Formulation and In Vitro, In Vivo Evaluation of Extended- release Matrix Tablet of Zidovudine: Influence of Combination of Hydrophilic and Hydrophobic Matrix Formers

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ABSTRACT

The aim of the present study was to prepare and characterize extended-release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. Release kinetics was evaluated by using *United States Pharmacopeia (USP)*-22 type I dissolution apparatus. Scanning electron microscopy was used to visualize the effect of dissolution medium on matrix tablet surface. Furthermore, the in vitro and in vivo newly formulated sustained-release zidovudine tablets were compared with conventional marketed tablet (Zidovir, Cipla Ltd, Mumbai, India). The in-vitro drug release study revealed that either Eudragit preparation was able to sustain the drug release only for 6 hours (94.3% ± 4.5% release). Combining Eudragit with ethyl cellulose sustained the drug release for 12 hours (88.1% ± 4.1% release). Fitting the in vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. In vivo investigation in rabbits showed sustained-release pharmacokinetic profile of zidovudine from the matrix tablets formulated using combination of Eudragits and ethylcellulose. In conclusion, the results suggest that the developed sustained-release tablets of zidovudine could perform therapeutically better than conventional dosage forms, leading to improve efficacy and better patient compliance.

KEYWORDS: anti-HIV drug, Zidovudine, matrix tablets, sustained release, mechanism, scanning electron microscopy.

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. UNAIDS 2004 report on the global AIDS epidemic showed 5.1 million children and adults to be infected with human immunodeficiency virus (HIV)/AIDS. It is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment.[1-3]

Zidovudine (AZT), the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of AZT is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.[4] After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 hours.[5] In the systemic circulation, it is first converted to AZT triphosphate, which is pharmacologically active and prevents the replication of the HIV virus. The biological half-life of AZT-triphosphate is 4 hours, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Since AZT acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of AZT is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration.

AZT is absorbed throughout the GIT. The drug is freely soluble at any pH and hence judicious selection of release-retarding excipients is necessary for achieving constant in vivo release. The most commonly used method of modulating the drug release is to include it in a matrix system.[6] No study has been done so far for preparing the AZT matrix tablets, although, Sanchez-Lafuente et al[7] have investigated matrix tablet of anti-HIV drug didanosine. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[8] The hydrophilic polymers selected for the present study were Eudragit RLPO and RSPO. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms.[9] However, the

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use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system.[10] Hence, in the present work, an attempt has been made to formulate the extended-release matrix tablets of AZT using hydrophilic matrix material (Eudragit RLPO and RSPO) in combination with hydrophobic ethylcellulose.

Materials and Methods

Materials

AZT was obtained as a gift sample from Cipla Ltd (Mumbai, India). Eudragit RLPO, RSPO, polyvinyl pyrrolidone (PVP-K90) and ethylcellulose were obtained as gift samples from S. Zhaveri & Co (Mumbai). High-performance liquid chromatography (HPLC) grade distilled water, acetic acid, and acetonitrile were procured from E. Merck (Mumbai). All other chemicals and reagents used in the study were of analytical grade.

Preparation of the Matrix Tablets

Matrix tablets were prepared by wet granulation method as reported by Bettini et al.[11] AZT (300 mg) was dry blended with appropriate quantity of polymer(s) and granulated using 5% wt/vol ethanolic solution of PVP-K90. The wet mass was passed through a No. 10 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour and sieved (No. 16/22 sieve). The oversized granules (retained on No. 16 sieve) were kept aside. The undersize granules (passed from No. 22 sieve) were mixed with granules (retained on No. 16 sieve) in a ratio of 1:9 as fines.[12] This granule mixture was blended with magnesium stearate (1.2% wt/wt) and compressed using double punch tableting machine, equipped with beveled flat-faced punches of 8-mm diameter (Cadmach Machinery Co, Ahmedabad, India). The formulation ingredients of various batches are summarized in Table 1.

Table 1. Composition of Sustained Release Matrix Tablets of AZT (300 mg)*

Batch	Eudragit RLPO (mg)	Eudragit RSPO (mg)	Ethylcellulose (mg)	Magnesium Stearate (mg)
A	120			5
B		120		5
C		60	60	5
D	60		60	5
E	30	30	60	5

*Tablet weight: 425 mg.

Characterization of Granules

Prior to compression, granules were evaluated for their characteristic parameters. Moisture content was determined using moisture balance equipped with an infrared unit (IEC, Mumbai). Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation.[13]

$$CI = (TD - BD) \times 100/TD \quad (1)$$

where, TD is the tap density and BD is the bulk density.

The drug content in granules was determined by extracting an accurately weighed amount of powdered granules (100 mg) with water. The solution was filtered through 0.45-μm membrane and absorbance was measured at 266 nm after suitable dilution.

Characterization of Tablets

The properties of the compressed matrix tablet, such as hardness, friability, weight variation, and content uniformity were determined using reported procedure.[14] Briefly, hardness was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation and uniformity of drug content were performed according to the IP procedures.[14] Content uniformity was determined by weighing 10 tablets individually, and the drug was extracted in water. The drug content was determined as described for granules.

In Vitro Drug Release Studies

The in vitro dissolution studies were performed using *USP*-22 type I dissolution apparatus at 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for first 2 hours and the phosphate buffer saline pH 7.4 from 3 to 12 hours (900 mL), maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer (DU640B, Backman, Fullerton, CA) at 266 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate.

Kinetic Analysis of Dissolution Data

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation.[15] These models fail to explain drug release mechanism due to swelling (upon hydration) along

with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems[16]:

$$Log\ (M_t/M_f) = Log\ k + n\ Log\ t \qquad (2)$$

where, M_t is the amount of drug release at time t; M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release.

To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch according to the Equation 2. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.[17]

Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold[18]):

$$MDT = (n/n+1).k^{-1/n} \qquad (3)$$

where n = release exponent and k = release rate constant.

Scanning Electron Microscopy

Tablet samples (batch E) were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with gold and visualized under scanning electron microscope (SEM) (Leica, Bensheim, Switzerland).

Determination of Swelling: Eroding Behavior

The swelling-eroding behavior of matrix tablets was determined by the method reported by Al-Taani and Tashoush.[19] Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of in vitro drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were placed in a vacuum oven at 40°C and after 48 hours tablets were removed and weighed. Swelling (%) and erosion (%) was calculated according to the following formula, where S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix

$$\%\ Swelling = S/R \times 100 \qquad (4)$$

$$\%\ Erosion = (T - R)/T \times 100 \qquad (5)$$

In Vivo Evaluation

Rabbits (New Zealand, White) of either sex weighing (2.8-3.2 kg) were divided into 4 groups, each consisting of 6 animals. First group received conventional tablets of AZT. Second, third, and fourth groups received the formulated matrix tablets of batch C, D, and E, respectively. The tablets were put behind the tongue to avoid their destruction due to biting. Food was withdrawn from the rabbits 12 hours before drug administration and until 24 hours postdosing. All rabbits had free access to water throughout the study. The Institutional Animal Ethical Committee approved the protocol for this study.

Blood samples were collected from marginal ear vein at defined time intervals. Blood collected was centrifuged at 2000 rpm for 10 minutes (Remi Equipment, Mumbai, India) and drug concentration after deproteinization with acetonitrile was determined by HPLC assay (Waters, Milford, MA).

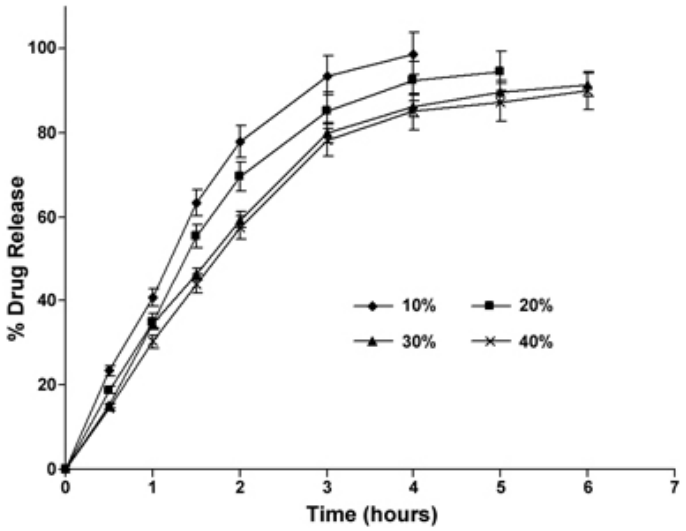

Figure 1. In vitro release profiles showing the effect of different concentration of RLPO on zidovudine release from matrix tablets. Data are represented as mean ± SD (n = 3).

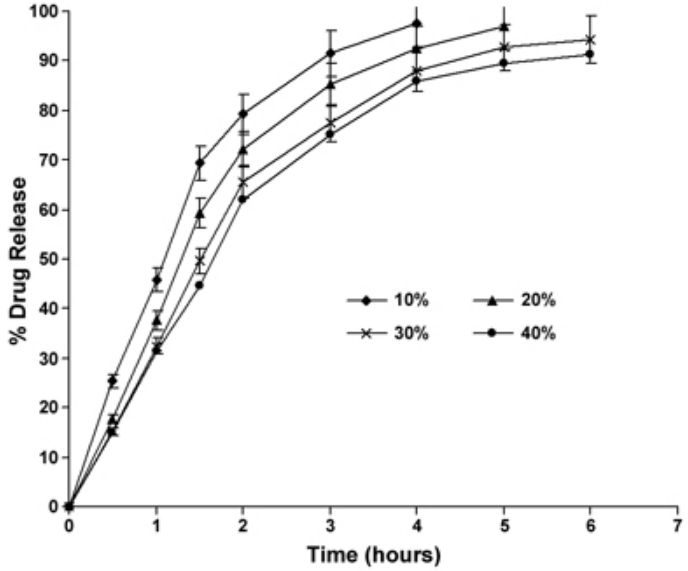

Figure 2. In vitro release profiles showing the effect of different concentration of RSPO on zidovudine release from matrix tablets. Data are represented as mean ± SD (n = 3).

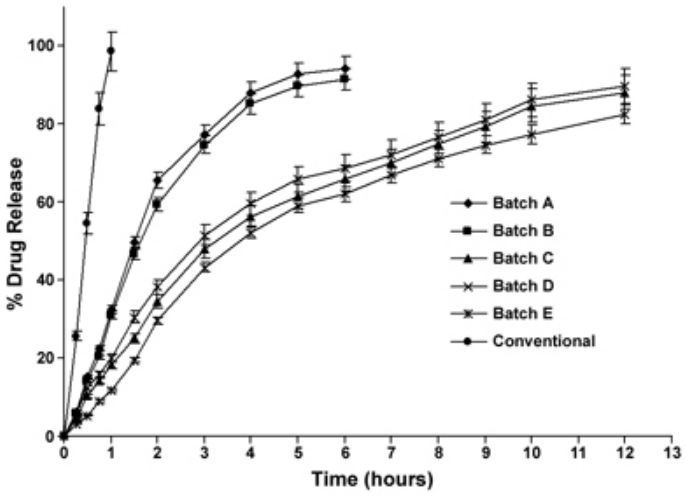

Figure 3. Percentage drug release of zidovudine from different batches of matrix tablet in comparison to marketed conventional formulation. Data are represented as mean ± SD (n = 3).

HPLC Assay

The quantitative determination of drug in plasma was performed by HPLC assay using acetonitrile, 0.1% acetic acid (25:75 vol/vol) mixture as mobile phase delivered at 1.0 mL/min by Waters 515 pump. Twenty microliters of injection volume was eluted in C-18 column (4.6 × 150 mm) at room temperature. The column eluant was monitored at 265 nm using diode array UV detector (model 2487, Waters).[3,20]

Statistical Analysis

The data was subjected to ANOVA followed by studentized range test for analyzing the statistical difference using the software PRISM (Graphpad, San Diego, CA). A confidence limit of $P < .05$ was fixed for interpretation of the results.

Results and Discussion

Figures 1 and 2 show the effect of different concentrations of Eudragit RLPO or RSPO (10%, 20%, 30%, and 40% wt/wt of drug) on release rate of AZT. The drug release was slower from tablets containing Eudragit RLPO or RSPO as compared with that from conventional tablets. No significant difference ($P < .05$) in release rate was observed between tablets containing either 10% or 20% of Eudragit RLPO or RSPO. However drug release decreased significantly ($P < .05$) when 30% of either Eudragit preparation was used individually in tablet formulation (91.3 ± 4.4 and 94.3 ± 4.5 at 6 hours for RLPO and RSPO, respectively). Further increase in concentration of Eudragits did not significantly effect ($P < .05$) the release rate. On this basis, 30% of Eudragit RLPO or RSPO was selected for further studies. The optimized batches were designated as A and B. The composition of different matrix tablets is summarized in Table 1.

Table 2. Characterization of Granules and Matrix Tablets of AZT*

Parameters	A	B	C	D	E
Granules					
Angle of repose (°)	28 ± 1.1	25 ± 0.8	27 ± 0.9	22 ± 0.6	28 ± 1.2
Bulk Density (g/mL)	0.63	0.53	0.39	0.48	0.36
Tap Density (g/mL)	0.78	0.65	.053	0.61	0.50
Carr's Index	19.2 ± 0.5	18.5 ± 0.5	26.4 ± 1.1	21.3 ± 0.6	28.0 ± 1.2
Moisture content (%)	2.1 ± 0.3	2.4 ± 0.3	1.9 ± 0.2	2.8 ± 0.4	2.3 ± 0.2
Total drug content (%)	98.0 ± 3.6	99.0 ± 3.9	98.5 ± 3.7	99 ± 4.1	98.0 ± 3.8
Tablets					
Weight variation (%)	± 3.0	± 2.0	± 4.0	± 3.0	± 2.0
Friability (%)	0.24	0.32	0.11	0.22	0.19
Hardness (kg/cm^2)	6.5 ± 0.1	7.2 ± 0.2	8.1 ± 0.2	8.2 ± 0.3	10.1 ± 0.4
Content uniformity (%)	98.3 ± 4.3	99.2 ± 4.0	98.5 ± 3.5	99.4 ± 4.3	98.7 ± 4.0

*All values represent mean ± SD (n = 3).

Table 3. Mathematical Modeling and Drug Release Kinetics of AZT Conventional and Sustained-Release Matrix Tablets*

Batch	r^2†				Log k‡	n§	Order of Release
	Zero Order	First Order	Higuchi	Korsmeyer Model			
A	0.8412	0.7418	0.9837	0.9340	3.4533	0.7113	Non-Fickian
B	0.7912	0.7195	0.9856	0.9373	3.4437	0.7218	Non-Fickian
C	0.7641	0.8052	0.9434	0.9772	2.7947	0.7885	Non-Fickian
D	0.9102	0.7805	0.9341	0.9872	3.1659	0.7486	Non-Fickian
E	0.8952	0.8084	0.9317	0.9989	2.5929	0.8375	Non-Fickian
Conventional	0.4892	0.9256	0.8321	0.7524	4.6670	1.4460	Super case II

*Analyzed by the regression coefficient method.

†Correlation coefficient Fickian.

‡Kinetic constant incorporating structural and geometric characteristic of the tablet.

§Diffusional exponent indicative of the mechanism of drug release.

The granules for matrix tablet were prepared according to the formula given in Table 1 and characterized with respect to angle of repose, moisture content, bulk density, and total drug content (Table 2). Angle of repose was less than 30° for all the batches of granules indicating satisfactory flow behavior. Moisture content of less than 2% indicates optimum drying of granules. Other parameters for granules were also determined and found to be in acceptable range.

The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness, and content uniformity according to procedure specified in *Indian Pharmacopoeia*. The weight variation and friability was less than 4% and 0.4%, respectively. Good uniformity in drug content was found among different batches of the tablets, and the drug content was more than 95% (Table 2).

The release pattern of AZT from conventional marketed tablet and from different batches of formulated matrix tablet is illustrated in Figure 3. The conventional formulation showed complete dissolution (98.5% ± 5.1% drug release) in 1 hour (0.1N HCl). Tablets containing release modifiers exhibited slow release of AZT as compared with conventional tablets. Both batch A containing 30% RLPO and batch B containing 30% RSPO showed more than 90% drug release in 6 hours. Batch C, D, and E containing combination of Eudragits and ethylcellulose showed 88.1 ± 4.1, 89.8 ± 3.8, and 82.4% ± 3.5% drug release, respectively in 12 hours (Figure 3).

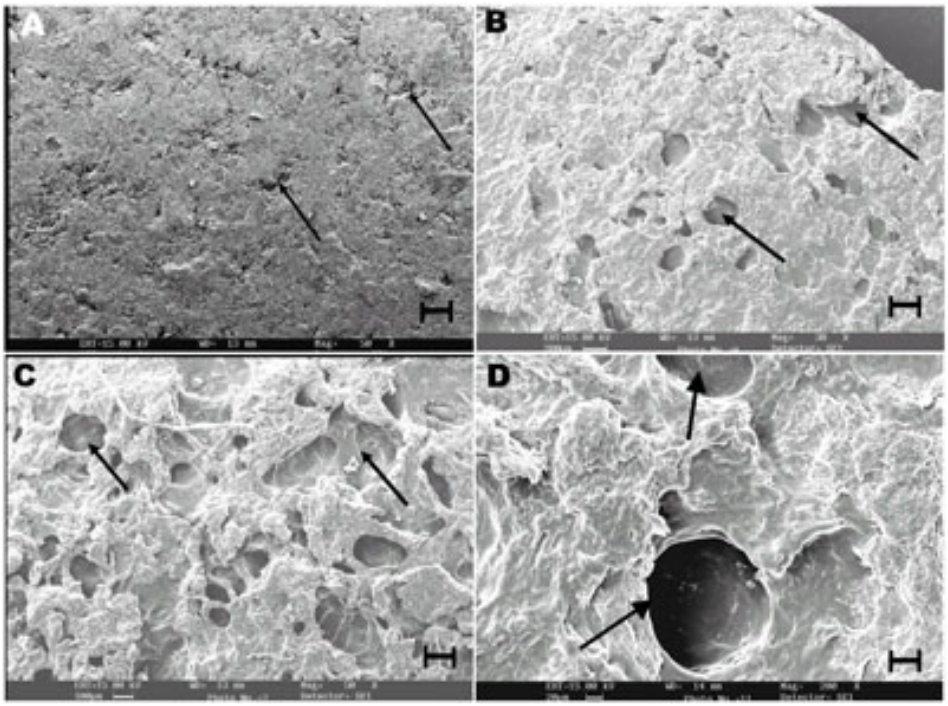

Figure 4. SEM photomicrographs of optimized matrix tablet (batch E) showing surface morphology after 0 hours (A, 5000×), 2 hours (B, 6000×), 5 hours (C, 5000×), and 10 hours (D, 4000×) of dissolution study. (Arrow indicates the formation of pores on matrix surface.)

Table 4. Dissolution Parameters of AZT Release From Matrix Tablets*

Batch	$t_{25\%}$ (hours)	$t_{50\%}$ (hours)	$t_{75\%}$ (hours)	*MDT
A	0.8 ± 0.1	1.5 ± 0.1	2.9 ± 0.2	1.5 ± 0.1
B	0.7 ± 0.1	1.6 ± 0.1	2.7 ± 0.2	1.5 ± 0.2
C	1.2 ± 0.1	3.0 ± 0.2	8.1 ± 0.4	1.9 ± 0.2
D	1.6 ± 0.2	3.1 ± 0.2	9.1 ± 0.4	2.6 ± 0.2
E	1.7 ± 0.2	3.1 ± 0.2	10.0 ± 0.5	3.3 ± 0.3
Conventional	0.4 ± 0.1	0.6 ± 0.1	0.8 ± 0.1	0.6 ± 0.1

*MDT indicates mean dissolution time. All values represent mean ± SD (n = 3).

Tablet containing Eudragit RLPO (batch A) and those containing Eudragit RSPO (batch B) required 1.5 hours to release 50% of AZT and 6.0 hours for releasing >90% AZT. Inclusion of ethylcellulose in the matrix almost doubled (3.1 and 12 hours) the time required for releasing 50% and 90% of drug (batch E). This may be owing to a more rigid complex formed by Eudragits in presence of ethylcellulose, which helped in retaining the drug in matrix and did not allow rapid diffusion of soluble drug from the matrix. The hydrophobic nature of ethylcellulose seems to have contributed toward reduction in the penetration of the solvent molecules into the matrix.

As indicated in Figure 3, tablets containing Eudragit (batches A and B) alone showed initial burst release during first hour (32.4% ± 2.1% and 31.0% ± 1.6%, respectively, for batches A and B). This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core.[21] However, when hydrophilic Eudragit was combined with hydrophobic ethyl cellulose (batches C, D, and E) no burst release was observed (less than 20% drug release in 1 hour).

AZT has pH-independent solubility and is absorbed uniformly throughout the GIT. The successful sustained-release formulation must show pH-independent release, so that release of AZT starts from upper GIT and continues for 10 to 12 hours up to the lower GIT. Eudragit RLPO and RSPO contain quaternary ammonium groups in their structure.[9] The solubilization of these quaternary ammonium groups in acidic pH leads to formation of pores in the matrix, thereby releasing AZT in the acidic pH. Ethylcellulose may have a tendency to mask these quaternary ammonium groups to some extent, thereby modifying release of the drug. Batches C, D, and E showed less than 20% release (no burst release) in 1 hour, whereas more than 30% release (burst release) occurred in batches A and B. This can be attributed to the masking of quaternary ammonium groups by ethylcellulose in batches C, D, and E.

It is reported in the literature that more than 30% release of drug in the first hour of dissolution indicates the chance of dose dumping. The results showed probability of dose dumping from matrix tablets prepared without ethylcellulose (batches A and B). The addition of ethylcellulose reduced the chances of dose dumping. AZT has a very narrow (0.4-4.0 μmol/L) therapeutic index.[22] The commercially available conventional tablet produces initial high plasma concentration owing to absence of release modifiers, which may cause unwanted toxic effects like bone marrow depression that sometimes leads to withdrawal of drug therapy.[23] Hence, it is essential to maintain the plasma level within the therapeutic index for eliminating these toxic effects. The tablets formulated using combination of Eudragits and ethylcellulose did not show any burst release (in vitro) indicating reduced possibility of dose dependent toxicity (in vivo).

The release rate kinetic data for all the models is shown in Table 3. Drug release data of conventional tablet was fitted in first order equation (r^2 = 0.9256), while drug release data of batch A and B matrix tablets showed good fit into the Higuchi equation (r^2 = 0.9837 and 0.9856, respectively). Tablets of batches C, D, and E showed high linearity with Korsmeyer equation (r^2 = 0.9772, 0.9872, and 0.9989, respectively) and indicated combined effect of diffusion and erosion mechanisms for controlled drug release. Value of release exponent "n" determined from the various matrices ranged from 0.7113 to 0.8375, and the log k values ranged from 2.5929 to 3.4533 (Table 3). The value of "n" and log k was found to vary with type and concentration of polymers.

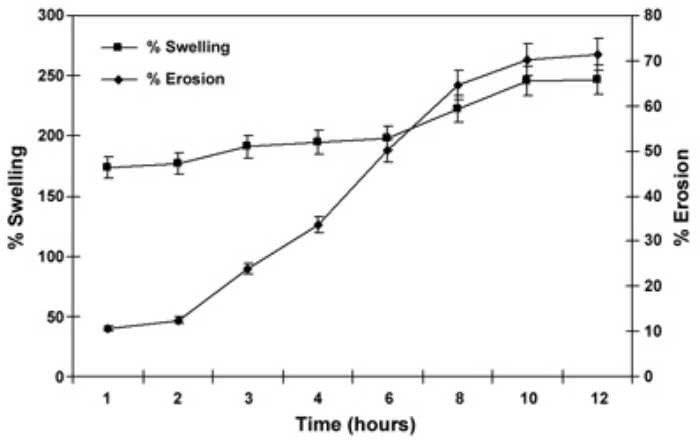

Figure 5. Swelling-eroding behavior of optimized batches of matrix tablet (batch E). Data are represented as mean ± SD (n = 3).

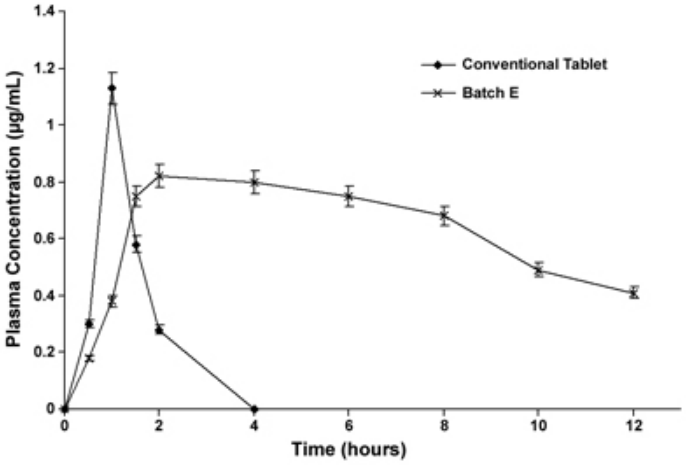

Figure 6. Plasma concentration-time profiles of optimized batch of matrix tablet (batch E) and conventional tablet after oral administration. Data are represented as mean ± SD (n = 6).

SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (batch E). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix (Figure 4A-D). SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time. SEM photomicrograph of the surface of fresh tablet (Figure 4A) did not show any pores. Photomicrographs at 2, 5, and 10 hours revealed pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of matrix tablets (Figure 4B-D). Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of AZT from formulated matrix tablets.

The time taken to release 25% (t_{25}), 50% (t_{50}), and 75% (t_{75}) of drug from different tablets was determined (Table 4). Tablets containing combination of Eudragits and ethylcellulose (batch E) required 1.7 ± 0.13 and 10 ± 0.48 hours to release 25% and 75% of drug, respectively. These values were significantly higher than those obtained in matrix tablets prepared with either Eudragit alone (batches A and B). This indicated sustained release nature of the combination of both Eudragits and ethylcellulose.

Mean dissolution time (MDT) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Tablets prepared with combination of Eudragits and ethylcellulose showed higher MDT value (3.3 ± 0.3 hours) in comparison to tablet prepared with Eudragit RLPO or RSPO (batches A and B, 1.5 ± 0.1 hour and 1.5 ± 0.2 hours, respectively). This finding can be attributed to the water-repelling property of ethylcellulose, which retarded drug release from the matrix.[24]

Figure 5 represents the matrix erosion (%) as well as swelling (%) as a function of time. It is clear that the matrices underwent both swelling and erosion at the same time after placement in the dissolution media. Since both swelling and erosion occurred simultaneously in the matrix, constant release can be obtained in such types of matrices.[25] Constant release in such situations occurs because the increase in diffusion path length due to swelling is compensated by continuous erosion of the matrix.[18]

Plasma concentration and pharmacokinetic parameters after oral administration of formulated matrix tablets and conventional tablet are summarized in Figure 6 and Table 5. No sustained blood level of AZT was evident after oral administration of the conventional formulation. Although, plasma concentration-time profile was characterized by significantly ($P < .05$) higher plasma concentration after 0.9 hours of administration, and then the plasma concentration declined rapidly. The formulated matrix tablets (batch E) showed significantly lower C_{max} than conventional tablet ($P < .05$) and required significantly more time to reach C_{max} (t_{max} 3.8 ± 0.4 hours) as compared with conventional tablets (t_{max} 0.9 ± 0.2 hours). However, these tablets maintained constant plasma concentration up to 12 hours. Due to low therapeutic index (0.4-4.0 µmol/L), AZT is known to exhibit dose-dependent side effects resulting in withdrawal of therapy. The smooth and extended absorption phase coupled with maintenance of plasma concentration for longer duration after administration in matrix tablets suggests reduced chance of dose-dependent side effects of AZT.

Table 5. Pharmacokinetic Parameters of AZT After Administration of Conventional and Matrix Tablets*

Formulation Code	AUC (µg.h/mL)	C_{max} (µg)	t_{max} (hours)	RB
Conventional Tablet	1.35 ± 0.1†	1.13 ± 0.3†	0.9 ± 0.2†	100.0%
Batch C	3.34 ± 0.2	0.85 ± 0.1	3.8 ± 0.4	310.8%
Batch D	3.21 ± 0.2	0.87 ± 0.1	3.8 ± 0.5	298.7%
Batch E	3.68 ± 0.2	0.82 ± 0.1	4.0 ± 0.5	342.9%

*AUC indicates area under the curve; and RB, relative bioavailability in comparison to conventional zidovudine tablets;. All values represent mean ± SD (n = 6).

†Significantly different from matrix tablets ($P < .05$).

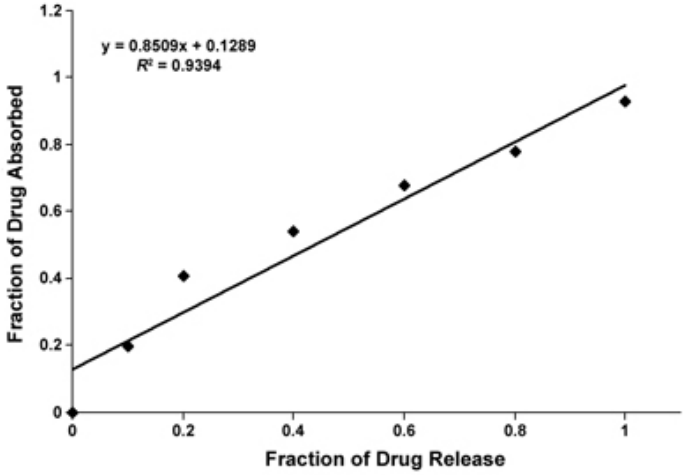

Figure 7. Fraction of drug absorbed versus fraction of drug release (in vitro-in vivo correlation for optimized batch (E) of matrix tablets).

A good correlation between the dissolution profiles and bioavailability was observed. In vitro-in vivo correlation was determined by plotting a graph showing the fraction of drug absorbed versus the fraction of drug released in vitro. A high value of correlation coefficient ($r^2 = 0.9394$) suggested good correlation between in vitro-in vivo data (Figure 7).

CONCLUSION

Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of AZT. The investigated sustained-release matrix tablet was capable of maintaining constant plasma AZT concentration through 12 hours. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional AZT tablets.

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