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RANOLAZINE: A REVIEW ON ANALYTICAL METHOD AND ITS DETERMINATION IN SYNTHETIC MIXTURE

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Abstract:
Ranolazine is a piperazine derivative is a new anti-ischemic drug for the treatment of angina. Ranolazine is to inhibit late I_{Na} thus preventing sodium overload of the cell. As a consequence, Ranolazine prevents reverse mode sodium–calcium exchange and thus diastolic accumulation of calcium possibly resulting in improved diastolic tone and improved coronary blood flow.
This review article represents the various analytical methods which have been reported for estimation of Ranolazine in synthetic mixture. The Spectrophotometric techniques like fluorescent assay and area under curve spectroscopy; Chromatographic methods like HPLC, HPTLC and RP HPLC, GC, LC-MS, LC-MS/MS were reported.
Key words: *Ranolazine, RP- HPLC, GC, LC-MS, LC-MS/MS*

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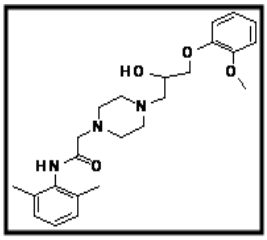
INTRODUCTION [1]:

Ranolazine is -(2,6-dimethylphenyl)-2{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl piprazine-1-yl}acetamide is piprazine derivative appears as white to off white crystalline powder.The drug is freely soluble in Methanol. Ranolazine is a strong base with pKa values of 13.6 [2], Six-membered Piprazine Ring. Ranolazine melts at 122-124 ^{0}C [3].



Chemical formula: $C_{24}H_{33}N_3O_4$
Molecular weight: 427.54 g/mol

Fig1: Structure of Ranolazine

Mechanism Of Action [4,5]

Ranolazine a piperazine derivative is a new anti-ischemic drug for the treatment of angina. Ranolazine

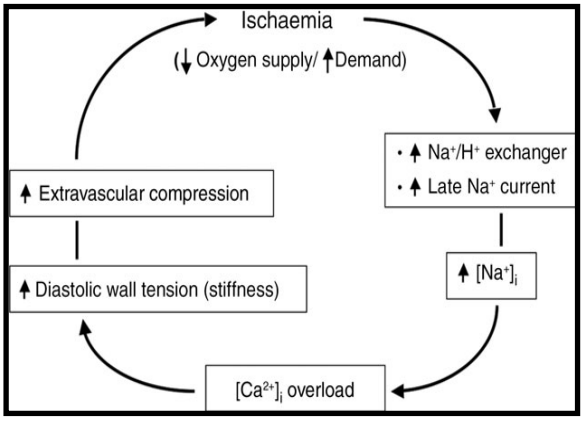


Fig 2: Mechanism of Ischaemia

is to inhibit late I_{Na} thus preventing sodium overload of the cell. As a consequence, ranolazine prevents reverse mode sodium–calcium exchange and thus diastolic accumulation of calcium possibly resulting in improved diastolic tone and improved coronary blood flow.

As a late I_{Na} inhibitor, ranolazine was also shown to increase action potential duration and thus modestly QT interval by 2–5 ms. This effect, however, is not heart rate-dependent and cannot be exaggerated during bradycardia. Furthermore, Ranolazine does not induce early after depolarization and does not increase dispersion of depolarization across the left ventricular wall [4].

It is act via selective inhibition of the late inward sodium current (I_{Na}) in cardiac muscle cells. This reduces intracellular sodium accumulation and calcium overload, and consequently improves myocardial relaxation and decreases left ventricular diastolic stiffness [5].

Ranolazine is administered orally and metabolize by CYP3A and excreted in intestine (5%) and in urine.

Combination of Ranolazine [6]

Ranolazine+Dronederone

Marketed formulation of Ranolazine [7]

Ranexa, Caroza, Rolazine

1. **Analytical Method**

A. **Compendial Method:**

Ranolazine is not official in Pharmacopoeia.

B. **Reported Method:**

I. Chromatographic Methods:

The high-pressure liquid chromatography (HPLC) for Ranolazine estimation. GC method for residual solvent determination in Ranolazine. HPTLC method is widely used chromatographic methods in the analysis of Ranolazine in Formulation. LC-MS/MS, LC-MS and UHPLC use for estimation of Ranolazine in Plasma. RP HPLC method also developed for determination of concentration of Ranolazine in human serum and also for simultaneous determination of Ranolazine and Dronederone.

Table 1: Summary of Chromatographic Method of Ranolazine

Title	Method	Mobile phase	Stationary phase	Wave Length	Reference
Ranolazine in bulk & marketed formulation	HPLC & UV	Methanol : 0.5% tri ethyl amine pH 6 with orthophosphoric acid (75:25)	-	271	8
Estimation of Ranolazine HCL in Tablet Dosage Form	RP-HPLC	Buffer : Acetonitrile(60:40),(pH adjust with triethylamine	Inertsil ODS C18	224 nm	9
Determining Related Substances in Compatibility Studies in novel Formulation for Ranolazine.	HPLC	Phosphate buffer pH 7.0 : methanol (350:650 v/v)	Supelcosil C18 column	220 nm	10
Estimation of Ranolazine in tablet dosage form	RP-HPLC	Sodium dihydrogen phosphate buffer (pH adjust to 5 with dilute orthophosphoric acid): Acetonitrile (600:400)	X-terra C_{18} column	210 nm	11
Estimation of Ranolazine in Bulk and Tablet Dosage Form	RP-HPLC	Ammonium acetate buffer pH-4 : Acetonitrile : methanol(30:50:20)	ODS C_{18} column	200 nm	12
Estimation of Ranolazine in bulk and P'ceutical formulation	RP-HPLC	Sodium dihydrogen phosphate buffer pH adjust to 5 with dilute orthophosphoric acid: Acetonitrile (600:400)	X-terra RP_{18} column	225 nm	13
Determination of Related Component and Assay of Ranolazine	LC	-	C_{18} column	210 nm	14
Determination of Ranolazine HCL in bulk and dosage form	LC	Methanol : water (99:1 %,V/V)	HiQ Sil C_{18} HS	273 nm	15
Quantitation of Ranolazine in rat plasma	LC	-	C_{18} column	-	16
Quantitation of Ranolazine in rat plasma	LC	Acetonitrile : water : formic acid : 10% *n*-butylamine (70:30:0.5:0.08, v/v/v/v)	Nova-Pak C_{18} column	-	17
Determination of Ranolazine in human plasma	HPLC	Acetonitrile: 0.1% formic acid(90:10)	Agilent-ZORBAX C_{18} column	-	18
Estimation of Ranolazine in Human Plasma	LC	methanol–10mM ammonium acetate (60:40 v/v, pH 4.0)	Zorbax extend C_{18} column	-	19

Continue …..

Ranolazine HCL in bulk and tablet dosage form	HPTLC	Chloroform: methanol : toluene (5 : 1 : 1 v/v/v)	silica gel aluminium plate 60 F – 254	273 nm	20
Estimation of Ranolazine	HPTLC	methanol **:** 10mM ammonium acetate solution (6:4 V/V)	Aluminium plates precoated with Silica gel G 60 F254	271 nm	21
Estimation of Ranolazine	RPHPLC	phosphate buffer pH 3.5 : Acetonitrile 65:35 (v/v)	Agilent Eclipse XDB C_{18} column	272 nm	22
Estimation of Ranolazine and eleven phase I metabolites	LC-MS	-	Source-Finnigan MAT TSQ 700 MS	-	23
Analysis of Ranolazine and Desmethyl ranolazine	LC-MS/MS	-	Chiralcel ODH Column	-	24
Quantitation of ranolazine in human plasma	U-HPLC-MS/MS	Acetonitrile : aqueous ammonium acetate solution(40:60, V/V)	BEH C_{18} column	-	25
Quantitation of ranolazine and its three metabolites	LC-MS/Ms	methanol: 5 mM ammonium acetate	Gemini C_{18} column	-	26
Estimation of Ranolazine in human plasma	LC-MS/MS	Methanol : water containing formic acid (1.0%, v/v) (65:35, v/v)	Peerless Cyano column	-	27
Semi preparative resolution of ranolazine enantiomers	LC	Methanol	cellulose tris(3,5dimethyl phenylcarbamate) Chiral stationary phases	-	28
Method for Ranolazine dihydrochloride and its degradation product	RPHPLC	Methanol : Acetonitrile : phosphate buffer (pH 3.6,6.3 mM) (4 : 3 : 3, V/V)	C_{18} column	220 nm	29
Estimation of ranolazine in dog urine	LC-MS	-	-	-	30
Determination of ranolazine in rat plasma	LC-MS	Methanol : 10 mM ammonium acetate (76 : 24 V/V)	C_{18} column	-	31
Determination of Ranolazine drug substance and drug product	RP-UPLC	monobasic sodium buffer : acetonitrile	Acquity BEH RP_{18} column	-	32
Determination of residual solvents in Ranolazine	GC	-	HP-INNOWAX column	-	33

Table 3: RP HPLC Method for Simultaneous Estimation of Ranolazine and Dronederone

Title	Method	Mobile phase	Stationary phase	Wave length	Ref.
Simultaneous estimation of Ranolazine and Dronederone in bulk and pharmaceutical dosage forms.	HPLC	0.02N NH2PO4 buffer (pH 4) : Acetonitrile (50 :50 V/V)	ODS column	282 nm	43
Simultaneous estimation of Ranolazine and Dronederone in bulk	RPHPLC	Ammonium acetate buffer (pH 4) : Acetonitrile (50 : 50 V/V)	X-terra C18 column	275 nm	44

II.UV Spectroscopic Method

First order derivative spectroscopy and Area Under curve spectroscopic technique was developed for simultaneous determination of Ranolazine. Calorimetry and Visible spectroscopy was developed for estimation of Ranolazine.

Table 2: Summary of UV Spectroscopic Method

Title	Method	Wavelength	Linearity and R^2	Recovery	REF.
Estimation of Ranolazine in bulk drug and pharmaceutical formulation	UV method	272 nm	10-100 µg/ml	99.77-100.33 %	34
Estimation of Ranolazine in bulk and pharmaceutical dosage form	First order derivative spectroscopic method	263 nm and 282 nm	10-35 µg/ml and 0.9992	-	35
Estimation of ranolazine in API and tablet formulation	Area under curve method	261nm and 281 nm	75-200 µg/ml and 0.998	99.42-99.97 %	36
Estimation of ranolazine in bulk and formulation	Novel spectrometric method	272 nm	10 – 100 µg/ml	99.345-100.43 %	37
Estimation of ranolazine in bulk	Nanodrop spectrometric method	272 nm	12.5-2000 µg/ml	-	38
Development for some amide group containing drugs using Bougainvillea spectabilis bract extracts	Colorimetry	418 nm	5-25 µg/ml	-	39
Determination of ranolazine in bulk and synthetic mixture	Colorimetry	731 nm	525 mg/ml	-	40
Estimation of ranolazine in formulation	Visible spectroscopy	510 and 525 nm	-	-	41

III. FTIR and DSC method [42]:
Prepare micro particles were characterized for micromeritics properties, polymer drug compatibility by FTIR, DSC, and SEM.
The yield of micro particles was up to 90 % and more than 98 % and having diameter of 285 µm.

DISCUSSION

Presented systematic review covers the current analytical methods for the determination of Ranolazine and its combination in pharmaceutical and biological samples like serum and plasma. HPLC method were found to be most widely use for Ranolazine. Various chromatographic conditions are presented in table.

CONCLUSION

The sensitivity, specificity, and better separation efficiency enable HPLC to be used frequently for simultaneous qualitative and quantitative determination of Ranolazine. The presented information is useful for the future study for researcher involved in formulation development and quality control of Ranolazine.

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