Research Article

Development and Optimization of Push Pull Osmotic Tablets of Lamotrigine Using Design of Experiments

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ABSTRACT

The purpose of the research was to develop and optimize the osmotic drug delivery system of Lamotrigine, an anticonvulsant drug using Design of Experiments. Design Expert was used to study the impact of formulation variables of core tablets and the functional coating variables in two different stages. The Push-pull osmotic drug delivery system was selected as a suitable system since Push-pull osmotic drug delivery system is the preferred system for the highly insoluble drugs like lamotrigine. The formulation development reveals that the Polyethylene oxide of drug layer and the push layer, sodium chloride of push layer and polyethylene glycol of the functional coating impacted the release profile at 24 hours of the osmotic drug delivery system.

Keywords: Design of experiments, Lamotrigine, Push-pull osmotic drug delivery system.

INTRODUCTION

Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens.[1–3] Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food intake or that are dependent on patient age.[2–4] One of the most promising technologies is the orally controlled osmotic drug delivery system.[4–6]

Adherence to treatment is an important determinant of clinical outcomes for patients in a wide range of clinical settings. Particularly in CNS drugs were patients often require treatment for months or years and premature discontinuation of treatment can have serious consequences for patient health and quality of life. Patients fail to take medication as directed for many different reasons: they may feel better and may decide that treatment is no longer necessary; they may experience disagreeable side effects; they may find medication schedules inconvenient; they may be unable to afford to fill their prescriptions; they may simply forget to take their medication; or they may be concerned that taking pills may betray desired confidentiality about being ill and needing treatment, as opposed to an injection, which takes place in the privacy of the doctor's office. Regardless of the specific reason for treatment non adherence, the failure of patients to continue to take medication as prescribed contributes to high rates of relapse, hospitalization, and in some patients (e.g., patients with major depressive disorder, bipolar disorder, or schizophrenia) an increased risk of death.[7]

Poor treatment adherence can be especially difficult in patients with mental illness. Psychotic disorders may profoundly affect patient insight into the severity of the condition or the effects of treatment, and non adherence to treatment has been described as the single most common cause of relapse and re hospitalization in patients with CNS drugs. Patients with depression often experience significant medication side effects well before the beneficial treatment effects begin to emerge, and patients with bipolar disorder may find their manic episodes rewarding. Many studies have found that large numbers of mentally ill patients often go days or weeks with unfilled prescriptions. However, even when patients have adequate supplies of medication, they may not take their medications as needed.

During the last several years, a number of new "extended release" or "sustained release" medication formulations have entered psychiatry practice. Many medications that once required two or three daily doses are now available in once-daily formulations. These new formulations offer patients greater convenience and privacy, many controlled clinical trials have also shown that extended-release agents are associated with improved tolerability, greater patient adherence to treatment, reduced total treatment costs, and better long-term clinical outcomes. Osmotic drug delivery systems are one of the extended drug delivery system having advantages over other extended drug delivery systems, like the zero order rate delivery, minimal side effects, minimal effect of food on the delivery, unaffected delivery regardless of pH conditions of the GIT.

Lamotrigine tablets are available as immediate release and sustained release dosage formulations. In 2009 GlaxoSmithKline received FDA Approval for an extended-release version of lamotrigine branded Lamictal

XR. Lamictal XR tablets are a novel preparation of lamotrigine, delivered in a tablet with an enteric coating that GlaxoSmithKline has branded DiffCORE.[8-9]

In the present work, an osmotic drug delivery of lamotrigine was developed which will have a zero order drug delivery rate so the plasma concentration of the drug will remain constant throughout the treatment period ensuring a better result in the management of convulsive disorders.

MATERIALS AND METHODS

The lamotrigine was received as gift sample from Alembic Pharmaceuticals Limited; Butylated hydroxyl toluene, Sodium lauryl sulfate, Sodium chloride was received from Merck; Polyethylene Oxide and cellulose acetate was received from signet; Polyvinyl pyrrolidone was received from ISP; Dibasic calcium phosphate from Innophos; Magnesium stearate from Ferro; iron oxide and Propylene glycol from Alembic Limited; Triethyl citrate from Vertellus performance.

Study of formulation factors (core tablet)

Method of preparation

The type of Osmotic Drug delivery System used for work was Push Pull osmotic system. In this system we have used the bi-layer core tablets surrounded by a semi-permeable membrane with a Mechanical-drilled orifice developed to deliver drugs independently of their solubility, the tablet-core composition contains mainly polymers and drugs. It allows drug delivery through the orifice as either a solution or dispersion under the hydrodynamic pressure generated by the swelling of the so-called 'push-layer'.

The method of manufacturing of the Push Pull osmotic system involves the wet granulation of both drug and the push layer followed by the compression in to bi layer tablet using tablet compression machine. The compressed tablets are coated with the semi-permeable membrane using suitable solvent system in the perforated automatic coating pan. Finally the coated tablets were drilled manually using mechanical drills.

Design of Experiment

A 2^{4-1} partial factorial Design of Experiments (DOE) with three center points was used to study the impact of the four formulation factors of the core tablets of osmotic drug delivery system on the response variables. The details of formulation trials planned using the Design of experiments for the formulation variables of core tablets in the osmotic drug delivery systems are provided in the Table 1.

Evaluation of tablet diameter, tablet thickness

The tablet diameter and thickness was estimated using vernier caliper.

Determination of assay

Assay of prepared osmotic system was carried out by Chromatographic method using HPLC.

In-vitro dissolution

The formulated tablets are further evaluated for their in-vitro dissolution profile in 6.8 phosphate buffer using USP-II with a volume of 900ml at 75 RPM. The dissolution profile was carried for 24 hours at periodical intervals.

Study of formulation factors (coating)

Coating Procedure

The Cellulose acetate was dissolved in Ethanol and dichloromethane using mechanical stirrer. Once the cellulose acetate was dissolved completely to form clear solution, propylene glycol and Triethyl citrate (TEC) was added and stirred for 15-30 min.

The prepared solution was uniformly coated on to the compressed bi-layered tablets using perforated coating pan to provide suitable weight gain.

Design of experiments for the coating optimization

A 2^2 full factorial Design of Experiments (DOE) with three center points was used to study the impact of these three formulation factors (Coating) on the response variables. The formulas for the designed trials were given in the Table 2.

RESULTS AND DISCUSSION

An osmotically regulated oral tablet of lamotrigine was developed with an intention to make a successful once daily dosing for the treatment of convulsant. In this present work the formulation development as well as optimization was carried out with the help of design of experiments.

The push pull type of osmotic systems was selected as lamotrigine proved to be highly water insoluble drug. The formulation development and optimization was carried out in two parts,

1) The development and optimization of core tablets and

2) Optimization of coating.

For the development and optimization of core tablets a 2^{4-1} partial factorial design was chosen. Eleven trails were carried out including 3 centre points. The formula of the trial 1-11 was given in the Table 1. The developed tablets were evaluated for thickness, tablet diameter and assay. The dissolution of each formulation was carried out and the result was given in the Figure 1.

The R^2 value of the formulations ranges from 0.9843 – 0.9974. The ANOVA analysis of effect of formulation factors on the R^2 was proven that none of the formulation factor at the selected range was having a significant effect on the release rate (R^2). The results of the study is tabulated and provided in the Table 3.

Table 1: Formulation details to study the effect of formulation variables of the core tablets of Osmotic drug delivery system.

Ingredients	Trial - 1	Trial - 2	Trial - 3	Trial - 4	Trial - 5	Trial - 6	Trial - 7	Trial - 8	Trial - 9	Trial - 10	Trial - 11
	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
Drug layer											
Lamotrigine	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Dibasic Calcium Phosphate	68.23	43.20	53.83	53.83	64.48	64.48	39.45	53.83	43.20	39.45	68.23
PEO 200 K (WSR N 80)	25.00	50.00	37.50	37.50	25.00	25.00	50.00	37.50	50.00	50.00	25.00
Sodium chloride	3.75	3.75	5.63	5.63	7.50	7.50	7.50	5.63	3.75	7.50	3.75
BHT	0.03	0.05	0.04	0.04	0.03	0.03	0.05	0.04	0.05	0.05	0.03
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Push layer											
PEO 5000 K (WSR Coagulant)	75.00	37.50	56.25	56.25	75.00	37.50	75.00	56.25	75.00	37.50	37.50
Dibasic Calcium Phosphate	7.63	45.16	30.14	30.14	15.13	45.16	7.63	30.14	15.13	52.66	52.66
Sodium chloride	15.00	15.00	11.25	11.25	7.50	15.00	15.00	11.25	7.50	7.50	7.50
BHT	0.08	0.04	0.06	0.06	0.08	0.04	0.08	0.06	0.08	0.04	0.04
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Iron oxide Red	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Functional coating											
Cellulose acetate 398-6	21	21	21	21	21	21	21	21	21	21	21
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
DCM	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Propylene Glycol	2	2	2	2	2	2	2	2	2	2	2
TEC	2	2	2	2	2	2	2	2	2	2	2
Total Weight of Coating	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Total tablet weight	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**

Table 2: Formulation details to study the effect of Propylene glycol and TEC in functional coating

Ingredients	Trial - 12	Trial - 13	Trial - 14	Trial - 15	Trial - 16	Trial - 17	Trial – 18
Core tablet							
Lamotrigine	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Dibasic Calcium Phosphate	39.45	39.45	39.45	39.45	39.45	39.45	39.45
PEO 200 K (WSR N 80)	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Sodium chloride	7.50	7.50	7.50	7.50	7.50	7.50	7.50
BHT	0.05	0.05	0.05	0.05	0.05	0.05	0.05
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Push layer							
PEO 5000 K (WSR Coagulant)	75.00	75.00	75.00	75.00	75.00	75.00	75.00
Dibasic Calcium Phosphate	7.63	7.63	7.63	7.63	7.63	7.63	7.63
Sodium chloride	15.00	15.00	15.00	15.00	15.00	15.00	15.00
BHT	0.08	0.08	0.08	0.08	0.08	0.08	0.08
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Iron oxide Red	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Functional coating							
Cellulose acetate 398-6	21	23	19	21	21	21	21
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
DCM	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Propylene Glycol	1	1	3	2	3	2	2
TEC	3	1	3	2	1	2	2
Total Weight of Coating	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Total weight of the coated tablet	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**	**275.0**

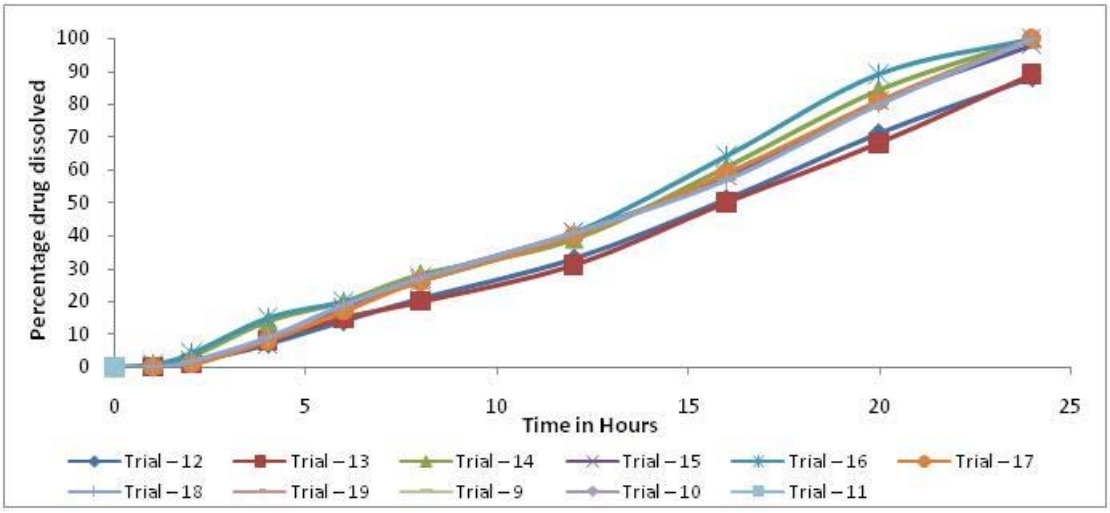

Figure 1: Dissolution profile of the trials used to optimize the core tablet of lamotrigine Osmotic drug delivery system

Table 3: Evaluation for the formulation trials to study the effect of formulation variables of the core tablets of Osmotic drug delivery system

	Trial - 1	Trial - 2	Trial - 3	Trial - 4	Trial - 5	Trial - 6	Trial - 7	Trial - 8	Trial - 9	Trial - 10	Trial - 11
Tablet Diameter	8.2 - 8.3 mm										
Tablet thickness	4.2 - 4.5 mm										
Orifice diameter	0.8 mm										
Assay	99.7	99.7	99.7	99.7	99.7	99.7	99.7	99.7	99.7	99.7	99.7
R^2 (Zero order)	0.9974	0.9921	0.9958	0.9926	0.9961	0.9909	0.9952	0.9906	0.9891	0.9854	0.9843

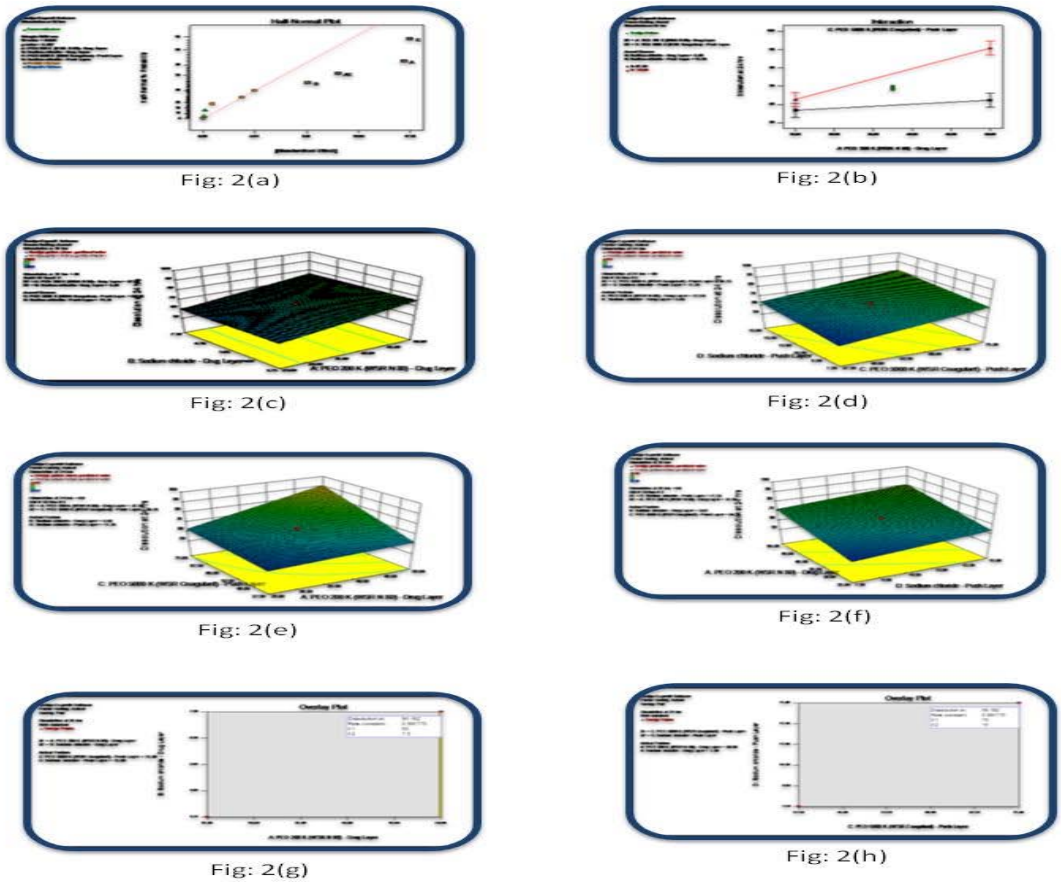

Figure 2: The effect of various formulation factors of core tablets on the release up to 24 hrs

Table 4: Initial evaluation of the Formulation details based on the DoE to study the effect of Propylene glycol and TEC in functional coating

	Trial - 12	Trial - 13	Trial - 14	Trial - 15	Trial - 16	Trial - 17	Trial – 18
Tablet Diameter	8.2 - 8.3 mm						
Tablet thickness	4.2 - 4.5 mm						
Orifice diameter	0.8 mm						
Assay	100.8	100.8	100.8	100.8	100.8	100.8	100.8
Rate Constant (R^2)	0.9903	0.9859	0.9917	0.995	0.9896	0.9945	0.994

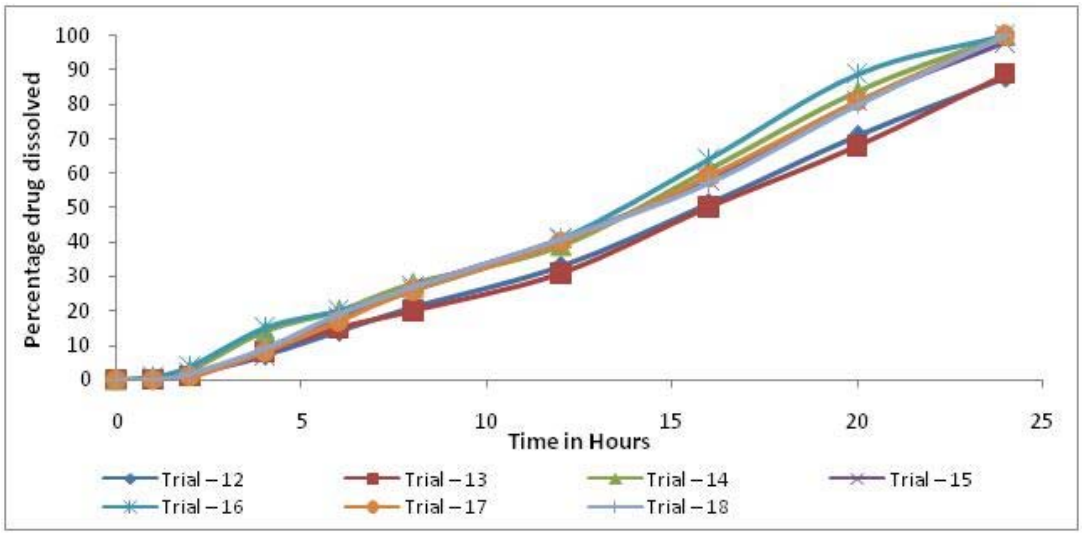

Figure 3: Dissolution profile of the formulation trials study the effect of formulation variables in functional coating

The effect of formulation factors on the release up to 24 hrs were studied with the help of ANOVA analysis. From the ANOVA analysis it was proved that the model selected was significant and the PEO in the drug layer (P =0.0003), Push layer (P = 0.0003), sodium chloride in the push layer (P = 0.0088), Interaction factor AC (P=0.0027) were identified as the significant factors affecting the release up to 24 hrs of lamotrigine from the tablets. A graphical representation of significant factors was shown as the Half normal plot in Figure 2 (a).The significant effect of interaction AC on release up to 24 hrs was shown in the Figure 2(b). Interactions occur when the effect of one factor depends on the level of the other. They cannot be detected by the traditional One-Factor-at-a-time (OFAT) experimentation. The figure shows two lines bracketed by least significant difference (LSD) bars at their end. The lines are not parallel, indicating quite different effects on the dissolution at 24 hours. When PEO-Push layer is low, the line is close to flat indicating the dissolution is unaffected by PEO- Drug layer. It could be concluded from the interaction plot that the high concentration of PEO-Drug layer & high concentration of PEO-Push layer would increase the dissolution profile.

The effect of various formulation factors on the release of lamotrigine up to 24 hrs were shown in the form of 3 D response plots. The Figure 2(c) of the formulation variable in drug layer clearly indicates no change in the dissolution profile by altering the concentration of variable B. However the change in concentration of Factor A has greater impact in the Dissolution profile. The Figure 2(d) of the formulation variable in push layer clearly indicates change in the dissolution profile by altering the concentration of variable D and C.

The Figure 2(e) of the formulation variable in drug and push layer, clearly indicates change in the dissolution profile by altering the concentration of variable A and C. The Figure 2(f) of the formulation variable in drug and push layer, clearly indicates change in the dissolution profile by altering the concentration of variable A and D.

Graphical Optimization of the core tablets

The optimization of the significant formulation factor was done with the help of overlay plot. The design space was identified to achieve the optimization. It is comprised of the contour plots from each response laid on top of each other. The overlay plot Figure 2(g) & (h) clearly mentions the effect of the formulation variables of the core tablets on the responses studied. The yellow zone indicates the all responses were achieved simultaneously and the grey zone indicates that one or more responses failed to meet the predefined criteria.

Study and optimization of formulation factors (coating)

Study and optimization of the formulation factors (coating) was done with the help of 2^2 full factorial Design of Experiments (DOE) with three center points. The impact of two formulation factors (Coating) on the response variables like dissolution at 24 hrs and zero

order rate constant were studied. The evaluation data of trial 12-18 was tabulated in Table 4. The dissolution profile up to 24 hr of trial 12-18 was given in the Figure 3.

A half normal plot of effect of factors on the dissolution up to 24 hrs was shown in the Figure 4(a). From the graph it was evident that the effect of A is very big relative to B. In a statistical sense, standout effect of factor A should be considered significant. In other words, we need to focus on the factor A and its effect on the response. ANOVA analysis also revealed the significance of factor A with a probability of 0.0092.

In order to represent the effect of factor A (TEC) and factor B (propylene glycol) on the release up to 24 hrs graphically a response surface plot was created and shown in the Figure 4(b). The surface plot of the formulation variable in drug layer clearly indicates no change in the dissolution profile by altering the concentration of variable B. However the change in concentration of Factor A has greater impact in the Dissolution profile.

Graphical Optimization of Coating

This is commonly done with the help of an overlay graph. It is comprised of the contour plots from each response laid on top of each other. The overlay plot (Figure 4(c)) clearly mentions the effect of the formulation variables of the coating on the responses studied. The yellow zone indicates the all responses were achieved simultaneously and the grey zone indicates that one or more responses failed to meet the predefined criteria.

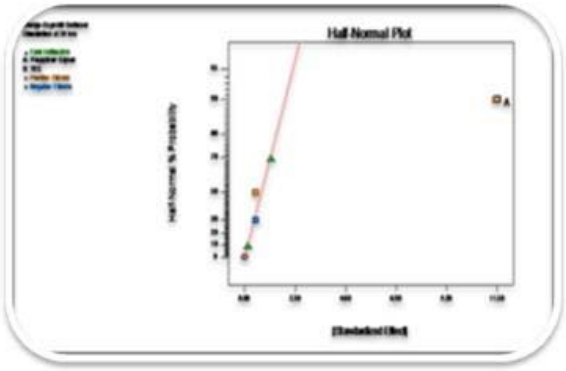

Figure 4(a)

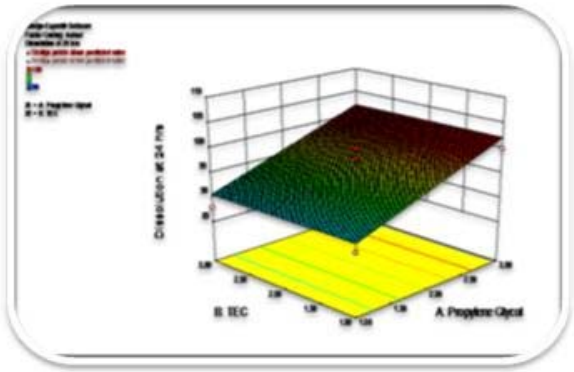

Figure 4(b)

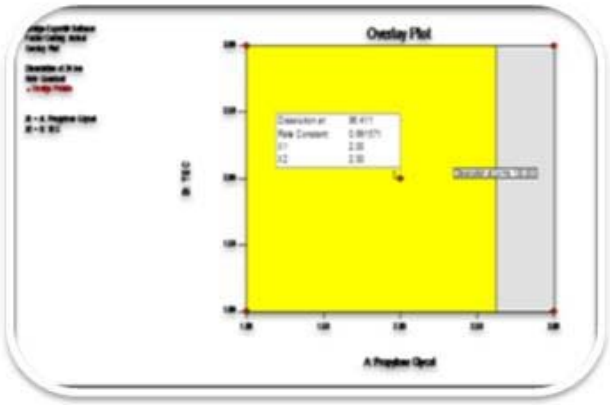

Figure 4(c)

Figure 4: The effect of various formulation factors of coating on drug release up to 24 hrs

CONCLUSION

Osmotically regulated oral tablet of lamotrigine was successfully developed and optimized with minimal number of trails and maximum understanding of the effects of formulation variables and the interaction effects of the formulation variables with the help of design of experiments. The formulation factors both core and coating were optimized with the help of overlay plots. The developed push pull osmotic tablets proved to be successful in delivering the drug in a controlled manner i.e at a zero order rate upto 24 hrs ensuring the once daily dosing for the treatment of convulsive disorders.

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