A Review on liquid chromatographic method for estimation of Dabigatran, Apixaban and Ticagrelor

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Abstract: **In the present era, the best common analytical method used for quantification of the drug is Reverse phase high-pressure liquid chromatography because of advantages like high accuracy, high sensitivity, and least time-consuming. DABIGATRAN is in a class of anticoagulant drugs. It is a direct thrombin inhibitor that prevents the formation of blood clots in the body. Dabigatran is also used to prevent strokes and severe blood clots in the individuals with atrial fibrillation without heart valve disease. APIXABAN is a specific novel anticoagulant drug which is used for treatment of thromboembolism. Apixaban is an oral anticoagulant and direct, selective inhibitor of factor Xa, which is used to decrease the risk of venous thrombosis, stroke and systemic embolization in patients with atrial fibrillation. TICAGRELOR is a cyclopentytriazolopyrimidine-based platelet aggregation inhibitor that is used orally. It's a P2Y12 receptor antagonist that suppresses platelet activation and accumulation triggered by P2Y12 and ADP receptor in myocardial infarction.**

In this study, we will look at all documented HPLC and LC-MS methods for determining specific anticoagulant medicines including dabigatran, Apixaban, and Ticagrelor in their pure form, combination form with other drugs, combined form with degradation products, and in biological fluids.

Keywords: **RP-HPLC, LC-MS, Dabigatran, Apixaban, Ticagrelor.**

I. INTRODUCTION

A. ANTICOAGULANTS:

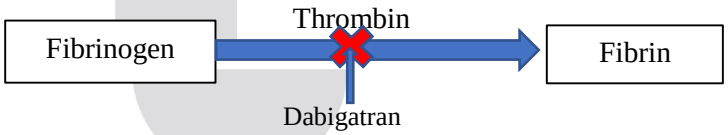
Anticoagulants are the medications that stop the blood from thickening or clotting. The new oral anticoagulants are first-in-class direct-acting medicines that target coagulation factor Xa or Thrombin. All over the world, these medications were recently licensed for the prevention and treatment of venous thromboembolism in individuals who had elective hip or knee arthroplasty. Dabigatran, Rivaroxaban, Apixaban, and Edoxaban are currently used anticoagulants all over the world.

a) DABIGATRAN:

Dabigatran is a specific potent oral anticoagulant medicine. Based on the results of the Randomized Evaluation of Long-Term Anticoagulant Therapy trial, which compared warfarin to dabigatran the European Union approved it in 2008, and the Food and Drug Administration approved it in 2010 [1]. It is highly selective potent thrombin inhibitor that is formulated as a prodrug, Dabigatran etexilate, and marketed under the brand name "Pradaxa". It's licensed for prevention and treatment of venous thrombosis after the orthopaedic surgery. It is used for prophylaxis of embolic strokes and pulmonary embolisms in individuals suffer from nonvalvular atrial fibrillation [2].

MECHANISM OF ACTION:

Dabigatran is a competitive, potent thrombin inhibitor. It is binds to the catalytic site on the thrombin molecule. It inhibits the serine protease enzyme which allow the conversion of fibrinogen to fibrin during the coagulation process. its inhibition prevents the formation of a clot [3].



DRUG PROFILE [4]:

Chemical name: ethyl-N-{[2-({[4-((E)-amino{[(hexyloxy)carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H-benzimidazol-5-yl] carbonyl}-Npyridin-2-yl-β-alaninate methane sulfonate

Molecular formula: $C_{35}H_{45}N_7O_8S$

Molecular weight: 723.86 gm/mol

Appearance: A yellow white coloured powder. Solubility of a saturated solution in pure water is 1.8 mg/mL

Chemical structure:

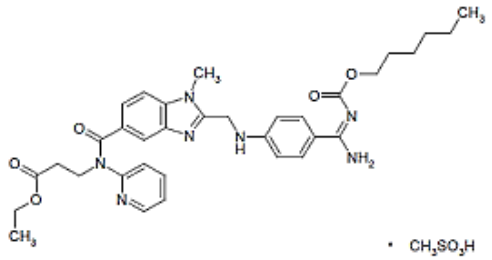


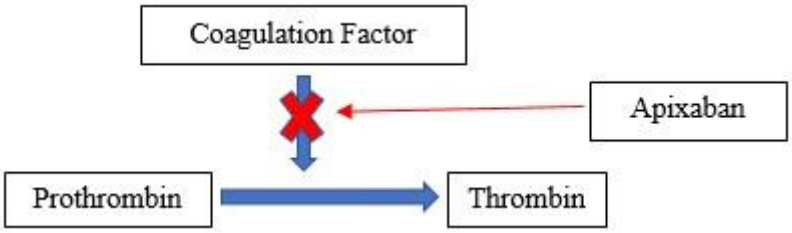
Fig. 1: Chemical structure of dabigatran etexilate mesylate

b) APIXABAN:

Apixaban is a novel specific anticoagulant drug. It is a potent inhibitor of coagulation factor Xa indicated for the prevention of venous thromboembolism in individuals with non-valvular atrial fibrillation. It is sold under the brand name "Eliquis". In December 2012 and January 2010, Apixaban was approved in the USA and Europe, respectively. Further it is suggested for prevention of stroke and serious blood clots in individuals with atrial fibrillation that not due to heart valve defect. It was designed by Aderis Pharmaceuticals and it was co-developed by Pfizer and Bristol-Myers Squibb [5].

MECHANISM OF ACTION:

Apixaban is a direct, reversible, potent inhibitor of coagulation factor Xa. It directly inhibit factor Xa which is involved in the conversion of prothrombin to thrombin and preventing the formation of clots [6].



DRUG PROFILE [7]:

Chemical name: 1-(4-methoxyphenyl)–7–oxo–6–[4–(2–oxopiperidin-1-yl) phenyl]–4,5,6,7–tetrahydropyrazolo [3,4–c] pyridine–3–carboxamide

Molecular formula: $C_{25}H_{25}N_5O_4$

Molecular weight: 459.4971 gm/mol

Appearance: white to pale yellow powder, stored at temperature ranging from 20 to 25 ºC

Solubility: 0.028 mg/mL at 24°C in water

Chemical structure:

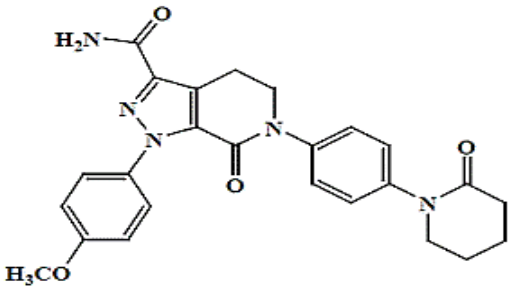


Fig.2: Chemical Structure of Apixaban

B. ANTIPLATELET DRUGS:

Antiplatelet drugs are medications that decrease platelet aggregation and inhibit thrombus formation. Antiplatelet drugs target the production of thromboxane, which is secreted by platelets and causes blood to clot**.** Antiplatelet medications are currently indicated for prevention and treatment of stroke, myocardial infarction, angina pectoris, venous thromboembolism and other several diseases and disorders. Example of antiplatelet drug are clopidogrel, ticagrelor, prasugrel [8].

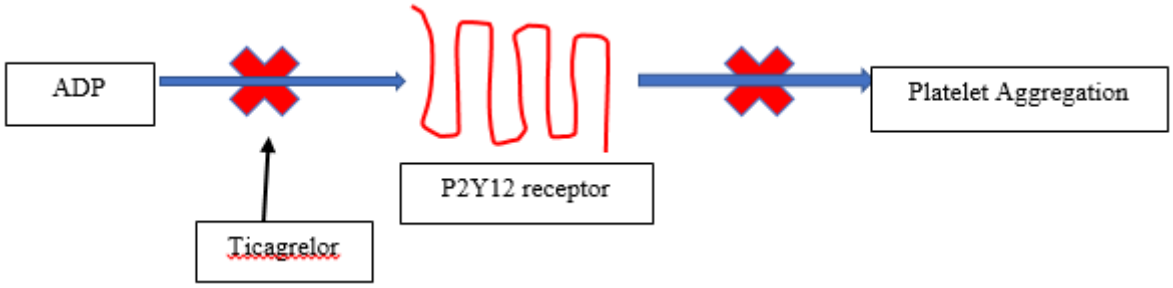
a) TICAGRELOR:

Ticagrelor is an antiplatelet medication. It is a direct acting P2Y12 receptor antagonist. Ticagrelor non-selectively and reversibly interact with P2Y12 receptor at a distinct site from that of adenosine diphosphate. This slowdown signal transduction and platelet activity, thus inhibit development of a pathologic thrombus. It was discovered by Astra Zeneca, and approved for use by the US Food and Drug Administration in 2011. The drug was licensed for use by The European commission in 2011. In the United States it is sold under the trade name Brilinta® whereas in Europe it is sold under trade name Brilique®. It

is indicated for reduction of clinical thrombotic events in patients with acute coronary syndrome. It is also used to lower the risk of cardiovascular mortality, myocardial infarction, and stroke [9].

MECHANISM OF ACTION:

After oral treatment, ticagrelor, a cyclopentyltriazolopyrimidine class medication, has antiplatelet effects. Ticagrelor reversibly binds to the P2Y12 receptor at a distinct site from that of adenosine diphosphate and prevent binding of adenosine diphosphate to P2Y12 receptor and thus slowdown platelet activation and thrombus formation [9].



DRUG PROFILE [10]:

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

Molecular formula: $C_{23}H_{28}F_2N_6O_4S$

Molecular weight: 522.568 gm/mol

Appearance: White crystalline powder, melting point 138-140°C

Solubility: Soluble in acetonitrile, methanol and ethanol

Chemical structure:

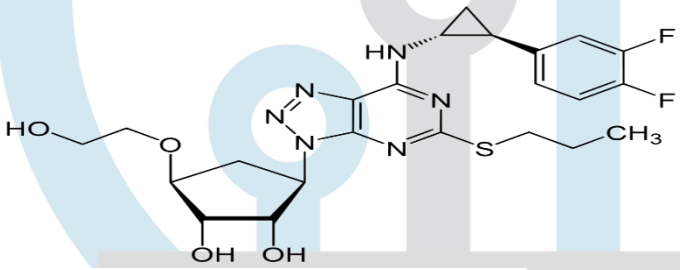


Fig.3: Chemical Structure of Ticagrelor [11].

We go over all of the HPLC and LC-MS methods that have been published for the determination of Dabigatran, Apixaban, and Ticagrelor in Pharmaceutical Dosage form and In Plasma. In Table No.1 We compile a list of all liquid chromatographic methods for the estimation of Dabigatran. In Table No.2 we give the overview of liquid chromatographic methods for estimation of Apixaban And in Table No.3 We compile a list of all liquid chromatographic methods for estimating Ticagrelor that have been published.

Table 1: Summary of HPLC and LC-MS Methods for Estimation of Dabigatran

Sr. No.	Matrix	Method	Stationary phase	Mobile phase	Detection	Linearity, LOD, LOQ (µg/mL) And Regression coefficient:	Rt / FR	Ref
1	Bulk Drug	HPLC	Inertsil ODS 3V column (250 mm × 4.6 mm, 5 µm)	Acetonitrile And 0.1% of trimethylamine with 20 mM ammonium formate (pH is maintained to 5 with the help of formic acid)	Photodiode array (PDA) detector 255nm	a) 0.211-2.250 µg/mL b) 0.070 µg/mL c).211µg/mL d) r^2=.9997	A)36.37 min B) 1.0 mL /Min	[11]
2	Pharmaceutical Dosage form	HPLC	Princeton SPHER-l00 C18 (250 mm ×, 4.6 mm,5 µm)	Phosphate buffer with pH adjusted to 2.5 and acetonitrile (67%:33%)	Photodiode array detector 225nm	A) 0.38-4.5 µg/mL B) 0.38 µg/mL C) 4.50 µg/mL D) r^2=.9962	A)25.89 min B) 1.0 mL/min	[12]

3	Capsule	HPLC	Zorbax C18 (250 mm × 4.6 mm, 5 µm)	Acetonitrile and Triethylamine 0.1%, pH 6.0 adjusted with phosphoric acid: (65%:35% v/v)	Photodiode array (PDA) detector 225nm	A) 10–70 µg/mL B) 0.04 µg/mL C)10 µg/mL D) r^2=.9991	A) 6.31 min B)1.0 mL/ min	[13]
4	Capsule	HPLC	Inertsil ODS-3V, (150 mm × 4.6 mm,5 µm)	Ammonium formate buffer and Acetonitrile	Photodiode array (PDA) detector 220nm	A) 0.12-42 µg/mL B) 0.12 µg/mL C) 0.41 µg/mL D) r^2=.9997	A)10.17 min B)1.0 mL/ min	[14]
5	Capsule	HPLC	Phenomenex Luna C18 (250 mm x 4.6 mm, 5 µm)	Methanol: Water (70:30)	UV-Visible Detector (SPD-20A)	A)0-25 µg/mL B)0.000451 µg/mL C) 0.00137 µg/mL D) r^2=.9981	A) 4.60 min B)1.2mL/min	[15]
6	Tablet	HPLC	Eclipse XDB C8 (250 mm x 4.6 mm, 5 µm)	Acetonitrile And 0.01 M o-phosphoric acid having (pH 2.6) (40:60 v/v)	UV/Vis detector 225nm	A) 5-100 µg/mL B) 0.067 µg/mL C) 0.221 µg/mL D) r^2 =0.9975	A)3.238±0.2 B) 1.5 mL /min	[16]
7	Capsule	RP-HPLC	Phenomenex Kinetex EVO C18 (250 mm x 4.6 mm, 5 µm)	Triethylammonium phosphate buffer (pH 2.0):methanol:acetonitrile (30:30:40 v/v)	UV detector 254nm	A) 10- 30 µg/mL B)1.09 ng/mL C)3.32 ng/mL D) r^2=0.9958	A)3.73 min B) 0.6 mL/min	[17]
8	API	RP-HPLC	Neosphere C8 (150 mm × 4.6 mm)	Methanol: phosphate Buffer (0.01 M) 60:40 v/v	PDA 225	A)1-5 µg/mL B)0.014 µg/mL C)0.040 µg/mL D) r^2=0.999	A) 4.4±0.05 min B)1 mL/min	[18]
9	API	RP-HPLC	Kinetex C8 column (250 mm × 4.6 mm, 5 µm)	Methanol: water in ratio of 70:30 (v/v)	996 PDA detector 230nm	A) 120-180 µg/mL B) …. C) …. D) r2 =0.996	Flow Rate -1 mL/min	[19]
10	API	HPLC	Inertsil C8, (250 mm x 4.6 mm, 5 µm)	Ammonium formate buffer and HPLC grade acetonitrile.	Photo diode array 255nm	A) … B) …. C) …. D) 1	A)2.6 min B)1mL/ min	[20]
11	API	HPLC	Poroshell 120 EC -18 column (150 mm × 4.6 mm, 2.7 µm)	Methanol: Hexane-1 Sulfonic acid sodium salt monohydrate (6.5 ± 0.05)	UV detector 230 nm	A) B) 0.01%w/w C) 0.035%w/w D) r^2=0.9999	A)26.57min B)0.6mL/min	[21]
12	Bulk Form	RP-HPLC	Unisol C18 (150 mm × 4.6 mm, 3 µm)	Ammonium acetate buffer Methanol and (10:90 v/v)	PDA Detector 226nm	A)20-100 µg/mL B)1.5 µg/mL C)2.5l µg/mL D) $r^{2=}$.999	A)2.52 min B)1mL/min	[22]
13	Capsule	RP-HPLC	Zorboc C18 (100 mm × 4.6 mm, 3.5 µm)	Acetonitrile: Water (70:30%v/v)	225 nm	A)20 -100 µg /mL B)1.38 µg/mL C)4.17 µg /mL D) $r^{2=}$.998	A)3 min B)1mL/min	[23]
14	Capsule	RP-HPLC	Waters Symmetry C18 (250 mm × 4.6 mm; 5 µm)	Triethylamonium phosphate buffer(ph2.5) And Acetonitrile (40:60v/v)	UV detector 313nm	A)15-45 µg /mL B)39.19 µg /mL C)118.88 µg /mL D) r^2=.999	A)2.44 min B) 1mL/min	[24]
15	Bulk	HPLC	XTerra C18 (150 mm × 4.6 mm, 5 µm)	Acetonitrile and Buffer (55%:45%)	PDA detector 334 nm	A)10-50 µg/mL B) … C) … D) r^2=.9998	A)2.163 min B)1mL/min	[25]
16	Human Plasma	UHPLC	Acquity UPLC HSS T3(100 mm ×	(A) Acetonitrile (B) 0.1% formic acid	MS/MS (positive	A) 5.0-800 nmol/L B)0.5 nmol/L	A)3 min B) 0.6 mL/min	[26]

			2.1 mm,1.8 µm) & (5 mm × 2.1 mm,1.8 µm precolumn)		Ionization electrospray	C)2.5 nmol/L D) r^2 >0.995		
17	Human Plasma	HPLC	RP C18 column Zorbax Eclipse plus (100 mm × 2.1 mm, 3.5 µm)	(A) 0.1% formic acid in methanol B) Ammonium acetate 2 mmol/ 0.05% formic acid	MS/MS (positive Ionization electrospray)	A) 5-100 µg/mL B) C)3 ng/mL D) $r^{2=}$.9996	A)5.2 min B)0.3 mL/min	[27]
18	Human Plasma	UHPLC	Acquity UPLC BEH C8 column (100 × 2.1 mm, 1.7 µm)	(A) 2.5mM ammonium formate at pH 3.0 (B) acetonitrile	MS/MS (positive Ionization electrospray)	A) 23 to 750ng/mL B) ≥.025ng m/L C) D) r^2 >.999	A)4.57 min B)300 µL/min	[28]
19	Human Plasma	UPLC MS	RP column Waters, Acquity UPLC BEH Phenyl (50 mm × 2.1 mm, 1.7 µm)	95%/5% water:methanol containing 0.1% formic acid and 2mM ammonium acetate	MRM MS (positive Ionization electrospray	A)0.8 and 800 µg/L B)0.21 µg/L C)0.46 µg/L D) r^2 <.99	A) 2.5 min B)0.35 mL/min	[29]
20	Human Plasma	HPLC	Waters Xterra C8 Column (50 mm× 3 mm, 3 µm)	Acetonitrile: Water (30:70, v/v) pH maintained to 3.0 using 0.05% formic acid solution.	MS/MS (positive ionization electrospray)	A)1.00–600.00 ng/mL B) C) LLOQ-1ng m/L D) $r^{2>}$.9999	A)5 min B)0.3 mL/min for 2 min and then 0.7 mL/min	[30]
21	Human Plasma	UHPLC	A) Poroshell 120, EC-C18 (50 mm × 3.0 mm, 2.7 µm) B) Guard column EC-C18, (5mm × 3.0 mm, 2.7 µm)	Acetonitrile and water (90/10 V/V%)	UV-Visible Detector 294nm	A) 20 to 300 ng/mL B) 4 to 5 ng/mL C) 15 to 19 ng/mL D) r^2>.999	A)1.83 min B)0.7 mL/min	[31]
22	Human Plasma	HPLC-DAD	C18 column (55 mm × 4 mm, 3 µm)	Acetonitrile: 0.1% of Formic acid in water (90:10, v/v)	diode array detection 300nm	A)0.066–5.28 gm/ mL, B)5.28 gm /mL, C) 0.066 gm/mL D) r^2=.994	A) 1.6 min B) 1.0 mL/ min	[32]
23	Human Plasma	HPLC	Acquity UPLC BEH C18 column (100 mm × 2.1 mm; 1.7 µm)	(A) Distilled water containing 0.1% formic acid and 0.07 g of ammonium acetate (B) acetonitrile with 0.1% formic acid	MS/MS (positive Ionization electrospray)	A) 2.5 to 500 ng/mL B) …. C) LLOQ-2.5 ng/mL D) r^2 > 0.995	A)1.45 min B) 0.3 mL/min	[33]

Table 2: Summary of HPLC and LC-MS Methods for Estimation of Apixaban

Sr. No.	Matrix	Method	Stationary phase	Mobile Phase	Detection	Linearity, LOD, LOQ and Correlation coefficient	Retention Time and Flow Rate	Ref
1	Bulk Drug and Tablet	RP-HPLC	C18 INERTSIL ODS-2 Column (250 mm ×4.6 mm×5 um)	Buffer: ACN) in the ratio of 55:45(v/v)	PDA 280nm	A) 1-3 µg/mL B)0.30 µg/mL C)0.60 µg/mL D) r^2=.999	A) 5.2 min B)1 mL/min	[34]
2	Bulk	RP-HPLC	Chiralapk IA (250 mm x 4.6 mm, 5 µm)	n-Hexane, Tolune, methanol & ethanol (65%,15%,10%& 10% v/v)	UV & PDA detector 290nm	A) B)0.19% C)0.057% D) r^2=.9993	A)32 min B) 1mL/min	[35]
3	Tablet	RP-HPLC	Purospher Star RP-18e (250 mm x 4.6 mm, 5 µm)	Water& Acetonitrile (60:40 v/v)	UV detector 280 nm	A)5-30 µg/mL B) 1.020 µg/mL C) 3.091 µg/mL D) r^2=.999	A)5.66 min B) 1mL/min	[36]
4	Bulk	RP-HPLC	Hypersil BDS C-18 column, (250 mm × 4.6 mm, 5 µm)	Phosphate buffer–methanol 60:40 (*v*/*v*)	PDA detector 220nm	A) 0.01–0.22 µg/mL B) 0.05 µg/mL C)0.15 µg/mL D) r^2=.9997	A)13.6 min B)1 mL/min	[37]
5	Bulk	RP-HPLC	C18 column (100 mm × 4.6 mm, 2.7 µm)	Phosphate buffer And Acetonitrile	PDA 225nm	A) ……. B) 0.050 µg/mL C)0.075 µg/mL D) r^2=.99979	A)1 min B) 1 mL/min	[38]
6	Pharmaceutical Dosage Form and Bulk	RP-HPLC	Reverse Phase C18 column (250 µm × 4.6 mm, 5 µm) [Inertsil® ODS-3V]	0.02 M phosphate buffer pH 5.5 Acetonitrile (20:80 v/v)	UV detector 279nm	A) 5-30 µg/mL B) 18.180 µg/mL C) 59.09 µg /mL D) r^2=.997	A)4.1 min B)0.8 mL/min	[39]
7	Tablet	RP-HPLC	Waters X-bridge C18, (250 x 4.6 mm, 5µm)	Water: Acetonitrile (50:50)	UV detector 259 nm	A) 0-25 µg/mL B)0.49 µg/mL C)1.49 µg/mL D) r^2=.999	A)3.4 min B)1 mL/min	[40]
8	Tablet	RP-HPLC	Zorbax RX C18 (250 mm × 4.6 mm; 5µm)	0.03 M Ammonium acetate and acetonitrile in the ratio 90:10 v/v	UV detector 280 nm	A).10-1.62 µg/mL B).333 µg/mL C).090 µg/mL D) r^2=.999	A)13.05 min B) 1mL/min	[41]
9	Bulk	RP-HPLC	Inertsil® CN-3 and an XBridge® C8, both (150mm ×4.6 mm, 5 µm)	Methanol and water (50.2:49.8 v/v)	Diode array detector 220nm	A) 1–35 µg/mL B) ... C) ... D) r^2=.999	A) B)1.015 mL/min	[42]
10	API and Tablet	RP-HPLC	Waters X-bridge C18(250 mm x 4.6 mm, 5 µm)	Acetonitrile and Water (50:50, v/v)	UV detector 259 nm	A) 5 to 25 µ/mL B) ... C) …. D) r^2.999	A)3.42 min B)1mL/min	[43]
11	Pharmaceutical dosage form	RP-HPLC	C18 column (100 mm × 4.6 mm, 2.7 µm) {Sigma Aldrich ascentis express}	Phosphate buffer and acetonitrile	PDA detector 225nm	A)1-7 ppm B)0.2887ppm C)0.8749ppm D) r^2.995	A)3.305 min B)0.8-1.3 mL/min	[44]
12	Bulk	HPLC	Kromasil C18 column (250 mm × 4.6 mm, 5µm)	Sodium acetate and acetonitrile in the ratio (50:50%V/V)	……	A)10-50 µg/mL B)0.36 µg /mL C)1.09 µg/mL D) r^2>.994	B)1 mL/min	[45]

13	Tablet and Bulk	RP-HPLC	C18(150 mm x 4.6 mm, 5µm)	Water: Acetonitrile in the ratio of 55:45(v/v)	UV detector 281 nm	A) 50-150 µg/mL B) 44.18 µg/mL C) 58.12 µg/mL D) r^2=.994	A) 4.960 min B)1 mL/min	[46]
14	Plasma	LC-MS-MS	Zorbax SB C18 column (50 mm × 4.6 mm, 3.5 µm)	0.1% formic acid: methanol (15:85, v/v)	Electrospray ionization	A) 1.02–301.3 ng/mL B) LLOQ-(1.02 ng/mL C) …. D) r^2>.99	A) 0.75±0.3 min B)0.75 mL/min	[47]
15	Human Plasma	LC-MS	Hypersil Beta Basic C18 column, (100 mm × 4.6 mm, 5 µm)	Acetonitrile:2 mmol aquous solution of ammonium acetate (80%:20% v/v)	Electrospray ionization	A) 1-250 ng/mL B) LLOD-0.05 ng/mL C)…. D) r^2>.99	A) B)0.50 mL/min	[48]
16	Human Plasma	LC-MS-MS	Thermo Beta basic-8, (100 mm x 4.6 mm, 5µm)	Acetonitrile: Ammonium formate buffer pH 4.2 (70:30 v/v)	Multiple reaction Monitoring	A) 1.0- 301.52 ng/mL B) LLOQ-1.0 ng/mL C)…. D)r^2>.99	A) ... B)1 mL/min	[49]
17	Human Plasma	LC-MS	Waters, XBridge C8 (30 mm× 2.1 mm, 10 µm) and Waters, Acquity UPLC BEH C18, 50 mm × 2.1 mm ,1.7 µm)	0.1% formic Acid v/v and 2m mol/L ammonium acetate	Electrospray ionization	A) 0.25–760 µg/L B) LOD-0.12 µg/lL C) r^2>.99	A) …. B)0.1 mL/min	[50]
18	Human Plasma	UPLC-MS	Thermo Hypersil Gold C18 column (150 mm ×2.1 mm, 1.9 µm)	Solution containing 0.1% formic acid in methanol and 2.5 mMole ammonium formate (pH 3.0)	Electrosparyio nization	A) 1–500 ng/mL B) LLOQ- 1ng/mL C)r^2>.997	A) B)0.35 mL/min	[51]
19	Human Plasma	UHPLC-PDA	Kinetex EVO C18 (100 mm x 2.1 mm, 2.6 µm)	Methanol and 10 mMole phosphate buffers (pH 3 maintained with o-phosphoric acid)	PDA detection	A) 0.001-5.0 µg/mL B) LOD- 0.003 µg/mL C) r^2>.9997	A) …. B)0.7 mL/min	[52]
20	Human plasma	UHPLC-MS-MS	Acquity UPLC HSS T3 (100 mm ×2.1 mm, 1.8 µm) Acquity UPLC HSS T3 (5 mm x 2.1 mm, 1.8 µm)	Milli Q H2O with 0.1% formic acid &Acetonitrile	Electrospray ionization	A) 5.0-800 nmol/l B) LOD-0.25 nmol/l C)LOQ-2.5 nmol/l D)r^2>0.995	A)0.6 mL/min B)1.5 min	[26]

Table 3: Summary Of HPLC-MS Method for Determination of Ticagrelor

Sr. No.	Matrix	Method	Stationary phase	Mobile Phase	Detection	Linearity, LOD, LOQ (µg/mL) and Correlation coefficient	Retention Time and Flow Rate	Ref
1	Pharmaceutical Dosage Form	RP-HPLC	Phenomenex C18 column (250 mm × 4.6 mm; 5µm)	Acetonitrile and methanol (70:30% v/v)	SPD-20A photo diode array detector 254nm	A) 20-100µg/mL B) 0.382 µg/mL C)1.158 µg/mL D) r^2=0.9967	A)4.503min B)1 mL/min	[53]

2	Tablet	RP-HPLC	Kromasil C18 column (250 mm × 4.6 mm, 5 µm)	Aqueous buffer (containing 0.5 mL formic acid and triethylamine each in water) and acetonitrile in the ratio of 50:50 v/v	UV/VWD detector 256nm	A) 1-7 ppm B) 0.2887 ppm C)0.8749 ppm D) r^2=0.9956	A) 3.372 min. B) 1.3 mL/min	**[54]**
3	Tablet	UPLC	Acquity UPLC BDS C8 column (150 mm x 4.6 mm, 5 µm)	Acetonitrile and Buffer 0.1% OPA (2.2 pH) in the ratio of 40:60	TUV detector 240nm	A) 15-150 µg/mL B)0.45 µg/mL C)1.35 µg/mL D) r^2=0.999	A) 0.942 min B) 1.0 mL/min	**[55]**
4	Pharmaceutical Formulation	RP-HPLC	ZORBAX Eclipse Plus 300SB C18 column (250 mm x 4.6 mm, 5.0 µm)	20mMole Potassium dihydrogen o-phosphate buffer and Acetonitrile (60:40 v/v)	PDA detector 225nm	A) 40-160 µg/mL B)0.05 µg/mL C) 0.20 µg/mL D) r^2=0.9995	A)5.94 Min B) 1.0 mL/min	**[56]**
5	Pharmaceutical Dosage form	RP-HPLC	Symmetry C18 column (250 mm × 4.6 mm, 5µm)	Methanol: Phosphate buffer (PH maintained to 4 with orthophosphoric acid) (75:25 v/v)	UV detector 256nm	A) 5-50 µg/mL B)0.4 µg/mL C)1.28 µg/mL D) r^2=0.999	A) 2.750 min B) 1.0 mL/min	**[57]**
6	Pharmaceutical Formulation	RP-HPLC	Shimadzu HPLC C18G (250 mm × 4.6 mm)	Methanol acid and water in the ratio of 20:80 v/v	UV detector 254nm	A)10-100 µg/mL B)0.2 µg/mL C)0.6 µg/mL D) r^2=0.999	A)5.786 min B) 1.0 mL/min	**[58]**
7	Bulk	RP-HPLC	Primesil C18 column (250 nm, 4.6 nm, 5µm)	Methanol and Water (0.05% OPA) (95:05 v/v)	UV detector 252 nm	A) 5-25 µg/mL B) 0.2125 µg/mL C) 0.6440 µg/mL D) r^2=0.997	A)4.5 min B) 1.0 mL/min	**[59]**
8	Tablet	RP-HPLC	Hypersil BDS C18 column (100 mm × 4.6 mm, 5µm)	Phosphate buffer pH 3.0 and acetonitrile (70.30)	254nm	A)22.5-135 µg/mL B)0.092 µg/mL C).281 µg/mL D) r^2=0.999	A)3.215 min B) 1.0 mL/min	**[60]**
9	Bulk	LC-HPLC	Unisol C18 column (100 mm × 4.6 mm, 5µm)	Ammonium acetate buffer pH 4.5 acetonitrile (40:60) v/v	PDA detector 250nm	A)10-50 µg/mL B) 1.5 µg/mL C) 2.5 µg/mL D) r^2=.99	A)3.88 min B) 1.0 mL/min	**[61]**
10	Tablet	RP-HPLC	Develosil ODS UG-5 C18 (150mm × 4.6mm, 5 µm)	Potassium dihydrogen phosphate buffer: acetonitrile (60:40, v/v) with pH 3.0 adjusted with phosphoric acid	PDA detector 280nm	A)20-80 µg/mL B)0.05 µg/mL C)0.15 µg/mL D) r^2=.9992	A)5.35 min B) 1.0 mL/min	**[62]**
11	Tablet	RP-HPLC	X-Select CSH Phenyl-Hexyl column (150 mm × 4.6 mm, 3.5 µm	70% methanol in water	PDA 100 detector 298nm	A) 10-60 µg/mL B) 0.611 µg/mL C) 2.038 µg/mL D) r^2=0.9990	A) B) 1.0 mL/min	**[63]**

12	Bulk And tablet	RP-HPLC	Phenomenex Luna C18 column (250 mm × 4.6 mm, 5 µm)	Methanol: Acetonitrile: water (40:30:30% v/v/v)	PDA detector 280nm	A)20-150 µg/mL B).53 µg/mL C)1.61 µg/mL D) r^2=.99	A) B)0.9 mL/min	**[64]**
13	Synthetic Mixture	RP-HPLC	Pearless C-18 column (250 mm x 4.6 mm, 5 µm)	Acetonitrile: 10% aqueous Ortho-phosphoric pH 4.0 (60:40% v/v)	UV detector 249nm	A) 9-54 µg/mL B) 0.274 µg/mL C).565µg/mL D) r^2=.9989	A)5.2 min B) 1.0 mL/min	**[65]**
14	Tablet	RP-HPLC	Thermo C18 (250 mm × 4.6 mm, 5 µm)	20 mM KH2PO4: acetonitrile (pH 3.0 with OPA) in the ratio of 20:80 v/v	UV Detector 282nm	A) 5-25 µg/mL B)0.35 µg/mL C)0.95 µg/mL D) r^2=.999	A) 8.102± 0.3 min B)1.0 mL/min	**[66]**
15	Bulk	RP-HPLC	Cosmocil, C18 column (250 mm x 4.6 mm, 5 µm)	Acetonitrile :0.1% formic acid (45:55%v/v)	PDA detector 254nm	A)2-14 µg/mL B).362 µg/mL C)1.095 µg/mL D) r^2=.9994	A) 16.479 min B) 1.0 mL/min	**[67]**
16	Bulk	RP-HPLC	C18 Pursuit and C8 Luna column (50 mm × 3 mm, 3 µm)	Acetonitrile and 75mMole ammonium acetate pH 8.25 (55%:45% v/v)	DAD detection 225nm	A) 5.0 - 60.0 µg/mL B)0.08 µg/mL C)0.15 µg/mL D) r^2=1	A) B)0.95 mL/min	**[68]**
17	Plasma and Pharmaceutical formulations	UPLC	C18 column (100 mm × 4 mm, 3µm)	Phosphoric acid solution And Acetonitrile (adjusted to pH 3.0 using triethylamine) (55:45, v/v)	PDA detector 254nm	A) 0.5–200 µg/mL B) 0.032 µg/mL C)0.167 µg/mL D) r^2=.9996	A)3.5 min B)0.7 mL/min	**[69]**
18	Tablet	RP-HPLC	C18 (250 mm x 4.6 mm, 5µm)	Acetonitrile &Methanol (85:15 v/v)	PDA detector 255nm	A) 5-25 µg/mL B)0.20 µg/mL C)0.61 µg/mL D) r^2=.9999	A)3.12min B)1 mL/min	**[70]**
19	Plasma	LC-MS-MS	Phenomenex Luna® C18 (50 x 2 mm; 3µm)	0.1% formic acid in water–acetonitrile (20:80, v/v)	MS detection	A) 2–1,500 ng/mL B) LLOQ-2 ng/mL D) r^2=0.9991	A)1.03 min B)0.2 mL/min	**[71]**
20	Plasma	LC-MS	Ultimate XB-C18 column (150 mm × 2.1 mm, 3 µm)	Aqueous ammonium acetate (0.025 mM)/acetonitrile (35: 65, v: v)	Electrospray ionization	A) 0.5–2,000 ng/mL B) LLOQ-0.5 ng/mL	A)3.50 min B)0.25 mL/min	**[72]**
21	Plasma	LC-MS-MS	Kinetex XB C18 column (100 mm × 2.1 mm; 2.6 µm)	Aqueous solution of 0.1% formic acid and 0.1% of formic acid in Acetonitrile (57%:43% v/v)	Electrospray ionization	A) 1.25–2000 ng/mL B) LLOQ-1.25 ng/mL	A)4.50 min B)0.37 mL/min	**[73]**
22	Plasma	HPLC-MS-MS	Zorbrax SB-C8 (150 mm × 3 mm; 3.5 µm)	Acetonitrile and water at 0.1% formic acid (85:15; v/v)	Electrospray ionization	A) 2 to 5000 µg/L B)2 µg/L	A)1.8 min B) 450 µL/min.	**[74]**
23	Plasma	UPLC	Eclipse XDBC18 column (150 mm × 4.6 m, 5 µm)	0.1% Formic acid and Acetonitrile	MRM	A)2.5-1000 ng/mL B)0.5 ng/mL C) 2.5ng/mL D) r^2=.99	A)3 min B)1mL/min	**[75]**

CONCLUSION:

This study summarises the reported HPLC-MS methods for estimating Dabigatran, Apixaban, and Ticagrelor that have been developed and validated. This review concluded that various Spectroscopic and Chromatographic methods for estimating Dabigatran, Apixaban, and Ticagrelor were available. It was observed that in most chromatographic methods Acetonitrile, water, Methanol, and Phosphate buffer used a mobile phase to produce a greater resolution. It was found that in most of reported methods detection was by PDA and UV detector in Bulk and Pharmaceutical Dosage Form. The estimation of Dabigatran, Apixaban, and Ticagrelor in plasma was done by LC-MS by using electrospray ionization. The flow rate is kept constant at 1.0 mL/min in most of the described HPLC techniques to achieve a good resolution time. Furthermore, the majority of the HPLC methods discussed have the potential to be used in clinical studies of drug combinations, multidrug pharmacokinetics, and interactions. As a result, all methods were discovered to be simple, accurate, cost-effective, precise, and repeatable.

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