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A REVIEW ON CHROMATOGRAPHIC AND SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF RIVAROXABAN AND TICAGRELOR

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ABSTRACT

RIVAROXABAN is a drug which belongs to class of anticoagulant. Rivaroxaban is approved for the prevention of strokes and systemic embolism in atrial fibrillation. It is useful in prevention blood clot and treatment of deep venous thrombosis. TICAGRELOR is a platelet aggregation inhibitor which is an antagonist of the P2Y12 receptor of thrombotic events in acute coronary syndrome or myocardial infarction with ST elevation Combination of Rivaroxaban and Ticagrelor was Proved to be effective in Atrial fibrillation compare to Rivaroxaban and Ticagrelor monotherapy. This review entails different method developed for determination of the Rivaroxaban and Ticagrelor like UV-spectroscopy, liquid chromatography, HPTLC and HPLC.

KEYWORDS: Rivaroxaban, Ticagrelor, UV- Spectroscopy, HPLC (High Performance Liquid Chromatography), HPTLC (High Performance Thin Layer Chromatography), LC (Liquid Chromatography).

INTRODUCTION[1-3]

RIVAROXABAN is a drug which belongs to class of anticoagulant. Rivaroxaban is approved for the prevention of strokes and systemic embolism in atrial fibrillation. It is useful in prevention blood clot and treatment of deep venous thrombosis. Rivaroxaban is highly selective Xa inhibitor with oral bioavability and it inhibits both free Factor Xa inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II), and no effects on platelets have been demonstrated.

TICAGRELOR is a platelet aggregation inhibitor which is an antagonist of the P2Y12 receptor of thrombotic events in acute coronary syndrome or myocardial infarction with ST elevation.

Ticagrelor is a P2Y12 Platelet Inhibitor. The mechanism of action of ticagrelor is as a Phenylalanine Hydroxylase Activator, and P2Y12 Receptor Antagonist, and Cytochrome P450 3A4 Inhibitor, and Cytochrome P450 3A5 Inhibitor, and P-Glycoprotein Inhibitor. The physiologic effect of ticagrelor is by means of Decreased Platelet Aggregation.

Combination of Rivaroxaban and Ticagrelor was studied under clinical trial for the Atrial fibrillation compare to Rivaroxaban and Ticagrelor monotherapy. Rivaroxaban and Ticagrelor was proved to be effective in patient with Atrial Fibrillation undergoing percutaneous coronary intervention (PCI). Atrial Fibrillation is defined as an abnormal heart rhythm which characterize by irregular and rapid beating of atria This abnormal beating become longer and constant over time.

Reported methods are categorized depending on the following considerations

1. Single component analyzed by UV-spectroscopy methods and chromatographic method.
2. Analysis of Rivaroxaban and Ticagrelor in combination with other drugs by UV-spectroscopy methods and chromatographic method.

Reported Method For Estimation Of Rivaroxaban:[4-19]

Sr. No.	Drug	Method	Description	Ref No.
1	Rivaroxaban	**UV Spectroscopy**	**Detection Wavelength:** 270nm **Linearity range:** 2-20 µg/mL. **Correlation coefficient:**0.9991	**4**
2	Rivaroxaban in Pharmaceutical dosage forms	**RP-HPLC method**	**Detection Wavelength:**249 nm **Detector:** UV detector **Linearity Range:**0.005 - 40.0 µg mL-1 µg/ml **Mobile phase:** ACN: Water (55:45 v/v) **Stationary Phase:** Phenomenex Luna C18 column (250 mm length, 4.6 mm was used at 40 o C) **Flow Rate:**1.2 ml/min	**5**
3	Rivaroxaban in bulk and tablet dosage forms	**RP-HPLC method**	**Detection Wavelength:** 218 nm **Detector:** UV detector **Linearity Range:** 1-120 µg/mL	**6**

			Mobile phase: 0.1M sodium acetate and methanol (60:40 v/v) **Stationary Phase:** ACE-Ciano column (250 mm x 4.6 mm, 5 µm particle size) **Flow rate:** 1 mL/min **Correlation coefficient:** 0.9992. **LOD:** 0.194 µg/mL **LOQ:** 0.648 µg/mL	
4	Rivaroxaban in tablet formulation	**RP-HPLC method**	**Detection Wavelength:** 234 nm **Detector:** UV detector **Linearity Range:** 50, 75, 125, 150, 175, 200 µg/ml **Mobile phase:** Acetonitrile: Methanol:Ortho phosphoric acid (90:8:2) **Stationary Phase:** C-18 column (250x4.6mm, 5µm in particle size) at ambient temperature coupled with a guard column of silica **Flow rate:** 1.5 mL/min **Correlation coefficient:** 0.997 **LOD:** 0.75ppm **LOQ:** 2.47ppm **Retention Time:**3.326min.	**7**
5	Rivaroxaban in formulation	**RP-HPLC Method**	**Detection wavelength:**248 nm **Detector:** UV detector **Mobile Phase:** potassium dihydrogen orthophosphate buffer : Acetonitrile (60-40v/v) **Stationary Phase:** HIBAR- 5µ C18 column **Flow Rate:**1 ml/min **Linearity Range:**1-5 mcg/ml **Retention Time:** 7.45 min **Regression Coefficient:** 0.9978	**8**
6	Rivaroxaban in Pharmaceutical Dosage Form	**HPLC method and DISSOLUTION method**	**Detection Wavelength:** 270 nm **Detector:** UV detector **Mobile Phase:** Acetonitrile: KH2PO4 50 mM(40:60, v/v) **Flow Rate:**1 mL min−1 **Linearity Range:**1 mL min−1 **Regression Coefficient:** 0.999 **LOQ:** 0.58 µg mL−1 **LOD:** 0.19 µg mL−1	**9**
7	Rivaroxaban and its alkaline Degradates in Bulk Powder and its Tablets	**HPLC, TLC densitometry, first derivative**	**Detection wavelength:** 280 nm **Mobile Phase:** 1.2% w/v potassium dihydrogen phosphate : acetonitrile (70:30, v/v) **Flow Rate:**1.5 ml/min	**10**

			Linearity Range: 10-70 µg/ml **LOD:** 1.03 **LOQ:** 3.15	
8	Rivaroxaban in human plasma	**HPLC Method**	**Detection Wavelength:** 280 nm **Detector:** UV detector **Mobile Phase:** Acetonitrile: Water (55: 45, v/v) **Flow Rate:**1 mL min−1 **Linearity Range:**0.01–4.00 µg mL^{-1} **Regression Coefficient:** 0.9993 **LOD:** 0.005 µg mL−1 **LOQ:** 0.01 µg mL−1	**11**
9	Rivaroxaban in pure, pharmaceutical formulation and human plasma samples	**RP-HPLC Method**	**Mobile Phase:** water : acetonitrile **Stationary phase:** XDB C18(150 * 4.6) mm column **Flow Rate:**1 ml/min **Linearity range:** 0.05-20 µg/ml **Correlation Coefficient:**0.9999 **LOD:** 0.015 µg/ml **LOQ:** 0.046 µg/ml	**12**
10	Rivaroxaban in bulk	**RP-HPLC and base degradation study**	**Detection wavelength:**250 nm **Detector:** PDA detector **Mobile Phase:** Methanol: Acetonitrile (50:50, v/v) **Flow Rate:**1 ml/min **Linearity Range:** 20-100 µg/ml **Regression Coefficient:** 0.99995	**13**
11	Rivaroxaban and related substance	**Stability indicating UPLC method**	**Detection Wavelength:** 248 nm **Detector:** photodiode array **Stationary Phase:** An Inertsil C8, 150 mm × 4.6 mm, 3.0 µm column (Agilent, USA) was used as the stationary phase **Mobile Phase:** Buffer: Acetonitrile (90:10) **Linearity range:** 15-150 µg/ml **Flow rate:** 0.45 ml/min **Regression Coefficient:** 0.999	**14**
12	Rivaroxaban in Tablet Dosage Form	**HPLC method**	**Detection wavelength:**251 nm **Detector:** UV detector **Mobile Phase:** ACN : Water (55:45v/v) **Stationary Phase:** C18 column (phenomenex 250 * 4.6mm 5 µm miniated at 35˚ c) **Flow Rate:**1.2 ml/min **Linearity Range:** 50-40 µg mL^{-1} **Retention Time:** 3.8 min	**15**

13	Rivaroxaban in pharmaceutical formulations	**Stability indicating RP-HPLC method**	**Detection Wavelength:** 249 nm **Mobile Phase:** ACN: Water (70:30v/v) **Stationary Phase:** C18 column (150 * 4.6mm 5 µm miniated at 40˚ c) **Flow Rate:**0.7 ml/min **Linearity Range:** 0.04-200 µg/ml **Retention Time:** 2.9 min **Regression Coefficient:** 0.9992	**16**
14	Rivaroxaban from its tablet dosage form	**HPTLC method**	**Detection Wavelength:** 249 nm **Detector:** PDA detector **Mobile Phase:** Methanol: toluene: triethanolamine (7:2.5:0.5) **Stationary Phase:** Silica gel F254 TLC plates under pure nitrogen steam linomat TLC spotter. **Linearity Range:** 500-3000 ng/spot (v/v/v) **Regression Coefficient:** 0.997	**17**
15	Rivaroxaban and clopidogrel bisulphate in pharmaceutical application	**HPLC Method for simultaneous estimation**	**Detection Wavelength:** 220 nm **Mobile Phase:** buffer (0.05MKH_2PO_4): Methanol (30:70v/v) **Stationary Phase:** BDS hypersil C_{18} 250mm Ã-4.6 mm 5Ãµ **Flow rate:** 1 ml/min **Linearity rang:** 50%-150% **Retention time:** Clopidogrel: 2.39 min Rivaroxaban: 4.04 min **Regression Coefficient:** Clopidogrel: 0.999 Rivaroxaban: 0.999	**18**
16	Rivaroxaban, Apixaban, Edoxaban in rat plasma	**UPLC-MS/MS**	**Mobile Phase:** Acetonitrile and 0.1% formic acid in water **Flow rate:** 0.4 ml/min **Linearity rang:** Rivaroxaban: 1-200 ng/ml Apixaban: 1-100 ng/ml Edoxaban: 1-500 ng/ml **Retention time:** 3.5 min **Regression Coefficient:** Rivaroxaban: 0.9948 Apixaban: 0.9971 Edoxaban: 0.9956 (lower) **LOQ:** 10ng/ml	**19**

Reported Method for Estimation of Ticagrelor[20-33]

Sr. No.	Drug	Method	Description	Ref No.
1	Ticagrelor in bulk form	**UV Spectroscopy**	**Detection Wavelength:** 224nm and 254 nm **Solvent:** Methanol **Linearity range:** 2-7 µg/mL. **Correlation coefficient:**0.998 **LOD:** 0.05 µg/mL **LOQ:** 0.20 µg/mL	**20**
2	Ticagrelor in bulk and marketed formulation	**Stability indicating method of UV**	**Detection Wavelength:**237 nm **Solvent:** Methanol and O-phosphoric acid (20:80) **Linearity Range:**2-10 µg/ml **Regression Coefficient:**0.9855 **LOD:** 0.199 µg/ml **LOQ:** 0.66 µg/ml	**21**
3	Ticagrelor drug in pharmaceutical formulation	**UV-Vis spectroscopy**	**Detection Wavelength:** 222 nm **Solvent:** Methanol : Water (1:1v/v) **Linearity Range:** 8-32 µg/mL **Correlation coefficient:** 0.9994 **LOD:** 0.30 µg/mL **LOQ:** 0.90 µg/mL	**22**
4	Ticagrelor in bulk form	**RP-HPLC method**	**Detection Wavelength:** 254 nm **Detector:** UV detector **Linearity Range:** 5-25 µg/ml **Mobile phase:** water: Methanol 95:05v/v **Stationary Phase:** C-18 column (length 250nm diameter 4.6nm,5µm in particle size) at ambient temperature coupled with a guard column of silica **Flow rate:** 1 mL/min **Correlation coefficient:** 0.997 **LOD:** 0.2125 µg/ml **LOQ:** 0.6440 µg/ml **Retention Time:** 3.326min.	**23**
5	Ticagrelor in bulk	**Method development and validation**	**Detection wavelength:**254 nm **Detector:** PDA/UV detector **Mobile Phase:** Acetonitrile: water (60:40v/v) **Flow Rate:**1 ml/min **Linearity Range:** 0.1-1 µg/ml **Retention Time:** 5.9 min **Regression Coefficient:** 0.997 **LOD:** 0.083 µg/ml **LOQ:** 0.25 µg/ml	**24**

6	Ticagrelor tablets	**RP-HPLC method**	**Detection Wavelength:** 256 nm **Mobile Phase:** Aqueous buffer (containing 0.5 ml formic acid and triethylamine):Acetonitrile (50:50v/v) **Flow Rate:**1 mL min−1 **Linearity Range:**1.3 mL min−1 **Regression Coefficient:** 0.9956 **Retention time:** 6 min	**25**
7	Ticagrelor in pharmaceutical dosage formulation	**RP-HPLC method**	**Detection wavelength:** 254 nm **Detector:** PDA **Mobile Phase:** Acetonitrile: Methanol (70:30v/v) **Flow Rate:**1 ml/min **Linearity Range:** 10-100 µg/ml **Retention time:** 7 min **Regression coefficient:** 0.9967 **LOD:** 0.971 µg/ml **LOQ:** 2.94 µg/ml	**26**
8	Ticagrelor in bulk and its formulation	**Stability indicating HPLC Method**	**Detection Wavelength:** 254 nm **Mobile Phase:** Phosphate buffer PH-3: Acetonitrile (70:30v/v) **Stationery phase:** Hypersil BDS C18 column (100 mm * 4.6 mm, 5 & micron) **Flow Rate:**1 mL min **Linearity Range:**22.5-135 µg/ml **Regression Coefficient:** 0.999	**27**
9	Ticagrelor and its organic impurities	**HPLC Method for simultaneous estimation analysis**	**Detection Wavelength:** 270 nm **Detector:** PDA **Mobile Phase:** Acetonitrile: ammonium acetate 50mM **Stationary phase:** Zorbax plus C8 column (150 * 4.6mm, 5 µm) **Flow Rate:**0.7 ml/min **Correlation Coefficient:**0.99	**28**
10	Ticagrelor in bulk	**LC-MS compatible RP-HPLC method**	**Detection wavelength:**250 nm **Detector:** PDA detector **Mobile Phase:** ammonium acetate buffer: Acetonitrile (40:40, v/v) **Flow Rate:**1 ml/min **Linearity Range:** 10-50 µg/ml **Retention time:** 3.88 min **Regression Coefficient:** 0.99 **LOD:** 1.5 µg/ml **LOQ:** 2.5 µg/ml	**29**
11	Ticagrelor hydrochloride	**HPLC-LC method**	**Detection wavelength:**225 nm **Detector:** PDA detector and auto sampler **Mobile Phase:** Acetonitrile: 20mM potassium dihydrogen ortho phosphate	**30**

			buffer (40:60v/v) **Stationary Phase:**ZORBAX eclipse plus 300SBC18 column (50 * 4.6mm 5 µm) **Flow Rate:**1 ml/min **Retention Time:** 3.8 min **Regression coefficient:** 0.9995 **LOD:** 0.05 µg/ml **LOQ:** 0.20 µg/ml	
12	Ticagrelor and its metabolite deshydroxyethoxy ticagrelor in human plasma	**UPLC method**	**Mobile Phase:** Acetonitrile: 0.1% Formic acid **Stationary Phase:** eclipse XDBC18 column (4.6mm*150mm) **Linearity range:** Ticagrelor: 2.5-1000 µg/ml deshydroxyethoxy ticagrelor: 1:300 µg/ml **Flow Rate:**1 ml/min **Retention Time:** 3 min **Regression coefficient:** 0.99 **LOD:** Ticagrelor: ng/ml deshydroxyethoxy ticagrelor: 0.2 ng/ml	**31**
13	Ticagrelor in tablets	**Stability indicating HPLC method**	**Detection Wavelength:** 249 nm **Mobile Phase:** ACN: Water (70:30v/v) **Stationary Phase:** C18 column (150 * 4.6mm 5 µm miniated at 40˚ c) **Flow Rate:**0.7 ml/min **Linearity Range:** 0.04-200 µg/ml **Retention Time:** 2.9 min **Regression Coefficient:** 0.9992	**32**
14	Ticagrelor in tablets	**Stability indicating HPLC method**	**Mobile Phase:** Acetonitrile: Water with 0.5% triethylamine (57:43v/v) **Stationary Phase:** C18 column (250*4.6mm, 5 µm **Linearity Range:** 45:105 µg/ml **Flow rate:** 0.7 ml/min **Regression Coefficient:** 0.9990	**33**

CONCLUSION

These reviews portray the reported Spectroscopic and Chromatographic methods developed and validated for estimation of Rivaroxaban and Ticagrelor. According to this review it was concluded that for Rivaroxaban and Ticagrelor different Spectroscopic and Chromatographic methods are available for single and combination. The mobile phase containing Phosphate buffer, Methanol and Acetonitrile were common for most of the chromatographic method to provide more resolution. For chromatographic method flow rate is observed in the range 0.6 - 2 ml/min to get good resolution time. For most of the Spectroscopic methods common

solvent is Phosphate buffer and Methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

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