FORMULATION AND EVALUATION OF MONOLITHIC MATRIX TABLETS OF ZIDOVUDINE BY USING NATURAL GUMS

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ABSTRACT
In the present investigation, an attempt was made to formulate and characterize the oral sustained release monolithic matrix tablets of Zidovudine order to improve efficacy, reduce the frequency of administration and better patient compliance. Monolithic Matrix tablets of Zidovudine were formulated using different concentrations of hydrophilic polymers such as HPMCK4M, xanthum gum, and carrageenan gum. The powder blend was evaluated for precompression properties. The sustained release matrix tablets were prepared by Wet granulation method. The tablets were evaluated for thickness, weight variation test, hardness, friability, and drug content and they were further evaluated for the in-vitro release of drug over a period of 12 hours. The drug release from optimized formulation F10 followed zero-order kinetics via non-Fickian (anomalous) diffusion. FTIR studies revealed that there was no interaction between the drug and excipients. In conclusion, the results indicated that the prepared sustained-release monolithic matrix tablets of Zidovudine could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

Keyword: monolithic matrix tablets,zidovudine,FTIR,drug release kinetics

I. INTRODUCTION
Monolithic Matrix System
In pharmaceutical CRDDS, matrix based systems 1 are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute throughout the matrix core of the release retardant . Alternatively, drug-release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wet granulation or beads. Zidovudine is a nucleoside analog reverse-transcriptase inhibitor (NRTI), used mainly for the treatment of HIV/AIDS infection 2. The most preferred route for this drug is oral delivery in form of tablets. Hence, in the present study, an attempt has been made to develop the sustained-release monolithic matrix tablets of Zidovudine using hydrophilic polymer HPMC K4M, xanthum gum and carrageenan gum the sustained pattern of it was evaluated by in-vitro drug release for 12 hours 3. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi’s kinetics, Korsmeyer’s equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics 4,5.

METHODOLOGY

Materials: zidovudine pure drug was obtained as a gift sample from hetero labs and xanthum gum,carrageenan gum,HPMC K4M,PVP K 30 and other excipients used in the formulation were obtained from merck specialties Pvt Ltd,Mumbai,india.

Construction of Standard Graph of Zidovudine
Accurately weighed amount of 100 mg of Zidovudine was transferred into a 100 ml volumetric flask. Methanol was added to dissolve the drug and the primary stock solution was made by adding 100 ml of methanol. This gives a solution having concentration of 1 mg/ml of Zidovudine stock solution. From this primary stock 10 ml was transferred in to another volumetric flask and made up to 100 ml with 6.8 pH phosphate buffer and this gives secondary stock solution. From this secondary stock 0.2, 0.4, 0.6, 0.8 and 1mL was taken separately and made up to 10 ml with 0.1N HCl and 6.8 pH phosphate buffer seperately. The absorbance was measured at 272 nm using a UV spectrophotometer.

Preparation of 0.1N HCl
A 8.65 ml of Conc. HCl was placed in a 1000 ml volumetric flask and the volume was made up with water and pH was adjusted to 1.2.
Preparation of Standard Solution Zidovudine

Accurately weighed 100mg of Zidovudine was placed in a 100mL volumetric flask and 50mL of 0.1 N HCl was added to dissolve the drug. The volume was made up to 100mL with 0.1 N HCl to give 1000 μg/mL of solution(stock solution -I). A 10mL aliquot from stock solution -I was taken and diluted to 100mL in a volumetric flask to get 100μg/mL (stock solution -II). Aliquots of 0.2, 0.4, 0.6, 0.8 and 1mL of Zidovudine standard solution of 100mcg/mL (stock solution-II) was taken and diluted to 10mL to obtain concentrations from 2 to 10μg/mL with 0.1 N HCl. The absorbances of solutions were determined at 272nm against respective media solutions as blank and a standard curve was plotted.

Preparation of Zidovudine Matrix Tablets

All the matrix tablets, each containing 32 mg of Zidovudine, were prepared by Wet granulation method and also to study the effect of various ratios of different types of polymers on the drug release.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 150mg with different drug polymer ratios like 1:0.5 1:1, 1:1.5 and combination of polymers. The various polymers used were HPMC K4M, xanthum gum, and carrageenan gum. MCC was used as a diluent for the preparation of matrix tablets.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Formulation Code</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>50</td>
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<tr>
<td>Xanthum gum</td>
<td>25</td>
</tr>
<tr>
<td>HPMC K4</td>
<td>-</td>
</tr>
<tr>
<td>Carrageenan gum</td>
<td>-</td>
</tr>
<tr>
<td>PVP K30</td>
<td>10</td>
</tr>
<tr>
<td>Water</td>
<td>q.s</td>
</tr>
<tr>
<td>Lactose mono hydrate</td>
<td>60</td>
</tr>
<tr>
<td>Talc</td>
<td>2</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>1</td>
</tr>
<tr>
<td>Total ( mg)</td>
<td>150</td>
</tr>
</tbody>
</table>

Evaluation of Precompression Blend

Angle of Repose

The angle of repose of precompression blend was determined by the funnel-method. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

\[
\tan \theta = \frac{h}{r}
\]

Where, \( h \) and \( r \) are the height and radius of the powder cone, \( \theta \) is the angle of repose.

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (\( W \)) was carefully poured into the graduated cylinder and volume (\( V_0 \)) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 tabs and after that the volume (\( V_f \)) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

\[
\text{Bulk density} = \frac{W}{V_0}
\]

\[
\text{Tapped density} = \frac{W}{V_f}
\]

Where, \( W \) = Weight of the powder

\( V_0 = \) Initial volume

\( V_f = \) final volume
Compressibility Index (Carr’s Index)

Carr’s index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is 6.

\[
CI = \frac{(TD-BD) \times 100}{TD}
\]

Where, TD is the tapped density and BD is the bulk density.

Hausner’s Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties 6. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr’s index.

\[
\text{Hausner’s Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Evaluation of Matrix Tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using vernier caliper. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). The friability was calculated as the percentage weight loss.

\[
\% \text{Friability} = \frac{(W_1 - W_2) \times 100}{W_1}
\]

Where \(W_1\) = Initial weight of the 20 tablets.

\(W_2\) = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

Weight Variation Test

To study weight variation individual weights (\(W_i\)) of 20 tablets from each formulation were noted using electronic balance. Their average weight (\(W_A\)) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

\[
\% \text{weight variation} = \frac{(W_A - W_i) \times 100}{W_A}
\]

Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount.

In-vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: \(n = 3\), USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml of and the phosphate buffer pH 6.8 up to 24 hours and temperature was maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. And drug content in each sample was analyzed by UV-visible spectrophotometer at 272 nm.

Kinetic Analysis of Dissolution Data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration 7. The first order Eq. (2) describes the release from system where release rate is concentration dependent 8. Higuchi 4 described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

\[
C = K_0 t \tag{1}
\]

Where, \(K_0\) is zero-order rate constant expressed in units of concentration/time and \(t\) is the time.

\[
\log C = \log C_0 - K_1 t / 2.303 \tag{2}
\]

Where, \(C_0\) is the initial concentration of drug and \(K_1\) is first order constant.
\( Q = K_H t^{1/2} \)  

Where, \( K_H \) is the constant reflecting the design variables of the system.

\( Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \)  

Where, \( Q_t \) is the amount of drug remained in time \( t \), \( Q_0 \) is the initial amount of the drug in tablet and \( K_{HC} \) is the rate constant for Hixson-Crowell rate equation.

**Swelling and Erosion Studies**

Swelling and eroding behavior was determined by a method similar to that reported by Avachat and Vikram\(^\text{10}\). It was estimated according to following equation

\[ Q = 100 \left( \frac{W_w - W_i}{W_i} \right) \]

Where \( Q \) is the percentage swelling, and \( W_w \) and \( W_i \) are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.

The degree of erosion (expressed as percentage erosion of the polymer content, \( E \)) was determined using following equation.

\[ E = 100 \left( \frac{W_i - W_f}{W_i} \right) \]

where \( W_i \) is the final mass of the same dried and partially eroded sample.

**Fourier Transform Infrared Spectroscopy (FTIR) Studies**

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm\(^{-1}\).

**RESULTS:**

**PRE-FORMULATION STUDIES**

Characterization of active pharmaceutical ingredient:

In preformulation studies, characterization of API (appearance, identification test by FTIR, assay) was performed and it was found that all are within the range specified in the pharmacopoeia.

**Calibration Curve of Zidovudine:**

Standard graph of Zidovudine was constructed using 6.8 pH phosphate buffer. Various concentrations 2 to 10 \( \mu g/mL \) were prepared. The absorbance of prepared concentrations was measured at 272(0.1N HCl) nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented.

\[ y = 0.094x \]

\[ R^2 = 0.999 \]

**Calibration Curve of Zidovudine in 6.8pH:**

Standard graph of Zidovudine was constructed using 6.8 pH phosphate buffer. Various concentrations 2 to 10 \( \mu g/mL \) were prepared. The absorbance of prepared concentrations was measured at 272(6.8 pH) nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented.
Precompression parameters

Before preparation of floting tablets of Zidovudine, the powder mass is evaluated for flow properties. The results of flow properties are shown in below Table 2. All the prepared formulations showed good flow properties.

Table 2 precompression parameters

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>Carr's Index</th>
<th>Hausner Ratio</th>
<th>Angle of Repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.55</td>
<td>0.65</td>
<td>1.25</td>
<td>0.25</td>
<td>23.45</td>
</tr>
<tr>
<td>F2</td>
<td>0.54</td>
<td>0.62</td>
<td>1.19</td>
<td>0.16</td>
<td>19.65</td>
</tr>
<tr>
<td>F3</td>
<td>0.56</td>
<td>0.64</td>
<td>1.23</td>
<td>0.18</td>
<td>22.35</td>
</tr>
<tr>
<td>F4</td>
<td>0.54</td>
<td>0.63</td>
<td>1.12</td>
<td>0.11</td>
<td>20.69</td>
</tr>
<tr>
<td>F5</td>
<td>0.50</td>
<td>0.67</td>
<td>1.24</td>
<td>0.22</td>
<td>20.82</td>
</tr>
<tr>
<td>F6</td>
<td>0.53</td>
<td>0.64</td>
<td>1.23</td>
<td>0.18</td>
<td>20.72</td>
</tr>
<tr>
<td>F7</td>
<td>0.51</td>
<td>0.67</td>
<td>1.24</td>
<td>0.19</td>
<td>20.89</td>
</tr>
<tr>
<td>F8</td>
<td>0.52</td>
<td>0.69</td>
<td>1.3</td>
<td>0.23</td>
<td>20.78</td>
</tr>
<tr>
<td>F9</td>
<td>0.56</td>
<td>0.68</td>
<td>1.21</td>
<td>0.17</td>
<td>20.66</td>
</tr>
<tr>
<td>F10</td>
<td>0.52</td>
<td>0.66</td>
<td>1.16</td>
<td>0.16</td>
<td>22.3</td>
</tr>
<tr>
<td>F11</td>
<td>0.51</td>
<td>0.62</td>
<td>1.18</td>
<td>0.18</td>
<td>24.6</td>
</tr>
<tr>
<td>F12</td>
<td>0.52</td>
<td>0.63</td>
<td>1.2</td>
<td>0.19</td>
<td>25.8</td>
</tr>
</tbody>
</table>

Post compression parameters:

The results of the weight variation, hardness, thickness, friability, and drug content of the Tablets are given in table.
Table 3. Post compression parameters

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness</th>
<th>Weight variation (mg)</th>
<th>Friability (%)</th>
<th>Hardness</th>
<th>%Drug content</th>
<th>Swelling Index±SD</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.41</td>
<td>150.65</td>
<td>0.16</td>
<td>5.4</td>
<td>96.19</td>
<td>22.4</td>
</tr>
<tr>
<td>F2</td>
<td>2.45</td>
<td>149.67</td>
<td>0.18</td>
<td>5.5</td>
<td>99.69</td>
<td>24.07</td>
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<tr>
<td>F3</td>
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<td>0.17</td>
<td>5.3</td>
<td>99.77</td>
<td>23.67</td>
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<td>F4</td>
<td>2.35</td>
<td>151.05</td>
<td>0.25</td>
<td>5.6</td>
<td>100.38</td>
<td>28.63</td>
</tr>
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<td>F5</td>
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</tr>
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<td>0.25</td>
<td>5.5</td>
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<td>29.45</td>
</tr>
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<td>2.46</td>
<td>149.13</td>
<td>0.42</td>
<td>5.0</td>
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<td>0.02</td>
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<td>31.2</td>
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<td>32.5</td>
</tr>
<tr>
<td>F12</td>
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<td>0.14</td>
<td>5.5</td>
<td>98.6</td>
<td>34.4</td>
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</table>

Dissolution Profiles of Formulations:

2a). [Graph 1]

2b). [Graph 2]
Table 4. In vitro release profile of drug with various polymers

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
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</tr>
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<td>1</td>
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<td>28.15</td>
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<td>46.98</td>
<td>49.60</td>
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<td>26.92</td>
<td>55.8</td>
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<td>88.92</td>
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<td>-</td>
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<td>95.3</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

KINETIC ANALYSIS OF DISSOLUTION DATA:
To analyse the drug release mechanism the in-vitro release data was fitted into various release equations and kinetic models zero order, first order, Higuchi and Korsmeyer Peppas model. The release kinetics of Optimized formulation F 10 is shown in table 5

TABLE 5 dissolution kinetics data of optimized formulae

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mathematical models (kinetics)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero order</td>
</tr>
<tr>
<td>F10</td>
<td>r^2</td>
</tr>
<tr>
<td></td>
<td>0.942</td>
</tr>
</tbody>
</table>
Graphs of the release kinetics of the optimized formulae

3a.

3b.

3c.

3d.
Discussion

The present investigation was undertaken to formulate and Sustained release tablets of Zidovudine.

Sustain release Tablets:

Using various polymers like xanthum gum and carrageenan gum, HPMC K4M, tablets were prepared along with other additives. Wet granulation method was used for the preparation of tablets. A total number of 12 formulations were prepared and evaluated.

To retain tablet for long period, most of the excipients selected must be water soluble by nature. This excipient was used a bulking agent to achieve the desired tablet weight. Talc was employed as a lubricant and magnesium stearate used as glidant.

Pre compressional studies:\n
The results obtained by evaluating the powder blends of drug and excipients are shown in table no Bulk density and tapped density were found in the range 0.52-0.56 g/cc and 0.62-0.69 g/cc respectively. The value of hausner’s ratio was in between 1.16-1.25 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 19.65-25.8 showing that blend of powder mass was Good flowing.
Weight variation and Thickness:
The average weight in all the formulations was found to be 146.7mg to 151.3 mg. In all 15 formulations no tablets were outside the ±10% of tablet weight in weight variation test. The thickness varies between 2.4 to 2.72mm. In all formulations tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 5 to 6 kg/cm² for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 96.5% and 100.38% of Zidovudine, which was within the acceptable limits.

In vitro dissolution:
The dissolution rate was found to increase linearly with increasing concentration of polymer. The optimized formulations are xanthum gum with HPMC K4M combination containing tablets (F10). Formulation have recorded drug 98.6 respectively in 12 hrs.

Drug Release Kinetics:
In vitro drug release data of all the Sustained formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi’s and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table and plots shown in figures 2 a,b,c,d. From the above data, it can be seen that all the formulations have displayed first order release kinetics (‘r’ values in the range of 0.900 to 0.965). From Higuchi and Peppas data, it is evident that the drug is released by non-fickian diffusion mechanism (n<0.5).

CONCLUSION
Success of the In vitro drug release studies recommend the product for further in vivo studies, which may improve patient compliance. From the results, formulation F10 containing Zidovudine, xanthum gum and HPMC K4M evolved as the optimized formulation and it releases more than 97% drug in 12hrs. IR spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation. The optimized formulation F10 can be considered as a promising Sustained Drug delivery system of Zidovudine providing nearly zero order drug release over a period of 12 hrs.

References