THE INFLUENCE OF pH ON DRUG RELEASE FROM ZIDOVUDINE MATRICES CONTAINING DIFFERENT GRADES OF HYDROXYPROPYL METHYL CELLULOSE

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ABSTRACT

The present study examines the effect of multimedia dissolution profile on the drug release of sustained release hydrophilic matrices of zidovudine containing combination of different grades of hydroxypropyl methylcellulose. Zidovudine the first anti-HIV compound approved for clinical use is widely used for the treatment of AIDS either alone or in combination with other antiviral agents. Matrices were prepared using combination of different grades of HPMC viz, HPMCK4M and HPMCK15M to sustain the release of the drug. Multimedia dissolution studies were performed to mimic the in-vivo condition by doing in-vitro test. The pH/buffer selection is based on the exposure of drug from stomach to intestine/colon. The study ensures the impact of pH changes on dissolution and release of drug substance for absorption. Matrices also provide quite regulated release of the drug zidovudine over an extended period of time.

Key words: Multimedia, Dissolution, Matrices, pH.

INTRODUCTION

Zidovudine, the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of it is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 hours. In the systemic circulation, it is first converted to zidovudine triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of zidovudine -triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Since zidovudine acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of zidovudine is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of zidovudine immediately after intravenous or oral administration. Zidovudine is absorbed throughout the GIT. The drug is freely soluble at any pH and hence judicious selection of release retarding excipients is necessary for achieving constant in vivo release. The most commonly used method of modulating the drug release is to include it in a matrix system [1-6].

Multimedia dissolution is to mimic the in-vivo condition by doing in-vitro test and pH/buffer selection is based on the exposure of drug from stomach to intestine/colon and to ensure the impact of pH changes on dissolution and release of drug substance for absorption [7-9].

Sustained release drug delivery system of zidovudine is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time by using different grades of Hydroxypropyl methylcellulose (HPMC) viz. HPMCK4M and HPMCK15M [10-14].

MATERIALS UNDER METHODS

Zidovudine was obtained as a gift sample and tablets were prepared by direct compression using HPMCK4M and HPMCK15M polymer combinations. Other excipients used were Magnesium stearate, Talc, MCC and dibasic calcium phosphate. The drug was analyzed by UV spectrophotometer (UV 1601 Shimadzu, Japan) at 266nm.

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RESULTS AND DISCUSSION

Physical properties of the tablets were found within the probable limits as shown in Table (1). The drug content was estimated from the absorbance obtained. Three tablets of zidovudine were placed into three different pH of phosphate buffer (pH2.4, pH 6.8 and pH 7.4). The USP dissolution apparatus was set at rotation 50 rpm and temperature of the assembly was set at 37°C. Absorbance was measured at 266 nm by collecting sample at different time intervals up to 12hrs. The percentage drug release was calculated at different time intervals at different pH and shown in Table (2). The graph was plotted between percent drug release and time for different dissolution media and shown in Fig (1).

Table 1. Physical characteristics of the tablets

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>HPMC K4M mg</th>
<th>HPMC K15M mg</th>
<th>Weight mg Mean ± SD</th>
<th>Hardness Kg Mean ± SD</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>15</td>
<td>120 ± 1.96</td>
<td>5.50 ± 0.12</td>
<td>0.50-0.08</td>
</tr>
</tbody>
</table>

Table 2. Result of dissolution studies with different pH

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Time hrs.</th>
<th>Absorbance (nm.)</th>
<th>pH2.4</th>
<th>pH6.8</th>
<th>pH7.4</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.4</td>
<td>6.8</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.161</td>
<td>0.168</td>
<td>0.222</td>
<td>12.78</td>
<td>13.5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.186</td>
<td>0.194</td>
<td>0.438</td>
<td>16.16</td>
<td>16.53</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.214</td>
<td>0.224</td>
<td>0.573</td>
<td>19.68</td>
<td>22.24</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>0.321</td>
<td>0.361</td>
<td>0.692</td>
<td>31.69</td>
<td>36.24</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>0.431</td>
<td>0.582</td>
<td>0.732</td>
<td>45.22</td>
<td>61.2</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>0.446</td>
<td>0.612</td>
<td>0.811</td>
<td>46.27</td>
<td>65.52</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>0.567</td>
<td>0.68</td>
<td>0.904</td>
<td>60.97</td>
<td>84.1</td>
</tr>
</tbody>
</table>

Fig 1. Percent drug release V/s Time in different pH media

CONCLUSION

The release profile of zidovudine from the matrices increased continuously with time, and the amount of drug release best seen in acidic media (pH=7.4). The cumulative amount of drug release is higher at pH 7.4 than that of pH 6.8 by 11.4 % and then that of pH 2.4 by 24.53 %. This increase in drug release at higher pH can be attributed to pH dependent solubility of stavudine. As the pH increases, the solubility of zidovudine increases which might increase drug release from matrices.

REFERENCES