



Received on 26 August, 2014; received in revised form, 21 November, 2014; accepted, 27 December, 2014; published 01 April, 2015

FORMULATION DEVELOPMENT AND EVALUATION OF LAMOTRIGINE SUSTAINED RELEASE TABLETS USING 3^2 FACTORIAL DESIGN

Raghavendra Kumar Gunda*, J. N. Suresh Kumar, Ch Ajay Babu and M. V. Anjaneyulu

Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt) - 522601, Andhra Pradesh, India

Keywords:

Lamotrigine, Factorial Design, Sustained Release Tablet, HPMC K4M, HPMC K100M, Non Fickian Mechanism

Correspondence to Author: Raghavendra Kumar Gunda

Assistant Professor,
Department of Pharmaceutics,
Narasaraopeta Institute of
Pharmaceutical Sciences,
Narasaraopet, Guntur (Dt.) - 522601,
A.P., India


E-mail: raghav.gunda@gmail.com

ABSTRACT: The main objective of present investigation is to formulate the sustained release tablet of lamotrigine using 3^2 factorial design. Lamotrigine, a weakly basic and anticonvulsant drug belongs to BCS Class II, having high permeability and poor solubility. The sustained release tablets of lamotrigine were prepared employing different concentrations of HPMC K4M and HPMC K100M in different combinations as a rate retarding polymer by wet granulation technique using 3^2 factorial design. The quantity of polymers, HPMC K4M and HPMC K100M required to achieve the desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$) and 50% ($t_{50\%}$) were selected as dependent variables. Totally nine formulations were designed and are evaluated for hardness, friability, diameter, thickness, % drug content, *In-vitro* drug release. From the Results it was concluded that all the formulation were found to be within the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for $t_{50\%}$, $t_{10\%}$, k_1 . According to SUPAC guidelines the formulation (F_5) containing combination of 12.5% HPMC K4M and 12.5% HPMC K100M, is the most similar formulation (similarity factor $f_2=85.01$ & No significant difference, $t=-0.0102$) to marketed product (Lamictal). The selected formulation (F_5) follows Higuchi's kinetics, and the mechanism of drug release was found to be Anomalous type (Non-Fickian, $n=0.841$).

INTRODUCTION: Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. The frequency with which a rapidly absorbed and distributed drug must be given in a conventional dosage form is dependent upon intrinsic properties of the drug, viz. elimination half-life ($t_{1/2}$)¹.

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration². Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules into a matrix in slowly disintegrating or inert porous material containing a hydrophilic rate controlling polymer^{3, 4, 5}.

Cellulose ethers such as hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (Na CMC),

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.6(4).1746-52</p>
<p>Article can be accessed online on: www.ijpsr.com</p>	
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1746-52</p>	

copolymers of acrylic-methacrylic acid (Eudragits) such as Eudragit RL and RS and some natural gums like guar gum and xanthan gum are widely used hydrophilic polymers as release retardant⁶.

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process.

Lamotrigine is an anti epileptic drug and it is approved in the united states for the treatment of partial seizures and bipolar disease, belongs to class-II under BCS Classification and exhibit oral Bioavailability of about 98%^{7, 8}. It is available as immediate release and sustained release formulations in the market with different strengths such as 25 mg, 50 mg and 100 mg. In 2009 GSK received FDA approval for extended release version of Lamotrigine (Lamictal-XR)^{9, 10}. In the present work, lamotrigine was selected as a model drug and is formulated into sustained release (SR) tablet with an aim to enhance patient compliance.

Chemically lamotrigine is 6-(2, 3-dichlorophenyl)-1,2,4- triazine-3,5-diamine. Lamotrigine inhibits sodium currents by selectively binding to the inactivated state of the sodium channel and subsequently suppresses the release of the excitatory amino acid, glutamate¹¹. Hence, the objective of this research work was to prepare sustained release tablet of lamotrigine using hydroxypropyl methylcellulose (HPMC) of different grades K4M and K100M (their concentrations were optimised) by wet granulation method and applied the different kinetic models to study the drug release mechanisms.

A 3² full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of HPMC K4M and HPMC K100M on the dependent variables, i.e. $t_{50\%}$, $t_{10\%}$, k_1 (Time taken to release 50% of drug, Time taken to release 10% of drug from dosage form, first order rate constant respectively)

MATERIALS AND METHODS:

Materials used in this study were obtained from the different sources. Lamotrigine was a gift sample from Aurobindo pharma Ltd, Hyderabad, India. HPMC K4M and HPMC K100M were procured from colorcon Asia Pvt Ltd, Goa. Other excipients such as mannitol and magnesium stearate were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Lamotrigine Sustained Release Tablets:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses¹².

A selected three level, two factor experimental design (3² factorial design) describe the proportion in which the independent variables HPMC K4M, HPMC K100M were used in formulation of lamotrigine sustained release (SR) Tablets. The time required for 10% ($t_{10\%}$) and 50% ($t_{50\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p < 0.05$) for Final Equations. Polynomial equations were developed for $t_{50\%}$, $t_{10\%}$, k_1 (step-wise backward Linear Regression Analysis).

The three levels of factor X₁ (HPMC K4M) at a concentration of 7.5%, 12.5%, 17.5%. three levels of factor X₂ (HPMC K100M) at a concentration of 7.5%, 12.5%, 17.5% (% with respect to total tablet weight) was taken as the rationale for the design of the lamotrigine SR tablet formulation. Totally nine lamotrigine sustained release tablet formulations were prepared employing selected combinations of the two factors i.e X₁, X₂ as per 3² Factorial and evaluated to find out the significance of combined effects of X₁, X₂ to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form.

Preparation of Lamotrigine Sustained Release Tablets:

All the ingredients were weighed accurately and passed through 40# sieve, blended in a Poly bag

except magnesium stearate for 10 minutes. The obtained mixture was wet massed using water (qs) for granulation and was passed through 20# sieve in order to form granules. These granules were dried and were passed through 30# sieve. These dried granules were lubricated with magnesium stearate, which was previously passed through 60# Sieve. The lubricated granules were punched in to tablets using rotary tablet punching machine (RIMEK), Ahmedabad).

Experimental Design:

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMC K4M was taken as X_1 and concentration of HPMC

K100M was taken as X_2 . Experimental design was given in the Table 1. Three levels were selected and coded as $-1=7.5\%$, $0=12.5\%$, $+1=17.5\%$. Formulae for all the experimental batches were given in Table 2¹³.

TABLE 1: EXPERIMENTAL DESIGN LAYOUT

Formulation Code	X_1	X_2
F ₁	1	1
F ₂	1	0
F ₃	1	-1
F ₄	0	1
F ₅	0	0
F ₆	0	-1
F ₇	-1	1
F ₈	-1	0
F ₉	-1	-1

TABLE 2: FORMULAE FOR THE PREPARATION OF LAMOTRIGINE SUSTAINED RELEASE TABLETS AS PER EXPERIMENTAL DESIGN

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
Lamotrigine	200	200	200	200	200	200	200	200	200
Mannitol	58	78	98	78	98	118	98	118	138
HPMC K4M	70	70	70	50	50	50	30	30	30
HPMC K100M	70	50	30	70	50	30	70	50	30
Purified Water	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total Weight	400	400	400	400	400	400	400	400	400

Evaluation of Lamotrigine Sustained Release Tablets:

Hardness:¹⁴

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm² is considered adequate for mechanical stability.

Friability:¹⁴

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

$$\text{Friability (\%)} = \frac{[(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100}{}$$

Content Uniformity:¹⁴

In this test, 20 tablets were randomly selected and the percent drug content was determined, the

tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay:

Weighed and finely powdered not less than 20 tablets were taken and transfer an accurately weighed portion of the powder equivalent to about 200 mg of lamotrigine in to a 100 ml volumetric flask. Add approximately 60ml of methanol and shake and sonicate for 10 min to complete the extraction and dilute the methanolic solution with water to make up the volume. From this, pipette out a 2ml aliquot into a 100ml volumetric flask, dilute with mobile phase up to required volume and mixed well. The obtained solution was filtered through the whatman filter paper and the absorbance of solution was measured at 254 nm using UV-visible spectrophotometer.

Thickness and Diameter:¹⁴

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet

between two arms of the vernier calipers. The similar procedure was followed to measure the diameter.

In-vitro Dissolution Study:

The *In-vitro* dissolution study for the lamotrigine sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for 12 hours at 50 rpm and temperature $37\pm 0.5^\circ\text{C}$. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 254 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

Kinetic modeling of drug release:

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release^{15, 16, 17}.

RESULTS AND DISCUSSION:

Sustained release tablets of lamotrigine were prepared and optimized by 3^2 factorial design in order to select the best combination of different rate retarding polymers, HPMC K4M, HPMC K100M and also to achieve the desired prolong/sustained release of drug from the dosage form. The two factorial parameters involved in the development of formulations are, quantity of HPMC K4M & HPMC K100M polymers as independent variables (X_1 , X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$ & K_1 as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 200 mg of lamotrigine were prepared as a sustained release tablet dosage form by wet granulation technique as per the formulae given in **Table 2**.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean diameter, mean thickness as per official methods and results are given in **Table 3**. The hardness of tablets was in the range

of 4.3-5.0 Kg/cm². Weight loss in the friability test was less than 0.52%. Drug content of prepared tablets was within $97\pm 3.56\%$. *In-vitro* Dissolution studies were performed for prepared tables using 0.1 N HCl as a dissolution media. The *In-vitro* dissolution profiles of tablets are shown in **Fig.1** and the dissolution parameters are given in **Table 4**.

Much variation was observed in the dissolution rate (K_1), $t_{10\%}$, $t_{50\%}$ due to formulation variables. Formulation F₅ containing 50 mg of HPMC K4M, 50 mg of HPMC K100M showed promising dissolution parameter ($K_1=0.123$, $t_{10\%}= 0.856$ h, $t_{50\%} = 5.635$ h). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation¹⁸.

The *In -vitro* dissolution data of lamotrigine SR formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release.

The results of linear regression analysis including regression coefficients are summarized in **Table 4** and plots shown in **Fig.1, 2, 3, 4**. It was observed from the above that dissolution of all the tablets followed first order kinetics (except F₇) with coefficient of determination (R^2) values above 0.946. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.973-0.996, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism.

Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.406- 0.915 (except F₆=0.178, F₈=0.237) that shows Non-Fickian diffusion mechanism. Polynomial equations were derived for k_1 , $t_{50\%}$ and $t_{10\%}$ values by backward stepwise linear regression analysis. The dissolution data of factorial formulations F₁ to F₉ are shown in **Table 5**.

Polynomial equation for 3² full factorial designs is given in Equation

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \dots$$

Where, Y is dependent variable, b₀ arithmetic mean response of nine batches, and b₁ estimated coefficient for factor X₁. The main effects (X₁ and X₂) represent the average result of changing one factor at a time from its low to high value. The interaction term (X₁X₂) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X₁² and X₂²) are included to investigate non-linearity. The equations for K₁, t_{10%} and t_{50%} developed as follows,

$$Y_1 = 0.387 - 0.256X_1 - 0.321X_2 + 0.194X_1X_2 \text{ (for } K_1)$$

$$Y_2 = 0.949 + 0.364X_1 + 0.393X_2 - 0.557X_1X_2 \text{ (for } t_{10\%})$$

$$Y_3 = 6.25 + 2.45X_1 + 4.30X_2 - 3.580X_1X_2 \text{ (for } t_{50\%})$$

The positive sign for co-efficient of X₁ in Y₂ and Y₃ equations indicates that, as the concentration of HPMC K4M increases, t_{10%} and t_{50%} value increases. In other words the data demonstrate that both X₁ (amount of HPMC K4M) and X₂ (amount of HPMC K100M) affect the time required for drug release (t_{50%} and t_{70%}). From the results it can be concluded that, and increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X₁ and X₂ levels. The final best (Optimised) formulation (F₅) is compared with marketed product (Lamictal) shows similarity factor (f₂) 85.016, difference factor (f₁) 2.422 (There is no significant difference in drug release because t_{cal} is < 0.05).

TABLE 3: POST-COMPRESSION PARAMETERS FOR THE FORMULATIONS

S.No.	Formulation Code	Hardness (kg/cm ²)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug Content (%)
1	F ₁	4.6	9.51	5.00	0.44	97.21±5.6
2	F ₂	4.5	9.50	5.10	0.51	97.26±3.4
3	F ₃	4.9	9.51	4.95	0.37	97.20±1.5
4	F ₄	4.8	9.50	5.12	0.49	97.01±2.0
5	F ₅	4.9	9.50	5.11	0.35	97.00±4.5
6	F ₆	5.0	9.51	5.00	0.31	97.00±5.6
7	F ₇	4.3	9.50	5.21	0.49	97.15±4.5
8	F ₈	4.6	9.50	5.10	0.41	97.22±1.8
9	F ₉	4.6	9.51	5.10	0.39	97.08±3.2

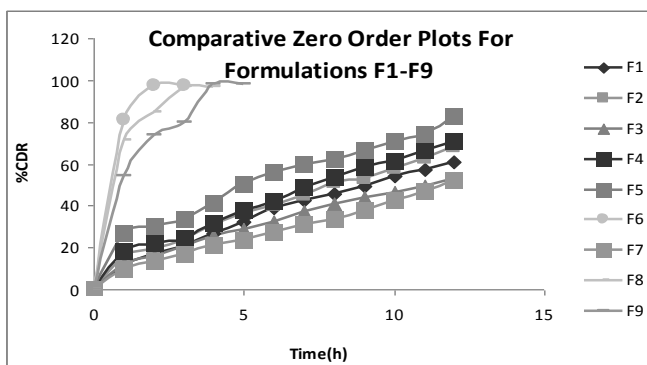


FIG. 1: COMPARATIVE ZERO ORDER PLOTS OF F₁-F₉

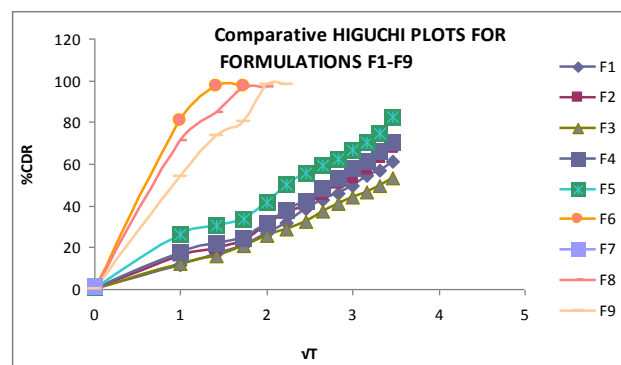


FIG. 3: COMPARATIVE HIGUCHI PLOTS OF F₁-F₉

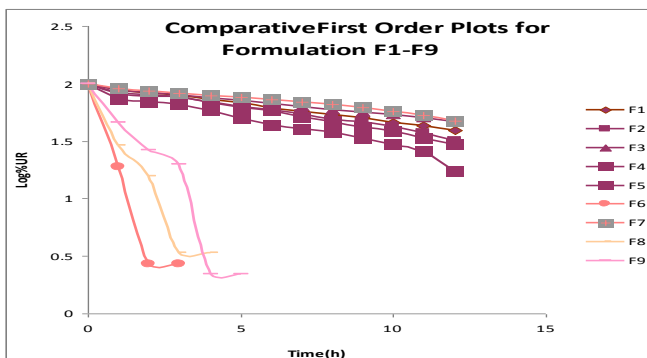


FIG. 2: COMPARATIVE FIRST ORDER PLOTS OF F₁-F₉

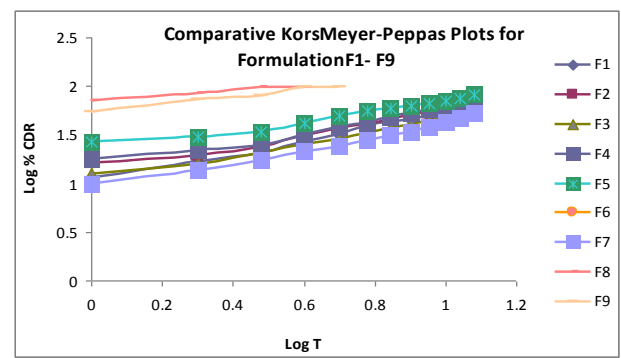


FIG. 4: COMPARATIVE KORSMEYER-PEPPAS PLOTS

TABLE 4: REGRESSION ANALYSIS DATA OF 3² FACTORIAL DESIGN FORMULATIONS OF LAMOTRIGINE

S.No	Formulation Code	Kinetic Parameters											
		Zero Order			First Order			Higuchi			Korsmeyer-Peppas		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F ₁	6.26	4.818	0.990	1.99	0.03	0.998	6.55	18.54	0.986	0.840	0.915	0.980
2	F ₂	8.16	5.120	0.988	1.989	0.037	0.994	5.545	19.74	0.987	0.909	0.883	0.977
3	F ₃	7.041	4.037	0.986	1.980	0.025	0.997	3.996	15.67	0.991	0.866	0.823	0.982
4	F ₄	8.842	5.382	0.988	1.99	0.041	0.994	5.546	20.74	0.986	0.937	0.877	0.975
5	F ₅	15.93	5.74	0.967	1.97	0.053	0.984	0.863	22.77	0.993	1.053	0.841	0.944
6	F ₆	22.65	30.83	0.855	1.869	0.555	0.947	7.1	59.61	0.964	1.915	0.178	0.931
7	F ₇	4.153	3.893	0.994	1.995	0.024	0.989	5.65	14.738	0.973	0.798	0.8378	0.991
8	F ₈	26.01	21.87	0.856	1.917	0.387	0.971	8.235	50.05	0.968	1.85	0.237	0.981
9	F ₉	22.42	17.92	0.911	2.062	0.354	0.96	2.311	47.81	0.995	1.733	0.406	0.988
10	MP	17.32	5.719	0.960	1.961	0.054	0.985	0.119	22.895	0.995	1.066	0.8406	0.934

F₁ to F₉ are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Marketed Product.

TABLE 5: DISSOLUTION PARAMETERS OF LAMOTRIGINE SUSTAINED RELEASE TABLETS 3² FULL FACTORIAL DESIGN BATCHES

S.NO	Formulation Code	Kinetic Parameters			
		t _{1/2} (h)	t ₁₀ (h)	K(h ⁻¹)	r
1	F ₁	9.164	1.393	0.076	0.998
2	F ₂	7.986	1.214	0.087	0.994
3	F ₃	11.761	1.788	0.059	0.997
4	F ₄	7.256	1.103	0.095	0.994
5	F ₅	5.635	0.856	0.123	0.984
6	F ₆	0.542	0.082	1.279	0.947
7	F ₇	12.575	1.911	0.055	0.989
8	F ₈	0.776	0.118	0.893	0.971
9	F ₉	0.851	0.129	0.814	0.96
10	MP	5.584	0.849	0.124	0.985

CONCLUSIONS: The present research work envisages the applicability of hydrophilic polymers such as HPMC K4M and HPMC K100M in the design and development of sustained release tablet formulations of lamotrigine utilizing the 3² factorial design. From the results it was clearly understood that as the polymer concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods.

The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be Non Fickian, anomalous type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F₅ may be used once a day administration in the management of epilepsy.

ACKNOWLEDGEMENTS: The authors would like to thank Management, Principal, Teaching,

Non-teaching Staff of Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (D.t), A.P., India for providing support for successful completion of research work.

REFERENCES:

1. Sood A, Panchagnula R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. *Int J Pharma* 2003; 261: 27-41.
2. Agoram B, Woltosz BWS, Bolger MB. Predicting the impact of physiological and biochemical processes oral drug bioavailability. *Adv Drug Delivery Rev.* 2001; 50: 41-67
3. Bravo SA, Lamas MC, Salamon CJ. *In-vitro* studies of diclofenac sodium controlled-release from bio-polymeric hydrophilic matrices. *J Pharm Pharma Sci* 2002; 5: 213-219.
4. Basak SC, Jayakumar RBM, Lucas MK. Formulation and release behavior of sustained release Ambroxol hydrochloride HPMC matrix tablet. *Indian J Pharma Sci* 2006; 68(5): 594-597.
5. Dandagi, PM, Mastiholimat VS, Patil MB, Manvi FV, Gagad AP, Sharma R. Development and evaluation of Theophylline and Salbutamol sulphate sustained release matrix tablets. *Indian J Pharma Sci* 2005; 67(5): 598-602
6. Arthur HK. *Handbook of Pharmaceutical Excipients*. 3rd ed. London: American Pharmaceutical Association; 2000. pp. 463-464.

7. L. Mladena, P. Ana, G. K. Svetlene and G. B. Ksenija, Comparison of Dissolution Profiles and Serum Concentrations of Two Lamotrigine Tablet Formulations; *Drugs in R & D*; 2011; 11(1), 53-60.
8. <http://en.wikipedia.org/wiki/Lamotrigine>
9. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.drugDetails>
10. http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020241s10s21s25s26s27,020764s3s14s18s19s20lbl.pdf
11. The Science and Practice of Pharmacy, Remington part-I, 20th Edition-2000, Published by Philadelphia college of pharmacy & Science. p.558
12. Kharia, et al, Design and Optimization of Floating Drug Delivery System of Acyclovir, *Indian J. Pharm. Sci.*, 2010, 72 (5): 599-606
13. Ramesh C. Nagarwal, et al, In Situ Forming Formulation: Development, Evaluation, and Optimization Using 3^3 Factorial Design, *AAPS Pharm Sci Tech*, 2009; Vol. 10, No. 3, 977-984.
14. K.P.R. chowdary, et al, optimization of valsartan tablet formulation by 2^3 factorial design, *JGTPS*, 2014; Volume 5, Issue 1, 1374-1379.
15. Notari RE. Biopharmaceutics and clinical pharmacokinetics. 4th ed. New York: Marcel Dekker Inc; 1987. p. 6-21.
16. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci* 1963; 51:1145-9.
17. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv* 1985; 60:110-1.
18. Dortunc B, Gunal N. Release of acetazolamide from swellable Hydroxypropylmethylcellulose matrix tablets. *Drug Dev Ind Pharm* 1997; 23:1245-9.

How to cite this article:

Gunda RK, Kumar JNS, Babu CA and Anjaneyulu MV: Formulation Development and Evaluation of Lamotrigine Sustained Release Tablets Using 3^2 Factorial Design. *Int J Pharm Sci Res* 2015; 6(4): 1746-52. doi: 10.13040/IJPSR.0975-8232.6 (4).1746-52.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)