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DESIGN OF A GASTRORETENTIVE SYSTEM OF AN ANTI-EPILEPTIC DRUG USING FACTORIAL DESIGN

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ABSTRACT

Introduction: Gastroretention of drugs with problems like absorption window in stomach or upper part of duodenum, instability in alkaline pH, short half-life has proven to be more therapeutically efficacious because of increased retention time in stomach. Materials and methods: Detailed Drug-excipient compatibility studies were performed at different temperature and humidity conditions. Swellable polymers like HPMC and Ethyl cellulose were used for preparation of matrix tablets with effervescent materials like sodium bicarbonate and Citric acid anhydrous. Direct compression was used for preparation of matrix tablets. 2^2 Factorial Design was utilized to optimize the polymer concentration. Also, In-vivo Gastroretention study has been performed in rabbit. Result and discussion: Carbopol 971P and Citric acid monohydrate were found to be incompatible with Lamotrigine. The quantities of HPMC and Ethyl cellulose were optimized. The tablet was found to be sufficiently floating in rabbit. Conclusion: The matrix tablets with sufficient floating time and sustained release upto 24 hrs were successfully prepared.

Keywords: Matrix tablets, Swelling Index, Carbopol 971P, Factorial Design.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed [1, 2]. 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 (Rouge et al., 1996). To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as, floating drug dosage systems (FDDS) (Baumgarter et al., 2000; Bulgarelli et al., 2000; Timmermans and Moes, 1994), swelling or expanding systems (Chen and Park, 2000), mucoadhesive systems (Akiyama et al., 1998; Chickering et al., 1997), modified-shape systems (Kedzierewicz et al., 1999), high-density systems (Rouge et al., 1998), and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used [2, 3].

FDDS 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. This results in increased gastric retention time and reduced fluctuation in plasma drug concentration [1]. While the system is floating in the gastric content, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds) (Baumgarter et al., 2000; Chen and Park, 2000, Johnson et al., 1997), highly swellable hydrocolloids and light mineral oils (Desai and Bolton, 1993; Murata et al., 2000). Multiple unit systems (Iannuccelli et al., 1998; Ichikawa et al., 1991; Rouge et al., 1998) and hollow systems prepared by solvent evaporation methods (El-Kamel et al., 2001; Kawashima et al., 1992; Thanoo et al., 1993) have also been developed [3, 4].

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 [5, 6]. It exerts its anticonvulsant effect by stabilizing presynaptic neuronal membranes. It inhibits sodium currents by selectively binding to the sodium channel and subsequently suppresses the release of the excitatory amino acid, glutamate. Various tablet formulations of Lamotrigine have been approved for marketing, for instance, conventional compressed instant release (IR) tablets comprising 25 mg, 50 mg, 100 mg, 150 mg or 200 mg of active ingredient [5]. These 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 [5, 7, 8]. Also, the drug is unstable in the alkaline pH of the small intestine and has absorption window in the stomach [9]. Hence, by formulating Lamotrigine as FDDS, the drug is completely absorbed from the stomach and its instability in small intestine is prevented.

MATERIALS AND METHODS

Materials

Hydroxypropyl methyl cellulose (HPMC) K100M CR and Ethyl cellulose 10 Premium (Colorcon, Goa) were kindly supplied by Watson Pharma Pvt. Ltd., Ambernath. Lamotrigine (Jubilant Organosys, Germany) was also 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.

Methods

Preformulation studies

Drug – Excipient compatibility studies

FTIR studies: The detailed Drug : Excipient compatibility studies were done by keeping the Drug – Excipient mixtures at different temperature and humidity conditions like 25°C/60% RH, 40°C/75% RH, 50°C and controlled samples at 2°- 8° for 1 months. A variety of excipients were kept with the drug to find out compatible excipients and then to use them instead of incompatible excipients. The samples were analysed till 1 month. The compatibility testing was carried out by using KBr pellet method. The scans of samples were compared with the IR scans of samples taken initially and that of Placebo. The sample details are given in Table I.

Table I: The sample details of Drug : Excipients compatibility study

Sr. No.	Sample Name
1	Pure Drug
2	Drug : HPMC K4M
3	Drug : HPMC K15M
4	Drug : HPMC K100M
5	Drug : Ethyl Cellulose 10
6	Drug : Aerosil

7	Drug : Talc
8	Drug : Microcrystalline Cellulose PH 102 (MCC PH 102)
9	Drug : FD & C Brilliant blue II
10	Drug : Mannitol
11	Drug : Polyvinylpyrrolidone (PVP K90)
12	Drug : Sodium bicarbonate
13	Drug : Citric acid monohydrate
14	Drug : Citric acid anhydrous
15	Drug : Lactose Spray dried (SD)
16	Drug : Magnesium stearate
17	Drug : Carbopol 971P
18	Placebo

DSC Studies [10]: DSC shows the fast evaluation of possible incompatibilities, because it shows the change in appearance, shift of melting endotherms and exotherms and variations in corresponding enthalpies of reaction. The thermal analysis was performed on Shimadzu DSC instrument in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature of 30° C to 200° C.

pH – dependent solubility studies [11]**:** excess amount of drug was dissolved in the 100 ml of each of the buffers and kept on orbital shaker for 24 hrs at 37°C at 150 rpm. The buffers used are pH 1, pH 2, pH 3, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, pH 7.5 phosphate buffer and water. The solutions are then filtered and absorbances are taken at 269.8 nm with suitable dilutions with water.

Solution stability [12]**:** The solution stability was done to check the stability of drug in acidic pH for 24 hrs. The standard solution of Lamotrigine in 0.01N HCl was prepared and its absorbance was taken initially and at 24 hrs. The solutions were kept at room temperature and at 37°C in volumetric flask.

PREPARATION OF FLOATING MATRIX TABLETS

Preparation of floating matrix tablets was done by direct compression technique. All materials were sifted through 30# except magnesium stearate. The drug was mixed with the polymers and the effervescent mixture as per table II. The powder blend was then blended in

a suitable octagonal blender for 20 minutes. The powder blend was then further blended with magnesium stearate for not more than 5 minutes. The tablets were punched on multi – punch compression machine (Cadmach Machinery Limited, Ahmedabad, India). The details of the formulation are given in Table II.

Table II: Composition of formulations

Ingredients	L1	L2	L3	L4
	Contents (mg/tab)			
Lamotrigine	50	50	50	50
Citric acid anhydrous	15	15	15	15
Sodium Bicarbonate	100	100	100	100
HPMC K100M	210	180	180	210
Ethyl Cellulose 10	9	9	12	12
Lactose SD	149.5	179.5	176.5	146.5
Magnesium stearate	2.5	2.5	2.5	2.5
Total Tablet weight	**536**	**536**	**536**	**536**

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 to 400 nm to determine the λ max using 0.01 N HCl as blank in UV Spectrophotometer (Shimadzu 1800). The λ max 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 λ max 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 λ max of 269.8 nm using 0.01N HCl as blank (Table III and Figure 1)

Table III: Linearity

Concentration (µg/mL)	Absorbance
5	0.1123
10	0.2329
20	0.4814
30	0.7208
40	0.9998

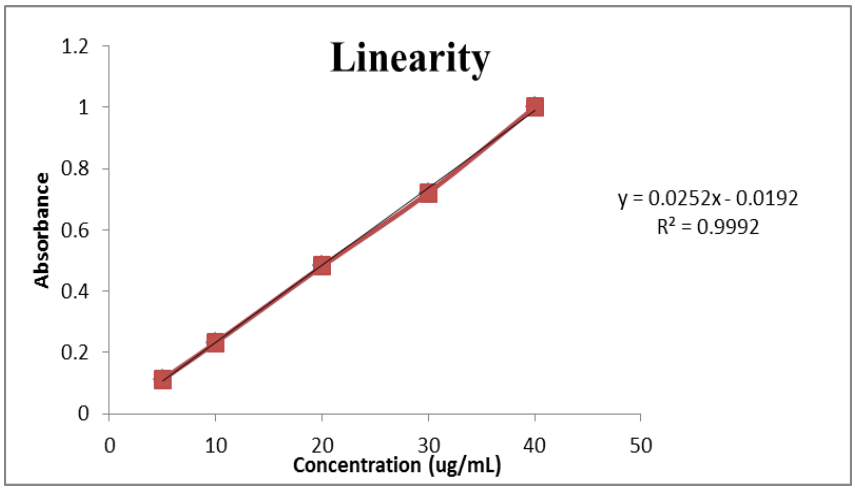


Figure 1: Linearity

EVALUATION OF GRANULES

The granules were prepared by direct compression and analysed for following tests:

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation 1:

$$\text{Tan } \theta = h/r \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where, h and r are the height and radius of the powder cone.

Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 20 gms of granules from each formulation was introduced into a

100 ml measuring cylinder. The cylinder was placed in the automatic Tapped density apparatus (Electrolab). After the initial volume was observed, the cylinder was tapped. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula (2) and (3).

LBD = weight of the powder/volume of the packing …… (2)

TBD = weight of the granules/tapped volume of the packing …… (3)

Compressibility Index: The compressibility index of the granules was determined by Carr's compressibility index.

Carr's compressibility index (%) = [(TBD-LBD) X100] / TBD …….. (4)

Hausner's Ratio [13]: Hausner's Ratio is an ease of index of powder flow. It is calculated by using the following formula:

Hausner's Ratio = Tapped Density/ Bulk Density…… (5)

EVALUATION OF FLOATING TABLETS

Uniformity of Weight [14]: Twenty tablets were selected randomly and the average weight was determined. The individual tablet was weighed and was compared to the average weight.

Tablet Dimension: Thickness and longitudinal diameter were measured using a calibrated digital vernier calliper (Aerospace). Three tablets of each formulation were picked randomly and thickness was measured individually. The tablets were examined under magnifying lens for the shape of the tablet.

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Dr. Scheulniger digital Hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability test [15]: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability (%F) was then calculated by

% Friability = (Initial weight – Final Weight)/ Initial Weight X 100…… (6)

% friability of tablets <1% were considered acceptable.

Weight variation Test [16]: Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of tablet by U.S. Pharmacopoeia (Table IV).

Table IV: Standard limit value in weight variation test

Average weight of Tablet	Percentage Deviation
130 mg or less	±10
>130mg and <324mg	±7.5
324mg or more	±5.0

In all formulations, the tablet weight is 536 mg. Hence ±5.0 maximum difference is allowed.

In vitro buoyancy studies [16]: 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 [17]: The swelling index of tablets was determined in 0.01N 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:

Swelling Index =

(Weight of tablet at time t – Initial Weight of tablet) / Initial Weight of tablet X 100 ... (7)

Test for Content Uniformity: Tablet containing 50 mg of drug is dissolved in 50 ml of Methanol taken in volumetric flask. The solution is 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 is 50 mg per tablet.

In-vitro Dissolution Study: The release rate of drug from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.01N hydrochloric acid, at 37 ± 0.5°C and 50 rpm [18]. A sample (5 ml) of the solution was withdrawn from the dissolution

apparatus at specific time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.01N hydrochloric acid. 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:** Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Korsmeyer - 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 formulation L2 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 [19]:** Barium sulphate loaded tablets were prepared by adopting the procedure as described before except using barium sulphate instead of drug. 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 hr. 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

2^2 Factorial Designs [20, 21, 22, 23]:

A 2^2 Factorial Design was used in the present study. In this design, 2 factors were evaluated each at 2 levels and the experimental trials were carried out with all possible 4 combinations. The quantity of HPMC K100M CR (X1) and Ethyl cellulose 10 (X2) were taken as independent factors (Table V) and % Drug release at 12 hrs, 24 hrs and time required to for 60% drug dissolution (t60%) were selected as dependent factors. The resulting data were

fitted into Stat Ease, Inc. (Minneapolis, MN) Design Expert 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of Methocel K100M CR and Ethyl cellulose 10 on dependent variables.

Table V: Codes for Factorial Design Table

Coded Values	Actual Values	
	X1 (mg)	X2 (mg)
-1	180	9
+1	210	12

RESULTS AND DISCUSSIONS

Preformulation studies

Drug – Excipient Compatibility Studies

FTIR Studies: The different drug – excipient mixtures showed the major peaks of Lamotrigine, except mixture of drug with Carbopol 971P and Citric acid monohydrate. The IR study concluded that there was no incompatibility between Lamotrigine and any of the excipients except Carbopol 971P and Citric acid monohydrate. The IR scans of Carbopol 971P and Citric acid monohydrate with Lamotrigine showed disappearance of the major peaks of drug, with shifting of some of the peaks. Incompatibility between Carbopol and Lamotrigine can be attributed to the complex formation between them [24]. The Overlay IR scans are provided from figure No. 2-11.

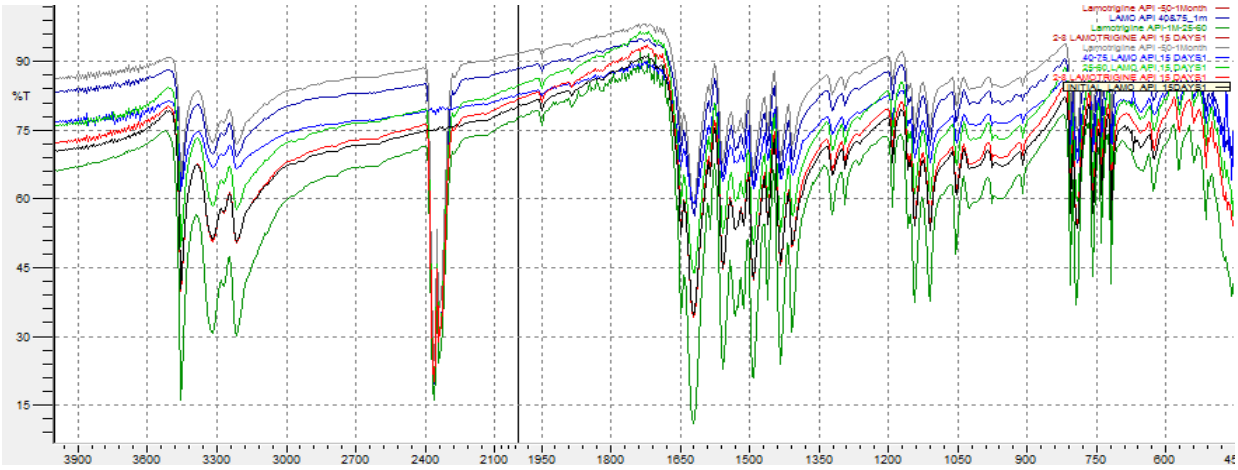


Figure 2: Overlay IR scan of Pure Drug at different temperature and Humidity conditions

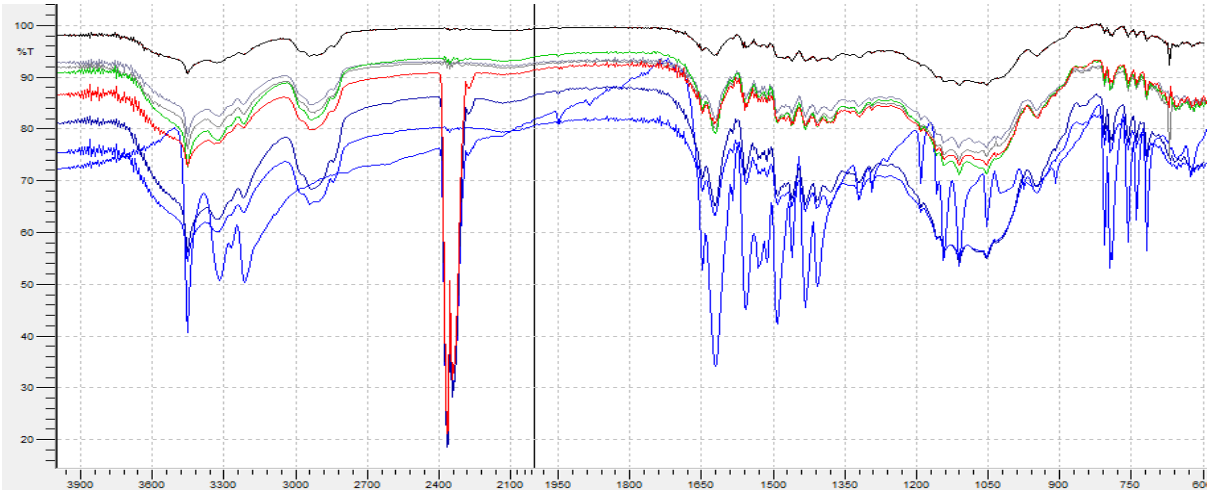


Figure 3: Overlay IR scan of Drug with Drug : HPMC K100M at different temperature and Humidity conditions

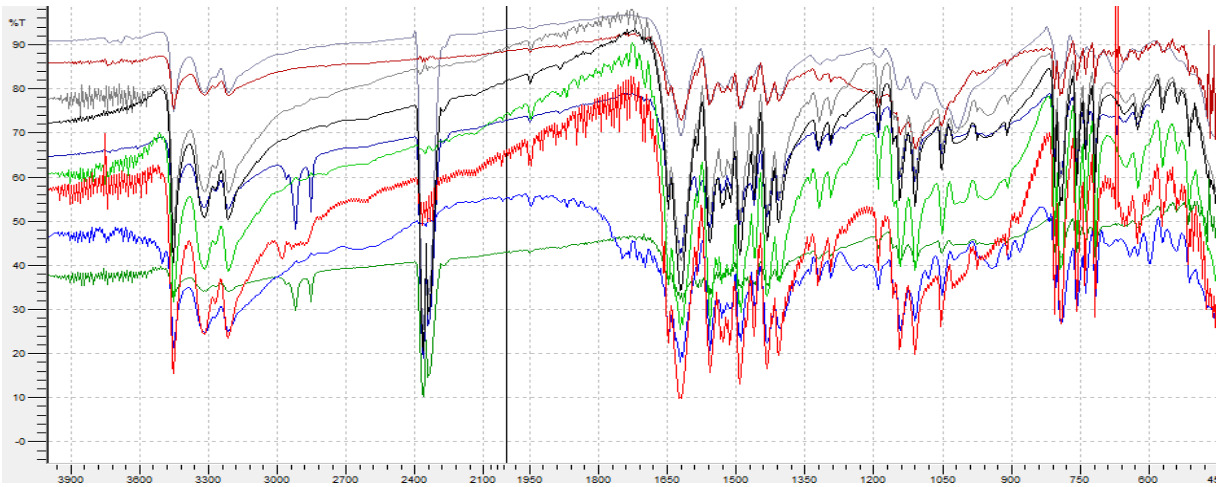


Figure 4: Overlay IR scan of Drug with Drug : Ethyl cellulose at different temperature and Humidity conditions

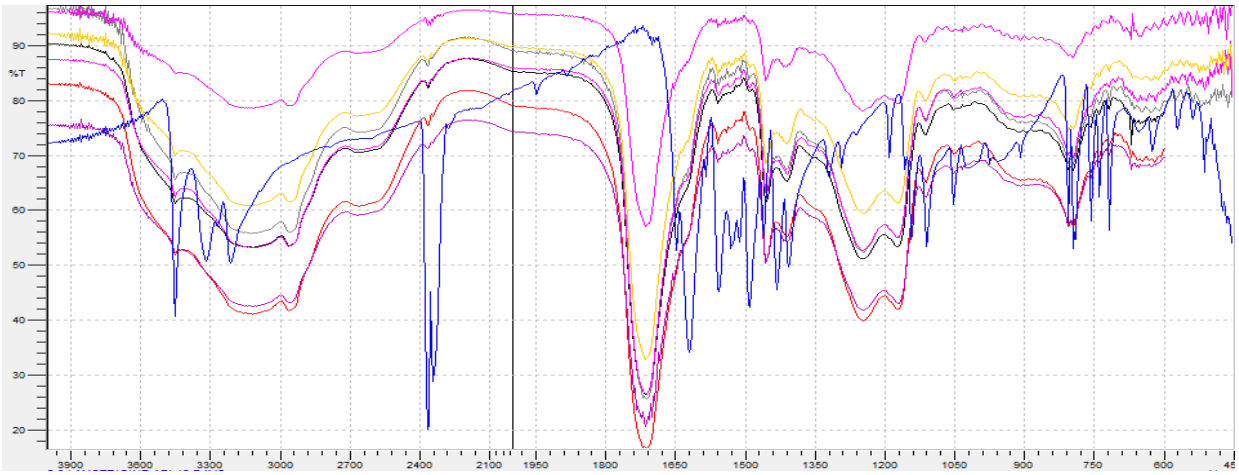


Figure 5: Overlay IR scan of Drug with Drug : Carbopol 971P at different temperature and Humidity conditions

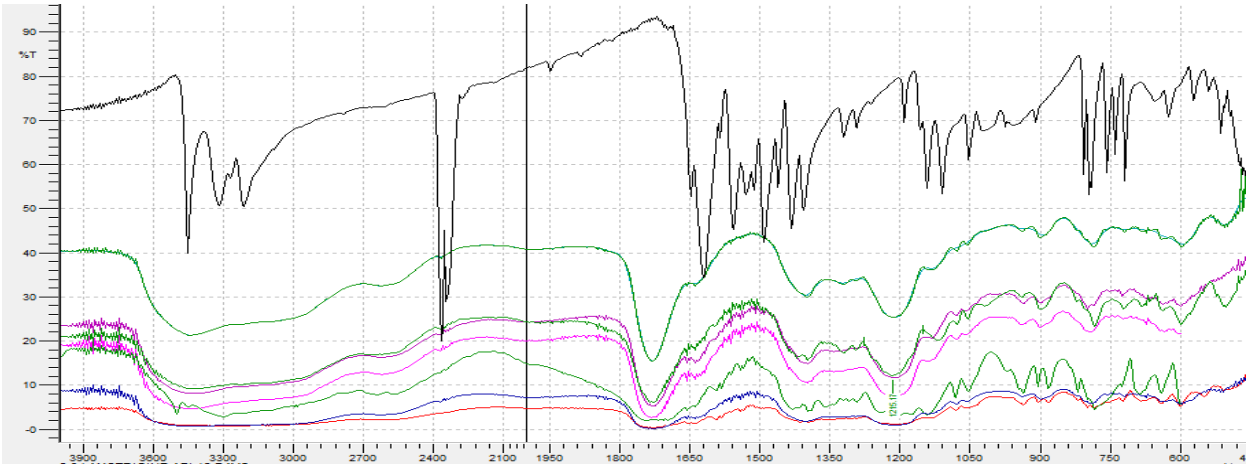


Figure 6: Overlay IR scan of Drug with Drug : Citric acid monohydrate at different temperature and Humidity conditions

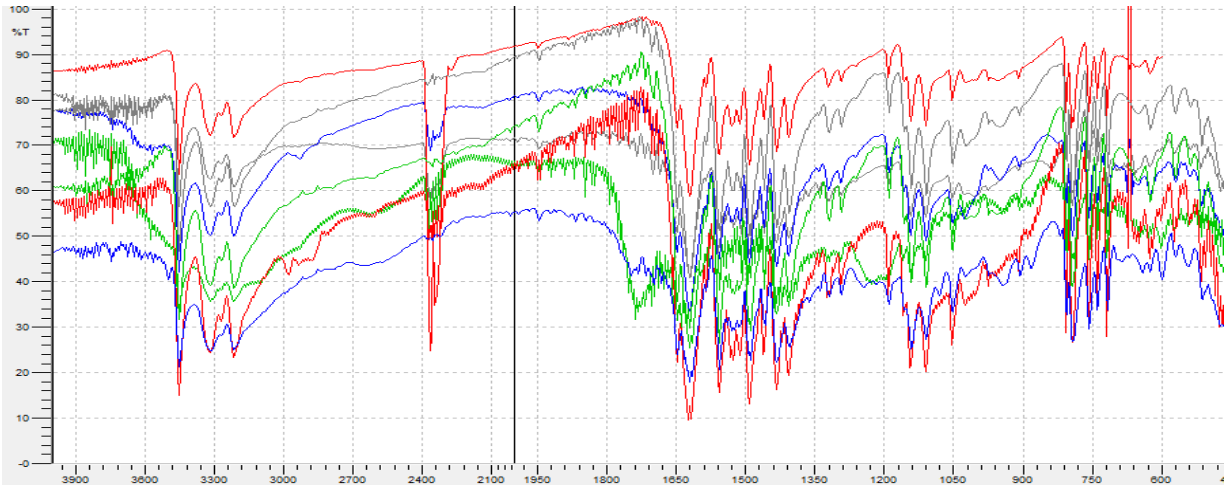


Figure 7: Overlay IR scan of Drug with Drug : Citric acid anhydrous at different temperature and Humidity conditions

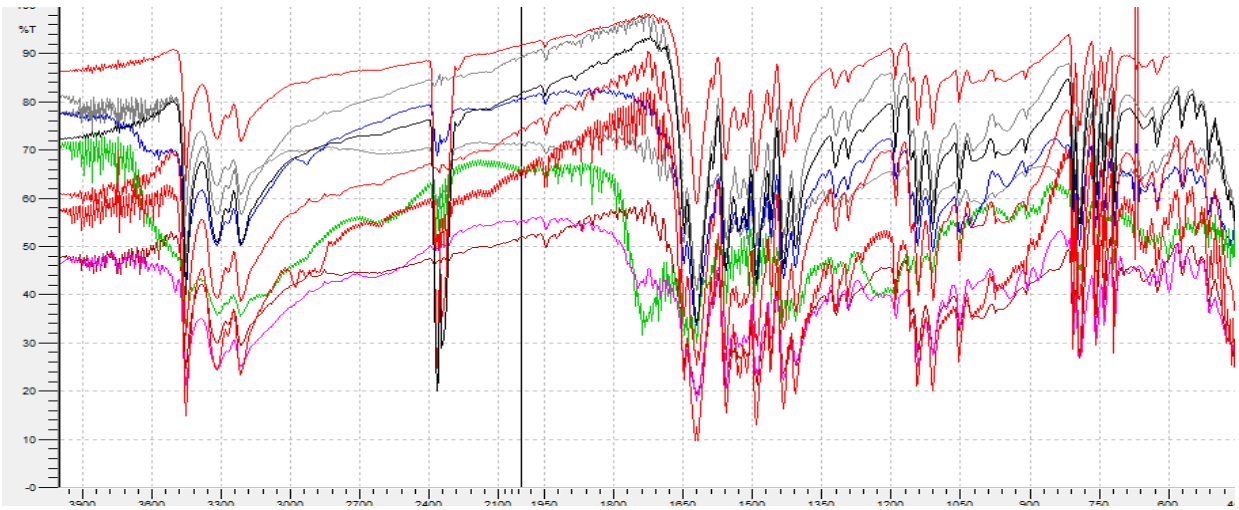


Figure 8: Overlay IR scan of Drug with Drug : Sodium Bicarbonate at different temperature and Humidity conditions

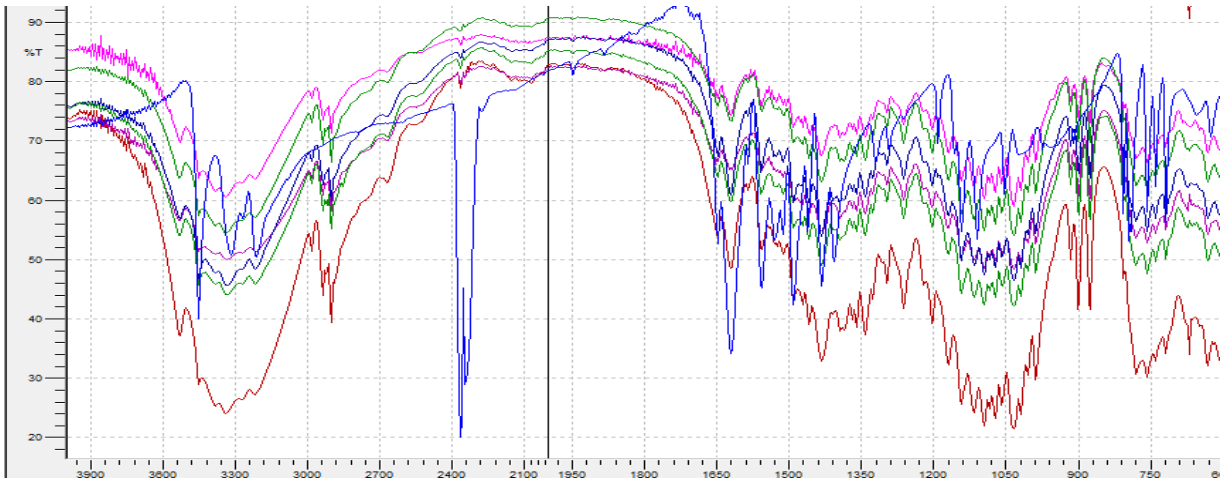


Figure 9: Overlay IR scan of Drug with Drug : Lactose SD at different temperature and Humidity conditions

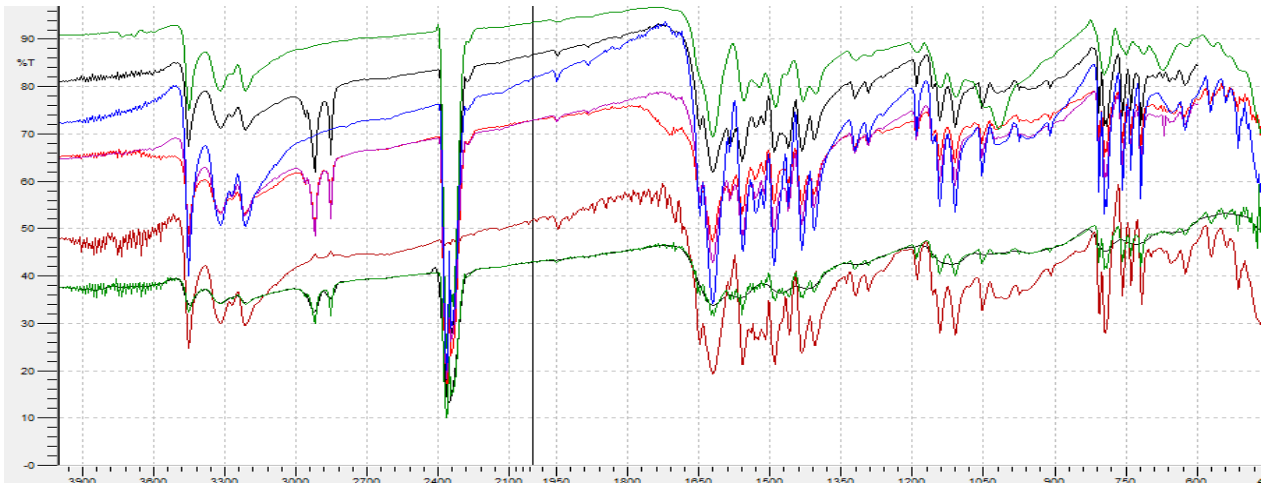


Figure 10: Overlay IR scan of Drug with Drug : Magnesium stearate at different temperature and Humidity conditions

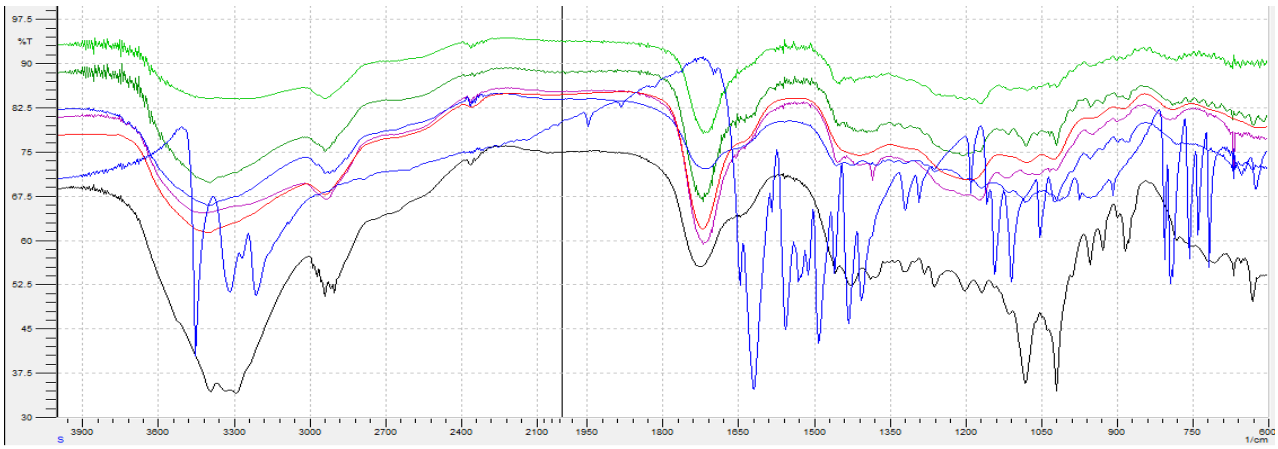


Figure 11: Overlay IR scan of Drug with Placebo at different temperature and Humidity conditions

DSC Studies: Figure 12 shows the DSC of drug in combination with HPMC K100M, Polymer mixture, Citric acid (monohydrate and anhydrous both), Carbopol, Lactose, pure drug alone and final tablet mixture. There is one main peak for Lamotrigine with peak maximum at 218.16°C, due to melting of Lamotrigine [11]. As shown in Figure 12, there was no difference in the melting point of Lamotrigine with the polymers and in the final formulation which ranged from 215°C to 225°C, showing no incompatibility, except Carbopol 971P and Citric acid monohydrate. The thermograms of Carbopol 971P with drug and Citric acid monohydrate with drug showed large deviation in the endothermic peak for Lamotrigine, concluding interaction between these excipients with drug.

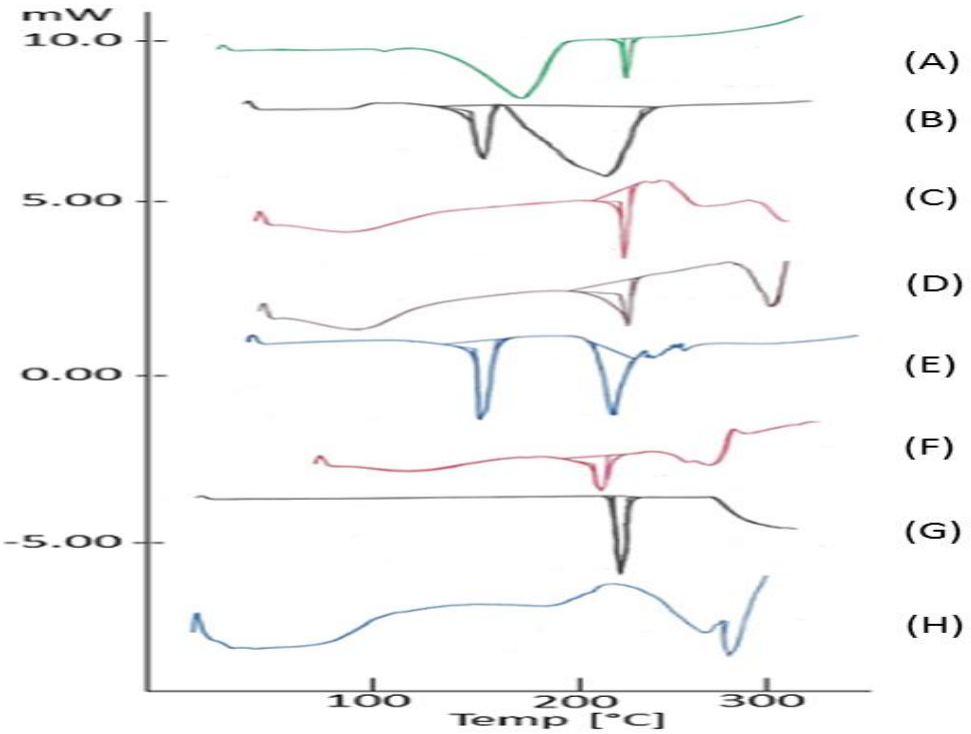


Figure 12: DSC Overlay scan of all samples

Where,

A – DSC of Citric acid anhydrous with drug

B – DSC of Citric acid monohydrate with drug

C – DSC of Polymer mixture with drug

D – DSC of HPMC K100M with drug

E – DSC of Lactose with drug

F – DSC of Final Tablet mixture with drug

G – DSC of Pure Drug

H – DSC of Carbopol with drug

pH – dependent solubility study : The pH – dependent solubility study shows that the drug was freely soluble in acidic conditions and its solubility decreases as the pH increases (Table VI).

Table VI: pH - dependent solubility

Buffer medium	Solubility (mg/mL)
0.1 N HCl	2.87
0.01 N HCl	2.74
0.001N HCl	0.44
pH 4.5 Acetate Buffer	1.44
Distilled Water	0.20
pH 6.8 Phosphate Buffer	0.21
pH 7.5 Phosphate Buffer	0.19

Solution stability: The solution stability was found to be for 24 hrs in 0.01N HCl at room temperature and at 37°C.

Table VII: Observations of Pre – compressional parameters

Formulation	Angle of Repose	LBD	TBD	Compressibility index (%)	Hausner's ratio
L1	26.59	0.38	0.45	14	1.16
L2	27.14	0.39	0.44	12	1.14
L3	28.31	0.41	0.46	13	1.15
L4	29.78	0.40	0.45	12	1.17

Table VIII: Formulation characteristics of Core Tablets.

Parameters	L1	L2	L3	L4
Average Weight (mg)	536.8	538	535.02	537.25
Longitudinal Diameter (mm)	14	14	14	14
Thickness (mm)	5.2	5.3	5.3	5.3
Hardness (Kp)	8-9	8-10	9-11	9-12
Friability (% w/w)	0.44	0.42	0.40	0.41
FLT (minutes)	3	5	10	5
Floating Time (hours)	20	24	18	24
Swelling index (%)	314.01	277.59	304.63	338.29
Assay (%)	100.2	101.1	99.7	96.5

Table IX: Dissolution profile of formulation batches

Time (Hrs.)	% Cummulative Release			
	L1	L2	L3	L4
0.5	9	15	10	7
1	11	20	13	9
2	13	22	17	12
4	15	23	20	14
6	19	28	24	17
8	24	36	31	21
10	33	50	42	26
12	44	64	52	32
16	64	83	62	51
20	80	90	69	62
24	91	101	80	70

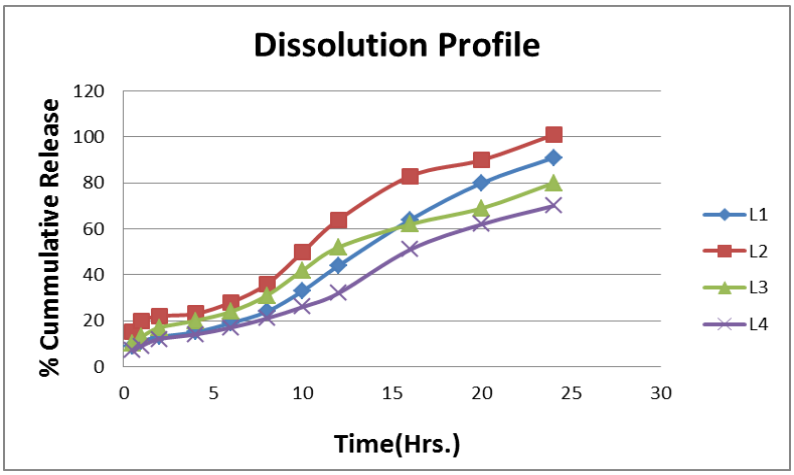


Figure 13: Dissolution Profile of formulation batches

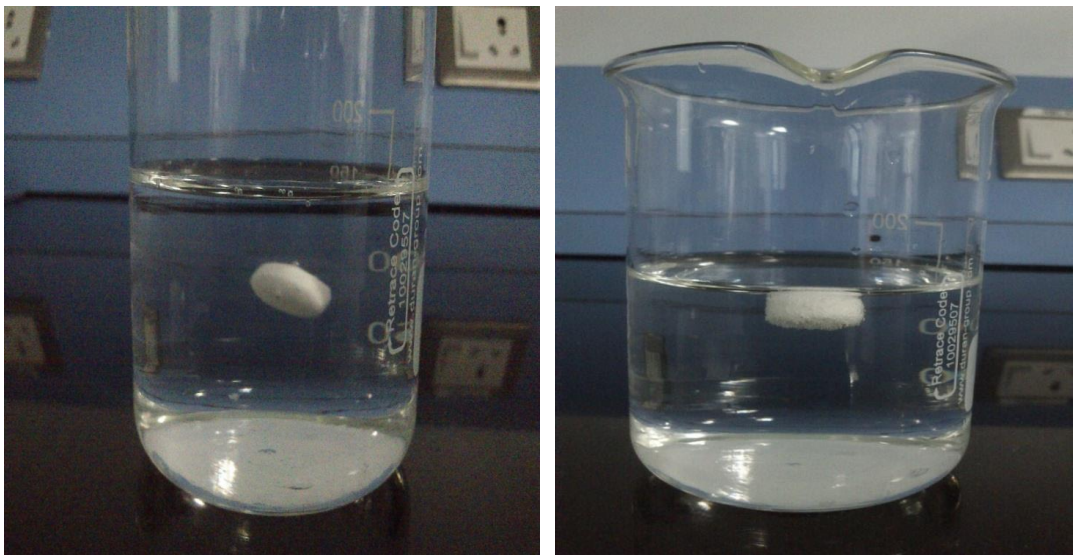
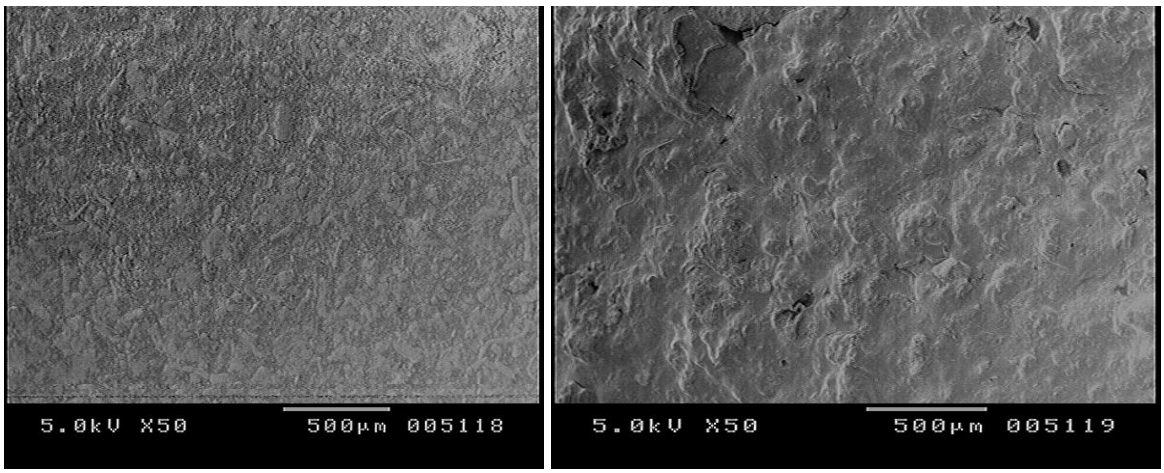


Figure 14: Images of Floating Matrix Tablets

Table X: In vitro drug release kinetic studies

Formulation	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			
L1	0.9885	0.9853	0.8923	0.4723	0.9455	0.8805	Zero order release
L2	0.9845	0.9537	0.9433	0.4546	0.9737	0.8220	Zero order release
L3	0.9881	0.9551	0.9483	0.4525	0.9825	0.8243	Zero order release
L4	0.9886	0.9823	0.8853	0.4403	0.9410	0.8695	Zero order release

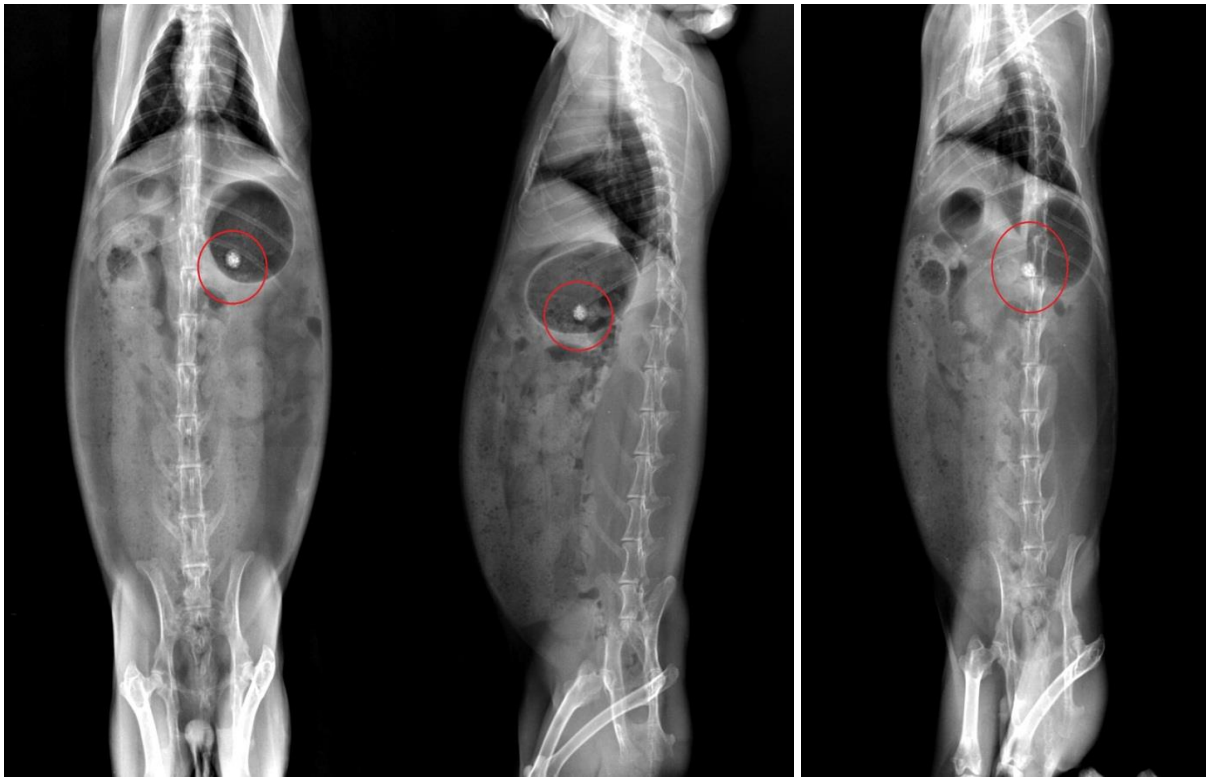
Scanning Electron Microscopy: The SEM images of the tablet were taken before and after dissolution. Figure 15 (a) showed intact surface without any perforations, channels, or troughs. After dissolution, the pores had formed throughout the matrix indicating, formation of a network in the swollen polymer through which the drug diffused to the surrounding medium (Figure 15 b). 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 L2.



(a) **(b)**

Figure 15: SEM of Tablet before Dissolution (a) and Tablet after Dissolution (b)

In – vivo gastroretention study: The X – Ray photographs of rabbit was taken at 1 hr, 12 hr and 24 hr. The amount of barium sulphate was sufficient enough to make tablets visible through the X – ray photograph. The tablet was found to be floating upto 24 hrs.



(a) (b) (c)

Figure 16: X – Ray radiograph of rabbits at 1 hr (a), 12 hr (b) and 24 hr (c)

Factorial Designs

For the 2^2 Factorial Design**,** The responses of formulation prepared by factorial designs are indicated in Table XI.

Table XI: Responses of the factorial batches

Batch Code	Coded values		% Release at 12 Hrs	% Release at 24 Hrs.	t60% (Hrs.)
	X1	X2			
L1	+1	-1	44	91	15.0
L2	-1	-1	64	101	11.2
L3	-1	+1	52	80	15.2
L4	+1	+1	32	70	19.2

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

% Drug Release at 12 hrs = + 48.00 - 10.00X1 – 6.00X2

% Drug Release at 24 hrs = + 85.50 - 5.00X1 - 10.50X2

t60% = +15.15 + 1.95X1 + 2.05X2

The fitted equations relate the 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 <0.001 for % Drug Release at 12 hrs and 24 hrs and 0.0177 for t60% indicates that the model is significant. The values of the correlation coefficient indicate a good fit. The data demonstrate that both X1 and X2 affect the drug release. The contour plot shows that as the amount of both the polymer decreases, the % drug release increases. This shows that the amount of polymer has inverse relationship with the drug release. The same relationship can be seen in the 3D – surface plot of t60%. As the polymer amount increases, the time required to release 60% of drug decreases. Therefore, as a general pattern both HPMC K100M and Ethyl Cellulose 10 concentration have a negative effect on response, i.e. increasing their concentration decrease % of drug released. Normal probability plot of the residuals (difference between the actual and predicted values) was a straight line and showed a normal distribution of the error.

Figures 17 - 19 show the plot of the percentage of HPMC K100M (X1) and the percentage of Ethyl Cellulose 10 (X2) versus % Release at 12 hrs, % Release at 24 hrs and t60% respectively. The plot was drawn using Stat-Ease Design Expert 8.0.7.1. The data demonstrate that both X1 and X2 affect the drug release at 12 hrs, 24 hrs and t60%.

Figures 20 - 22 show correlation plots between the observed and the predicted values of % Release at 12 hrs, 24 hrs and t60%. The linear correlation plots drawn between the predicted and the observed responses indicate excellent fitting of the model.

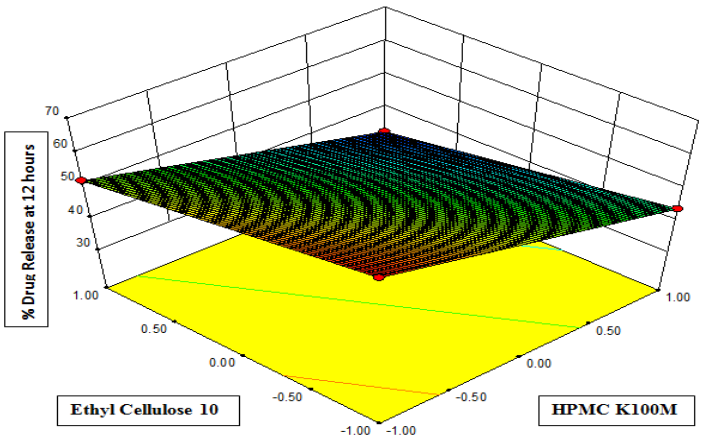


Figure 17: 3D - Surface plot for % Release at 12 hrs.

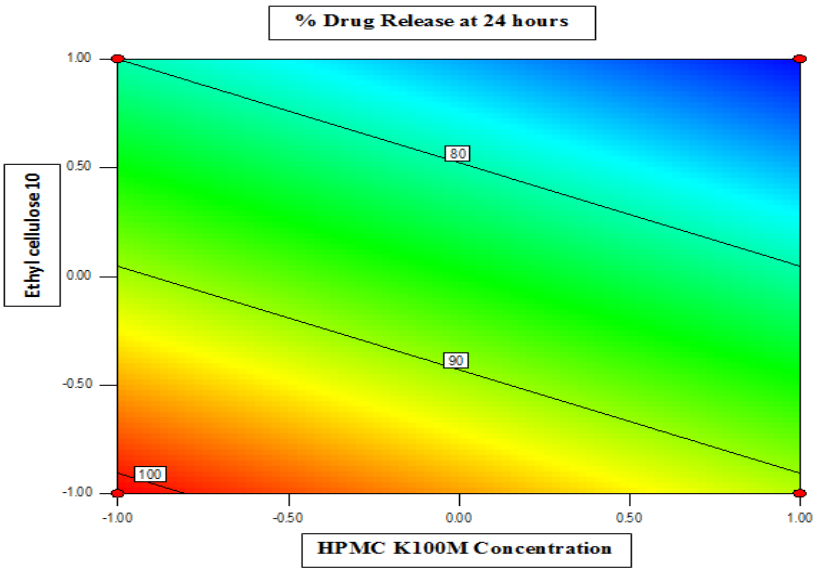


Figure 18: Contour plot % Drug Release at 24 hrs

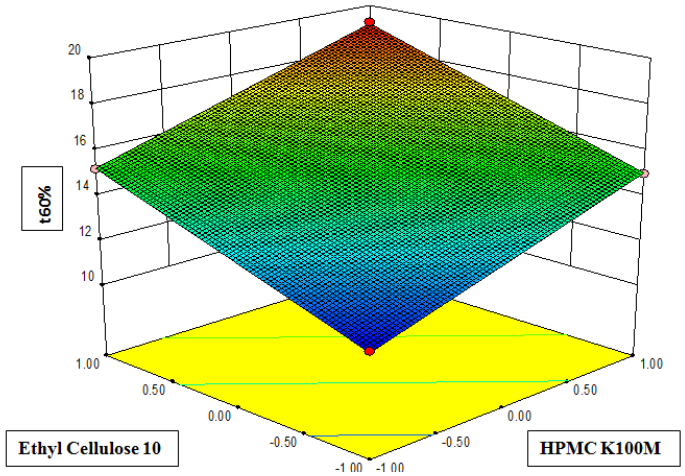


Figure 19: 3D Surface plot for Time required for 60% of Drug dissolution.

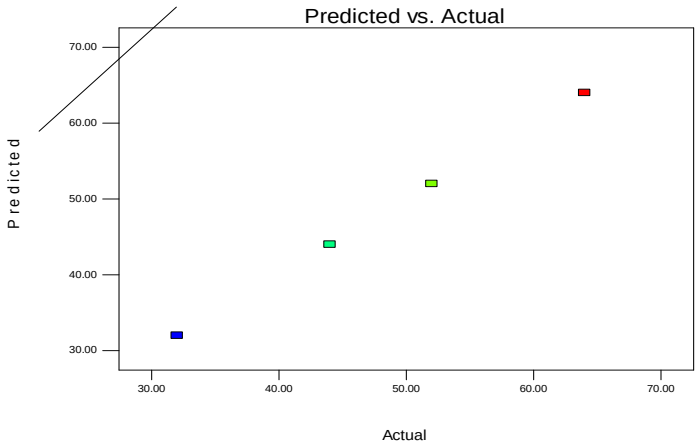


Figure 20: Linear Plots between observed and Predicted values of % Release at 12 hrs.

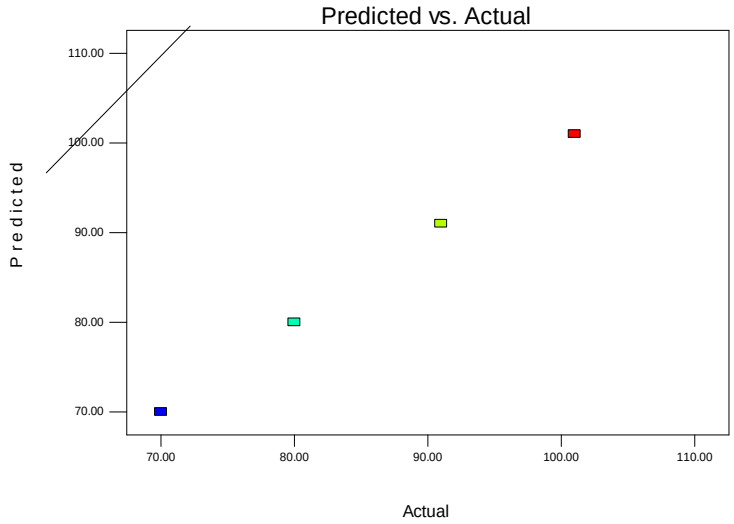


Figure 21: Linear Plots between observed and Predicted values of % Release at 24 hrs.

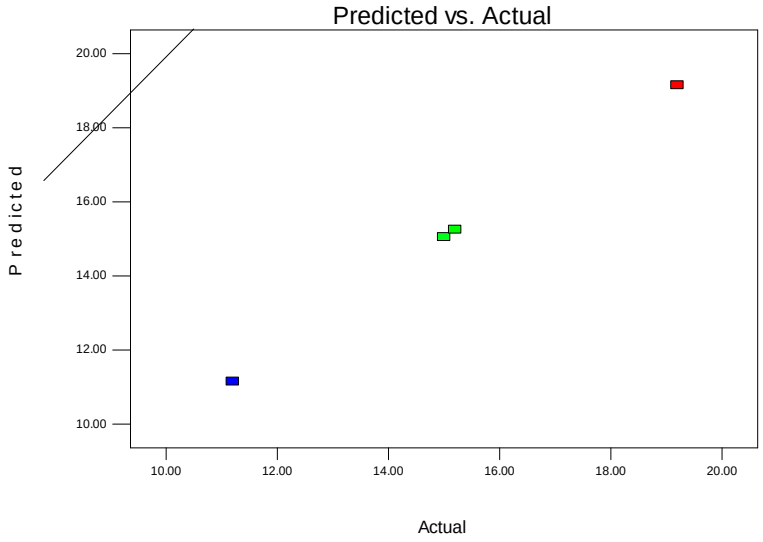


Figure 22: Linear Plots between observed and Predicted values of t60%

Table XII: Summary of results of regression analysis for responses % Release at 12 hrs., % Release at 24 hrs. and t60%

	% Release at 12 hrs.	% Release at 24 hrs.	t60%
R- squared	1.0000	1.0000	0.9997
Adj R – squared	1.0000	1.0000	0.9991
Pred R – squared	1.0000	1.0000	0.9950
Adeq Precision	-	-	92.376

Table XIII: ANOVA for % Release at 12 hrs.

Source	Sum of squares	df	Mean square	F Value	P Value	Model Significant/ Non significant Relative to Noise
Model	544.00	2	272.00	6.366E+007	<0.0001	Significant
A-HPMC K100M	400.00	1	400.00	6.366E+007	<0.0001	Significant
B-EC 10	144.00	1	144.00	6.366E+007	<0.0001	Significant
Residual	0.000	1	0.000	-	-	
Cor Total	544.00	3	-	-	-	

Table XIV: ANOVA for % Release at 24 hrs.

Source	Sum of squares	df	Mean square	F Value	P Value	Model Significant/ Non significant Relative to Noise
Model	541.00	2	270.00	6.366E+007	<0.0001	Significant
A-HPMC K100M	100.00	1	400.00	6.366E+007	<0.0001	Significant
B-EC 10	441.00	1	441.00	6.366E+007	<0.0001	Significant
Residual	0.000	1	0.000	-	-	
Cor Total	541.00	3	-	-	-	

Table XV: ANOVA for t60%.

Source	Sum of squares	df	Mean square	F Value	P Value	Model Significant/ Non significant Relative to Noise
Model	32.02	2	16.01	1601.00	0.0177	Significant
A-HPMC K100M	15.21	1	15.21	1521.00	0.0163	Significant
B-EC 10	16.81	1	16.81	1681.00	0.0155	Significant
Residual	0.010	1	0.010	-	-	
Cor Total	32.03	3	-	-	-	

The drug release from the system was found to be concentration independent. The FLT and total duration of floating was also found to be good. The batch L2 was found to be releasing maximum amount of the drug, with following zero order release mechanism. The factorial

design helped to optimize the quantities of both the polymers for releasing most of the drug at the end of end of 24 hrs.

CONCLUSION

The objective of this study was to formulate a floating matrix tablet of Lamotrigine with sufficient floating time and maximum % Cummulative release. The detailed IR study at different temperature and humidity conditions helped us to identify the incompatible polymers and hence not used further. The result of the dissolution profile revealed that increase in the proportion of polymer (HPMC K100M and Ethyl cellulose 10) was associated with decrease in the overall cumulative drug release rate. Batch L2 was found to be releasing 101% at the end of 24 hrs. Hence, this batch is taken as the optimized batch with acceptable attributes. The matrix tablet was found to have excellent physical characters and good matrix integrity. Hence the formulation L2 fulfils the objective of the study.

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