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RECENT ANALYTICAL TRENDS IN TICAGRELOR QUANTIFICATION IN PHARMACEUTICAL AND BIOLOGICAL MATRICES: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Ticagrelor is a direct-acting, reversible oral $P2Y_{12}$ receptor antagonist widely prescribed for the prevention of thrombotic events in patients with acute coronary syndromes. Given its clinical relevance, accurate quantification in both pharmaceutical and biological matrices is essential for quality control, pharmacokinetic profiling, and bioequivalence studies.

Objective: This review aims to systematically compile and evaluate the various analytical methods developed for the estimation of Ticagrelor, highlighting methodological advances, validation performance, and matrix-specific considerations.

Methods: Peer-reviewed literature from 2014 to 2024 was collected using scientific databases such as PubMed, ScienceDirect, and Google Scholar. Studies employing techniques such as UV spectrophotometry, RP-HPLC, UPLC, HPTLC, and LC-MS/MS were reviewed and compared based on sample matrix, method sensitivity, linearity, and sample preparation approaches.

Results: UV spectrophotometric methods offer simplicity and cost-effectiveness for routine analysis in bulk and dosage forms. RP-HPLC remains the most widely employed technique for tablet analysis due to its balance of precision, speed, and accessibility. In contrast, LC-MS/MS methods, especially those with triple quadrupole configurations, are preferred for plasma

analysis owing to their high sensitivity, with LLOQs as low as 0.78 ng/mL. Several methods incorporated quality by design (QbD), green solvents, and stability-indicating capabilities.

Conclusion: A diverse array of validated analytical techniques exists for Ticagrelor estimation, each suited for specific applications. However, opportunities remain for the development of faster, greener, and more automated methods for high-throughput analysis. This review offers a practical reference for researchers and analysts in pharmaceutical and clinical laboratories.

Keywords: Ticagrelor, RP-HPLC, LC-MS/MS, UV spectrophotometry, Bioanalysis, Sample Preparation, Method Validation

1. INTRODUCTION :

Ticagrelor, a member of the cyclopentyl-triazolopyrimidine class, is a potent oral antiplatelet agent that selectively and reversibly inhibits the $P2Y_{12}$ receptor. Unlike thienopyridines such as clopidogrel, Ticagrelor does not require metabolic activation, allowing for a faster onset of action and more predictable pharmacodynamics. It is primarily indicated in the management of acute coronary syndromes (ACS) and is often used in dual antiplatelet therapy with aspirin. The molecular structure of Ticagrelor is shown in **Figure 1**.

As its clinical use has grown, so has the need for reliable analytical methods to quantify Ticagrelor in bulk drug, pharmaceutical formulations, and biological matrices such as plasma. These methods support not only routine quality control and batch release but also therapeutic drug monitoring and pharmacokinetic studies during clinical trials. Over the past decade, numerous analytical techniques have been reported, ranging from simple UV spectrophotometric assays to more advanced liquid chromatography-tandem mass spectrometry (LC-MS/MS) procedures.

UV-visible spectrophotometric methods offer simplicity and affordability for estimation in tablet dosage forms **[5, 12, 13]**. RP-HPLC methods dominate pharmaceutical analysis due to their robustness and moderate sensitivity, with various modifications reported for improved linearity and precision **[1–4, 9–11]**. Stability-indicating HPLC and HPTLC methods have also been developed to assess degradation and impurity profiling **[6, 18]**.

In plasma and other biological matrices, LC-MS/MS has emerged as the method of choice due to its high sensitivity and specificity. Multiple studies have demonstrated the successful use of LC-MS/MS for bioanalytical quantification of Ticagrelor and its active metabolite AR-C124910XX **[3, 15, 19, 20]**. These methods often utilize solid-phase or protein precipitation techniques to ensure clean extraction and reproducible results.

This systematic review provides a comprehensive analysis of published analytical methods for Ticagrelor, with a focus on their performance characteristics, suitability for different matrices, and potential for application in routine pharmaceutical and clinical settings.

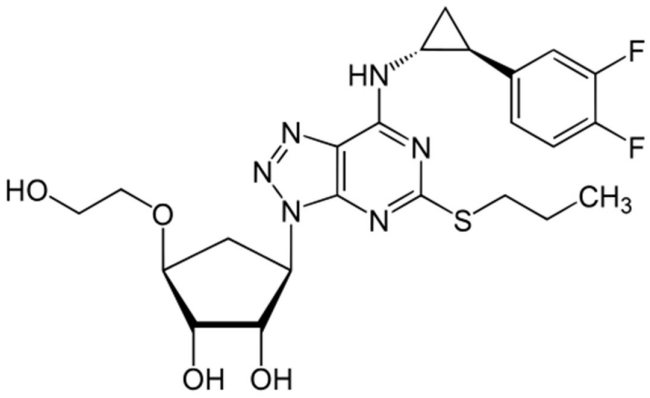

Figure 1: Chemical structure of Ticagrelor

2. PHYSIOCHEMICAL PROPERTIES:

Ticagrelor is chemically classified as a cyclopentyl-triazolo-pyrimidine derivative and functions as a selective, reversible $P2Y_{12}$ receptor antagonist. It is structurally distinct from thienopyridines (e.g., clopidogrel) and is administered orally in the treatment of acute coronary syndromes. Its IUPAC name is:

(1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

Ticagrelor is metabolized primarily by cytochrome P450 3A4 into an active metabolite, AR-C124910XX, which retains similar antiplatelet activity. The poor water solubility of Ticagrelor presents challenges for formulation and analysis, often necessitating the use of organic solvents such as methanol, acetonitrile, or DMSO during sample preparation. It is chemically stable under acidic and neutral pH but may undergo degradation under alkaline or oxidative conditions.

Given its BCS Class IV designation, the analytical determination of Ticagrelor in formulations and biological fluids demands highly sensitive and selective techniques. These physicochemical features are critical considerations during method development, particularly for extraction efficiency, chromatographic separation, and detection sensitivity. The key properties of Ticagrelor is shown in **Table 1**.

Table 1: Key Properties of Ticagrelor

Property	Value / Description
Molecular Formula	$C_{23}H_{28}F_2N_6O_4S$
Molecular Weight	522.57 g/mol
Appearance	White to off-white crystalline powder
Melting Point	Approximately 138–140 °C
Solubility	Practically insoluble in water; freely soluble in DMSO and ACN
Log P (octanol/water)	~2.3 (moderate lipophilicity)
pKa	Predicted ~1.5 (acidic OH), ~12.8 (basic nitrogen)
BCS Classification	Class IV (low solubility, low permeability)
Storage Conditions	Store in a cool, dry place; protected from light and moisture
UV Absorption Max (λ max)	~254 nm in methanol (used in UV/HPLC methods)

3. ANALYTICAL METHODS:

A wide range of analytical methods have been employed for the estimation of Ticagrelor in pharmaceutical dosage forms and biological matrices. These include UV-Visible spectrophotometry, RP-HPLC, UPLC, HPLC-DAD, HPTLC, and LC-MS/MS. Each method has its own set of advantages, limitations, and applications, depending on the sample matrix and analytical requirements.

3.1 Methods for Pharmaceutical Dosage Forms

3.1.1 UV-Visible Spectrophotometry

This method is based on the absorption of UV light by Ticagrelor in a suitable solvent. It is widely used due to its simplicity, cost-effectiveness, and suitability for routine quality control. λmax is typically around 254–255 nm. Solvents include methanol, ethanol, and water. These methods are not suitable for biological samples due to interference from plasma components. Methods have been reported with moderate sensitivity, such as LOD = 0.495 µg/mL and LOQ = 1.502 µg/mL **[12]**, and qualitative methods without LOD/LOQ **[13, 5]**.

3.1.2 Reversed-Phase HPLC (RP-HPLC)

RP-HPLC is the most commonly reported and validated technique for Ticagrelor quantification in tablet dosage forms due to its high precision, accuracy, and reproducibility. Mobile phases include combinations of methanol, acetonitrile, buffers (like phosphate or formic acid), and water. Most methods use C18 columns of different brands (Shim-Pack, Kromasil, Nova-Pak, etc.).Flow rates are generally set at 1.0 mL/min, with UV detection in the 220–280 nm range. LODs as low as 0.045 µg/mL have been reported **[16]**, with others reporting LODs around 0.204 µg/mL **[1]**, 0.05 µg/mL [5], and 0.070 µg/mL **[17]**. Stability-indicating methods capable of separating degradation products were also developed **[6, 9, 10]**. Simpler formulations without degradation studies are also available **[2, 4, 7, 8]**.

3.1.3 Ultra-Performance Liquid Chromatography (UPLC)

UPLC is an advanced version of HPLC that uses smaller particle-size columns to achieve better resolution and shorter run times. A method was developed using a

BEH C18 column (100×2.1 mm, 1.8 µm) with a buffer: ACN (65:35) mobile phase **[11]**. LOD and LOQ were reported as 0.32 µg/mL and 0.96 µg/mL, respectively. This technique is ideal for high-throughput environments.

3.1.4 HPLC-DAD

Diode Array Detection (DAD) provides wavelength flexibility and helps confirm the identity and purity of peaks.A method using C18 and ACN:Water (65:35) with detection at 255 nm was reported **[19]**. LOD = 0.090 µg/mL and LOQ = 0.270 µg/mL.Useful when peak purity is important, such as in method validation and degradation studies.

3.1.5 High-Performance Thin-Layer Chromatography (HPTLC)

HPTLC is a planar chromatography technique that is faster and less solvent-intensive than column-based methods. A validated method using Silica Gel 60 F254 and a solvent system of toluene:ethyl acetate:methanol:formic acid (6:3:0.5:0.5) was reported **[18]**. Detection at 254 nm with LOD = 0.080 µg/mL and LOQ = 0.240 µg/mL.Suitable for cost-effective, high-throughput estimation of drugs in solid dosage forms.

3.2 Bioanalytical Methods for Biological Matrices

3.2.1 RP-HPLC in Plasma

HPLC with UV detection can be used in plasma analysis, though it lacks the sensitivity of MS-based techniques. Deeksha *et al*. **[3]** used Vydac C18 with ACN:Water (60:40) and achieved LOD = 0.083 µg/mL, LOQ = 0.25 µg/mL.Another method used C18 with ACN:Methanol (60:40) and 254 nm detection **[14]**. These methods often require sample pre-treatment steps like protein precipitation.

3.2.2 LC-MS/MS (Triple Quadrupole MS)

LC-MS/MS is the gold standard for analyzing Ticagrelor in plasma due to its ultra-high sensitivity, specificity, and suitability for pharmacokinetic studies.Most methods use C18 columns with mobile phases like NH_4Ac:ACN or formic acid in water:ACN. Yadav *et al*. **[15]** developed a validated method using NH_4Ac:ACN, achieving accurate plasma quantification. Singh *et al*. **[20]** developed a triple quadrupole LC-MS method with LOD = 0.030 µg/mL and LOQ = 0.090 µg/mL, the most sensitive reported. Sample prep involved protein precipitation, ensuring clean extracts for injection. The summary of analytical methods for the estimation of Ticagrelor is presented in **Table 2**. The distribution of sample matrices used in Ticagrelor quantification from 2014 to 2023 is shown in **Figure 2**.

Table 2: Summary of Analytical Methods for the Estimation of Ticagrelor

No.	Matrix	Technique	Mobile Phase	Column (Stationary Phase)	Detection wavelength (nm)	Flow Rate (mL/min)	LOD (µg/mL)	LOQ (µg/mL)	Reference
1	Tablet	RP-HPLC	MeOH: ACN:0.1% OPA (90:5:5 v/v/v)	Shim-Pack C18 (250×4.5 mm, 5 µm)	255	1.0	0.204	0.618	1
2	Tablet	RP-HPLC	MeOH: Water (95:5 v/v)	Primesil C18 (250×4.6 mm, 5 µm)	252	1.0	NA	NA	2
3	Plasma	RP-HPLC	ACN : Water (60:40 v/v)	Vydac C18 (250×4.6 mm, 5 µm)	NA	1.0	0.083	0.25	3
4	Tablet	RP-HPLC	Buffer: ACN (50:50 v/v)	Kromasil C18 (250×4.6 mm, 5 µm)	256	1.3	NA	NA	4
5	Tablet	RP-HPLC	KH_2PO_4 buffer: ACN (60:40 v/v)	ODS UG-5 C18 (150×4.6 mm, 5 µm)	280	1.0	0.05	0.15	5
6	Tablet	RP-HPLC	0.1% FA in H_2O: MeOH (10:90 v/v)	Inertsil ODS-3V (150×4.6 mm, 5 µm)	220	1.0	NA	NA	6
7	Tablet	RP-HPLC	ACN: Water (80:20 v/v)	Qualisil BDS C18 (250×4.6 mm, 5 µm)	254	1.0	NA	NA	7
8	Tablet	RP-HPLC	NH_4: ACN (40:60 v/v)	Unisol C18 (100×4.6 mm, 5 µm)	250	1.0	NA	NA	8
9	Tablet	RP-HPLC (Stab.)	MeOH-acid: Water (20:80 v/v)	C18G (250×4.6 mm)	254	1.0	NA	NA	9
10	Tablet	RP-HPLC	Buffer: ACN (50:50 v/v)	Kromasil C18	256	1.3	NA	NA	10
11	Tablet	UPLC	Buffer: ACN (65:35 v/v)	BEH C18 (100×2.1 mm, 1.8 µm)	240	1.0	0.32	0.96	11
12	Tablet	UV-Vis	Methanol :Water (1:1 v/v)	NA	255	NA	0.495	1.502	12
13	Tablet	UV-Vis	Ethanol	NA	255	NA	NA	NA	13
14	Plasma	RP-HPLC	ACN: MeOH (60:40 v/v)	C18	254	1.0	NA	NA	14
15	Plasma	LC-MS/MS	NH_4Ac:ACN	C18	250	1.0	NA	NA	15
16	Tablet	RP-HPLC	ACN : Buffer (60:40 v/v)	Nova-Pak C18 (150×4.6 mm, 4 µm)	254	1.0	0.045	0.135	16
17	Tablet	RP-HPLC	Methanol : Water (70:30 v/v)	Symmetry C18 (150×4.6 mm, 5 µm)	260	1.0	0.07	0.21	17
18	Tablet	HPTLC	Tol:EtOAc:MeOH:FA (6:3:0.5:0.5 v/v/v)	Silica Gel 60 F254	254	NA	0.08	0.24	18
19	Tablet	HPLC-DAD	ACN:Water (65:35)	C18 (150×4.6 mm, 5 µm)	255	1.0	0.09	0.27	19
20	Plasma	LC-MS (Triple Q)	0.1% FA in Water:ACN (50:50)	C18 (50×2.1 mm, 1.7 µm)	250	0.5	0.03	0.09	20

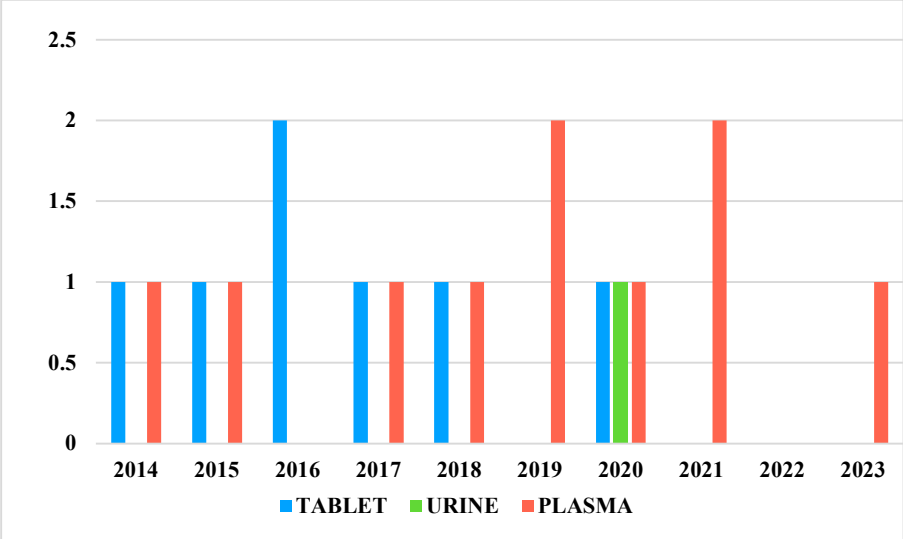

Figure 2: Sample matrices reported for Ticagrelor estimation between 2014 and 2023

4. DISCUSSION:

A comparative analysis of the compiled analytical methods reveals a clear trend in the selection of techniques based on sample matrix and sensitivity requirements. For pharmaceutical formulations, RP-HPLC continues to dominate due to its robustness, availability, and well-established validation procedures **[1–2, 4–11, 16–17]**. These methods offer LOD values ranging from 0.045 µg/mL **[16]** to 0.204 µg/mL **[1]**, demonstrating sufficient sensitivity for routine dosage form analysis. Several methods further incorporate stability-indicating capabilities, essential for impurity profiling and regulatory compliance **[6, 9, 10]**.

UV-spectrophotometric methods provide quick, low-cost alternatives for bulk and tablet analysis **[5, 12, 13]**. However, their application is limited due to lower sensitivity and specificity, particularly in complex formulations or when degradation products are present.

UPLC and HPLC-DAD techniques offer enhanced resolution and peak purity assessment, respectively, with the added advantage of faster run times **[11, 19]**. These techniques are especially suited for high-throughput pharmaceutical environments and method development laboratories.

For bioanalytical studies, LC-MS/MS methods using triple quadrupole mass analyzers are clearly superior, offering the lowest LODs (0.030 µg/mL) and high selectivity **[20]**. Such sensitivity is crucial in pharmacokinetic and therapeutic drug monitoring applications. These methods generally employ protein precipitation or liquid-liquid extraction for plasma cleanup **[3, 15, 20]**.

Although RP-HPLC has been employed for plasma analysis **[3, 14]**, it suffers from relatively higher detection limits and may

not be suitable for low-concentration pharmacokinetic phases.

Across methods, C18 columns were the stationary phase of choice due to their strong retention characteristics for moderately lipophilic drugs like Ticagrelor. Mobile phases primarily consisted of acetonitrile, methanol, buffers, and formic or phosphoric acids, optimized based on detection wavelength and peak shape. Despite a variety of validated methods available, opportunities still exist to improve environmental sustainability through green solvent usage, reduce manual intervention via automated extraction, and enhance reproducibility using QbD-based analytical design.

5. CONCLUSION:

This systematic review provides a comprehensive overview of the analytical techniques employed for the estimation of Ticagrelor in both pharmaceutical formulations and biological matrices. Among these, RP-HPLC remains the most widely used and validated method for dosage form analysis due to its balance of accuracy, cost-effectiveness, and ease of operation **[1–2, 4–11, 16–17]**. Stability-indicating RP-HPLC methods play a critical role in impurity profiling and regulatory compliance **[6, 9, 10]**.

For bioanalytical applications, particularly in plasma, LC-MS/MS stands out as the most reliable technique due to its superior sensitivity, specificity, and suitability for pharmacokinetic and therapeutic drug monitoring studies **[3,15, 20]**. While UV-spectrophotometry and HPTLC are advantageous for their simplicity and low operational cost **[5, 12, 13, 18]**, their limited sensitivity restricts their use to bulk and formulation studies only. Innovative approaches such as UPLC, HPLC-DAD, and green solvent systems are emerging as valuable tools, especially in high-throughput or environmentally conscious settings **[11, 19]**.

However, the lack of matrix flexibility and automation in many of the current methods indicates the need for continued development. In conclusion, a wide array of validated methods exist for Ticagrelor quantification, each with distinct advantages. Future research should focus on green chemistry principles, miniaturized sample preparation, and automation to further enhance analytical performance and environmental sustainability. This review offers a consolidated reference to guide method selection for researchers, analysts, and regulatory professionals working with Ticagrelor.

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CONFLICT OF INTEREST:

The authors declare that NO conflict of interest among us.

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