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 represent the various analytical methods which has 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.

Keywords: Ranolazine, synthetic mixture, analytical development

INTRODUCTION (1):

Ranolazine is -(2,6-dimethylphenyl)-2{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl piprazine-1-yl]acetamide is piperazine 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. Edaravone melts at 122-124 °C(3).

Figure: 1 Structure of Ranolazine
Mechanism of Action (4,5)
Ranolazine 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. 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 repolarization 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 are 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.

Figure 2: Mechanism of Ischaemia
### Table No.1: Summary of Chromatographic Method of Edaravone

<table>
<thead>
<tr>
<th>Title</th>
<th>Method</th>
<th>Mobile phase</th>
<th>Stationary phase</th>
<th>Wave Length</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranolazine in bulk &amp; marketed formulation</td>
<td>HPLC &amp; UV</td>
<td>Methanol : 0.5% triethyl amine pH 6 with orthophosphoric acid (75:25) Buffer</td>
<td></td>
<td>271</td>
<td>8</td>
</tr>
<tr>
<td>Estimation of Ranolazine HCL in Tablet Dosage Form</td>
<td>RP-HPLC</td>
<td>Acetonitrile(60:40), pH adjust with triethylamine</td>
<td>Inertsil ODS C18</td>
<td>224 nm</td>
<td>9</td>
</tr>
<tr>
<td>Estimation of Ranolazine in tablet dosage form</td>
<td>RP-HPLC</td>
<td>Sodium dihydrogen phosphate buffer (pH adjust to 5 with dilute orthophosphoric acid): Acetonitrile (600:400)</td>
<td>X-terra C18 column</td>
<td>210 nm</td>
<td>11</td>
</tr>
<tr>
<td>Estimation of Ranolazine in Bulk and Tablet Dosage Form</td>
<td>RP-HPLC</td>
<td>Ammonium acetate buffer pH 4 : Acetonitrile : methanol(30:50:20) Sodium dihydrogen phosphate buffer pH adjust to 5 with dilute orthophosphoric acid: Acetonitrile (600:400)</td>
<td>ODS C18 column</td>
<td>200 nm</td>
<td>12</td>
</tr>
<tr>
<td>Estimation of Ranolazine in bulk and Pharmaceutical formulation</td>
<td>RP-HPLC</td>
<td>-</td>
<td>X-terra RP C18 column</td>
<td>225 nm</td>
<td>13</td>
</tr>
<tr>
<td>Determination of Related Component and Assay of Ranolazine</td>
<td>LC</td>
<td>-</td>
<td>C18 column</td>
<td>210 nm</td>
<td>14</td>
</tr>
<tr>
<td>Determination of Ranolazine HCL in bulk and dosage form</td>
<td>LC</td>
<td>Methanol : water (99:1 %,V/V)</td>
<td>HiQ Sil C18 HS</td>
<td>273 nm</td>
<td>15</td>
</tr>
<tr>
<td>Quantitation of Ranolazine in rat plasma</td>
<td>LC</td>
<td>-</td>
<td>C18 column</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Quantitation of Ranolazine in rat plasma</td>
<td>LC</td>
<td>Acetonitrile : water : formic acid : 10% n-butylamine (70:30:0.5:0.08, v/v/v/v)</td>
<td>Nova-Pak C18 column</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>Determination of Ranolazine in human plasma</td>
<td>HPLC</td>
<td>Acetonitrile: 0.1% formic acid(90:10)</td>
<td>Agilent-ZORBAX C18 column</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Estimation of Ranolazine in Human Plasma</td>
<td>LC</td>
<td>methanol–10mM ammonium acetate (60:40 v/v, pH 4.0)</td>
<td>Zorbax extend C18 column</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Ranolazine HCL in bulk and tablet dosage form</td>
<td>HPTLC</td>
<td>Chloroform: methanol : toluene (5 : 1 : 1 v/v/v)</td>
<td>silica gel aluminium plate 60 F – 254</td>
<td>273 nm</td>
<td>20</td>
</tr>
<tr>
<td>Estimation of Ranolazine</td>
<td>HPTLC</td>
<td>methanol : 10mM ammonium acetate solution (6:4 V/V) phosphate buffer pH</td>
<td>Aluminium plates precoated with Silica gel G 60 F254</td>
<td>271 nm</td>
<td>21</td>
</tr>
<tr>
<td>Estimation of Ranolazine</td>
<td>RPHPLC</td>
<td>-</td>
<td>Agilent Eclipse XDB C18 column</td>
<td>272 nm</td>
<td>22</td>
</tr>
</tbody>
</table>
II. UV spectroscopic method

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

Table No.2: Summary of UV spectroscopic method

<table>
<thead>
<tr>
<th>Title</th>
<th>Method</th>
<th>Wavelength</th>
<th>Linearity and R²</th>
<th>Recovery</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimation of Ranolazine in bulk drug and pharmaceutical formulation</td>
<td>UV method</td>
<td>272 nm</td>
<td>10-100 µg/ml</td>
<td>99.77-100.33 %</td>
<td>34</td>
</tr>
<tr>
<td>Estimation of Ranolazine in bulk and pharmaceutical dosage form</td>
<td>First order derivative spectroscopic method</td>
<td>263 nm and 282 nm</td>
<td>10-35 µg/ml and 0.9992</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>Estimation of ranolazine in API and tablet formulation</td>
<td>Area under curve method</td>
<td>261 nm and 281 nm</td>
<td>75-200 µg/ml and 0.998</td>
<td>99.42-99.97 %</td>
<td>36</td>
</tr>
<tr>
<td>Estimation of ranolazine in bulk and formulation</td>
<td>Novel spectrometric method</td>
<td>272 nm</td>
<td>10 – 100 µg/ml</td>
<td>99.345-100.43 %</td>
<td>37</td>
</tr>
<tr>
<td>Estimation of ranolazine in bulk</td>
<td>Nanodrop spectrometric method</td>
<td>272 nm</td>
<td>12.5-2000 µg/ml</td>
<td>-</td>
<td>38</td>
</tr>
<tr>
<td>Development for some amide group</td>
<td>Colorimetry</td>
<td>418 nm</td>
<td>5-25 µg/ml</td>
<td>-</td>
<td>39</td>
</tr>
</tbody>
</table>
containing drugs using Bougainvillea spectabilis bract extracts

Determination of ranolazine in bulk and synthetic mixture

Estimation of ranolazine in formulation

III. FTIR and DSC method(42):

Prepare microparticles were characterized for micromeritic properties, polymer drug compatibility by FTIR, DSC, SEM.

The yield of microparticles was up to 90% and more than 98% and having diameter of 285 μm.

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

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

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 Ranolazne. The presented information is useful for the future study for researcher involved in formulation development and quality control of Ranolazine.

REFERENCES

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