Design and *in Vitro* Evaluation of Zidovudine Oral Controlled Release Tablets Prepared Using Hydroxypropyl Methylcellulose

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Oral controlled release matrix tablets of zidovudine were prepared using different proportions and different viscosity grades of hydroxypropyl methylcellulose. The effect of various formulation factors like polymer proportion, polymer viscosity and compression force on the *in vitro* release of drug were studied. *In vitro* release studies were carried out using United States Pharmacopeia (USP) type 1 apparatus (basket method) in 900 ml of pH 6.8 phosphate buffer at 100 rpm. The release kinetics were analyzed using Zero-order model equation, Higuchi's square-root equation and Ritger–Peppas' empirical equation. Compatibility of drug with various formulations excipients used was studied. *In vitro* release studies revealed that the release rate decreased with increase in polymer proportion and viscosity grade. Increase in compression force was found to decrease the rate of drug release. Matrix tablets containing 10% hydroxypropyl methylcellulose (HPMC) 4000 cps were found to show a good initial drug release of 21% in the first hour and extended the release upto 16 h. Matrix tablets containing 20% HPMC 4000 cps and 10% HPMC 15000 cps showed a first hour release of 18% and extended the release upto 20 h. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets followed non-Fickian or anomalous release. No incompatibility was observed between the drug and excipients used in the formulation of matrix tablets. The developed controlled release matrix tablets of zidovudine, with good initial release (17—25% in first hour) and which extend the release upto 16—20 h, can overcome the disadvantages of conventional tablets of zidovudine.

Key words controlled release; matrix tablet; zidovudine; hydroxypropyl methylcellulose

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages.[1] Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs.[2]

AIDS is considered to be an epidemic and according to estimates from the UNAIDS/WHO AIDS Epidemic Update, December 2005, 38.0 million adults and 2.3 million children were living with human immunodeficiency virus (HIV) at the end of 2005. The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient compliant anti-retroviral medications are available at affordable prices.[3] The major drawbacks of anti-retroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance and huge cost of the therapy.[4,5]

Zidovudine (AZT) is a potent antiviral agent used in the treatment of AIDS. Conventional formulations of AZT are administered multiple times a day depending on the dose (300 mg twice daily or 200 mg thrice daily) due to its short half-life ($t_{1/2}$=0.5 to 3 h).[6—8] Treatment of AIDS using conventional formulations of AZT is found to have many drawbacks such as adverse side effects due to accumulation of drug in multi-dose therapy,[9,10] poor patient compliance[11] and high cost. So, CR once daily formulations of AZT can overcome some of these problems.

Matrix based CR tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. The matrix tablets can be prepared *via* wet granulation or by direct compression.[12] Many polymers have been used in the formulation of matrix based CR drug delivery systems. Reports were found on the use of hydrophilic polymers like hydroxypropyl methylcellulose (HPMC), methylcellulose, sodiumcarboxy methylcellulose,[13] carbopols[14] and polyvinyl alcohol[15] for the preparation of CR formulations of different drugs. HPMC, a semisynthetic derivative of cellulose, is a swellable hydrophilic polymer. It contains methoxyl and hydroxypropyl substituents on its β-*o*-glucopyranosyl ring backbone, which makes it very resistant to changes in pH or ionic content of the dissolution medium. At pH values from 2 to 13, HPMC is relatively stable and the CR matrix formulations of any drug prepared using HPMC can show pH independent drug release if the drug has pH independent drug solubility.[16] Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs.[17—19] It is very suitable to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle.[20] Matrix tablets prepared using HPMC on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix.[21] The release of the drug from the CR matrices is influenced by various formulation factors like polymer viscosity, polymer particle size, drug to polymer ratio, drug solubility, drug particle size, compression force, tablet shape, formulation excipients, processing techniques and dissolution medium.[18,22]

The drug release from polymer matrix can be due to disentanglement or diffusion, depending on the polymer molecular weight and the thickness of the diffusion boundary layer.[23,24] Polymer dissolution plays an important role in regulating the drug release in case of lower viscosity grades of HPMC and for relatively water insoluble drugs.[25] Several kinetic models

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have been proposed to describe the release characteristics of a drug from controlled release polymer matrix. The following three equations hold the special position and are currently in common use due to their simplicity and applicability[26,27]:

Zero-order model equation:

$$M_t/M_\infty = K_o t \quad (1)$$

Higuchi's square-root equation:

$$M_t/M_\infty = K_H t^{1/2} \quad (2)$$

Ritger–Peppas' empirical equation:

$$M_t/M_\infty = K t^n \quad (3)$$

Where M_t/M_∞ is the fraction of drug released at any time t; K_o, K_H and K are release rate constants for Eqs. 1, 2 and 3 respectively. In Eq. 3, n is the diffusional exponent indicative of mechanism of drug release. In case of tablets (which are of cylindrical shape), a value of $n=0.45$ indicates Fickian or Case I release; $0.45<n<0.89$ for non-Fickian or anomalous release; $n=0.89$ for Case II release; and $n>0.89$ indicates Super Case II release.

Reports were found on the extended release of AZT from matrix tablets prepared using combination of hydrophilic (Eudragit) and hydrophobic (ethylcellulose) polymers.[28] The release of AZT was extended from 4 to 12 h. *In vitro* release of AZT from ceramic capsules prepared using tricalcium phosphate and alumino-calcium-phosphorous oxide for sustained action had been investigated by Benghuzzi and his coworkers.[29] Long-term sustained delivery of AZT *in vivo* by means of hydroxyapatite and tricalcium-phosphate ceramic implants was studied by Benghuzzi.[30] It was found that ceramic drug delivery systems can be effectively used in both sustaining and reducing the fluctuations of AZT concentration levels in blood and tissues.

However, no literature has been found on oral CR tablet formulations of AZT prepared using HPMC as a retardant material. Since AZT is known to have pH independent solubility, CR tablet formulations prepared using a polymer like HPMC, which has pH independent drug release characteristics (due to its pH independent swelling and erosion properties) would be ideal for obtaining desired drug release kinetics. The purpose of this study was to design oral CR tablet formulations of AZT using HPMC as the retarding polymer. The tablets were formulated by wet granulation method and their physical and *in vitro* release characteristics were evaluated. The effect of formulation factors like polymer proportion, polymer viscosity and compression force on the drug release characteristics were studied in order to optimize these variables.

Experimental

Materials AZT was obtained as gift sample from Strides Arcolab Limited, Bangalore, India. HPMC (4000, 15000, 100000 cps) was a gift sample from IPCA laboratories, Mumbai, India. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Analytical Method An in-house developed and validated UV spectrophotometric method (UV-VIS-NIR Spectrophotometer, V-570, Jasco, Tokyo, Japan), with 1 cm quartz cell, using pH 6.8 phosphate buffer at 266 nm was used for the estimation of drug in bulk, formulations and in dissolution samples.[31]

Characterization of Bulk Drug and Effect of Various Formulation Excipients The bulk drug was characterized by various tests of identification according to the certificate of analysis given by the supplier and analyzed by the above mentioned UV spectrophotometric method. The IR spectrum obtained (Infrared spectrophotometer; IR Report 100, Jasco, Tokyo, Japan) was compared with that of the standard. To study the compatibility of various formulation excipients with AZT, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1 : 1 and stored in air tight containers at 30±2 °C/65±5% RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR) (Fourier Transform Infrared Spectrometer, IR Prestige-21, Shimadzu, Kyoto, Japan) and differential scanning calorimetry (DSC) (Differential Scanning Calorimeter, DSC-60, Shimadzu, Kyoto, Japan). The solid admixtures were characterized every 6 months for a period of 1 year.

Formulation of Zidovudine Matrix-Embedded Tablets Matrix embedded CR tablet formulations of AZT were prepared using various proportions of different viscosity grade HPMC as the retarding polymer. The tablets were manufactured by wet granulation process using isopropyl alcohol as the binding agent. The drug and polymer (passed through 60# mesh) were mixed uniformly and granulated with isopropyl alcohol and dried in a tray drier at 40 °C. The dried granules were then passed through mesh 20#. The final granules were blended with talc (3% w/w of the dried granules weight) and magnesium stearate (1% w/w of the dried granules weight) and compressed on 16-station tablet compression machine (Rotary Tabletting Machine, CMB3-16, Cadmach, Ahmedabad, India) using round, flat face, beveled edge punches of 10-mm diameter at different compression forces. Three batches were prepared for each formulation with each tablet containing 300 mg AZT. The formula and physical characteristics of the prepared matrix embedded tablets are given in Table 1.

Physical Characterization of the Designed Tablets The drug content

Table 1. Formulation Components and Physical Characteristics of Designed Controlled Release Matrix Tablets of Zidovudine

Formulations	H4-1	H4-2	H4-2A	H4-2B	H4-3	H4-4	H15-1	H15-2	H15-3	HL-1	HL-2	HL-3
Components[a]												
Drug (mg)	300	300	300	300	300	300	300	300	300	300	300	300
HPMC (%)[b] 4000 cps	10	20	20	20	40	60	—	—	—	—	—	—
15000 cps	—	—	—	—	—	—	10	20	40	—	—	—
100000 cps	—	—	—	—	—	—	—	—	—	10	20	40
Physical properties												
Drug content (mg/tablet)[c]	300.5 (±1.1)	298.6 (±0.9)	301.9 (±0.7)	302.5 (±1.0)	299.8 (±0.9)	298.5 (±0.7)	301.3 (±0.6)	302.6 (±1.0)	299.5 (±0.6)	302.9 (±1.1)	300.5 (±0.8)	301.6 (±0.4)
Tablet weight (mg)	343.5	375.8	374.2	373.8	437.4	501.7	344.2	376.7	438.5	342.6	374.3	436.5
Weight variation (%)[d]	±2.0	±1.5	±2.2	±2.4	±1.9	±2.1	±2.0	±2.6	±2.3	±2.0	±2.6	±2.5
Hardness (kg/cm^2)[e]	7.4 (±0.4)	7.5 (±0.4)	4.0 (±0.4)	11.5 (±0.3)	7.5 (±0.3)	7.6 (±0.4)	7.5 (±0.3)	7.5 (±0.4)	7.3 (±0.3)	7.6 (±0.3)	7.5 (±0.4)	7.4 (±0.3)
Friability (%)	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5

a) Also contains 3% w/w talc and 1% w/w magnesium stearate as manufacturing additives and isopropyl alcohol was used as binding agent. *b*) % w/w of the drug weight, *c*) mean of triplicate with S.D., *d*) ± max. variation from the mean value, *e*) mean of 10 tablets with S.D. Formulations H4-2A, H4-2 and H4-2B contain same proportion (20% w/w of drug weight) of HPMC 4000 cps, but prepared with different compression forces to get different hardness levels and were used for studying the effect of compression force on drug release.

of the manufactured tablets of each batch was determined in triplicate. For each batch 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved in pH 6.8 phosphate buffer, and analyzed after making appropriate dilutions. The weight variation was determined by taking weight of 20 tablets using an electronic balance (Type ER182A, Afcoset, Mumbai, India). 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 a friability tester (FTA-20, Campbell Electronics, Mumbai, India) for 4 min at 25 rpm.

Release Rate Studies Release rate for all the designed formulations was studied up to 24 h using Tablet Dissolution Tester (Dissolution Tester (USP), TDT-08L, Electrolab, Mumbai, India), type 1 (basket method) in 900 ml of pH 6.8 phosphate buffer at 37.5±0.5 °C. The stirring speed was set at 100 rpm. At predetermined time intervals, a 10 ml sample was withdrawn and replaced with fresh dissolution media. After appropriate dilution the samples were analyzed. Cumulative percent of the drug released was calculated and the mean of six tablets from three different batches was used in data analysis.

Characterization of Release Kinetics The order and mechanism of AZT release from the CR matrix tablets were determined by fitting the release rate studies data into Eqs. 1, 2 and 3. The values of K, K_H, K_o, n, $t_{50\%}$ (time required for 50% of drug release) and r (correlation coefficient) were determined. Equations 1 and 2, fail to explain the drug release mechanism from polymeric matrices that undergo swelling and/or erosion during the dissolution process. In such cases based on the value of obtained by fitting the data into Eq. 3, we can describe the mechanism of drug release from the formulation.[28] In case of Fickian release mechanism, the rate of drug release is much lesser than that of polymer relaxation (swelling/erosion). So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian (anomalous) case, the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation. Case II release generally refers to the polymer relaxation.[26] Nature of release of the drug from the designed CR matrix tablets was inferred based on the correlation coefficients obtained from the plots of the three kinetic models.

Swelling and Eroding Behavior 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.[14] So swelling and erosion studies were carried out according to the method reported by Al-Taani and Tashtoush,[32] to understand the influence of swelling and erosion behavior 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:

$$\%\text{swelling} = S/R \times 100 \quad (4)$$

$$\%\text{erosion} = (T-R)/T \times 100 \quad (5)$$

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.

Batch Reproducibility and Stability on Storage Three batches of each formulation were prepared and their quality and respective *in vitro* release characters were evaluated under the same conditions to determine the batch reproducibility. To study the effect of storage on stability and release profile, the tablets of all formulations were sealed in airtight cellophane packets and stored at 30±2 °C/65±5% RH. Physical characteristics and drug release profile of the formulations were studied at 6 months and 1 year intervals for determining the effect of storage.

Release Profiles Comparison and Statistical Analysis The drug release profiles were compared using a model-independent method,[33] by determining the mean dissolution time (MDT) of the formulations being compared and subjecting the MDT values to one-way ANOVA for analyzing the statistical difference. A confidence limit of $p<0.05$ was fixed and the theoretical and calculated values of F (F_{crit} and F_{cal}) were compared for the interpretation of results. ANOVA was determined using software 'PRISM' (Graphpad, San Diego, U.S.A.). The MDT values were calculated by the following equation:

$$\text{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (6)$$

Where j is the sample number, n is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and t_{j-1} (easily calculated with the expression) $(t_j+t_{j-1})/2$) and ΔM_j is the additional amount of drug released between t_j and t_{j-1}.

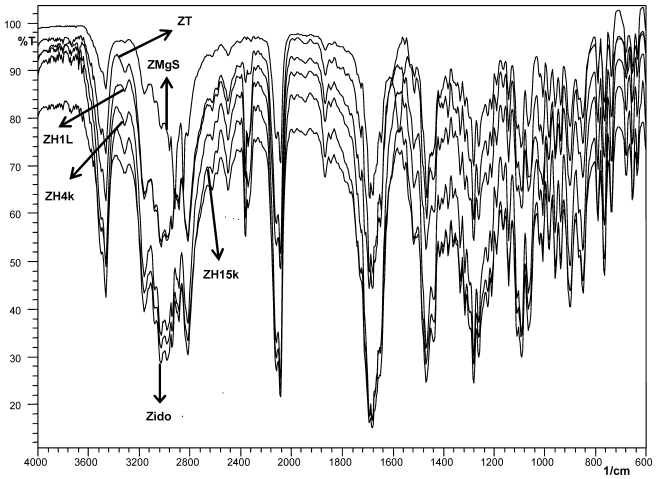

Fig. 1. FT-IR Spectra of Pure Zidovudine (Zido), Solid Admixture of Zidovudine with HPMC 4000 cps (ZH4k), Zidovudine with HPMC 15000 cps (ZH15k), Zidovudine with HPMC 100000 cps (ZH1L), Zidovudine with Magnesium Stearate (ZMgS) and Zidovudine with Talc (ZT)

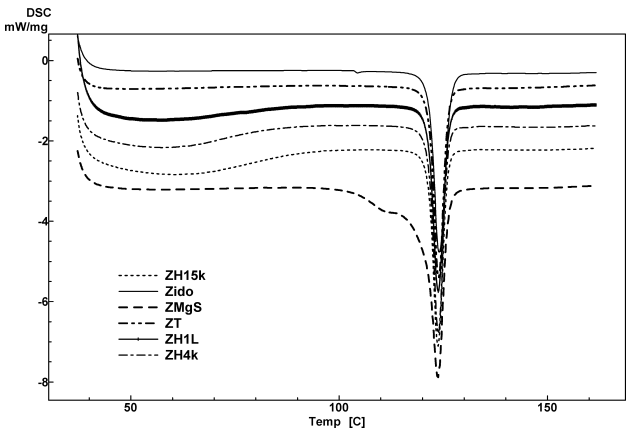

Fig. 2. DSC Thermograms of Pure Zidovudine (Zido) and Its Solid Admixture with HPMC 4000 cps (ZH4k), HPMC 15000 cps (ZH15k), HPMC 100000 cps (ZH1L), Magnesium Stearate (ZMgS) and Talc (ZT) at a Heating Rate of 10 °C/min Using Nitrogen Environment

Results and Discussion

Characterization of Bulk Drug and Effect of Various Formulation Excipients The supplied drug passed the various tests of identification and analysis as per the certificate of analysis given by the supplier. FT-IR spectra of pure AZT and solid admixtures of AZT with various excipients used in the preparation of CR tablet formulations, characterized after

Table 2. Release Kinetics Parameters and Mean Dissolution Time (MDT) Values of Designed Controlled Release Matrix Tablets of Zidovudine

Parameters		H4-1	H4-2	H4-2A	H4-2B	H4-3	H4-4	H15-1	H15-2	H15-3	HL-1	HL-2	HL-3
Ritger–Peppas empirical equation	$r^{a)}$	0.993	0.989	0.998	0.986	0.984	0.982	0.990	0.987	0.983	0.991	0.987	0.985
	$K^{b)}$ (% h^{-n})	21.72	18.27	25.06	15.80	14.72	12.05	18.33	14.91	11.28	15.52	11.49	8.46
	$n^{c)}$	0.581	0.603	0.568	0.622	0.644	0.675	0.598	0.634	0.699	0.606	0.655	0.699
	$t_{50\%}{}^{d)}$ (h)	4.19	5.33	3.37	6.38	6.66	8.23	5.35	6.74	8.39	6.89	9.42	12.66
Higuchi's square-root equation	$r^{a)}$	0.972	0.967	0.975	0.960	0.923	0.908	0.977	0.902	0.895	0.948	0.904	0.889
	$K_H{}^{e)}$ (% $h^{-0.5}$)	25.42	22.81	28.78	21.15	20.92	18.34	22.77	20.57	18.26	19.91	16.62	13.61
Zero-order model equation	$r^{a)}$	0.735	0.725	0.787	0.735	0.749	0.779	0.725	0.752	0.808	0.741	0.767	0.776
	$K_o{}^{f)}$ (% h^{-1})	7.96	6.37	9.96	5.35	5.26	4.65	6.34	5.20	4.66	5.05	4.22	3.46
MDT$^{g)}$ (h)		5.11	6.36	4.20	7.35	7.68	9.86	6.44	7.87	9.86	8.36	11.75	15.99

a) Correlation coefficients. *b*, *e*, *f*) Release rate constant for Ritger–Peppas empirical equation, Higuchi's square-root equation and Zero-order model equation respectively. *c*) Diffusional exponent indicative of release mechanism in Ritger–Peppas empirical equation. *d*) Time for 50% of the drug release. Reported value is the mean of 6 tablets with S.D. within ±0.11 h. *g*) Mean of 6 tablets with S.D. within ±0.15 h.

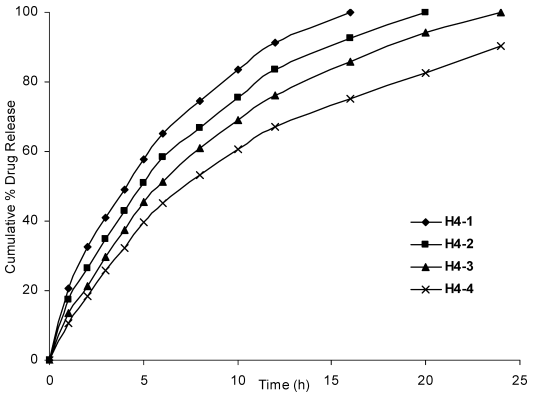

Fig. 3. Comparative Release Profile of Zidovudine from Controlled Release Matrix Tablets Prepared Using Different Proportions of HPMC 4000 cps

Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0.

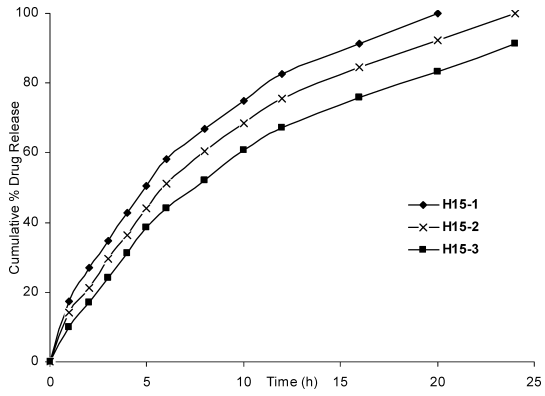

Fig. 4. Comparative Release Profile of Zidovudine from Controlled Release Matrix Tablets Prepared Using Different Proportions of HPMC 15000 cps

Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0.

6 months of storage, is given in Fig. 1. The characteristic peak of carbonyl group at 1694 cm^{-1} and azide group at 2012 cm^{-1},[34] present in all the spectrum indicates the stable nature of AZT in the solid admixtures. This was further supported by DSC studies. The DSC thermogram of pure AZT showed a sharp melting endotherm at 124 °C with a normalized energy of 92.5 J/g, as shown in Fig. 2. The thermograms of solid admixtures of AZT with various excipients, characterized after 6 months of storage, also had shown similar peak at 124 °C with almost the same normalized energy, indicating that AZT is unaffected in the presence of various excipients used in the preparation of CR tablets formulations. Similar results were obtained for the pure AZT and the solid admixtures of AZT with various excipients, when characterized after 1 year of storage using FT-IR and DSC.

Physical Characterization of the Designed Tablets The physical appearance, tablet hardness, friability, weight variation and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 1. Tablet hardness was found to be good (between 3.5—12.0 kg/cm^2) depending on the compression force applied and friability was less than 0.5% (w/w). The manufactured tablets showed low weight variation and a high degree of drug content uniformity indicating that the wet granulation method is an acceptable method for preparing good quality matrix tablets of AZT.

Release Rate Studies The kinetic parameters and MDT values for all the formulations are given in Table 2. A plot of cumulative percentage of drug released versus time for matrix embedded CR tablet formulations of AZT prepared using different proportions of HPMC 4000 cps, with hardness 7.0—8.0 kg/cm^2, is shown in Fig. 3. The initial percent released for the first hour varied between 10—21% for all the formulations. However, in the later stages the release was found to be slower and more controlled in the tablets with higher proportion of the polymer. The release of the drug from the tablets extended as the polymer proportion was increased form 10 to 60%. The release extended till 16 h in case of 10% (H4-1) to more than 24 h in case of 60% (H4-4) polymer proportion. In case of H4-4, around 90% drug release was observed after 24 h of dissolution because of the high polymer proportion used in the formulation. The release rate was significantly dependent on the proportion of polymer. Statistically significant increase ($p<0.05$, $F_{crit}(3,20)=3.09$ and $F_{cal}=2418.68$) was observed in the MDT values of formulations, as the polymer proportion increased.

Similar pattern was observed with matrix embedded CR tablet formulations of AZT prepared using HPMC 15000 and 100000 cps as the retarding polymer. The release rate decreased and the drug release extended as the polymer propor-

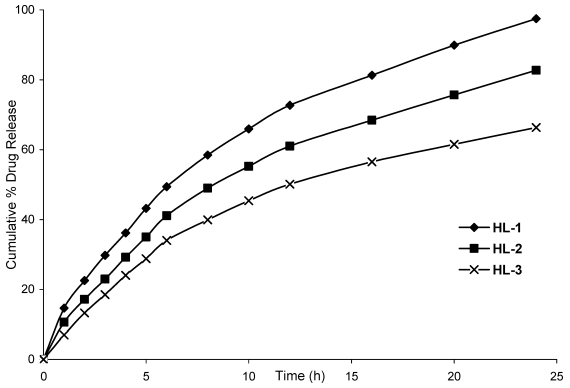

Fig. 5. Comparative Release Profile of Zidovudine from Controlled Release Matrix Tablets Prepared Using Different Proportions of HPMC 100000 cps

Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0.

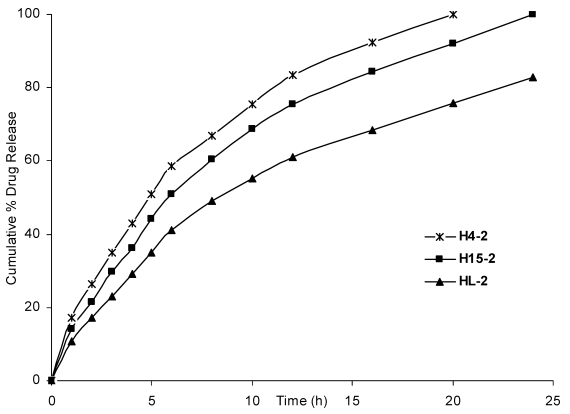

Fig. 6. Comparative Release Profile of Zidovudine from Matrix Tablets Prepared Using Different Viscosity Grades of HPMC at 20% w/w of Drug Weight

Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0.

tion was increased. In case of HPMC 15000 cps, the initial release for the first hour varied between 10—18% depending on polymer proportion, but the release was found to be more controlled in later stages in the tablets with higher proportion of the polymer (Fig. 4). The release of the drug extended from 20 h in case of 10% (H15-1) to beyond 24 h in case of 40% (H15-3). The MDT values increased significantly ($p<0.05$, $F_{crit}(2,15)=3.68$ and $F_{cal}=2133.09$) as the polymer proportion was increased from 10 to 40%. In formulations containing HPMC 100000 cps as the retarding polymer, the initial release for the first hour varied between 7—15% depending on polymer proportion (Fig. 5). However, the release was found to be much slower and controlled, extending it beyond 24 h in the tablets even with 10% (HL-1) of polymer proportion. The MDT values increased significantly ($p<0.05$, $F_{crit}(2,15)=3.68$ and $F_{cal}=11308.21$) as polymer proportion was increased from 10 to 40%. Similar results were reported in the literature by several research groups, when they studied the effect of polymer proportion on the release of drugs like propranolol hydrochloride, aminophylline and indomethacin from matrix tablets of HPMC.[35—37] The release rate of the drug from the matrix tablets decreased with increase in polymer proportion because of an increase in the gel strength as well as the formation of a gel layer with a longer diffusional path. This could have caused a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate.[21,38]

The n values for all the formulations ranged from 0.568 to 0.699 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. The poor correlation coefficients (r values ranged from 0.725 to 0.808) observed for the kinetic parameters based on Zero-order model equation were mainly due to the drug release mechanism. Based on the swelling and erosion studies, it was observed that the matrix tablets undergo swelling (Fig. 8) as well as erosion (Fig. 9) during the dissolution study, which indicated that polymer relaxation had a significant role in the drug release mechanism. The values of n increased as the proportion of polymer was increased. So, it can be inferred that the influence of polymer relaxation on the mechanism of drug release increased while that of drug diffusion on mechanism of drug release decreased with increase in polymer proportion.

The release rate was fastest from the formulation containing HPMC 4000 cps at 10% w/w of the drug weight (H4-1) with a K value of 21.72% $h^{-0.581}$ and $t_{50\%}$ value of 4.19 h. The release rate was slowest from the formulation containing HPMC 100000 cps at 40% w/w of the drug weight (HL-3) with a K value of 8.46% $h^{-0.699}$ and $t_{50\%}$ value of 12.66 h. The release rates of H4-2 and H15-1 were almost similar, and no significant difference ($p<0.05$, $F_{crit}(1,10)=4.96$) was found between K ($F_{cal}=1.87$), $t_{50\%}$ ($F_{cal}=0.35$), MDT ($F_{cal}=0.76$), initial release in first hour ($F_{cal}=2.14$) and duration of release ($F_{cal}=0.15$) values of these two formulations. Similarly, no significant difference ($p<0.05$, $F_{crit}(2,15)=3.68$) was observed in the values of K ($F_{cal}=3.57$), $t_{50\%}$ ($F_{cal}=2.93$), MDT ($F_{cal}=3.63$), initial release in first hour ($F_{cal}=3.02$) and duration of release ($F_{cal}=3.17$) values for formulations H4-3, H15-2 and HL-1, indicating that they showed similar release profiles. These results prove that the release profiles obtained with higher proportions of low viscosity HPMC (4000 cps) can be achieved with lower proportions of high viscosity HPMC (15000 or 100000 cps).

Effect of Viscosity of HPMC on Drug Release The effect of viscosity of HPMC on the drug release from formulations containing the same proportion of polymer (20% w/w of the drug weight) is shown in Fig. 6. As the viscosity of HPMC was increased from 4000 cps (H4-2) to 100000 cps (HL-2) the release rate extended from 20 h to beyond 24 h; the values of K decreased from 18.27% $h^{-0.603}$ to 11.49% $h^{-0.655}$; and the values of $t_{50\%}$ increased from 5.33 to 9.42 h. The MDT vales increased significantly ($p<0.05$, $F_{crit}(2,15)=3.68$ and $F_{cal}=5114.58$) with increase in polymer viscosity. This observation was in agreement with other reported works.[39] The release rate was faster with lower viscosity grades of HPMC probably due to lesser polymer entanglement and lesser gel strength and also larger effective molecular diffusional area at lower viscosity as compared to higher viscosity grades of HPMC.[39] The values of n increased as the viscosity of polymer was increased. So, it can be inferred that the influence of polymer relaxation on the mechanism of drug release increased while that of drug diffusion on mecha-

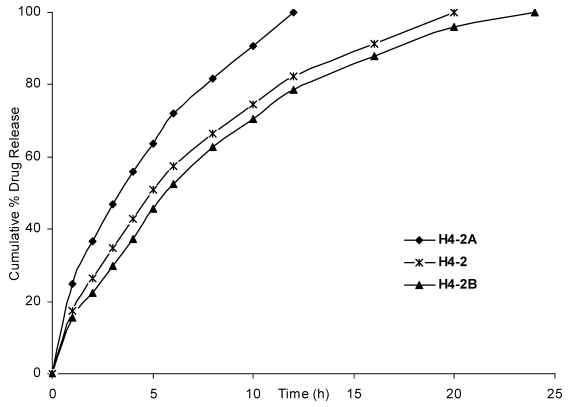

Fig. 7. Comparative Release Profile of Zidovudine from Matrix Tablets Prepared Using 20% w/w of HPMC 4000 cps with Different Compression Forces

Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0.

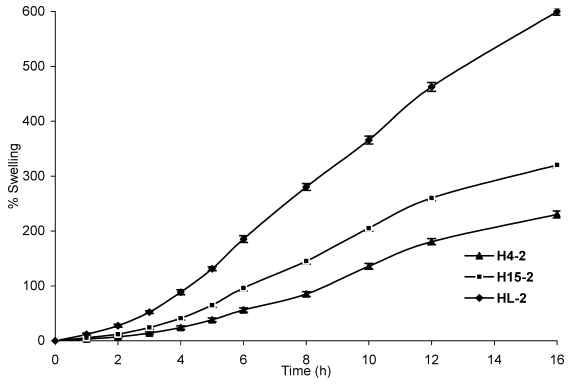

Fig. 8. Swelling Behavior of CR Matrix Tablets of Zidovudine Prepared Using Different Viscosity Grades of HPMC at 20% w/w of Drug Weight

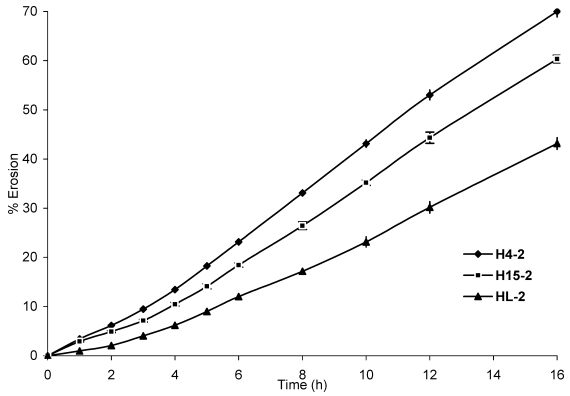

Fig. 9. Eroding Behavior of CR Matrix Tablets of Zidovudine Prepared Using Different Viscosity Grades of HPMC at 20% w/w of Drug Weight

nism of drug release decreased as the viscosity of polymer increased. It was observed from the swelling (Fig. 8) and erosion (Fig. 9) studies that the %swelling and %erosion of the matrix tablets was totally dependent on the viscosity of the polymer used. The %swelling increased with increase in polymer viscosity, while %erosion decreased with increase in polymer viscosity. This was because higher viscosity grades HPMC have higher and faster water absorption capacities and tend to swell rapidly than compared to the lower viscosity grades.[21] Moreover the matrix formed by higher viscosity grades HPMC would have more gel strength than the one formed by lower viscosity grades because of which the erosion would be lesser. Due to these reasons the diffusional path length increased and the diffusion coefficient of the drug through the matrix decreased as the viscosity grade of HPMC was increased.

Effect of Compression Force on Drug Release Several authors have reported the significance and influence of compression force on the hardness, apparent density and porosity of the tablet.[40,41] Increase in the compression force increases the hardness and the apparent density of matrix tablet, thereby reducing the matrix porosity in the tablet.[42] The relationship between pressure–density was reported to be dependent on material, compression speed, size and shape of the tooling.[43] It was also reported that the effect of compression force is more pronounced in lower viscosity grade HPMC polymers because they deform more readily to fill interparticulate voids than higher viscosity grade HPMC polymers.[35—37]

The effect of compression force on the drug release was studied by preparing tablets using the same polymer proportion (20%) and viscosity (HPMC 4000 cps) but with different compression forces to get tablets with different hardness levels, 3.5—4.5, 7.0—8.0 and 11.0—12.0 kg/cm^2. The release rate decreased with increase in compression force. Statistically significant difference was observed in the MDT values ($p<0.05$, $F_{crit}(2,15)=3.68$ and $F_{cal}=2171.39$) of the formulations prepared using different compression forces. The release of the drug from formulations prepared with less compression force (H4-2A) (Hardness 3.5—4.5 kg/cm^2) was found to be significantly much faster ($p<0.05$) (K value 25.06% h$^{-0.568}$; $t_{50\%}$ value 3.37 h) than compared to formulations prepared with higher compression forces (K values are 18.27% h$^{-0.603}$ and 15.80% h$^{-0.622}$ for hardness 7.0—8.0 kg/cm^2 (H4-2) and 11.0—12.0 kg/cm^2 (H4-2B) respectively; $t_{50\%}$ values are 5.33 h and 6.38 h for hardness 7.0—8.0 kg/cm^2 and 11.0—12.0 kg/cm^2 respectively). The effect of compression force on the release rate was found to be more pronounced at lesser compression forces than at higher compression forces. Similar results were obtained by another research group, when they studied the effect of compression force on drug release from binary polymer matrix systems. The drug release was found to be faster at less compression forces than at higher because of the relatively larger matrix porosity of the tablet, which allowed greater penetration of dissolution fluid into the matrix, thus enhancing polymer disentanglement and drug dissolution.[39] Compression force was found to have no effect on the release mechanism as the values of varied from 0.568 to 0.622, indicating that release mechanism still followed anomalous, non-Fickian diffusion, which is in agreement with earlier reported works.[18] Similarly, compression force was found to have no effect on the drug release mechanism and the drug release followed non-Fickian diffusion from formulations prepared using HPMC 15000 (n varied from 0.601 to 0.654 from formulation prepared using 20% HPMC 15000 cps as the compression force was increased from 3.5—4.5 kg/cm^2 to 11.0—12.0 kg/cm^2) as well as HPMC 100000 cps (n varied from 0.614 to 0.673 from formulation containing 20% HPMC 100000 cps as the compression force was increased from 3.5—4.5 kg/cm^2 to

11.0—12.0 kg/cm^2). Based on the above results obtained, it can be inferred that compression force had no effect on the drug release mechanism irrespective of the viscosity of HPMC used in the CR matrix tablets.

Reproducibility and Stability on Storage No significant difference was observed in the drug release profile of different batches of each CR matrix tablet formulations of AZT, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics were unaltered for up to 1 year of storage and there were no significant changes in the physical characteristics of all the formulations, suggesting that AZT was stable in HPMC matrices.

Conclusions

CR matrix tablets of AZT conforming to good quality were prepared using HPMC by wet granulation method. Release rate of the drug from the matrix tablets was dependent on proportion as well as viscosity of HPMC used. The effect of compression force on the drug release was more pronounced at lesser compression forces than at higher compression forces. Drug release was found to follow non-Fickian or anomalous release mechanism. The designed CR matrix tablets of AZT (formulations H4-1, H4-2 and H15-1), which release 17—25% of drug in first hour and extend the release up to 16—20 h, can overcome the disadvantages associated with conventional tablet formulations of AZT.

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