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Development and Evaluation of Lamivudine Extended Release Trilayer Matrix Tablets by Response Surface Methodology

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ABSTRACT

The present study was aimed to develop and optimize extended release (ER) matrix tablets of Lamivudine trilayer tablets to achieve zero-order drug release for prolonged period of time. 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. The release profile of the optimized formulation (HF23) was described by the Zero-order and Higuchi model. The results indicate that the approach used could lead to a successful development of extended release formulation of short biological half-life drug. These results also demonstrated the suitability of three-layered tablet formulation of Lamivudine to provide controlled release for prolonged period of time and improved linearity for Lamivudine in comparison to marketed product in the effective management of AIDS with patient compliance.

Keywords: Lamivudine, Trilayer matrix tablet, HPMC, Xanthan gum, Geomatrix

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INTRODUCTION

Compressed hydrophilic matrices have become popular as modified release dosage forms for oral administration in terms of clinical efficacy and patient compliance. Matrix system is often used for manufacturing sustained release dosage forms easy of production[1]. 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 tabletting[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 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 METHOD

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 method (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

Sr 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	16	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 trials of extended release trilayered matrix tablets of lamivudine

Ingredients	AF23	BF23	CF23	DF23	EF23	FF23	GF23	HF23
Middle Active Layer (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
MCC	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 trilayered 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

Hardness of ten randomly picked tablets was determined using Monsanto hardness tester.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche Friabilator. This was operated for 4 min at a speed of 25 rpm. The tablets were removed from the Friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,% Friability = (Loss in weight/ Initial weight) X 100.

Weight variation

The weight variation test was performed as per the USP. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

Drug content / Assay

Five tablets were weighed individually and powdered. Then the powder of tablet equivalent to 200mg was weighed and dissolved in phosphate buffer pH 6.8, the solution was filtered and diluted using phosphate buffer pH 6.8 and then the drug content was analyzed using UV spectrophotometer at 271nm.

Swelling & Erosion studies

Swelling experiment was conducted on the prepared tablets using USP dissolution apparatus II at rotational speed of 50 rpm. The medium used was 900ml phosphate buffer pH 6.8 at 37^0C. The swelling study was done upto 10h. The tablets were removed using a small basket and swollen weight of each tablet was determined. The percentage of swelling was calculated according to the formula:

Percentage of swelling = (S/R) X 100

***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 500ml 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. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Samples were accurately weighed and heated in sealed aluminium pans at a rate of 10°C/min between 25 and 350°C temperature rang under nitrogen atmosphere. Empty aluminium pan was used as a reference.

SEM studies:

The surface and shape characteristics of Tablets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

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 m. The tablets were characterized for the hardness, friability, drug content.

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.

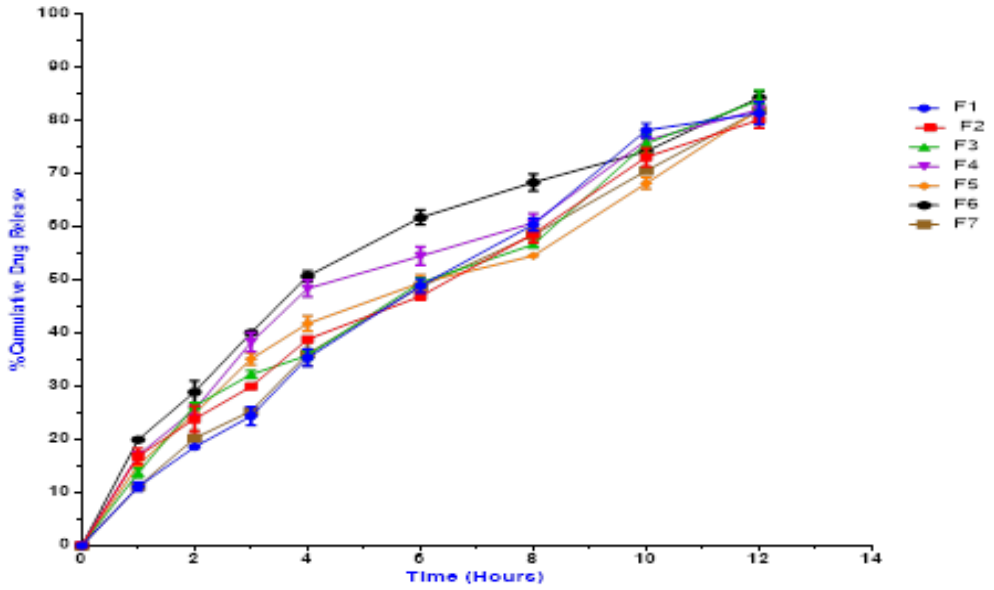

Figure 1: *In vitro* dissolution studies of lamivudine middle active layer tablets F1-F7

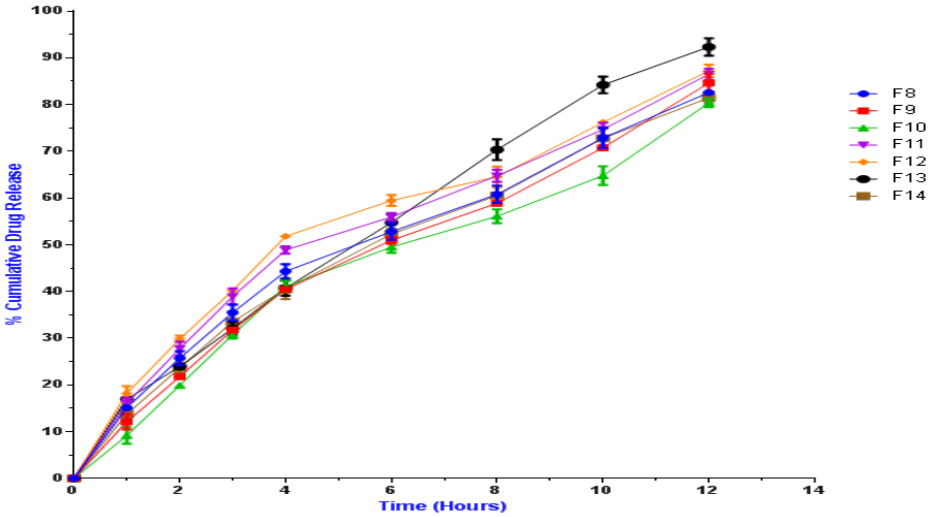

Figure 2: *In vitro* dissolution studies of lamivudine middle active layer tablets F8-F14

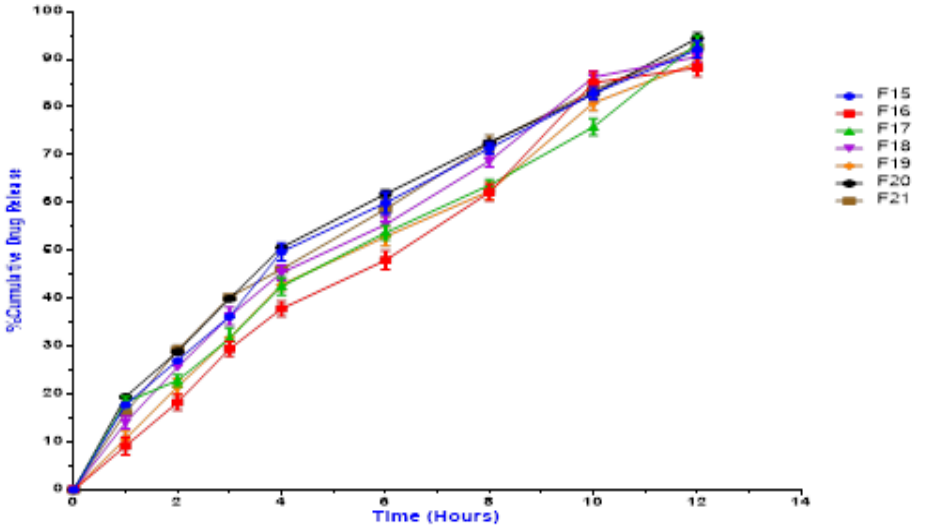

Figure 3: *In vitro* dissolution studies of lamivudine middle active layer tablets F15-F21

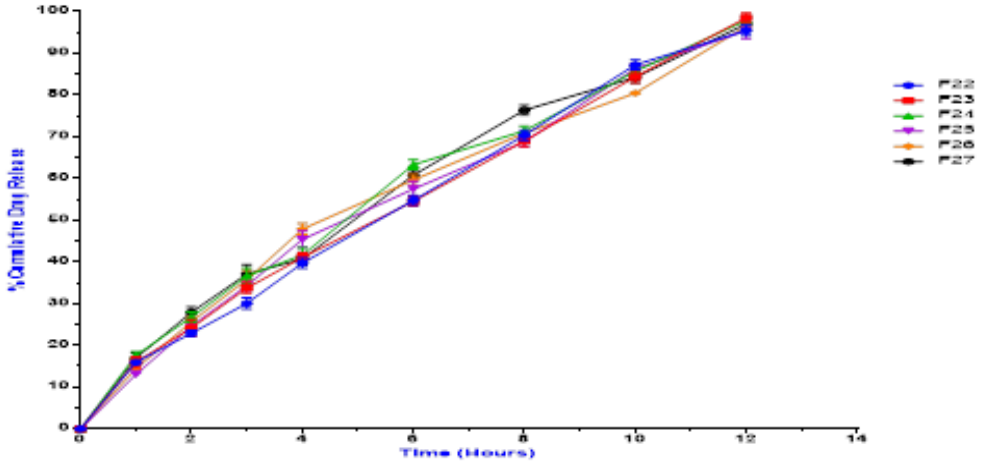

Figure 4: *In vitro* dissolution studies of lamivudine middle active layer tablets F22-F27

Figure 6: Lamivudine trilayer matrix tablets

Evaluation of of trilayer matrix tablets of Lamivudine

The evaluation parameters of all the tablets were found to be within the limits and summarized in **Table 3.**

The drug content of all formulation is in between 94-99.23%; drug content depends on angle of repose because if the angle of repose was good then drug content is also uniform because if the flow property is good then the drug is evenly distributed in the formulation.

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.

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**. 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

Release order kinetics

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 (**Table 5).** This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.817 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

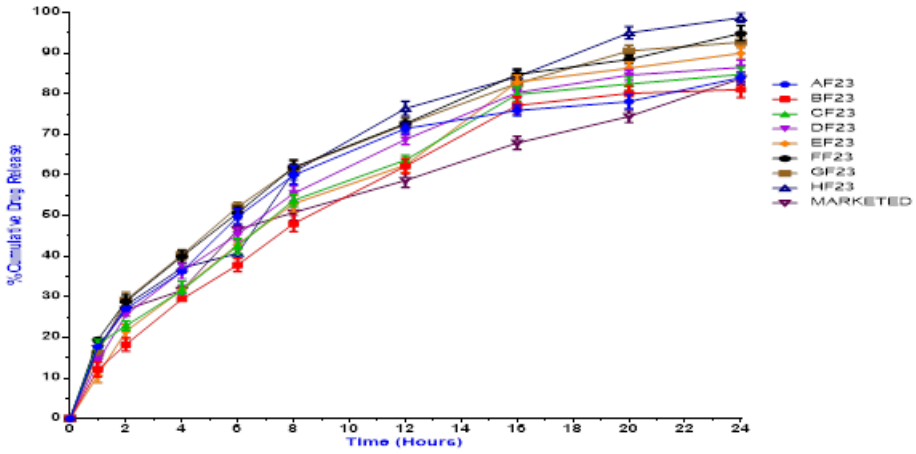

Figure 5*: In vitro* dissolution studies of lamivudine trilayer extended release tablets AF23-HF23

In vitro drug release for marketed product

From the above results it is apparent that the regression coefficient value closer to unity in case of First order plot i.e.0.967 indicates that the drug release follows a first order mechanism (**Table 5**). This data indicates a lesser amount of linearity when plotted by the zero-order equation. Hence it can be concluded that the major mechanism of drug release follows first order kinetics. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modelling such as Higuchi and Korsmeyer-Peppas plots. Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.823 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

Table 5: Release kinetics of optimized formulation of Lamivudine Trilayered tablets

S/No	Formulation	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	n
1	HF23	0.994	0.912	0.956	0.988	0.817
2	Marketed	0.923	0.967	0.925	0.945	0.823

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 6 &7**).

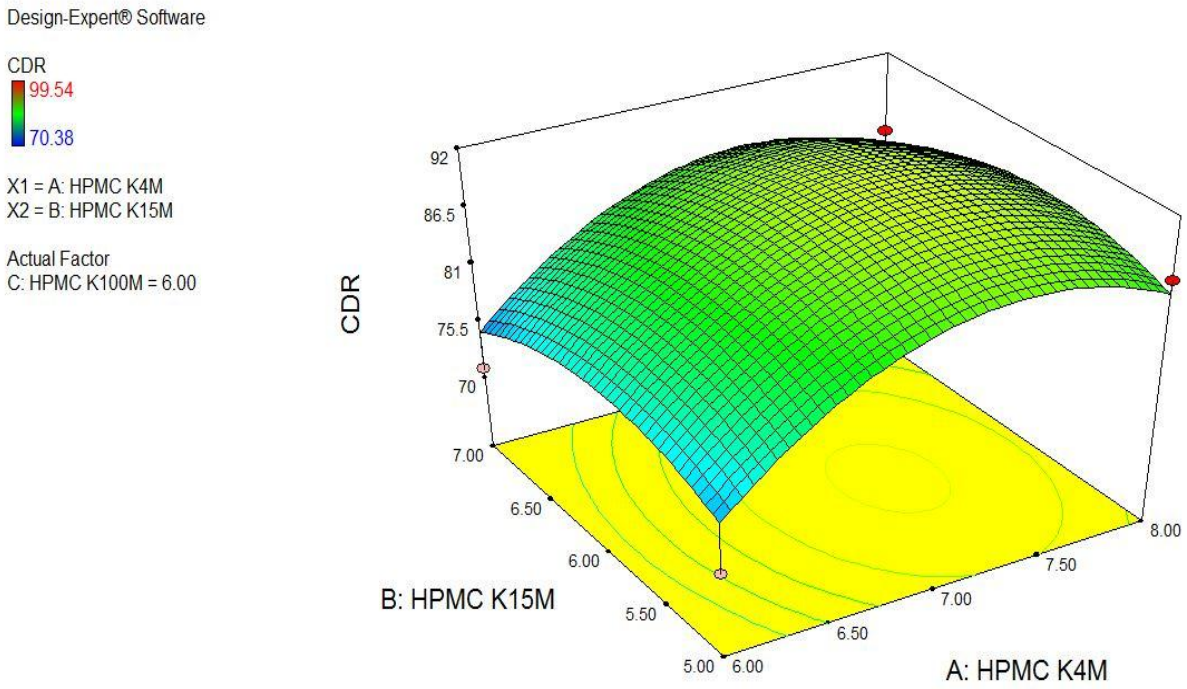

Figure 6: Response surface plot showing the influence of amount of polymer on the release profile of lamivudine for % Cumulative Drug Release.

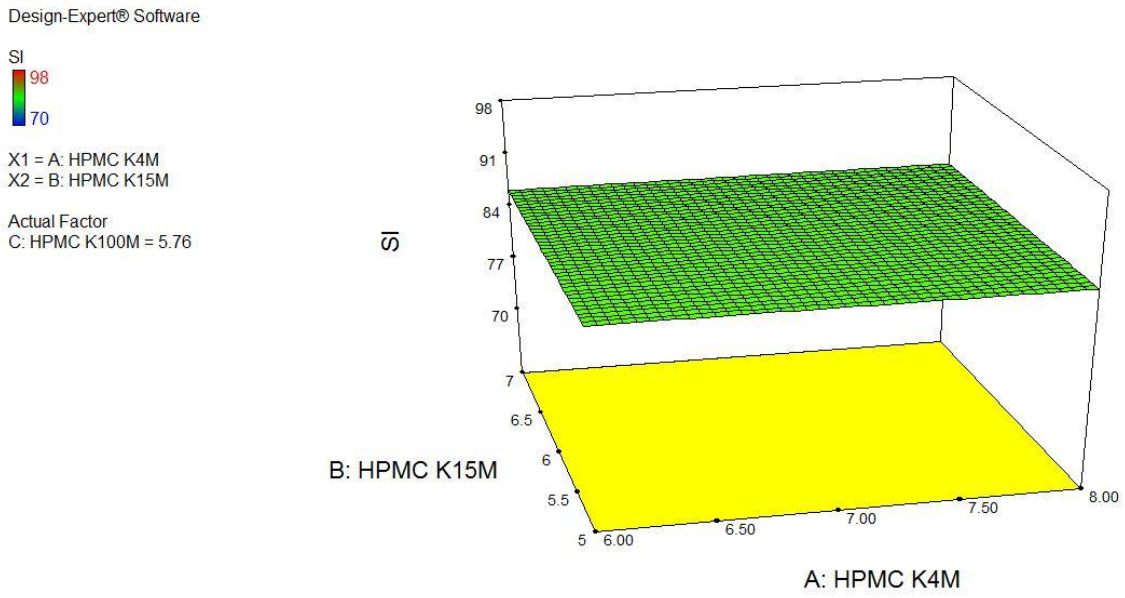

Figure 7: Response surface plot showing the influence of amount of polymer on Swelling Index of lamivudine

Characterization

FT-IR:

Overall there was no alteration in peaks of Lamivudine pure drug (**Figure 8**) and optimized formulation (**Figure 10**), suggesting that there was no interaction between drug & excipients. FT-IR spectrum of pure drug and other polymers are shown in (**Figure 9**). 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.

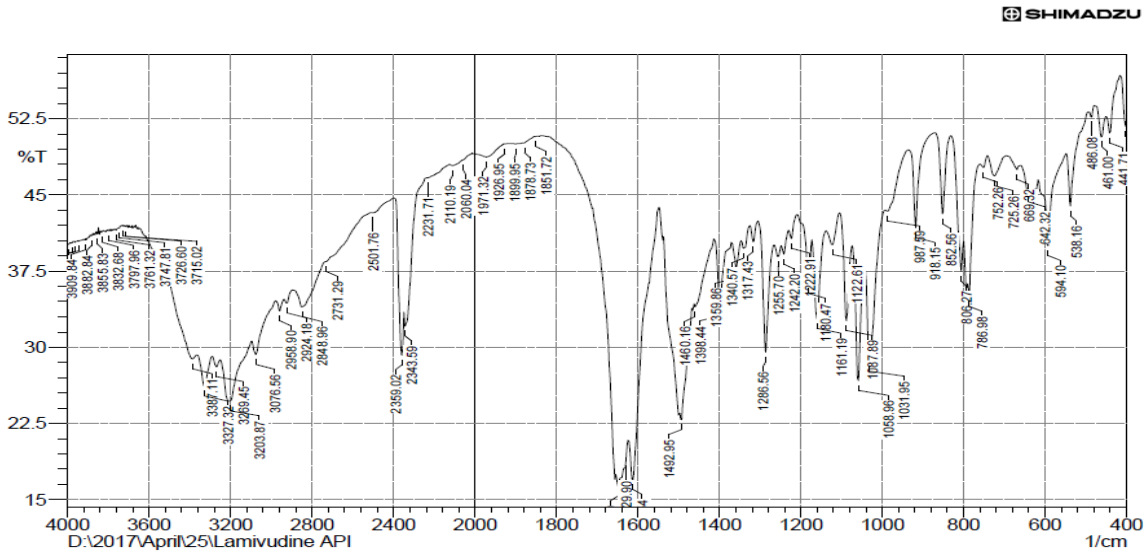

Figure 8: FT-IR spectrum of pure drug Lamivudine

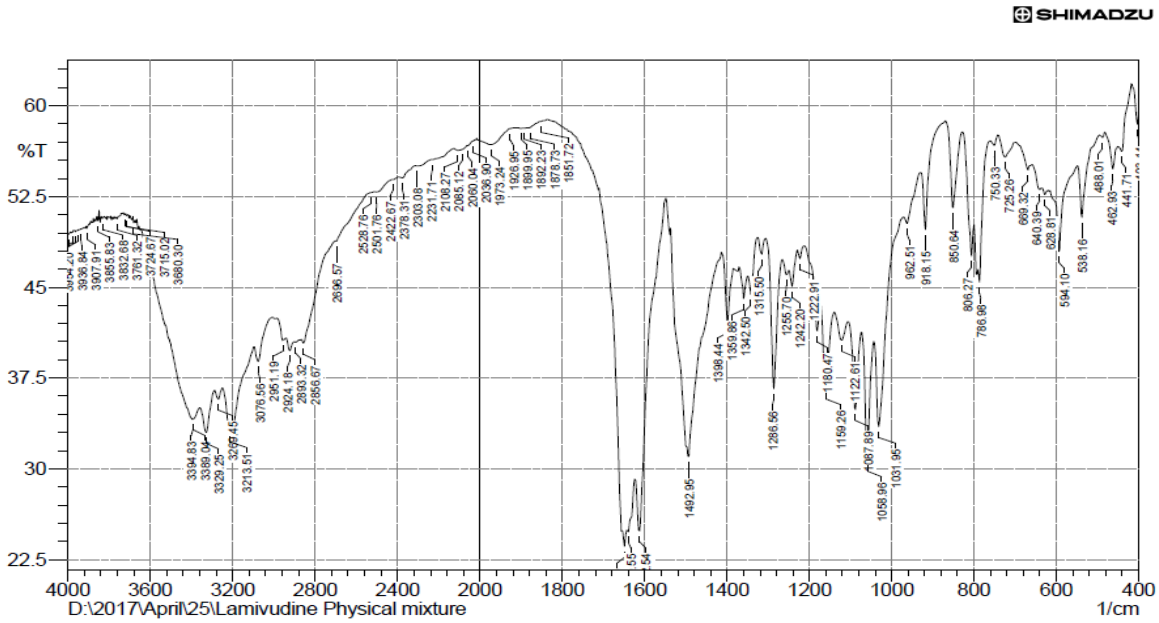

Figure 9: FT-IR spectrum of pure drug and other polymers

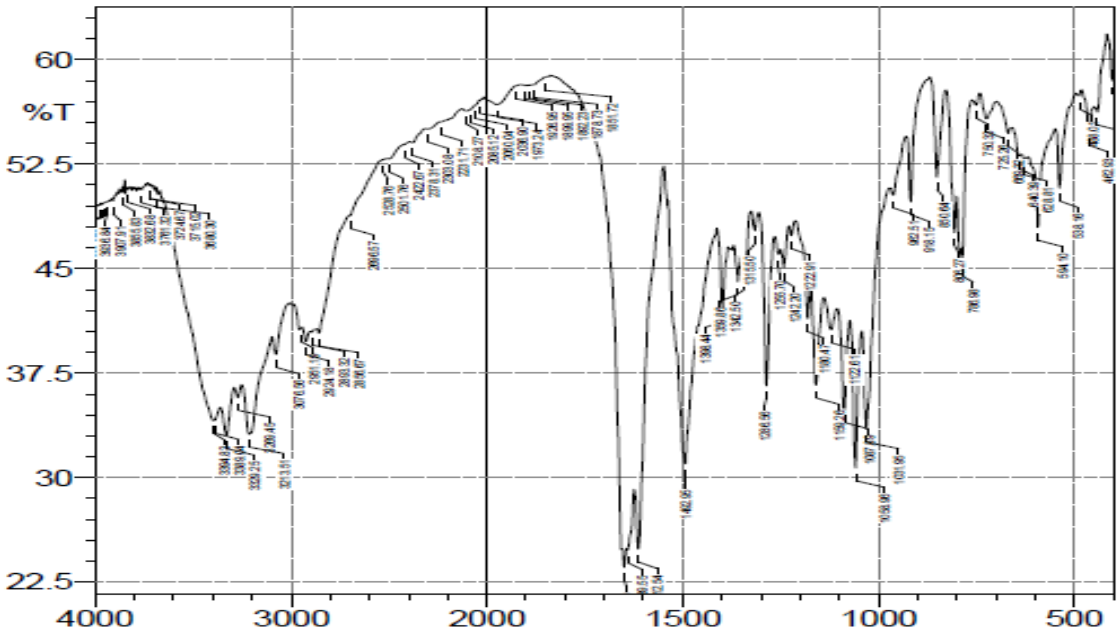

Figure 10: FT-IR spectrum of optimized formulation HF23

DSC studies:

DSC was used to detect interaction between Lamivudine and excipients. The thermogram of Lamivudine exhibited a sharp endotherm melting point at 161^{0}C. The thermo gram of optimized formulation of Entacapone exhibited a sharp endotherm melting point at 163 ^{0}C.The DSC thermo gram retained properties of Lamivudine, as well as polymer properties. There is no considerable

change observed in melting endotherm of drug in optimized formulation (**Figure 11)**. It indicates that there is no interaction between drug & excipients used in the formulation.

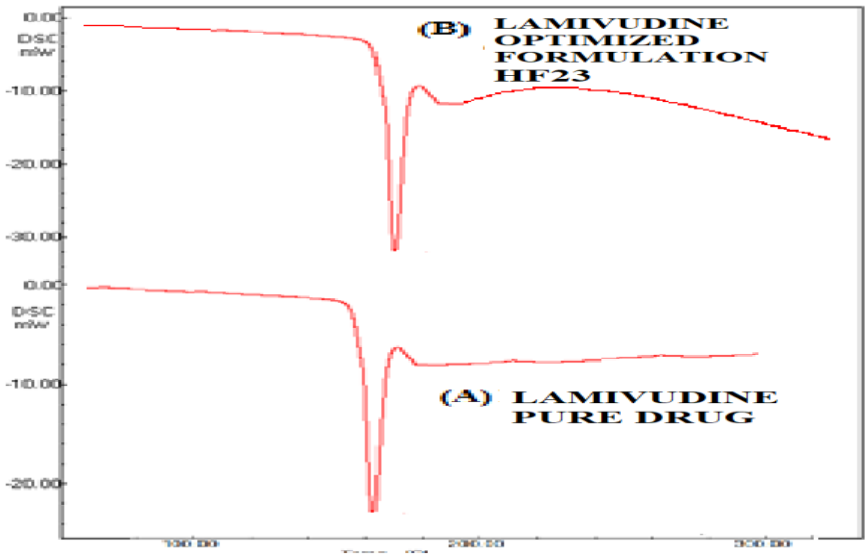

Figure 11: DSC thermogram of Entacapone pure drug (A) and optimized formulatin HF23 (B)

SEM studies:

SEM further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized formulation (HF23). Initially, tablet matrix showed swelling with pore formation that is clearly visible from SEM image. At the end of 24 h, the matrix was intact and pores had formed through it. SEM images also show the formation of gel structure indicating swelling and pore formation on the tablet surface (**Figure 12**).

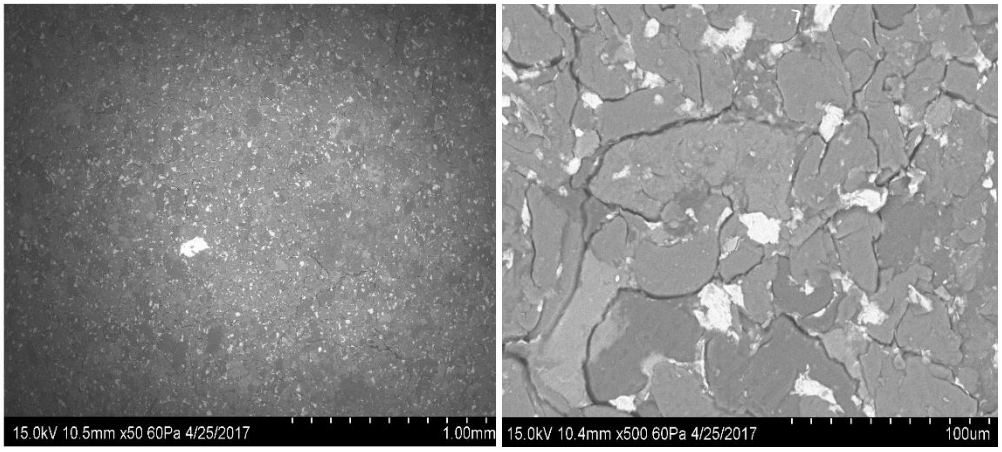

Figure 12: SEM studies for optimized HF23

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.

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 order 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. The release profile of the optimized formulation (HF23) was described by the Zero-order and Higuchi model. The results indicate that the approach used could lead to a successful development of a extended release formulation of the drug. These results also demonstrated the suitability of three-layered tablet formulation of Lamivudine to provide controlled release for prolonged period of time and improved linearity for Lamivudine in comparison to marketed product in the effective management of AIDS with patient compliance.

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