A Review on Analytical Methods for Ivabradine determination in Pharmaceutical Dosage Forms

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ABSTRACT

Ivabradine is a specific heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Ivabradine is a novel heart rate lowering medicine for the symptomatic management of stable angina pectoralis and symptomatic chronic heart failure. In multicenter clinical trials, it has been proved that Ivabradine is superior to beta-blocking agents during complex therapy of chronic heart failure accompanied with its beneficial effects related to cardiac remodeling, improvement of the currency of heart failure and diminution of patients rehospitalisation. It is suggested that Ivabradine as a newer agent is a valuable perspective drug for the treatment of congestive heart failure. This review is useful for the future study for researcher involved in formulation development and quality control of Ivabradine.

This review article represents the various analytical methods which have been reported for estimation of Ivabradine in pharmaceutical dosage form. The spectrophotometric techniques and Q-absorbance ratio method were reported by the various authors. Many researchers also worked in chromatographic areas like Thin layer chromatography, High performance liquid chromatography, and High performance thin layer chromatography. Ivabradine is also studied by various hyphenated techniques .We reviewed and reported almost all analytical methods with more emphasis on chromatographic mrthodsfor Ivabradine.

Keywords: Ivabradine, heart rate-lowering drug, hyphanatd Techniques

INTRODUCTION

Ivabradine is a specific heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Chemically 3-[3-({[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7yl] methyl} methylamino) propyl]-1, 3, 4, 5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin -2-One and available in the form of hydrochloride salt Ivabradine is the new class of drugs that have the ability of slowing the depolarization slope, reducing heart rate and show the activity similar to that of β-blockers. Ivabradine is freely soluble in water, methanol, and acetonitrile. The drug is a basic drug and having pKa values≈ 8.02 (O'Neil MJ., 2006, Sulfi et al., 2006 , Seerapu et al., 2010).

An increase in heart rate is a common occurrence in cardiac pathophysiology, particularly in heart failure, mediated by β-adrenergic receptors (βARs) following activation of the sympathetic nervous system. Although an elevated heart rate may initially compensate for insufficient cardiac output, sustained tachycardia usually leads to adverse haemodynamic consequences. Ivabradine is a novel pharmacological agent specifically inhibiting the hyperpolarization-activated pacemaker *If*–current (*If*) that underlies the rate of spontaneous diastolic depolarization in Sino atrial pacemaker cells. This drug is introduced in medical practice in the last decade is a pure heart rate-slowing agent. A large number of studies in patients with cardiovascular disease have demonstrated that heart rate is a very important and major independent risk factor for prognosis, because lowering of heart rate reduces cardiac work and diminished myocardial oxygen requirement. It was shown that ivabradine a selective inhibitor of the hyperpolarisation activated sodium channel (If) is involved in pacemaker generation and responsiveness of the sino-atrial node resulting in the heart rate reduction without negative inotropic action. Ivabradine in chronic heart failure improves diastolic function and attenuates cardiac tissue

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hypoxia. Long-term reduction of heart rate induced by Ivabradine reduced remodeling and preserved nitric oxide (NO) bioavailability, resulting from processes triggered early after reduction of heart rate. (Sulfi et al., 2006).

Structure of Ivabradine

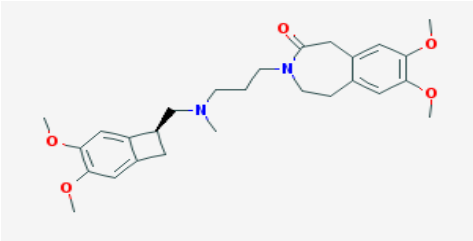

Fig.1 Structure of Ivabradine

Mechanism of action-

Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, and inhibit the *If*–current (*If*) which reduces the cardiac pacemaker activity of the sinus node which decreases heart rate without an effect on ventricular repolarization or myocardial contractility. Ivabradine is recommended for angina pectoris and symptomatic chronic heart failure. Ivabradine inhibit the "funny" channel pacemaker current (*If*) in the sinoatrial node in a dose-dependent fashion, resulting in a lower heart rate and thus more blood to flow to the myocardium. When we use calcium channel blockers and beta blockers for lowering heart rate, they are good in action but show adverse effects due to their negative ionotropic effects. Therefore, Ivabradine is designed as a "pure" heart rate-lowering drug. It causes no serious adverse effects. (Corlanor® is a first-in-class, HCN channel blocker that lowers heart rate).

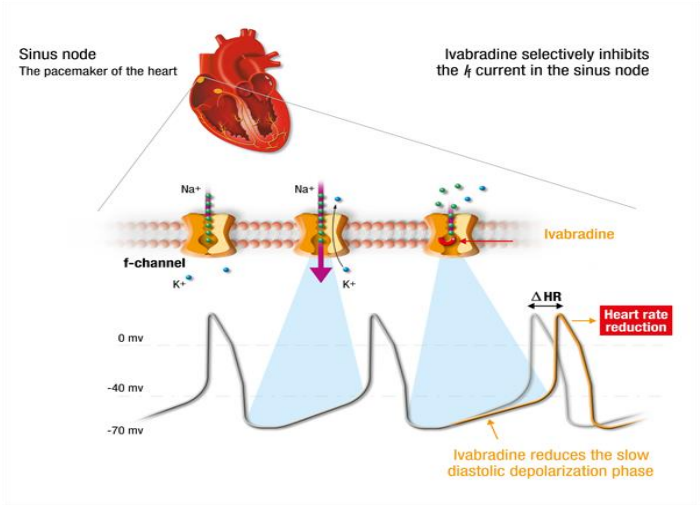

Fig.2 Mechanism of Ivabradine

ANALYTICAL METHODS

I. Chromatographic method

Table no. 1 Summary of chromatographic methods for Ivabradine

Sr. no	Title	Method	Mobile phase	Stationary Phase	Wavelength	Ref
1	Development and validation of RP-HPLC method for the estimation of Ivabradine hydrochloride in tablets.	RP-HPLC	Methanol:25mm phosphate Buffer (60:40 *v/v*), adjusted to pH 6.5 with orthophosphoric acid	SS Wakosil C18AR, 250×4.6 mm, 5 µm column	285 nm	Seerapu et al., 2010
2	Development and validation of stability-indicating HPTLC method for Ivabradine HCL.	HPTLC	Chloroform: Methanol (1:1 *v/v*)	Aluminum Plate precoated with Silica Gel 60 F254	286 nm	Damle et al., 2015
3	Development and validation of RP-HPLC method for analysis of Ivabradine	RP-HPLC	Buffer (pH-7.3), methanol and acetonitrile (55:15:30	C18 column (VP-ODS, 150 x 4.6 mm, 5	-----	Rahman et al., 2012

	hydrochloride in tablet dosage forms.		*v/v*)	µm)		
4	Chromatographic analysis of ivabradine on polar, nonpolar and chemically modified adsorbents by HPTLC.	HPTLC	Aqueous (methanol–water and acetonitrile–water) and non-aqueous (methanol–acetonitrile and methanol–dimethyl sulfoxide)	High-performance TLC plates	-----	Piotr P et al., 2013
5	Determination of the related substances in Ivabradine hydrochloride and its tablets by HPLC.	HPLC	n-hexane and isopropanol (0.1% triethylamine) (60:40)	Chiral hplc column	286 nm	Xiaoli Y et al, 2011
6	Development of validated RP-HPLC method for simultaneous estimation of Carvedilol and Ivabradine.	RP- HPLC	Acetonitrile: Phosphate Buffer pH 3 adjusted with o-Phosphoric acid (75:25)	Hypersil ODS C18 in isocratic mode	275 nm.	Patel H et al .,2015
7	Quantitative determination and validation of Ivabradine HCL by stability indicating RP-HPLC method and spectrophotometric method in solid dosage form.	RP-HPLC	0.5% Formic Acid (pH=7.0): Acetonitrile (65: 35 *v/v*)	Inertsil ODS-3V [250 mm × 4.6mm] 5m column	286 nm	Maheshwaria S et al., 2010
8	Determination of Ivabradine hydrochloride in the human plasma and the bioequivalence study by LC-MS/MS.	LC-MS/MS	methanol: water (containing 5 mol·L-1ammonium formate and 0. 1% formic acid)	METHODS C18column (150 mm × 4. 6 mm, 3. 5 µm)	----	Yan-yan et al ., 2014
9	Validated stability-indicating high performance thin layer chromatographic method for determination of Ivabradine hydrochloride in bulk and marketed formulation: An application to kinetic study.	HPTLC	Ethyl acetate: 0.389 M ammonium acetate in methanol (1:5, *v/v*) as solvent system	Precoated silica gel 60 F_{254} aluminuim plates (10×10 cm 100 um thickness)	287 nm	Motisariya M.H.,2013
10	Validated stability indicating chromatographic methods for determination of Ivabradine Hydrochloride in the presence of its acidic degradation Product.	TLC HPLC	Methanol: chloroform: water (8:1:1 *v/v*) Methanol: acetonitrile: phosphate buffer pH 3 (50:40:10 *v/v*)	Aluminium sheet of silica gel 60 F254 C18 column	286 nm 230nm	Nadia M. M et al.,2016

11	Characterization of degradation products of Ivabradine by LC-HR-MS/MS: a typical case of exhibition of different degradation behavior in HCl and H_2SO_4 acid hydrolysis.	LC-HR-MS/MS	Ammonium Formate (10 mm, pH 3.0) and acetonitrile	Phenomenex Luna C18 (250 × 4.6 m m, 5.0 µm) column	286 nm	Patel et al., 2015
12	Simultaneous determination of ivabradine and its metabolites in human plasma by liquid chromatography--tandem mass spectrometry.	Tandem Mass Spectrometry	Liquid chromatography--tandem mass spectrometry	C18 column	----	MaryseFrançois-Bouchard et al.,2000

II. UV Spectroscopic Method

First order derivative spectroscopy and Area Under the curve spectroscopic technique was developed for simultaneous determination of Ivabradine was developed

Table no 2. Summary of Spectroscopic methods for Ivabradine

Sr.No	Title	Method	Wavelength	Linearity (ug/ml) and R^2	Recovery	Ref
1	Rapid and selective UV spectrophotometric and RP-HPLC methods for dissolution studies of Ivabradine controlled release formulations.	UV	286 nm	5-60 µg/ml 0.9998	-----	Panda et al., 2014
2	Q-absorbance ratio spectrophotometric method for simultaneous determination of atenolol and ivabradine hydrochloride in synthetic mixture	Q-absorbance ratio	286.04 nm and 276 nm	2-10 µg/ml 0.998	100.47 ± 0.348	Patil et al., 2016

DISCUSSION

The presented systematic review covers the current analytical methods for the determination of Ivabradine and its combination in pharmaceutical and biological samples like serum and plasma. HPLC method were found to be most widely use for Ivabradine. 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 Ivabradine. The presented information is useful for the future study for researcher involved in formulation development and quality control of Ivabradine.

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Conflict of Interest: None.

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