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 methods for 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’Neill MJ., 2006, Sulf 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 (BARs) 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-slwing 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 ivabr

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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](image)

**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 inotropic 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](image)

**ANALYTICAL METHODS**

I. Chromatographic method

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Title</th>
<th>Method</th>
<th>Mobile phase</th>
<th>Stationary Phase</th>
<th>Wavelength</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Development and validation of RP-HPLC method for the estimation of Ivabradine hydrochloride in tablets.</td>
<td>RP-HPLC</td>
<td>Methanol:25mm phosphate Buffer (60:40 v/v), adjusted to pH 6.5 with orthophosphoric acid</td>
<td>SS Wakosil C18AR, 250×4.6 mm, 5 μm column</td>
<td>285 nm</td>
<td>Seerapu et al., 2010</td>
</tr>
<tr>
<td>2</td>
<td>Development and validation of stability-indicating HPTLC method for Ivabradine HCL.</td>
<td>HPTLC</td>
<td>Chloroform: Methanol (1:1 v/v)</td>
<td>Aluminum Plate precoated with Silica Gel 60 F254</td>
<td>286 nm</td>
<td>Damle et al., 2015</td>
</tr>
<tr>
<td>3</td>
<td>Development and validation of RP-HPLC method for analysis of Ivabradine</td>
<td>RP-HPLC</td>
<td>Buffer (pH-7.3), methanol and acetonitrile (55:15:30)</td>
<td>C18 column (VP-ODS, 150 x 4.6 mm, 5</td>
<td>-----</td>
<td>Rahman et al., 2012</td>
</tr>
<tr>
<td>No.</td>
<td>Method Description</td>
<td>Column Details</td>
<td>Mobile Phase</td>
<td>Detection Wavelength</td>
<td>Reference</td>
<td></td>
</tr>
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</tr>
<tr>
<td>4</td>
<td>Chromatographic analysis of ivabradine on polar, nonpolar and chemically modified adsorbents by HPTLC.</td>
<td>HPTLC</td>
<td>Aqueous (methanol–water and acetonitrile–water) and non-aqueous (methanol–acetonitrile and methanol–dimethyl sulfoxide)</td>
<td>High-performance TLC plates</td>
<td>-----</td>
<td>Piotr P et al., 2013</td>
</tr>
<tr>
<td>5</td>
<td>Determination of the related substances in Ivabradine hydrochloride and its tablets by HPLC.</td>
<td>HPLC</td>
<td>n-hexane and isopropanol (0.1% triethylamine) (60:40)</td>
<td>Chiral hplc column</td>
<td>286 nm</td>
<td>Xiaoli Y et al, 2011</td>
</tr>
<tr>
<td>7</td>
<td>Quantitative determination and validation of Ivabradine HCL by stability indicating RP-HPLC method and spectrophotometric method in solid dosage form.</td>
<td>RP-HPLC</td>
<td>0.5% Formic Acid (pH=7.0): Acetonitrile (65: 35 v/v)</td>
<td>Inertsil ODS-3V [250 mm × 4.6mm] 5m column</td>
<td>286 nm</td>
<td>Maheshwar S et al., 2010</td>
</tr>
<tr>
<td>8</td>
<td>Determination of Ivabradine hydrochloride in the human plasma and the bioequivalence study by LC-MS/MS.</td>
<td>LC-MS/MS</td>
<td>methanol: water ( containing 5 mol-L-1ammonium formate and 0. 1% formic acid)</td>
<td>METHODS C18column (150 mm × 4. 6 mm, 3. 5 μm)</td>
<td>----</td>
<td>Yan-yan et al , 2014</td>
</tr>
<tr>
<td>9</td>
<td>Validated stability-indicating high performance thin layer chromatographic method for determination of Ivabradine hydrochloride in bulk and marketed formulation: An application to kinetic study.</td>
<td>HPTLC</td>
<td>Ethyl acetate: 0.389 M ammonium acetate in methanol (1:5, v/v) as solvent system</td>
<td>Precoated silica gel 60 F254 aluminium plates (10×10 cm 100 um thickness)</td>
<td>287 nm</td>
<td>Motisariya M.H.,2013</td>
</tr>
<tr>
<td>10</td>
<td>Validated stability indicating chromatographic methods for determination of Ivabradine Hydrochloride in the presence of its acidic degradation Product.</td>
<td>TLC and HPLC</td>
<td>Methanol: chloroform: water (8:1:1 v/v)</td>
<td>Aluminium sheet of silica gel 60 F254 C18 column</td>
<td>286 nm 230nm</td>
<td>Nadia M. M et al.,2016</td>
</tr>
</tbody>
</table>
Characterization of degradation products of Ivabradine by LC-HR-MS/MS: a typical case of exhibition of different degradation behavior in HCl and H₂SO₄ acid hydrolysis.


**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>
<thead>
<tr>
<th>Sr.No</th>
<th>Title</th>
<th>Method</th>
<th>Wavelength</th>
<th>Linearity (µg/ml) and R²</th>
<th>Recovery</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapid and selective UV spectrophotometric and RP-HPLC methods for dissolution studies of Ivabradine controlled release formulations.</td>
<td>UV</td>
<td>286 nm</td>
<td>5-60 µg/ml 0.9998</td>
<td>-----</td>
<td>Panda et al., 2014</td>
</tr>
<tr>
<td>2</td>
<td>Q-absorbance ratio spectrophotometric method for simultaneous determination of atenolol and ivabradine hydrochloride in synthetic mixture</td>
<td>Q-absorbance ratio</td>
<td>286.04 nm and 276 nm</td>
<td>2-10 µg/ml 0.998</td>
<td>100.47 ± 0.348</td>
<td>Patil et al., 2016</td>
</tr>
</tbody>
</table>

**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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