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ANALYTICAL METHODS OF TICAGRELOR: A REVIEW

G. Nikitha and A. Ajitha *

Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Analysis, CMR College of Pharmacy, Medchal, Hyderabad – 501401, Telangana, India.

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Correspondence to Author:
Ajitha Azhakesan

Department of Pharmaceutical Analysis, Faculty of Pharmaceutical Analysis, CMR college of Pharmacy, Medchal, Hyderabad – 501401, Telangana, India.

E-mail: ajithaazhakesan27@gmail.com

ABSTRACT: Ticagrelor is a platelet aggregation inhibitor. It is used for the prevention of stroke, heart attack, and other events in people with the acute coronary syndrome, meaning problems with the blood supply in the coronary arteries. It acts as a platelet aggregation inhibitor by antagonising the P2Y 12 receptor. Its half-life is up to 12 h with the hepatic type of metabolism and biliary excretion. This review provides the pharmacokinetic and pharmacodynamics of the Ticagrelor, which also includes the review on pharmaceutical analytical techniques like High-performance liquid chromatography, Reverse phase - High-performance liquid chromatography, Bio-analytical techniques, UV spectrometry with the impurities, pharmaceutical dosage forms, bulk, and its formulations used for determination and validation. This review helps us to get updated information on validation of drug-Ticagrelor till current date.

INTRODUCTION: Ticagrelor is a platelet aggregation inhibitor. Ticagrelor is used to treat the acute coronary syndrome. Ticagrelor directly inhibits the Adenosine Diphosphate (ADP) receptors which prevent signal transduction and platelet activation without first undergoing hepatic activation [1-2]. It is a small molecule, and the Average weight of Ticagrelor is 522.568, and its chemical formula is $C_{23}H_{28}F_2N_6O_4S$. The chemical name of Ticagrelor(1S, 2S, 3R, 5S)-3-[7-[[(1R, 2S)-2-(3, 4-difluorophenyl) cyclopropyl]amino]-5-propylsulfanyltriazolo[4,5-d] pyrimidin -3-yl]-5-(2-hydroxy-ethoxy) cyclopentane-1, 2-diol [3]. Ticagrelor has a plasma half-life of approximately 8 h, while the active metabolite has a plasma half-life of approximately 12 h [4]. The chemical structure of Ticagrelor was given in below **Fig. 1**.

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Pharmacokinetic: Pharmacokinetic involves Absorption, Distribution, Metabolism & Excretion.

Absorption: Ticagrelor is an orally administered, reversibly binding, and direct-acting P2Y12 receptor antagonist [5].

Distribution: - Volume of distribution of ticagrelor is 88 L [4].

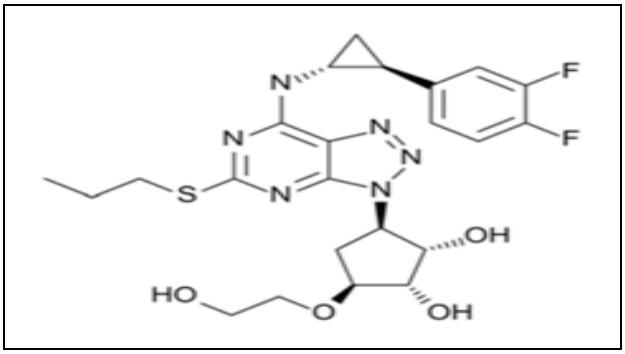

FIG. 1: STRUCTURE OF TICAGRELOR

Metabolism: Ticagrelor is metabolized by the cytochrome P450 (CYP) enzyme to AR-C124910XX, a metabolite that possesses equivalent antiplatelet potency as the parent drug [5].

Excretion: The primary route of ticagrelor elimination is hepatic metabolism [6]. Ticagrelor is mainly excreted in the faeces, with renal excretion laying only a minor role; the primary route of excretion for the active metabolite is most likely biliary secretion [7].

Pharmacodynamics: The inhibition of platelet aggregation (IPA) by ticagrelor is acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist [6].

Drug Interactions: Ticagrelor and AR-C124910XX are principally metabolized by CYP3A4 and, minorly, by CYP3A5 enzymes [7].

Mechanism of Action: Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation.

Ticagrelor and its active metabolite are approximately equipotent [6].

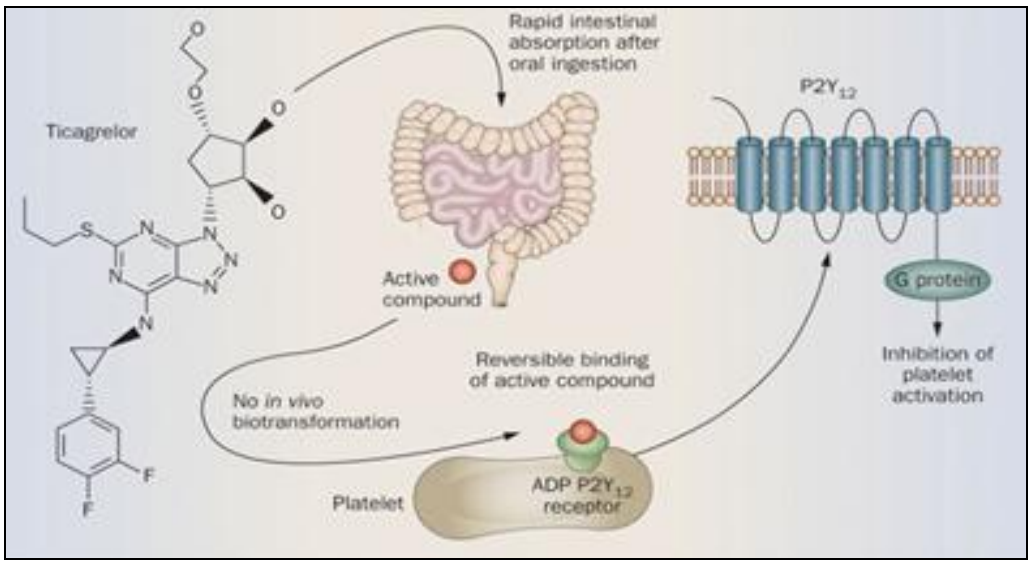

Fig. 2: MECHANISM OF ACTION OF TICAGRELOR

TABLE 1: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR BY HPLC METHOD

Sl. no	Research work	Description	Ref.no
1	Application of Quality by Design to optimize a stability-indicating LC method for the determination of ticagrelor and its impurities	Detector: Diode array detectors Detection: 225 nm	8
2	Analytical Method Development and Validation of Ticagrelor from Bulk and Formulation	Stationary Phase: C18 (250 x 4.6 mm i.d., 5μ) Mobile phase: ACN: Methanol (85:15 v/v) Flow rate 1.0 ml/min Detector : PDA Run time 7 min Correlation Co-efficient: 0.999 LOD : 0.20 μg/ml LOQ : 0.61 μg/ml	9
3	A chiral stationary phase HPLC method for determining ticagrelor isomers in ticagrelor tablets	Stationary phase: CHIRALPAK IA (250 mm×4.6 mm, 5 μm) Mobile phase: n-hexane-methanol-ethanol-acetic acid (800:100:100:1) Flow rate: 0.8 mL·min^{-1} Detection: 255 nm Correction coefficients : >0.999 LOD: 0.1 μg·mL^{-1} LOQ: 0.2~0.4 μg·mL^{-1}	10
4	Method Development, Validation and Impurity Profiling of Ticagrelor by Acid Degradation Method	Forced degradation under acidic condition Stationary phase: Cosmocil C18 (250 x 4.6 mm i.d., 5 μ) Mobile phase: 0.1% Formic acid:ACN(55:45%v/v)	11

		Flow rate : 1.0 ml/min Detection : 254 nm Acid degradant isolation Stationary phase: Thermo (100 x 10mm i.d., 5µ) Hypersil Flow rate: 4.0 ml/min	
5	HPLC method for simultaneous analysis of ticagrelor and its organic impurities and identification of two major photodegradation products	Stationary phase: Zorbax Plus C_8 column (150 × 4.6 mm, 5.0 µm) Mobile phase: of acetonitrile: ammonium acetate 50 mM (57:43v/v) Detector: photodiode array detector Detection: 270 nm Flow rate: 0.7ml/min Correlation coefficient : > 0.99	12
6	Determination of the New Antiplatelet Agent Ticagrelor in Tablets by Stability-Indicating HPLC Method	Stationary phase : Phemomenex® C18 column (250 x 4.6 mm, 5 µm) Mobile phase: acetonitrile: water with 0.5% triethylamine (57:43 v/v) Flow rate: 7.0, at 0.7 ml/min Injection volume: 20 µl	13
7	A Validated Stability- indicating HPLC method for determination of Ticagrelor in bulk and its formulation	Stationary phase: Hypersil BDS C18 column (100 mm Ã— 4.6 mm, 5 Î¼) Mobile phase: phosphate buffer: acetonitrile(70: 30 V/V) correlation coefficient : 0.999 Flow rate: 1.0 ml/min Retention time: 3.215 min. Detection: 254 nm	14

Table 1 helps to seek the Literature review of Ticagrelor on the HPLC method with its impurities and bulk and its formulation.

Table 2 helps to seek the Literature review of Ticagrelor on the RP-HPLC method with its bulk and formulation, and dosage form.

TABLE 2: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR BY RP-HPLC METHOD

S. no	Research work	Description	Ref.no
1	RP-HPLC and UV spectrophotometric methods for the estimation of Ticagrelor in pharmaceutical formulations	Stationary phase : Thermo C18 (250 × 4.6 mm, 5µm) mobile phase : KH2PO4: acetonitrile (20:80 v/v) Flow rate : 1.0 ml/min retention time : 8.102 ± 0.3 min correlation coefficient : 0.999	15
2	Development and validation of stability indicating RP-HPLC Method for the estimation of Ticagrelor in the formulation	Stationary phase: C18G (250 × 4.6 mm) Mobile phase: methanol acid: water (20:80 v/v) Flow rate : 1.0 ml/min Detection: 254 nm retention time : 5.786 min correlation coefficient 0.99	16
3	A Novel Validated RP-HPLC method for the estimation of Ticagrelor in Bulk and Pharmaceutical Dosage Forms	Stationary phase : symmetry C18 column (250mmx4.6mm, 5µm) mobile phase : Methanol: phosphate buffer (75:25v/v) Detector : VWD detector Detection : 256 nm Flow rate : 1.0 ml/min retention time : 2.750 min correlation coefficient 0.999 LOD : 0.4 µg/ml LOQ : 1. 28 µg/ml	17

4	Analytical method development and validation studies of ticagrelor tablets by RP-HPLC	Stationary phase: Kromasil, 250×4.6 mm, 5 µ mobile phase: aqueous buffer (containing 0.5 ml formic acid and triethylamine each in water) and acetonitrile in the ratio of 50:50 v/v flow rate : 1.3 ml/min detection : 256 nm run time: 6 min Retention time: 3.372 min. range: 20-90 ppm correlation coefficient : 0.9956 specific recovery: 99.93% % RSD of precision: 0.069.	18
5	An LC-MS compatible RP-HPLC method for the determination of ticagrelor in bulk	Stationary phase : Unisol C18 column (100 mm × 4.6 mm, 5 µ) mobile phase : ammonium acetate : acetonitrile (40: 60 V/V) correlation coefficient : 0.99 Flow rate : 1.0 ml/min Detection : 250 nm retention time : 3.88 min	19
6	Analytical method development and validation of stability-indicating assay method of Ticagrelor tablets by using RP-HPLC	Stationary phase : Develosil ODS UG-5 C18 (150 X 4.6mm, 5µ particle size) mobile phase : potassium dihydrogen phosphate buffer: acetonitrile (60:40, v/v) flow rate : 1 ml/min Detector : PDA detector Detection : 280 nm retention time : 5.35 min correlation coefficient : 0.9992 LOD : 0. 05 µg/ml LOQ : 0.15 µg/ml	20
7	A new-RP-HPLC method development and validation for the estimation of ticagrelor in bulk and formulation and its extension to dissolution studies	Stationary phase : Qualisil BDS C18 column (250mm × 4.6 mm, 5 μm particle size) mobile phase : Acetonitrile : Water (80: 20 v/v) Flow rate : 1.0 ml/min Detector : UV detector Detection : 254 nm retention time : 4.30 min correlation coefficient : 0.991	21
8	Analytical method development and validation for the estimation of a Ticagrelor in drug substance by RP-HPLC method	Stationary phase : C18 column (Inertsil ODS 3V 150*4.6, 5um) mobile phase : 0.1%v/v Formic acid in water : Methanol (10:90) Flow rate : 1.0 ml/min Detector : UV detector detection : 220 nm retention time : 2.71 min	22
9	Method development and validation for the estimation of a Ticagrelor in bulk and comparison with other published methods	Stationary phase: C18 Vydac Monomeric 120A (5.0 micron, 250 x 4.6mm) mobile phase : Acetonitrile: Water Milli Q (60:40v/v) Detector: PDA detector Flow rate : 1.0 ml/min correlation coefficient 0.997 LOD : 0.083 µg/ml LOQ : 0.25 µg/ml	23
10	Development and validation of RP- HPLC method for determination of ticagrelor in pharmaceutical dosage formulation	Stationary phase : phenomenex C18 mobile phase : acetonitrile : methanol (70:30% v/v) Flow rate : 1.0 ml/min Detector : SPD-20A photo diode array detector	24

		Detection : 254 nm retention time : 3.793 min run time : 7 min correlation coefficient 0.9967	
11	An improved assay method for the estimation of Ticagrelor hydrochloride by reverse phase liquid chromatography	Stationary phase : on ZORBAX Eclipse Plus 300SB C18 (250 x 4.6mm, 5.0 micron) mobile phase : Acetonitrile : 20mM Potassium dihydrogen ortho phosphate buffer (40:60 v/v) flow rate : 1.0 ml/min correlation coefficient : 0.9995 LOD : 0.05µg/ml LOQ : 0.20µg/ml	25
12	Development and validation of RP-HPLC method for estimation of Ticagrelor in bulk form	Stationary phase : Primesil C18 column (Length: 250nm, Diameter:4.6nm) mobile phase: methanol and Water (95:05 v/v) retention time: 4.5 min correlation coefficient : 0.997	26

TABLE 3: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR BIO-ANALYTICAL METHOD

S. no	Research work	Description	Ref. no
1	Liquid Chromatography-Tandem Mass Spectrometry Method for Ticagrelor and its Active Metabolite Determination in Human Plasma: Application to a Pharmacokinetic Study	Mobile phase : formic acid 0.1% : acetonitrile Elution : < 4 min Quantification : <2 ng/mL	27
2	Ultra-fast liquid chromatography method for the determination of ticagrelor in pharmaceutical formulations and spiked plasma samples	Stationary phase : C18 column (100 × 4mm, 3µm) mobile phase : acetonitrile : phosphoric acid solution(55:45, v/v) flow rate : 0.7 mL/min detection wavelength : 254 nm Detector : photo-diode array Retention time : 3.5 min correlation coefficient : 0.9996	28
3	Simultaneous quantification of ticagrelor and its active metabolite, AR-C124910XX, in human plasma by liquid chromatography-tandem mass spectrometry: Applications in steady-state pharmacokinetics in patients	Stationary phase : Acclaim™ RSLC 120 C18 column (2.2 µm, 2.1 × 100 mm) mobile phase: acetonitrile-water containing 0.1% formic acid	29
4	Development and Validation of Simple LC-MS-MS Assay for the Quantitative Determination of Ticagrelor in Human Plasma: its Application to a Bioequivalence Study	Stationary phase : a Phenomenex Luna® mobile phase : 0.1% formic acid in water-acetonitrile (20:80, v/v) Flow rate: 0.2 mL/min. retention time : 1.03 min correlation coefficient (r) : ≥ 0.9991 range : 2-1,500 ng/mL Intra & inter-day precisions : 1.0% - 4.9% & 1.8% - 8.7% accuracy : 97.0% -105.9% & 97.5% to 102.9%,	30
5	Validated liquid chromatography-tandem mass spectrometry method for quantification of ticagrelor and its active metabolite in human plasma	Stationary phase: Dikma C_{18} Mobile phase : Acetonitrile and 5 mM ammonium acetate Flow rate : 0.5 mL/min correlation coefficient : ≥0.994 intra- and inter-day precisions : within 12.61% accuracy : within ±7.88%	31

6	Development of an LC-MS/MS method for simultaneous determination of ticagrelor and its active metabolite during concomitant treatment with atorvastatin	Stationary phase: Kinetex XB-C18 c Range : 1.25-2000 ng/mL Mobile phase : water and acetonitrile with 0.1% formic acid, 57:43, v/v	32
7	Bioanalytical method development and validation of Ticagrelor by RP-HPLC	Stationary phase : phenomenex C18 column mobile phase : acetonitrile : methanol (60:40% v/v) Detector : SPD-20-A photo-diode array flow rate : 1 ml/min detection wavelength : 254 nm Retention time : 4.503 min Run time : 10 min correlation coefficient : 0.9992	33
8	Simultaneous Determination of Ticagrelor and Its Metabolites in Human Plasma and Urine Using Liquid Chromatography-Tandem mass spectrometry	Stationary phase : Ultimate XB-C18 column (2.1 mm × 150 mm, 3 μm) mobile phase : aqueous ammonium acetate (0.025 mM):acetonitrile (35 : 65, v:v) intra- and inter-assay precisions : ≤14.6% range : 98.3–110.7%	34
9	Simultaneous quantification of ticagrelor and its metabolite deshydroxyethoxy ticagrelor in human plasma by ultra-performance liquid chromatography electrospray ionization-tandem mass spectrometr	Stationary phase : Eclipse XDB-C8 5μm 4.6*150mm mobile phase : Acetonitrile : 0.1% Formic acid flow rate : 1.0 ml/min run time : 3.0 min correlation coefficient : 0.99 LOD : 0.5 ng/Ml	35
10	Determination of unbound ticagrelor and its active metabolite (AR-C124910XX) in human plasma by equilibrium dialysis and LC-MS/MS	ranges : 5-5000 ng/ml	36
11	Determination of ticagrelor and two metabolites in plasma samples by liquid chromatography and mass spectrometry	detection: atmospheric pressure chemical ionization run time: 2 min range : 5-5000 ng/mL LOQ : 5 ng/ml	37
12	Ultra-fast liquid chromatographic method for the determination of ticagrelor in pharmaceutical formulations and spiked plasma samples	Stationary phase : C18 column (100 × 4mm, 3μm) mobile phase : acetonitrile and phosphoric acid solution(55:45, v/v) flow rate : 0.7 ml/min Detection : 254 nm Detector : photodiode array detector (PDA) retention time : 3.5 min correlation coefficient : 0.9996	38

Table 3 helps to seek the Literature review of Ticagrelor on Bio-Analytical method with its formulation and plasma samples.

Table 4 helps to seek the Literature review of Ticagrelor on UV-Spectrophotometric method with its dosage form and bulk and formulation.

TABLE 4: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR UV-SPECTROPHOTOMETRIC METHOD

Sl. no	Research work	Description	Ref.no
1	Development and Validation of UV Spectrophotometric Method for the Estimation of Ticagrelor (Oral Antiplatelet (OAP) in Pharmaceutical Dosage Form	λmax : 255 nm correlation coefficient : 0.9999 LOD : 0.18962 LOQ : 0.57462	39
2	Analytical Method Development and Validation of Ticagrelor from Bulk and Formulation	λmax : 255 nm	9

3	Method Development and validation of ticagrelor an antiplatelet drug by spectrometry in bulk drug and pharmaceutical formulation	λ max : 430nm correlation coefficient : 0.999	40
4	RP-HPLC and UV spectrophotometric methods for the estimation of Ticagrelor in pharmaceutical formulations	λ max : 282 nm correlation coefficient : 0.999	41
5	Development and Validation of new spectrophotometric method for the determination of Ticagrelor in bulk and pharmaceutical formulation	λmax : 414 nm range : 50-400µg/ml correlation coefficient : 0.999 LOD : 0.32 LOQ : 1.09	42
6	Assaying the Antiplatelet Ticagrelor by Validated UV Spectrophotometric method with performance equivalent to HPLC	λ max: 255nm correlation coefficient : 0.9996	43
7	UV-Vis spectrophotometric assay determination of oral antiplatelet ticagrelor drug in pharmaceutical formulation: Application to content uniformity	λmax: 222 nm Mobile phase : methanol: water (1:1 v/v) Beer's Range : 8 - 32 (µg/ml) Detector : UV detector Correlation coefficient = 0.9994 LOD : 0.30 (µg/ml) LOQ : 0.90 (µg/ml)	44
8	A validated stability indicating method of UV-Spectrophotometry for the estimation of ticagrelor in bulk & marketed formulation	λmax: 237nm correlation coefficient : 0.9855	45
9	Development and validation of a UV spectrophotometric method for the determination of ticagrelor in bulk form.	λmax : 224 &255 nm range : 2-7µg/mL correlation coefficient : 0.998 LOD : 0.05 µg/ml LOQ : 0.20 µg/ml	46

TABLE 5: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD

S. no	Research work	Description	Ref.no
	Development and validation of stability indicating UPLC method for the estimation of ticagrelor in bulk and its tablet dosage form	Stationary phase: BEH C_{18}100 mm x 2.1 mm, 1.8 µ. mobile phase : buffer: acetonitrile (65:35) flow rate : 1.0 ml/min detection : 240 nm correlation coefficient : 0.999 LOD : 0.32 µg/ml LOQ : 0.96 µg/ml	**47**

TABLE 6: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TICAGRELOR HIGH-PERFORMANCE THIN LIQUID CHROMATOGRAPHY METHOD

S. no	Research work	Description	Ref. no
1	Stability indicating HPTLC method for the estimation of ticagrelor in bulk and in pharmaceutical dosage form	Stationary phase: aluminum plates precoated with silica gel 60 F254 mobile phase : toluene: Ethyl acetate: Acetic acid (5:4:1V/V/V) LOD : 0.826 ng/ band LOQ : 2.64 ng/band	48

Table 5 helps to seek the Literature review of Ticagrelor on Ultra performance liquid chromatography method with its bulk and tablet dosage form.

Table 6 helps to seek the Literature review of Ticagrelor on the High-performance thin liquid chromatography method with its pharmaceutical dosage form.

TABLE 7: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF SIMULTANEOUS TICAGRELOR AND RIVAAOXABAN UV SPECTROPHOTOMETRIC METHOD

S. no	Research work	Description	Ref.no
1	Development and validation of first UV spectrophotometric method and RP-HPLC method for simultaneous estimation of rivaroxaban and ticagrelor in synthetic mixture	λ max : 249nm Correlation coefficient : 0.9989	49

Table 7 helps to seek the Literature review of Simultaneous Ticagrelor and rivaroxaban on UV spectrophotometric method with a synthetic mixture

Table 8 helps to seek the Literature review of Simultaneous Ticagrelor and rivaroxaban on RP-HPLC method with a synthetic mixture

TABLE 8: ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF SIMULTANEOUS TICAGRELOR AND RIVAAOXABAN RP-HPLC METHOD

S. no	Research work	Description	Ref.no
1	Development and validation of first UV spectrophotometric method and RP-HPLC method for simultaneous estimation of rivaroxaban and ticagrelor in synthetic mixture	Stationary phase : Pearless C-18 column (4.6 x 250 mm, 5µ particle size) mobile phase : Acetonitrile: 10% Ortho-phosphoric acid (60:40% v/v) flow rate : 1.0 ml/min Detection : 249 nm Correlation coefficient : 0.9991	49

CONCLUSION: These reviews furnish the outline of chromatographic, bio-analytical, and spectro-scopic methods developed and validated for the estimation of ticagrelor. Consequently this all methods were found to be simple, accurate, and precise. This information certainly helps the researchers for their research work and to the students who would like to know them extensively.

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