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In vivo evaluation of lamivudine extended release trilayer matrix tablets

Rangu Nirmala[1*], Gande Suresh[2*]

[1]*Research Scholar, Mewar University, Chittorgarh, Rajasthan, India*
[2]*Research Supervisor, Mewar University, Chittorgarh, Rajasthan, India*

***Corresponding Author: Rangu Nirmala**
Email: rangunirmal@gmail.com

ABSTRACT

The objective of the present study was aimed to develop and optimize extended release (ER) matrix tablets of Lamivudine trilayer tablets by direct compression and consist of middle active layer and barrier layers were prepared with different concentrations of hydrophilic and hydrophobic polymers. The tablets were also evaluated for physicochemical characteristics and release kinetics. The physicochemical characteristics of the prepared tablets were satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (HF23) was described by the Zero-order and Higuchi model. From in vivo bioavailability studies, $AUC_{0-\ inf}$ for optimized formulation was higher than the marketed formulation. Statistically, AUC_{0-t} of the optimized formulation was significantly higher ($p<0.05$) as compared to marketed formulation. The present study demonstrated that formulation of Lamivudine trilayer matrix tablet is a highly effective strategy for enhancing the prolonged drug release and bioavailability.

Keywords: Lamivudine, AIDS, Trilayer matrix tablet, Xanthan gum, Geomatrix, Bioavailability studies

INTRODUCTION

Matrix system is often used for manufacturing sustained-release dosage forms easy of production [1]. The basic characteristic of the systems is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage forms. A number of design options are available to control or modulate drug release from a drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tableting [2, 3, 4].

The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate [5, 6]. In the device, the coat layers prevent the water penetration through the protected core for some

duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release [7, 8].

The use of naturally occurring biocompatible gums has been the focus of recent research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymers matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance [9]. Xanthan gum (XG) is soluble in water, anionic hetero polysaccharide and to be sensitive to pH and ionic strengths. It swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse [10] and is used for the fabrication of matrices with uniform drug release characteristics [11, 12].

Geomatrix technology

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release [13].

Lamivudine is a potent hydrophilic antiviral agent indicated for the treatment of AIDS and belongs to BCS Class III drug with high solubility and low permeability. However, the main limitation to the therapeutic effectiveness of lamivudine is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability [14].

The short half life of Lamivudine necessitated for fabricating extended release matrix tablets to provide a therapeutic amount of drug and maintain the desired drug concentration i.e. the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specific period of time. Sustained release tablets are intended to take once or twice daily, when compared with conventional dosage forms that may have to take three or four times daily to achieve the same therapeutic effect. The objective of the present study was to develop a trilayered tablet of Lamivudine with different hydrophobic and hydrophilic polymers. The results indicate that the optimized trilayered Lamivudine tablet can be successfully used for treatment of AIDS.

MATERIALS AND METHODS

Materials

Lamivudine pure drug was generous gift from Hetero drugs Ltd, Hyderabad, India. HPMC K 4 M, HPMC K 15 M and HPMC K 100 M were obtained from Rubicon labs, Mumbai. MCC, EC, Xanthan gum and Carnauba wax were gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Methods

Formulation of controlled release Lamivudine trilayer matrix tablets

The trilayered matrix tablets of Lamivudine were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24 h.

Preparation of middle active layer of lamivudine trilayered tablets

Twenty-seven formulations (F1-F27) for active layer were prepared by direct compression method using 3^3 Response surface methods (3 variables and 3 levels of polymers) by using Design of experiment Relia Soft software product with polymers like different HPMC grades. All the formulations were varied in concentration of polymers, magnesium stearate constituted in all the formulations. These materials were screened through #60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12 mm diameter flat punches on a sixteen-station rotary tablet press. Formulation of active layer was depicted in Table 1. The prepared tablets were subjected to dissolution studies [15].

Table 1: Formulation trials of middle active layer of lamivudine

F.NO	LAMIVUDINE	HPMC K4M	HPMC K15M	HPMC K100M	PVP K-30	MCC	MG STEARATE	TOTAL
F1	300	24	20	16	8	28	4	**400**
F2	300	32	20	16	8	20	4	**400**
F3	300	24	28	16	8	20	4	**400**
F4	300	32	28	16	8	12	4	**400**
F5	300	24	20	24	8	20	4	**400**
F6	300	32	20	24	8	12	4	**400**
F7	300	24	28	24	8	12	4	**400**
F8	300	32	28	24	8	04	4	**400**
F9	300	24	28	24	8	12	4	**400**
F10	300	32	24	20	8	12	4	**400**
F11	300	28	20	20	8	20	4	**400**
F12	300	28	28	20	8	12	4	**400**
F13	300	28	24	16	8	20	4	**400**
F14	300	28	24	24	8	20	4	**400**
F15	300	28	24	20	8	16	4	**400**
F16	300	28	20	24	8	16	4	**400**
F17	300	28	20	16	8	24	4	**400**
F18	300	28	28	20	8	12	4	**400**
F19	300	32	20	20	8	16	4	**400**
F20	300	28	28	16	8	16	4	**400**
F21	300	32	24	16	8	16	4	**400**
F22	300	32	24	20	8	12	4	**400**
F23	**300**	**32**	**28**	**20**	**8**	**08**	**4**	**400**
F24	300	24	24	20	8	20	4	**400**
F25	300	32	24	24	8	08	4	**400**
F26	300	24	24	16	8	24	4	**400**
F27	300	28	24	16	8	20	4	**400**

Preparation of upper and lower layers of lamivudine trilayered tablets

The barrier layers were formulated employing hydrophobic swellable polymer natural wax i.e. carnauba wax the swelling erosion modeling fillers which include water soluble MCC, EC and Xanthan gum. The procedure adopted to make the compacts was via direct compressions. For the first procedure the wax, xanthan gum and the filler were mixed in mortar and lubricated with magnesium stearate [16]. Formulation of upper and lower layers was depicted in Table 2.

Table 2: Formulation trails of extended release trilayered matrix tablets of lamivudine

INGREDIENTS	AF23	BF23	CF23	DF23	EF23	FF23	GF23	HF23
MIDDILE ACTIVE LAYAER (F23) (400 mg)								
Lamivudine	300	300	300	300	300	300	300	300
HPMC K 4 M	32	32	32	32	32	32	32	32
HPMC K 15 M	28	28	28	28	28	28	28	28

HPMC K 100 M	20	20	20	20	20	20	20	20
PVP K30	08	08	08	08	08	08	08	08
MCC	08	08	08	08	08	08	08	08
Magnesium stearate	04	04	04	04	04	04	04	04
UPPER AND LOWER LAYER (125 mg)								
Carnauba wax	20	25	30	35	40	42.5	45	50
Xanthan gum	40	40	38	35	35	32.5	30	30
Ethyl cellulose	12	10	14	12	15	12	12	12
Micro Crystalline Cellulose	50	47	40	40	32	35	35	30
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Formulation of extended release tryilayered tablets of Lamivudine

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of die cavity; (12 mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (650 mg). Then the pre-weighed amount of powder equivalent to bottom layer (125mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and the granules equivalent to 400 mg of the drug was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre-weighed (125 mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test [17].

Evaluation of trilayer matrix tablets of Lamivudine

Hardness, Thickness, Friability, Weight variation, Content Uniformity and *In Vitro* Swelling Studies were conducted.

In-vitro drug release profile

In vitro drug release studies for developed trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 271nm.

Drug release order kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer.

Stability studies

The stability study of the formulated trilayer tablets were carried out under different conditions according to ICH guidelines using stability chamber (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content.

Pharmacokinetic studies of Lamivudine

Animal Preparation

Male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^{0}C, Relative Humidity 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee **(IAEC NO: IAEC/1657/CMRCP/T2/Ph.D-16/61).**

In vivo study design [18]

The Rabbits were randomly divided into two groups each group contains six animals. The group A was received prepared Lamivudine matrix Tablets (650 mg), marketed product was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24hrs post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at −20°C until analysis.

HPLC method

For HPLC C8 column with 5µm particle size and the mobile phase containing water: tetrahydrofuran: acetonitrile (45.83: 20.83: 33.34 % v/v/v), Oyster BDS premium C18 (250 mm × 4.6 mm, 5 µm) analytical column in isocratic mode at room temperature and UV detection at 245 nm. The compounds were eluted at a flow rate of 1.15 ml min-1. Internal standard didanosine was used. The retention times of lamivudine and didanosine were found to be 2.01 ± 0.003, 3.01 ± 0.001min respectively [19].

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max} i.e., T_{max} and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$

RESULTS AND DISCUSSION

Preparation of middle active layer

The matrix tablets of Lamivudine were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles. From the above results, among all the formulations the formulation F23 was decided as optimized formulation for active layer based on the highest drug release i.e. 98.54±1.15 within 12hrs when compared with other preparations (Figure 1 - 4). Formulation F23 was choosen as active layer for trilayer matrix tablets.

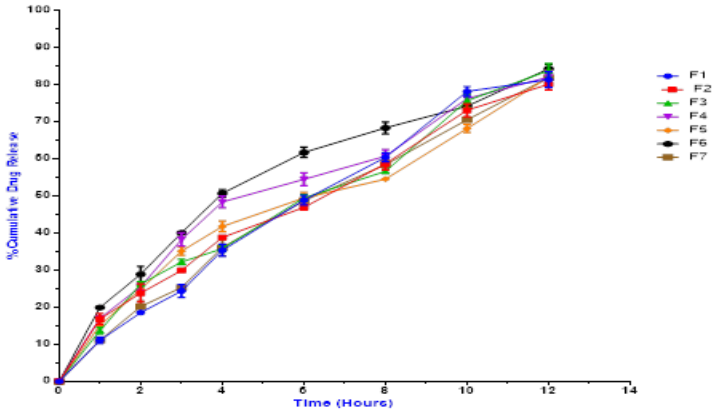

Figure 1: *In vitro* dissolution studies of lamivudine middle active layer tablets F1-F7

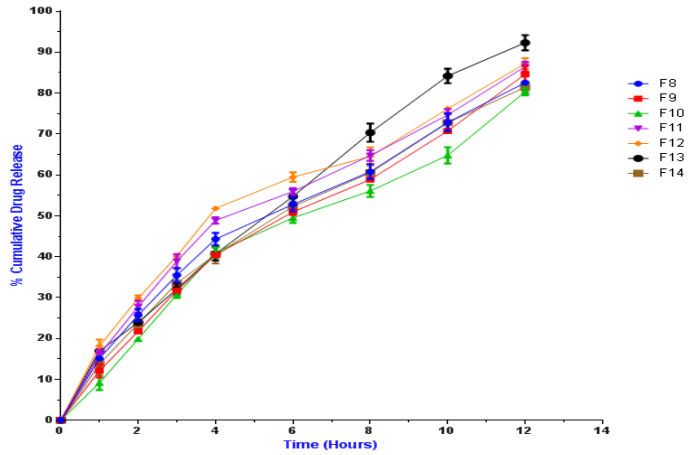

Figure 2: *In vitro* dissolution studies of lamivudine middle active layer tablets F8-F14

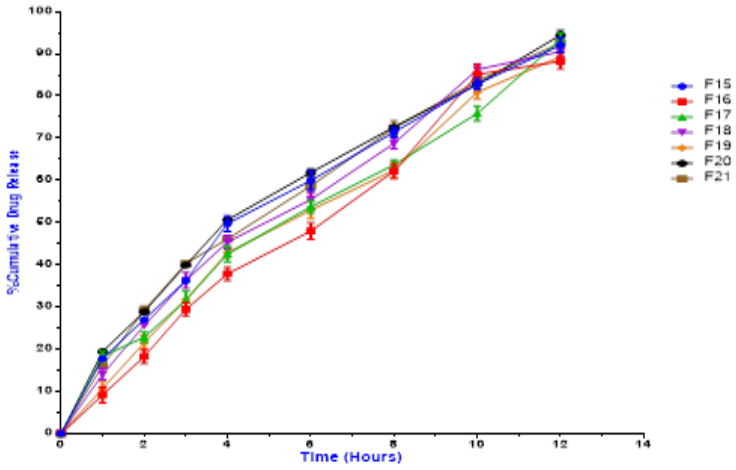

Figure 3: *In vitro* dissolution studies of lamivudine middle active layer tablets F15-F21

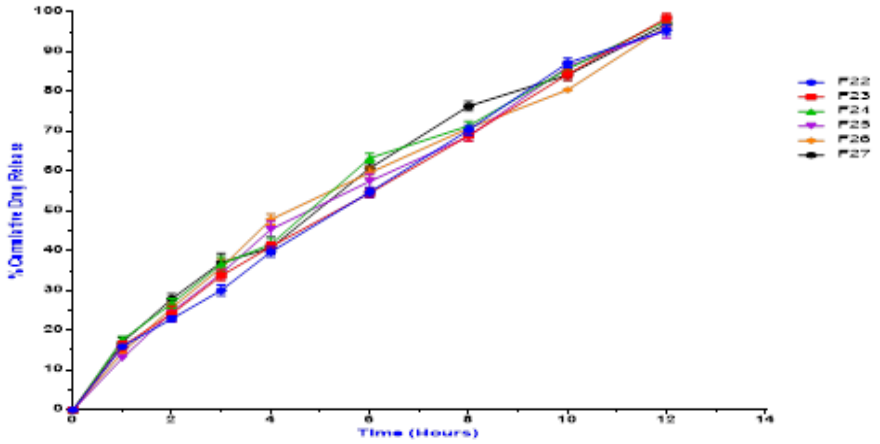

Figure 4: *In vitro* dissolution studies of lamivudine middle active layer tablets F22-F27

Evaluation of of trilayer matrix tablets of Lamivudine

The prepared trilayer tablets were shown in Figure 5 and the evaluation parameters were found to be within the IP limits (Table 3).

The Swelling study of trilayered matrix tablet of lamivudine was given in Table 3, showed that the swelling index of the tablet increases with increase in time upto 12 hours, this may be attributed to the fact that the erosion of biodegradable polymer Xanthan gum. This indicates that the drug will remain in intestinal region till drug is released completely from the delivery system and promotes evacuation after its release.

Figure 5 : Lamivudine trilayer matrix tablets

Table 3: Physico chemical evaluation properties of Lamivudine trilayered Tablets

F.NO	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	**Friability (%)	# Content uniformity (%)	Swelling index (%)
AF23	651.65±1.2	6.0±0.12	7±0.12	0.52±0.01	95.23±0.63	83±0.76
BF23	648.69±0.8	6.1±0.06	8.1±0.06	0.55±0.02	97.04±0.06	83±0.72
CF23	648.04±0.5	6.1±0.06	7.1±0.06	0.63±0.03	95.56±0.14	82±0.64
DF23	651.05±0.0	6.2±0.12	7.2±0.12	0.72±0.01	94.11±1.01	88±0.81
EF23	650.54±0.4	6±0.00	7±0.00	0.62±0.02	94.23±0.8	73±1.03
FF23	650.78±0.4	6.3±0.10	7.1±0.06	0.66±0.01	95.45±0.31	82±0.84

GF23	650.65±0.3	6.1±0.10	7.1±0.10	0.58±0.02	94.11±0.49	80±0.72
HF23	**650.57±0.2**	**6.3±0.25**	**7.3±0.40**	**0.69±0.01**	**99.23±0.51**	**95±0.79**

*Values are expressed in mean± SD :(n=20)
**Values are expressed in mean± SD :(n=10)
#Values are expressed in mean± SD :(n=3)

In vitro dissolution studies of trilayer matrix tablets of Lamivudine:

The release of Lamivudine from different formulations was carried out and the results are depicted in Table 4 and figure 6. The trilayer tablets extended the drug release upto 24 hrs. The highest drug release was found in the formulation HF23 i.e 98.12% within 24 h. HF23 was found to be optimized formulation based on the dissolution and other evaluation parameters. The marketed product drug release was found to be 90.78% upto 24h.

Table 4: *In vitro* Drug Release Profile for Prepared Extended release trilayered Tablet of lamivudine (AF23-HF273)

Time (h)	AF23	BF23	CF23	DF23	EF23	FF23	GF23	HF23	Marketed
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	**0±0**	0±0
1	17.77±0.04	12.14±1.85	18.35±1.11	14.05±1.32	10.68±1.78	19.46±0.18	16.12±0.22	**16.95±0.25**	21.33±1.73
2	27.04±0.15	18.26±1.66	22.87±1.18	25.60±0.48	21.54±1.68	28.87±0.59	29.23±0.96	**27.93±1.28**	29.84±1.68
4	36.24±0.18	29.45±0.52	31.64±2.22	36.30±1.88	31.76±0.18	39.97±0.46	40.34±0.28	**37.09±2.21**	38.24±0.18
6	49.78±1.85	37.86±0.63	42.56±1.85	45.40±1.56	42.89±1.15	50.67±0.61	52.12±0.17	**40.72±0.51**	43.56±1.15
8	59.98±2.24	48.04±0.98	53.78±1.56	55.50±1.86	52.98±1.98	61.89±0.86	61.72±1.85	**60.77±0.18**	51.78±1.98
12	71.44±1.18	62.18±1.78	63.69±1.18	68.76±1.28	62.43±1.77	72.67±0.19	72.45±1.72	**76.36±0.16**	62.60±1.77
16	75.88±1.29	77.14±2.18	79.89±1.75	80.27±1.28	82.90±1.65	84.78±0.32	82.56±1.11	**84.23±0.25**	73.89±1.65
20	78.07±1.75	80.27±1.85	82.43±1.62	84.58±1.32	86.32±0.52	88.45±0.11	90.58±0.45	**95.02±0.48**	81.43±0.52
24	83.98±1.24	81.04±1.98	84.78±1.26	86.50±1.81	89.98±1.58	94.89±1.86	92.72±1.35	**98.12±1.15**	90.78±1.52

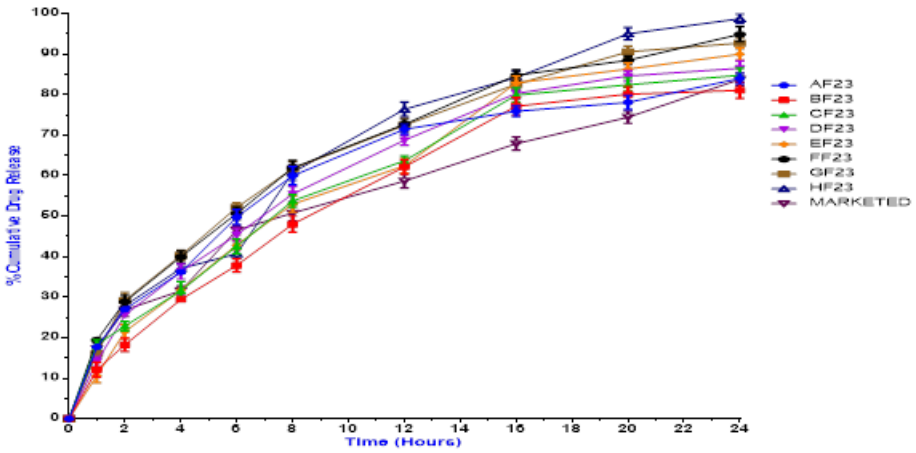

Figure 6*: In vitro* dissolution studies of lamivudine trilayer extended release tablets AF23-HF23

Release order kinetics for optimized (DF8) Formulation

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.994 indicates that the drug release follows a zero order mechanism and Higuchi model.

Design of Experiment

This method is mainly used to explain the effect of one factor on other factor, whether this effect is significant or not, if significant how it influences the response. In this present work the effect of one factor (HPMC K 100M) on other two factors (HPMC K 4M, HPMC K 15M) was explained.

In the above graph the effect of HPMC K100M on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of HPMC K100M on % cumulative drug release. The formulations with all 3 factors shown % drug release in between 70.38-99.54. The less amount of drug release is the effect of factor (HPMC K100M**)** on response. There is a negligible effect on Swelling Index of formulations because all formulations have excellent Swelling property and there is slightly influence on Swelling Index by HPMC K 100M (Figure 7&8).

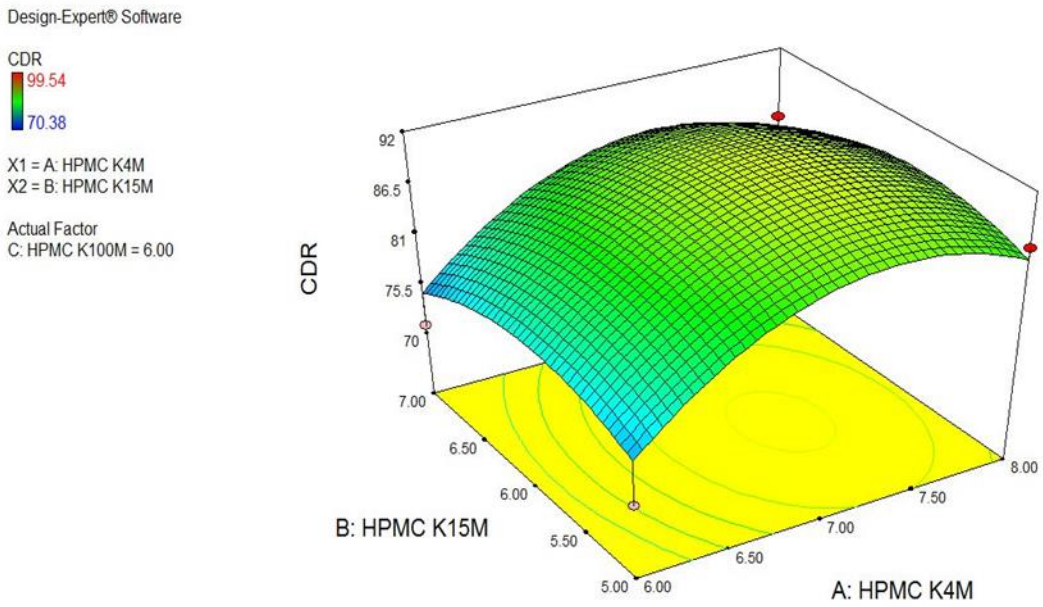

Figure 7: Response surface plot showing the influence of amount of polymer on the release profile of lamivudine for % Cumulative Drug Release.

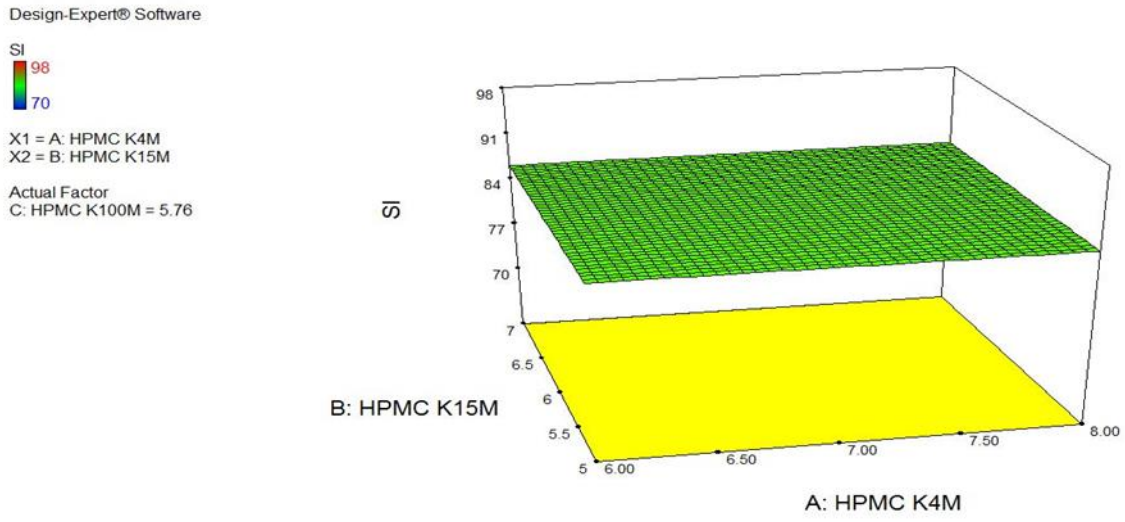

Figure 8: Response surface plot showing the influence of amount of polymer on Swelling Index of lamivudine

Characterization

FT-IR

Overall there was no alteration in peaks of Lamivudine pure drug (Figure 9). and optimized formulation (Figure 11), suggesting that there was no interaction between drug & excipients. FT-IR spectrum of pure drug and other polymers are shown in (Figure 10). There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug indicating absence of any interaction.

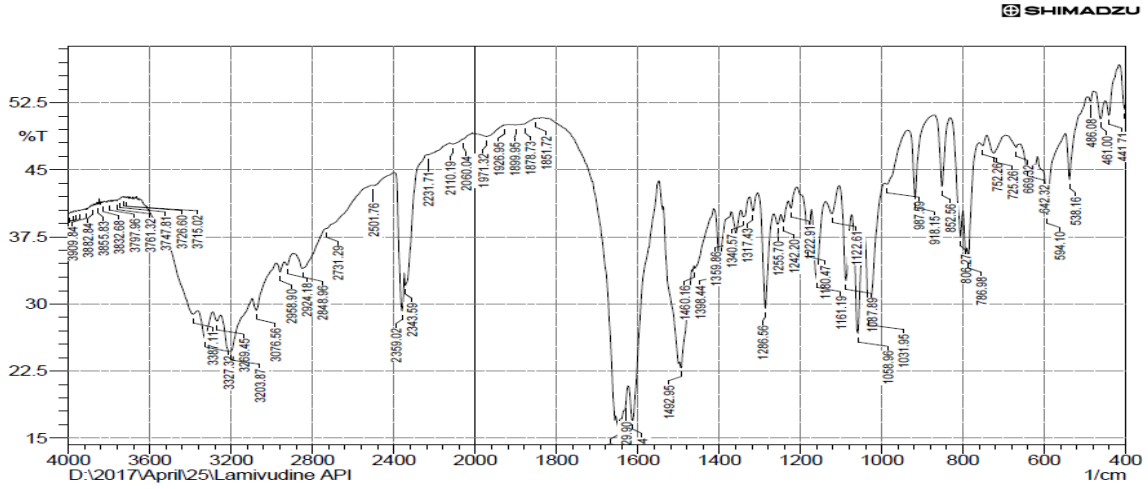

Figure 9: FT-IR spectrum of pure drug Lamivudine

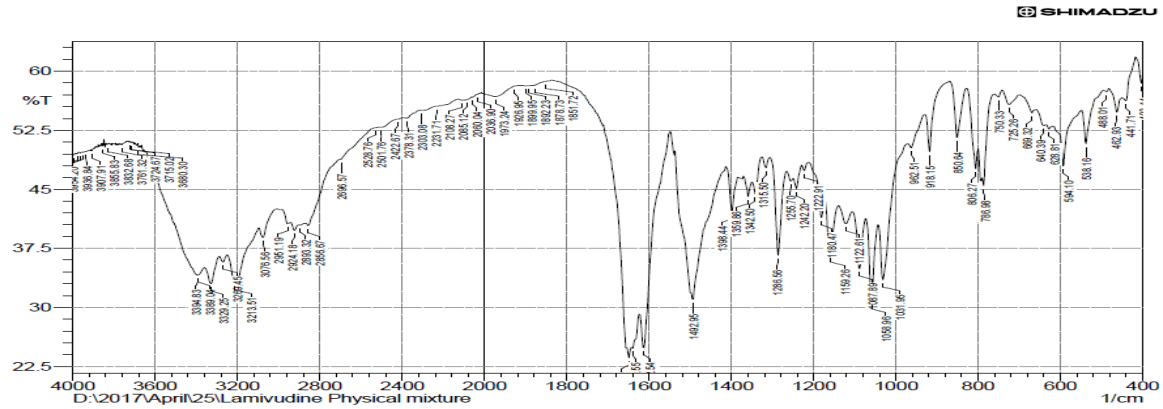

Figure 10: FT-IR spectrum of pure drug and other polymers

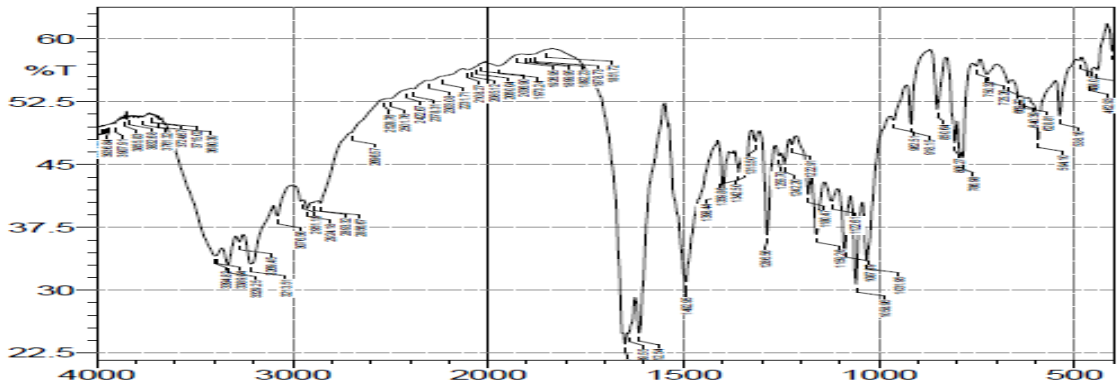

Figure 11: FT-IR spectrum of optimized formulation HF23

Stability studies

Optimized formulation HF23 was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

Bioavailability Parameters

From in vivo bioavailability studies, C_{max} of optimized formulation was higher than the marketed product, 62.11±0.16µg/ml and 45.12±0.15µg/ml respectively. T_{max} of the optimized formulation (8.00±0.14h) suggests slower absorption. This delayed absorption of test preparation is most likely due to the sustained release of the drug. The half-life of the marketed drug (6.15±0.05h) was low which indicates rapid removal of the drug from plasma. This was also supported by the high elimination rate constant value. The optimized formulation exhibited higher half-life (10.5±0.0144h) and low elimination rate constant values indicating slower drug disposition and prolonged effect. However, the $AUC_{0-\infty}$ values for the two formulations (optimized 687.75±1.14µg h/ml and marketed product 458.14±1.02µg h/ml) were significantly different. AUC_{0-t} of the optimized trilayer tablet was significantly higher ($p<0.05$) as compared to marketed product and the results are summarized in Table 5 and figure 12, which shows the higher bioavailability with sustained release of optimized formulation of Lamivudine.

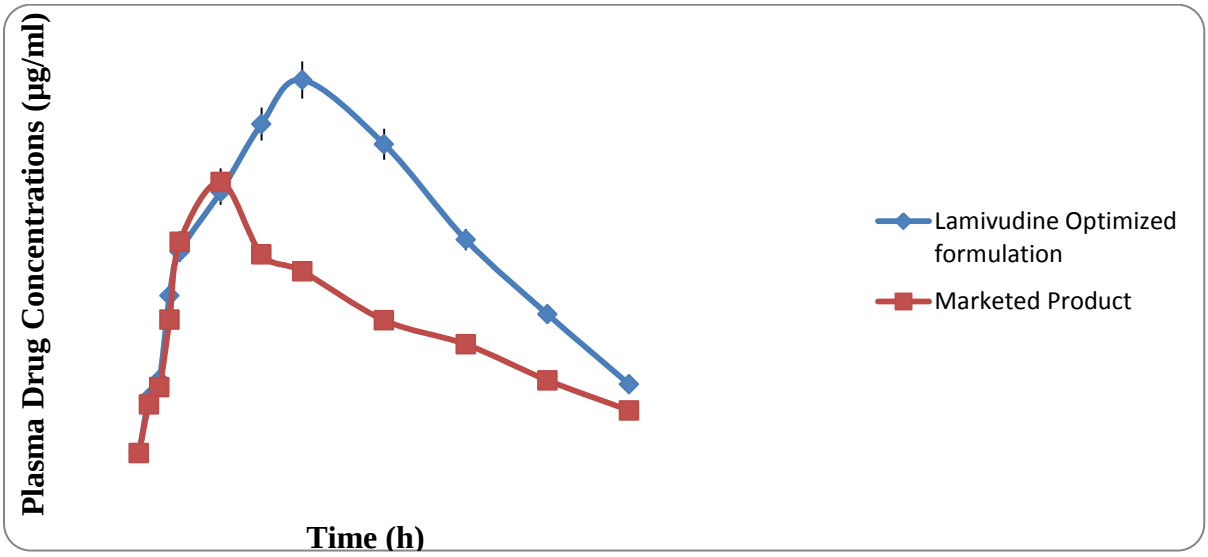

Figure 12: Plasma Concentrations of Lamivudine Optimized formulation and Marketed Product at different time intervals

Table 5: Comparison of pharmacokinetic parameters of Lamivudine Optimized formulation and marketed product

Parameters	Lamivudine optimized formulation	Marketed product
C_{max} (µg/ml)	62.11±0.16	45.12±0.15
AUC $_{0-t}$ (µg h/ml)	410.65±1.12	252.25±1.02
$AUC_{0-\infty}$ (µg h/ml)	687.75±1.14	458.14±1.02
T_{max} (h)	8.00±0.14	4.02±0.12
t $_{1/2}$ (h)	10.5±0.014	6.15±0.05

SUMMARY AND CONCLUSION

It was concluded that trilayer matrix tablets of Lamivudine could be successfully prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF23 was found to be optimized formulation Lamivudine tablets were prepared by direct compression and consist of middle active layer with different grades of HPMC, MCC and PVP K30, upper and lower layers were prepared with Carnauba wax, xanthan gum, EC and MCC. The tablets were also evaluated for physicochemical characteristics and release kinetics. The physicochemical characteristics of the prepared tablets were satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. From in vivo bioavailability studies, $AUC_{0-\ inf}$ for optimized formulation was higher than the marketed formulation. Statistically, AUC_{0-t} of the optimized formulation was significantly higher ($p<0.05$) as compared to marketed formulation. The present study demonstrated that formulation of Lamivudine trilayer matrix tablet is a highly effective strategy for enhancing the prolonged drug release and bioavailability.

REFERENCES

[1]. Merkus FWHM. Controlled and rate-controlled drug delivery. Boca Raton FL, CRC Press, USA; 1986, 15-47.
[2]. Conte U, Maggi L. Multi-layer tablets as drug delivery devices. Pharm Tech 2, 1998, 18–25.
[3]. Chidambaram N, Porter W, Flood K, Qiu Y. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J. Control. Release 52, 1998, 149–158.
[4]. Efentakis M, Politis S. Comparative evaluation of various structures in polymer-controlled drug delivery systems and the effect of their morphology and characteristics on drug release. Eur. Polym. J 42, 2006, 1183–1195.
[5]. Conte U, Maggi L, Colombo P, La Manna A. Multi-layered hydrophilic matrices as constant release devices. J Control Rel 26, 1993, 39-47.
[6]. Yihong Qui, Chidambaram N, Kolette F. Design and evaluation of layered diffusional matrices for zero order sustained-release tablets. J Control Rel 51, 1998, 123-130.
[7]. Conte U, Maggi L. Modulation from Geomatrix multi-layer matrix tablets containing drugs of different solubility. Biomaterials 17(9), 1996, 889-896.
[8]. Yihong Q, Kolette F. Design of sustained release matrix system for a highly water-soluble compound ABT-089. Int J Pharm 157, 1997, 46-52.
[9]. Tobyn MJ, Stani forth JN, Baichwal AR, Mc Call TW. Prediction of physical properties of a novel polysaccharide-controlled release system. Int J Pharm 128, 1996, 113-22.
[10]. Talukdar MM, Mooter VD, Augustijns P, Maga TT, Verbeke N, Kinget R. In vitro evaluation of xanthan gum as potential excipients for oral controlled release matrix tablet formulation. Int J Pharm 169, 1998, 105-13.
[11]. Talukdar MM, Vercammen JP. Evaluation of xanthan gum as a hydrophilic matrix for controlled release dosage forms. Drug Dev Ind Pharm 19, 1993, 1037-46.
[12]. Hong Wen, Kinam Park. Oral controlled release formulation design and drug delivery. Theory to practice, Wiley publication, New Jercy; 2010, 94-95.
[13]. Praveen Kumar T, Pallavi Y, Deepthi K, Narayana Raju P. Formulation and evaluation of Entacapone sustained release matrix tablets. The Pharma Innovation 3(8), 2014, 80-88.
[14]. Kieburtz KD, Seidlin M, Lambert JS, Dolin R, Reichman R, Valentine F. Extended follow-up of peripheral neuropathy in patients with AIDS and AIDS-related complex treated with dideoxyinosine. J Acquir Immune Defic Syndr 5, 1992, 60-4.
[15]. Pavan Kumar Potturi, Y. Sudhakar, Formulation and In vitro/In vivo evaluation of controlled release Entacapone trilayer matrix tablets by geomatrix, *Int J of Drug Deli*, 7, 2015, 155-166.
[16]. Conte L, Maggi. Multi-layered hydrophilic matrices as constant release devices Geomatrix TM Systems. J Control Release 26(1), 1993, 39–47.

[17]. Sung in Hong, Seaung Youl Oh. Dissolution kinetics and physical Characterization of three-layered tablet with poly (ethylene oxide) core matrix capped by Carbopol. Int J Pharm 356, 2008, 121–129.

[18]. Dheeraj Baviskar, Rajesh Sharma and Dinesh Jain, Formulation and In vitro/In vivo Evaluation of Sustained Release Diltiazem Matrix Tablets, Tropical Journal of Pharmaceutical Research June 12(3), 2013, 311-316.

[19]. B. Naga Sandhya, A. Manikanta Kumar, Mahesh K Nasare, P. Vijay Kumar, Jetta Satish and Prakash. V. Diwan. RP-HPLC method for simultaneous estimation of lamivudine, didanosine and efavirenz in pharmaceutical dosage forms, Der Pharmacia Lettre, 5(3), 2013, 148-155.