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Original Article

GASTRORETENTIVE DRUG DELIVERY SYSTEM OF LAMOTRIGINE: *IN VIVO* EVALUATION

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ABSTARCT

Objective: The aim of this study was to develop intragastric bilayer floating tablets of an anti-convulsant drug Lamotrigine using simple and convenient methods in an attempt to provide extended release profile with the floating efficiency.

Methods: Detailed Drug - excipient compatibility studies were performed at different temperature and humidity conditions using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). The floating bilayer tablets were prepared using Direct compression (DC). HPMC K100M, Ethyl cellulose and sodium alginate were used for extending the drug release. The polymer contents were optimized using factorial design. In-vivo gastroretention studies were performed in fasted rabbit.

Results: The floating tablets were found to be having acceptable hardness and friability. 99% dissolution of the final optimized batch was achieved up to 24 hrs. The tablets were found to be floating for 24 hrs in rabbit.

Conclusion: It is concluded that Lamotrigine can be given for extended release profile. This study has solved the problem of alkaline instability of Lamotrigine and has a great industry prospect.

Keywords: Lamotrigine, Bilayer tablet, Sodium alginate, 2^3 Factorial Design, Gastroretention.

INTRODUCTION

The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [1].

Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To solve these problems, floating drug delivery systems (FDDS) are very popular. They have a lower density than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating in the gastric content, the drug is released slowly from the system at a desired rate.

Lamotrigine, an antiepileptic agent, belonging to phenyltriazine class, is used as a monotherapy and as an adjunct with other antiepileptic agents for the treatment of partial seizures and primary and secondary generalized tonic – clonic seizures. It is also used for seizures associated with the Lennox – Gastut syndrome [2,3].

It inhibits sodium currents by selectively binding to the sodium channel and subsequently suppresses the release of the excitatory amino acid, glutamate. The conventional marketed IR tablets are administered once, twice, or three times daily. The peak plasma concentration of the drug is 1.4 to 4.8 hours following oral administration. The drawback in conventional tablets is that fluctuation in the level of plasma drug concentration which leads to inability to maintain appropriate therapeutic level which results in adverse events occurring in patients or alternatively the rate of increase in plasma concentration in the initial stages before the peak plasma concentration is achieved [2,3]. Also, the drug is unstable in the alkaline pH of the small intestine and has absorption window in the stomach [4]. Hence, FDDS of Lamotrigine will solve the problem of alkaline instability in stomach.

MATERIALS AND METHODS

Chemicals

Hydroxypropyl methyl cellulose (HPMC) K100M CR, Ethyl cellulose 10 and Sodium alginate were kindly supplied by Watson Pharma Pvt. Ltd., Ambernath. Lamotrigine was obtained as gift sample from Watson Pharma Pvt. Ltd. India. Remaining all the excipients and materials used were also provided by Watson Pharma Pvt. Ltd. The reagents used were of analytical grades.

Drug - Excipient compatibility study

The drug - excipients mixtures were kept at different temperature and humidity conditions like 25°C/60% RH, 40°C/75% RH and 50°C for 1 months. The study was carried out by using KBr pellet method. The scans of samples were compared with the FTIR scans of samples taken initially and that of Placebo.

Preparation of floating matrix tablets

The bilayer floating tablets were prepared by direct compression technique. All materials were sifted through 30# except magnesium stearate. The effervescent mixture and the drug-polymer mixture were weighed separately in order to avoid any contamination. The individual powder mixtures were blended in a suitable octagonal blender for 30 minutes. These powder blends were then further blended with magnesium stearate for not more than 5 minutes. The effervescent mixture was compressed first and evaluated for desirable floating with placebo layer. The finalized composition was then incorporated into the drug mixture and the final characteristics were observed. The bilayer tablets were punched on multi – punch compression machine (Cadmach Machinery Limited, Ahmadabad). The details of the floating layer batches and extended release batches are given in table 1 and 2 respectively.

Analysis of drug

Determination of analytical wavelength

A standard stock solution of 10 µg/mL of Lamotrigine was prepared. This solution was scanned between 200 - 400 nm to determine the λmax using 0.01 N HCl as blank in UV Spectrophotometer (Shimadzu

1800). The λmax was found to be 269.8 nm which was taken as the analytical wavelength.

Specificity

The specificity was checked by dissolving 536 mg of placebo in 900 mL of 0.01 N HCl and sonicated for 30 minutes. The solution was then filtered using Whatmann filter paper and the UV absorbance was taken at λmax of 269.8 nm using 0.01 N HCl as blank. The method is found to be specific as no interference from the placebo is observed.

Linearity

Appropriate aliquots were withdrawn from the standard stock solution into different volumetric flasks and diluted with water so as to prepare the solutions of 5, 10, 20, 30 and 40 µg/mL The absorbances of these solutions were taken at λmax of 269.8 nm using 0.01 N HCl as blank.

Evaluation of Granules

The prepared granules were evaluated for angle of repose, bulk density, Compressibility index and Hausner's ratio [5].

Evaluation of floating tablets

The tablets were evaluated for Uniformity of weight, tablet dimension, Hardness [6], Friability test [7] and weight variation test [8].

In vitro buoyancy studies [8]

The time between introduction of dosage form and its buoyancy on simulated gastric fluid, pH 1.2 and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT).

Determination of Swelling index [9]

The swelling index of tablets was determined in 0.01 N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 hr. The swelling index, expressed as a percentage, and was calculated from the following equation:

$$\text{Swelling Index} = \frac{\text{(Weight of tablet at time t – Initial weight of tablet)}}{\text{Initial weight of tablet}} \times 100$$

Table 1: Composition of floating layer batches

Batch No.	FL1	FL2	FL3	FL4	FL5
Floating layer					
HPMC K100M	120	120	120	120	120
Citric acid anhydrous	40	20	15	10	5
Sodium Bicarbonate	40	120	100	80	50
FD & C Brilliant Blue I	0.5	0.6	0.6	0.5	0.4
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5
Total (Floating layer)	201	261.1	236.1	211	176
Extended release layer (placebo)					
Lactose SD	239.4	239.4	239.4	239.4	239.4
Ethyl cellulose 10	9	9	9	9	9
HPMC K100M	60	60	60	60	60
Magnesium Stearate	0.6	0.6	0.6	0.6	0.6
Total (Extended release)	309	309	309	309	309
Total	**510**	**570.10**	**545.10**	**520**	**485**

Table 2: Composition of Extended release batches

Batch no.	LH1	LH2	LH3	LM1	LM2	LM3	LM4	LS1	LS2	LS3
Floating layer										
HPMC K100M	120	120	120	120	120	120	120	120	120	120
Citric acid anhydrous	15	15	15	15	15	15	15	15	15	15
Sodium Bicarbonate	100	100	100	100	100	100	100	100	100	100
FD & C Brilliant Blue I	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Total (Floating layer)	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**	**236.6**
Extended release layer										
Lamotrigine	50	50	50	50	50	50	50	50	50	50
Lactose SD	204.4	189.4	174.4	179.5	149.5	146.5	176.5	167.5	116.5	91.5
HPMC K100M	45	60	75	60	90	90	60	60	90	90
Ethyl cellulose 10	-	-	-	9	9	12	12	12	12	12
Sodium Alginate	-	-	-	-	-	-	-	9	30	55
Magnesium Stearate	0.6	0.6	0.6	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (Extended release)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Total	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**	**536.6**

Test for Content uniformity

Tablet containing 50 mg of drug was dissolved in 50 ml of methanol taken in volumetric flask.

The solution was kept under sonication for few minutes. The solution was filtered, 2 ml of filtrate was taken in 100 ml of volumetric flask and diluted up to mark with methanol and analyzed spectrophotometrically at 307 nm. The concentration of Lamotrigine in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 50 mg per tablet.

In-vitro dissolution Study

The release rate of drug from floating tablets were determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.01 N hydrochloric acid, at 37 ± 0.5°C and 50 rpm [10]. A 5 ml

sample was withdrawn from the dissolution apparatus at specific time intervals and sink condition was maintained. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.01 N HCl. Absorbance of these solutions was measured at 269.8 nm using a UV-visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile. All the studies were performed in triplicate.

In vitro drug release kinetic studies

In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Korsemeyer - Peppas model, Higuchi square root model and Hixon-Crowell model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS excel statistical function.

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) of intact tablet of final formulation was taken before and after dissolution of 24 hours. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and floating.

In – vivo gastroretention study [11]

Barium sulphate loaded tablets were prepared by replacing drug with barium sulphate. Healthy rabbit weighing approximately 2.3 Kg was used to assess *in vivo* floating behaviour. Ethical clearance for the handling of experimental animals was obtained from the institutional animal ethical committee (IAEC) of the institute. The animal was fasted for 12 hrs. The rabbit was made to swallow barium sulphate loaded tablets with 30 ml of water. During the experiment, rabbit was not allowed to eat but water was provided. At predetermined time intervals, the radiograph of abdomen was taken using an X-ray machine.

Factorial design and optimization [12]

A 2^3 Factorial design was used in the present study. In this design, 3 factors were evaluated each at 2 levels and the experimental trials were carried out with all possible 8 combinations. The quantity of Ethyl cellulose 10 (A), HPMC K100M CR (B), and Sodium alginate (C) were taken as independent factors (table 3) and % Drug release at 6 hrs (Y_6), 12 hrs (Y_{12}), 24 hrs (Y_{24}) and time required to for 60% drug dissolution (t60%) were selected as dependent factors.

The resulting data were fitted into Design Expert version 8 and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of HPMC K100M CR and Ethyl cellulose 10 on dependent variables.

Dissolution of Lamictal XR

The extended release dosage form of Lamotrigine is available as 'Lamictal XR' marketed by GlaxoSmithKline. It is the only available extended release tablet of Lamotrigine. Hence, the multimedia dissolution of Lamictal XR was carried out in 0.01 N HCl for 2 hrs and then in USP pH 6.8 phosphate buffer with 0.5% SLS as OGD media specified by US FDA. It was done to observe a comparative scenario between the dissolution profile of Lamictal XR and the optimized gastroretentive batch with respect to time.

Table 3: Codes for Factorial Design

Sr. No.	Independent factors	Level 1	Level 2
1	Ethyl cellulose 10	-1 (3%)	+1 (4%)
2	HPMC K100M	-1 (20%)	+1 (30%)
3	Sodium alginate	-1 (3%)	+1 (10%)

Table 4: Observations of Pre – compressional parameters of all the batches

Formulation	Angle of repose (°)	Bulk density (g/ml)	Tap density (g/ml)	Compressibility index (%)	Hausner's ratio
LH1	27.75	0.38	0.45	19	1.20
LH2	26.54	0.39	0.44	18	1.25
LH3	26.49	0.39	0.48	16	1.19
LM1	28.24	0.39	0.42	17	1.23
LM2	27.54	0.38	0.43	19	1.19
LM3	27.51	0.40	0.46	18	1.21
LM4	28.04	0.39	0.44	19	1.18
LS1	29.58	0.39	0.42	18	1.20
LS2	27.61	0.34	0.45	17	1.24
LS3	28.86	0.40	0.46	19	1.21

Table 5: Formulation characteristics of Core tablets

Parameters	LH1	LH2	LH3	LM1	LM2	LM3	LM4	LS1	LS2	LS3
Average Weight (mg)	536.8	535.1	537.5	537.3	538.6	537.2	536.1	538.8	539.7	537.4
Longitudinal Diameter (mm)	14	14	14	14	14	14	14	14	14	14
Thickness (mm)	5.75	5.80	5.80	5.76	5.75	5.82	5.75	5.70	5.72	5.71
Hardness (Kp)	7-9	7-9	7-9	7-9	7-9	7-9	7-9	7-9	7-9	7-9
Friability (% w/w)	0.42	0.43	0.45	0.42	0.43	0.45	0.40	0.43	0.45	0.42
Floating Lag Time (minutes)	5	6	5	4	6	5	6	7	6	6
Floating Time (hours)	24	24	24	24	24	24	24	24	24	24
Swelling index (%)	280.65	300.38	261.87	249.31	258.16	252.14	256.81	189.36	190.64	192.78
Assay (%)	99.8	100.2	99.7	99.3	99.8	100.6	98.8	100.4	100.2	99.8

RESULTS AND DISCUSSIONS

Drug – Excipient Compatibility studies

The FTIR scans of pure drug, final formulation at different conditions and placebo were compared (Fig. 1). The study concluded that there was no incompatibility between Lamotrigine and any of the excipients. This was confirmed by the DSC scans (Fig 2).

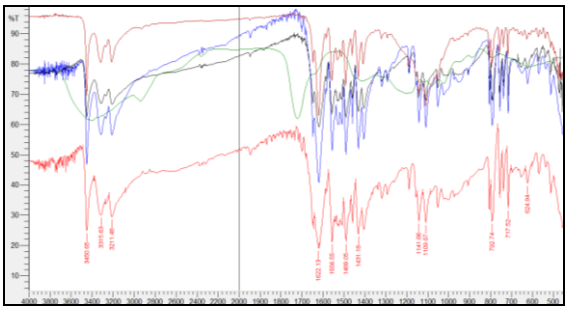


Fig. 1: Overlay FT-IR scans of Final tablet mixture at various conditions, pure drug (----) and placebo (----)

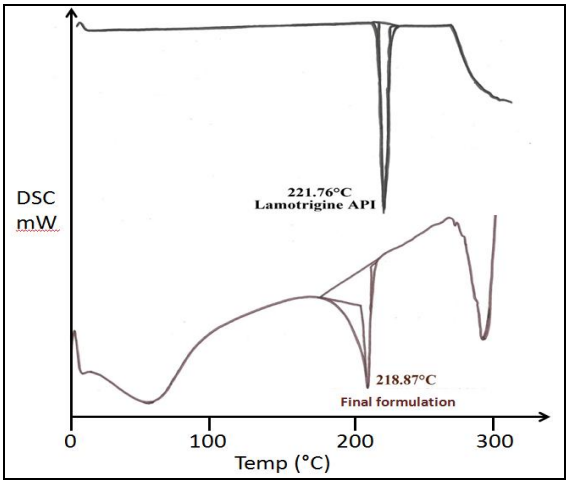


Fig. 2: DSC scans of Lamotrigine and Final formulation

The Pre – compressional parameters of the granular blend and Formulation characteristics of the tablets are given in the table 4 and 5

Table 6: Regression Analysis of different models for final formulation LS1

Coefficient of correlation (R^2) values						
Zero order model	**First order model**	**Korsemeyer-Peppas model**		**Higuchi model**	**Hixon-Crowell model**	**Proposed mechanism of release**
		(R^2)	**N**			
0.9985	0.9653	0.8923	0.4723	0.9455	0.8805	Zero order release

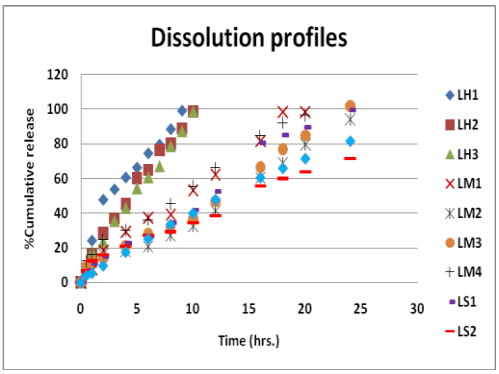
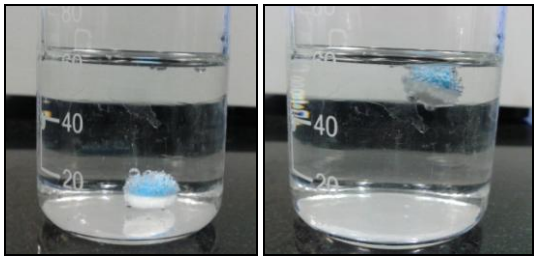


Fig. 3: Dissolution profiles of all the batches



(a) **(b)**

Fig. 4: Images of floating tablet at 0 min (a) and at 7 mins(b)

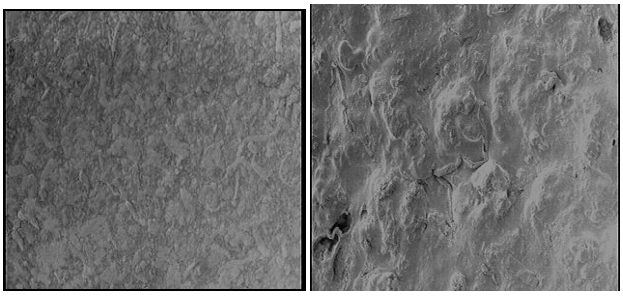
Mathematical modeling of kinetic release

The data analysis was carried out for the final optimized batch LS1 by fitting the data into different models and the results are given in Table 6. It was concluded that the formulation followed zero order model showing regression of 0.9985.

Scanning Electron Microscopy

The SEM images of the tablet were taken before and after dissolution. Fig. 5a showed intact surface without any perforations, channels, or troughs. After dissolution, the pores had formed throughout the matrix indicating, formation of a network in the swollen polymer through which the drug diffused to the surrounding medium (Fig 5b).

Thus, SEM study confirmed the diffusion mechanisms (because of swelling) along with zero order release rate to be operative during drug release from the optimized formulation LS1.



(a) **(b)**

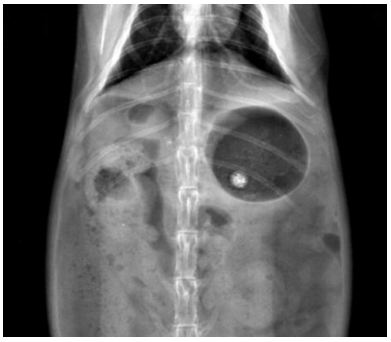
Fig. 5: SEM of Lamotrigine tablet surface before (a) and after the dissolution (b)

In – vivo gastroretention study

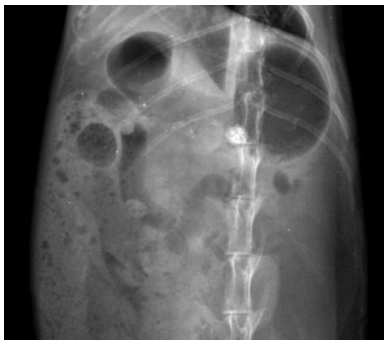
The X – Ray radiographs of rabbit were taken at 1 hr, 12 hr and 24 hr. The tablet was found to be floating up to 24 hrs (Fig. 6).

Factorial designs

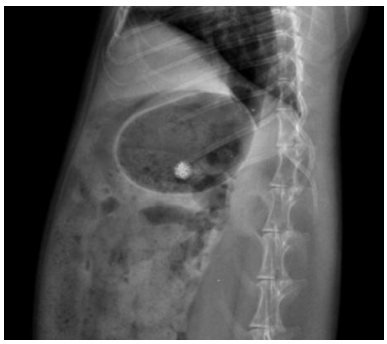
For the 2^3 Factorial design, the responses of formulation prepared by factorial designs are indicated in table 7.



(a)



(b)



(c)

Fig. 6: X – Ray radiographs of rabbit at 1 hr (a), 12 hr (b) and 24 hr (c)

The data clearly shows that the % release at 6 hrs, % release at 12 hrs, % release at 24 hrs and t60% are dependent on the independent variables chosen. This can be seen in the contour plot of % release at 6 hrs, 12 hrs and 24 hrs. The fitted equation relating the response % release at 6 hrs, 12 hrs, 24 hrs and t60% to the transformed factors are,

Drug release 6 hours = + 27.77- 1.51*A + 1.34*B + 2.36*C – 1.87*AB – 1.30*AC + 0.91*BC

Adjusted R-Squared = 0.9976Predicted R-Squared = 0.9778

Drug release 12 hours = + 52.41 – 2.65*A - 1.79*B + 1.14*C – 3.42*AB – 3.81*AC – 1.42*BC

Adjusted R-Squared = 0.9985Predicted R-Squared = 0.9986

Drug release 24 hours = + 90.00 –1.61*A – 3.17*B – 1.15*C – 3.94*AB – 3.71*AC – 0.69*BC

Adjusted R-Squared = 0.9968Predicted R-Squared = 0.9708

Time required for 60% drug release = + 13.21 + 1.26*A + 0.44*B + 0.34*C + 1.14*AB

+ 0.49*AC + 0.26*BC

Adjusted R-Squared = 0.9972Predicted R-Squared = 0.9743

The fitted equations relate all the responses to the transformed factor. The polynomial equations can be used to draw conclusions after considering the sign and magnitude of the main effect signify the relative influence of each factor on the response. The p value of 0.0349 for % drug release at 6 hrs, 0.0271 for % drug release at 12 hrs, 0.0400 for % drug release at 24 hrs and 0.0376 for t60% indicates that the model is significant. The values of the correlation coefficient indicate a good fit. The data demonstrate that A, B and C affect the drug release. The contour plots show that as the amount of the A decreases, the % drug release increases. This shows that the amount of Ethyl cellulose has inverse relationship with the drug release. In case of t60%, as the polymer amount increases, the time required to release 60% of drug also increases. Normal probability plot of the residuals was a straight line and showed a normal distribution of the error.

Figures 7-10 show the plot of the percentage of A, B and C versus % release at 6 hrs, 12 hrs, 24 hrs and t60% respectively. The plot was drawn using Stat-Ease Design Expert 8.0.7.1. The data demonstrate that A, B and C affect the drug release at 6 hrs, 12 hrs, 24 hrs and t60%. The drug release from the system was found to be concentration independent. The lag time and total duration of floating was also found to be good. The batch LS1 was found to be releasing maximum amount of the drug, with following zero order release mechanism. The statistical optimization of above mentioned responses helps for the better understanding of concentration to be used for the three polymers. Hence, the formulation factors are statistically optimized.

Table 7: Responses of the factorial batches

Batch Code	Coded values			% release at 6 hrs (Y_6)	% release at 12 hrs (Y_{12})	% release at 24 hrs (Y_{24})	t60% (hrs)
	A	B	C				
D1	1	-1	1	27.77	40.56	75.59	17.1
D2	1	-1	-1	28.89	59.89	93.95	12.2
D3	1	1	-1	23.69	48.56	86.97	15.0
D4	-1	-1	-1	26.72	56.32	99.53	12.3
D5	-1	1	1	23.24	46.97	87.72	13.1
D6	-1	-1	1	36.99	60.13	94.40	11.4
D7	-1	1	-1	27.99	53.25	90.36	11.1
D8	1	1	1	26.86	53.63	91.47	13.5

Dissolution of Lamictal XR: The dissolution profile shows that the Lamictal XR was releasing up to 18 hrs in 0.01 N HCl while the final formulation releases up to 24 hrs in the same media. The complete drug is not released in the USP pH 6.8 phosphate buffer. Thus, the final formulation was found to be in correlation with the Lamictal XR in 0.01 N HCl (Fig. 11).

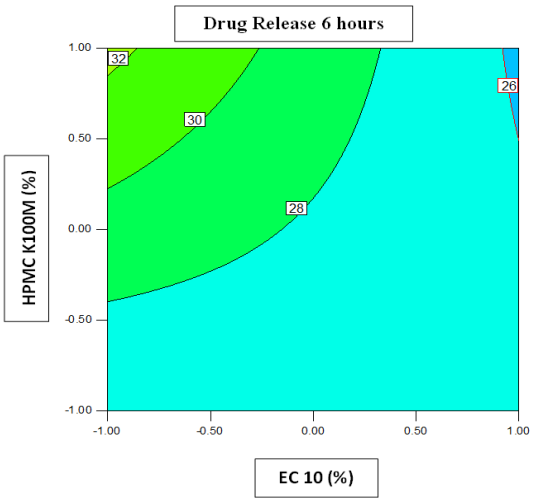


Fig. 7: Contour plot for Y_6

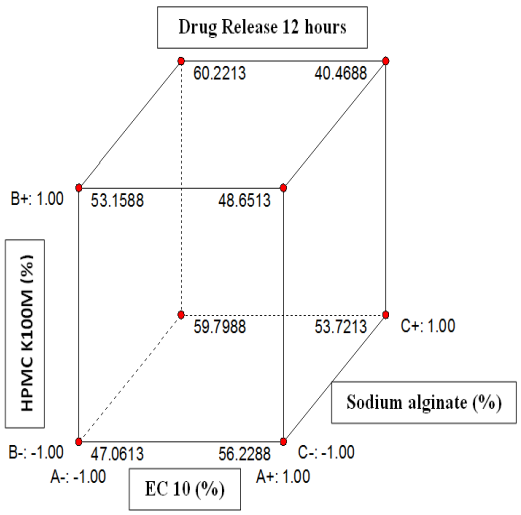


Fig. 8: 3D Scatter plot for Y_{12}

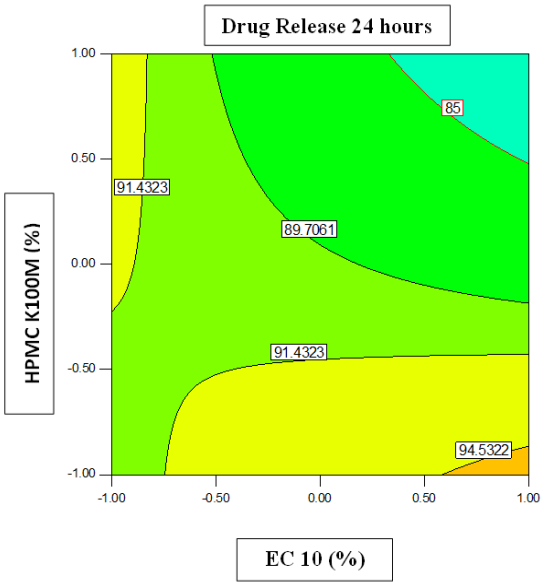


Fig. 9: Contour plot for Y_{24}

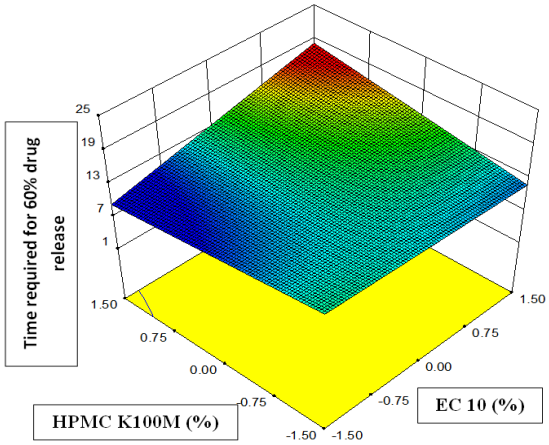


Fig. 10: 3D - Surface plot of t60%

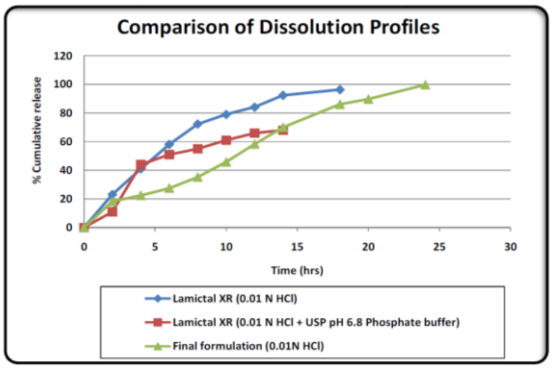


Fig. 11: Comparative dissolution profile of Lamictal XR and final formulation

CONCLUSION

The objective of this study was to formulate a bilayer floating tablet of Lamotrigine with sufficient floating time and desired drug release. Batch LS1 was found to be releasing 99% at the end of 24 hrs Hence, this batch is taken as the optimized batch having desired properties. The bilayer tablet was found to have excellent physical characters and good matrix integrity. Hence the formulation LS1 fulfils the objective of the study.

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