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RESEARCH ON ANALYTICAL METHODS OF ANALYSIS OF RANOLAZINE: A REVIEW

Priyanka Dilip Patil

Professor, Department of Quality Assurance Technique.

KYDSCT's College of Pharmacy, Sakegaon,

Tal: Bhusawal, Dist: Jalgaon, India.

Abstract : New antianginal drugs examines are focusing on promising concentrations in order to develop new prescription contenders. Fundamental and biochemical strategy feeble connection between seriousness of torment and level of oxygen hardship in the heart muscle, for instance at times, angina can be very extreme, and in the mid twentieth century this was a known indication of looming demise, can accept an essential activity in the distinctive evidence of these goals. Compounding angina assaults, abrupt beginning angina very still, and angina enduring over 15 minutes are indications of flimsy angina (normally gathered with comparative conditions as the intense coronary disorder). As these may go before a respiratory failure, they require critical clinical consideration and are, all in all, rewarded in comparative design to myocardial localized necrosis. The pharmaceutical undertakings are centered around new drug improvement due to the overall affirmation of this unsafe security from the correct now available antianginal treatment. The HPLC, UV and HPTLC methods are available for the assessment of Ranolazine the starting late used prescription for intestinal sickness are studied in this articles.

Keywords- Antianginal Drugs, Ranolazine, analysis.

1. INTRODUCTION

Angina pectoris is a clinical indication that outcomes from coronary atherosclerotic coronary illness. An intense anginal assault (optional angina) is thought to happen in view of an unevenness between myocardial oxygen flexibly and request attributable to the powerlessness of coronary blood stream to increment with respect to increments in myocardial oxygen prerequisites. This is commonly the aftereffect of extreme coronary vein atherosclerosis. Angina pectoris (variation, essential angina) may likewise happen because of vasospasm of enormous epicardial coronary vessels or one of their significant branches. Furthermore, angina in specific patients may result from a blend of coronary vasoconstriction, platelet collection, plaque break, and an expansion in myocardial oxygen request (crescendo or flimsy angina). According to the World Cardiovascular maladies Report (2019), an expected 17.9 million individuals passed on from cardiovascular illnesses in 2016, speaking to 31% of every worldwide demise. Of these passing, 85% are because of coronary failure and stroke. **[1, 4, 6 -7]**

Antianginal drugs [5-9]

Antianginal medications may soothe assaults of intense myocardial ischemia by expanding myocardial oxygen gracefully or by diminishing myocardial oxygen request or both. Three gatherings of pharmacological specialists have been demonstrated to be powerful in lessening the recurrence, seriousness, or both of essential or optional angina. These specialists incorporate the nitrates, β-adrenoceptor enemies. What's more, calcium section blockers. To comprehend the gainful activities of these specialists, it is essential to be acquainted with the central point managing the harmony between myocardial oxygen gracefully and request.

The Classes are,

Vasodilators compounds (VC):-

The contractile movement of a wide range of muscle is controlled essentially by the reversible phosphorylation of myosin. Along with actin they take an interest in a course of biochemical occasions that are a piece of the procedures of muscle compression and unwinding. Nitrates shows vasodilating impact, which brings about decrease of fringe obstruction during myocardial constrictions. The vasodilator meds under this class joins nitrates, calcium blocker, for example, Isosorbide dinitrate, Pentaerythritol tetranitrate,

Isosorbide mononitrate and Nitroglycerin, and so on.

Cardiac depressants compounds (CDC):-

Cardiac depressants compounds (CDC) like calcium blocker, and beta-blocker, for instance, verapamil, calcium particles assume a significant job in the guideline of numerous cell forms, for example, synaptic transmission and muscle constriction. Calcium channel blockers lessen or forestall the expansion of free cytosolic calcium particles by meddling with the vehicle of calcium particles through these pores. Ex. Atenolol, Propranolol, Metoprolol, Diltiazem and Verapamil, and so on.

Miscellaneous compounds (MC):-

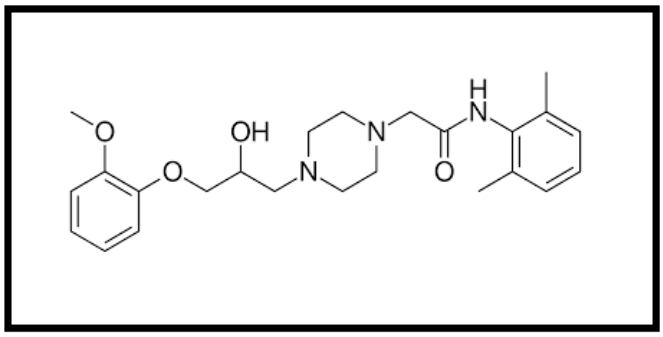
Miscellaneous compounds (MC) acts non-aerodynamically, forestalls corruption of layer unsaturated fats by lipid peroxidation decreases myocardial O_2 request - pFOX inhibitor and furthermore represses superoxide cytotoxicity - shields myocin from unsafe impacts of ischemia. What's more, it squares late internal sodium flows in cardiomyocytes. In the ischemic myocardium, late internal sodium flows add to a rise in intracellular sodium, which prompts an expansion in intracellular calcium through the sodium-calcium exchanger. Calcium over-burden in ischemic cells prompts hindered unwinding, cardio protective additionally restrains unsaturated fat oxidation. The various compounds under this characterization consolidates Ivabradine, Ranolazine and Trimetazidine, and so on.

Angina pectoris is the consequence of myocardial ischemia brought about by an unevenness between myocardial blood gracefully and oxygen request. It is a typical introducing side effect (commonly, chest torment) among patients with coronary artery disease (CAD). Roughly 9.8 million Americans are assessed to encounter angina yearly, with 500,000 new instances of angina happening each year. Individuals with a normal age of 62 years, who have moderate to extreme degrees of angina (reviewing by classes II, III, and IV) have a 5-year endurance pace of around 92%. **[1]** This overview moreover analyzes present day and front line distinctive consistent approaches to manage antianginal cure like ranolazine, methodology improvement with UV, HPLC, HPTLC, GC-MS and LC-MS including the various methodologies.

Ranolazine (ROZ) [2,3 & 10] :-

Ranolazine (ROZ) is hinders persevering or late internal sodium current in heart muscle in an assortment of voltage-gated sodium channels. Repressing that present prompts decreases in intracellular calcium levels. This thus prompts diminished pressure in the heart divider, prompting decreased oxygen necessities for the muscle. Ranolazine likewise shows its consequences for the postponed rectifier current, it promptly invigorates myogenesis, it diminishes a genius oxidant irritation/oxidative condition, and actuates the calcium flagging pathway. The chemical name of ranolazine is N-(2, 6-dimethylphenyl) -2-{4-[2-hydroxy -3-(2-methoxyphenoxy) propyl] piperazin-1-yl} acetamide. The atomic equation of ROZ is $C_{12}H_{33}N_3O_4$ and sub-atomic load of ROZ is 427.537 g/mol.

It has the following structural formula

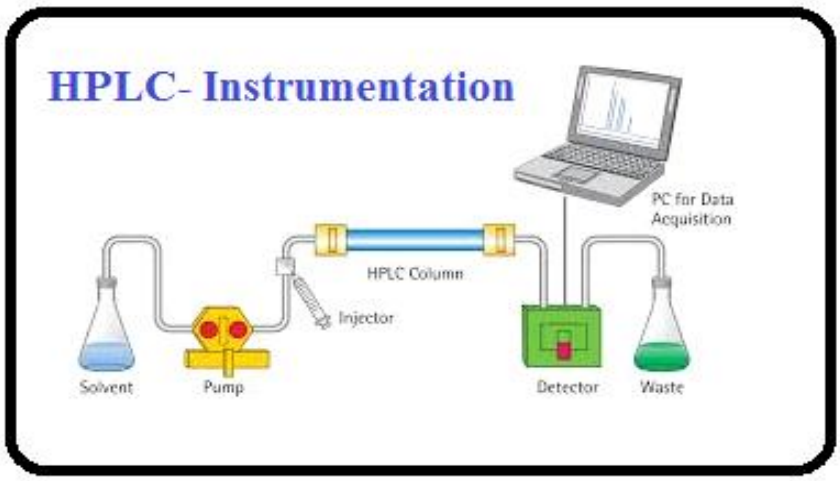


Ranolazine is white to off-white solid with a dissolvability in natural solvents, for example, dichloromethane and methanol, sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone, slightly soluble in ethyl acetate, iso-propanol, toluene, and ethyl ether; and very slightly soluble in water. The partition coefficient (log p) for ROZ is 2.07 and Pka is 2.2.

Ranolazine is a piperazine subordinate is another enemy of ischemic medication for the treatment of angina. Ranolazine is to restrain late INa accordingly forestalling sodium over-burden of the cell. As an outcome, ranolazine forestalls switch mode sodium–calcium trade and hence diastolic amassing of calcium perhaps bringing about improved diastolic tone and improved coronary blood stream. This audit article speaks to the different expository strategies which has been accounted for estimation of Ranolazine in manufactured blend. **[5,7-10]**

HPLC METHOD OF ANALYSIS OF ANTIANGINAL DRUGS:-

High Performance Liquid Chromatography (HPLC) is a separation system, it disconnects mix containing in any event two sections under high pressure. In HPLC Stationary stage is full in one completion of fragment which is attached to a wellspring of pressurized liquid versatile stage. HPLC is a speediest creating logical method for the examination of the prescription. Its ease, high distinction and wide extent of affectability makes it ideal for the examination of various drugs in the two estimations structure and regular fluids. A couple HPLC procedures were represented the examination of antianginal cure in the mass, portion structure and characteristic fluids**. [11-13]**



A summary of research take a shot at a few expository techniques (HPLC, UV, HPTLC, UPLC and MS) announced for the ranolazine alone and in blend is give in Table 1.

2. Conclusion

In spite of the way that couple of indicative procedures (HPLC, UV, HPTLC, UPLC and MS) are represented there is a continued with necessity for developing continuously beneficial, sensitive, precise and accurate systems for the assessment of the ranolazine alone and in blend in the portion structures and in the natural fluids. The introduced data is valuable for the future examination for analyst associated with definition improvement and quality control of Ranolazine.

Table 1- a summary of research work on the analytical methods for the estimation of ranolazine alone and in the combination.

Sr. No.	Drug	Method	Instrument, Mobile Phase, RT, Flow Rate & Results of Validation	Reference
1.	Ranolazine	UV-Method	**M.Phase :-** Methanol **λmax :-** 272 nm **Results :-** R^2-0.999, Slope and intercept- 0.0061 and - 0.0118 Detection Limit (µg/mL)- 0.27 Quantification limit (µg/mL)- 0.82	A. Sharma et.al.**[14]**
2.	Ranolazine	UV-Method	**M.Phase :-** 0.2% v/v ortho phosphoric acid **λmax** :- 271 nm **Results :-** R^2-0.999, Slope and intercept- 0.006 and 0.0048 LOD - 0.807 µg/ml LOQ - 2.4460 µg/ml	D. Shirisha et.al**[15]**
3.	Ranolazine	UV-Method	**M.Phase :-** Methanol and distilled water **λmax :-** 263 nm & 282 nm. **Result-** R^2-0.9992, LOD - 0.0072 LOQ - 0.021	J. Ramesh et.al.**[16]**
4.	Ranolazine	UV-Method	**M.Phase :-** Water **λmax :-** 447 nm, **Result-** R^2-0.9997, Slope and intercept- 0.0482 and 0.0171 % RSD – 1.140 % Recovery- 99.99	G. Naveen Kumar et.al.**[17]**
5.	Ranolazine	UV-Method	**M.Phase** :- Synthetic mixture **λmax :-** 272 nm. **Result :-** R^2-0.9995, Slope and intercept- 0.0005 and 0.0104 % RSD :- less than 2 , % Recovery:- 92.18-96.17	R. Singh et.al.**[18]**
6.	Amiodarone Hydrochloride and Ranolazine	UV-Method	**M.Phase** :- synthetic mixture **λmax :-** 263 nm & 249 nm. **Result :-** R^2-0.9996 for ADH & 0.9996 for ROZ LOD :- 0.712 µg/ml and 0.823 µg/ml LOQ:- 0.235 µg/ml and 0.271 µg/ml	V. Patel et.al.**[19]**
7.	Ranolazine	UV-Method & HPLC.	**M.Phase** :- 0.05M HCl **λmax :-** 272 nm. **Result :-** Slope and intercept- 0.00587 and 0.00093 R^2-0.9993, LOD :- 0.25 µg/ml , LOQ:- 1.00 µg/ml. **HPLC:** **M.Phase** :- Acetonitrile: 20 mM Ammonium acetate buffer (55 : 45, v / v) Flow Rate :- 1.0 ml/min at 270 nm **Result:-** R. Time :- 3.8 min., R^2-0.9995 . LOD :- 0.5 ng/ml LOQ :- 0.5 ng/ml	C. Nishith et.al.**[20]**

8.	Ranolazine and Dronedarone	LC-UV	**M.Phase** :- Acetonitrile: 0.02N NH2PO4 buffer (50:50, v / v) Flow Rate :- 1.0 ml/min at 282 nm **Result:-** R. Time :- 0.25 & 0.16 min., R^2-0.9999. LOD :- 0.39 and 0.58 ng/ml LOQ :- 1.19 and 1.76 ng/ml	A. Nahid et.al.**[21]**
9.	Ranolazine	LC-UV	**M.Phase** :- Acetonitrile – Sodium di-hydrogen phosphate monohydrate buffer (40:60 v/v) Flow Rate :- 1.0 ml/min at 225 nm **Result:-** R. Time :- 4.0 min., R^2-0.9999. LOD :- 1.03 ng/ml LOQ :- 0.34 ng/ml	G. Ramanaiah et.al.**[22]**
10.	Ranolazine	HPLC.	**M.Phase** :- Methanol-acetonitrile-phosphate buffer (pH 3.6; 6.3 mM) (4:3:3, v/v/v) Flow Rate :- 1 ml/min at 254 nm **Result:-** R. Time :- 1.82 min., R^2-0.9999. LOD :- 0.04 µg/ml , LOQ:- 0.12 µg/ml.	T. Laha et.al.**[23]**
11.	Ranolazine	HPLC.	**M.Phase** :- Methanol- phosphate buffer (pH-7) (65:35 v/v) Flow Rate :- 1 ml/min at 220 nm **Result:-** R. Time :- 10.49 min., R^2- 0.9999. LOD :- 0.0273 µg/ml LOQ:- 0.0818 µg/ml	V. Sureshbabu et.al.**[24]**
12.	Ranolazine	HPLC.	**M.Phase** :- Buffer- acetonitrile (90:10 v/v) and Acetonitrile- water (90:10 v/v) Flow Rate :- 1 ml/min **Result:-** R. Time :- 11.94 min., R^2-0.999. LOD :- 1000 µg/ml LOQ:- 1000 µg/ml	A. Madhavi et.al.**[25]**
13.	Ranolazine enantiomers	LC-UV.	**M.Phase** :- Methanol Flow Rate :- 1.0 ml/min **λmax :-** 254 nm. **Result:-** R. Time :- 4.7 & 6.4 min., R^2-0.997 & 0.999. LOQ:- 0.8 & 1.1 µg/mL	X. Luo et.al.**[26]**
14.	Ranolazine	RP-HPLC.	**M.Phase** :- Potassium dihydrogen phosphate monohydrate:methanol: acetonitrile (40:40:20) v/v Flow Rate: - 1.2 ml/min at 225 nm. **Result:-** R. Time :- 4 min., R^2-0.9998. LOD:- 0.34 µg/mL LOQ: - 1.03 µg/mL.	B. Gade et.al.**[27]**
15.	Ranolazine	HPLC in dog plasma sample.	**M.Phase** :- Acetonitrile-water(7 mmol·L-1 ammonium acetate,3.5 mmol·L-1 acetic acid and 1‰ triethylamine) (50:50) Flow Rate: - 0.8 ml/min at 230 nm. **Result:-** R. Time :- min., R^2- 0.9998 % Recovery: - 88%-105%.	L. Xia et.al.**[28]**

16.	Ranolazine	RP-HPLC.	**M.Phase** :- Sodium di-hydrogen phosphate buffer : Acetonitrile (60:40) v/v) Flow Rate :- 1.0 ml/min **Result:-** R. Time :- 4 min., R^{2-} 0.9998 LOD:- 0.34 µg/mL LOQ: - 1.03 µg/ml.	G. Lakshmi Priya et.al.**[29]**
17.	Ranolazine	HPLC in Synthetic sample.	**M.Phase** :- hexane : 2-propanol (90 : 10) Flow Rate :- 1 ml/min **Result:-** R^{2-} >0.988 % RSD :- less than 2 , % Recovery:- 92.18-96.17	G. Sawant et.al.**[30]**
18.	Ranolazine	LLE-HPLC in human plasma	**M.Phase :-** Acetonitrile: phosphate buffer (pH 2, 20 mM) (40:60 v/v) **λmax :-** 225nm **Results :-** R. Time :- 3.73 min., R^{2-}0.998. LOQ: 80 µg/ml,	V. Nalawade et.al.**[31]**
19.	Ranolazine	RP-UPLC Method	**M.Phase :-** Acetonitrile-Sodium dihydrogenphosphate (pH7.3;0.01 M)-Triethylamine (10:90:0.1,v/v/v) **λmax :-** 223 nm **Results :-** R^{2-}0.9975, R. Time :- 10.25 Detection Limit – 0.006 Quatification limit – 0.15	V. Malati et.al.**[32]**
20.	Ranolazine	HPLC-FD, HPLC-UV, LC-MS/MS in clinical pharmacokinetics	**HPLC-FD** **M.Phase :-** Methanol-Potassium phosphate monobasic 0.01 mol/L - Acetonitrile (45 : 40 : 15, v/v/v) **Flow rate**; - 1 ml/min. **λmax :-** 229 nm **HPLC** **M.Phase:-** N-heptane/2-propanol/alcohol [ethanol]/diethylamine (60 : 15 : 25 : 0.2, v/v/v/v) **Flow rate** ;- 1 ml/min. **λmax :-** 229 nm **LC-MS/MS** **M.Phase :-** Water containing 0.1% formic acid & Acetonitrile containing 0.1% formic acid **Flow rate** ;- 1 ml/min. **λmax :-** 223 nm	M. Jerling et.al.**[33]**
21.	Ranolazine	LC- MS/MS in plasma	**M.Phase** :- 0.125 % v/v trifluoroacetic acid in water adjusted to pH 3 with ammonia Flow Rate: - 1. ml/min. **HPLC :-** R. Time: - 27.41 min. R^{2-} 0.998, Recovery:- 85%,	A. Penman et.al.**[34]**
22.	Ranolazine	LC-MS/MS in dog plasma	**M.Phase:-** Acetonitrile 0 05% acetic acid (60:40, v/v) Flow Rate: - 2 ml/min. **HPLC :-** R^{2-}0.999, Recovery:- 80-91%, Absolute bioavability -72.6% Peak concentration – 4.32 µg/mL	X. Lin et.al.**[35]**

23.	Ranolazine	LC-MS/MS in human plasma	**M.Phase** :- Acetonitrile-0.1% formic acid (90:10). Flow Rate :- 1.0 ml/min. **HPLC :-** R. Time :- 6 min R^{2-} 0.9998 Recovery:- 75% LOQ:- 20 ng/ml	B. Shaobo et.al.**[36]**
24.	Ranolazine	HPLC- MS in human plasma	**M.Phase** :- Methanol–10mM Ammonium acetate (60:40 v/v) Flow Rate :- 1.0 ml/min. **HPLC :-** R. Time :- 1.93 min LOD :- 1 ng/mL LOQ:- 10 ng/mL	L. Zhao et.al.**[37]**
25.	Ranolazine	LC- EI-MS in Rat plasma	**M.Phase** :- Methanol–10 mM Ammonium acetate, (76:24 v/v). Flow Rate :- 1.0 ml/min **HPLC :-** R. Time :- 4.2 min Recovery :- 82.77–86.54%. LOQ:- 46 ng/mL	J. Zhong et.al.**[38]**
26.	Ranolazine	LC–MS–MS in human plasma	**M.Phase** :- Acetonitrile–Water–Formic acid– 10% N-butylamine (70:30:0.5:0.08, v/v/v/v) Flow Rate :- 5 µl/min **HPLC :-** R. Time :- 1.12 min R^{2-} 0.995. LOQ:- 5 µg/ml	L. Tian et.al.**[39]**
27.	Ranolazine	LC-MS/Ms in human plasma	**M.Phase** :- :- Methanol–Water containing formic acid (1.0%, v/v) (65:35, v/v) Flow Rate :- 1.0 ml/min **Result:-** R. Time :- 4.38 min., R^{2-}0.9937. LOQ:- 5.0 ng/ml	U. Bhaumik et.al.**[40]**
28.	Ranolazine and its three metabolites	LC-MS/Ms in human plasma.	**M.Phase** :- 5 mM Ammonium acetate aq.- Methanol. Flow Rate :- 0.5 ml/min **Result:-** R. Time :- 4.04 min., R^{2-}0.9998. Recovery:- 84.2 -108% LOQ:- 4 ng/ml	Y. Wang et.al.**[41]**
29.	Ranolazine and its metabolites desmethyl ranolazine	DLLME and LC-MS/MS	**M.Phase** :- :- Hexane:Ethanol (60/40, v/v) Flow Rate :- 10 µl /min **Result:-** R. Time :- 5.66 & 13.54 min for ROZ 3.36 & 4.10 min. for DROZ R^{2-}0.9873 & 0.9891 for ROZ 0.9953 & 0.9944 for DROZ LOQ:- 25 and 10 ng/ml	R. Almeida et.al.**[42]**
30.	Ranolazine	LC-APCI-MS in human plasma.	**M.Phase** :- Aqueous ammonium acetate (20 raM)and trifluoroacetic acid (TFA, 0.12%) : methanolic ammonium acetate (20 mM) and TFA (0.12%) (40: 60 v/v) Flow Rate :- 1 ml/min **Result:-** R. Time :- 2.38 min., R^{2-}0.996. Inter-assay variation:- 18.5%	W. Herron et.al.**[43]**

31.	Ranolazine	LC-APCI-MS in dog plasma.	**M.Phase** :- :- Acetonitrile-0.05%formic acid (60:40v/v) Flow Rate :- 0.3 ml/min **Result:-** R. Time :- 3.8 min. R^{2-}0.998. LOD:- 0.002 mg/mL LOQ:- 0.01 mg/mL	Y. Liang et.al**.[44]**
32.	Ranolazine	U-HPLC–MS/MS in human plasma.	**M.Phase** Acetonitrile - Aqueous ammonium acetate solution (40:60, v/v). Flow Rate :- 0.35 ml/min **Result:-** R. Time :- 1.01 min., R^{2-} _≥ 0.997. Recovery:- 85 – 100.4% LOQ:- 1.0 ng/ml	Q. Tan et.al**.[45]**
33.	Ranolazine	DRIFTS-Method	**M.Phase** :- Potassium bromide Detection :- 4000 and 650 cm^{-1} Std. Peak:- Carbonyl peak around 1689 cm. **Result:-** Resolution :- 8, R^{2-}0.9987. RSD:- 0.957-1.001 Recovery:- 95.58–97.12%	B. Bhongade et.al**.[46]**
34.	Ranolazine	HPTLC Method	**M.Phase :-** Chloroform : Methanol : Toluene (5 : 1 : 1 v/v/v) **λmax :-** 273nm **Results :-** Rf value:- 0.15 to 0.79 R^{2-}0.9999, LOD:- 250 ng/spot LOQ;- 440 ng/spot	A. Khedkar et.al**.[47]**
35.	Ranolazine	HPTLC-MS	**M.Phase** :- Butanol–Acetic acid–water (6:2:2 v/v) **λmax :-** 270 nm **Results :-** Rf value:- 0.56 R^{2-}0.9999, LOD:- 14.9 ng/band LOQ;- 49.67 ng/band	S. Abburu et.al**.[48]**
36.	Ranolazine	Headspace GC	**S.Phase** :- DB-624 capillary column (30m×0.32mm×1.8µm) Detector :- FID % RSD :- 1.1-3.7% Recovery:- 98.1%-105.5%	O. Yahua et.al**.[49]**
37.	Ranolazine	Headspace GC	**S.Phase:-** HP-INNOWAX column Solvent :- Water Detector :- FID % RSD of precision and accuracy:- less than 8% Recovery:- 87.1%-105.6%.	Y. Yl et.al**.[50]**

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