CHAPTER V

FORMULATION DEVELOPMENT OF TABLETS OF LAMIVUDINE AND ZIDOVUDINE COMBINATION

INTRODUCTION TO ORAL SOLID DOSAGE FORMS AND TABLETS

Drugs can be administered through different routes. However, of all the routes of administration, oral route of administration is most convenient for administering drugs for systematic effect because of ease of administration by manufacturing and dosage adjustments. Parental route is not routinely used because of difficulty in self-administration and hence hospitalization may be required. Topical route is recently developed and is employed for only few drugs like nitroglycerine, scopolamine, for systematic effect. Topical route has limitations in its ability to allow effective drug absorption for systematic drug action. Parenteral administration is employed in case of emergency and in which the subject cannot swallow 90% of all drugs used to produce systemic effect are administered by oral route.

Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are as follows: tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed.

By comparison liquid oral dosage forms such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one lose
medication in 5-30ml. Such dosage measurements are typically error by a factor ranging from 20-50% when the drug is itself administered by patient. Liquid oral dosage forms have other disadvantage and limitations. They are more expensive to ship, breakage or leakage is more serious problem for liquids. Drugs are generally less stable in liquid form.

Solid dosage forms of tablets and capsules are more commonly employed. The tablets have advantages than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed.

The adulteration can be easily found if it is done in either liquid form or solid form since deformation takes place. If it is done in liquid form and powders cannot be added to the tablet if once they are formed. The major disadvantage of capsules over tablet is their higher cost.

The disadvantage of tablets includes difficulty in swallowing is seen to effect nearly 35% of population. This disorder is also associated with number of medical conditions including stroke, parkinsons disease, aids, head and neck radiation therapy and other neurological disorder including cerebral palsy. Many elder persons will have difficulty in taking conventional dosage forms because of tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular and nervous tissues. In some cases such as motion sickness, sudden episode of allergic attack of coughing and unavailability of water swallowing tablets may become difficult. The release of the drug comparatively slows since the tablets are harder and take about 15 min
to disintegrate. If they disintegrate slowly the release of the drug is affected and will take longer time to produce therapeutic action.

Drug substances are most frequently administered orally by means of solid dosage forms such as tablets and capsules. Large scale production methods used for their preparation require the presence of other materials in addition to the active ingredients. Additives may also be included in the formulations to enhance the physical appearance, improve stability and aid in disintegration after administration. Care must be taken in the selection and evaluation of additives and preparation methods to ensure that the physiological availability and therapeutic efficacy of the active ingredients will not be diminished.

In a limited number of cases it has been shown that the drug substances solubility and other physical characteristics have influenced its physiological availability from a solid dosage forms. These characteristics include its particle size amorphous or crystalline, whether solvated or non-solvated, and its polymorphic form. After clinically effective formulations or obtained, variations among dosage units of a given batch, as well as batch-to-batch differences are reduced to a minimum through proper in process controls and good manufacturing practices.

**Tablets:**

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Tablets remain popular as a dosage form
because of the advantages afforded both to the manufacturer (eg: simplicity and economy of preparation, stability and convenience in packing, shipping, dispensing) and the patient (eg: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration. Although tablets are more frequently discoid in shape, round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance presence and the intended method of administration.

The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistance to shock and abrasion and to withstand handling during manufacturing, packing, shipping and use. Hardness and friability test measure this property.

2. Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.

3. The drug content of the tablet must be bioavailable.

4. This property is measured by the dissolution test.

5. Tablet must be elegant in appearance and must have characteristic shape, color and other markings necessary to identify the product.

6. Tablets must retain all these functional attributes which include drug stability and efficacy.

Excipients in tablet formulation and their functions:

Diluents or filter – Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
**Binders or granulating agents** – Provide cohesiveness to powders, thus providing necessary bonding to form granules.

**Disintegrants** – Facilitate breakup or disintegration of the tablet when placed in aqueous environment.

**Antifrictional agents:**

**Lubricants** – Reduce the friction during tablet formation in a die and also during ejection from die cavity.

**Antiadherents** – Reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.

**Glidants** – Promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between particles.

**Miscellaneous:**

**Wetting agents**: Aid water uptake during disintegration and assist drug dissolution.

**Dissolution retards** – Retards the dissolution of active pharmaceutical ingredients.

**Dissolution enhancers** – Enhance the dissolution rate of active pharmaceutical ingredients.

**Adsorbents** – Retains large quantities of liquids without being wet this property allows many oils, fluid extracts to be incorporated into tablets.

**Buffers** – Provide suitable micro environmental pH to get improved stability or bioavailability.
**Antioxidants** – Prevents oxidation and maintains the product stability.

**Chelating agents** – Protect against auto oxidation. They act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.

**Preservatives** - Prevent growth of micro organisms.

**Colours and Flavours** – Provides attractiveness, increase patient compliance and product identification.

**Tablet manufacturing methods:**

**Wet granulation:**

Most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing, drying and compression.

**Limitations:**

1. The greatest disadvantage of wet granulation is its cost. If is an expensive process because of labour, time, equipment, energy and space requirements.

2. Loss of material during various stages of processing.

3. Stability may be major concern for moisture sensitive or thermolabile drugs.

4. Multiple processing steps add complexity and make validation and control difficult.

5. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.
**Procedure**

1. The active ingredient and excipients are weighed and mixed.
2. The wet granulate is prepared by adding the liquid binder adhesive to the powder blend and mixing thoroughly.
3. Screening the damp mass through a mesh to form pellets or granules.
4. Granules are dried by using tray dryer or fluid bed dryer.
5. After the granules are dried, they are passed through a screen to form uniform size granules.
6. Lubricants and other excipients are added to the granules and mixed thoroughly.
7. The granules are compressed into tablets.

**Dry granulation :**

In this process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. Two methods are used for drygranulation. The most widely used method is slugging, where the powder is precompressed and the resulting tablet or slug are milled to yield the granules. The other method is to precompress the powder with pressure rolls using a machine such as chilosonator.

**Advantages**

1. The main advantage of dry granulation or slugging are that is uses less equipments and space.
2. It eliminates the need for binder solution, heavy mixing equipment.
3. It also eliminates time consuming drying step required for wet granulation.

4. Slugging can be used for advantages in the following situations.

5. For moisture sensitive material

6. For heat sensitive material.

**Disadvantages**

1. It requires a specialized heavy duty tablet press to form slug.

2. It does not permit uniform colour distribution.

3. The process tends to create more dust than wet granulation, increasing the potential contamination.

**Steps in dry granulation:**

1. Milling of drugs and excipients.

2. Mixing of milled powders

3. Compression into large, hard tablets to make slug.

4. Screening of slugs.

5. Mixing with lubricant an disintegrating agent.

6. Tablet compression

**Direct compression**

The term “direct compression” is defined as the process by which tablets are compressed directly from powder mixture of active pharmaceutical ingredient and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.
Advantages:

1. The most important advantage of direct compression is economical process, reduced processing time, reduced labour cost, fewer manufacturing steps and less number of equipments are required.
2. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolavile and moisture sensitive API.
3. The chances of batch-to-batch variation are negligible because the unit operations required for manufacturing processesis fewer.

Disadvantages:

1. Problems in the uniform distribution of low dose drugs.
2. High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.
3. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability.
4. Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.

[Aulton Michael E 2007]

Steps in direct compression

1. Drying of materials (drug+excipients)

4. Tablet compression.

**Evaluation of tablets:**

**Physical appearance** – The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing,

**Thickness** – Thickness was determined for 20 preweighted tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablets thickness should be controlled within a +/- 5% variation of standard.

**Weight variation** – 20 tablets were selected randomly from a batch and were weighed individually and then average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

**Weight variation of tables**

<table>
<thead>
<tr>
<th>Average Weight of Tablets (mg)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 or less</td>
<td>10%</td>
</tr>
<tr>
<td>130 or 324</td>
<td>7.5%</td>
</tr>
<tr>
<td>&gt; 324</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Hardness test** – The crushing load which is the force required to break the tablet in the radial direction was measured using schluenziere hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in KP or kg.
**Percentage friability** – In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

If the tablet weight is >650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The % Friabilator should be not more than 1% w/w of the tablets being tested.

The % friability is expressed as the loss of weight and is calculated by formula

\[
\text{% friability} = \left( \frac{w_o - w_f}{w_o} \right) \times 100
\]

*Wo – initial weight of tablets
*Wf – final weight of tablets

**Disintegration time**: It is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a 10 mesh sieve. The basket is raised and lowered 28 – 32 times per minutes in a medium of 900 ml which is maintained at 37. Six tablets were placed in each of the tubes and the time required per compete passage of tablets fragments trough the 10 mesh was considered as the disintegration time of the tablet.

**Percentage water content** – Karl Fischer reagent (sulphur dioxide and iodine dissolved in pyridine and methanoal) is used to determine water content of the
tablet using karl fisher titrator

**Dissolution studies** - Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions

**Stability studies** – The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity etc.
STUDIES ON FORMULATION DEVELOPMENT OF TABLETS OF LAMIVUDINE AND ZIDOVUDINE COMBINATION

Combined drug therapy with anti-retroviral drugs is more efficient for treating HIV related diseases. Combination of lamivudine and zidovudine is a preferred option for treating HIV and AIDS. Though this combination is used widely, there are only a few combined drug formulations available in the market. The objective of the present study is to develop tablet formulations containing lamivudine and zidovudine combination and to evaluate the prepared tablets for various physical characteristics including dissolution rate. The HPLC method developed for the simultaneous estimation of lamivudine and zidovudine is used in the dissolution rate study to estimate the two drugs simultaneously. The results are presented in this Chapter.

EXPERIMENTAL

Materials

Lamivudine and zidovudine were gift samples from M/s Hetero Pharmaceuticals, Hyderabad.

Crospovidone and Crosscarmellose sodium were gift samples M/s Natco Pharma Ltd., Hyderabad.

Potato Starch (SD Fine Chem), Acacia IP, Sucrose, PVP K30 (Loba Chemie), Lactose I.P, Talc and Magnesium stearate were procured from commercial sources.
Zidolam, a commercial tablet formulation containing lamivudine and zidovudine was procured from local market.
All other materials used were of Pharmacopoeial grade.

Methods
Formulation and Preparation of Tablets:
Tablets each containing lamivudine (150 mg) and zidovudine (300 mg) were formulated employing commonly used tablet excipients. A total of six tablet formulations were prepared by wet granulation method as per the formulae given in Table 5.1.

Preparation of Tablets by Wet Granulation Method
The required quantities of lamivudine, zidovudine, lactose, half the quantity of potato starch and the binder were mixed thoroughly in a mortar by following geometric dilution technique. Water was added and mixed thoroughly to form dough mass. The wet mass was pressed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60\(^\circ\) C for 4 h. Dried granules were passed through mesh No. 16 to break aggregates. Crospovidone or Crosscarmellose sodium and lubricants talc and magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were then compressed into 600 mg tablets on a 16-station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a
hardness of 5-6 kg/cm² using 11 mm flat punches. In each case 100 tablets were compressed.

**Evaluation of Tablets**

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

**Dissolution Rate Study on Tablets**

Dissolution rate of (i) lamivudine and (ii) zidovudine from the tablets prepared was studied in water (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. A temperature of 37±1°C was maintained throughout the study. One tablet containing 150 mg of lamivudine and 300 mg of zidovudine was used in each run. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted with the mobile phase and assayed for lamivudine and zidovudine by the HPLC method developed. Dissolution samples (2.0 ml) were suitably diluted with the mobile phase and injected into the HPLC column for the simultaneous determination of lamivudine and zidovudine.

The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount of
drug dissolved. For comparison dissolution of lamivudine and zidovudine from Zidolam tablets was also studied. All dissolution rate experiments were conducted in triplicate (n=3).

**Analysis of Results**

Dissolution data were subjected to analysis as per zero order and first order kinetics. Three dissolution parameters namely PD$_{10}$ (Percent dissolved in 10 min), T$_{50}$ (Time for 50 % dissolution) and K$_1$ (First order dissolution rate constant) were calculated from the dissolution data.

**Table 5.1: Formulae of Lamivudine and Zidovudine Tablets Prepared**

<table>
<thead>
<tr>
<th>Ingredient (mg/Tablet)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Potato Starch</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Acacia</td>
<td>12</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sucrose</td>
<td>--</td>
<td>12</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>PVP K30</td>
<td>--</td>
<td>--</td>
<td>12</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Gelatinized Starch</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>12</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>Crosscarmellose Sodium</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>30</td>
</tr>
<tr>
<td>Lactose</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Talc</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Total Weight (mg)</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
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</table>
Table 5.2: Physical Characteristics of the Tablets Prepared

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (Kg/sq.cm)</th>
<th>Friability (% wt. loss)</th>
<th>D.T. (min-sec)</th>
<th>Weight Variation (%)</th>
<th>Drug Content (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lamivudine</td>
</tr>
<tr>
<td>F1</td>
<td>5.0 – 6.0</td>
<td>0.85</td>
<td>2 - 40</td>
<td>± 2.5</td>
<td>148.5</td>
</tr>
<tr>
<td>F2</td>
<td>5.5 – 6.0</td>
<td>0.62</td>
<td>3 - 40</td>
<td>± 1.5</td>
<td>149.2</td>
</tr>
<tr>
<td>F3</td>
<td>4.5 – 5.5</td>
<td>0.91</td>
<td>3 - 20</td>
<td>± 2.4</td>
<td>150.8</td>
</tr>
<tr>
<td>F4</td>
<td>5.0 – 5.5</td>
<td>0.74</td>
<td>4 - 50</td>
<td>± 1.2</td>
<td>151.2</td>
</tr>
<tr>
<td>F5</td>
<td>5.5 – 6.5</td>
<td>1.05</td>
<td>1 - 25</td>
<td>± 2.2</td>
<td>149.7</td>
</tr>
<tr>
<td>F6</td>
<td>5.0 – 6.0</td>
<td>0.95</td>
<td>1 - 30</td>
<td>± 1.8</td>
<td>148.2</td>
</tr>
<tr>
<td>C</td>
<td>6.0 – 6.5</td>
<td>0.87</td>
<td>2 - 50</td>
<td>± 2.5</td>
<td>148.8</td>
</tr>
</tbody>
</table>

F1-F6: Formulated Tablets; C: Commercial Tablets

Table 5.3: Lamivudine Dissolution Profiles of Formulated and Commercial Tablets

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Percent Lamivudine Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>47.45</td>
</tr>
<tr>
<td>10</td>
<td>60.6</td>
</tr>
<tr>
<td>20</td>
<td>70.25</td>
</tr>
<tr>
<td>30</td>
<td>78.2</td>
</tr>
</tbody>
</table>

F1-F6: Formulated Tablets; C: Commercial Tablets
Table 5.4: Zidovudine Dissolution Profiles of Formulated and Commercial Tablets

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Percent Zidovudine Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>59.8</td>
</tr>
<tr>
<td>10</td>
<td>72.8</td>
</tr>
<tr>
<td>20</td>
<td>82.4</td>
</tr>
<tr>
<td>30</td>
<td>90.6</td>
</tr>
</tbody>
</table>

F1-F6: Formulated Tablets; C: Commercial Tablets

Fig 5.1: Lamivudine Dissolution Profiles of Formulated and Commercial Tablets
Fig 5.2: First Order Plots of Lamivudine Dissolution of Formulated and Commercial Tablets

Fig 5.3: Zidovudine Dissolution Profiles of Formulated and Commercial Tablets
Fig 5.4: First Order Plots of Zidovudine Dissolution of Formulated and Commercial Tablets

Table 5.5: Lamivudine Dissolution Parameters of the Tablets Formulated and Commercial

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Disintegration Time (min)</th>
<th>Release Rate Constant (min⁻¹)</th>
<th>Correlation Coefficient (r) in First Order Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD₁₀ (%)</td>
<td>T₅₀ (min)</td>
<td>K₁ x 10⁻¹</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>60.60</td>
<td>15.2</td>
<td>0.4559</td>
</tr>
<tr>
<td>F2</td>
<td>59.28</td>
<td>15.2</td>
<td>0.4569</td>
</tr>
<tr>
<td>F3</td>
<td>64.35</td>
<td>11.7</td>
<td>0.5918</td>
</tr>
<tr>
<td>F4</td>
<td>43.25</td>
<td>25.3</td>
<td>0.2741</td>
</tr>
<tr>
<td>F5</td>
<td>65.25</td>
<td>13.0</td>
<td>0.5316</td>
</tr>
<tr>
<td>F6</td>
<td>64.46</td>
<td>13.3</td>
<td>0.5210</td>
</tr>
<tr>
<td>C</td>
<td>56.51</td>
<td>15.9</td>
<td>0.4333</td>
</tr>
<tr>
<td>Formulation</td>
<td>Dissolution Parameter</td>
<td>Correlation Coefficient (r) in First Order Model</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD(_{10}) (%)</td>
<td>T(_{50}) (min)</td>
<td>K(_1) x 10 (min(^{-1}))</td>
</tr>
<tr>
<td>F1</td>
<td>72.80</td>
<td>9.7</td>
<td>0.7097</td>
</tr>
<tr>
<td>F2</td>
<td>71.90</td>
<td>9.1</td>
<td>0.7588</td>
</tr>
<tr>
<td>F3</td>
<td>76.25</td>
<td>8.0</td>
<td>0.8588</td>
</tr>
<tr>
<td>F4</td>
<td>47.60</td>
<td>18.6</td>
<td>0.3730</td>
</tr>
<tr>
<td>F5</td>
<td>75.92</td>
<td>7.4</td>
<td>0.9305</td>
</tr>
<tr>
<td>F6</td>
<td>74.35</td>
<td>7.9</td>
<td>0.8782</td>
</tr>
<tr>
<td>C</td>
<td>70.12</td>
<td>10.2</td>
<td>0.6746</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

The objective of the present study is to develop tablet formulations containing lamivudine and zidovudine combination and to evaluate the dissolution rate of combined drug formulation by using the HPLC method developed for simultaneous determination of lamivudine and zidovudine in the dissolution study.

Tablets each containing lamivudine (150 mg) and zidovudine (300 mg) were formulated employing commonly used tablet excipients. Binder is a critical ingredient in tablet formulation influencing the disintegration time and dissolution rate of the tablets. Four binders namely (i) acacia, (ii) sucrose, (iii) PVP K30 and (iv) starch paste (i.e., gelatinized starch) were used in the formulation of combined drug tablets. Their influences on various physical properties and dissolution rate of combined drug tablet formulations were evaluated. Disintegrant is another critical ingredient in tablets. The effect of three disintegrants namely (i) potato starch, (ii) crospovidone and (iii) croscarmellose sodium on the disintegration and dissolution rate of combined drug tablet formulations was also evaluated. A total of six tablet formulations were prepared as per the formulae given in Table 5.1. The tablets were prepared by wet granulation method.

The physical characteristics of the tablets prepared are given in Table 5.2. Hardness of the tablets was in the range 4.5 – 6.5 Kg/sq.cm. Friability of the tablets was less than 1.05% in all the cases. Tablet weight variation was within ±2.5%. The tablets contained both the drugs, lamivudine and zidovudine within 100±3 % of the labeled claim. Tablets formulated with superdisintegrants,
crosopovidone and crosscarmellose sodium (F5 and F6) disintegrated rapidly within 1 min 30 seconds. Whereas the tablets formulated employing potato starch as disintegrant (F1, F2, F3, F4) disintegrated relatively slowly and the disintegration time of these tablets was in the range 2 min 40 seconds - 4 min 50 seconds. All the tablets prepared as well as commercial tablets fulfilled the official (IP 2010) specifications of uncoated tablets with regard to weight variation, hardness, friability, drug content and disintegration time.

Dissolution rate of lamivudine and zidovudine from the formulated and commercial tablets was studied in water as prescribed in IP 2010 for zidovudine tablets. As lamivudine is a water soluble drug its dissolution was also studied in water. Lamivudine and zidovudine content of the dissolution samples were determined by the HPLC method developed. The dissolution profiles are given in Tables 5.3 – 5.4 and in Figs. 5.1 – 5.4. The dissolution parameters are summarized in Tables 5.5 – 5.6.

The dissolution of both the drugs from the tablets formulated depended on the binder and disintegrant used. Lamivudine and zidovudine dissolution from the tablets followed first order kinetics with correlation coefficient (r) values in the range 0.9284 – 0.9804. The dissolution rate (K₁) values were calculated from the slopes of the first order linear plots (Figs. 5.2, 5.4) in each case. Dissolution rate (K₁) of both lamivudine and zidovudine depended on the binder used. Though all the binders were used at the same concentration as the formulae (2%), variations were observed in the dissolution rate of the drugs from the tablets. Among the four
binders PVP K30 gave relatively rapid and higher dissolution and starch paste (gelatinized starch) gave low dissolution. The order of increasing dissolution rate (K₁) observed with various binders is as follows:

\[
PVP \text{ K}30 > \text{Sucrose} > \text{Acacia} > \text{Starch paste}
\]

The same order was observed with both the drugs.

Tablets formulated employing superdisintegrants (F5, F6) gave faster dissolution of the two drugs than those formulated with potato starch (F1) as disintegrant.

All formulated tablets, except formulation F4, gave higher dissolution rate of the medicaments than the commercial formulation. IP 2010 described a dissolution of NLT 70 % in 30 min for lamivudine and NLT 80% in 30 min for zidovudine. All formulated tablets except formulation F4 and commercial formulation tested fulfilled the official (IP 2010) dissolution rate test specification. Overall, formulations F3, F5 and F6 gave very rapid dissolution of both the drugs and as such they are considered as best combined drug formulations developed. Formulation F3 contains PVP K30 as binder and potato starch as disintegrant. Formulation F5 contains acacia as binder and crospovidone as disintegrant. Formulation F6 contains acacia as binder and crosscarmellose sodium as disintegrant. The dissolution characteristics of these formulations are better than those of commercial formulations tested.

Based on the results discussed above, PVP K30, sucrose and acacia are recommended as binders and crospovidone and crosscarmellose sodium as
disintegrants for the formulation development of combined drug tablets containing lamivudine and zidovudine.