Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

SPATIO TEMPORAL RELEASE OF LAMOTRIGINE BY BUOYANT GASTRORETENTIVE DRUG DELIVERY: DEVELOPMENT AND EVALUATION.

RAJA SEKHAR REDDY POONURU[1]*, G. CHANDRASEKHARA RAO[2]

[1]Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences, Vidyanagar, Hanamkonda-506001, Andhra Pradesh, India., [2]Department of Pharmaceutics, Yalamarthy College of Pharmacy, Tarluwada, Visakhapatnam- 530052, India.
Email: yuppieraj@gmail.com

Received: 14 March 2014 Revised and Accepted: 29 March 2014

ABSTRACT

Objective: The present study involves formulation and evaluation of gastro retentive drug delivery systems of lamotrigine

Methods: Gastro retentive drug delivery systems were prepared by developing buoyancy by usage of effervescent and non effervescent strategies utilising gas generating materials and low density porous materials respectively. The finished tablets were subjected to floating studies, dissolution studies, release kinetic studies and stability studies.

Results: The optimized tablets of lamotrigine, F4 showed floating lag time of 30 seconds and total floating time more than 12 hours with *in vitro* percentage release of 89.43% at the end of 12hours. The kinetic studies showed that the release was by zero order and is best fit to Peppas model showing the release by non- Fickian diffusion implying that both diffusion and erosion controlled the drug release. The n value greater than 0.89 indicates super case II transport mechanism which refers to the erosion of the polymeric chain. The optimized formulation when subjected to stability studies showed no significant differences in drug content and release profile.

Conclusion: This design of the study will be helpful for the spatial and temporal control over the release from the dosage form making the bioavailability to improvise with better patient compliance.

Keywords: Lamotrigine, Gastro retention, Absorption window, Direct compression, Floating tablet.

INTRODUCTION

Lamotrigine is an atypical anticonvulsant drug which is chemically 3, 5-diamino-6-(2, 3-dichorophenyl)-1, 2, 4-triazine currently used both in monotherapy and combination therapy in patients with partial and secondary generalized seizures [1, 2]. Lamotrigine is a successful molecule to treat epilepsy. However Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are caused by unregulated plasma concentrations of the antiepileptic drug lamotrigine [3, 4, 5, 6]. The percentage of benign skin reactions ranges between 8% and 11% [7]. The severity of the skin rash range from simple non symptomatic erythema to severe, life-threatening Stevens-Johnson's syndrome [8, 9, 10, 11]. This can be controlled by formulating lamotrigine as a controlled drug delivery system. Moreover the drug shows proper absorption profile with maximum absorption when it is retained between the stomach and the ascending part of the colon. Lamotrigine shows pH dependant solubility [12]. The phenomena of improvised absorption with increased gastric residence time along with pH-dependant solubility with high solubility at low pH make it suitable for formulation as a gastro retentive drug delivery system [13].

Lamotrigine has biological half life more than 36 hours but still is preferred to be formulated as sustained release dosage form because of less chances of toxicity if the concentration of drug in plasma is prevented from sudden hiking [14]. Existing formulations of lamotrigine provide immediate release with t max ranging from 1.4 h to 4.8 h and result into a release profile exhibiting cyclic peaks and troughs [15]. Gastro retentive drug delivery systems retain in the stomach for longer duration of time and hence the bioavailability of the drugs is improved preferentially by letting the drug absorbed from proximal gastro intestinal tract [16].

MATERIALS AND METHODS

Materials

Lamotrigine was gifted by Dr. Reddy's labs India ltd, Hyderabad. HPMCK4M, HPMCE4M and HPMCK100 LV CR were obtained from Colorcon, Verna, Goa, India as gift samples. Sodium bicarbonate was purchased from S.D. Fine Chem ltd. Mumbai, India Micro crystalline cellulose is obtained as a gift sample from SPI Pharma Bengaluru, India. Porous calcium silicate was gifted by Tomita Pharmaceutical Co., Ltd. Japan and Zeolite was gifted by R.A. Chem., Hyderabad, India. Directly compressible lactose was obtained as gift sample from DMV-Fonterra Excipients, Whitefield, Bengaluru, India. All other materials used were of analytical grade.

Experimental Methods

Pre formulation study

Prior to formulation of any dosage form it is necessary to undertake preformulation studies to understand the physic chemical properties of the drug and the blend to have better idea on what should be done to overcome the problems in the existing marketed formulations helping in the design of novel methodologies.

Solubility study [17]

Excess of lamotrigine was added to vials containing solvents and then the vials were shaken for 48 hours on a rotary shaker and the solubility was observed by using ultra violet spectrophotometry at 244 nm with relevant dilutions after filtering.

Excipients compatibility study

Any formulation requires suitable excipients to organise the drug performance and they are needed to be added in proper proportions. IR spectroscopy was used to know and understand the selectivity and compatibility of excipients.

Infrared spectrophotometer (IR)

Infrared spectrums were recorded within a range of 4000 to 400cm^{-1} wavelength region.

The samples to be tested are compressed into disc by mixing with potassium bromide in Potassium bromide press and then are exposed to light in the path and spectrums were obtained [18].

Preparation of floating matrix tablets of Lamotrigine

Weighed quantity of lamotrigine and the diluents, microcrystalline cellulose or directly compressible lactose were sifted through sieve with mesh number 22 and then taken into a poly bag, HPMC K4M, HPMC K100LV CR and sodium bicarbonate were passed through sieve of mesh number 40. The above pre-lubricated blend was mixed with weighed quantity of magnesium stearate after passing through sieve of mesh number 60, the contents of the poly bag were mixed thoroughly and then tablets were prepared by direct compression method using 8 mm diameter standard flat-face punches using Rimek mini press, M/S: Karnavati engineering, Ahmadabad., maintaining a hardness of 5.5 kg/cm^2. Tablets of non effervescence type were also formulated and tableted the same way but by replacing sodium bicarbonate with either porous calcium silicate or zeolite as shown in table 1.

Table 1: Composition of Lamotrigine floating matrix tablets

Ingredients	Effervescent type									Non Effervescent type			
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Lamotrigine	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K100 LV CR	20	20	20	20	-	-	10	20	20	20	20	20	20
HPMCK4M	40	40	40	40	40	40	40	50	60	40	-	40	-
HPMC E 4 M	-	-	-	-	20	20	10	0	0	-	40	-	40
Sodium bicarbonate	10	20	30	30	20	30	20	20	20	-	-	-	-
Micro crystalline cellulose	78	68	58	0	68	58	68	58	48	-	-	-	-
Porous Calcium Silicate	-	-	-	-	-	-	-	-	-	50	50	-	-
Zeolite	-	-	-	-	-	-	-	-	-	-	-	50	50
Directly Compressible Lactose	-	-	-	58	-	-	-	-	-	38	38	38	38
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200	200

HPMC=Hydroxy propyl methyl cellulose

Evaluation of dry Blend

F1to F13 were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index.

Angle of repose [19]

The powder blend is made to flow through a fixed funnel kept above the graph paper at a height, h, of 2 centimetres placed on horizontal surface. Angle of repose can be determined by following equation:

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of base of the pile.

Bulk density and tapped density

2 grams of powder from each formula was filled in a 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued till no change in the volume was observed. Loose bulk density and tapped bulk density were determined by using the following formulae.

Loose bulk density: Weight of the powder/volume of the packing.
Tapped bulk density: Weight of the powder/tapped volume of the packing.

Compressibility index

Carr's Compressibility index of the powder blend was determined by the formula

$$\text{carr's index}(\%) = \frac{\text{Tapped density} - \text{loose bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio can be determined by the following equation,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Loose bulk density}}$$

Evaluation of tablet characteristics

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Following parameters were evaluated.

Weight variation [20]

Twenty (20) tablets from each batch were individually weighed in grams (g) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Weight variation permissible limits

Average weight (mg)	% Deviation allowed
130 or less	10
130-323	7.5
More than 324	5

Tablet hardness [21]

10 tablets were selected randomly and hardness was measured using a Monsanto hardness tester in kg/cm^2 and the average hardness and standard deviation was reported.

Friability [22]

Twenty (20) tablets were weighed from each batch and were rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The

tablets were re-weighed after dedusting loss in weight is recorded. Friability was then calculated using formula.

$$\mathbf{F} = \frac{[\mathbf{1} - \mathbf{Wo}]}{\mathbf{Wt}} \times \mathbf{100}$$

Where, W0 is Weight of tablet before test and W**t** is Weight of tablet after test.

Content uniformity [23]

From each formulation batch ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of 0.1N HCL was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with 0.1N HCL. The solution was filtered and suitable dilutions were prepared with 0.1N HCL. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 244 nm by using UV-Visible spectrophotometer.

Buoyancy / Floating Test [24]

The *in vitro* buoyancy was done by determining both floating lag time and total floating time. The tablet were placed in a 100-ml, beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is stated to be the total floating time.

Water uptake studies [25]

The swelling nature of tablets can be studied by weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of 0.1 N HCl which was maintained at 37°C + 0.5°C, rotated at 50 rpm. At predetermined intervals the tablets were withdrawn and weighed. Percentage swelling of the tablet was determined using the formula

$$\%\mathbf{WU} = \frac{\mathbf{Wt} - \mathbf{Wo}}{\mathbf{Wo}} \times \mathbf{100}$$

Where, Wt is the weight of the swollen tablet, Wo is the initial weight of the tablet.

Dissolution Study of tablets [26]

The tablet was placed inside the dissolution vessel containing 900 ml of 0.1 N HCL. 5ml samples were withdrawn at each interval replacing with 5ml of dissolution medium after each sampling. The release studies were conducted with 6 tablets, & the mean values were plotted versus time. Each sample was analyzed at 244 nm using double beam UV Visible Spectrophotometer. The dissolution study for marketed formulation was also performed in the same manner.

Kinetics of in-vitro drug release [27, 28]

To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order, Higuchi and Korsemeyer-Peppas.

Zero-order,

It can be represented by the following equation;

$$\mathbf{Qt} = \mathbf{Qo} + \mathbf{Ko\ t}$$

Where, Qt = amount of drug released in time, t;

Qo = initial amount of drug in the solution;

k_0 = zero order release constant.

Graph: % of drug remained to be released vs. time.

First-order,

It can be represented by the following equation;

$$\mathbf{Log\ Qt} = \mathbf{Log\ Qo} + \frac{\mathbf{Kt}}{\mathbf{2.303}}$$

Where, Qt = amount of drug released in time, t;

Q0 = initial amount of drug in the solution;

k = first order release constant.

Graph: logarithmic value of % drug remained to be released vs. time.

Higuchi,

Simplified Higuchi model can be expressed by following equation:

$$\mathbf{Qt} = \mathbf{KHt}^{1/2}$$

Where, kH = Higuchi diffusion constant;

Qt = fraction of drug dissolved in time, t.

Graph: cumulative % release of the drug vs. square root of time.

Korsmeyer peppas,

$$\mathbf{Log}\ \frac{\mathbf{Mt}}{\mathbf{Mo}} = \mathbf{Km} + \mathbf{n\ logt}$$

Where Mt / M0= fraction of drug released at time, t;

km = the rate constant

n = release exponent. The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent $n \leq 0.45$ indicates Fickian diffusion; $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion; n = 0.89 indicates case II (relaxational) transport and $n > 0.89$ indicates super case II transport mechanism. Anomolous diffusion or non-Fickian diffusion refers to both diffusion and erosion controlled drug release. Case-II or Super case-II transport refers to the erosion of the polymeric chain.

Similarity factor (f2) [29]**.**

For each dissolution run, a mean of six determinations was recorded for the reference and test methods both of which were matched for similarity in drug release profiles by calculating the similarity and difference factors. A comparison of the similarity and difference factors was

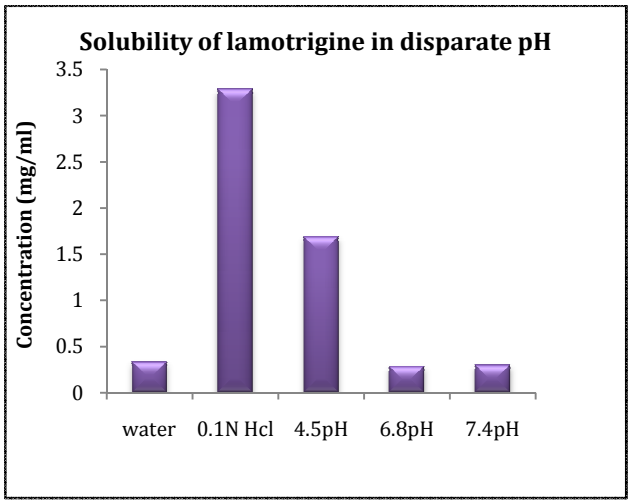

Fig. 1: Solubility of Lamotrigine in different pH

Obtained using the formula

$$\mathbf{f2} = \mathbf{50} \times \mathbf{log}\ \{[\mathbf{1} + \tfrac{\mathbf{1}}{\mathbf{n}} \sum (\mathbf{Rt} - \mathbf{Tt})^{\mathbf{2}}]^{-0.5} \times \mathbf{100}\}$$

Rt and Tt are the cumulative percentage dissolved at each of the selected "n" time points of the reference and test product, respectively..

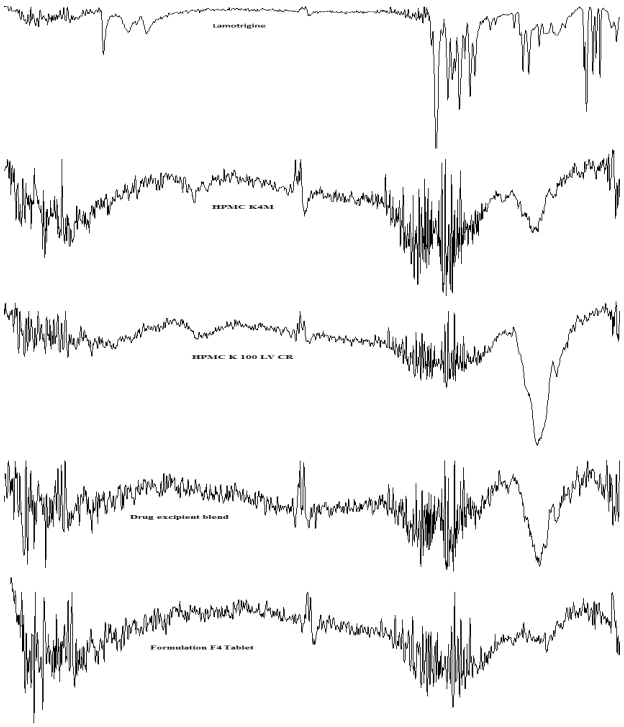

Fig. 2: FTIR Spectra of a) Lamotrigine b) HPMC K4M c) HPMC K100LV d) Drug polymer blend and e) Formulation F4 Tablet.

Stability study [30]

In present study, stability studies were carried at 40^{0}C and 75% RH for 90 days for optimized formulation. For stability study, the tablets were placed in desiccators maintained at 75%RH.

After 90 days the tablets were retested for any physical change or change in release profile.

RESULTS AND DISCUSSION

Preformulation Studies

Lamotrigine showed pH dependant solubility as observed from the data as shown in Figure 1.

Drug- excipient compatibility studies by using IR graphs

From the IR spectra, it was found that there is no significant change in wave number plain drug spectra and spectra of drug with excipient **(as shown in Figure 2)**. So there is no Drug and excipient interaction.

Micromeritic properties of drug and excipient blend

Micromeritic properties of pure drug and polymer blend were tested and the values were **as shown in Table 2**. Angle of repose for all the formulations were within the range of 26.9 ± 1.08 to 34.9 ± 1.11 indicating that the flow properties were good. The Carr's index was within the range of 8.17 ± 0.77 to 14.94 ± 0.33 indicating good compressibility. The Hausner's ratio ranged between 1.08 ± 0.31 to1.15 ± 0.54 showing that the blend showed good flow.

Evaluation of Tablet characteristics

The floating tablets of lamotrigine tablets were evaluated for diameter variation, thickness, hardness, friability, drug content, weight variation. Weight of the tablet was fixed at 200mg and all batches found to be showing values within the acceptance limits. Hardness of the tablets of all batches was within the permissible limit range. The thickness of floating tablets ranged from 3.00 ± 0.01 to 3.98 ± 0.01 mm and linearly correlated with the weight of the tablets. Friability test showed that the values of friability are within the limit. Drug content uniformity for all formulations was determined and the percent of active ingredient ranged from 98.45 ± 1.2 to 100.32 ± 2.21 indicating that the values were within the limits (as shown in Table 3)

Table 2: Micromeritic properties of lamotrigine formulations

Code no.	Bulk density	Tap density	Carr's compressibility index	Hausner's ratio	Angle of repose
F1	365.7 ± 0.65	412.9±0.2	11.43±0.5	1.12±0.68	30.8±0.3
F2	352.6 ± 0.2	407.4±0.31	13.45±0.3	1.15±0.54	34.2±0.2
F3	357.3 ± 1.01	405.9±0.24	11.97±0.2	1.13±1.02	32.3±0.25
F4	362.8 ± 0.45	411.2±0.11	11.77±0.14	1.13±0.73	32.6±1.02
F5	358.1 ± 0.58	413.2±0.12	13.33±0.62	1.15±0.38	34.1±0.6
F6	353.2 ± 0.46	414.25±0.5	14.73±0.54	1.17±0.28	34.9±1.11
F7	378.2 ± 0.35	431.4±0.62	12.33±0.22	1.14±0.66	34.3±0.54
F8	353.9 ±0.26	416.1±0.44	14.94±0.33	1.17±0.57	34.8±0.21
F9	355.6 ± 0.24	410.3±0.21	13.33±0.17	1.15±0.38	32.6±0.32
F10	365.2 ± 0.78	401.2±0.87	8.97±0.81	1.09±0.85	27.6±1.15
F11	369.4 ± 0.63	402.3±0.32	8.17±0.77	1.08±0.31	26.9±1.08
F12	366.9 ± 0.23	405.4±0.24	9.49±0.67	1.10±0.49	28.4±1.21
F13	359.8 ± 0.41	403.2±0.13	10.76±0.38	1.12±0.62	29.4±1.45

All values are expressed are average ± SD (n=3)

Buoyancy determination

The floating lag time and total floating time were determined by using 0.1 N Hydrochloric acid. The floating lag time was determined by noting the time required for the tablet to float from the time of insertion into the dissolution medium. The floating lag time was in the range of 30 to 110 seconds. The floating lag time and the total floating time values are represented in table 3 and the floating pictures are shown in figure 3.

Water uptake studies

The swelling index was calculated for 8 hours time. As time increased, the swelling index increased, because weight gain by tablet was increased proportionally with rate of hydration. **(As represented in Figure 4)**. Swelling index for f4 formulation has shown relatively a higher value than other formulations. The formulations F10 to F13 showed an increase in swelling index initially but later the values declined abruptly which might be due to the erosion of tablets.

In vitro dissolution testing

Dissolution studies of the tablet formulations were conducted using 0.1N HCL as dissolution medium. In vitro dissolution study of formulations from F1to F9 with gas generating mechanism and F10 to F13 with porous materials was conducted in 0.1N HCL and the percent of drug release from formulations were noted. The formulations F1 to F9 containing HPMC K4 M, HPMC E4M and HPMC K100LV have entrapped the carbon dioxide released by effervescence and floated well compared to the formulations F10 to F13 containing porous materials. More over the non effervescent type formulations could float soon but could not float well for the desired period of time and the drug release happened to complete

by 8 hours. The Drug release was controlled for 12hrs in F4 formulation due to the presence of combination of HPMC K4M and HPMC K100LV polymers and also shown 89.43 % of drug release. This formulation also floated for the desired 12 hours time and also shown very low floating lag time making it to be considered as the best formulation. In the formulations as the concentration of sodium bicarbonate increased the floating lag time has decreased. The in vitro dissolution testing was performed and values were obtained **(as represented in Figure 5, 6)** and the results were expressed as mean ± S.D (n=3).

Table 3: Physicochemical properties of all batches

Formula code	Diameter (mm)	Thickness (mm)	Hardness (Kg-cm)	Friability (%)	Content uniformity (%)	Weight variation (mg)	Floating lag time (seconds)	Total floating time (h)
F1	7.99 ± 0.040	3.02 ± 0.01	5.5 ± 0.47	0.96	98.45 ± 1.2	248.6 ± 1.29	110	>12
F2	7.98 ± 0.006	3.01 ± 0.01	5.4 ± 0.32	0.72	99.32 ± 1.36	250.4 ± 0.95	70	>12
F3	7.99 ± 0.067	3.02 ± 0.06	5.4 ± 0.54	0.91	99.24 ± 2.3	251.6 ± 0.98	47	>12
F4	7.98 ± 0.070	3.02 ± 0.01	5.3 ± 0.42	0.86	98.67 ± 2.7	251.1 ± 1.37	30	>12
F5	7.98 ± 0.056	3.00 ± 0.01	5.5 ± 0.35	0.79	100.2 ± 1.32	249.6 ± 1.49	60	9
F6	7.98 ± 0.006	3.12 ± 0.01	5.5 ± 0.54	0.97	99.65 ± 1.64	249.5 ± 1.19	53	10
F7	7.99 ± 0.067	3.98 ± 0.01	5.5 ± 0.54	0.72	98.72 ± 1.47	250.5 ± 1.19	117	8
F8	7.98 ± 0.072	3.04 ± 0.06	5.3 ± 0.42	0.72	98.88 ± 1.82	250.5 ± 1.19	49	10
F9	7.98 ± 0.065	3.02 ± 0.01	5.4 ± 0.32	0.72	100.32 ± 2.21	249.5 ± 1.19	51	9
F10	7.98 ± 0.057	3.00 ± 0.05	5.4 ± 0.30	0.89	98.73 ± 1.24	249.5 ± 0.98	21	6
F11	7.97 ± 0.061	3.11 ± 0.01	5.3 ± 0.48	0.94	99.21 ± 1.32	249.6 ± 1.08	32	7
F12	7.98 ± 0.071	3.01 ± 0.01	5.3 ± 0.41	0.85	99.67 ± 1.45	250.8 ± 0.958	36	7
F13	7.99 ± 0.005	3.11 ± 0.01	5.4 ± 0.53	0.95	98.53 ± 1.91	249.3 ± 1.01	38	8

All values are expressed average ± SD (n=3)

***In vitro* Buoyancy determination**

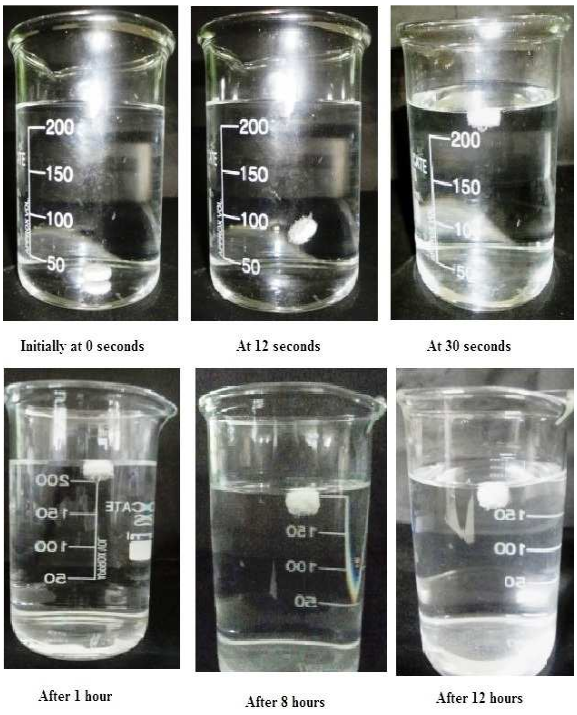

Fig. 3: floating lag time and floating time of F4 formulation

Dissolution Profile Modeling

The release mechanism was determined by calculating the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations **(as shown in Table 4)**.

The regression coefficient (R^2) values of release data of all formulations obtained by curve fitting method for zero order, first-order, and Higuchi and Korsmeyer-Peppas model. For the optimized formulation F4, the R^2 value of zero order is 0.986.

Swelling index of formulation

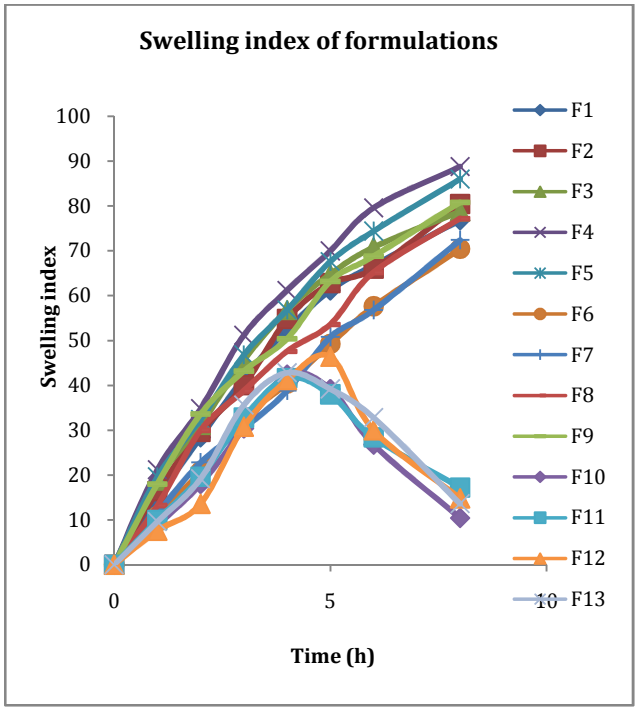

Fig. 4: Swelling index of formulations

The n value of optimized formulation F4 is 0.981 which is nearer to 1 indicating that the drug release mechanism is of non-Fickian diffusion following super case II mechanism. The f2 value was found to be 56.99 indicating that the release was similar to marketed product but was showing zero order release kinetics as shown in figure7.

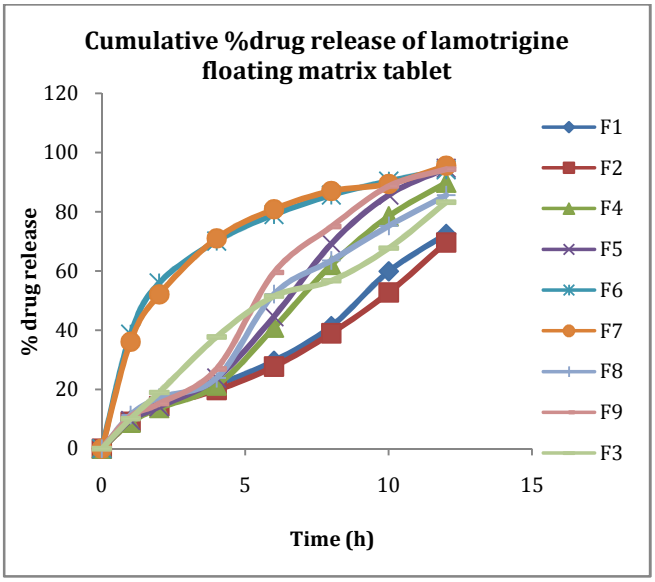

Fig. 5: Cumulative % drug release of formulations F1 to F9 (effervescent type)

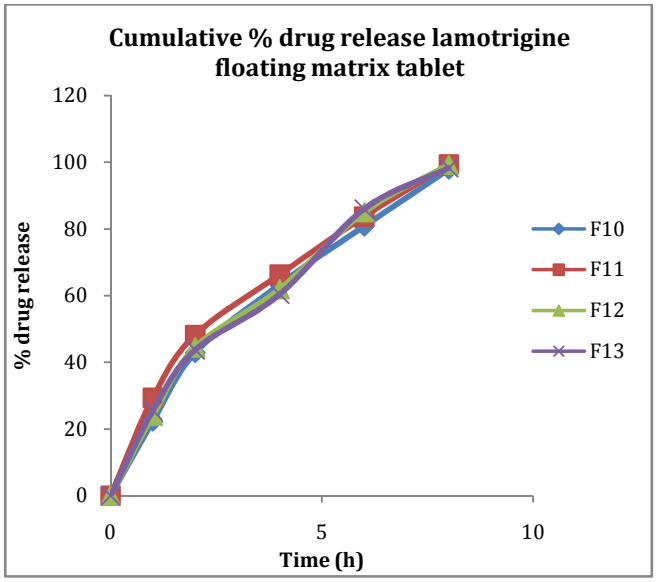

Fig. 6: Cumulative % drug release from Formulations (non effervescent type) F10-F13

Table 4: Regression coefficient (R^2) values for different kinetic models for all formulations

Formulation	R^2- values					
	First order	Zero order	Higuchi	Hixson -Crowell	Korsmeyer Peppas	n value
F1	0.907	0.976	0.848	0.939	0.958	0.780
F2	0.899	0.975	0.839	0.933	0.959	0.786
F3	0.949	0.965	0.938	0.979	0.991	0.829
F4	0.875	0.986	0.827	0.931	0.969	0.981
F5	0.853	0.984	0.833	0.925	0.971	0.989
F6	0.961	0.415	0.929	0.848	0.978	0.347
F7	0.966	0.485	0.946	0.879	0.975	0.385
F8	0.946	0.980	0.885	0.975	0.962	0.859
F9	0.914	0.974	0.868	0.963	0.966	0.959
F10	0.865	0.922	0.977	0.968	0.987	0.690
F11	0.806	0.862	0.994	0.954	0.993	0.569
F12	0.811	0.919	0.978	0.955	0.988	0.640
F13	0.873	0.915	0.978	0.972	0.991	0.667

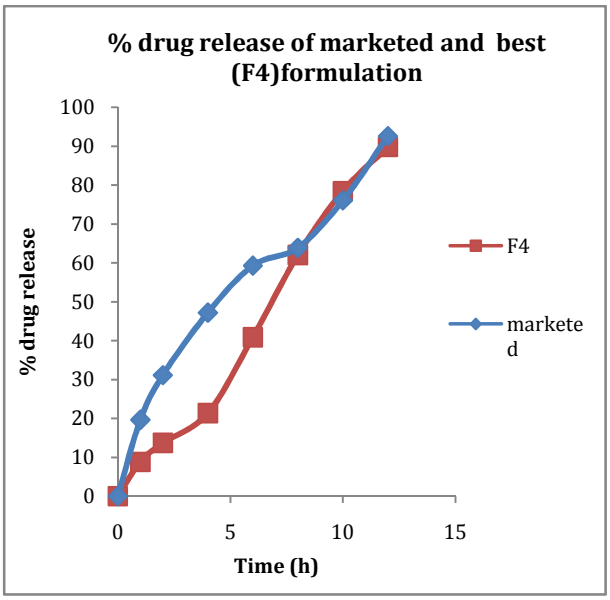

Fig. 7: Comparison of release from marketed product and F4 formulation

Stability studies

Stability studies have shown that there was no significant change in the drug content, release rate of the drug or buoyancy characters of the optimized formulation F4 when exposed to 40^{0}C at 75% relative humidity.

CONCLUSION

Tablets were prepared and the addition of gel-forming polymer HPMC (K4M) and gas-generating agent, sodium bicarbonate, and porous calcium silicate as low-density excipient provided the buoyancy and drug release. The prepared tablets could float within 3min and maintain for more than 12 h. The formulation F4 gave best results with a floating lag time of 30 seconds and total floating time more than 12 hours and also showed good release pattern of the drug with 89.43% of drug release followed a zero order profile with greater R^2 value 0.986 and n value >0.89 indicating non fickian diffusion. Floating lag time decreased with increase in sodium bicarbonate, increase in amount of HPMC K4M and replacement of microcrystalline cellulose by directly compressible lactose. Formulated tablets showed satisfactory results for their evaluation like hardness, weight variation, floating lag time, total floating time, and in vitro drug release. Finally, it can be concluded that Lamotrigine with pH dependant solubility and good absorption window at duodenum makes it a good candidate for the preparation of floating drug delivery systems.

ACKNOWLEDGEMENT

Authors are thankful to Doctor Reddy's Laboratories Hyd. for providing gift sample of Lamotrigine, Colorcon, Verna, Goa for providing the release controlling polymers, Tomita Pharmaceutical Co., Ltd. Japan for gifting Porous calcium silicate. The authors are also thankful to Mr. T. Jayapal Reddy, chairman, St. Peter's Institute of pharmaceutical Sciences, for providing required equipment and laboratory to carry on the research.

REFERENCES

1. Menachem E.B. New antiepileptic drugs and non-pharmacological treatments. Curr Opin Neurol. 2000; 13:165–170.
2. Brodie M J. Lamotrigine. Lancet 1992; 339: 1397–1400.
3. Bowden CL, Asnis GM, Ginsberg LD, Bentley B, Leadbetter R,White R. Safety and tolerability of lamotrigine for bipolar disorder. Drug Safety. 2004; 27:173-184.
4. Vincent D, Sylvie R R. DRESS syndrome. Joint Bone Spine. 2014; 81: 15–21.
5. Patrice C, Philippe M, Vincent D, Olivier M, Chris S, Laetitia F, et al. The DRESS Syndrome: A Literature Review. Am J Med. 2011; 124: 588–597.
6. Vincent D, Sylvie R R, Philippe M, Annick B. Le DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms. Rev Rhum 2011; 78: 197–200.
7. Ketter TA, Wang PW, Chandler RA, Alarcon AM, Becker OV, Nowakowska C, et al. Dermatology precautions and slower titration yield low incidence of lamotrigine treatment emergent rash. J Clin Psychol.2005; 66: 642-5.
8. Sach B, Ronnau AC, Ruzicka T, Gleichmann E, Schuppe HC. Lamotrigine and toxic epidermal necrolysis. Lancet1996; 348: 1597.
9. Fogh K, Mai J. Toxic epidermal necrolysis after treatment with lamotrigine (Lamictal). Seizure. 1997; 6: 63–65.
10. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine-induced severe cutaneous adverse reaction. Epilepsia.1998; 39: 22–26.
11. Guberman AH, Besag FM, Brodie MJ. Lamotrigine-associated rash: risk/benefit consideration in adults and children. Epilepsia.1999; 40: 985–991.
12. Mohana Raghava SK, Lakshmi PK, Balasubramaniam J. Design of a novel bilayered gastric mucoadhesive system for localized and unidirectional release of lamotrigine. Saudi Pharm. J.2013; 21: 45-52.
13. Grasela TH, Fiedler-Kelly J, Cox E, Womble GP, Risner ME, Chen C. Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. J Clin Pharmacol. 1999; 39: 373-384.
14. Morkhade DM, Fulzele SV, Gum Copal, Gum Damar. Novel Matrix forming Materials for Sustained Drug delivery. Int J of Pharm Sci 2004; 53-58.
15. Cheng CL, Chou CH, Hu OY. Determination of lamotrigine in small volumes of plasma by high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci. 2005; 817:199–206.
16. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastroretentive drug delivery system for ofloxacin: In vitro and in vivo evaluation. Int J Pharm. 2005; 304:178–84.
17. Pavan KG, Prasad GS. Physicochemical properties of lamotrigine and its compatibility with various inactive ingredients to formulate Lamotrigine orally disintegrating tablets Int. J. Pharm. Biologica Archives. 2013; 4: 94-95.
18. Silverstein RM, Webster FX. Spectrophotometric identification of organic compounds. Willy J. and Sons Inc. 2003; 71-109.
19. Carr RL. Evaluating Flow Properties of Solids. Chem. Eng. 1965; 72, 163–168.
20. The Indian Pharmacopoeia. Ministry of Health and Family Welfare. Govt. of India. The Controller of publication: New Delhi, 1996; 2,736.
21. Fell JT, Newton JM. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 1970; 59: 688–691.
22. Rudnic ED, Schwartz JB. Oral solid dosage form. Remington, The science and practice of pharmacy; Beringer, p, 21st Eds; 2nd; B. I. Publications Pvt Ltd. 2006; 1: 900.
23. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy; Eds; 3rd; Varghese Pub. House: Bombay, 2003; 297-299.
24. Zou H, Jiang X, Kong L, Gao S. Design and evaluation of a dry coated drug delivery system with floating pulsatile release.J.Pharm. Sci.2008; 97:263-273.
25. Srivastava. AK, Wadhwa S, Ridhukar D, Mishra. Oral sustained delivery of Atenolol from floating matrix tablets formulation and evaluation. Drug Develop and Industrial Pharm. 2005; 31: 367-374.
26. Banker GS, Anderson, NR. Tablets. The theory and practice of industrial pharmacy: Lachman L, Lieberman HA, Kanig JL. Eds; 3rd; Varghese Pub. House: Bombay, 2003; 297-299.
27. Londhe S, Gattani S, Surana S. Development of floating drug delivery system with biphasic release for Verapamil Hydrochloride: In-vitro and In-vivo evaluation. J. Pharm. Sci. and Tech. 2010; 2: 361-367.
28. Varahala Setti ML, Vijaya Ratna J. Preparation and evaluation of controlled-release tablets of carvedilol. Asian J Pharm. 2009; 3: 252-256.
29. Honey G, Nishant V, and Vikas R. A Novel Approach to Optimize and Formulate Fast Disintegrating Tablets for Nausea and Vomiting. AAPS PharmSciTech. 2008; 9: 774–781.
30. Carstensen JT. Drug stability principles and practice. Eds; 3rd; Marcel Dekker, Inc: New York, 145-189.