A COMPREHENSIVE REVIEW OF "ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR RANOLAZINE IN BULK AND PHARMACEUTICAL DOSAGE FORMS"

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Abstract: Ranolazine, a piperazine-derived compound, is a novel therapeutic agent used in the management of chronic angina. Its primary mechanism involves suppression of the late sodium current (INa), thereby preventing intracellular sodium accumulation and subsequent calcium overload. By reducing reverse sodium–calcium exchange, ranolazine limits diastolic calcium buildup, which improves ventricular relaxation and enhances coronary blood flow. Unlike conventional antianginal drugs, its action is mediated through sodium-dependent calcium pathways rather than direct effects on heart rate or blood pressure. This review summarises the analytical techniques reported for the estimation of ranolazine in bulk drug and pharmaceutical dosage forms. Methods include spectrophotometric approaches such as UV, visible, and fluorescence spectroscopy, as well as chromatographic techniques including HPLC, RP-HPLC, HPTLC, GC, LC-MS, and LC-MS/MS.

Keywords: Ranolazine; Anti-ischemic; Angina; HPLC; HPTLC.

INTRODUCTION

Ranolazine, a derivative of piperazine, is widely recognised as an antianginal agent. Chemically, it is identified as N-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]-1-yl piperazine] acetamide. The compound is crystalline in nature, readily soluble in methanol, and exhibits strong basicity due to its six-membered piperazine ring, with a pKa value of 13.6. Its melting point lies between 122-124 °C.

Pharmacologically, ranolazine reduces calcium influx indirectly by inhibiting the late sodium current, thereby decreasing sodium entry into ischemic myocardial cells. This mechanism lowers intracellular calcium via the sodium–calcium exchanger, improving diastolic relaxation and coronary perfusion. Importantly, its antianginal and anti-ischemic effects occur without significant changes in blood pressure or heart rate.

For patients who show inadequate response to conventional antianginal therapies, ranolazine can be administered either alone or in combination with other agents. In the United States, extended-release formulations have been approved for the treatment of chronic angina. The drug is available in multiple dosage forms, including film-coated and extended-release tablets, with recommended doses ranging from 500 to 1000 mg twice daily. [1,2,3]

Drug Profile

Ranolazine

Overview

Ranolazine acts by selectively inhibiting the late phase of inward sodium current in ischemic cardiac myocytes. This inhibition reduces intracellular sodium levels, which in turn decreases calcium influx through the sodium–calcium exchanger. The reduction in intracellular calcium helps lower ventricular wall tension and myocardial oxygen demand. Importantly, ranolazine achieves these effects without altering heart rate or systemic blood pressure, making it distinct from conventional antianginal agents.

General Information

Drug Name: Ranolazine

Brand Names: Ranexa, Corvera (extended-release)

Category: Anti-anginal drug

Chemical Name: N-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]-1ylpiperazine] acetamide

Molecular Formula: $C_{24}H_{33}N_3O_4$

Molecular Weight: 427.5 g/mol

Appearance: White to off-white crystalline powder

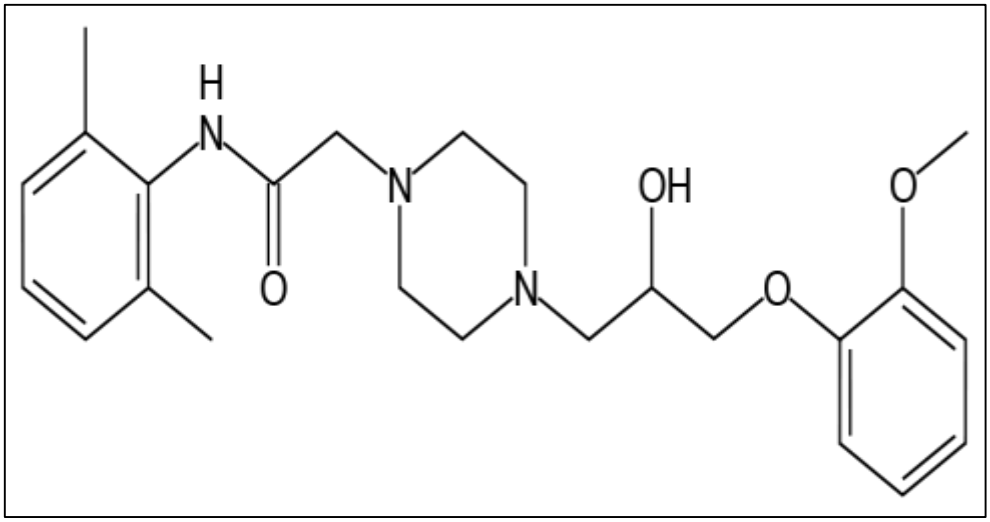

Fig 01. Structure of Ranolazine

Mechanism of action:

Although the precise mechanism of ranolazine is not fully understood, its anti-anginal and anti-ischemic effects are primarily attributed to inhibition of the late sodium current in ischemic cardiac myocytes. This action reduces intracellular sodium levels, thereby limiting calcium influx through the sodium–calcium exchanger. The resulting decrease in intracellular calcium lowers ventricular wall tension and myocardial oxygen demand, improving diastolic relaxation and coronary perfusion.

Clinical evidence supports these effects. In the MARISA trial, 191 patients with exercise-limiting angina were randomised to receive ranolazine at doses of 500 mg, 1000 mg, or 1500 mg twice daily, or placebo, for one week. Ranolazine significantly prolonged exercise duration compared to placebo, without affecting blood pressure or heart rate.

At higher concentrations, ranolazine also inhibits rapid delayed rectifier potassium current, leading to delayed action potential and QT interval prolongation. Additionally, it modulates myocardial metabolism by reducing fatty acid oxidation, enhancing glucose utilization, lowering lactic acid production, and thereby improving cardiac efficiency. (4)

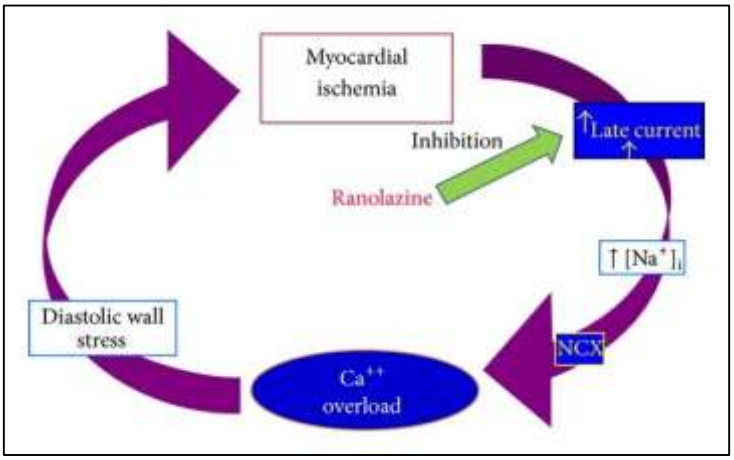

Fig 02: mechanism of action

Pharmacology

Pharmacodynamics

At therapeutic concentrations, ranolazine exerts its effects by modulating both sodium and potassium ion channel currents. The drug specifically inhibits the late phase of inward sodium current during cardiac repolarisation, a mechanism that has been extensively studied. Excess activity of this late sodium current in pathological states enhances sodium–calcium exchange, leading to elevated cytosolic calcium levels.

This intracellular calcium overload is considered a key contributor to impaired left ventricular relaxation during ischemia and reperfusion. Elevated calcium not only compromises diastolic function but also increases myocardial wall tension, thereby worsening oxygen demand. By attenuating late sodium current, ranolazine reduces calcium accumulation, helps to restore ventricular relaxation and improves overall cardiac efficiency.

Pharmacokinetics

- **Absorption**: Steady-state plasma concentrations are achieved within three days, with peak levels occurring between 2–6 hours post-dose.
- **Distribution:** The apparent volume of distribution ranges from 85 to 180 L, indicating extensive tissue penetration.
- **Metabolism**: Ranolazine undergoes rapid hepatic metabolism, primarily via CYP3A4, with CYP2D6 contributing to a lesser extent. More than 100 metabolites have been identified in urine, and over 40 in plasma.
- **Elimination:** Approximately 75% of the administered dose is excreted renally, while the remainder is eliminated through faeces. The drug's half-life averages around seven hours. [5,6,7,8]

Clinical Research

- **Ranolazine in Stable Angina**
  Multiple randomised controlled trials have demonstrated that ranolazine, either alone or in combination with conventional antianginal agents, reduces angina frequency, improves exercise tolerance, and decreases nitro-glycerine use. The MARISA trial enrolled 191 patients with stable angina and randomised them to receive ranolazine at doses of 500, 1000, or 1500 mg twice daily, or placebo, for a week. Results showed significant improvement in exercise duration without changes in blood pressure or heart rate. [9,10]
- **Ranolazine in Incomplete Revascularisation**
  The RIVER-PCI trial evaluated ranolazine in 2651 patients with stable angina who had undergone percutaneous coronary intervention (PCI) but had incomplete revascularisation. The primary endpoint was time to ischemia-driven revascularisation or hospitalisation without revascularisation. No significant difference was observed between the ranolazine and placebo groups (26% vs. 28%, $p = 0.48$). [11]
- **Ranolazine in Acute Coronary Syndrome**
  The MERLIN-TIMI 36 trial investigated ranolazine in 6560 patients presenting with non-ST-elevation acute coronary syndrome within 48 hours of symptom onset. Participants were randomised to receive intravenous ranolazine followed by 1000 mg orally twice daily, or placebo. The composite endpoint of death, myocardial infarction, or recurrent ischemia showed a reduction in ischemic events, though mortality benefits were not significant.
- **Ranolazine in Microvascular Angina**
  In a double-blind, randomised crossover study, 81 patients with microvascular angina were assigned to ranolazine or placebo. Cardiac MRI was used to assess left ventricular volume and myocardial perfusion reserve index (MPRI). Patients with impaired coronary flow reserve (CFR < 2.5) but no obstructive epicardial disease demonstrated improved myocardial perfusion and reduced angina symptoms with ranolazine therapy.
- **Diabetes and Comorbidities**
  Angina frequently coexists with other chronic conditions, particularly diabetes mellitus. Data from the National Health and Nutrition Examination Survey (NHANES) revealed that nearly half (48.9%) of patients with coronary artery disease (CAD) and diabetes also reported angina symptoms. For this population, it is advantageous to employ antianginal therapies that not only alleviate ischemic symptoms but also exert favourable effects on glycaemic control. Ranolazine has shown promise in this regard, offering dual benefits in cardiovascular and metabolic management.

Dosage Forms and Administration

Ranolazine is commercially available as film-coated and extended-release tablets in strengths of 500 mg and 1000 mg.

- **Adult Dosing**

  Initial dose: 500 mg twice daily.

  Titration: May be increased to 1000 mg twice daily, which represents the maximum recommended dose. [12,13,14]

  Tablets should be swallowed whole; they must not be chewed, split, or crushed due to their film-coated design. Administration is independent of meals, as food does not significantly affect absorption or systemic exposure. Pharmacokinetic parameters include a half-life of approximately seven hours, attainment of steady-state concentrations within three days, and peak plasma levels occurring between 2–5 hours post-dose. [15]

- **Dose Adjustments**

  When co-administered with moderate CYP3A inhibitors (e.g., erythromycin, verapamil, diltiazem), the dose should not exceed 500 mg twice daily. P-glycoprotein inhibitors such as cyclosporine may elevate plasma concentrations of ranolazine; therefore, dosing should be individualised based on clinical response. [16]

Adverse Effects

The most commonly reported adverse reactions include headache, dizziness, nausea, constipation, blurred vision, palpitations, tinnitus, and dyspepsia. Peripheral oedema and anorexia have also been observed. Serious but less frequent adverse events encompass thrombocytopenia, leukopenia, angioedema, renal impairment, eosinophilia, pulmonary fibrosis, syncope, hematuria, bradycardia, hypotension, orthostatic hypotension, and pancytopenia. Rare cases of ranolazine-induced myopathy have been documented, though prognosis is generally favourable upon discontinuation. [17]

Postmarketing Reports

Additional adverse effects include dermatitis, paresthesia, tremors, hallucinations, dysuria, and impaired coordination. Neurological symptoms are typically dose-dependent and resolve after cessation of therapy.

Drug–Drug Interactions

- Ranolazine undergoes hepatic metabolism primarily via CYP3A4, with CYP2D6 contributing to a lesser extent. It is also a substrate for P-glycoprotein.
- Contraindications: Strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) markedly increase ranolazine plasma levels and should not be used concurrently.
- Precautions: Moderate CYP3A4 inhibitors (e.g., verapamil, erythromycin, fluconazole, diltiazem) elevate ranolazine concentrations; dosing should be limited to 500 mg twice daily with close monitoring.
- CYP3A4 Inducers: Agents such as Rifampicin, carbamazepine, phenytoin, and St. John’s wort reduce ranolazine exposure and are not recommended.
- Special Populations: Ranolazine is contraindicated in patients with hepatic cirrhosis, though no specific dose adjustments are required for mild to moderate hepatic impairment.

Interaction with Metformin

Co-administration of ranolazine (1000 mg twice daily) increases plasma concentrations of Metformin. Patients receiving this combination should not exceed 1700 mg of metformin daily, and blood glucose levels should be monitored regularly.

Toxicity

High doses of ranolazine may produce dose-dependent adverse effects such as hallucinations, nausea, vomiting, tremors, dizziness, and dysphagia. In cases of overdose, supportive care and ECG monitoring are recommended. Due to its ~62% plasma protein binding, ranolazine is not effectively removed by hemodialysis. [18]

Overview of Analytical methods for the determination of Ranolazine in Biological and Pharmaceutical samples

The distribution of typical analytical techniques for ranolazine is shown in a pie chart. The most common techniques used in research with ranolazine, such as mass spectrometry, UV-visible spectroscopy, and HPLC, are shown in Fig. no:03.

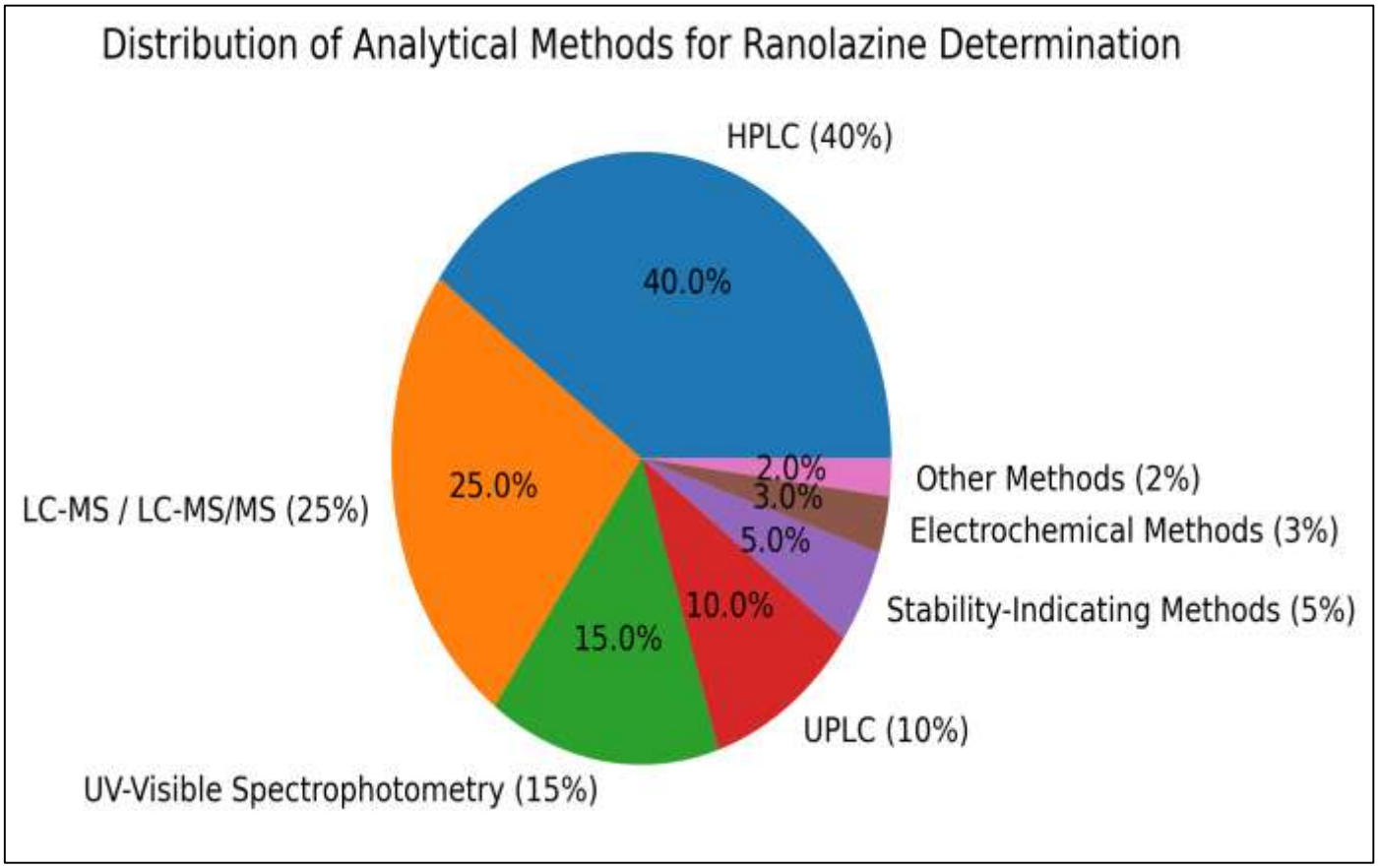

Fig 03: distribution of analytical method for ranolazine determination

- HPLC (High pressure liquid chromatography)40% LC-MS / LC-MS/MS (Liquid Chromatography-
- Mass Spectrometry) 25% UV-Visible Spectrophotometry 15%
- UPLC (Ultra-Performance Liquid Chromatography) 10% Stability-Indicating Methods (Forced
- Degradation Studies) 5% Electrochemical Methods (e.g., Voltammetry) 3%
- Other Methods (e.g., TLC, Capillary Electrophoresis) 2%

I. Chromatographic Methods

Ranolazine is predominantly quantified using high-performance liquid chromatography (HPLC). Gas chromatography (GC) has also been applied for its determination. Among pharmaceutical formulations, high-performance thin-layer chromatography (HPTLC) is a widely employed technique for Ranolazine analysis. Advanced hyphenated methods such as LC-MS/MS, LC-MS, and UHPLC have been utilised to assess ranolazine concentrations in biological matrices, particularly plasma. Additionally, a reverse-phase HPLC (RP-HPLC) procedure has been developed for estimating ranolazine levels in human serum, as summarised in Table 1.

Table No.1: Chromatographic Method of Ranolazine

Title	Method	Mobile phase	Stationary phase	Wave Length
Ranolazine in bulk and marketed formulation [8]	HPLC and UV	Methanol: 0.5% tri ethyl amine, pH 6 with orthophosphoric acid (75:25)	-	271 nm
Estimation of Ranolazine HCL in Tablet Dosage Form [9]	RP-HPLC	Buffer: Acetonitrile (60:40) pH adjusted with triethylamine	Intersil ODS C18	224 nm
Determining Related Substances in Compatibility Studies in Novel Formulation for Ranolazine. [10]	HPLC	Phosphate buffer pH 7.0: methanol (350:650 v/v)	Supelcosil C18 column	220 nm
Estimation of Ranolazine in tablet dosage form [11]	RP- HPLC	Sodium dihydrogen phosphate buffer (pH adjusted to 5 with dilute orthophosphoric acid): Acetonitrile (600:400	X-terra C18 column	210 nm
Estimation of Ranolazine in Bulk and Tablet Dosage Form [12]	RP -HPLC	Ammonium acetate buffer pH-4: Acetonitrile: Methanol (30:50:20)	ODS C18 column	200 nm
Estimation of Ranolazine in bulk and pharmaceutical formulation [12]	RP -HPLC	Sodium dihydrogen phosphate buffer pH adjusted to 5 with dilute orthophosphoric acid: Acetonitrile (600:400)	X-terra RP18 column	225 nm
Determination of Related Component and Assay of Ranolazine [13]	LC	-	C18 column	210 nm
Determination of Ranolazine HCl in bulk and dosage form [14]	LC	Methanol: water (99:1 %, V/V)	HiQ Sil C18 H S	273 nm
Quantitation of Ranolazine in rat plasma [15]	LC	-	C18 column	-
Quantitation of Ranolazine in rat plasma [16]	LC	Acetonitrile: water: formic acid: 10% n butylamine (70:30:0.5:0.08, v/v/v/v)	Nova-Pak C18 column	-
Determination of Ranolazine in human	HPLC	Acetonitrile:0.1% formic acid (90:10)	Agilent ZORBAX C18 column	-

plasma [17]				
Estimation of Ranolazine in Human Plasma [18]	LC	Methanol–10mM acetate (60:40 v/v, pH 4.0)	Zorbax Extend C18 column	-
Ranolazine HCL in bulk and tablet dosage form [19]	HPTLC	Chloroform: methanol: toluene (5 :1: 1 v/v/v)	silica gel aluminum plate 60 F – 254	273 nm
Estimation of Ranolazine [20]	HPTLC	Methanol: 10mM ammonium acetate solution (6:4 V/V)	Aluminum plates precoated with Silica gel G 60 F254	271 nm
Estimation of Ranolazine [21]	RP-HPLC	Phosphate buffer pH 3.5: Acetonitrile 65:35 (v/v)	Agilent Eclipse XDB C18 column	272 nm
Estimation of Ranolazine and eleven phase I metabolites [22]	LC-MS	-	Source- Finnigan MAT TSQ 700 MS	-
Analysis of Ranolazine and Dimethyl Ranolazine [23]	LC MS/MS	-	Chiralcel ODH Column	-
Quantitation of ranolazine in human plasma [24]	UPLC-MS	Acetonitrile aqueous ammonium acetate solution (40:60, V/V)	BEH C18 column	-
Quantitation of ranolazine and its three metabolites [25]	LC-MS	Methanol: 5 mM ammonium acetate	Gemini C18 column	-
Estimation of Ranolazine in human plasma [26]	LC -MS	Methanol water containing formic acid (1.0%, v/v) (65:35, v/v)	Peerless Cyano column	-
Semi-preparative resolution of ranolazine enantiomers [27]	LC	Methanol	Cellulose tris (3, 5-dimethylphenylcarbamate) Chiral stationary phases	-
Method for Ranolazine dihydrochloride and its degradation product [28]	RPHPLC	Methanol: Acetonitrile: phosphate buffer (pH 3.6,6.3 mM) (4: 3 :3, V/V)	C18 column	220 nm
Estimation of ranolazine in dog urine [29]	LC-MS	-	-	-
Determination of ranolazine in rat plasma [30]	LC-MS	Methanol:10 m ammonium acetate (76: 24 V/V)	C18 column	-

II. UV spectroscopic method

Ultraviolet (UV) spectroscopic approaches have also been explored for the quantification of ranolazine. Techniques such as first-order derivative spectroscopy and the area-under-curve (AUC) method were developed for this purpose. In addition, colourimetric analysis and visible spectrophotometry have been employed for estimating ranolazine concentrations. These methods are summarised in Table 2.

Table No.2: UV spectroscopic method

Title	Method	Wavelength	Linearity and R^2
Estimation of Ranolazine in bulk drug and pharmaceutical formulation [34]	UV method	272 nm	10-100 µg/ml
Estimation of Ranolazine in bulk and pharmaceutical dosage form [35]	First-order derivative spectroscopic method	263 nm and 282 nm	10-35 µg/ml and 0.9992
Estimation of ranolazine in API and tablet formulation [36]	Area under the curve method	261nm and 281 nm	75-200 µg/ml and 0.998
Estimation of ranolazine in bulk and formulation [37]	Novel spectrometric method	272 nm	10 – 100 µg/ml
Estimation of ranolazine in bulk [38]	Nanodrop spectrometric method	272 nm	12.5-2000 µg/ml
Development for some amide group-containing drugs using Bougainvillaea spectabilis bract extracts [39]	Colorimetry	418 nm	5-25 µg/ml
Determination of ranolazine in bulk and synthetic mixture [40]	Colorimetry	731 nm	5-25 mg/ml
Estimation of ranolazine in formulation [41]	Visible spectroscopy	510 and 525 nm	-

Table No.3: RP HPLC Method for simultaneous estimation of Ranolazine and Dronedarone

Title	Method	Mobile phase	Stationary phase	Wave length
Simultaneous estimation of Ranolazine and Dronedarone in bulk and pharmaceutical dosage forms. [43]	HPLC	0.02N NH2PO4 buffer (pH4) Acetonitrile (50 :50 V/V)	ODS column	282 nm
Simultaneous estimation of Ranolazine and Dronedarone in bulk [44]	RPHPLC	Ammonium acetate buffer(pH4): Acetonitrile (50: 50 V/V)	X-terra C18 column	275 nm

FTIR Method (Fourier Transform Infrared Spectroscopy)

Fourier transform infrared (FTIR) spectroscopy is employed to characterise ranolazine by measuring absorption of infrared radiation across different wavelengths. The resulting spectra provide insights into the molecule's functional groups, revealing characteristic bond vibrations and molecular interactions.[18]

DSC Method (Differential Scanning Calorimetry)

Differential scanning calorimetry (DSC) is utilised to evaluate the heat flow of a material as a function of temperature, thereby identifying phase transitions. This technique is widely applied to study thermal properties, including melting behaviour, degradation patterns, and crystallisation processes. [21]

Conclusion

This review highlights the diverse analytical methodologies reported for the assay of ranolazine, along with essential drug information such as its mechanism of action, pharmacodynamics, and pharmacokinetics. A wide spectrum of techniques has been employed for the quantification of ranolazine in biological matrices and pharmaceutical dosage forms. The survey of published literature indicates that spectrophotometric approaches are among the simplest and most cost-effective options for routine estimation in formulations. Chromatographic methods, including HPLC-UV, RP-HPLC, LC, HPTLC, and GC, provide reliable accuracy at relatively lower cost compared to advanced detection systems. The compiled information serves as a valuable resource for researchers engaged in formulation development and quality control of ranolazine.

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