Design and Study of Lamivudine Oral Controlled Release Tablets

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ABSTRACT

The objective of this study was to design oral controlled release matrix tablets of lamivudine using hydroxypropyl methylcellulose (HPMC) as the retardant polymer and to study the effect of various formulation factors such as polymer proportion, polymer viscosity, and compression force on the in vitro release of drug. In vitro release studies were performed using US Pharmacopeia type 1 apparatus (basket method) in 900 mL of pH 6.8 phosphate buffer at 100 rpm. The release kinetics were analyzed using the zero-order model equation, Higuchi's square-root equation, and the Ritger-Peppas empirical equation. Compatibility of the drug with various excipients 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 60% HPMC 4000 cps were found to show good initial release (26% in first hour) and extended the release up to 16 hours. Matrix tablets containing 80% HPMC 4000 cps and 60% HPMC 15 000 cps showed a first-hour release of 22% but extended the release up to 20 hours. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore 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 lamivudine, with good initial release (20%-25% in first hour) and extension of release up to 16 to 20 hours, can overcome the disadvantages of conventional tablets of lamivudine.

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INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by 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 preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs.[2]

AIDS is considered to be an epidemic, and according to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) *AIDS Epidemic Update 2005*, 38 million adults and 2.3 million children were living with the 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 antiretroviral medications are available at affordable prices.[3] The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost.[4,5]

Lamivudine (LAM) is a potent antiviral agent used in the treatment of AIDS. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life ($t_{1/2}$ = 5-7 hours).[6,7] Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose therapy,[8] poor patient compliance, and high cost. CR once-daily formulations of LAM can overcome some of these problems.

Matrix-based CR tablet formulations are the most popular and easiest to formulate on a commercial scale. The matrix tablets can be prepared via wet granulation or by direct compression.[9] Many polymers have been used in the formulation of matrix-based CR drug delivery systems. Reports were found on usage of hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), methylcellulose, sodium carboxymethylcellulose,[10] carbopols,[11] and polyvinyl alcohol[12] for the purpose of CR formulations of different drugs. HPMC, a semisynthetic derivative of cellulose, is a

swellable and hydrophilic polymer. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs.[13-15] It is very suitable to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle.[16] 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.[17] The release of the drug from the CR matrices is influenced by various formulation factors, such as 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.[14,18] The drug release from the polymer matrix can be due to disentanglement or diffusion, depending on the polymer molecular weight and the thickness of the diffusion boundary layer.[19,20] Polymer dissolution plays an important role in regulating the drug release in the case of lower viscosity grades of HPMC and for relatively water-insoluble drugs.[21] Several kinetic models have been proposed to describe the release characteristics of a drug from a CR polymer matrix. The following 3 equations are commonly used, because of their simplicity and applicability[22,23]: Equation 1, the zero-order model equation; Equation 2, Higuchi's square-root equation; and Equation 3, the Ritger-Peppas empirical equation.

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

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

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

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

However, there appears to be no literature on CR tablet formulations of LAM. The purpose of this study was to design oral CR tablet formulations of LAM using HPMC as the retarding polymer. The tablets were formulated by wet granulation, and their physical and in vitro release characteristics were evaluated. The effect of formulation factors such as polymer proportion, polymer viscosity, and compression force on the release characteristics was studied in order to optimize these variables.

MATERIALS AND METHODS

LAM was obtained as gift sample from Strides Arcolab Limited (Bangalore, India). HPMC (4000, 15 000, 100 000 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 271 nm was used for the estimation of drug in bulk, formulations, and dissolution samples.

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 infrared (IR) spectrum obtained (IR spectrophotometer; IR Report 100, Jasco) was compared with that of the standard. To study the compatibility of various formulation excipients with LAM, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and then stored in airtight containers at 30°C ± 2°C/65% relative humidity (RH) ± 5% RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR) (IR Prestige-21, Shimadzu, Kyoto, Japan) and differential scanning calorimetry (DSC) (DSC-60, Shimadzu). The solid admixtures were characterized every 6 months for a period of 1 year.

Formulation of Lamivudine Matrix-Embedded Tablets

Matrix-embedded CR tablets of LAM were prepared using various proportions of different viscosity grade HPMC as the retarding polymer. The tablets were manufactured by the wet granulation process using distilled water as the binding agent. The drug and polymer (passed through No. 60 mesh) were mixed uniformly and granulated with distilled water and dried in a tray drier at 60°C. The dried granules were then passed through No. 20 mesh. The final granules were blended with talc (3% wt/wt of the dried granules' weight) and magnesium stearate (1% wt/wt of the dried granules' weight) and compressed on a 16-station tablet compression machine (rotary tableting machine, CMB3-16, Cadmach, Ahmedabad, India) using 10-mm punches at different compression forces. Three batches were prepared for each formulation, with each tablet containing 200 mg LAM. The formula and physical characteristics of the prepared matrix-embedded tablets are given in Table 1.

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

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													
Drug (mg)		200	200	200	200	200	200	200	200	200	200	200	200
HPMC (%)† (cps)	4000	40	60	60	60	80	100	—	—	—	—	—	—
	15 000	—	—	—	—	—	—	40	60	80	—	—	—
	100 000	—	—	—	—	—	—	—	—	—	40	60	80
Physical properties													
Drug content (mg/tablet)‡		200.1 (± 0.8)	199.4 (± 0.7)	201.6 (± 0.6)	201.5 (± 0.9)	199.9 (± 0.9)	198.7 (± 0.8)	201.3 (± 0.7)	200.6 (± 1.0)	199.1 (± 0.8)	200.9 (± 1.0)	201.2 (± 0.8)	201.4 (± 0.8)
Tablet weight (mg)		293.4	335.8	333.7	330.4	374.2	418.5	296.4	332.8	376.1	295.4	334.1	373.6
Weight variation (%)§		± 1.7	± 1.3	± 2.0	± 2.2	± 1.5	± 1.9	± 2.0	± 2.1	± 1.9	± 2.3	± 1.9	± 1.4
Hardness (kg/cm^2)‖		7.4 (± 0.4)	7.5 (± 0.4)	4.0 (± 0.4)	11.5 (± 0.4)	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

*HPMC indicates hydroxypropyl methylcellulose. Formulation components also contain 3% wt/wt talc and 1% wt/wt magnesium stearate as manufacturing additives, and distilled water was used as a binding agent. Formulations H4-2A, H4-2, and H4-2B contain the same proportion (60% wt/wt of drug weight) of HPMC 4000 cps but were prepared with different compression forces to get different hardness levels and were used for studying the effect of compression force on drug release.
†Percentage wt/wt of the drug weight.
‡Mean of triplicate with SD.
§Weight variation ± maximum variation from the mean value.
‖Mean of 10 tablets with SD.

Physical Characterization of the Designed Tablets

The drug content of the manufactured tablets of each batch was determined in duplicate. 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 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) for 4 minutes at 25 rpm.

Release Rate Studies

Release rate for all the designed formulations was studied up to 24 hours using a tablet dissolution tester (Dissolution Tester [US Pharmacopeia] TDT-08L, Electrolab, Mumbai, India), type 1 (basket method), in 900 mL of pH 6.8 phosphate buffer at 37.5°C ± 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 medium. After appropriate dilution the samples were analyzed. Cumulative percentage of the drug released was calculated, and the mean of 6 tablets from 3 different batches was used in data analysis.

Characterization of Release Kinetics

The order and mechanism of LAM release from the CR matrix tablets were determined by fitting the release rate studies data into Equations 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 dissolution. In such cases, based on the value of n obtained by fitting the data into Equation 3, we can describe the mechanism of drug release from the formulation.[24] In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation (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.[22] 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 3 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 is low; it increases significantly as the polymer matrix imbibes more and more water and forms a gel, as 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 lesser degree on

polymer particle size.[13] So swelling and erosion studies were performed according to the method reported by Al-Taani and Tashtoush,[25] to understand the influence of swelling and erosion behavior on drug release and also to determine the effect of polymer viscosity on 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 the 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 formulas:

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

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

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 characteristics 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°C ± 2°C/65% RH ± 5% RH. Physical characteristics and release profiles of the formulations were studied at 6-month and 1-year intervals for the effect of storage.

Release Profiles Comparison and Statistical Analysis

The drug release profiles were compared using a model-independent method,[26] by determining the mean dissolution time (MDT) of the formulations being compared and subjecting the MDT values to 1-way analysis of variance (ANOVA) to examine the statistical difference. A confidence limit of $P < .05$ 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 PRISM software (GraphPad, San Diego, CA). The MDT values were calculated by the following equation:

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

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}.

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 LAM and solid admixtures of LAM with various excipients used in the preparation of CR tablet formulations, characterized after 6 months of storage, are given in Figure 1. The characteristic peak of the carbonyl group (present in the cytidine nucleus) at 1650 cm^{-1}; a band of peaks at 3319, 3271, and 3197 cm^{-1} owing to amino and hydroxyl groups; and peaks at 1286 and 1161 cm^{-1} owing to asymmetrical and symmetrical stretching of the C-O-C system (present in the oxathiolane ring), respectively, in all the spectrum, indicate the stable nature of LAM in the solid admixtures of the drug with various excipients. This finding was further supported by DSC studies. The DSC thermogram of pure LAM showed a sharp melting endotherm at 177°C with a normalized energy of 103.9 J/g, as shown in Figure 2. The thermograms of solid admixtures of LAM with various excipients, characterized after 6 months of storage, also showed a similar peak at 177°C with almost the same normalized energy, indicating that LAM is unaffected in the presence of various excipients used in the preparation of CR tablet formulations. Similar results were obtained for the pure LAM and the solid admixtures of LAM with various excipients, when characterized after 1 year of storage by FTIR and DSC.
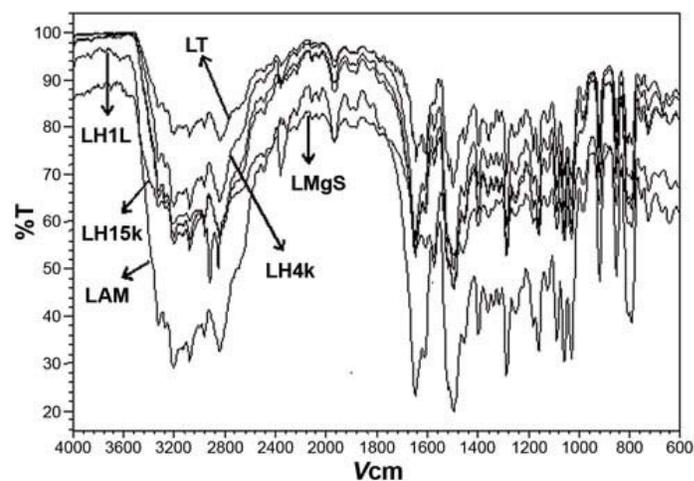
Figure 1. Fourier transform infrared spectra of pure lamivudine (LAM), solid admixture of LAM with hydroxypropyl methylcellulose (HPMC) 4000 cps (LH4k), LAM with HPMC 15 000 cps (LH15k), LAM with HPMC 100 000 cps (LH1L), LAM with magnesium stearate (LMgS), and LAM with talc (LT).
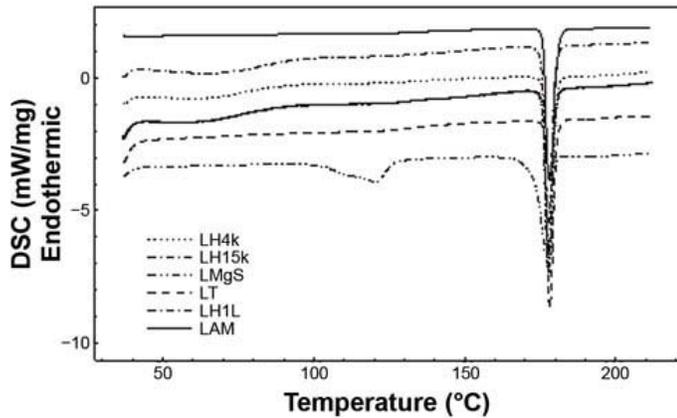
Figure 2. Differential scanning calorimetry (DSC) thermograms of pure lamivudine (LAM) and its solid admixture with hydroxypropyl methylcellulose (HPMC) 4000 cps (LH4k), HPMC 15 000 cps (LH15k), magnesium stearate (LMgS), talc (LT), HPMC 100 000 cps (LH1L), at a heating rate of 10°C/min using nitrogen environment.

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 and 12 kg/cm^2) depending on the compression force applied, and friability was less than 0.5% (wt/wt). The manufactured tablets showed low weight variation and a high degree of drug content uniformity, indi-

cating that wet granulation is an acceptable method for preparing good-quality matrix tablets of LAM.

Release Rate Studies

The kinetic parameters and MDT values for all the formulations are given in Table 2. A plot of cumulative percentage released vs time for matrix-embedded CR tablets of LAM prepared using different proportions of HPMC 4000 cps, with hardness 7 to 8 kg/cm^2, is shown in Figure 3. The initial percentage released for the first hour varied between 16% and 33% for all the formulations. However, in the later stages, the release was found to be slower and more controlled in the tablets with a higher proportion of the polymer. The release of the drug from the tablets extended as the polymer proportion was increased from 40% to 100%. The release extended from 10 hours in the case of 40% (H4-1) to more than 24 hours in the case of 100% (H4-4) polymer proportion. In the case of H4-4, 100% drug release was not observed after 24 hours of dissolution because of the high polymer proportion used in the formulation. The release rate was significantly dependent on the proportion of polymer. A statistically significant increase ($P < .05$, F_{crit} (3, 20) = 3.09 and F_{cal} = 1115.05) was observed in the MDT values of formulations as the polymer proportion increased.

A similar pattern was observed with matrix-embedded CR tablet formulations of LAM prepared using HPMC 15 000 and 100 000 cps as the retarding polymer. The release rate decreased and the drug release extended as the polymer

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

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
	r^*	0.994	0.977	0.990	0.980	0.982	0.974	0.991	0.984	0.980	0.983	0.961	0.960
Ritger-Peppas empirical equation	$K†$ (% h^{-n})	32.53	27.25	33.80	24.17	23.13	18.76	28.60	23.44	20.08	21.68	17.53	15.21
	$n‡$	0.505	0.512	0.489	0.523	0.525	0.545	0.533	0.546	0.558	0.595	0.604	0.615
	$t_{50\%}§$ (h)	2.34	3.27	2.22	4.04	4.34	6.03	2.85	4.01	5.12	4.07	5.63	6.92
Higuchi's square-root equation	r^*	0.995	0.979	0.995	0.982	0.984	0.978	0.992	0.976	0.980	0.987	0.970	0.971
	$K_H \|$ (% h$^{-0.5}$)	32.72	26.37	32.49	23.91	23.57	20.21	30.40	23.91	21.60	27.11	22.47	20.03
Zero-order model equation	r^*	0.616	0.568	0.673	0.532	0.546	0.555	0.691	0.523	0.532	0.705	0.587	0.604
	$K_o¶$ (% h^{-1})	12.47	8.17	12.55	6.98	6.62	5.12	10.49	6.78	5.49	8.11	5.53	4.91
MDT# (h)		3.14	4.29	3.06	5.52	5.69	6.72	3.64	5.26	6.67	4.87	6.61	9.01

*Correlation coefficients.

†Release rate constant for Ritger-Peppas empirical equation.

‡Diffusional exponent indicative of release mechanism in Ritger-Peppas empirical equation.

§Time for 50% of the drug release. Reported value is the mean of 6 tablets with SD within ± 0.14 hours.

‖ Release rate constant for Higuchi's square-root equation.

¶Release rate constant for zero-order model equation.

#Mean of 6 tablets with SD within ± 0.19 hours.
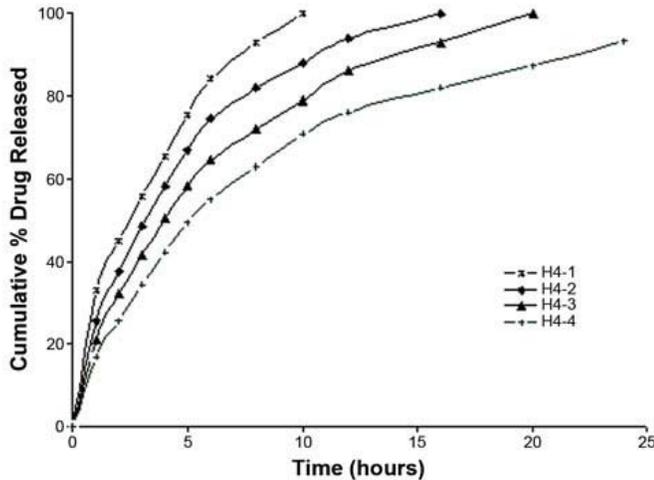
Figure 3. Comparative release profile of lamivudine from controlled release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 4000 cps. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.
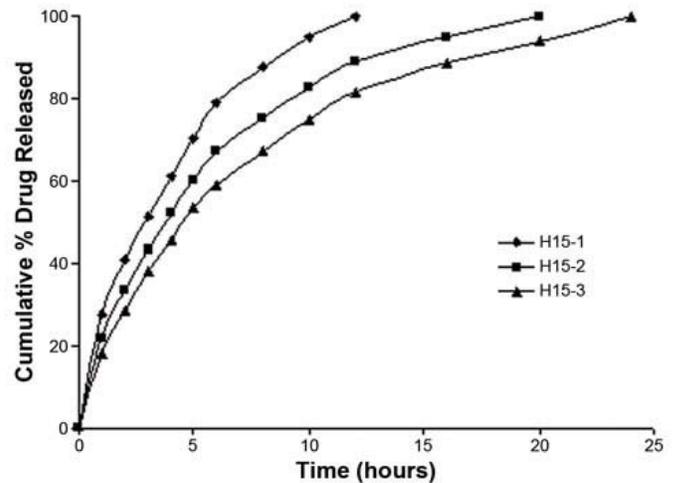
Figure 4. Comparative release profile of lamivudine from controlled release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 15 000 cps. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.

proportion was increased. In the case of HPMC 15 000 cps, the initial release for the first hour varied between 18% and 28% depending on polymer proportion, but the release was found to be more controlled in later stages in the tablets with a higher proportion of the polymer (Figure 4). The release of the drug extended from 12 hours in the case of 40% (H15-1) to 24 hours in the case of 80% (H15-3). The MDT values increased significantly ($P < .05$, F_{crit} (2,15) = 3.68 and F_{cal} = 697.72) as the polymer proportion was increased from 40% to 80%. In formulations containing HPMC 100 000 cps as the retarding polymer, the initial release for the first hour varied between 12% and 20% depending on polymer proportion, but the release was found to be more controlled in later stages in the tablets with a higher proportion of the polymer (Figure 5). The release of the drug extended from 16 hours in the case of 40% (HL-1) to more than 24 hours in the case of 80% (HL-3), with a maximum of 89% release at 24 hours in 80%. The MDT values increased significantly ($P < .05$, F_{crit} (2,15) = 3.68 and F_{cal} = 1249.97) as the polymer proportion was increased from 40% to 80%. Similar results were reported in the literature by several research groups that studied the effect of polymer proportion on the release of drugs like propranolol hydrochloride, aminophylline, and indomethacin from matrix tablets of HPMC.[27-29] The release rate of the drug from the matrix tablets decreased with an 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.[17,30]

The *n* values for all the formulations ranged from 0.489 to 0.615, 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 and polymer relaxation. The poor correlation coefficients (*r* values ranged from 0.523 to 0.705) observed for the kinetic parameters based on the zero-order model equation were mainly due to the drug release mechanism. Because the values of *n* were closer to 0.5, in most cases, good correlation coefficients (*r* values ranged from 0.970 to 0.995) were obtained for the kinetic parameters based on Higuchi's square-root equation. But it cannot be concluded that the drug release was totally based on diffusion, which generally is the case
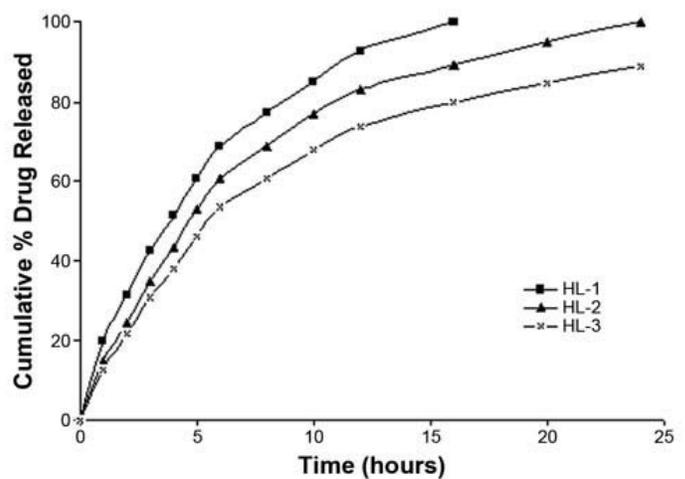
Figure 5. Comparative release profile of lamivudine from controlled release matrix tablets prepared using different proportions of hydroxypropyl methylcellulose 100 000 cps. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.

E6
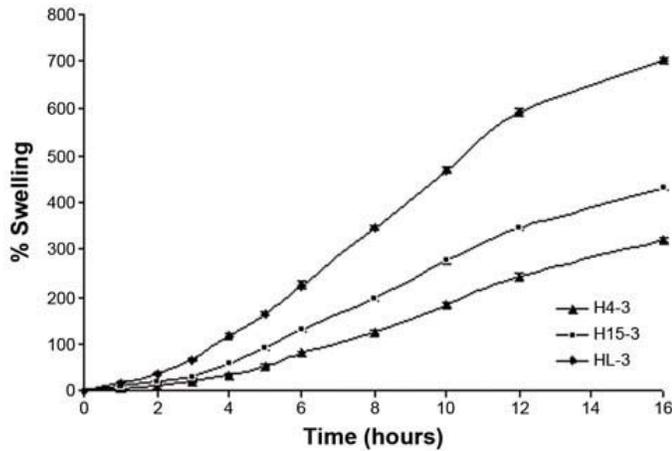
Figure 6. Swelling behavior of controlled release matrix tablets of lamivudine prepared using different viscosity grades of hydroxypropyl methylcellulose at 80% wt/wt of drug weight.
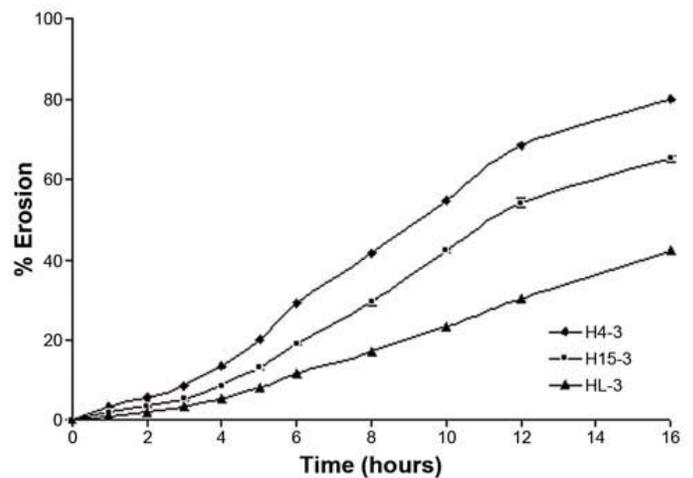
Figure 7. Eroding behavior of controlled release matrix tablets of lamivudine prepared using different viscosity grades of hydroxypropyl methylcellulose at 80% wt/wt of drug weight.

in Higuchi's square-root kinetics. Based on the swelling and erosion studies, it was observed that the matrix tablets undergo swelling (Figure 6) as well as erosion (Figure 7) during the dissolution study, which indicates that polymer relaxation had a role in the drug release mechanism. However, it can be concluded that the effect of diffusion on drug release was more than the effect of polymer relaxation as the values of n were nearer to 0.5.

The release rate was fastest from the formulation containing HPMC 4000 cps at 40% wt/wt of the drug weight (H4-1) with a K value of 32.53% hours$^{-0.505}$ and t$_{50\%}$ value of 2.34 hours. The release rate was slowest from the formulation containing HPMC 100 000 cps at 80% wt/wt of the drug weight (HL-3) with a K value of 15.21% hours$^{-0.615}$ and t$_{50\%}$ value of 6.92 hours. The decrease in release rate in formulations with lower viscosity grades was more pronounced and significant as the polymer proportion was increased, as compared with that of formulations with higher viscosity grades.

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 (60% wt/wt of the drug weight) is shown in Figure 8. As the viscosity of HPMC was increased from 4000 cps (H4-2) to 100 000 cps (HL-2), the release rate extended from 16 hours to 24 hours; the values of K decreased from 27.25% hours$^{-0.512}$ to 17.53% hours$^{-0.604}$; and the values of t$_{50\%}$ increased from 3.27 hours to 5.63 hours. The MDT values increased significantly ($P < .05$, F_{crit} (2,15) = 3.68 and F_{cal} = 459.08) with increase in polymer viscosity. This observation was in agreement with other reported works.[31] The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusional area at lower viscos-

ity as compared with higher viscosity grades of HPMC.[31] It was observed from the swelling (Figure 6) and erosion (Figure 7) studies that the percentage swelling and percentage erosion of the matrix tablets was totally dependent on the viscosity of the polymer used. The percentage swelling increased with increase in polymer viscosity, while the percentage erosion decreased with increase in polymer viscosity. This was because higher viscosity grades of HPMC have higher and faster water absorption capacities and tend to swell more rapidly compared with the lower viscosity grades.[17] Moreover, the matrix formed by the higher viscosity grade HPMC would have more gel strength than the one formed
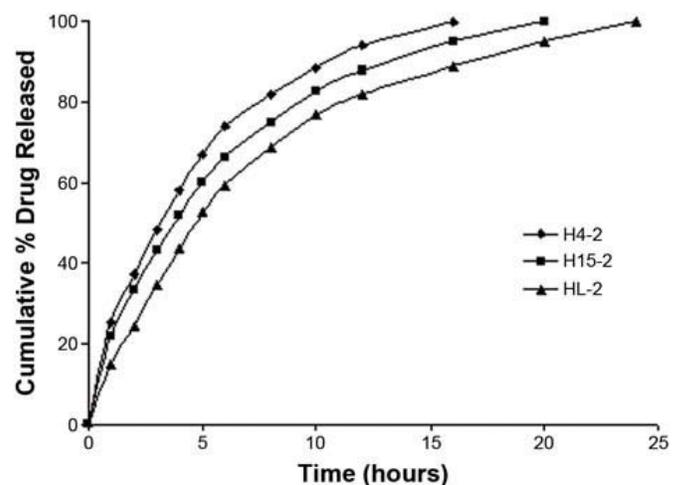
Figure 8. Comparative release profile of lamivudine from matrix tablets prepared using different viscosity grades of hydroxypropyl methylcellulose at 60% wt/wt of drug weight. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.

by the lower viscosity grade because of which, the erosion would be less. For these reasons the diffusional path length increased and the diffusion coefficient of the drug through the matrix decreased as the viscosity grade of the 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.[32,33] An increase in the compression force increases the hardness and the apparent density of the tablet, thereby reducing the matrix porosity in the tablet.[34] The relationship between pressure and density was reported to be dependent on material and also on the compression speed and size and shape of the tooling.[35] 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.[27-29]

The effect of compression force on the drug release was studied by preparing tablets using the same polymer proportion (60%) and viscosity (HPMC 4000 cps) but with different compression forces to obtain tablets with different hardness levels, 3.5-4.5, 7-8, and 11-12 kg/cm^2 (Figure 9). The release rate decreased with an increase in compression force. A statistically significant difference was observed in the MDT values ($P < .05$, F_{crit} (2,15) = 3.68 and F_{cal} = 792.85) 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 faster ($P < .05$; K value 33.80% hours$^{-0.489}$; t$_{50\%}$ value 2.22 hours) than the release of the drug from formulations prepared with higher compression forces (K values are 27.25% hours$^{-0.512}$ and 23.57% hours$^{-0.523}$ for hardness 7-8 kg/cm^2 [H4-2] and 11-12 kg/cm^2 [H4-2B], respectively; t$_{50\%}$ values are 3.27 hours and 4.20 hours for hardness 7-8 kg/cm^2 and 11-12 kg/cm^2, respectively). The effect of compression force on the release rate was found to be more pronounced at lower compression forces than at higher compression forces. Similar results were obtained by other researchers, who studied the effect of compression force on drug release from binary polymer matrix systems. The drug release was found to be faster at lower compression forces than at higher ones 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.[31] Compression force was found to have no effect on the release mechanism, as the values of *n* varied from 0.489 to 0.523, indicating that the release mechanism still followed anomalous, non-Fickian diffusion, which is in agreement with earlier reported works.[14]

Batch Reproducibility and Stability on Storage

No significant difference was observed in the release profile of different batches of each CR matrix tablet formulation of LAM, 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 any of the formulations, suggesting that LAM was stable in HPMC matrices.

CONCLUSIONS

CR matrix tablets of LAM conforming to good quality were prepared using HPMC by the 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 lower compression forces than at higher compression forces. Drug release was found to follow a non-Fickian or anomalous release mechanism. The designed CR matrix tablets of LAM, which release 20% to 30% of drug in the first hour and extend the release up to 16 to 20 hours, can overcome the disadvantages associated with conventional tablet formulations of LAM.

Figure 9. Comparative release profile of lamivudine from matrix tablets prepared using 60% wt/wt of hydroxypropyl methylcellulose 4000 cps with different compression forces. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.

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