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RESEARCH ARTICLE

NATURAL CHEMISTRY

FORMULATION AND DEVELOPMENT OF EXTENDED RELEASED TABLET OF LAMOTRIGINE

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ABSTRACT

The present study was to develop once-daily extended release tablet of Lamotrigine, an Anti-convulsant. It is a phenyl triazines derivative showing effective anti-convulsant properties mainly used in effective in preventing seizure spread in the maximum electroshock (MES). The tablets were prepared by the wet granulation method. Lamotrigine using hydrophilic matrix material (Methocel K4M & Methocel K100LV) in combination with hydrophobic material (Eudragit L-30D-55) were used, which can release the drug upto 24hrs in predetermined rate. Diluents used were lactose monohydrate and magnesium starate as lubricant. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The formulated tablets were also characterized by physical and chemical parameters. The granules showed satisfactory flow properties, compressibility, and drug content. The in-vitro release rate profile showed the higher concentration of 04-50ERT polymer in tablet, the combination of hydrophilic in core and hydrophobic in coating polymer showed less result than use of a single polymer.


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KEY WORDS

Lamotrigine, Extended release tablet (ERT), Hydrophilic, Hydrophobic.

INTRODUCTION

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.

Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. The advantages of extended release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction in overall health care costs. The rate of drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings and controlling drug diffusion rates from dosage forms. Generally the different techniques employed to fabricate the modified release dosage forms are coated beads, granules and microspheres, multi tablet system, micro encapsulated drug, complex formation, ion exchange resins, and embedding drug in slowly eroding or hydrophilic matrix system.

The use of polymeric matrix devices to control the release of a variety of therapeutic agents has become increasingly important in the development of modified release dosage forms. This device may be a swellable, hydrophilic monolithic systems, erosion controlled monolithic systems or non erodible systems. The hydrophilic gel forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping. [1, 2, 3]

Lamotrigine is a newer anti-convulsant drug effective in preventing seizure spread in the maximum electroshock (MES). It is rapidly and completely absorbed after oral administration with negligible first-pass metabolism and requires multiple dosing (2-3 times daily) for maintaining therapeutic effect throughout the day. Lamotrigine drug is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of Anti-convulsant drug to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces.

In vitro pharmacological studies suggest that Anti-convulsant drug inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). Hence, to reduce the frequency of administrations and to improve patient compliance, lamotrigine is suitable candidate for making extended release dosage form.

Lamotrigine is water soluble drug so selection of polymer should be properly done. Preparation of extended release formulation by matrix technique is commonly employed method because of ease of preparation, flexibility and cost efficiency. In the present study, the polymer hypromellose (Methocel K 100 LV low viscosity with controlled release), Methocel E 4M (High viscosity with controlled release), Diluents used were lactose

monohydrate and magnesium starate as lubricant in core formulation and also coating polymer use as Polymethacrylates (Eudragit L 30 D55).

The objective of the present study is to formulate once-daily extended release formulation of lamotrigine, to study effect of polymer viscosity, polymer ratios and combination of hydrophilic as well as hydrophobic polymers on the pattern of drug release by in vitro dissolution testing and to compare it with theoretical release profile.

MATERIALS AND METHODS

HPMC K100 LV, HPMC E4M, Lactose monohydrate, Magnesium starate, Polymethacrylates (Eudragit L 30 D55), Triethyl citrate, Talc, Polyoxyethylene sorbitan fattyacid ester (Polysorbate 80), Calcium silicate, Colloidal silicon dioxide , Povidone (PVK 30), Aerosil, Iron oxide yellow/Red all the ingredients were of analytical grade.

Selection of Granulation Procedure:

Wet Granulation Procedure: was used for manufacturing Lamotrigine Extended-Release Tablets, for following reasons

1. To improve the API flow, compressibility characteristics by forming the granules.
2. Match the innovator dissolution profile.

Wet granulation was carried out by two ways:

a. Wet Granulation using Non-Aqueous Solvent
b. Wet Granulation using Aqueous Solvent: Using Rapid mixer granulator (RMG), Fluidized Bed Procedure: (FBP) or RMG with spray granulation.

Due to residual solvent issue, first approach i.e. Wet granulation using Non-aqueous solvent was not evaluated.

Therefore wet granulation using aqueous solvent was selected.

In Rapid mixer granulator (RMG) with binder pouring method problems like formation of hard granules due to high percentage of polymer concentration was observed and it was difficult to mill the granules.

Therefore alternate method, which simulates Fluid Bed Granulator, was selected; Rapid mixer granulator (RMG) with Top Spray Granulation was finalized to carry out further trials with wet granulation using aqueous solvent. [4]

Wet Granulation Method

Preparation of the core tablet by using aqueous wet granulation process

1. All the ingredients were weighed.
2. Lamotrigine, Methocel K100LV Premium CR, Methocel E4M and Lactose monohydrate sifted through 40 #.
3. Dry mix was granulated by purified water in Rapid Mixer Granulator (RMG) with spraying gun (1 mm diameter) keeping following parameters:
4. Granules were dried in FBD at 60ºC inlet temperature for 35 mins.
5. Co-milling the granules 10 # (0502), passed through 20# and the retentions further co-milled 12# (1575) followed by 18# (1016) and finally passed through 20#. LOD = 3.13 % at 105ºC.
6. B.D= 0.56 gm/ml and % fines (below 60#)= 43
7. Granules were lubricated with Magnesium stearate (60# passed) in Double Cone Blender for 3 mins.
8. The lubricated was compressed blend in to Tablets by using suitable tooling.
9. The prepared granules of were compressed on a 16 station Cad Mac Rotary compression machine by using 9.5 mm, SC, circular shape, plain punches.

Table 1
RMG Parameter.

Impeller Speed (rpm)	Chopper speed (rpm)	Stage of granulation	Time (sec)	Pump (rpm)	Air Atom. kg/cm^2
150rpm	Off	Dry mixing	300		
150rpm	Off	Solvent addition (30%)	75	38-42	0.2-0.3
200rpm	500rpm	Kneading	60		
150rpm	Off	Extra solvent (10%)	30	38-42	0.2-0.3
200rpm	500rpm	Kneading	60		
150rpm	Off	Discharge	15		

pray rate: 32-34 gm/min

FORMULATION BATCHES FOR 01-50ERT TO 04-50ERT
***Selection of suitable matrix polymer, its quantity and suitable coating system*:**

Table 2
Composition of core formulation.

Sr. No.	Ingredients	% of polymer use in 01-50ERT	01-50ERT Mg/tab	% of polymer use in 02-50ERT	02-50ERT Mg/tab	% of polymer use in 03-50ERT	03-50ERT Mg/tab	% of polymer use in04-50ERT	04-50ERT Mg/tab
				INTRAGRANULAR					
1	Lamotrigine API	14.28	50	14.28	50	14.28	50	14.28	50
2	Methocel K100LV	15	52.5	17	59.5	17	59.5	17	59.5
3	Methocel E4M	**22.0**	77.0	**24.0**	84.0	**24.0**	84.0	**24.0**	84.0
4	Lactose monohydrate	48.22	168.77	44.21	154.75	44.21	154.75	44.21	154.75
5	Purified water	40% of Dry mix	q.s	40% of Dry mix	q.s	40% of Dry mix	q.s	40% of Dry mix	q.s
				EXTRAGRANULAR					
6	Magnesium Stearate	0.5	1.75	0.5	1.75	0.5	1.75	0.5	1.75
	Total weight	**100**	**350**	**100**	**350**	**100**	**350**	**100**	**350**

Coating of Core Tablets:

Table 3
Composition of coating formulation.

Ingredients	
Solution A	**Solution B**
Methacrylic acid copolymer (Eudragit L 30D-55)	Purified water
Purified water	Polysorbate 80
Triethyl citrate	Talc
	Iron oxide red
	Calcium Silicate or PVP k30 and Aerosil 200 as per batch

Quantity of coating polymer is taken depending upon the percentage of coating required to batch.

Preparation Method
Preparation of Solution A
1. Eudragit L 30 D-55 was weighed and the dispersion was diluted with purified water
2. Triethyl citrate was added to above dispersion and stirred about 15 minutes

Preparation of Solution B:
1. Talc, Polysorbate 80, Iron oxide red, PVP k30 and Aerosil 200 or Calcium silicate were added to purified water and mixed well under stirring for 15 mins.

Preparation of final Eudragit Coating Suspension
Solution B was poured into solution A and mixed well for 15 mins under stirring, to make 18-20% w/w final suspension. The dispersion was finally passed through a 60 mesh and kept aside.

Table 4
Coating parameter

Inlet temp. (^{0}C)	Exhaust temp. (^{0}C)	Atomization (bar)	Spray rate, (g/min)	Pan rate (rpm)	Weight gain (%)	Curing (mins)
40-45	32-35	2.0 – 2.5	2 – 4	9-11	3%	10

EVALUATION PARAMETER OF LAMOTRIGINE ER TABLET

Physical Characterization of Granules:
All physical tests of granules were performed like Bulk density, Tapped density, Compressibility index, Hausner's ratio and Loss on drying, PSD by sieve analysis. [5]

Tablet Evaluation:
Prepared tablets were evaluated for certain physical properties like Tablet wt. variation, hardness, thickness, friability, dissolution study, Assay, etc.

1. ***Average Weight:*** 20 Tablets were taken randomly and weighed accurately and calculated the average weight of the tablets from each batch was calculated.

2. ***Hardness/ Crushing Strength***: The term hardness indicates the ability of a Tablet to withstand mechanical shocks while handling. It is generally expressed in Kg/cm^2 or in Newton (N). Hardness of an extended release tablet was measured using hardness testers. [5]
3. ***Thickness:*** Three samples were selected randomly and thickness was measured using "Mitutoyo" Vernier caliper. [5]
4. ***Friability:*** To achieve % friability within limits for a chewable tablet is a challenge to the formulator. Friability test is performed to assess the effect of friction and mechanical shocks, which may often cause Tablet to chip, cap, laminate or break. [5]

Method: Samples of 20 Tablets were taken. Tablets were de-dusted prior to testing. Tablet samples were accurately weighed, and were placed in the drum of friability tester (Electrolab). Drum was rotated for 100 revolutions. Tablets were dedusted and reweighed.

$$\% F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where, $W_{initial}$ – Initial weight of Tablets
W_{final} – Weight of Tablets after completing tests

5. ***Dissolution Test***: This test provides evaluation of physiological availability of drug candidate. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of Reference-Listed Drug. Therefore similarity factor (f_2) is recommended by various regulatory committees that demonstrated the similarity in the percent (%) dissolution of test product with reference product. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100.

The similarity factor (f) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) difference of drug percent dissolved between the test and reference product.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

Dissolution tests were performed in a USP Dissolution Tester Apparatus I, II and III at 37 ± 0.5°C.

6. ***Assay:*** This method is used to analyze or quantify a substance in a sample. Assay is an analytical process to determine not only the presence of substance and the amount of substance but also the biological and pharmacological potency of a drug.
7. ***Stability Study:*** The effects of temperature and humidity on the physical and chemical characteristics of the Tablet were evaluated by carrying out the stability studies on the prepared formulation. [5, 6, 7]

Table 5
Stability Study

Pack	Unit per pack	Condition
		40°C±2°C/75%RH± 5%RH (Accelerated)
Container pack:		
40 cc HDPE white opaque bottle	30 Tablets	1 Month
Unit dose pack:		
PVC/PVDC clear (60gsm) with Alu lid	10 Tablets	1 Month

COMPARISON OF FORMULATION WITH MARKETED FORMULATION:

The different dissolution profile of optimized Lamotrigine formulation batches was compared with that of marketed Lamotrigine ER tablet (LAMICTAL XR) for t50% (time for 50% drug release) and f2 (similarity factor). The in-vitro drug release for 24 hr of marketed formulation was shown in table.

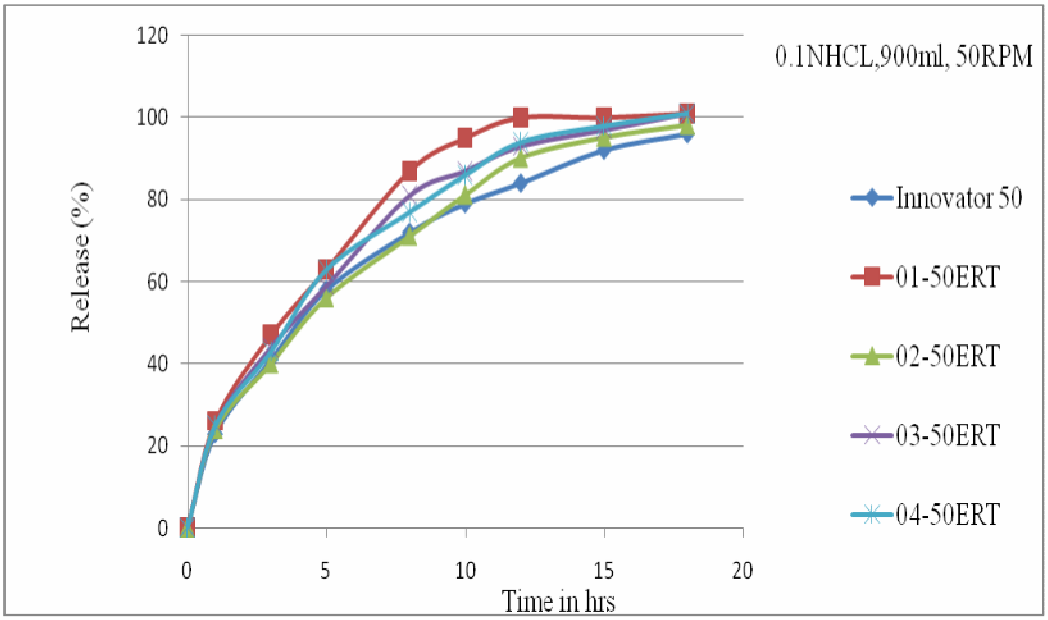
Dissolution In: USP-2 / 0.1N HCl 900ml/ 50 RPM
Batches: Innovator 50, 01-50ERT, 02-50ERT, 03-50ERT and 04-50ERT, Core tablet

Table 6
Dissolution in Core Tablet.

Time in hrs	Innovator 50	01-50ERT	02-50ERT	03-50ERT	04-50ERT
0	0	0	0	0	0
1	23	26	24	25	25
3	41	47	40	44	43
5	58	63	56	59	63
8	72	87	71	81	77
10	79	95	81	87	86
12	84	100	90	93	94
15	92	100	95	97	98
18	96	101	98	101	101
Core wt.	295mg	350mg	350mg	350mg	350mg
F2		**49**	**77**	**61**	**62**

Graph 1

Dissolution Profile of Core Tablet of Batch no. 01 to 04-50 ERT in 0.1 N HCl



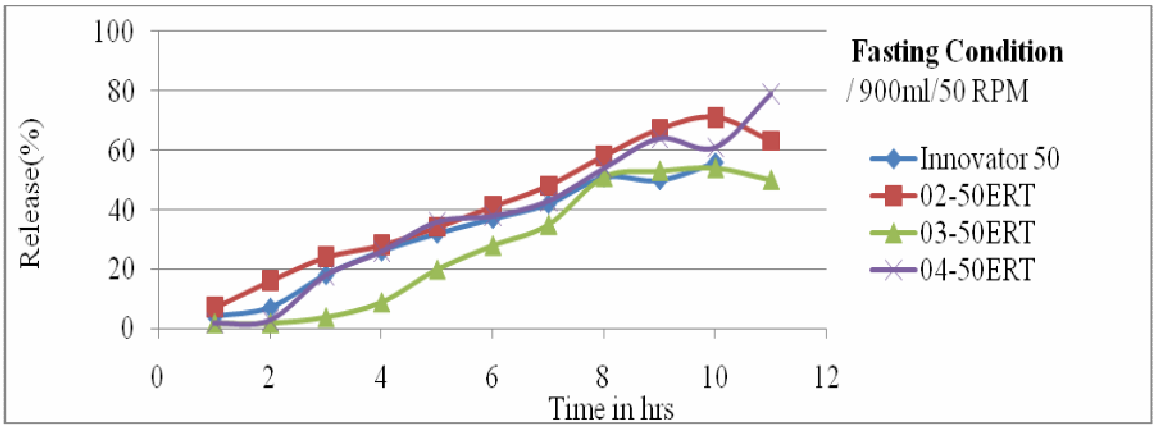
Dissolution: USP-2/ First 1 hr 0.1N HCL then 1hr 4.5 pH Acetate buffer followed by 6.8 Phosphatebuffer. **(Fasting Condition)** / 900ml/50 RPM

Table 7

Dissolution in Fasting Condition

Time in hrs	Innovator 50	02-50ERT	03-50ERT	04-50ERT
1hr-0.1N HCL	4	7	2	2
1hr-4.5 pH Acetate	7	16	2	3
1hr-6.8 Phos.	18	24	4	18
3hr-6.8	26	28	9	26
6hr-6.8	32	34	20	36
8hr-6.8	37	41	28	38
10hr-6.8	42	48	35	43
13hr-6.8	51	58	51	54
16hr-6.8	50	67	53	64
18hr-6.8	56	71	54	61
F2		**63**	**50**	**79**

Graph 2
Dissolution Profile of Coated Tablet of Batch no. 02 to 04-50 ERT in Fasting Condition.

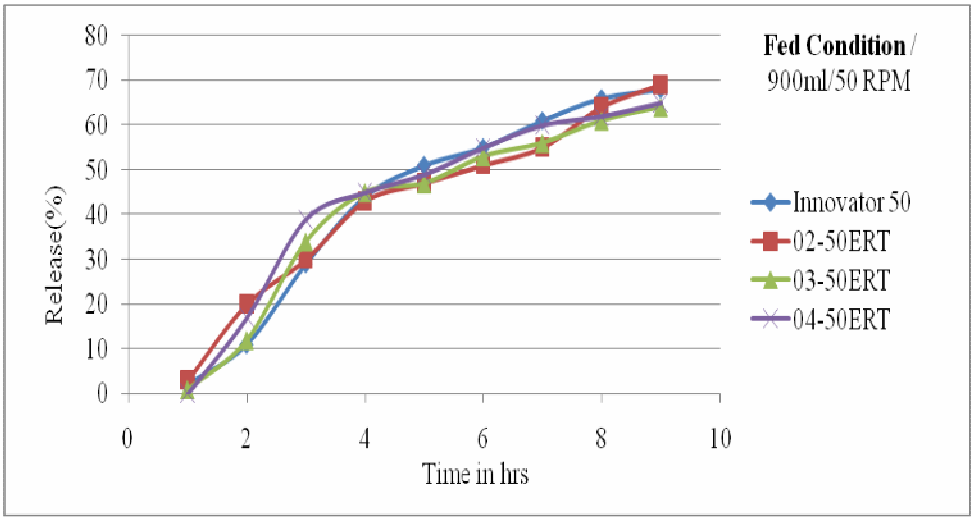


***Dissolution in*: First 2 hr 4.5 pH Acetate buffer then 2hr 0.1N HCL followed by 6.8 Phosphate buffer.**
(Fed Condition) / 900ml/50 RPM

Table 7
Dissolution in Fed Condition

Time in hrs	Innovator 50	02-50ERT	03-50ERT	04-50ERT
2hr-4.5 pH Acetate	2	3	1	0
2hr-0.1N HCL	11	20	12	17
1hr-6.8 Phos	29	30	34	39
4hr-6.8	44	43	45	45
6hr-6.8	51	47	47	49
8hr-6.8	55	51	53	55
11hr-6.8	61	55	56	60
14hr-6.8	66	64	61	62
16hr-6.8	68	69	64	65
F2		**67**	**72**	**74**

Graph 3
Dissolution Profile of Coated Tablet



Batch no. 01 to 04-50 ERT in Fed Condition.

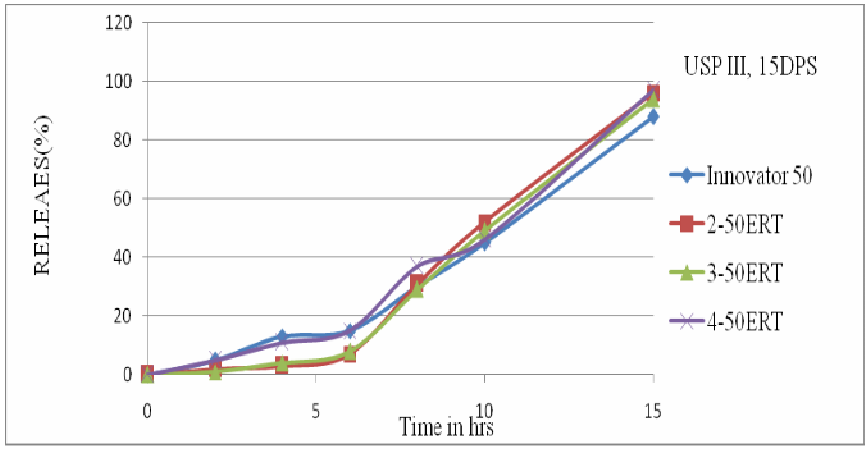
Dissolution Apparatus: USP III (Reciprocating cylinder)
Buffer: First 2 hr 0.1N HCL then 2hr 4.5 pH Acetate buffer then 2hr 5.5 pH Acetate buffer followed by 9hr in 6.8 Phosphate buffer. 250ml, **Speed:** 15 DPM.

Table 8
Dissolution in USP III

Time in hrs	Innovator 50	02-50ERT	3-50ERT	4-50ERT
0	0	0	0	0
2hr-0.1N HCL	5	2	1	5
2hr-4.5 Acetate	13	3	4	11
2hr-5.5 Acetate	15	7	8	15
2hr-6.8 Phos.	30	31	29	37
2hr-6.8 Phos.	45	52	49	46
5hr-6.8 Phos.	88	96	94	97
Time in hrs	**Innovator 50**	**02-50ERT**	**3-50ERT**	**4-50ERT**

Graph 4

Dissolution Profile of Coated Tablet of Batch no. 02 to 04-50 ERT in USPIII.



RESULT AND DISCUSSION

Tablet In process Result:

Table 9

In Process Blend Results of Lamotrigine ER Tablets

BatchNo.	Angle of Repose(Degrees)	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Compre-ssibility Index(%)	Hausner Ratio	LOD (% L)
01-50ERT	35.26	0.604	0.760	20.54	1.250	2.78
02-50ERT	32.94	0.545	0.656	16.92	1.204	2.08
03-50ERT	32.94	0.538	0.621	13.33	1.154	1.89
04-50ERT	34.17	0.547	0.664	17.64	1.214	2.50

Compression of Tablet Evaluation Result:

Table 10

Tablet Evaluation Result

Batch No.	Average weight (mg)	Hardness (N)Average	Thickness (mm)Average	Friability (%)
01-50ERT	348	79	4.6	0.12
02-50ERT	347	82	4.85	0.15
03-50ERT	349	87	4.9	0.14
04-50ERT	350	98	4.9	0.14

PSD by Sieve Analysis:

Table 11
Sieve Analysis Result

Mesh Size	08-50 ERT	09-50 ERT	10-50 ERT	11-50 ERT
20	3.3	1.0	7.1	2.0
30	19.7	7.2	28.3	15.2
40	13.3	17.8	26.1	17.0
60	4.7	21.8	15.3	20.5
80	3.0	16.3	7.0	14.4
100	11.2	8.0	3.2	6.5
Collector	44.5	26.7	10.3	24.1

Assay Results of Batch no.02 to 03-50ERT

Table 12
Assay Result

B.No.	Innovator	02-50ERT	03-50ERT	04-50ERT
Assay	96.3	98.6	101.6	97.3

Table 13
Impurity Data and Assay Result

Impurities	Initial	40°C± 2°C and 75 %RH± 5%RH 1 Month	
		40 cc HDPE white opaque bottle	PVC/PVDC clear (60gsm) with Alu lid
Impurity A	0.012	0.013	0.011
Impurity B	0.012	0.016	0.013
Impurity C	0.010	0.020	0.012
Highest Unknown	0.03	0.045	0.053
Total Unknown	0.120	0.119	0.122
Total RS	**0.139**	**0.128**	**0.192**
Assay	**97.3**	**97.1**	**96.2**

CONCLUSION

Drug release of Batch no.02-50ERT and subsequent reproducible trials 03-50ERT and 04-50ERT with 24% Methocel E4M was found better than 001-50ERT-with 22% Methocel E4M and compression and coating parameters found satisfactory result. Batch no.04-50ERT tablets coated with 20% calcium silicate as wicking agent in enteric coating system at 3 % weight gain showed better release profile and drug release was observed comparable to innovator.

DISCUSSION

The present study concludes that combination of hydrophilic polymer in core such as Hydroxy propyl methyl cellulose k 100, E4M and hydrophobic polymer in coating such as Methacrylic acid copolymer (Eudragit L 30D-55) can be utilized for designing and development of controlled release solid dosage form. Using selected polymers the developed controlled release table of Lamotrigine drug was found to be equivalent with regard to dissolution profile in all the buffers with marketed product. The best formulation 04-50ERT has shown a drug release NLT 60-80 % in 18hr was in accordance with the USP dissolution criteria for extended release Lamotrigine formulation.

There was an excellent agreement for the dissolution profile of the formulation 04-50ERT and marketed product (LAMICTAL XR) In conclusion, in the present research, extended release tablet formulations of Lamotrigine were successfully prepared for a once daily administration.

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