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Formulation And Evaluation Of Controlled Release Matrix Tablet Of An Antiviral Drug

Harsha Sonaye*, Shagufta Khan, Pritish Kurumkar[a]

Department of Pharmaceutics, Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha. 442001. Maharashtra, India.
[a]Department of Pharmaceutics, NCRD's Sterling Institute of Pharmacy, Nerul East, Navi Mumbai. 400706. Maharashtra, India.

***Corres.Author: harsha_20054@rediffmail.com**
Mob. 9970794970

Abstract: Most of antiviral drugs have short half life due to rapid elimination therefore consequent treatment with such drugs requires four to five time administrations a day by conventional oral delivery system. The present research work is planned with the objectives to formulate controlled release matrix tablet of Lamivudine using polymer Eudragit RS100 and RL100 and HPMC K100M that can control the release of drugs, to study effect of polymer on drug release kinetics and drug polymer ratio on release. In vitro release study the initial drug released of formulations containing Eudragit RS100 and RL100 characterized by an initial faster release phase followed by more or less marked decrease in the release rate. As expected Eudragit RS100 showed the lowest drug release being the lowest water permeability on the other hand Eudragit RL100 shows more release as compared to Eudragit RS100 due to its good water permeability. And also this may be due to initial burst effect caused by surface erosion or disaggregation of matrix tablets prior to gel layer formation around the tablet core hence the release pattern of that formulations were not within the desirable limit. Due to presence of quaternary ammonium groups in Eudragit RS100 and RL100, the solubilization of these groups in acidic pH leads to formation of pores in the matrix, thereby releasing Lamivudine in the acidic pH. HPMC K100M played an important role in retarding the release rate and when combined with Eudragit RL100 and RS100 forms a firm gel layer and helps in formation of pores on the tablet surface which modifying release rate from matrix.
Keywords: Controlled release matrix tablets, Lamivudine, Eudragit RS100, Eudragit RL100, Hydrorxy propyl methyl cellulose K100M.

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]

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). 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, 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. 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 hydroxypropylmethylcellulose (HPMC), methylcellulose, sodium carboxymethylcellulose, carbopols, and polyvinyl alcohol 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. It is very suitable to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle. 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. 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. 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. 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. 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: Equation 1, the zero-order model equation; Equation 2, Higuchi's square-root equation; and Equation 3, the Ritger-Peppas empirical equation.

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

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

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

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.[3]

MATERIALS AND METHODS

LAM was supplied as gift sample from Arch Pharmalabs Limited (Mumbai,India). Eudragit RS100, Eudragit RL100 and HPMC K100M were a gift sample from Colorcon Asia Private Limited (Goa, India). All other chemicals and reagents used were of pharmaceutical or analytical grade.

Analytical Method

A validated Double Beam UV Spectrophotometer Model No. UV 2401 PC, Shimadzu Corporation, Singapore using pH 1.2 acid buffer 279.4 nm and pH 6.8 phosphate buffer at 271 nm were 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 UV spectrophotometric method. The infrared (IR) spectrum obtained FTIR Spectrophotometer Model -84005 Shimadzu Asia Pacific Pvt. Ltd., Singapore was compared with that of the standard. To study the compatibility of various formulation excipients with LAM, solid admixtures were stored at 40 ± 20^oC temperature with relative humidity of $75 \pm 5\%$ for three months. The sampling was done after

every one month and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release.

Formulation of Lamivudine Matrix-Embedded Tablets

Matrix-embedded CR tablets of LAM were prepared by varying polymer: drug ratio using different matrix forming polymers like HPMC K100M, Eudragit RS100 and Eudragit RL100.[4] Drug, polymers (passed through No. 60 mesh) and other excipients were mixed thoroughly and compressed on a Single Punch Tablet Compression Machine (Model No. H/416/95 Cadmach Machinery Pvt .Ltd., Ahmedabad, India) directly by using 10 mm flat punch die. Batches were prepared for each formulation, with each tablet containing 200 mg LAM. The compositions of the prepared matrix-embedded tablets are given in **Table 1.**

Table 1: Composition of Lamivudine Tablets

Composition	Lamivudine (mg)	Eudragit RL100 (mg)	Eudragit RS100 (mg)	HPMC K100M (mg)
F1	200	50	50	-
F2	200	75	50	-
F3	200	100	50	-
F4	200	50	75	-
F5	200	75	75	-
F6	200	100	75	-
F7	200	50	100	-
F8	200	75	100	-
F9	200	100	100	-
F10	200	50	50	20
F11	200	75	50	20
F12	200	100	50	20
F13	200	50	75	20
F14	200	75	75	20
F15	200	100	75	20
F16	200	50	100	20
F17	200	75	100	20
F18	200	100	100	20
F19	200	25	125	20
F20	200	125	25	20

Weights are given for one tablet

Physical Characterization of the Designed Tablets

The weight variation was determined by taking 20 tablets using Electronic Weighing Balance (Model No. AW-220 and BX – 6205 Shimadzu Corporation, Japan).[5] Hardness was measured using Pfizer hardness tester. For each batch three tablets were tested. Friability was determined by taking 10 tablets were weighed and placed in a Friability Tester (Model No. EF2 USP Electrolab Pvt. Ltd Goregaon (E), Mumbai.) and tablets were rotated at 25rpm for 4 minutes.[6] Thicknesses and Diameter were determined by selecting 3 samples randomly from each batch and thickness was measured using Digital Tablet Tester.

Release Rate Studies

The *in vitro* release of lamivudine from formulated tablets was carried out in acid buffer pH 1.2 for 2 hours and then continued in phosphate buffer pH 6.8 for 10 hours. The studies were performed in USP dissolution apparatus type II, (Dissolution Test Apparatus**,** Model No.DA-3, Veego Scientific Devices, and Mumbai) at 37 ± 0.5° C and 50 rpm speed. Samples were taken at hourly interval and analyzed for lamivudine content at 279.4 nm for acid buffer pH 1.2 and 271.0 nm for phosphate buffer pH 6.8 respectively by using UV–visible spectrophotometer (Mode No. UV 2401 PC, Shimadzu Corporation, Singapore).[7-14]

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 equation 1, 2 and 3. The values of K, K_t, K_0, n, $t_{1/2}$ (time required for 50% drug release). And 'n' (correlation coefficient) were determined. Equation 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, can describe the mechanism of drug release from the formulation. 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 depending 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 nature of drug release of drug from the design CR matrix tablets was inferred based on the 3 kinetic models.

Swelling and Eroding Behavior

The mechanism of drug release from hydrophilic polymeric matrices involves solvent penetration, hydration and swelling of 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 increase significantly as the polymer imbibes more and more water and form a gel, as time progresses. The hydration rate of polymer matrix, and thereby the gel formation and subsequent erosion, depend significantly on polymer proportion, viscosity and to a lesser degree on polymer particle size. So swelling and erosion studies were performed according to the method reported by Al-Taani and Fashtoush, 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. The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of *in vitro* drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were placed in a oven at 40°C and after 48 hours tablets were removed and weighed. % Swelling and % erosion was calculated according to the following formula, where S is the weight of the matrix after swelling, R is the weight of the eroded matrix, and T is the initial weight of the matrix.[3]

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

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

Scanning Electron Microscopy

Tablet samples were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. 20 Samples were coated with platinum and visualized under scanning electron microscope (SEM Model No. 6380-A).[15-17]

Release 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 condition to determine the batch reproducibility. To study the effect of storage on stability and release profile each batch of 20 tablets was wrapped in aluminum foil of thickness 0.04 mm and stored at 40 ± 2^0C temperature with relative humidity of $75 \pm 5\%$ for three months. The sampling was done after every one month and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release.[18-19]

RESULTS

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 use in the preparation of CR tablet formulation, characterized after 6 months of storage, are given in Fig. 1.[20]

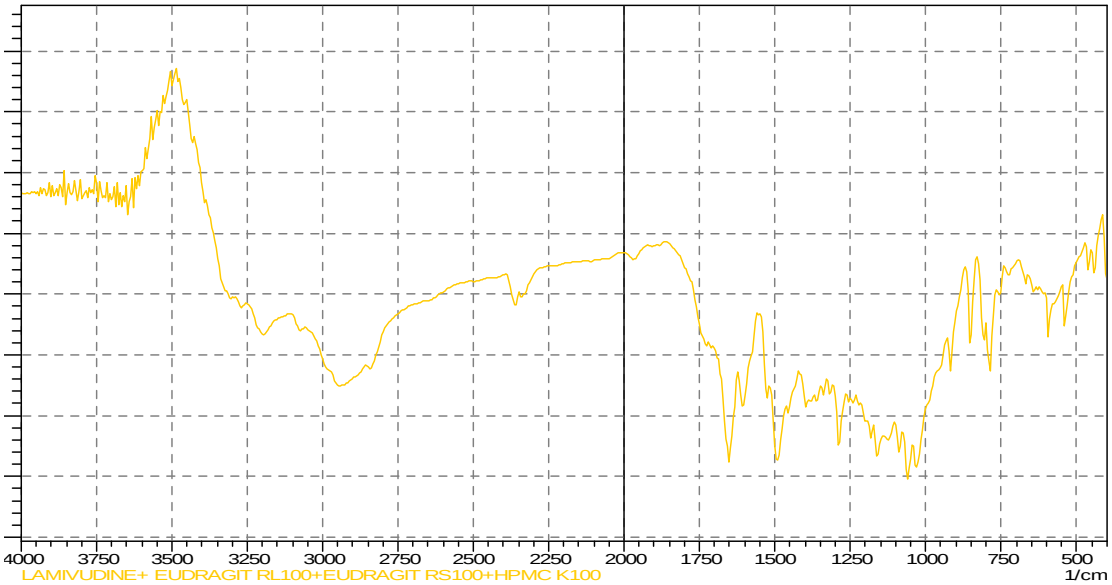


Figure 1: FTIR of Formulation (F16) contains Lamivudine, Eudragit RL 100, Eudragit RS 100 and HPMC K100M

Physical Characterization of the Designed Tablets

The physical characterization, hardness, friability, thickness, diameter and drug content uniformity of all tablet formulations were observed in **Table 2.**

Table 2: Evaluation physical characteristics of Lamivudine Tablets

Formulations	Hardness* (kg/cm^2)	Friability* (%w/w)	Thickness* (mm)	Diameter* (mm)	% Drug Content*
F1	5.2±0.05	0.512±0.015	2.40±0.11	10.02±0.67	99.50±0.55
F2	5.0±0.11	0.529±0.036	2.45±0.15	10.02±0.52	98.63±0.54
F3	4.8±0.05	0.563±0.019	2.52±0.12	10.03±0.34	97.26±0.42
F4	4.9±0.05	0.552±0.010	2.43±0.20	10.02±0.45	98.52±0.46
F5	4.8±0.13	0.562±0.019	2.50±0.15	10.02±0.76	99.21±0.41
F6	4.7±0.15	0.578±0.013	2.55±0.46	10.03±0.23	98.53±0.52
F7	4.8±0.05	0.567±0.007	2.51±0.14	10.03±0.58	99.23±0.55
F8	4.7±0.05	0.573±0.019	2.54±0.13	10.01±0.26	98.12±0.45
F9	4.6±0.07	0.589±0.003	2.57±0.11	10.03±0.52	97.14±0.48
F10	7.2±0.11	0.430±0.004	2.41±0.10	10.02±0.32	98.26±0.43
F11	6.9±0.11	0.445±0.031	2.46±0.13	10.03±0.60	95.23±0.52
F12	6.8±0.08	0.452±0.032	2.52±0.16	10.03±0.55	97.15±0.51
F13	7.0±0.12	0.438±0.015	2.44±0.19	10.02±0.54	98.36±0.49
F14	6.8±0.05	0.457±0.036	2.51±0.12	10.02±0.51	99.43±0.45
F15	6.7±0.11	0.472±0.019	2.56±0.15	10.03±0.43	98.25±0.46
F16	6.8±0.12	0.456±0.010	2.52±0.14	10.02±0.48	99.26±0.51
F17	6.7±0.11	0.468±0.019	2.55±0.12	10.03±0.52	99.12±0.53
F18	6.5±0.08	0.486±0.013	2.58±0.11	10.01±0.35	98.36±0.54
F19	6.8±0.07	0.451±0.009	2.52±0.20	10.02±0.52	97.14±0.51
F20	6.8±0.05	0.454±0.011	2.53±0.12	10.02±0.54	96.12±0.45

***Results are mean of three observations ± S.D.**

Release Rate Studies

Comparative release profile of lamivudine from controlled release matrix tablets prepared using different proportions of Eudragit RL 100, Eudragit RS 100 and HPMC K100M of formulations F1 to F20 are given in Fig. 2, Fig. 3, Fig. 4 and Fig. 5. Each data point represents the average of 6 tablets from 3 batches with SD within ± 2.0.

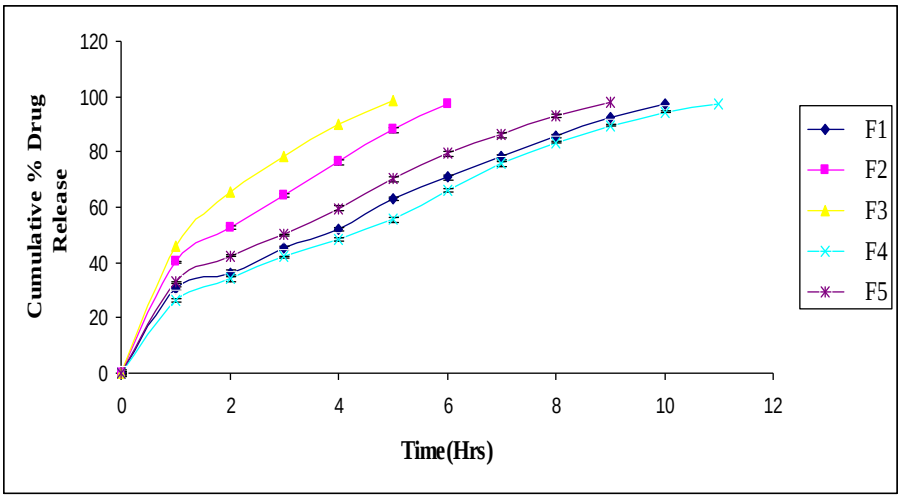


Figure 2: *In Vitro* Drug Release Profiles of Formulations F1-F5 for 12 Hrs

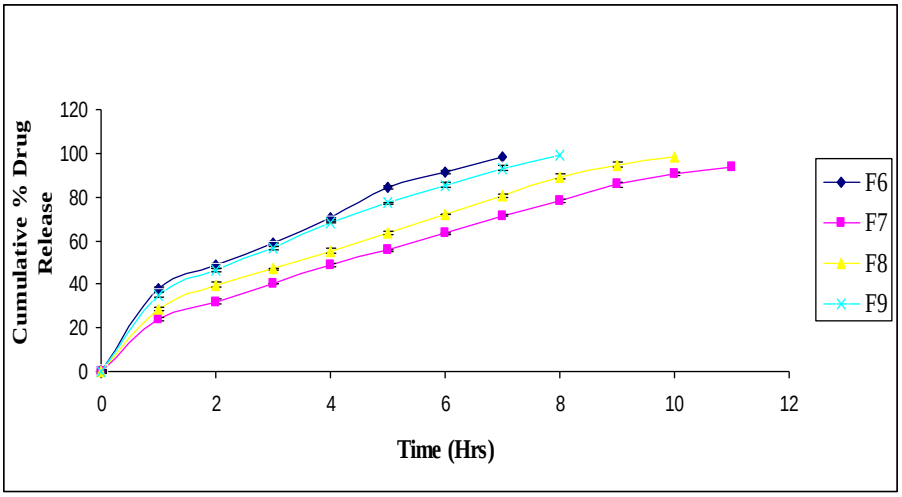


Figure 3: *In Vitro* Drug Release Profiles of Formulations F6-F9 for 12 Hrs

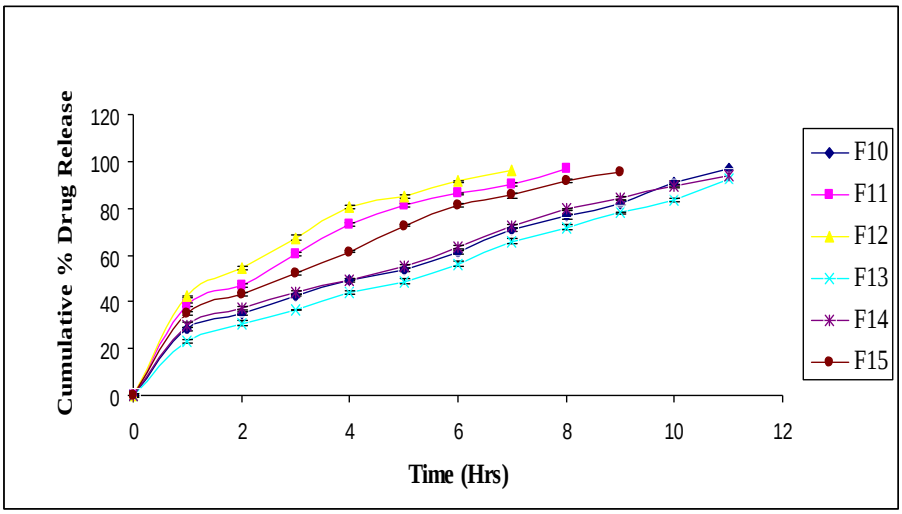


Figure 4: *In Vitro* Drug Release Profiles of Formulations F10-F15 for 12 Hrs

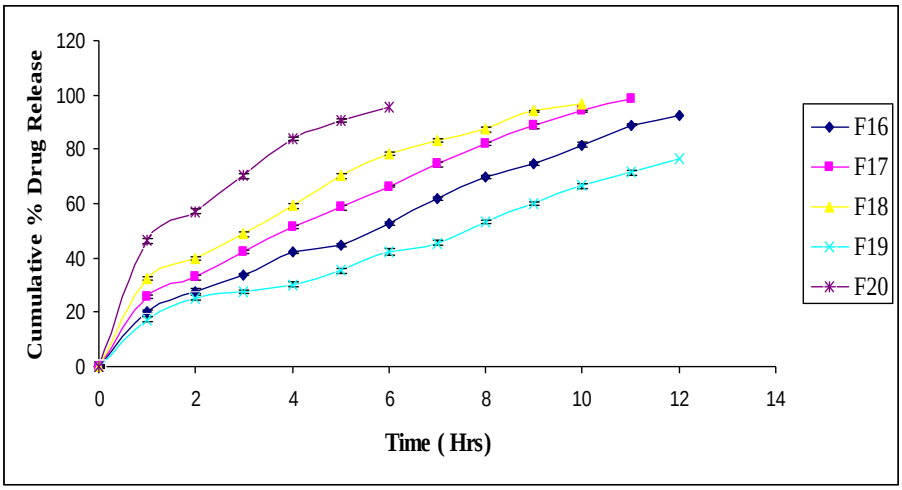


Figure 5: *In Vitro* Drug Release Profiles of Formulations F16-F20 for 12 Hrs

Characterization of Release Kinetics

The Kinetic treatment of data of dissolution profiles of formulations F16 is given in Table 3. A plot of cumulative percentage drug release vs. time for matrix-embedded CR tablets of LAM prepared using different proportions of Eudragit RL 100, Eudragit RS 100 with hardness 4.6 to 7.8 kg/cm^2, is shown in Table 3.

The 'n' values for 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.

Table 3: Kinetic Treatment of Data of Dissolution Profiles of Formulations F16

F16	Zero Order	First Order	Hixon Crowell	Korsmeyer Peppas	Higuchi Plot
R^2 Value	0.812	0.765	0.908	-0.249	0.983
Slope	0.120	0.002	0.010	0.639	0.272
Intercept	9.929	0.975	3.186	-2.182	3.007

Swelling and Eroding Behavior

Based on the swelling and erosion studies the matrix tablets undergo swelling (Fig. 6, Fig. 7, Fig. 8 and Fig. 9) as well as erosion (Fig. 10, Fig. 11, Fig. 12 and Fig. 13) during the dissolution study, which indicates that polymer relaxation had a role in the drug release mechanism.

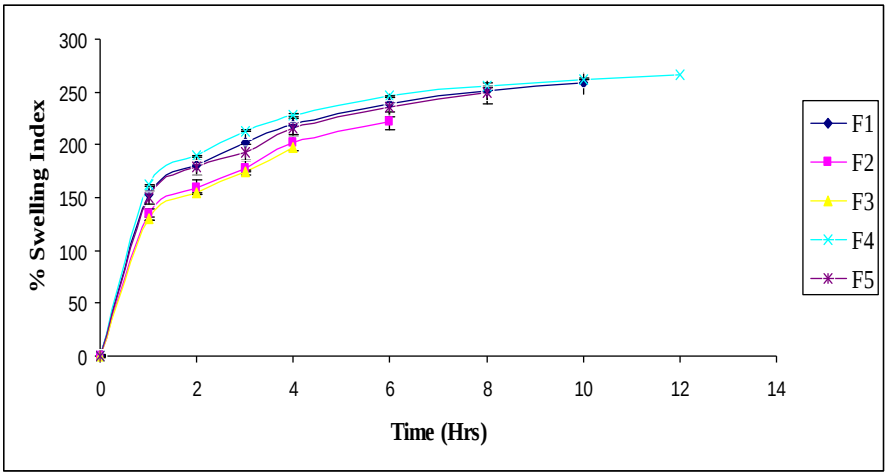


Figure 6: % Swelling Indices of Formulations F1-F5

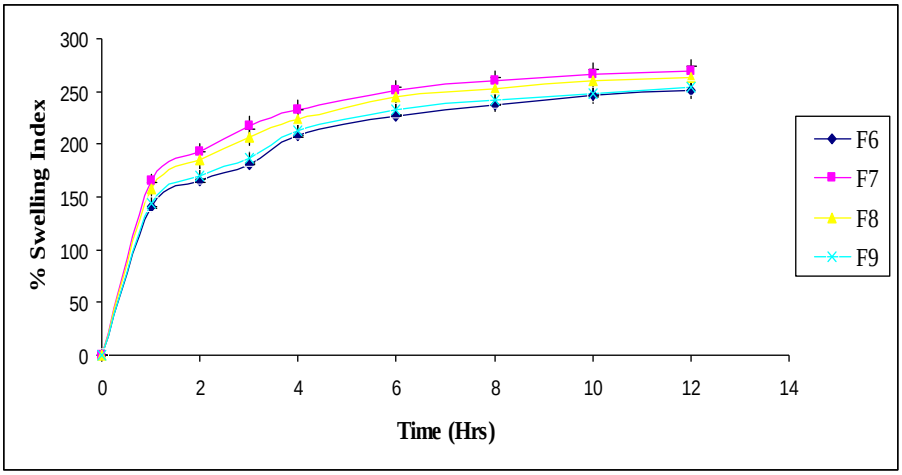


Figure 7: % Swelling Indices of Formulations F6-F9

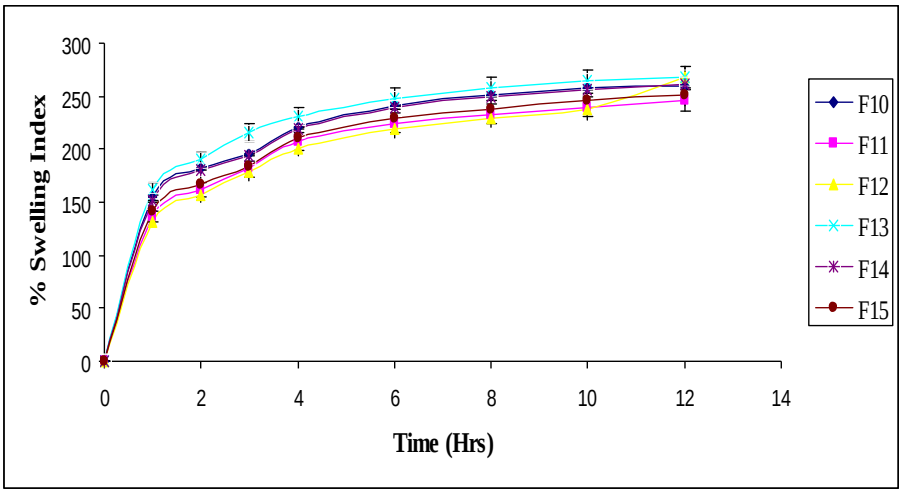


Figure 8: % Swelling Indices of Formulations F10-F15

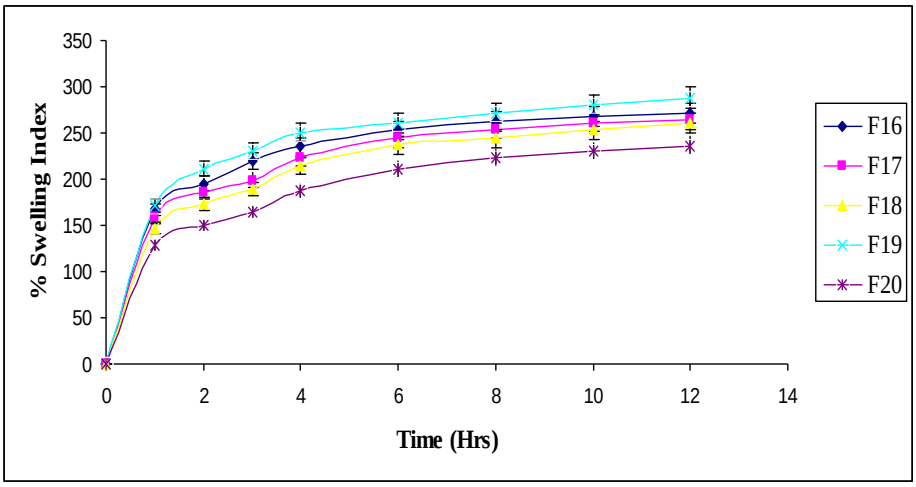


Figure 9: % Swelling Indices of Formulations F16-F20

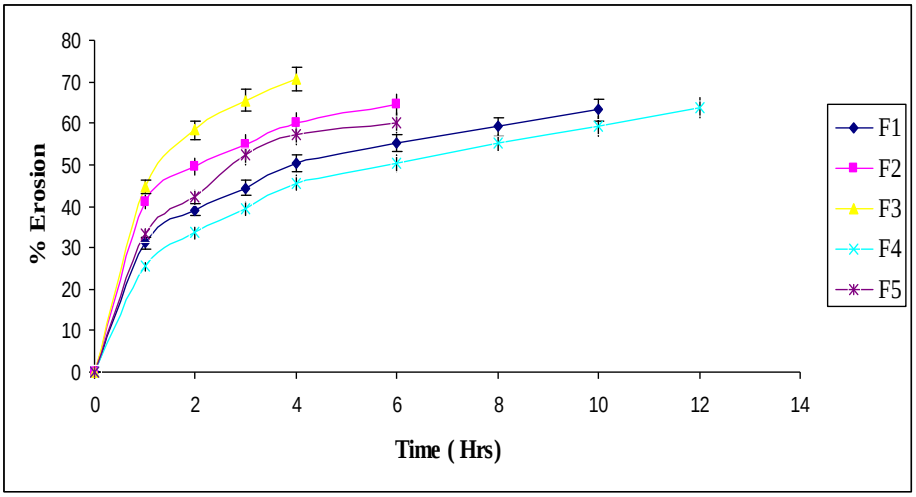


Figure 10: % Erosion of formulations F1-F5

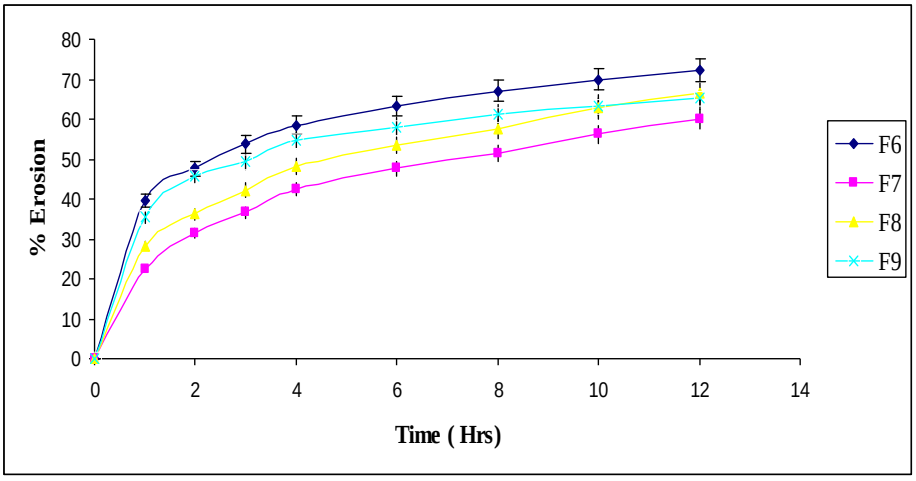


Figure 11: % Erosion of Formulations F6-F9

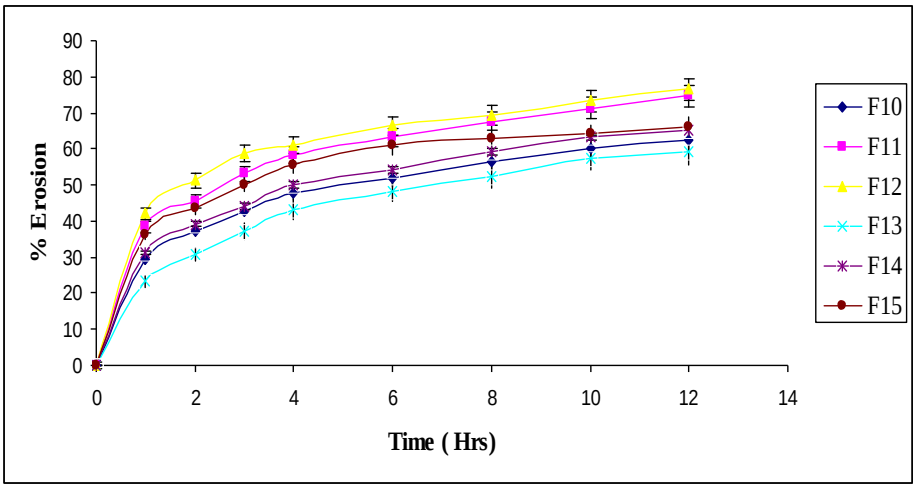


Figure 12: % Erosion of Formulations F10-F15

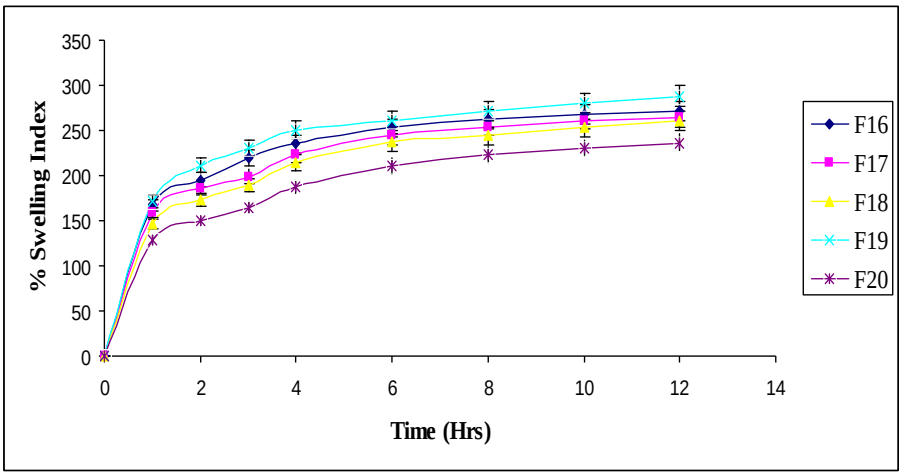


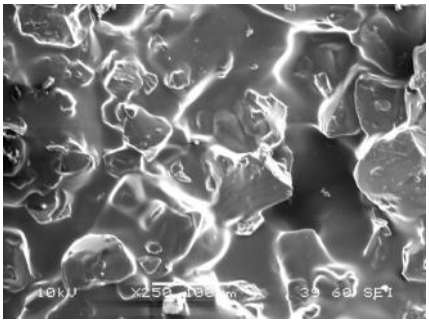
Figure 13: % Erosion of Formulations F16-F20

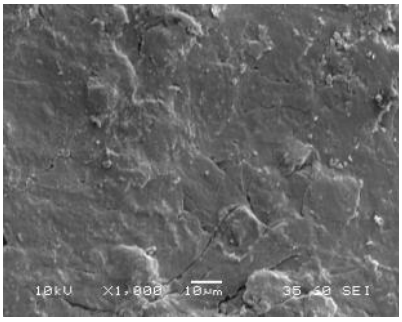
Scanning Electron Microscopy

SEM study revealed that both diffusion and erosion mechanisms to be operative during drug release from the optimized formulations F16 of matrix tablets. SEM photomicrographs of the matrix tablets taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix (Fig. 14).

Release Reproducibility and Stability on Storage

Formulations F16 was given desirable release and were as optimized formulations and hence were selected for stability studies. Observations are shown in Fig. 15.

A 

B 

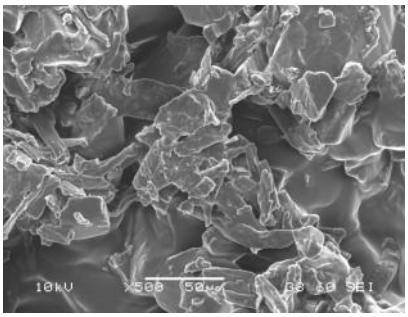
C 

Figure 14: SEM Photomicrographs of Optimized Matrix Tablet (Batch F16) Showing Surface Morphology after 0 Hrs (A), 2 Hrs (B) and 10 (C) Hrs of Dissolution Study.

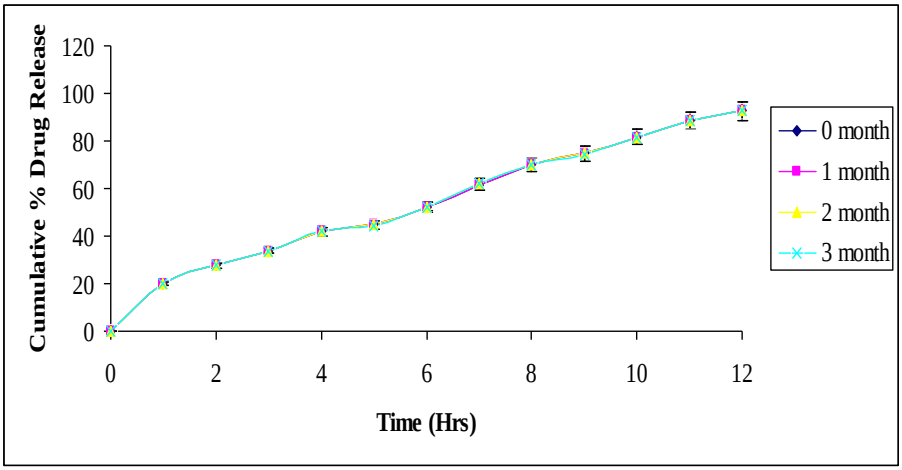


Figure 15: *In Vitro* Release Profiles of Formulation F16 Kept for Stability 40° ± 2°C and 75±5% RH for 3 months

DISCUSSION

From the characterization of preformulation studies, it was concluded that the drug sample of Lamivudine complies with the compendial specification for identification and other tests therefore Lamivudine drug was suitable for present studies.

FTIR of Lamivudine shows characteristic peaks at 3323.12 cm^{-1} & 3305.76 cm^{-1} due to asymmetric & symmetric N-H group stretching. Peaks at 1571.88 cm^{-1} due to N-H group deformation. 1608.52 cm^{-1} due to C=N group stretching, 1637.45 cm^{-1} due to C=O group stretching. Aliphatic C-H stretching found at 2997.17cm^{-1}, 2960.53cm^{-1} & 2837.09 cm^{-1} and 1456.16 cm^{-1} owing to C-H group deformation (scissoring). Formulation

clearly showed retention of these characteristic peaks of the drug (Fig. 1), thus it revealed that no interaction found between drug and polymer.

Standard calibration curve of Lamivudine was obtained in acid buffer pH 1.2 and phosphate buffer pH 6.8 at wavelength 279.4 nm and 271.0 nm. Standard calibration curve of lamivudine in acid buffer pH 1.2 and in phosphate buffer pH 6.8 obeyed Beer-Lamberts law in concentration range of 2-20 µg/ml respectively. Bulk characterization of drug and polymer suggested that the properties were well within the ranges given in the compendia.

All the tablets of different formulations showed acceptable results with respect to weight variation, drug content uniformity, friability, etc. Tablets found to be good hardness was within the range of 4.5 to 7.5 Kg/cm^2 (Table 2). Friability 1% (w/w) that indicates the ability of tablets to withstand shocks which may be encountered during transport. The manufactured tablets showed low weight variations.

The in vitro release rate patterns of all formulations are studied in Fig. 2, Fig. 3, Fig. 4 and Fig. 5. Fig. 2 and Fig. 3 showed the effect of different ratios of Eudragit RL100 and Eudragit RS100 on release rate of lamivudine. Formulation F7 showed 93.58% drug release in 11 hrs as compared with formulation F1 to F8 and F9.

Fig. 5 showed the effect of different ratios of Eudragit RL100, Eudragit RS100 and HPMC K100M on release rate of lamivudine. Formulation F16 showed 92.53 % drug release in 12 hrs as compared with formulation F10 to F19 and F20. The composition of different matrix tablets are summarized in Table 1 and 2.

The initial drug released of F1-F9 formulations containing Eudragit RS100 and Eudragit RL100 (Fig. 2 and 3) characterized by an initial faster release phase followed by more or less marked decrease in the release rate. As expected Eudragit RS100 showed the lowest drug release being the lowest water permeability on the other hand Eudragit RL100 shows more release as compared to Eudragit RS100 due to its good water permeability. And also this may be due to initial burst effect caused by surface erosion or disaggregation of matrix tablets prior to gel layer formation around the tablet core hence the release pattern of F1 – F9 formulations were not within the desirable limit.

The release of lamivudine starts from upper GI tract and continues for 10 to 12 hrs upto the lower GI tract. Eudragit RS100 and Eudragit RL100 contain quaternary ammonium group in their structure. The solubilization of these quaternary ammonium groups in acidic pH leads to formation of pores in the matrix, thereby releasing lamivudine in the acidic pH. HPMC K100M played an important role in retarding the release rate. HPMC K100M when combined with Eudragit RL100 and Eudragit RS100 forms a firm gel layer along with Eudragit RL100 and Eudragit RS100 and helps in formation of pores on the tablet surface. Also because of its tendency to mask the quaternary ammonium groups of Eudragit RL100 and Eudragit RS100 to some extent thereby modifying release rate from matrix.

From kinetic treatment of dissolution data, it was concluded that the release mechanism of Lamivudine from matrix tablets, the dissolution data were subjected to the Korsmeyer and Peppas diffusion model. The ‘n’ values for formulations F16 was found to be 0.614 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. R^2 value (i.e., 0.982) was maximum for Higuchi plot. Therefore release kinetics fitted the Higuchi plot.

Scanning electron microscopy (SEM) of tablet surface at different time intervals also showed that erosion of matrix increased with time. SEM photomicrographs of the surface of fresh tablet (Fig. 14A) did not show any pores. From SEM photomicrographs revealed that after 0, 2 and 10 hours pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of matrix tablet.

Both Eudragit RL 100 and Eudragit RS 100 were having the properties of swelling and erosion. Formulation F3 showed lowest % swelling (198.1%) and highest % erosion (70.78%) as compared to the formulation F1-F9 as it contains more amount of Eudragit RL 100 which was more water permeable. Similarly, F19 showed highest % swelling (287.9%) and lowest % erosion (56.22%) as compared to the formulation F10 – F20 as it contains more amount of Eudragit RS 100 which was less water permeable and more % w/w of HPMC K100M.

From stability study data (Fig. 15), it was concluded that formulations F16 had not found statistically significant difference ($P > 0.05$) in drug content, *in vitro* dissolution and all other parameters. This showed that the formulations F16 was stable.

CONCLUSION

Result of present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating controlled release matrix tablets of lamivudine. The controlled release matrix tablet was capable of maintaining slow drug release up to 12 hours. Thus if these findings translate into *in vivo* studies, constant plasma concentration with reduced frequency of administration may be possible.

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