Design, Development and Study of Effects of Process Variables on In Vitro Drug Release of Zidovudine Extended Release Matrix Tablets

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Abstract

The aim of present study was to prepare and characterize extended release matrix tablets of Zidovudine using hydrophilic polymers Carbopol 974P and HPMC K4M alone or combination with each other by wet granulation method. The in vitro dissolution studies were carried out using USP XXIV dissolution apparatus -1(paddle) type and as well the effects of variables such as different dissolution medium, different hardness and different intensity of agitation on drug release were studied. The in vitro dissolution study revealed that combination of Carbopol 974P: HPMC K4M (3:2) extended drug release for nearly 12 hour. In conclusion, the results suggest that the developed extended release tablets of Zidovudine could perform therapeutically better than conventional dosage forms, may lead to improved efficacy and patient compliance.

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Key Words
HPMC K4 M, matrix tablet,
Carbopol 974P,
Controlled release, Zidovudine.
INTRODUCTION

When acquired immune deficiency syndrome (AIDS) first emerged, no one foresaw how the epidemic would spread across the world and how it would change many millions of lives. There was no real idea of what caused it and, consequently, no real idea of how to protect against it. Human immunodeficiency virus (HIV) has devastated families, communities, and whole continents\(^1\). HIV is a lentivirus and like all viruses of this type, it attacks the immune system. Lentivirus is part of a larger group of viruses known as retroviruses\(^2\). They have been found in a number of different animals, including cats, sheep, horses and cattle. However, the origin of HIV is the simian immunodeficiency virus (SIV) that affects monkeys\(^3\).

There are now 40 million people living with AIDS worldwide and globally 24.8 million people have died of AIDS since the beginning of the epidemic and it is estimated that 68 million will die of AIDS by 2020. HIV/AIDS is recognized as a global emergency demanding the attention of all public sectors – not just health. Millions of people around the world die from it every year, and millions more become newly infected. That is why combating it is one of the eight Millennium Development Goals and a top priority in bilateral and multilateral development aid\(^3\).

Antiretroviral agents effective against the human immunodeficiency virus (HIV) have emerged in recent past. HIV is characterized by an extremely high rate of replication and genetic variation. Drug resistant strains may be present even prior to initiation of treatment with antiretroviral agents and emerge rapidly during the course of treatment. This is a challenging task in the management of HIV infection and justifies the use of a multi drug approach directed at multiple targets, rather than mono
therapy. A number of virus-mediated steps in the HIV-1 replication cycle have been targeted for chemotherapeutic inhibition. Markers for monitoring the progress of HIV infection have improved, with the availability of sensitive methods for quantitative detection of plasma viral load. The assessment of disease progression and determination of the efficacy of currently available antiretroviral drugs can be done effective.

Zidovudine (AZT, 3'-azido-3'deoxythymidine) is a thymidine analogue. It is widely used in treatment of AIDS either alone or in combination with another antiviral drug. The main limitation to therapeutic effectiveness of AZT is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability. It is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of $1.27 \, \mu M$. The biological half-life of AZT-triphosphate is 3-4 hrs, thus necessitating frequent administration (3 to 4 time a day) to maintain constant therapeutic drug levels. Since its antiviral effect is time dependent, an adequate zero-order delivery of AZT is desired for maintaining antiAIDS effect and avoiding the toxic side effect like granulocytopenia and severe anemia usually associated with excessive plasma level of AZT immediately after intravenous or oral administration.

The most commonly used method of modulating the drug release is to include it in matrix system. Several polymers have been used in the formulation of matrix tablet based controlled release drug delivery system. Reports were found on usage of polymers like hydroxypropyl methylcellulose (HPMC), carbopol 934P, methylcellulose and sodium carboxy methylcellulose and polyvinyl alcohol for the purpose of CR.
formulations of different drugs. However, no literature has been found on oral CR tablets of AZT prepared using carbopol 974P as a retardant material. Since AZT is known to have pH independent solubility, CR tablets formulations prepared using a polymer like carbopol 974P and HPMC K4M would be ideal for obtaining desired drug release kinetics. The purpose of this study was to design oral extended release tablets of AZT using carbopol 974P and HPMC K4M as the retarding polymers. The tablets were formulated by wet granulation method and their physical properties and in vitro release characteristics were evaluated.

MATERIALS AND METHODS

AZT was obtained as a gift sample from ICPA Health products ltd, (Ankleshwar, India). Carbopol 974P, HPMC K4M were obtained as a gift sample from ICPA Health products ltd, (Ankleshwar, India). All other chemicals and reagents used in the study were of analytical grade.

Drug-excipients compatibility studies

Drug-excipients compatibility studies were performed using by Fourier Transform Infrared Spectroscopy (FT-IR) and Differential scanning calorimetry (DSC). The drug and physical mixture was subjected FT-IR analysis by KBr pellet method using FT-IR (Perkin Elmer, spectrum-100, Japan). Differential scanning calorimetry was performed on pure sample of Ziduvidine and physical mixture using Schimadzu DSC-50 apparatus. Differential scanning calorimetric thermograms of 2 to 3 mg samples were recorded at a heating rate of 5°C /min in an open aluminum pan over the range of 25-250°C.

Preparation of matrix tablets

Matrix tablets were prepared by wet granulation method. AZT (300 mg)
was dry blended with appropriate quantity of polymer(s) and granulated using PVP-K30 solution of isopropyl alcohol. After enough cohesiveness was obtained the mass was passed through a sieve No. 10 and dried at 40°C for 30 minutes. The dried granules were passed through sieve No. 16 to get uniform granules and again were dried at 40°C for 2 hrs. The granules were sieved (No. 16/22 sieve). The oversized granules (retained on No. 16 sieve) were kept aside. The undersized granules (passed from No. 22 sieve) were mixed with granules (retained on No. 16 sieve) in a ratio of 1:9 as fines. This mixture was blended with talc and magnesium stearate which was previously passed through a sieve No. 60. The granules were compressed by double punch tablet machine using 12 mm standard concave punch\textsuperscript{13,14}. The formulation ingredients of various batches are summarized in table 1.

**Characterization of tablets**

The properties of the compressed tablet, such as diameter, thickness, hardness, friability, weight variation and drug content were evaluated using reported procedure. Briefly, hardness was determined by using Inlap hardness tester. Friability was determined using Roche friability apparatus. Weight variation test was performed according to the USP procedure \textsuperscript{15}. Drug content was determined by colorimetric method which was described by Basavaiah \textsuperscript{16}.

**Estimation of drug content**

From each batch of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 300 mg was transferred into a 250 ml volumetric flask, 100 ml of phosphate buffer pH 7.4 was added and the solution was sonicated for about 30 min. The solution was made up to 100 ml with phosphate buffer pH 7.4, filtered and suitable dilutions were made with phosphate buffer pH 7.4. Same concentration of the
standard solution was also prepared by taking 100 mg of drug in a 100 ml volumetric flask made up to volume with phosphate buffer pH 7.4. The drug content was estimated by measuring the absorbance of both standard and sample solutions at 267 nm using UV/Vis spectrophotometer (Systronics 2201) 17.

In vitro release studies

In vitro drug release of formulations was studied up to 12 hrs using Tablet Dissolution Tester (Dissolution Tester (USP), TDL-06N, Electrolab, Mumbai) type 1 (Paddle method) in 900 ml of distilled water at 37°C ± 0.5. The stirring speed was set at 50 rpm. At predetermined time intervals, a 5 ml sample was withdrawn and replaced with fresh dissolution media. After appropriate dilution with water, the samples were analyzed UV/Vis spectrophotometer (Systronics 2201) at 267 nm. The release studies were conducted in triplicate 17.

Evaluation of Release Characteristics

The release of the active ingredient from the preparation in the gastrointestinal tract is affected by many physiological factors including the mechanical force exerted by the digestive tract in relation to its movement, and the volume, composition, pH, surface tension, and viscosity of the gastrointestinal fluid. Therefore, the in vitro release behavior should be investigated under as many conditions as possible to understand possible effects of gastrointestinal variables on in vivo release. To achieve stable blood concentrations, it is generally desirable to prepare prolonged release dosage forms whose release rates are minimally pH dependent. Therefore, release of the active ingredient should be evaluated at multiple levels of pH, such as 1.2, 4.0 and 6.8, representing typical gastrointestinal pH variation. Considering the variation in gastrointestinal motility, agitation
rates should be studied at more than two levels like 50, 100 and 200 rpm, when the paddle method is used, at an appropriate pH. It is also desirable.

determined time interval by using different dissolution medium such as 0.1N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer and water.

Tab 1. Formula of Zidovudine Matrix Tablets

<table>
<thead>
<tr>
<th>Composition*</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1 (mg)</td>
</tr>
<tr>
<td>Zidovudine IP</td>
<td>300</td>
</tr>
<tr>
<td>Lactose monohydrate IP</td>
<td>108</td>
</tr>
<tr>
<td>Carbopol 974P</td>
<td>-</td>
</tr>
<tr>
<td>HPMC-K4M</td>
<td>168</td>
</tr>
<tr>
<td>PVP</td>
<td>9</td>
</tr>
<tr>
<td>Talc</td>
<td>9</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>6</td>
</tr>
</tbody>
</table>

* Total weight per tablet was 600 mg

to perform release tests using different apparatus

**pH challenge studies**

The pH challenge study on dissolution of final selected formulation was performed up to 12 hrs at the pre-

*Effect of Hardness on dissolution rate*

The tablet hardness has an impact on release profile, increasing the hardness generally causes slowing of dissolution at a constant drug level because
increase in binding agent (excipient level). The effect of hardness on dissolution rate of final selected formulation was performed. The study was carried on two different hardness of tablet each type contains same concentration of the drug (300 mg of zidovudine).

**Effect of intensity of agitation on in vitro release rate**

The tablets of optimized batch were studied to observe the effect of agitation on dissolution which was being carried out at 50, 100 and 150 rpm. The dissolution was carried out in water for 12 hrs.

**Release Kinetics**

To study the mechanism of drug release from the matrix tablets, the release data were fitted to the following Eqns: Zero-order Eqns\(^{18}\) : \(Q_t = k_0 t\) where \(Q\) is the amount of drug release at time \(t\), and \(k_0\) is the release rate; First-order equation \(^{19}\):

\[
\log C = \log C_0 - \frac{K_t}{2.303} \]

where \(K_t\) is the release rate constant; Higuchi square root equation \(^{20}\): \(Q = K_{H} t^{1/2}\) Where \(Q\) is the amount of drug release at time \(t\), and \(K_{H}\) is the Higuchi rate constant. Korsemeyer and peppas equation \(^{21}\):

\[
\frac{M_t}{M_{\infty}} = K_t^n\]

where \(\frac{M_t}{M_{\infty}}\) is the fractional release of drug in time \(t\), \(K\) is a constant incorporating structural and geometric characteristic of the controlled release devices, and \(n\) is the diffusion release exponent indicative of mechanism of release. The value of \(n\) is 0.5 for Fickian transport, more than 0.5 and less than 1 for non-Fickian transport, and 1 for case II transport (zero order).

**RESULTS AND DISCUSSION**

The present investigation was undertaken to fabricate and evaluate the extended release formulation of Zidovudine using matrix technique. The FTIR spectral analysis showed that there was no significant appearance or disappearance of any characteristics
peaks of pure drug Zidovudine and in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers (Fig. 1). The DSC spectral analysis also revealed the same (Fig. 2). The matrix tablets of Zidovudine were prepared by wet granulation method and evaluated. Table 2 shows the data obtained from the evaluation of tablets. Physical parameters observed in the present study were good. Weight variation observed in range of 602.1±1.18 to 604.3±1.68 mg. Hardness was found in range of 5.2±0.43 to 6.4±0.91 kg/cm². Friability was found in range of 0.49% to 0.69%. Diameter and Thickness was found range of 12±0.01 to 12±0.04 mm, 5.9±0.06 to 6.4±0.038 mm, respectively.

Drug content was determined and results (98.3±0.43%w/w to 101.1±1.12%w/w) were found satisfactory and within limit of USP.
Pharmacopoeia for all formulated batches of zidovudine matrix tablets.

Fig 1. IR Study of drug and physical mixture IR spectra of (a) Zidovudine; (b) carbopol 974P; (c) HPMC K4M and (d)physical mixture

Fig 2. DSC thermograms of (a) Zidovudine and (b) physical mixture

The in vitro drug release profile showed that formulation F4 showed extended release profile compared to other formulations and also showed good initial burst release compared to other formulation (fig. 3). Formulation F4 was selected as optimized formulation and effect of process variables on in vitro drug release was studied on F4.

The results showed that matrix tablets slow release profile in acidic medium compared to other dissolution medium like phosphate buffer pH 6.8, water and phosphate buffer pH 7.4. It may be due to carbopol getting easily ionized, having a great influence on the drug release rate by changing the pH value (fig. 3)\textsuperscript{10}.

Result of effect of hardness on in vitro dissolution study revealed that the rate of drug release, in case of hardness 7-8 kg kg/cm\textsuperscript{2} is slow in comparison to that of hardness 5-6 kg/cm\textsuperscript{2}(fig. 5). Effect of agitation intensity on in vitro drug release rate (fig. 6) data showed that increase in agitation, increases the in vitro drug release rate and concluded that agitation may important when hydrophilic polymer are used in tablets.
The release from the formulation F4 was also comparable to that of a commercially available conventional tablet which showed better release profile than conventional marketed tablet (fig. 7). Investigation of the order and mechanism of drug release by plotting the in vitro data of optimized formulation F4 for zero and first order,
Higuchi and Korsmeyer pappas equation were the observed slope values and regression co-efficient showed that the formulation F4 follow zero order (fig. 7) and release mechanism of drug through polymeric membrane was observed anomalous transport (Non-fickian) diffusion (n=0.6533), which is also confirmed by Higuchi plot (fig. 8). This anomalous behavior would be attributed to the presence of HPMC, a nonionic polymer not affected by pH variation, which interacted with the carbomer to control the drug release, which is ideally suited for controlled release in solid dosage forms. This is probably due to the stronger hydrogen bonding between the carboxyl groups of Carbopol and hydroxy groups of HPMC which leading to stronger crosslinking between two polymers and diminish the release fluctuations. These general effects are supported by the data presented in Figs. 1 and 2.
CONCLUSION

It can be concluded that the formulation of extended release matrix tablets of Zidovudine containing Carbopol 974P and HPMC K4M (Formulation F4 (3:2)) could be successfully formulated. As it fulfils all the requirements of extended release tablets, this study encourages long term stability study on formulation F4 and preclinical trials.

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