage form.

Methods: A simple, selective, validated and well-defined stability that shows isocratic RP-HPLC methodology for the quantitative determination of Ticagrelor. The chromatographic strategy utilized Phenomenex C18, 250 mm x 4.6 mm i.d.5µm particle size, using isocratic elution with a mobile phase consists of Acetonitrile and Phosphate Buffer (0.01M) (pH-3.2) was taken in the ratio of 35: 65% v/v. A flow rate of 1.0 ml/min and a detector wavelength of 245nm utilizing the UV detector were given in the instrumental settings. Validation of the proposed method was carried out according to an international conference on harmonization (ICH) guidelines.

Results: LOD and LOQ for the active ingredients were established with respect to test concentration. The calibration charts plotted were linear with a regression coefficient of R2>0.999, means the linearity was within the limit. Recovery, specificity, linearity, accuracy, robustness, ruggedness was determined as a part of method validation and the results were found to be within the acceptable range.

Conclusion: The proposed method to be fast, simple, feasible and affordable in assay condition. During stability tests, it can be used for routine analysis of the selected drugs.

Key Words: Ticagrelor, RP-HPLC, Method Development, Validation, Accuracy, Precision.

INTRODUCTION

Ticagrelor is an oral antiplatelet drug that is used with low dose aspirin to decrease the risk of myocardial infarction and stroke in patients with acute coronary syndromes. Ticagrelor has been linked to rare instances of hypersensitivity reactions accompanied by mild liver injury[1]. Ticagrelor, or AZD6140, was first described in the literature in 2003. Ticagrelor is an ADP derivative developed for its P2Y12 receptor antagonism. Unlike Clopidogrel, Ticagrelor is not a prodrug. It is marketed by Astra Zeneca as Brilinta in the US6 and Brilique or Possia in the EU. Ticagrelor is indicated to reduce the risk of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction[2]. Ticagrelor is also indicated to reduce

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the risk of a first myocardial infarction or stroke in high-risk patients with coronary artery disease. Ticagrelor Chemically is (1S, 2S, 3R, 5S)-3-[7-[[(1R, 2S)-2-(3, 4-difluoro phenyl) cyclo propyl] amino]-5-propyl sulfanyl triazolo [4, 5-d] pyrimidin-3-yl]-5-(2-hydroxy ethoxy) cyclo pentane-1, 2-diol[3]. The Chemical Structure of Ticagreloris showing in following

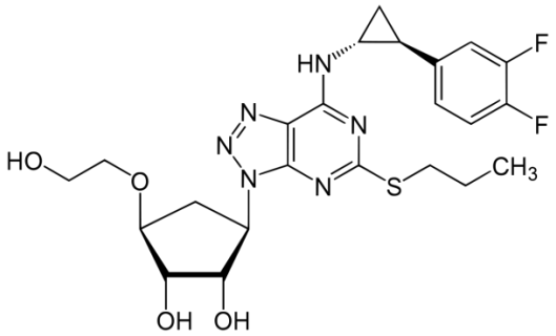


Fig-1: Chemical Structure of Ticagrelor

MATERIALS AND METHODS

Equipments:

Table-1: List of Equipments

S. No.	Instruments/Equipments/Apparatus
1.	HPLC WATERS with Empower2 Software with Isocratic with UV-Visible Detector.
2.	T60-LABINDIA UV – Vis spectrophotometer
3.	High Precision Electronic Balance
4.	Ultra Sonicator (Wensar wuc-2L)
5.	Thermal Oven
6.	Symmetry C18 Column, 250 mm x 4.6 mm and 5µm particle size
7.	PH Analyser (ELICO)
8.	Vaccum Filtration Kit (Labindia)

Chemicals and Reagents:

Table-2: List of Chemicals used

S. No.	Name	Grade	Manufacturer/Supplier
1.	HPLC grade water	HPLC	Sd fine-Chem ltd; Mumbai
2.	Methanol	HPLC	Loba Chem; Mumbai.
3.	Ethanol	A.R.	Sd fine-Chem ltd; Mumbai
4.	Acetonitrile	HPLC	Loba Chem; Mumbai.
5.	DMSO	A.R.	Sd fine-Chem ltd; Mumbai
6.	DMF	A.R.	Sd fine-Chem ltd; Mumbai

HPLC Instrumentation & Conditions: The HPLC system employed was HPLC WATERS with Empower2 Software with Isocratic with UV-Visible Detector4.

Standard Preparation for UV-Spectrophotometer Analysis:

The Standard Stock Solutions – 10 mg of Ticagrelor standard was transferred into 10 ml volumetric flask, dissolved & make up to volume with Methanol. Further dilutions were done by transferring 1 ml of the above solution into a 10ml volumetric flask and make up to volume with methanol to get 10ppm concentration. It scanned in the UV spectrum in the range of 200 to 400nm. This has been performed to know the maxima of Ticagrelor, so that the same wave number can be utilized in HPLC UV detector for estimating the Ticagrelor5.

DIFFERENT TRIALS FOR CHROMATOGRAPHIC CONDITIONS

Table-3: Different Chromatographic Conditions

Column Used	Mobile Phase	Flow Rate	Wave length	Observation	Result
Develosil C18, 250 mm x 4.6 mm and 5µm Column	Acetonitrile : Water = 65 : 35	0.8 ml/min	245nm	Base line noise is high	Method rejected
Develosil C18, 250 mm x 4.6 mm and 5µm Column	Acetonitrile : Water = 55 : 45	0.8ml/min	245nm	Tailing is more	Method rejected
Zorbax C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Acetonitrile = 30 : 70	0.9 ml/min	245nm	Extra peaks	Method rejected
Phenomenex C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Acetonitrile = 60 : 40	1.0 ml/min	245nm	Good sharp peak	Method accepted
Symmetry C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Acetonitrile = 50 : 50	1.0 ml/min	245nm	Improper peak separation	Method rejected
Symmetry C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Phosphate Buffer (0.01M) (pH-2.8) = 40 : 60	1.0 ml/min	245nm	Tailing peaks	Method rejected
Symmetry C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Phosphate Buffer (0.02M) (pH-3.2) = 60 : 40	1.0 ml/min	245nm	Tailing peaks	Method rejected
Symmetry C18, 250 mm x 4.6 mm and 5µm Column	Methanol : Phosphate Buffer (0.02M) (pH-3.8) = 70 : 30	1.0 ml/min	245nm	Proper Peak	Method Accepted

Preparation of 0.01M Phosphate Buffer (pH-3.2): Prepare 800 mL of distilled water in a suitable container. Add 1.36086g of Potassium dihydrogen Phosphate to the solution to the solution. Adjust solution to final desired pH 3.2 using diluted solution of orthophosphoric acid and add distilled water until volume is 1 Liter.

Preparation of Mobile Phase: Mix a mixture of 0.01M Phosphate Buffer (pH-3.2) 750 ml (75%) and 350 ml Acetonitrile HPLC (35%) and degas in ultrasonic water bath for 15 minutes. Filter through 4.5 µ filter under vacuum filtration6.

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Ticagrelor working standard into a 10ml of clean dry volumetric flasks add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette out 0.1ml of Ticagrelor from the above stock solutions into a 10ml volumetric flask and dilute up to the mark with Diluent.

RESULTS AND DISCUSSION

Method Development

Optimized Chromatographic Conditions:

The method was developed using HPLC WATERS equipped with Auto Sampler. The chromatographic conditions were optimized to achieve effective separation, satisfactory peak resolution, and reproducible results during the quantitative estimation of the drug using the RP-HPLC method. The analysis was carried out using a Phenomenex C18 column (250 mm × 4.6 mm i.d., 5 µm particle size) as the stationary phase. The mobile phase consisted of acetonitrile and 0.01 M phosphate buffer adjusted to pH 3.2 in a ratio of 35:65% v/v. The mobile phase was pumped through the column at a constant flow rate of 1.0 mL/min to ensure consistent and efficient elution of the analyte. The detection wavelength was set at 245 nm using a UV detector for suitable analytical response. A sample injection volume of 10 µL was maintained to ensure reproducibility throughout the analysis. The column temperature was maintained at ambient conditions, and the total chromatographic run time was fixed at 7 minutes. These optimized chromatographic conditions were selected for the reliable, accurate, and precise estimation of the drug in bulk and marketed pharmaceutical dosage forms.

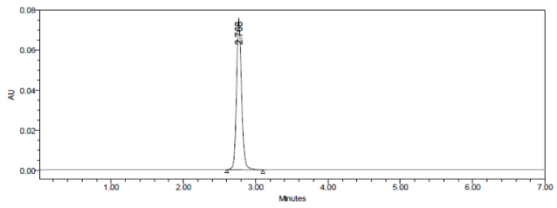


Fig-2: Optimized Chromatogram for Ticagrelor

Observation: The selected and optimized mobile phase was Methanol: Phosphate Buffer (70: 30% v/v) and conditions optimized were flow rate (1.0 ml/minute), wavelength (245nm), Run time was 07 mins. Here the peak has shown better theoretical plate count and symmetry7. The proposed chromatographic conditions were found appropriate for the quantitative determination of the Ticagrelor drug.

Method Validation

System Suitability Test

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. Following system suitability test parameters were established8. The data are shown in Table-4.

Table-4: Data of System Suitability Test

S. No.	Injection No.	RT	Area	Height	USP Plate Count	USP Tailing
1	Injection 1	2.786	715268	47844	5857	1.36
2	Injection 2	2.784	716584	46985	5986	1.38
3	Injection 3	2.768	715364	47258	5784	1.35
4	Injection 4	2.789	714895	47152	5896	1.34
5	Injection 5	2.784	716587	47258	5749	1.36
6	Injection 6	2.781	718549	47985	5657	1.39
Mean			716207.8		5821.5	1.36
S.D			1347.976			
%RSD			0.18821			

Table-5: Acceptance Criteria and Result:

S.No.	Parameter	Limit	Result
1	Tailing factor	T ≤ 2	1.36
2	Theoretical plate	N > 2000	5821.5

Accuracy:

Recovery Study: To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of Ticagrelor were taken and 3 replications of each has been injected to HPLC system9-10. From that percentage recovery values were calculated from the linearity equation y = 74143x + 7294.9. The results were shown in table-6.

Table-6: Accuracy Readings

Sample ID	Concentration (µg/ml)		Peak Area	% Recovery of Pure drug	Mean % Recovery	
	Amount Injected	Amount Recovered				
S1 : 80 %	8	8.013	601425	100.162	Mean = 100.195%	% Mean Recovery = 100.364 %
S2 : 80 %	8	8.012	601396	100.150		
S3 : 80 %	8	8.022	602123	100.275		
S4 : 100 %	10	10.038	751584	100.380	Mean = 100.356	
S5 : 100 %	10	10.039	751642	100.390		
S6 : 100 %	10	10.030	750969	100.300		
S7 : 120 %	12	12.057	901253	100.475	Mean = 100.541	
S8 : 120 %	12	12.073	902431	100.608		
S9 : 120 %	12	12.065	901864	100.541		

Observation: From the Accuracy Method, we observed that the mean %Recovery of the drug is 99.686 which are within the range of 98-102%.

Precision:

Repeatability

The precision of each method was ascertained separately from the peak areas & retention times obtained by actual determination of six replicates of a fixed amount of drug

Ticagrelor (API). The percent relative standard deviation was calculated for Ticagrelor11-12.

Table-7: Results of Repeatability readings

HPLC Injection Replicates of Ticagrelor	Retention Time	Peak Area	Theoretical Plates	Tailing Factor
Replicate – 1	2.777	716984	5986	1.36
Replicate – 2	2.795	715698	5897	1.37
Replicate – 3	2.789	716859	5869	1.39
Replicate – 4	2.797	718548	5967	1.37
Replicate – 5	2.797	714895	5984	1.35
Replicate – 6	2.799	715986	5879	1.38
Average		716495	5930.333	1.37
Standard Deviation		1268.126		
% RSD		0.17699		

Observation: From the Precision method, we observed that the %RSD of the Peak Area is 0.176 which are within the acceptable range as per ICH guidelines30.

Intermediate Precision:

The Intermediate Precision consists of two methods13-14: -

Intra Day: In Intra Day process, the 80%, 100% and 120% concentration are injected at different intervals of time in same day.

Inter Day: In Inter Day process, the 80%, 100% and 120% concentration are injected at same intervals of time in different days.

Intra-Day:

Table-8: Peak results for Intra-Day Precision

S. No.	Name	RT	Area	Height	USP Tailing	USP Plate Count	Injection
1	Ticagrelor	2.784	716587	48685	1.38	5954	1
2	Ticagrelor	2.768	717845	48698	1.39	5935	2
3	Ticagrelor	2.786	716857	46989	1.36	5798	3
4	Average		717096.3	48124	1.376	5895.66	
5	S.D		662.2698				
6	% RSD		0.092354				

Inter-Day:

Table-9: Peak results for Inter-Day Precision

S. No.	Name	RT	Area	Height	USP Tailing	USP Plate Count	Injection
1	Ticagrelor	2.780	716987	49867	1.34	5968	1
2	Ticagrelor	2.794	718695	48574	1.33	5998	2
3	Ticagrelor	2.775	718542	48569	1.39	5859	3
4	Average		718074.7	49003.33	1.353333	5941.667	
5	S.D		945.0483				
6	% RSD		0.131609				

Observations: The intra & inter day variation of the method was carried out for standard deviation & % RSD (% RSD < 2%) within a day & day to day variations for Ticagrelor revealed that the proposed method is precise.

Linearity & Range:

To evaluate the linearity, serial dilution of analyte was prepared from the stock solution was diluted with mobile phase to get a series of concentration ranging from 6-14µg/ml. The prepared solutions were sonicated. From these solutions, 10µl injections of each concentration were injected into the HPLC system and chromatographed under the optimized conditions15. Calibration curve was constructed by plotting the mean peak area (Y-axis) against the concentration (X-axis).

Table-10: Linearity Concentrations of Ticagrelor

S. No.	Concentration (in ppm)	Peak Area
1	0	0
2	6	457896
3	8	607574
4	10	752268
5	12	896587
6	14	1036579

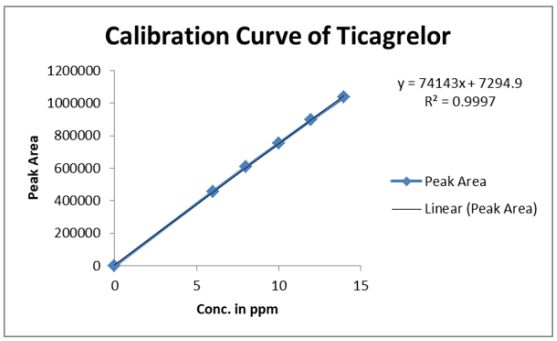


Fig-3: Calibration Curve of Ticagrelor

Observation: We observed that the calibration curve showed good linearity in the range of 6-14 µg/ml, for Ticagrelor with correlation coefficient (R2) of 0.9997. A typical calibration curve has the regression equation of y = 74143x + 7294.9 for Ticagrelor16-17.

Specificity: Specificity of the pharmaceutical analysis is the ability to measure accurately and specifically the concentration of API, without interference from other active ingredients, diluents, mobile phase. Solutions of mobile phase, sample solution, standard solution were injected into liquid

chromatography. Retention times of samples and standard were compared18.

Method Robustness: Influence of small changes in chromatographic conditions such as change in flow rate 1ml (± 0.1ml/min), Wavelength of detection 245nm (±2nm) & organic phase content in mobile phase 60 (±5%) studied to determine the robustness of the method are also in favour of (Table-11, % RSD <2%) the developed RP-HPLC method for the analysis of Ticagrelor (API) 19.

Table-11: Results of Method Robustness Test

Change in Parameter	Theoretical Plates	Tailing Factors
Flow (1.1 ml/min)	5954	1.35
Flow (0.8 ml/min)	6188	1.39
More Organic (70+5)	5748	1.41
Less Organic (70-5)	6185	1.48
Wavelength of Detection (250 nm)	6184	1.69
Wavelength of detection (240nm)	6247	1.47
Temperature (30 0C)	6324	1.34
Temperature (20 0C)	6985	1.32

LOD & LOQ: The detection limit (LOD) and quantization limit (LOQ) may be expressed as:

L.O.D. = 3.3(SD/S).

L.O.Q. = 10(SD/S)

Where, SD = Standard deviation of the response

S = Slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte.

The Minimum concentration level at which the analyte can be reliable detected (LOD) & quantified22 (LOQ) were found to be 0.507 & 1.539 µg/ml respectively20.

Estimation of Ticagrelor in Pharmaceutical Dosage Form

Twenty tablets were taken and the I.P. method was followed to determine the average weight. Above weighed tablets were finally powdered and triturated well. A quantity of powder equivalent to 10 mg of drug were transferred to 10 ml volumetric flask, and 8 ml of mobile phase was added and solution was sonicated for 15 minutes, there after volume was made up to 10 ml with same solvent. Then 1ml of the above solution was diluted to 10 ml with HPLC grade methanol21-23. The solution was filtered through a membrane filter (0.45 µm) and sonicated to degas24. From this stock solution (1.0 ml) was transferred to five different 10 ml volumetric flasks and volume was made up to 10 ml with same solvent system31-34. The solution prepared was injected in five replicates into the HPLC system and the observations were recorded. A duplicate injection of the standard solution was also injected into the HPLC system and the peak areas were recorded. The data are shown in Table-12.

ASSAY

$$\% \text{ Assay} = AT/AS \times WS/DS \times DT/WT \times P/100 \times AW/LC \times 100$$

Where:

AT = Peak Area of Ticagrelor obtained with test preparation

AS = Peak Area of Ticagrelor obtained with standard preparation

WS = Weight of working standard taken in mg

WT = Weight of sample taken in mg

DS = Dilution of Standard solution

DT = Dilution of sample solution

P = Percentage purity of working standard

Results obtained are tabulated below25-26:

Table-12: Assay of Ticagrelor

Brand name of Tablets/Capsules	Labelled amount of Drug (mg)	Mean (±SD) amount (mg) found by the proposed method (n=5)	Assay + % RSD
Brilinta Tablets (AstraZeneca)	90mg	89.685 (± 0.487)	99.389 % (± 0.635)

Observation: The %Purity of Brilinta Tablets containing Ticagrelor was found to be 99.389% (± 0.635).

SUMMARY AND CONCLUSION

In the present investigation, a simple, sensitive, accurate, precise, and reproducible RP-HPLC method was successfully developed and validated for the quantitative estimation of Ticagrelor in bulk drug and marketed pharmaceutical dosage forms. The chromatographic conditions were optimized using a Phenomenex C18, 250 mm x 4.6 mm i.d., 5µm particle size with a mobile phase consisting of Acetonitrile and 0.01 M phosphate buffer (pH 3.2) in the ratio of 35:65% v/v. The flow rate was maintained at 1.0 mL/min, with UV detection at 245 nm, an injection volume of 10 µL, and a total run time of 7 minutes. The retention time of Ticagrelor was found to be approximately 2.768 minutes. The method exhibited good linearity over the concentration range of 6–14 ppm, with percentage recovery within 98.0–102.0%, indicating

satisfactory accuracy. System suitability, precision, robustness, and ruggedness studies demonstrated acceptable results, with percentage RSD values within the prescribed limits. The developed method was found to be economical, reliable, and suitable for routine quality control analysis of Ticagrelor in bulk and pharmaceutical dosage forms. Therefore, the proposed RP-HPLC method can be effectively employed for the routine quantitative determination of Ticagrelor in bulk and pharmaceutical formulations.

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