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Research Article

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Controlled Release Matrix Tablets of Zidovudine: Effect of Formulation Variables on the *In Vitro* Drug Release Kinetics

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Abstract. The purpose of this research was to design oral controlled release (CR) matrix tablets of zidovudine (AZT) using hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) and carbopol-971P (CP) and to study the effect of various formulation factors on *in vitro* drug release. Release studies were carried out using USP type 1 apparatus in 900 ml of dissolution media. Release kinetics were analyzed using zero-order, Higuchi's square root and Ritger–Peppas' empirical equations. Release rate decreased with increase in polymer proportion and compression force. The release rate was lesser in formulations prepared using CP (20%) as compared to HPMC (20%) as compared to EC (20%). No significant difference was observed in the effect of pH of dissolution media on drug release from formulations prepared using HPMC or EC, but significant difference was observed in CP based formulations. Decrease in agitation speed from 100 to 50 rpm decreased release rate from HPMC and CP formulations but no significant difference was observed in EC formulations. Mechanism of release was found to be dependent predominantly on diffusion of drug through the matrix than polymer relaxation incase of HPMC and EC formulations, while polymer relaxation had a dominating influence on drug release than diffusion incase of CP formulations. Designed CR tablets with pH independent drug release characteristics and an initial release of 17–25% in first hour and extending the release up to 16–20 h, can overcome the disadvantages associated with conventional tablets of AZT.

KEY WORDS: controlled release; matrix tablets; release kinetics; zidovudine.

INTRODUCTION

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 (1,2). 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 (3,4), poor patient compliance (5) and high cost. So, CR once daily formulations of AZT can overcome some of these problems.

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 (6). 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 of high-potency drugs (7).

Several polymers have been used in the formulation of matrix based CR drug delivery systems. Reports were found on usage of polymers like hydroxypropyl methylcellulose (HPMC), methylcellulose and sodiumcarboxy methylcellulose (8), ethyl cellulose (EC) (9,10), carbopols (CP) (11,12) and polyvinyl alcohol (13) for the purpose of CR formulations of different drugs. Several research groups have worked on CR of different drugs form matrix tablets prepared using HPMC (8,14–16), EC (9,10) and CP (12,17,18) as the retarding polymers. HPMC, a semi synthetic derivative of cellulose, is a swellable and hydrophilic polymer. It is a suitable polymer to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle (14). 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 (15). EC is an inert, hydrophobic polymer and is extensively used in the preparation of matrix type CR tablets of different drugs (19,20). The release of a drug from hydrophobic EC matrix occurs by dissolution and diffusion of the drug through water filled capillaries within the pore network (21). CP, a novel and toxicologically preferred carbomer, is a synthetic high molecular weight acrylic acid polymer cross linked with polyalkenyl polyether. Carbomer polymers readily hydrate,

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absorb water and swell quickly. Their hydrophilic nature and highly cross linked structure renders them suitable for CR drug delivery systems. The release of a drug from CP matrices occurs by swelling controlled diffusion process and/or by controlled relaxation of the polymer (17). The release of the drug from 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 (10,16).

Reports were found on the extended release of AZT from its matrix tablets prepared using combination of hydrophilic (Eudragit) and hydrophobic (ethylcellulose) polymers (22). 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 the sustained release had been investigated (23). Long-term sustained delivery of AZT in vivo by means of hydroxyapatite and tricalcium-phosphate ceramic implants was studied (24). 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 tablets of AZT prepared using HPMC, EC and CP separately as retardant materials. The purpose of this study was to design oral CR tablets of AZT using HPMC, EC and CP separately as the retarding polymers. The tablets were formulated by wet granulation method and their physical and *in vitro* release characteristics were evaluated. The effect of formulation factors like type of polymer, polymer proportion, compression force, dissolution medium and agitation speed on the release characteristics was studied in order to optimize these variables.

MATERIALS AND METHODS

AZT was obtained as gift sample from Strides Arcolab Limited, Bangalore, India. HPMC (Metocel K4M Premium), EC (ETHOCEL™ Standard Premium, 10 cps) and CP (Carbopol-971P NF) were obtained as gift samples 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 (25).

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% RH±5% RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR; 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 AZT Matrix Embedded Tablets

Matrix embedded CR tablets of AZT were prepared using various proportions of HPMC, EC and CP separately as the retarding polymer. The tablets were manufactured by wet granulation process using isopropyl alcohol (IPA) as the binding agent. The drug and polymer (passed through 60# mesh) were mixed uniformly and granulated with IPA and dried in a tray drier at 50 °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 I.

Physical Characterization of the Designed Tablets

The thickness and diameter of 20 tablets of each batch were measured using a screw gauge. The drug content 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 ten tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing ten 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 agitation 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

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

	Components in the CR Matrix Formulation[a]				Physical Properties					
Formulation	Drug (mg)	HPMC (%)[b]	EC (%)[b]	CP (%)[b]	Thickness (mm)[c]	Tablet weight (mg)[d]	Weight variation (%)[e]	Drug content (mg/tablet)[f]	Hardness (Kg/cm^2)[g]	Friability (%)
HP1	300	5	–	–	2.81±0.02	325.6	±1.8	300.4±1.5	7.4±0.4	<0.5
HP2	300	10	–	–	2.93±0.02	342.7	±0.9	298.5±1.2	7.5±0.3	<0.5
HP3	300	20	–	–	3.12±0.03	373.9	±1.5	301.7±0.9	7.6±0.3	<0.5
HP3-A	300	20	–	–	3.24±0.03	374.5	±1.3	300.1±2.1	3.9±0.3	<0.5
HP3-B	300	20	–	–	3.01±0.02	373.4	±2.5	301.5±0.8	11.5±0.5	<0.5
HP4	300	40	–	–	3.39±0.04	437.6	±1.4	299.4±1.5	7.5±0.4	<0.5
HP5	300	60	–	–	3.65±0.03	497.5	±0.9	297.2±1.9	7.3±0.3	<0.5
EC1	300	–	20	–	3.03±0.02	374.1	±2.1	302.8±1.6	7.6±0.4	<0.5
EC2	300	–	40	–	3.31±0.03	438.2	±1.7	300.7±1.2	7.4±0.3	<0.5
EC3	300	–	60	–	3.52±0.03	498.3	±0.9	299.3±0.7	7.6±0.2	<0.5
EC3-A	300	–	60	–	3.64±0.02	499.1	±1.1	300.4±1.7	4.0±0.3	<0.5
EC3-B	300	–	60	–	3.39±0.02	497.2	±2.1	301.8±1.2	11.4±0.3	<0.5
EC4	300	–	80	–	3.80±0.05	560.8	±1.6	302.7±2.1	7.4±0.4	<0.5
EC5	300	–	100	–	4.11±0.04	623.7	±1.2	298.5±1.4	7.5±0.4	<0.5
CP1	300	–	–	5	2.79±0.03	326.3	±2.0	299.1±0.9	7.3±0.3	<0.5
CP2	300	–	–	10	2.92±0.02	343.5	±1.6	301.7±0.8	7.6±0.3	<0.5
CP3	300	–	–	15	2.99±0.03	357.7	±1.3	300.3±1.1	7.5±0.5	<0.5
CP3-A	300	–	–	15	3.08±0.02	356.5	±2.2	301.4±1.9	3.9±0.4	<0.5
CP3-B	300	–	–	15	2.89±0.03	358.1	±0.9	302.6±1.8	11.6±0.3	<0.5
CP4	300	–	–	20	3.14±0.04	375.7	±1.5	298.8±1.7	7.6±0.3	<0.5
CP5	300	–	–	25	3.23±0.03	390.3	±1.7	301.7±1.4	7.5±0.4	<0.5

[a] Also contains 3% *w/w* talc and 1% *w/w* magnesium stearate as manufacturing additives and IPA was used as binding agent
[b] % *w/w* of the drug weight
[c] Mean of 20 tablets with SD
[d] Mean of 20 tablets
[e] ±max variation from the mean value of 20 tablets
[f] Mean of triplicate with SD
[g] Mean of ten tablets with SD. The diameter of all the tablets was found to be 10 mm

from three different batches was used in data analysis. To study the effect of agitation speed, *in vitro* release studies were also carried out at 50 rpm for some selected formulations and keeping the remaining test parameters same as mentioned above. To study the effect of dissolution media, *in vitro* release rate studies of some selected formulations were carried out in 900 ml of pH 1.2 (0.1 N HCl solution) and pH 4.5 phosphate buffer, maintaining the same agitation speed (100 rpm) and bath temperature as mentioned above.

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 the following equations:

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 (26,27).

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 n obtained by fitting the data into Eq. 3, we can describe the mechanism of drug release from the formulation (22). Incase 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). The values of K, K_H, K_o, n, $t_{50\%}$ (time required for 50% of drug release) and r (correlation coefficient) were determined. 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.

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% RH± 5% RH. Physical characters and release profile of the formulations were studied at 6 months and 1 year intervals for the effect of storage.

Release Profiles Comparison and Statistical Analysis

The drug release profiles were compared using two model-independent methods, mean dissolution time (MDT) and similarity factor (f_2) (28). The MDT values of the formulations being compared were determined and subjected the 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, USA). The MDT values were calculated by the following equation:

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (4)$$

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} .

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. FTIR spectra of pure AZT and solid admixtures of AZT with various excipients used in the preparation of CR tablets, characterized after 6 months of storage, is given in Fig. 1. The characteristic peak of carbonyl group at 1,694 cm^{-1} and azide group at 2,012 cm^{-1}, (29) 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 FTIR and DSC.

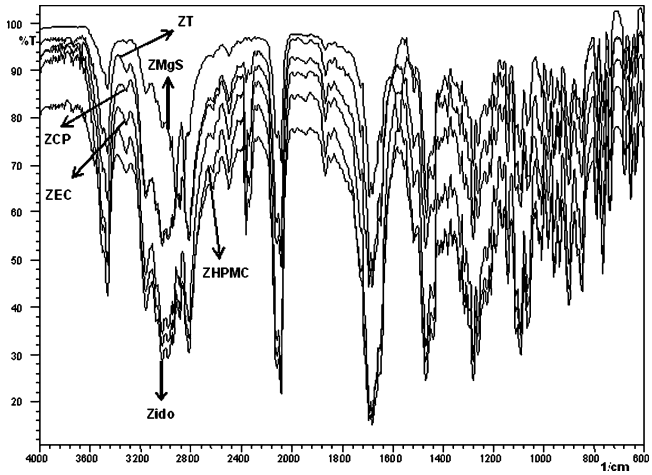

Fig. 1. FTIR spectrum of pure zidovudine (Zido), solid admixtures of zidovudine with HPMC (*ZHPMC*), zidovudine with EC (*ZEC*), zidovudine with CP (*ZCP*), zidovudine with magnesium stearate (*ZMgS*) and zidovudine with talc (*ZT*)

Physical Characterization of the Designed Tablets

The physical appearance, tablet hardness, friability, weight variation and drug content uniformity of all tablets were found to be satisfactory and reproducible as observed from the data in Table 1. The thickness of the tablets varied depending on the weight of tablet, bulk density of the dried granules and the compression force used. The diameter of all the tablets was found to be 10 mm. 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.

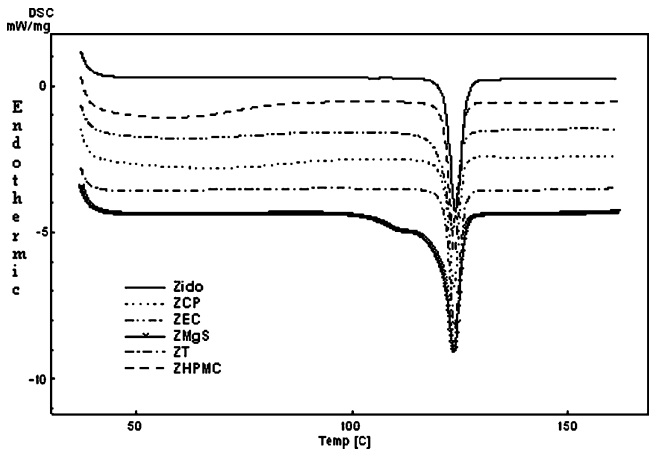

Fig. 2. DSC thermograms obtained for pure zidovudine and zidovudine solid admixtures with various excipients used in the preparation of controlled release tablets at a heating rate of 10 °C/min using nitrogen environment

Release Rate Studies

Effect of Polymer Proportion

The *in vitro* drug release profiles of matrix embedded CR tablets of AZT, in pH 6.8 phosphate buffer, prepared using different proportions of HPMC, EC and CP separately, with hardness 7.0–8.0 kg/cm^2, are shown in Fig. 3a, b and c respectively. The results of release rate and release mechanism elucidated from the mathematical treatment using Eqs. 1, 2 and 3 are given in Table II. In HPMC based formulations, the initial release for the first hour varied between 10–26% 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. The release of the drug extended from 12 h in case of 5% to beyond 24 h in case of 60% polymer. The release rate decreased with increase in polymer proportion. Statistically significant increase [$P<0.05$, F_{crit} (4,25)=2.76 and F_{cal}=3,038.77] was observed in the MDT values of the formulations, as the polymer proportion increased. The tablets formulations were found to swell to different extents forming a gel like structures during the drug release period depending upon the polymer proportion. The gel structure recovered at the end of dissolution study was found to be more eroded in formulations containing less proportion of polymer than compared to formulations containing higher proportions. The *n* values for HPMC based formulations ranged from 0.567 to 0.675, indicating that the release mechanism was non-Fickian. It can be inferred that the release was dependent on both drug diffusion as well as polymer relaxation. The value of n increased as proportion of polymer was increased indicating that the influence of polymer relaxation on mechanism of drug release increased with polymer proportion. 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 theophylline, diclofenac sodium, propranolol hydrochloride and aminophylline from matrix tablets of HPMC (15,16,30).

In formulations prepared using EC as the retarding polymer, the initial release for the first hour varied from 14–29% depending on polymer proportion. 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 from 12 h in case of 20% to beyond 24 h in case of 100% polymer. The

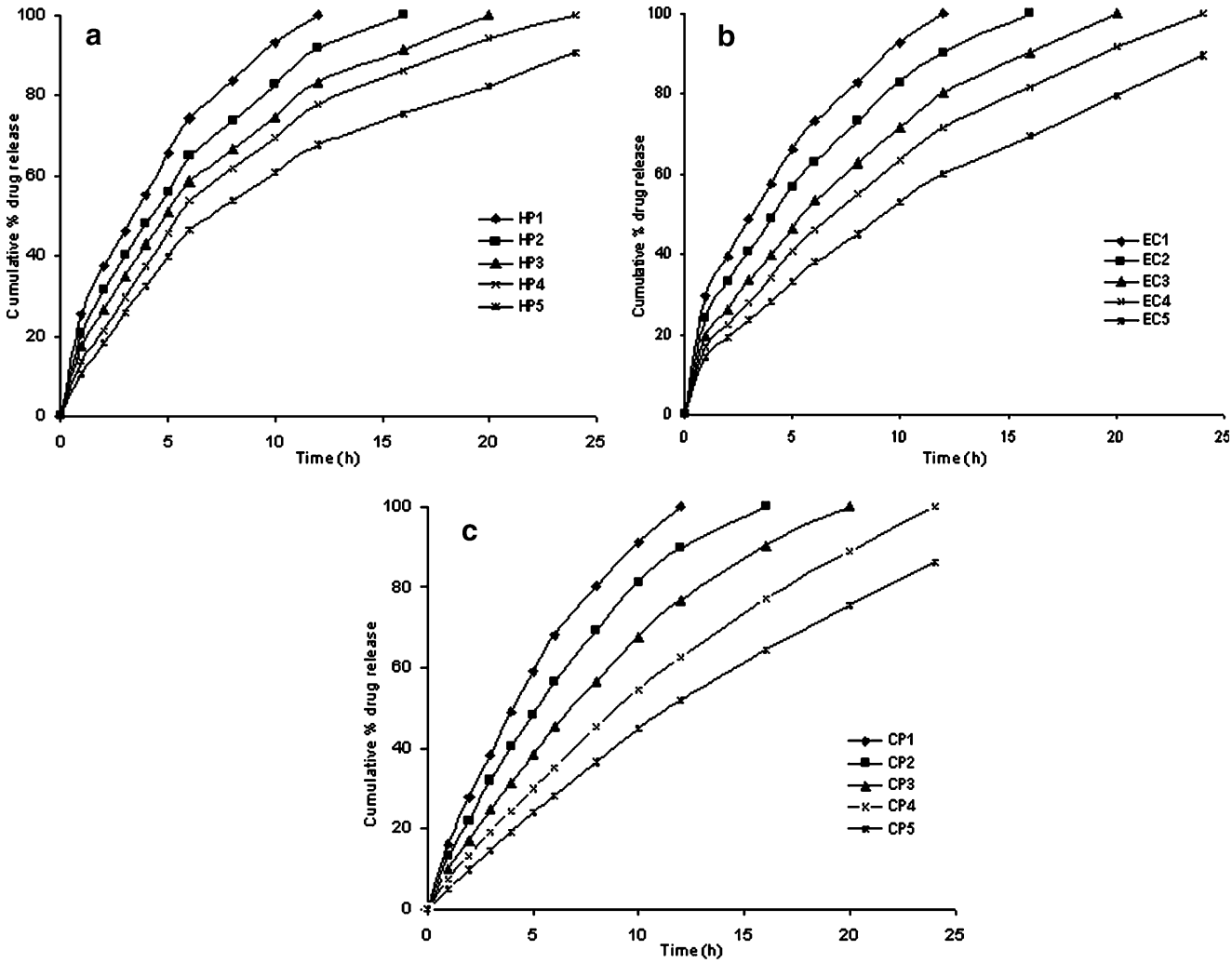

Fig. 3. Comparative release profiles of AZT from CR matrix tablets prepared using different proportions of **a** HPMC, **b** EC and **c** CP. Each data point represents the average of six tablets from three batches with SD within ±2.0

Table II. Release Kinetics Parameters and MDT Values of Designed Controlled Release Matrix Tablets of Zidovudine in Dissolution Media of pH 6.8 at 100 rpm

		Ritger–Peppas' Empirical Equation				Higuchi's Square-Root Equation		Zero-Order Model Equation	
Formulation	MDT Values	K^a (% h^{-n})	n^b	$t_{50\%}{}^c$ (h)	r^d	K^e (% $h^{-o.5}$)	r^f	K^g (% h^{-1})	r^h
HP1	4.19	25.19	0.5689	3.33	0.9948	28.77	0.9910	10.07	0.7974
HP2	5.11	21.23	0.5868	4.30	0.9846	25.41	0.9897	7.91	0.7570
HP3	6.36	18.25	0.6010	5.34	0.9895	22.81	0.9875	6.34	0.7247
HP3-A	4.24	25.05	0.5678	3.37	0.9878	28.48	0.9951	9.95	0.7821
HP3-B	7.33	15.79	0.6216	6.38	0.9858	21.14	0.9885	5.33	0.7282
HP4	7.88	14.78	0.6460	6.59	0.9911	20.91	0.9941	5.28	0.7380
HP5	9.86	12.10	0.6746	8.19	0.9814	18.34	0.9791	4.65	0.7696
EC1	3.96	28.74	0.5071	2.98	0.9968	29.14	0.9989	10.13	0.7449
EC2	5.19	23.47	0.5379	4.08	0.9952	25.42	0.9907	7.89	0.7591
EC3	6.93	18.22	0.5752	5.69	0.9937	22.09	0.9836	6.18	0.7801
EC3-A	5.13	22.52	0.5616	4.13	0.9945	25.52	0.9894	7.97	0.7456
EC3-B	7.75	16.33	0.5901	6.65	0.9939	20.42	0.9801	5.18	0.7664
EC4	8.44	15.43	0.5984	7.12	0.9853	19.80	0.9698	5.03	0.8010
EC5	10.94	12.99	0.6099	9.39	0.9868	16.94	0.9499	4.33	0.8116
CP1	4.65	18.57	0.7502	3.68	0.9957	27.47	0.8701	11.45	0.9408
CP2	5.97	13.62	0.7621	5.51	0.9938	23.75	0.8652	7.55	0.9574
CP3	7.83	10.38	0.7926	7.26	0.9955	20.21	0.8845	5.89	0.9614
CP3-A	4.96	15.98	0.7542	4.53	0.9985	26.27	0.8752	9.39	0.9453
CP3-B	9.27	8.46	0.8224	8.67	0.9910	18.88	0.8910	4.91	0.9712
CP4	10.03	7.62	0.8340	9.53	0.9976	17.14	0.8912	4.67	0.9833
CP5	12.75	5.33	0.9030	11.91	0.9961	14.95	0.8809	3.92	0.9799

[a,e,g] Release rate constants for Ritger–Peppas' empirical equation, Higuchi's square-root equation and Zero-order model equation respectively
[b] Diffusional exponent indicative of release mechanism in Ritger–Peppas' empirical equation
[c] Time for 50% of the drug release
[d,f,h] Correlation coefficients for Ritger–Peppas' empirical equation, Higuchi's square-root equation and Zero-order model equation respectively

release rate decreased with increase in polymer proportion. Statistically significant increase [$P<0.05$, F_{crit} (4,25)=2.76 and F_{cal}=6,146.42] was observed in the MDT values of the formulations, as the polymer proportion increased. The formulations prepared using EC remained intact over the drug release period and little/no swelling was observed. The *n* values for EC based formulations ranged from 0.507 to 0.609. Based on the *n* values obtained, the drug release was found to follow non-Fickian release mechanism. The drug release was chiefly dependent on drug diffusion than on polymer relaxation. This observation was in agreement with the other reported works, in which the drug release decreased from the matrix tablets of different drugs as the proportion of EC increased (9,31). In case of CP as the retarding polymer, the initial percent released for the first hour varied between 4–17% depending on polymer proportion. The release of the drug from the tablets extended from 12 h in case of 5% to beyond 24 h as in case of 25% polymer. The release rate decreased with increase in polymer proportion. Statistically significant increase [$P<0.05$, F_{crit} (4,25)=2.76 and F_{cal}= 8,315.22] was observed in the MDT values of the formulations, as the polymer proportion increased. Formulations containing CP were found to undergo rapid swelling process and form rigid gel like structures during the process of dissolution. The *n* values for CP based formulations ranged from 0.750 to 0.903. The release mechanism was found to change from non-Fickian release to Super Case II release as the proportion of polymer was increased, indicating that polymer relaxation had a greater influence on drug release mechanism than diffusion of drug through the matrix. At higher proportion of the polymer (25%), the drug release was totally based on polymer relaxation. Similar results were obtained when Jelena *et al.* have studied the effect of proportion of CP on the release of paracetamol from matrix based tablets (18).

Release rate of the drug from matrix tablets decreased with increase in polymer proportion irrespective of the type of polymer used. Incase of formulations containing HPMC or CP, release rate decreased 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. Incase of formulations containing EC, the release rate decreased with increase in polymer proportion because of more tortuous pathway and/or a less porosity inside the matrix having higher proportions of the polymer.

Effect of Type of Polymer

The *in vitro* drug release profiles of matrix embedded CR tablets of AZT, in pH 6.8 phosphate buffer, prepared using 20% of HPMC, EC and CP separately with hardness 7.0–8.0 kg/cm^2, is shown in Fig. 4. The release rate was fastest from formulations containing EC with a *K* value of 28.74% $h^{-0.507}$ and $t_{50\%}$ value of 2.98 h. The release rate was slowest form formulations containing CP with a *K* value of 7.62% $h^{-0.834}$ and $t_{50\%}$ value of 9.53 h. The formulations prepared using EC recovered at the end of dissolution process were intact with no swelling or erosion (indicating that release was controlled mainly due to diffusion of dissolved drug through pore network in polymer matrix), while formulations

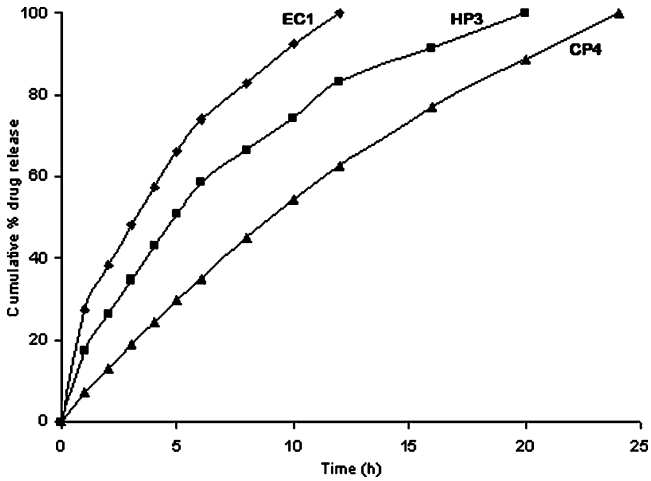

Fig. 4. Comparative release profile of AZT from CR matrix tablets prepared using 20% HPMC, EC and CP separately. Each data point represents the average of 6 tablets from three batches with S.D. within ±2.0

prepared using HPMC or CP were swollen and formed gel like structures (indicating that release was controlled mainly due to drug diffusion and/or polymer relaxation or disentanglement). The intensity of swelling was more and the swollen mass was more firmer incase of CP than compared to HPMC.

The release rate was fastest from formulations containing EC when compared to HPMC or CP, because of its low viscosity and smaller diffusional path of the drug inside the matrix due to its lesser swelling properties. In formulations containing CP the release of the drug was more controlled and retarded because of its faster hydration/swelling, longer diffusional path length, higher strength and rigidity of the gel as compared to HPMC, which forms a less rigid gel structure which can erode over the dissolution period.

Effect of Compression Force on Drug Release

The effect of compression force on the drug release was studied by preparing tablets using same type of polymer and same polymer proportion but with different compression

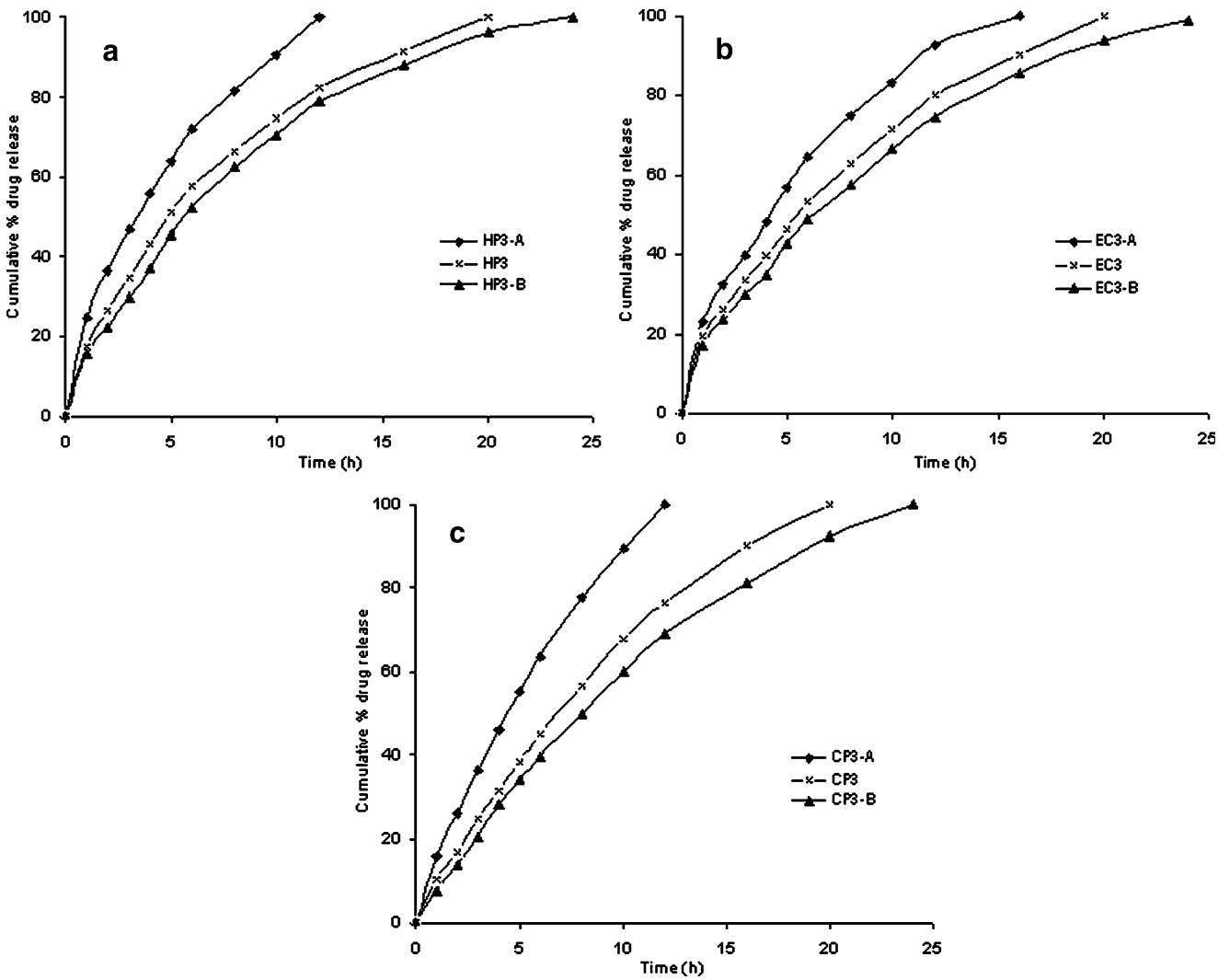

Fig. 5. Comparative release profiles of AZT from matrix tablets prepared using **a** 20% HPMC **b** 60% EC and **c** 15% CP separately, with different compression forces. Each data point represents the average of 6 tablets from three batches with SD within ±2.0

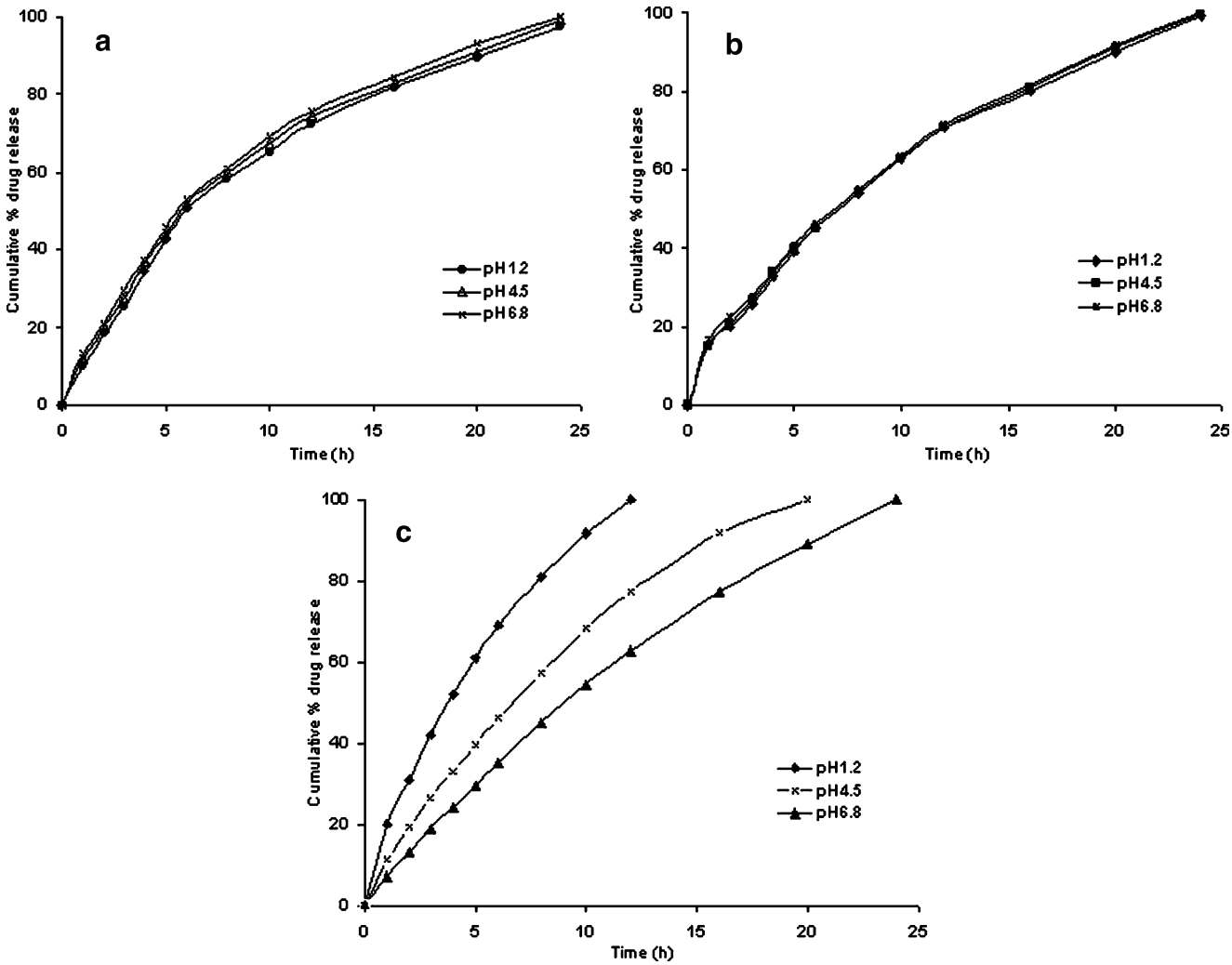

Fig. 6. Comparative releases profile of AZT from CR matrix tablets prepared using **a** 40% HPMC, **b** 80% EC and **c** 20% CP separately, in different dissolution media (pH 1.2, 4.5 and 6.8). Each data point represents the average of 6 tablets from three batches with SD within ±2.0

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 effect of compression force on the drug release from formulations prepared using 20% HPMC, 60% EC and 15% CP separately are shown in Fig. 5a, b and c respectively. The release of the drug from EC based formulations prepared with less compression force (hardness, 3.5–4.5 kg/cm^2) was found to be significantly much faster (K value 22.52% h$^{-0.561}$; $t_{50\%}$ value 4.13 h) than compared to EC based formulations prepared with higher compression forces (K values are 18.22% h$^{-0.575}$ and 16.33% h$^{-0.590}$ for hardness 7.0–8.0 kg/cm^2 and 11.0–12.0 kg/cm^2 respectively; $t_{50\%}$ values are 5.69 and 6.65 h for hardness 7.0–8.0 kg/cm^2 and 11.0–12.0 kg/cm^2 respectively). Similar results were observed in the effect of compression force on release rate of drug from both HPMC as well as CP based formulations. However, in formulations containing same type of polymer, compression force was found to have no effect on the release mechanism. The value of n varied from 0.568 to 0.622 in formulations containing HPMC and from 0.562 to 0.590 in formulations containing EC, indicating that drug diffusion had a dominating effect on the release mechanism than polymer relaxation. In formulations containing CP, the value of n varied from 0.754 to 0.822 indicating that polymer relaxation had a predominant effect of drug release mechanism than drug diffusion.

Release rate was found to decrease with increase in compression forces because of increase in hardness and apparent density of the tablet thereby a reduction in porosity and/or increase in tortuosity (31,32). Significant difference was observed in the release profiles of tablets compressed with different hardness till 7.0–8.0 kg/cm^2, but less significant difference was observed in the release profiles of tablets with different hardness beyond 7.0–8.0 kg/cm^2. This could be because of significant decrease in the porosity of the matrix with increase in hardness from 3.5–4.5 kg/cm^2 to 7.0–8.0 kg/cm^2, but beyond hardness level of 7.0–8.0 kg/cm^2 there was no significant change in the porosity of the matrix.

Effect of Dissolution Media on Drug Release

The effect of dissolution media (pH 1.2, 4.5 and 6.8) on the drug release from formulations prepared using 40% HPMC, formulations prepared using 80% EC and formulations prepared using 20% CP compressed with hardness of 7.0–8.0 kg/cm^2 are shown in Fig. 6a, b and c respectively. No significant difference was observed in the drug release from

Table III. Effect of pH of Dissolution Media and Agitation Speed on Drug Release Kinetics of Selected Controlled Release Formulations of Zidovudine

				Ritger–Peppas' Empirical Equation				Higuchi's Square-Root Equation		Zero-Order Model Equation		
Formulation	Media pH	Agitation Speed	MDT Values	K^a (% h^{-n})	n^b	$t_{50\%}$ [c] (h)	r^d	K^e (% $h^{-0.5}$)	r^f	K^g (% h^{-1})	r^h	Similarity Factor (f_2)
HP4	1.2	100	8.05	14.21	0.6494	6.93	0.9787	20.31	0.9775	5.07	0.7460	pH 1.2/6.8>70[i]
	4.5	100	7.98	14.47	0.6509	6.73	0.9915	20.72	0.9812	5.15	0.7610	pH 4.5/6.8>83[i]
	6.8	100	7.88	14.78	0.6460	6.59	0.9811	20.91	0.9941	5.28	0.7380	pH 1.2/4.5>82[i]
	6.8	50	10.02	11.23	0.6998	8.42	0.9758	18.22	0.9642	4.60	0.7819	Rpm 100/50<48[j]
EC4	1.2	100	8.61	14.26	0.6216	7.52	0.9945	19.43	0.9488	4.96	0.8040	pH 1.2/6.8>75[i]
	4.5	100	8.56	14.40	0.6225	7.38	0.9952	19.58	0.9509	5.04	0.8041	pH 4.5/6.8>85[i]
	6.8	100	8.49	15.43	0.5984	7.12	0.9853	19.80	0.9698	5.03	0.8010	pH 1.2/4.5>84[i]
CP4	1.2	100	4.45	20.21	0.6614	3.90	0.9833	27.70	0.9771	9.78	0.8641	pH 1.2/6.8<35[i]
	4.5	100	7.63	11.79	0.7501	6.96	0.9571	20.87	0.9571	5.96	0.9131	pH 4.5/6.8<48[i]
	6.8	100	10.03	7.62	0.8340	9.53	0.9976	17.14	0.8912	4.67	0.9833	pH 1.2/4.5<26[i]
	6.8	50	12.42	4.61	0.9664	11.76	0.9929	15.01	0.8845	3.98	0.9928	Rpm 100/50<51[j]
EC3	6.8	100	6.90	18.22	0.5752	5.69	0.9937	22.09	0.9836	6.18	0.7801	Rpm 100/50>84[j]
	6.8	50	6.96	16.88	0.5837	5.86	0.9951	21.66	0.9879	6.06	0.7878	

[a,e,g] Release rate constants for Ritger–Peppas' empirical equation, Higuchi's square-root equation and Zero-order model equation respectively.
[b] Diffusional exponent indicative of release mechanism in Ritger–Peppas' empirical equation.
[c] Time for 50% of the drug release.
[d,f,h] Correlation coefficients for Ritger–Peppas' Empirical Equation, Higuchi's square-root equation and Zero-order model equation respectively.
[i] Mean f_2 values calculated by comparing dissolution profiles obtained in different media, keeping the agitation speed same at 100 rpm.
[j] Mean f_2 values calculated by comparing dissolution profiles obtained in media of pH 6.8 and changing the agitation speed from 100 to 50 rpm.

formulations containing HPMC in different dissolution media based on the MDT and f_2 values obtained (Table III). No statistically significant difference [$P<0.05$, F_{crit} (2,15)=3.68 and F_{cal}=3.03] was observed in the MDT values for formulations containing 40% HPMC in different dissolution media. Similarly no statistically significant difference [$P<0.05$, F_{crit} (2,15)=3.68 and F_{cal}=3.51] was observed in the MDT values for formulations containing 80% EC in different dissolution media. The f_2 values determined by comparing drug release profiles in pH 1.2 with pH 6.8, pH 4.5 with pH 6.8 and pH 1.2 with pH 4.5 were found to be greater than 70, 83 and 82 respectively for HPMC based formulations; 75, 85 and 84 respectively for EC based formulations. But statistically significant difference [$P<0.05$, F_{crit} (2,15)=3.68 and F_{cal}= 7,469.67] was observed in the drug release from formulations containing CP. The drug release was fastest in pH 1.2 with a K value of 20.21% $h^{-0.661}$ and $t_{50\%}$ value of 3.90 h. The drug release was slowest in pH 6.8 with a K value of 7.62% $h^{-0.834}$ and $t_{50\%}$ value of 9.53 h. The values of n for CP formulations in pH 1.2 and 4.5 were found to be 0.661 and 0.750 respectively, indicating that the mechanism of drug release from the formulations in pH 1.2 and 4.5 was different compared to pH 6.8 (n value 0.834).

Whatever the possible difference in dissolution profiles of AZT CR matrix tablets due to difference in dissolution media that would be observed, it should be possibly due to differences in polymer characteristics in different media than due to the drug. This is because AZT has pH independent solubility. But, no significant difference was observed in the dissolution profiles of formulations prepared using HPMC as well as EC in different dissolution media. Because HPMC, a cellulose derivative with methoxyl and hydroxypropyl substituents on a β-*o*-glucopyranosyl ring backbone, is very resistant to changes in pH or ionic content of the medium. At pH values from 2 to 13, HPMC is relatively stable (33). Similarly EC, a cellulose derivative with ethoxyl substitution on anhydroglucose ring backbone, is insoluble in water and its release properties are less affected by the pH changes (34). So for a drug like AZT, which has pH independent solubility, release profiles from either HPMC or EC matrices would be independent of pH changes in dissolution media. The difference in the dissolution profiles of CP based formulations was due to the difference in the ionization of CP in different dissolution media because of which there was a difference in swelling, gel strength and diffusional path length of the matrix. The carboxylic groups that make up the carbomer backbone (pK_a=6.0) ionize very little in acidic media and polymer chain repulsion, by the negative charges of carboxylic groups, is at minimum (35). So the swelling and diffusional path length of the CP matrix was lesser in pH 1.2. As the pH of media increases, the ionization of carboxylic groups increases because of which swelling and diffusional path length of the CP matrix increases. Lesser the diffusional path length faster is the dissolution rate. Hence the drug release was fastest in pH 1.2 and slowest in pH 6.8.

Effect of Agitation Speed on Drug Release

The effect of agitation speed on the *in vitro* release profiles of drug from formulations prepared using HPMC (40%), EC (60%) and CP (20%) separately with similar

hardness (7.0–8.0 kg/cm^2), in 900 ml of pH 6.8 phosphate buffer is shown in Fig. 7a, b and c respectively. No significant difference was observed in the release rate with decrease in agitation speed from 100 rpm to 50 rpm from formulations containing EC as indicated by MDT values [$P<0.05$, F_{crit} (1,10)=4.96 and F_{cal}=0.19] and f_2 values ($f_2>84$). Statistically significant decrease was observed in the release rate with a decrease in agitation speed from 100 rpm to 50 rpm incase of HPMC [$P<0.05$, F_{crit} (1,10)=4.96 and F_{cal}=1,592.02]. Similarly the release rate decreased significantly with decrease in agitation speed incase of CP [$P<0.05$, F_{crit} (1,10)=4.96 and F_{cal}=249.46] based formulations. The value of K decreased from 14.78% $h^{-0.646}$ to 11.23% $h^{-0.701}$ and the value of $t_{50\%}$ increased from 6.59 to 8.42 h incase of HPMC; and value of K decreased from 7.62% $h^{-0.834}$ to 4.62% $h^{-0.966}$ and the value of $t_{50\%}$ increased from 9.53 to 11.76 h incase of CP formulations, as the agitation speed decreased from 100 to 50 rpm (Table III).

The decrease in release rate with decrease in agitation speed in HPMC as well as CP based formulations was due to decrease in the attrition of matrix structure formed by such swellable polymers at the swelling/dissolution front. So the gel structure that could be formed by HPMC or CP during the process of dissolution would swell and /or erode quickly at 100 rpm compared to 50 rpm because of which the release of drug due to diffusion and/or erosion was faster at 100 rpm than 50 rpm (32). Whereas in case of EC, no significant difference was observed in release rates because it is insoluble in water and does not undergo swelling or erosion processes. Moreover the release of drug form EC matrices is mainly due to diffusion through the pores of the matrix.

Batch Reproducibility and Stability on Storage

No significant difference was observed in the release profile of different batches of each CR matrix tablets of AZT, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics were unaltered 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, EC and CP matrices.

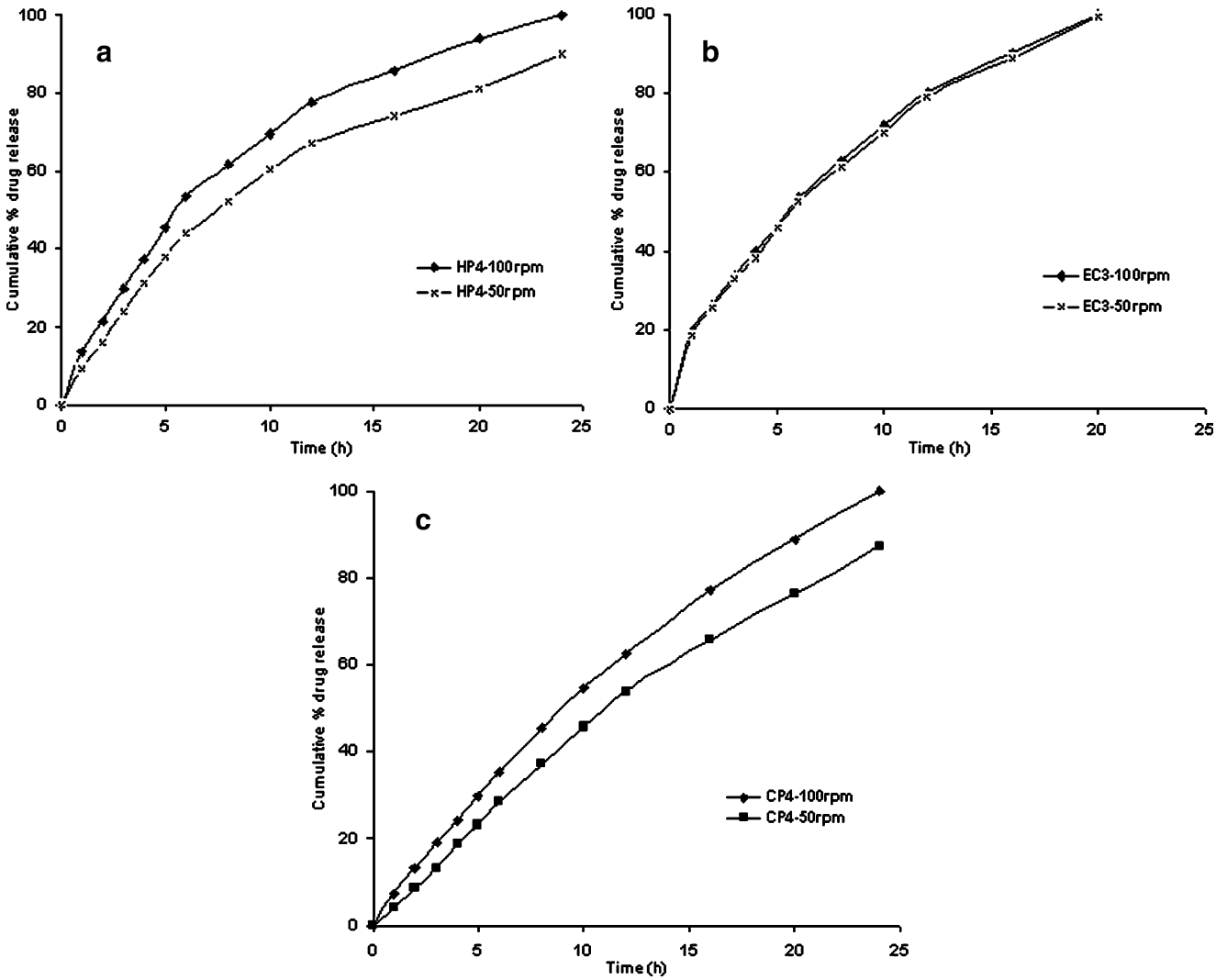

Fig. 7. Comparative release profiles showing the effect of agitation speed on release of AZT from CR matrix tablets prepared using **a** 40% HPMC, **b** 60% EC and **c** 20% CP separately. Each data point represents the average of 6 tablets from three batches with SD within ±2.0

CONCLUSIONS

CR matrix tablets of AZT of good quality were prepared by wet granulation method. Drug release was dependent on type of polymer used, polymer proportion and compression force. Change in agitation speed and pH of the media had an effect on drug release depending on the polymer used in matrix. Designed CR tablets, with pH independent drug release and a good initial release (17–25% in first hour) and extending the release up to 16–20 h, can overcome the disadvantages associated with conventional tablets of AZT.

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