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Formulation and Statistical Optimization of Controlled Release Matrix Tablet of Zidovudine

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The purpose of the present study is to develop and optimize controlled release matrix tablets containing zidovudine (AZT) as model drug by optimization technique. A 2^3 factorial design was employed in formulating the matrix tablets with taking concentration of hydroxy propyl methyl cellulose (HPMC) K4M (X_1), ethyl cellulose (X_2) and types of filler MCC or DCP (X_3) as independent variables. Three dependent variables were considered: time required for 50 % drug released ($t_{50\%}$), mean dissolution time (MDT) and release exponent (n). The main effect and interactive terms were quantitatively evaluated using mathematical model. The results indicated that X_2 and X_3 significantly affected the $t_{50\%}$, mean dissolution time and n value but the concentration of HPMC K4M was not significant in $t_{50\%}$. Regression analysis and numerical optimization were performed to identify the best formulation. Mathematical analysis of the release kinetics indicated that non-Fickian release was the predominant mechanism of drug release which implied both polymer erosion and relaxation during the entire course time. Scanning electron microscopy was used to visualize the effect of dissolution media on matrix tablet surface. No incompatibility was observed between the drug and excipients used in the optimized formulation of matrix tablets. Results suggest that the developed controlled-release tablets of zidovudine could perform therapeutically better than marketed dosage forms, leading to improve efficacy, controlling the release and better patient compliance.

Key Words: HPMC K4 M, Matrix tablet, Zidovudine, Controlled release.

INTRODUCTION

Acquired immuno deficiency syndrome (AIDS), which threatens to cause a great plaque in present generation creates the great problem of medical community today. It is crucial for the success of AIDS therapy to maintain the drug concentration consistently above its target anti retroviral concentration throughout the course of treatment[1].

Zidovudine (AZT) (3-azido-3'deoxythymidine) is a purine analogue, in which the 3-hydroxyl group is replaced by an azido group ($-N_3$). It is the first antiretroviral drug approved from clinical use in the treatment of AIDS either along or in combination

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with other antiviral agents. The main limitation of therapeutic effectiveness of AZT is dose dependent hameological toxicity, low therapeutic index, short biological half life and poor bioavailability. It is rapidly absorbed from gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 µg/L at 0.8 h. In the systemic circulation, it is first converted to AZT triphosphate, which is pharmacologically active and prevents the viral replications. The short biological half life of AZT-triphosphate is 3-4 h, thus frequent dosing is required to maintain constant therapeutic drug level. Since its antiretroviral effect is time dependent, an controlled release formulation of AZT is desired for maintaining anti AIDS effect and avoid the toxic effect like granulocytopenia and severe anemia usually associated with excessive plasma level of AZT immediately affect intravenous or oral administration.

Zidovudine is completely and rapidly absorbed through the GIT with a bioavailability of 65 %. As the drug is freely soluble in all pH, judicious selection of release retarding agent is necessary for constant *in vivo* release. Because of their simplicity and cost-effectiveness, hydrophilic based matrix tablets are widely used for oral controlled release formulations.

Non-ionic cellulose ether and most frequently hydroxy propyl methyl cellulose (HPMC) have been widely utilized for their application in oral sustained release drug delivery system. HPMC hydrates rapidly and forms a gelatinous layer around the tablet. The rate of drug release from HPMC matrix depends on various factors such as grades of polymer, solubility of drug, polymer content, particle size of drug and polymer as well as types of filler used in formulations[2].

The adjustment of the polymer concentration, viscosity grade and addition of different type and level of excipients to the HPMC matrices can modify kinetic of drug release[3]. However use of hydrophilic polymer along for controlling the drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through hydrophilic gel layer, hence use of hydrophobic polymer along with HPMC is desirable. Thus in present investigation an attempt has been made to formulate controlled release matrix tablets using different concentration of hydrophilic HPMC K 4 M and hydrophobic ethyl cellulose (EC) along with different types of filler (micro crystalline cellulose/dicalcium phosphate) and evaluated statistically the influence of these parameters on kinetic of drug release from matrix tablet using 2^3 full factorial design.

EXPERIMENTAL

Zidovudine was obtained as a gift sample from Mecleod's Pharma (Mumbai, India), HPMC K 4 M from Alkem laboratories (Mumbai, India), micro crystalline cellulose (MCC), Mg. sterate and dicalcium phosphate (DCP) from Loba Chem, Mumbai, India. All other ingredients used in the study were of analytical grade.

Experimental design: A 2-level full factorial design consists of 8 full factorial design points; according to the model, 8 experiments were conducted in total. This design generally involves dependent variables Y and independent variable X_1, X_2,

X_3. The three independent formulation variables selected for this study where X_1, concentration of HPMC K 4 M; X_2, concentration of EC and X_3, types of filler MCC (swellable) and DCP (insoluble). The level of independent variable are shown in Table-1. The dependent variables were Y_1, time required for 50 % drug release ($t_{50\%}$); Y_2, mean dissolution time (MDT), Y_3 release exponents (n).

TABLE-1
LEVEL OF INVESTIGATED VARIABLES

Coded values	Independent variables		
	Conc. of HPMC K 4 M in % (X_1)	Conc. of EC in % (X_2)	Types of filler (X_3)
-1	20	5	MCC
1	25	10	DCP

Preparation of matrix tablet: Matrix tablets were prepared at random following a 2^3 factorial design. Table-1 shows the level of variable according to experimental design. All ingredients were sieved through 40 mesh screens and mixed together through geometric mixing, then lubricated with magnesium stearate. Finally powder mixture were compressed in 10 station rotary tablet machine (Rimek Mini Press-I, Ahmedabad, India) using 12 mm standard flat faced punch. The formula and physical characteristics of the prepared matrix embedded tablets are given in Table-2.

TABLE-2
FORMULATION COMPONENTS AND PHYSICAL CHARACTERISTICS OF DESIGNED CONTROLLED RELEASE MATRIX TABLETS OF ZIDOVUDINE

Formulations	D1	D2	D3	D4	D5	D6	D7	D8
Component[a]								
Drug (mg)	300	300	300	300	300	300	300	300
HPMCK 4 M[b]	20	25	20	25	20	25	20	25
EC[b]	5	5	10	10	5	5	10	10
MCC	106.5	79.0	79.0	51.5	-	-	-	-
DCP	-	-	-	-	106.5	79.0	79.0	51.5
Physical properties								
Drug content mg/tab (%)[c]	99.6	98.4	101.8	98.8	98.9	101	100.8	101.3
mg/tab (%)[c]	±0.6	±0.5	±1.5	±1	±1	±1.3	±0.9	±0.7
Tablet weight (mg)	545.63	552.07	545.18	552.8	561.73	555.46	542.18	548.84
Weight variation (%)[d]	±1.7	±1.6	±2.0	±1.5	±0.9	±1.6	±1.0	±2.5
Hardness (kg/cm^2)[e]	7.3	7.0	7.1	7.7	7.3	6.9	6.6	7.5
	±0.5	±0.5	±0.5	±0.3	±0.5	±0.6	±1.03	±0.6
Friability (%)	0.12	0.35	0.43	0.31	0.27	0.43	0.42	0.38

[a]Also contain 6 mg/tab (550 mg) of mg state, [b]%w/w of tablet weight, [c]Mean of triplicate with S.D., [d]±Maximum variation from the near value, [e]Mean of 10 tablets with S.D.

Physical characterization of the designed tablets: The drug content of the manufactured tablets of each formulation was determined in triplicate. For each formulation 20 tablets were taken, weighed and finely powdered. An accurately

weighed quantity of this powder was taken and suitably dissolved in distilled water and analyzed after making appropriate dilutions. The weight variation was determined by taking weight of 20 tablets using an electronic balance (Sartorious, BT-2245). Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in Roche friabilator for 4 min at 25 rpm.

***In vitro* dissolution study:** The dissolution was performed by using USP XXIV type I apparatus of rotational speed 50 rpm. The dissolution medium consists 900 mL of 0.1 N HCl for first 2 h and for subsequent 10 h in distilled water (pH 7.0), maintained at 37 ± 0.5 ºC. 5 mL of aliquots were withdrawn at predetermined time interval and replaced with fresh dissolution media. After appropriate dilution the samples were analyzed by UV-spectrophotometric (Elico, India, SL164) at 269 nm. Cumulative per cent of the drug released was calculated and the mean of three tablets from different formulations were used in data analysis.

Kinetic of drug release: To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero order[4] and Higuchi[5] equations. These models fail to explain the release mechanism due to swelling (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well known exponential equation (Korsmeyer and Peppas[6]), which used to describe the drug release behaviour from polymeric matrices.

Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and lipoid[7]):

$$MDT = (n/n+1).\ K^{-1/n} \quad (1)$$

where n = release exponent, k = rate constant.

Swelling and eroding behaviour: The mechanism of drug release from hydrophilic polymeric matrices involves solvent penetration, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix and erosion of the gel layer. Initially, the diffusion coefficient of drug in the dehydrated polymer matrix will be less and increases significantly as the polymer matrix imbibes more and more water and forms a gel, as the time progresses. The hydration rate of the polymer matrix and thereby the gel formation and subsequent erosion depends significantly on polymer proportion, viscosity and to a less degree on polymer particle size[8]. So swelling and erosion studies were carried out according to the method reported by Al-Taani and Tashtoush[9] to understand the influence of swelling and erosion behaviour on drug release and also to determine the effect of polymer viscosity on the swelling and erosion. Matrix tablets were introduced into the dissolution apparatus under the standard set of conditions as specified for release rate studies. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45 °C to a constant weight. Swelling (%) and erosion (%) were calculated according to the following formula:

$$\text{Swelling (\%)} = S/R \times 100 \quad (2)$$

$$\text{Erosion (\%)} = (T\text{-}R)/T \times 100 \quad (3)$$

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.

RESULTS AND DISCUSSION

All the tablets of different formulations showed acceptable results with respect to weight variation, drug content uniformity, friability, *etc*. Hardness within the range of 6.0 to 7.5 kg/cm^2 (Table-2). All formulations showed less than 1 % (w/w) friability that indicates the ability of tablets to withstand shocks which may be encountered during transport. The manufactured tablets showed low weight variations and a high degree of drug content uniformity was found among different formulations of the tablets and drug content was more than 97 %.

The tablets prepared from 10 and 15 % of HPMC K 4 M with either of the filler have released the drug within 5-6 h. No significant difference was observed between tablet containing either 10 or 15 % HPMC K 4 M. The release was significantly decreased when 20 % polymer was used. However the dissolution profile of the above formulation extended up to 8 h. Hence to get the desire release pattern hydrophobic polymer was included in the matrix tablet.

In the present study, the influence of combination of hydrophilic and hydrophobic in different concentration and types of filler on drug release from matrix tablet was evaluated using 2^3 full factorial design. Release profiles from 8 formulation of 2^3 factorial design are shown in Figs. 1 and 2. It was cleared from the Fig. 1, as the concentration of HPMC K 4 M and ethyl cellulose increased the release pattern of the drug decreased. In formulations D1 and D2 the release pattern was more than the desire limit (97.01 ± 1.49 and 94.56 ± 1.41, respectively at 10 and 11 h), but the D3 and D4 has the desire release pattern (91.54815 ± 0.684873 and 82.49 ± 1.45, respectively at 12 h). However in formulations D5 to D8, the release patterns were slow as compared to above formulations, at the same polymeric concentration. The properties of the diluents impact the release pattern of the formulations. Water insoluble diluent DCP retarded the release pattern more than MCC (water swellable diluents) at the same polymeric composition. In D5 formulations the release pattern was fast (91.57 ± 1.34 % released at 11 h) but in D7 and D8 the drug release was slow, 79.25 ± 1.17 % and 74.71 ± 0.96 % drug released in 12 h, respectively. The D6 formulations has the release pattern within the desirable limit (91.57 ± 1.34 % at 12 h).

The results of diffusion exponent (n), time required to 50 % drug release ($t_{50\%}$) and mean dissolution time (MDT), showed wide variation (Table-3). All the data were statistically analyzed for response variable by using demo version software (sigma plot 10.0). The design was evaluated by a factorial linear first order model:

$$Y = b_0+b_1X_1+b_2X_2+b_3X_3+b_{12}X_1X_2+b_{13}X_1X_3+b_{23}X_2X_3 \quad (4)$$

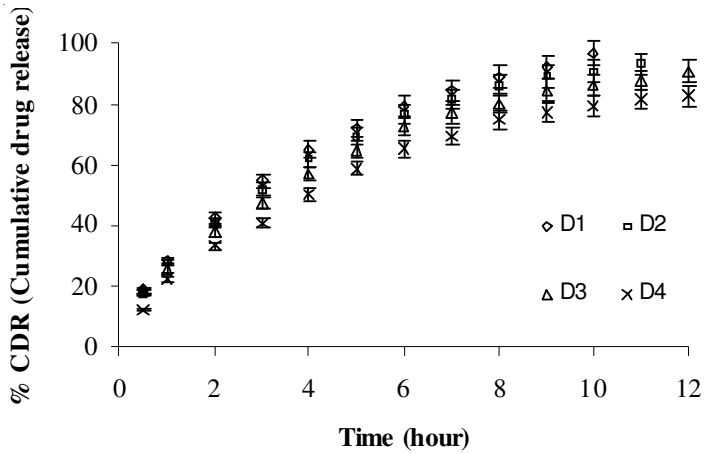

Fig. 1. *In vitro* release of AZT from formulation D1 to D4 (n = 3)

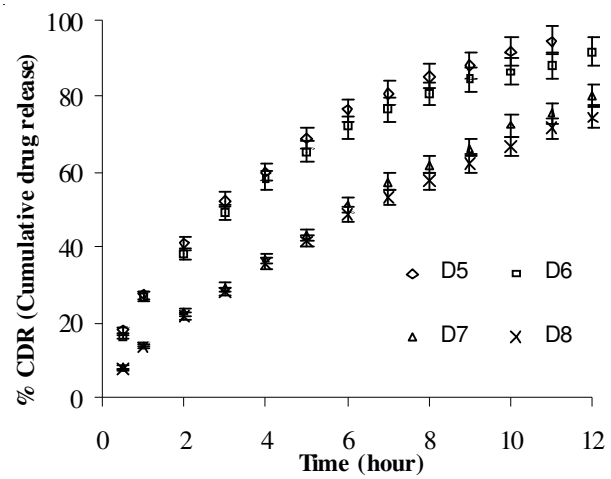

Fig. 2. *In vitro* release of AZT from formulation D5 to D8 (n = 3)

TABLE-3
RELEASE KINETICS AND DISSOLUTION PROFILE OF ALL FORMULATIONS

Formulation code	r^2			MDT	n	$t_{50\%}$
	Zero order	Higuchi	Korsmeyer			
D1	0.916	0.995	0.995	3.13±0.05	0.55	2.60±0.02
D2	0.899	0.991	0.990	3.14±0.06	0.54	2.79±0.02
D3	0.897	0.990	0.993	3.83±0.53	0.52	3.28±0.15
D4	0.908	0.989	0.986	3.58±0.09	0.59	4±0.15
D5	0.909	0.994	0.994	3.3±0.10	0.54	2.8±0.05
D6	0.897	0.991	0.989	3.50±0.10	0.54	3±0.15
D7	0.979	0.981	0.999	4.82±0.10	0.72	5.8±0.10
D8	0.976	0.984	0.999	4.70±0.10	0.70	6.25±0.10

The regression coefficients for each dependent variable in the regression model are summarized in Table-4.

TABLE-4
REGRESSION COEFFICIENTS OF THE RESPONSE

$Y_1 = 3.805 + 0.207\ X_1 + 1.005\ X_2 + 0.658\ X_3 + 0.108\ X_1X_2 - 0.0300\ X_1X_3 + 0.558\ X_2X_3$
$Y_2 = 3.697 + 0.0274\ X_1 + 0.429\ X_2 + 0.390\ X_3 - 0.0351\ X_1X_2 + 0.00488\ X_1X_3 + 0.248\ X_2X_3$
$Y_2 = 0.588 + 0.00687\ X_1 + 0.0434\ X_2 + 0.0351\ X_3 + 0.00912\ X_1X_2 - 0.00962\ X_1X_3 + 0.0384\ X_2X_3$

Concentration of hydrophobic agent (X_2) had the significant effect on the time required for 50 % drug release. As the concentration increase the above dependent variable increase significantly ($p < 0.05$), this is due to its prevention of entry of the dissolution fluid into the intact matrices. This has been reported that ethyl cellulose has higher fragmentation rate and extensive plastic deformation which result lower porosity and more sustained of the tablet even if lower compression force[10,11].

The factor X_3 (types of diluents) have the significant effect in X_1 value ($p < 0.05$). In case of formulation prepared using MCC as filler, due to its high swelling capability and disintegration properties, it can allowed faster penetration of dissolution medium. It can also create such an environment that more amount of drug get dissolved with in the gel matrix and subsequently behave as a soluble component and release from matrix *via* diffusion mechanism. However formulations containing DCP as water insoluble filler retarding the release pattern.

When the HPMC K 4 M (X_1) increased leads to retard the release pattern hence Y_1 value increased gradually because increased in strength of the gel layer around the tablets prevent penetration of liquid[12]. At lower level of X_2, Y_1 didn't show any significant changes when X_1 increased from -1 to +1 level but significant changes occurred when X_2 at high level and X_3 was at lower level (Fig. 3a). In case of DCP (X_3) Fig. 3b, higher level of EC leaded to significantly effect ($p < 0.05$) the Y_1 value.

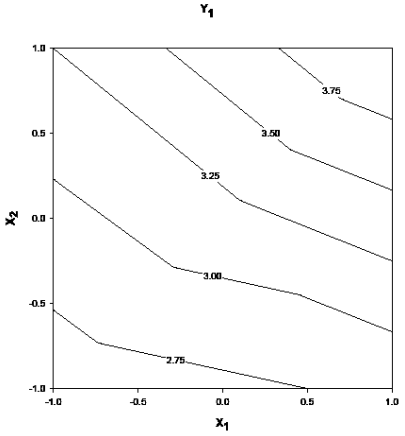

Fig. 3a. Contour graph showing the effect of concentration HPMC K 4 M (X_1) and ethyl cellulose on (X_2) on $t_{50\%}$ (Y_1), for MCC

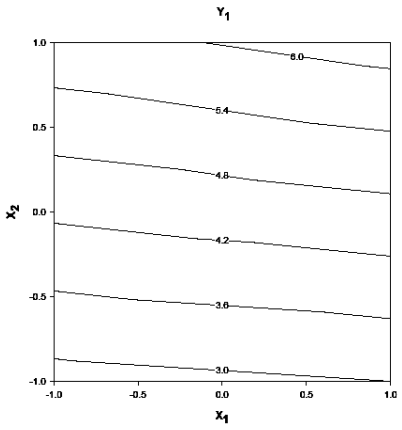

Fig. 3b. Contour graph showing the effect of concentration HPMC K 4 M (X_1) and ethyl cellulose on (X_2) on $t_{50\%}$ (Y_1), for DCP

The model form for Y_2 (MDT) was found to be insignificant ($p > 0.05$) with change in X_1 variable, with constant level of X_2 and X_3. Change in the concentration of ethyl cellulose (X_2) from its higher to lower level leaded to change the MDT value significantly ($p < 0.05$) with either of the diluents MCC or DCP. Alteration of X_3 value at constant level of X_1 and X_3 changed the MDT value significantly. In MCC the MDT values were lower because of swelling properties that cause easy diffusion of drug (Fig. 4a and 4b).

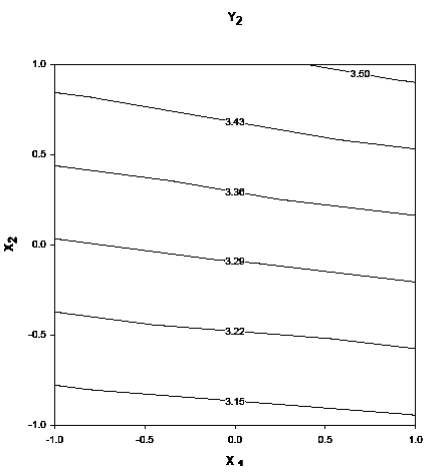

Fig. 4a. Contour graph showing the effect of concentration HPMC K 4 M (X_1) and ethyl cellulose on (X_2) on MDT (Y_2), for MCC

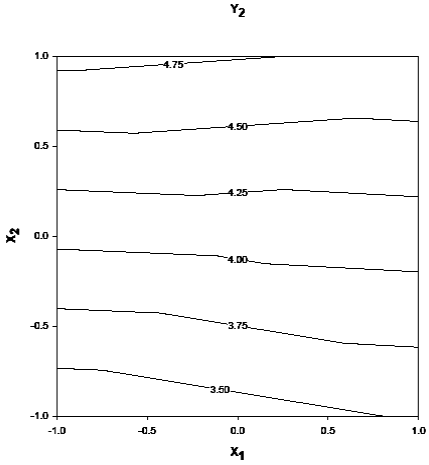

Fig. 4b. Contour graph showing the effect of concentration HPMC K 4 M (X_1) and ethyl cellulose on (X_2) on MDT (Y_2), for DCP

The release exponent (n) value changed significantly ($p < 0.05$) with change in all variables. As X_1 variable increased at lower level of X_2, the value decreased rather than increased. This behaviour is due to increase hydrophilic polymer load, which leads to increase intactness and viscosity of gel layer. Hence release pattern approached towards diffusion predominant mechanism, at lower level of X_1 which was unable to form the intact mass and hence more water penetration to the tablet core through the tortuous path caused bath diffusion and erosion of the polymer. At maximum level of X_2 (hydrophobic polymer), the minimum to maximum level of X_1, release exponent was increased due to more polymer erosion rather than diffusion. Formulations prepared using MCC as filler, due to its high swelling capability and disintegration properties, it can allowed faster penetration of dissolution medium. Hence created such an environment that more amount of drug get dissolved within gel matrix and subsequently behaved as soluble component and released from matrix *via* diffusion mechanism[13] thus lower the release exponent. In formulations containing DCP as filler showed higher value of 'n' at same level of X_1 and X_2 because of its insoluble nature, which prevent penetration of dissolution fluid in to the tablet core and hence erosion was the predominant mechanism.

Selection of the final formulation: Formulations prepared using MCC on diluents, 97.01 ± 1.49 and 94.5 ± 1.4 % drug released from D1 and D2 at time 10 and 11 h, but D3 and D4 the release pattern within 91.54 ± 0.68 and 82.4 ± 1.4 % drug released at 12 h. However formulation D5, 91.57 ± 1.34 % drug released at 11 h but D6 the release pattern was found to be desire level, but D7 and D8 has lower the released pattern when DCP was used as diluents. Taking $t_{50\%}$ and MDT values of formulations D3, D4 and D6, it was clear that D4 has significantly higher value 4 ± 0.15 h and 3.58 ± 0.09 h, which implied that D4 was the optimized formulation.

To know the kinetics of drug released, the dissolution data of D4 was treated according to the different model. Which showed best fill into Higuchi's equation (r^2 = 0.989). The value of n (0.594) indicating that the release mechanism was non-Fickian or anomalous release (0.45 < n < 0.89). It can be inferred that the release was dependent on both drug diffusion as well as polymer relaxation. Based on the swelling and erosion studies, it was observed that the matrix tablets undergo swelling (Fig. 5) as well as erosion (Fig. 6) during the dissolution study, which indicated that polymer relaxation had a significant role in the drug release mechanism.

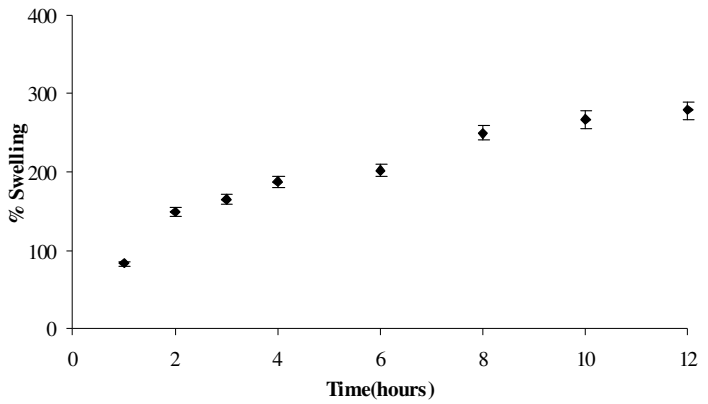

Fig. 5. Swelling behaviour of the optimized formulation

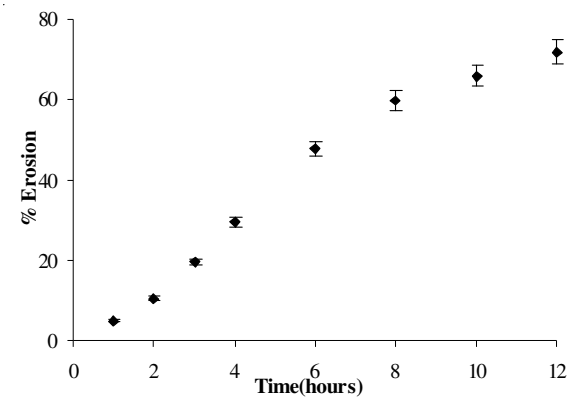

Fig. 6. Erodable behaviour of optimized formulation

SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet. 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. SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time indicated by the photomicrographs at 2 and 6 h revealing pores with increasing diameter. These photomicrograph also revealed the formation of gelling structure indicating the possibility of swelling of matrix tablets (Fig. 8a and b). 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.

Drug excipient interaction study: FT-IR spectra of pure AZT and solid admixtures of AZT with various excipients were scanned over a wavelength range of 4000 to 400 cm^{-1} using an FTIR 8400S model instrument. Drug-excipient interactions play a vital role in the release of drug from formulations. FTIR techniques have been used to study the physical and chemical interactions between drug and excipients used. It was found that there is no chemical interaction between AZT and the polymers used (Fig. 7). The characteristic peak of carbonyl group at 1694 cm^{-1} and azide group at 2012 cm^{-1}, present in all the spectrum indicates the stable nature of AZT in the solid admixtures.

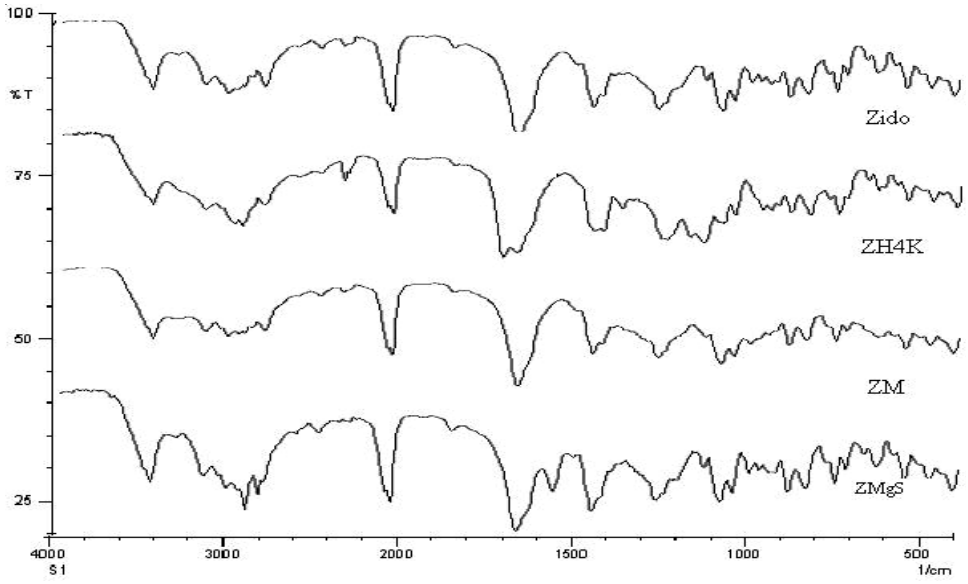

Fig. 7. FT-IR spectra of pure zidovudine (Zido), solid admixture of zidovudine with HPMC 4000 cps (ZH 4 K), zidovudine with MCC (ZM), zidovudine with magnesium stearate (ZMgS)

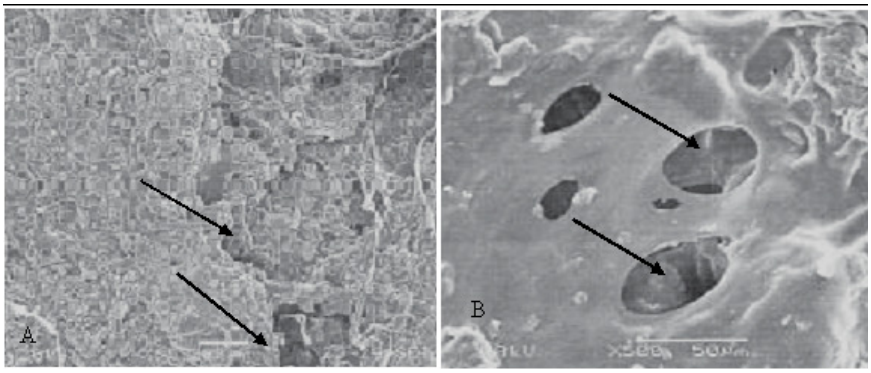

Fig. 8. SEM study of optimized matrix tablets showing surface morphology at 2 and 6 h of dissolution study (arrow indicated the formation of pores on matrix surface)

Reproducibility and stability on storage: No statistically significant differences were observed the release profiles of optimized formulations ($p > 0.05$) and also release kinetics were unaltered, indicating that the manufacturing process employed was reliable and reproducible. No significant physical characteristics were changed when stability study was done for six months at 40 ± 2 ºC and 75 ± 5 % RH, suggesting that AZT was stable in HPMC matrices.

Conclusion

It can be concluded that stable formulation could be developed by incorporating both hydrophilic and hydrophobic polymer in a definite proportion, so that sustained released profile is maintained for an extended periods of time.

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