Abstract
The current research was designed to develop controlled release osmotic pump tablets of stavudine a nucleoside reverse transcriptase inhibitor for the treatment of HIV infection. Wet granulation method was adopted for the development of tablets containing dose 80mg of stavudine. The coating membrane of core tablets were prepared by using cellulose acetate as wall forming agent, poly ethylene glycol as flux regulating agent, and sorbitol as pore forming agent. The formulated tablets were characterized by FTIR, DSC, pre compression parameters, post compression parameters, in vitro drug release study and scanning electron microscopy study. Among developed formulations SM5 Batch showed 96.06% of drug release in controlled manner at the end of 18hrs. The in vitro release kinetics data were fitted for different batches in various pharmacokinetic models such as zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell model. The optimized formulation was carried out for effect of pH in dissolution media, agitation intensity and osmotic pressure effect on dissolution media. Short term stability study (at 40±2°C/75±5% RH for three months) on the best formulation confirmed that there was no significant changes in thickness, weight variation, %friability, drug content and in vitro drug release.

Keywords: HIV infection, DSC wet granulation, in vitro drug release, stability study.

Introduction
Most conventional oral drug products are developed to release the active drug immediately after oral administration to gain rapid and complete systemic drug absorption, but it is unable to control the release of drug and effective concentration of drug at the target site. The bioavailability (1) of drug for conventional dosage forms depends on physiochemical properties of drug, presence of excipients, physiological factors such as presence or absence of food, pH of GI tract, GI motility etc. Hence to avoid the limitations of conventional dosage forms various modified release drug products have been developed to control the release rate of drug and the time of drug release. Among several types of modified release drug products extended release drug product in the form of controlled release cover a wide range of prolonged action which provide continuous release of their active ingredients at predetermined rate and predetermined time. Out of various controlled drug delivery system oral osmotic controlled drug delivery system have advantages like independent of pH and hydrodynamic condition of the body, agitation intensity, presence or absence of food etc. Osmotic controlled drug delivery system works on principle...
of osmotic pressure for controlled delivery of drugs in the form of zero order.

The present study is to develop controlled porosity osmotic pump (CPOP) tablets of stavudine. CPOP tablets comprise of a core including the drug, an osmotic agent, other additives and semi permeable membrane (SPM) with porogen. Water leachable substances (2) are present in SPM which get dissolved when it comes in contact with release media, creating in situ micropore formation generating osmotic pressure within CPOP tablet to release drug in controlled manner.

HIV infection is a serious and a pandemic disease which is transmitted (3) primarily via unprotected sexual intercourse, contaminated blood transfusions through hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. Person infected with HIV has a CD4+ count of less than 200 cells/μL in blood. The management of HIV infection can be controlled by antiretroviral therapy, male circumcision, needle exchange program, use of diaphragms, topical protection, use of condoms and alternative medicine (4). Stavudine is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against (5) Human Immunodeficiency Virus Type 1 (HIV-1) which is chemically 2’,3’-didehydro-3’-deoxythymidine. The active metabolite stavudine 5’ triphosphate is an inhibitor of the HIV reverse transcriptase and acts as a chain terminator during DNA synthesis. Stavudine is absorbed rapidly orally producing peak plasma concentration within 1 hour with 86% bioavailability and elimination half life of 1 to 1.5 hour following single or multiple doses (6). The conventional dose of stavudine 40mg twice daily. Converting twice daily regimen of stavudine into once daily formulation of controlled release dose enhances the effectiveness of antiretroviral therapy.

Materials and Methods

Materials: Stavudine was obtained from Hetero Drugs Pvt. Ltd. India. Mannitol (Qualigens Fine Chemicals, India) and Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, HPMC E5LV, polyethylene glycol (PEG) 400, 600, 1500, 4000, 6000, Magnesium stearate and talc were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Microcrystalline cellulose (MCC), PVP-K30 were purchased from Signet Pharma, Mumbai, India. All other solvents and reagents used were of analytical grade.

Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR): In this method individual samples (7) as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into disc by applying pressure of 10kg/cm² to form a transparent pellet in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm⁻¹ in FTIR spectrophotometer (Bruker, Germany).

Differential Scanning Calorimetry (DSC): Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC (Shimadzu DSC-50, Japan). Individual samples as well as physical mixture of drug and excipients were weighed to about 5mg in DSC pan. The sample pan was crimped for effective heat conduction and scanned (8) in the temperature range of 50-300°C. Heating rate of 20°C min⁻¹ was used and the thermogram obtained was reviewed for evidence of any interactions.

Methods

Preparation of osmotic pump tablets: Wet granulation technique was used to develop CPOP core tablets. Accurately weighed quantities of ingredients mentioned in Table 1 were sifted through sieve No. 30. Lubricant (magnesium stearate) and glidant (talc) were sifted through sieve No. 80. The ingredients were manually blended homogenously in a mortar by way of geometric dilution except lubricant and glidant. The mixture was moistened with aqueous solution and granulated through sieve No.30 and dried in a hot air oven at 60°C for sufficient time (3-4 hrs). The dried granules were passed through sieve No.30 and blended with talc and magnesium stearate.

Chinmaya Keshari Sahoo et al
The homogenous blend was then compressed into round tablets with standard concave punches using 10 station rotary compression machine (Mini press, Karnavati, India).

**Coating of Core Tablets**: The coating solution was prepared taking required ingredients from table 2 and acetone was added quantity sufficient maintaining proper viscosity of solution. The coatings of tablets were performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Hot air is supplied to tablet bed by rotating lower speed 5-8 rpm initially. The coating of tablets was carried out with the rotation speed of 10-12 rpm. The spray rate and atomizing air pressure were 4-6 ml/min and 1.75 kg/cm² respectively. Inlet and outlet air temperature were 50°C and 40°C respectively. Coated tablets were dried at 50°C for 12 hrs.

**Evaluation of granules**: The prepared granules were evaluated for pre compression parameters (9) such as angle of repose, bulk density, tapped density and compressibility index (Carr’s index). Fixed funnel method was used to determine angle of repose. The bulk density and tapped density were determined by bulk density apparatus (Sisco, India).

The Carr’s index (10) can be calculated by the following formula.

\[
\text{\% Carr’s index} = \frac{e_t - e_b}{e_t} \times 100
\]

Where \(e_t\) is the tapped density of granules and \(e_b\) is bulk density of granules.

The Hausner’s ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

**Evaluation of tablets (11)**

**Thickness**: The thickness of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan). The limit of the thickness deviation of each tablet is \(\pm 5\%\).

**Measurement of coat thickness**: Film was isolated from the tablets after 18hrs of dissolution and dried at 40°C for 1 hr. Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan)

**Hardness**: The hardness of tablets can be determined by using Monsanto hardness tester (Sisco, India).

**Friability**: Friability (12) of tablets was performed in a Roche friabilator (SISCO, India). Twenty tablets of known weight \((W_{\text{initial}})\) were de-dusted in plastic chamber of friabilator for a fixed time of 25 rpm for 4 minutes and weighed again of weight \((W_{\text{final}})\). The percentage of friability was calculated using the following equation.

\[
\text{Friability} = \left(1 - \frac{W_{\text{final}}}{W_{\text{initial}}}\right) \times 100\%
\]

### Table 1. Composition of Osmotic Pump Stavudine tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>SM1</th>
<th>SM2</th>
<th>SM3</th>
<th>SM4</th>
<th>SM5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD(mg)</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>MCC(mg)</td>
<td>175</td>
<td>155</td>
<td>135</td>
<td>115</td>
<td>95</td>
</tr>
<tr>
<td>PVPK30(mg)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>HPMC E5LV(mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mannitol(mg)</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Magnesium stearate(mg)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc(mg)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total weight(mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Controlled Release Systems of Stavudine for Treatment of HIV Infection
%Friability = \( 1 - \frac{W_{\text{final}}}{W_{\text{initial}}} \) \times 100 \hspace{1cm} (2)

Where, \( W_{\text{initial}} \) and \( W_{\text{final}} \) are the weight of the tablets before and after the test respectively.

**Weight variation test:** The weight variation test is performed by weighing 20 tablets individually calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

**Uniformity of drug content test:** Powder is made after triturating 10 CPOP tablets from each batch with mortar and pestle. The powder weight equivalent to one tablet was dissolved in a 100ml volumetric flask filled with 0.1N HCl using magnetic stirrer for 24hr. Solution was filtered through Whatman filter paper No. 1 diluted suitably and analysed spectro photometrically.

**Diameter of tablet:** The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan).

**In vitro dissolution studies:** The in vitro dissolution studies were carried out using USP apparatus type II (Lab India 8000) at 75 rpm. For the first 2 hr the dissolution medium was 0.1N HCl (pH1.2) and phosphate buffer pH 6.8 for remaining hours (900 ml), maintained at 37±0.5°C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer (UV-1800, Shimadzu, Japan).

**In vitro drug release kinetic studies:** In order to investigate the mode of release from tablets, the release data of formulation was analyzed zero order kinetics, first order kinetics, Higuchi model and Korsmeyer and Peppas equations.

**Effect of osmogen concentration:** Keeping all the parameters for a tablet constant different osmogen (16) concentrations were used to prepare tablets. The drug release was compared with the different osmogen concentration of formulated batches by using USP-II dissolution apparatus.

**Effect of pore former concentration:** SPM for various batches were prepared by taking different concentrations of pore former (17). The effect of pore former on in vitro release profile is compared as well as number of formation of micropores were observed.

**Effect of membrane thickness:** Tablets with varying coating thicknesses were developed to demonstrate the effect of coating thickness (18) on drug release. The drug release rate was measured using 0.1N HCl and phosphate buffer pH6.8 as a dissolution medium.

**Effect of osmotic pressure:** The effect of osmotic pressure was demonstrated by adding different amount of mannitol of an osmotic agent to produce 30 atm, 60 atm and 90 atm respectively in dissolution media 0.1N HCl for 2hrs and phosphate buffer pH 6.8. The drug release rate was measured using 0.1N HCl and phosphate buffer pH6.8 as a dissolution medium.

\[\text{Table 2. Coating Composition for Controlled porosity Osmotic Pump Tablets}\]

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>CA (g)</th>
<th>PEG 400 (g)</th>
<th>PEG 600 (g)</th>
<th>PEG 1500 (g)</th>
<th>PEG 4000 (g)</th>
<th>PEG 6000 (g)</th>
<th>Sorbitol (g)</th>
<th>Acetone (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM1</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>SM2</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>SM3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1.2</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>SM4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1.6</td>
<td>300</td>
</tr>
<tr>
<td>SM5</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>300</td>
</tr>
</tbody>
</table>

Chinmaya Keshari Sahoo et al
was carried out in USP type II (Paddle) apparatus at 75 rpm maintained at 37±0.5°C and compared for various dosage forms.

Effect of pH (20) : The effect of pH for developed formulations were observed by performing the release studies of optimized formulation in different media 0.1 N HCl(pH 1.2), pH 6.8 phosphate buffer and pH 7.4 phosphate buffer in USP type II dissolution apparatus at 75rpm. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of agitation intensity (21) : The effect of agitation intensity were observed by performing the release studies of optimized formulation in USP Type II(Paddle) dissolution apparatus containing 0.1NHCl for first 2hrs and phosphate buffer pH 6.8 for rest hours at different rotational speeds of 50,100 and 150rpm with maintaining temperature at 37±0.5°C. The samples were withdrawn at predetermined intervals and analyzed by UV spectrophotometer.

Scanning Electron Microscopy (SEM) : Coating membranes (22) of formulation were collected before and after complete dissolution of core contents and examined for their porous morphology (23) as well as mechanism of drug release by scanning electron microscope (Leica, Bensheim, Switzerland). Scans were taken at an
excitation voltage in SEM fitted with ion sputtering device.

**Accelerated stability studies (24)**: The packed tablets in airtight container were placed in stability chambers (Thermo lab Scientific equipment Pvt. Ltd., Mumbai, India) maintained at 40±2°C/75±5% RH conditions for accelerated testing) for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, in vitro drug release etc..

**Results and Discussion**

**FTIR studies**: In the optimized formulation SM5 peak at 3673.16, 1455.07, 1251.44, and 776.99 cm⁻¹ were due to presence of the polymer HPMCE5LV. In the formulation the peaks present due to mannitol were 2916.14, 1017.47 and 669.04 cm⁻¹. Peaks at 2986.64, 1648.56 and 1066.24 cm⁻¹ were due to presence of the drug stavudine in the optimized formulation. So from the study it can be concluded that the major peaks of drug

Chinmaya Keshari Sahoo et al
2986.64, 1648.56 and 1066.24 cm\(^{-1}\) remain intact and no interaction was found between the drug, polymer and osmogen. Hence drug-excipient mixture reveals that there is no incompatibility was observed between stavudine. It was found that there was no major shift in peaks of optimized formulation as a result of which drug-excipients were found to be compatible. It is shown in figure 1(a,b).

**Pre compression parameters:** All the compressible excipients for various batches were evaluated for angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio. The angle of repose was found in the ranges from 25.11\(^\pm\) 0.11 to 29.73\(^\pm\) 0.11 degrees, bulk density of pre-compression blends was found to be in the range of 0.467\(^\pm\) 0.12 to 0.474\(^\pm\) 0.06 gm/ml, tapped density in the range of 0.504 \(^\pm\) 0.13 to 0.519 \(^\pm\) 0.06 gm/ml, the Carr’s index values were in the range of 7.34\(^\pm\) 0.08 to 9.44\(^\pm\) 0.07 %, and the Hausner’s ratio was in the range between 1.07\(^\pm\) 0.06 to 1.10\(^\pm\) 0.05. All the values were found to be acceptable limits of pharmacopoeial specifications. It is given in Table 3.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (degree)(^\pm) S.D</th>
<th>Bulk density (gm/ml)(^\pm) S.D</th>
<th>Tapped density (gm/ml)(^\pm) S.D</th>
<th>Carr’s Index (%)(^\pm) S.D</th>
<th>Hausner’s Ratio(^\pm) S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM1</td>
<td>29.73 (^\pm) 0.11</td>
<td>0.472 (^\pm) 0.08</td>
<td>0.516 (^\pm) 0.06</td>
<td>8.52 (^\pm) 0.07</td>
<td>1.09 (^\pm) 0.08</td>
</tr>
<tr>
<td>SM2</td>
<td>28.92 (^\pm) 0.08</td>
<td>0.474 (^\pm) 0.06</td>
<td>0.518 (^\pm) 0.04</td>
<td>8.49 (^\pm) 0.05</td>
<td>1.09 (^\pm) 0.04</td>
</tr>
<tr>
<td>SM3</td>
<td>27.46 (^\pm) 0.12</td>
<td>0.470 (^\pm) 0.04</td>
<td>0.519 (^\pm) 0.06</td>
<td>9.44 (^\pm) 0.07</td>
<td>1.10 (^\pm) 0.05</td>
</tr>
<tr>
<td>SM4</td>
<td>28.12 (^\pm) 0.13</td>
<td>0.468 (^\pm) 0.11</td>
<td>0.508 (^\pm) 0.14</td>
<td>7.87 (^\pm) 0.12</td>
<td>1.08 (^\pm) 0.12</td>
</tr>
<tr>
<td>SM5</td>
<td>25.11 (^\pm) 0.11</td>
<td>0.467 (^\pm) 0.12</td>
<td>0.504 (^\pm) 0.13</td>
<td>7.34 (^\pm) 0.08</td>
<td>1.07 (^\pm) 0.06</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean S.D, \(^n=3\)

**Post compression evaluation tests:** The thickness of the tablet formulations was found to be in the range of 2.9\(^\pm\) 0.02 to 3.15\(^\pm\) 0.06 mm, the hardness values were in the range of 6.5\(^\pm\) 0.13 to 7.9\(^\pm\) 0.09 kg/cm\(^2\), the friability values were in range of 0.13\(^\pm\) 0.12 to 0.37\(^\pm\) 0.06, average weight of tablet was in the range of 400.6\(^\pm\) 1.06 to 403.2\(^\pm\) 1.13 mg, drug content of tablet was in the range of 98.45\(^\pm\) 1.06 to 101.23\(^\pm\) 1.05 and diameter of tablets values were ranges of 7.9\(^\pm\) 0.03 to 8.2\(^\pm\) 0.06 mm. All values were found to be in acceptable ranges for uncoated tablets. It is mentioned in Table 4a. Similarly for coated tablets it is shown in Table 4b.

**In vitro drug dissolution study:** The in vitro drug release characteristics were studied in 900ml of 0.1N HCl (pH 1.2) for a period of first 2 hrs and remaining hrs in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type). The cumulative percentage drug release for SM1, SM2, SM3, SM4 and SM5 core CPOP tablets were 77.56, 80.34, 83.01, 87.11 and 95.99 respectively of stavudine at the end of 12 hrs. It is shown in figure 5a. The cumulative percentage drug release for SM1, SM2, SM3, SM4 and SM5 coated CPOP tablets were 81.23, 82.98, 84.98, 87.52 and 96.06 respectively of stavudine at the end of 18 hrs. It is shown in figure 5b.

Controlled Release Systems of Stavudine for Treatment of HIV Infection
Table 4a. Post compression evaluation tests for core tablets

<table>
<thead>
<tr>
<th>Formulation code (FC)</th>
<th>Thickness of tablet (mm) ± S.D</th>
<th>Hardness (kg/cm²) ± S.D</th>
<th>Friability (%) ± S.D</th>
<th>Average weight of 1 tablet (mg) ± S.D</th>
<th>% Drug content (%) ± S.D</th>
<th>Diameter (mm) ± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM1</td>
<td>3.1±0.03</td>
<td>6.8±0.12</td>
<td>0.32±0.08</td>
<td>402.1±1.12</td>
<td>98.45±1.06</td>
<td>8.1±0.04</td>
</tr>
<tr>
<td>SM2</td>
<td>2.9±0.02</td>
<td>6.5±0.13</td>
<td>0.37±0.06</td>
<td>403.2±1.13</td>
<td>101.23±1.05</td>
<td>8±0.02</td>
</tr>
<tr>
<td>SM3</td>
<td>3.1±0.03</td>
<td>7.2±0.06</td>
<td>0.24±0.05</td>
<td>401.3±1.06</td>
<td>100±1.01</td>
<td>7.±0.03</td>
</tr>
<tr>
<td>SM4</td>
<td>3.12±0.04</td>
<td>7.4±0.07</td>
<td>0.18±0.11</td>
<td>401.2±1.08</td>
<td>99.07±1.09</td>
<td>8.2±0.06</td>
</tr>
<tr>
<td>SM5</td>
<td>3.15±0.06</td>
<td>7.9±0.09</td>
<td>0.13±0.12</td>
<td>400.6±1.06</td>
<td>99.69±1.07</td>
<td>8±0.01</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean S.D, a n = 10, b n = 20

Table 4b. Post Compression evaluation tests for coated tablets

<table>
<thead>
<tr>
<th>Formulation code (FC)</th>
<th>Thickness of tablet (mm) ± S.D</th>
<th>Coat thickness (μm) ±S.D</th>
<th>Hardness (kg/cm²) ± S.D</th>
<th>Friability (%) ± S.D</th>
<th>Average weight of 1 tablet (mg) ± S.D</th>
<th>% Drug content (%) ± S.D</th>
<th>Diameter (mm) ± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM1</td>
<td>3.15 ± 0.09</td>
<td>500.4 ± 3.6</td>
<td>6.9 ± 0.12</td>
<td>0.02 ± 0.08</td>
<td>402.13 ± 1.19</td>
<td>98.45 ± 1.06</td>
<td>8.1 ± 0.04</td>
</tr>
<tr>
<td>SM2</td>
<td>3.11 ± 0.08</td>
<td>401.9 ± 3.8</td>
<td>6.6 ± 0.13</td>
<td>0.07 ± 0.06</td>
<td>402.2 ± 1.15</td>
<td>101.23 ± 1.05</td>
<td>8.2 ± 0.08</td>
</tr>
<tr>
<td>SM3</td>
<td>3.21 ± 0.07</td>
<td>300.6 ± 3.4</td>
<td>7.3 ± 0.06</td>
<td>0.04 ± 0.05</td>
<td>403.2 ± 1.07</td>
<td>100 ± 1.01</td>
<td>8.1 ± 0.06</td>
</tr>
<tr>
<td>SM4</td>
<td>3.22 ± 0.05</td>
<td>201.1 ± 3.1</td>
<td>7.5 ± 0.07</td>
<td>0.02 ± 0.11</td>
<td>402.8 ± 1.05</td>
<td>99.07 ± 1.09</td>
<td>8.3 ± 0.07</td>
</tr>
<tr>
<td>SM5</td>
<td>3.25 ± 0.04</td>
<td>100.2 ± 3.3</td>
<td>8.1 ± 0.09</td>
<td>0.01 ± 0.12</td>
<td>401.7 ± 1.06</td>
<td>99.69 ± 1.07</td>
<td>8.2 ± 0.05</td>
</tr>
</tbody>
</table>

N.B. All values are expressed as mean S.D, a n = 10, b n = 20

Fig. 5a. In vitro release profiles showing stavudine core tablets release from various fabricated formulations SM1-SM5 (n=3)

Figure 5b: In vitro release profiles showing stavudine release from various fabricated formulations SM1-SM5 (n=3)
Kinetic model: All the formulations showed to be best expressed by Higuchi kinetics as the plots showed high linearity. The regression values (R^2) of Higuchi were higher for all the formulations comparing to other kinetic models. It can be concluded that all the developed formulations follow Higuchi kinetics. The release exponent n value of Korsmeyer-Peppas model was more than 0.45 in SM1 formulation which indicated a non-Fickian diffusion mechanism of drug release and SM2, SM3, SM4 and LM5 show Fickian diffusion mechanism. It is shown in table 5.

Effect of osmogen concentration: The various batches of stavudine were developed with various concentrations of osmogen. It was observed that osmogen enhances the drug release of drug and thus had a direct effect on drug release. The drug release profile was shown in figure 5(a,b).

Effect of pore former concentration: For uncoated tablet there was no membrane and no pore former, but the drug releases up to 12 hrs (Figure 5a). The core formulations were coated with various concentration of sorbitol with compared to CA. It confirms that as the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release. Release profile of various batches was shown in figure 5b.

Effect of membrane thickness: For uncoated tablet there was no membrane, but the drug releases up to 12 hrs (Figure 5a). Release profiles of stavudine from various batches varying the coating thickness were evaluated. It was clearly evident that drug release was inversely proportional to coating thickness of the semi permeable membrane. It is shown in figure 5b.

Effect of osmotic pressure: The drug release for SM5 was found to be 90.11% for 30 atm, 84.56% for 60 atm and 81.23% for 90 atm respectively. Hence it was concluded that drug release was inversely proportional to the osmotic pressure of release media. It is shown in figure 6.

Table 5. Fitting of IVDR data in various mathematical models

<table>
<thead>
<tr>
<th>Models</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
<th>Hixson-Crowell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batches</td>
<td>R^2</td>
<td>K_0</td>
<td>R^2</td>
<td>K_1</td>
<td>R^2</td>
</tr>
<tr>
<td>SM1</td>
<td>0.956</td>
<td>3.618</td>
<td>0.962</td>
<td>0.0737</td>
<td>0.985</td>
</tr>
<tr>
<td>SM2</td>
<td>0.949</td>
<td>3.643</td>
<td>0.958</td>
<td>0.0783</td>
<td>0.981</td>
</tr>
<tr>
<td>SM3</td>
<td>0.933</td>
<td>3.588</td>
<td>0.936</td>
<td>0.0829</td>
<td>0.970</td>
</tr>
<tr>
<td>SM4</td>
<td>0.917</td>
<td>3.623</td>
<td>0.943</td>
<td>0.0898</td>
<td>0.975</td>
</tr>
<tr>
<td>SM5</td>
<td>0.928</td>
<td>4.230</td>
<td>0.906</td>
<td>0.1473</td>
<td>0.984</td>
</tr>
</tbody>
</table>

Fig. 6. In vitro release profiles showing stavudine release from best SM5 in different osmotic pressures.
Effect of pH: The optimized formulation SM5 was evaluated for in vitro drug release studies in buffers with different pH like 0.1N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4. It was concluded that there was no significant difference in the release profile, demonstrating that the developed formulation showed pH independent release. It is shown in figure 7.

Effect of agitation intensity: The optimized formulation of SM5 batch was carried out in USP dissolution apparatus type-II at varying rotational speed (50, 100 and 150 rpm). It showed that the release of stavudine from core was independent of agitation intensity and the release from the developed formulation was independent of the hydrodynamic conditions of the absorption site. It is shown in figure 8.

SEM analysis: Fig. 9a suggesting that there is no evidence of development of pores in the membrane before dissolution study of SM5. On the other hand, figure 9b shows that more pore formation after dissolution. When comparison was studied of the membranes containing different levels of porogen, it was observed that the membrane that contained a higher level of porogen became more porous after dissolution studies.

Stability studies: From short term stability studies of optimized formulation SM5, it was confirmed that there was no significance changes in physical appearance, weight variation, % friability, drug content and % drug release. It is shown in table 6. In vitro release profiles showing stavudine release from best SM5 in accelerated stability conditions is shown in fig. 10.
Acknowledgements
The authors would like to acknowledge the contributions of Pharmaceutics Department, Faculty of Pharmacy, University College of Technology Osmania University, Hyderabad, Telangana, India for providing necessary facilities to carry out the research work. This study was part of a Ph.D thesis under Osmania University, Hyderabad.

Controlled Release Systems of Stavudine for Treatment of HIV Infection
References


