FORMULATION DEVELOPMENT OF LAMIVUDINE TABLETS - APPLICATION OF A NEW UV SPECTROPHOTOMETRIC METHOD DEVELOPED

K. P. R. Chowdary*, K. Ravi Shankar and Prathyusa. Ravi

Vikas Institute of Pharmaceutical Sciences, Nidigatla Road, Rajahmundry- 533103.

ABSTRACT

Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI) used as an antiretroviral drug. A new UV spectrophotometric method comparable to HPLC methods is developed for lamivudine and reported earlier. The objective of the present study is to evaluate the UV spectrophotometric method developed for lamivudine for its application in formulation development studies. Lamivudine tablets were formulated employing commonly used tablet excipients. The effect of two diluents and two disintegrants on the disintegration and dissolution rate of Lamivudine tablets was evaluated. The tablets were prepared by wet granulation method and evaluated for hardness, friability, drug content, disintegration time and dissolution rate characteristics. The drug content and dissolution rate of drug from the prepared tablets was determined by the UV spectrophotometric method developed. For comparison the dissolution rate of one market brand of Lamivudine tablets was also studied. All the tablets prepared fulfilled the official (IP2010) specifications of hardness, friability, drug content and disintegration time of uncoated tablets. All the dissolution parameters estimated (PD_{10}, DE30, and K_{1}) indicated rapid dissolution of Lamivudine from all the tablets formulated. Tablets formulated employing lactose as diluent (F_{1}, F_{2}) gave rapid and higher dissolution of Lamivudine when compared to those formulated employing DCP as diluent(F_{3}, F_{4}). With both the diluents, tablets formulated employing Primojel as disintegrant gave higher dissolution rate of Lamivudine than those formulated with potato starch as disintegrant. The market brand also gave rapid dissolution of Lamivudine. Among all, formulation F_{1} prepared using lactose as diluent and Primojel as disintegrant gave rapid and higher dissolution of Lamivudine when compared to all other formulations and also market brand. Hence lactose
as diluent and Primojel as disintegrant are recommended for the formulation of Lamivudine tablets with fast dissolution characteristics. Thus the UV spectrophotometric method developed could be applied in the formulation development research to evaluate the products formulated and to select the best.

KEYWORDS: Lamivudine, UV Spectrophotometric method, Formulation development.

INTRODUCTION
Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor (nRTI) used as an antiretroviral agent that inhibits replication of retroviruses in combination with zidovudine in the management of HIV (human immunodeficiency virus). It is marketed by GlaxoSmithKline with the brand names Zeffix, Heptovir, Epivir, and Epivir-HBV. Lamivudine is also used for treatment of chronic hepatitis B. Several analytical methods have been reported for the determination of lamivudine either individually or in combination with other anti-retroviral drugs in the dosage forms and in biological fluids. These methods include visible spectrometry,[1] high performance liquid chromatographic (HPLC)[2-10], liquid chromatographic mass spectrometric (LC-MS)[11-16], capillary electrophoretic[17-26] and HPTLC.[27] Literature on UV spectrophotometric methods for the estimation of Lamivudine is scanty. A new UV spectrophotometric method comparable to HPLC methods is developed for lamivudine and reported earlier.[28]

Analytical method development and formulation development are critical activities in pharmaceutical research in Pharma industry. One of the important applications of analytical method is in formulation development in addition to quality control. The objective of the present study is to evaluate the UV spectrophotometric method developed for lamivudine for its application in formulation development studies.

EXPERIMENTAL
MATERIALS
Lamivudine was a gift sample M/s Eisai Pharma technology Pvt Ltd, Visakhapatnam. Methanol, hydrochloric acid, sodium hydroxide, di hydrogen phosphate, Primojel, potato starch, acacia, lactose, di calcium phosphate, talc, magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.
METHODS

Preparation of Lamivudine Tablets by Wet Granulation Method: Lamivudine (50 mg) tablets were prepared by wet granulation method as per the formulae given in Table 1. The required quantities of drug, lactose, acacia, and potato starch were blended thoroughly in a dry mortar. Water (q.s) was added and mixed thoroughly to form dough mass. The mass was pressed through mesh No. 12 to obtain wet granules. After drying the wet granules at 60°C for 1 h, they were passed through mesh No. 16 to break the aggregates. To the dried granules, Primojel, talc and magnesium stearate (already screened through sieve No.100) were added and mixed thoroughly in a polyethylene bag. Then the granules were compressed into tablets using an 8-station RIMEK tablet punching machine employing 9 mm flat punches.

Evaluation of Tablets
Lamivudine tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as per official methods.

Hardness
The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm.\textsuperscript{[2]}

Friability
The friability of the tablets was measured in a Roche friabilator using the formula Friability (\%) = \left[ \text{Initial weight - Final weight} / \text{Initial weight} \right] \times 100

Drug Content
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Lamivudine was taken into 100 ml volumetric flask, dissolved in water and the solution was made up to 100ml and filtered through whatman filter paper No.1. The filtrate was collected and suitably diluted with water and assayed for Lamivudine at 280 nm.

Disintegration time
Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.
Dissolution Rate Study

Dissolution rate of Lamivudine from various tablets prepared was studied in 0.01N HCl (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Lab India Disso 8000) with a paddle stirrer at 50rpm. A temperature of 37±1°C was maintained throughout the study. One tablet containing 50 mg of Lamivudine was used in the test. Samples of dissolution fluid(5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted and assayed for Lamivudine at 280 nm. The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction was made in calculating the amount of drug dissolved. All dissolution rate experiments were conducted in duplicate (n=2).

Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE$_{30}$) values were estimated as suggested by Khan.[29]

RESULTS AND DISCUSSION

Lamivudine tablets were prepared by wet granulation method employing the commonly used tablet excipients as per the formulae given in Table 1. Two diluents namely lactose and DCP and two disintegrants namely potato starch and Pimojel were used in the formulation of various tablets with a view to evaluate the effect of diluent and disintegrants on the dissolution rate of lamivudine tablets. For comparison the dissolution rate of a market brand of Lamivudine namely lamivir tablets of M/s CIPLA Ltd., Sikkim was also evaluated.

The physical parameters of the Lamivudine tablets prepared are given in Table: 2. The drug content and dissolution rate of drug from the prepared tablets was determined by the UV spectrophotometric method developed. The hardness of the tablets was in the range 4.5-5.0 kg/cm.$^2$. Weight loss in the friability test was less than 0.92% in all the cases. Lamivudine content of the tablets prepared was within 100±3 %. The disintegration times were in the range 30 sec to 2 min- 20 sec. All the tablets prepared fulfilled the official (IP2010) disintegration time specification of uncoated tablets.

The dissolution rate of various Lamivudine tablets prepared was studied in 0.01N hydrochloric acid as prescribed in IP 2010. The dissolution profiles of various tablets prepared are shown in Fig.1. The dissolution parameters of Lamivudine tablets prepared are given in Table 3. The dissolution data were analyzed as per zero order and first order kinetics.
in each case. The correlation coefficient (r) values were higher in the first order model than in zero order models indicating that the dissolution of Lamivudine followed first order kinetics. The correlation coefficient (r) values in the first order model were found to be in the range of 0.920-0.985. The corresponding first order dissolution rate (K₁) values of various products were estimated from the slope of the first order linear regressions. Dissolution Efficiency (DE₃₀) values were calculated as described by Khan.²⁹ The dissolution parameters of various Lamivudine tablets are summarized in Table 3.

All the dissolution parameters estimated (PD₁₀, DE₃₀, and K₁) indicated rapid dissolution of Lamivudine from all the tablets formulated. Tablets formulated employing lactose as diluent (F₁, F₂) gave rapid and higher dissolution of Lamivudine when compared to those formulated employing DCP as diluent. (F₃,F₄). The dissolution rate (K₁) was found to be 0.0329, 0.0089, 0.0043, 0.0028 and 0.0175 min⁻¹ in the case of formulations F₁,F₂,F₃,F₄ and market tablets respectively. With both the diluents, tablets formulated employing Primojel as disintegrant gave higher dissolution rate of Lamivudine than those formulated with potato starch as disintegrant. The market brand also gave rapid dissolution of Lamivudine. Among all, formulation F₁ prepared using lactose as diluent and Primojel as disintegrant gave rapid and higher dissolution of Lamivudine when compared to all other formulations and also market brand. Hence lactose as diluent and Primojel as disintegrant are recommended for the formulation of Lamivudine tablets with fast dissolution characteristics.

Table 1: Formulae of Lamivudine Tablets Prepared by Wet Granulation Method

<table>
<thead>
<tr>
<th>Ingredient (mg/tab)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Primojel (4%)</td>
<td>9.2</td>
<td>-</td>
<td>9.2</td>
<td>-</td>
</tr>
<tr>
<td>Potato starch (15%)</td>
<td>-</td>
<td>34.5</td>
<td>-</td>
<td>34.5</td>
</tr>
<tr>
<td>Acacia (2%)</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Lactose (q.s)</td>
<td>107</td>
<td>81.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DCP (q.s)</td>
<td>-</td>
<td>-</td>
<td>107</td>
<td>81.7</td>
</tr>
<tr>
<td>Talc (2%)</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Magnesium stearate (2%)</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Total Weight (mg)</td>
<td>230</td>
<td>230</td>
<td>230</td>
<td>230</td>
</tr>
</tbody>
</table>
Table 2: Physical Parameters of Lamivudine Tablets Prepared by Wet Granulation Method and Commercial Tablet

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (% Wt loss)</th>
<th>Disintegration Time (min-sec)</th>
<th>Drug Content (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.0</td>
<td>0.83</td>
<td>0-30</td>
<td>95.8</td>
</tr>
<tr>
<td>F2</td>
<td>4.5</td>
<td>0.89</td>
<td>2-20</td>
<td>99.1</td>
</tr>
<tr>
<td>F3</td>
<td>5.0</td>
<td>0.88</td>
<td>2-10</td>
<td>98.5</td>
</tr>
<tr>
<td>F4</td>
<td>4.5</td>
<td>0.91</td>
<td>1-35</td>
<td>97.7</td>
</tr>
<tr>
<td>Lamivir HBV</td>
<td>5.0</td>
<td>0.91</td>
<td>1-40</td>
<td>98.9</td>
</tr>
</tbody>
</table>

Fig.1: Dissolution Profiles of Lamivudine Tablets Prepared by Wet Granulation Method and Commercial Tablet

Table 3: Dissolution Parameters of Lamivudine Tablets Prepared by Wet Granulation Method and Commercial Tablet

<table>
<thead>
<tr>
<th>Formulation</th>
<th>PD_{10} (%)</th>
<th>T_{50} (min)</th>
<th>T_{90} (min)</th>
<th>DE_{30} (%) (\bar{x} ± s d)</th>
<th>K_{1} (min^{-1}) (\bar{x} ± s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>77.3</td>
<td>2.5</td>
<td>50</td>
<td>68.28±0.11</td>
<td>0.0329±1.10</td>
</tr>
<tr>
<td>F2</td>
<td>76.47</td>
<td>3.0</td>
<td>40</td>
<td>71.31±0.11</td>
<td>0.00896±1.53</td>
</tr>
<tr>
<td>F3</td>
<td>71.49</td>
<td>4.05</td>
<td>&gt;60</td>
<td>61.77±1.89</td>
<td>0.00434±1.97</td>
</tr>
<tr>
<td>F4</td>
<td>68.65</td>
<td>4.0</td>
<td>&gt;60</td>
<td>60.07±1.23</td>
<td>0.00286±1.45</td>
</tr>
<tr>
<td>Lamivir</td>
<td>83.08</td>
<td>&lt;5</td>
<td>20</td>
<td>75.84±1.25</td>
<td>0.0174±1.25</td>
</tr>
</tbody>
</table>

CONCLUSIONS
1. All the lamivudine tablets prepared fulfilled the official (IP2010) specifications of hardness, friability, drug content and disintegration time of uncoated tablets.
2. Tablets formulated employing lactose as diluent (F₁, F₂) gave rapid and higher dissolution of Lamivudine when compared to those formulated employing DCP as diluent (F₃, F₄).
3. With both the diluents, tablets formulated employing Primojel as disintegrant gave higher dissolution rate of Lamivudine than those formulated with potato starch as disintegrant.
4. Among all, formulation F1 prepared using lactose as diluent and Primojel as disintegrant gave rapid and higher dissolution of Lamivudine when compared to all other formulations and also market brand.
5. Hence lactose as diluent and Primojel as disintegrant are recommended for the formulation of Lamivudine tablets with fast dissolution characteristics.
6. Thus the UV spectrophotometric method developed could be applied in the formulation development research to evaluate the products formulated and to select the best.

REFERENCES