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Design of Regioselective drug delivery system of Lamotrigine using Curdlan gum

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Abstract

Lamotrigine is exclusively dissolved and absorbed from upper region of gastrointestinal tract. Therefore, the present study was aimed to design a regioselective delivery system of lamotrigine to enhance its bioavailability. The study explores utilization of novel polymer, curdlan gum in the design of regioselective drug delivery system and its comparison with HPMC K100M. Lamotrigine tablets were prepared by direct compression and evaluated for parametric tests, floating ability, swelling index and release kinetic study. The tablets pass the parametric tests as per Indian Pharmacopoeia and shows significant floating ability with low floating lag time. Formulation F4 was selected as optimized formulation and was found to be stable for short term stability study as per International Council Harmonization guidelines. Hence, the study successfully explores curdlan gum to achieve the objective of regioselective drug delivery system.

Keywords: bioavailability, curdlan gum, floating, lamotrigine, regioselective

1. Introduction

Epilepsy is a frequent chronic neurological disorder with convulsions and can occur to anybody [1-3]. The epileptic convulsions take place due to enhanced neuronal activity in the brain [4]. Although patients are on antiepileptic treatment there are the chances of recurrence of convulsions [5, 6]. Few anti-epileptics are prescribed alone or in combination with other drugs. Lamotrigine is a better antiepileptic agent that overcomes convulsions [7]. It belongs to phenyltriazine class and also effective medication in the treatment of bipolar disorder. It produces its anticonvulsant activity by blocking voltage activated sodium channels. It also inhibits the glutamate and aspartate release to stabilize the activity of brain [8]. It was introduced in early 90's and used in Europe and in United States for several years proving excellent efficacy with enough tolerability [9]. However, Stevens Johnson syndrome, drug rash, eosinophilia and systemic symptoms and toxic epidermal necrolysis might be caused by unregulated plasma concentrations of lamotrigine even leading to mortality [10]. However, these toxic effects could be prevented by designing controlled release drug delivery system of Lamotrigine [11]. Furthermore, the drug shows the absorption window in stomach and upper part of small intestine. It shows pH dependent solubility which makes it suitable to formulate as a gastroretentive drug delivery system (GRDDS) [12].

A gastroretentive drug delivery system is useful for delivering the drug in upper part of gastrointestinal tract (GIT) and it is most efficient in presence of adequate food and fluid. This drug delivery system remains unaffected by gastric emptying rate and peristaltic movements of GIT [13-15]. The present research was aimed to design regioselective drug delivery system containing 50 mg of lamotrigine using curdlan gum and hydroxypropyl methylcellulose K100M (HPMC K100M) individually. Floating extended release polymeric matrix release the drug regioselectively in stomach and proximal part of small intestine. Curdlan gum, a novel high molecular weight polysaccharide produced by fermentation from non-pathogenic and non-toxicogenic strain of *Agrobacterium biovar* or *A. radiobacter* [16]. HPMC K100M, a semi-synthetic, inert, hydrophilic polymer and popular excipient of oral controlled release drug delivery system [17]. The present research explores the application of curdlan gum in such delivery system and its comparison with HPMC K100M in the formulation of controlling the release of drug from tablets.

2. Materials and Methods

Materials

Lamotrigine was a gift sample obtained from Panacea Biotech Ltd., Navi Mumbai, India.

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Curdlan gum and HPMC K100M were purchased from Nanjing Joyful Imp. / Exp. Co. Ltd., Jiangsu, China and Colorcon Asia Pvt. Ltd., Verna, India respectively. Spray dried lactose, sodium bicarbonate, magnesium stearate and talc were purchased from Nikhil Scientific Suppliers, Karad, India.

Methods

2.1 Formulation of floating tablets of lamotrigine:

Accurately weighed quantity of lamotrigine and other excipients were sifted through nominal aperture of 710 μm (No. 22 sieve) as shown in [Table 1]. The powder mixtures were mixed in double cone blender for 30 min. The blended mixtures were evaluated for micro meretic properties.

Table 1: Formulation of floating tablets of lamotrigine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Lamotrigine	50	50	50	50	50	50	50	50
Curdlan gum	50	75	100	125	-	-	-	-
HPMC K100M	-	-	-	-	50	75	100	125
Spray dried lactose	120	95	70	45	120	95	70	45
Sodium bicarbonate	25	25	25	25	25	25	25	25
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

* All weights were expressed in mg.

2.2 Evaluation of powder blends

2.2.1 Bulk density (BD)

Bulk density was determined by pouring the weighed powder blend (previously passed through No. 22 sieve) into a calibrated measuring cylinder and the powder surface was leveled with glass rod without applying any pressure. The bulk volume was recorded and the bulk density of powder blend was determined using Eq. (1) [18, 19]

$$\text{Bulk density} = \frac{\text{Bulk weight}}{\text{Bulk volume}} \quad (1)$$

2.2.2 Tapped density (TD)

Tapped volume of known mass of powder blend was determined by tapping the measuring cylinder till a constant blend volume was observed (Electrolab, ETD-1020). Tapped density was calculated using Eq. (2) [18, 19].

$$\text{Tapped density} = \frac{\text{Powder weight}}{\text{Tapped volume}} \quad (2)$$

2.2.3 Angle of repose (AR)

The funnel was fixed to a stand at a definite height and powder mixture was allowed to flow through it. The angle of repose was determined by measuring the height and radius of pile of powder using Eq. (3) [18, 19].

$$\theta = \tan^{-1}(h/r) \quad (3)$$

Where, θ– angle of repose, °
 h– height of pile, cm
 r– radius of pile, cm.

2.2.4 Carr’s index (CI)

Powder flow properties are indicated by Carr’s index (% compressibility index). It is calculated by using Eq. (4) [18, 19].

$$\text{Carr’s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

2.2.5 Hausner ratio (HR)

It is an indirect index of flow. Lower the Hausner ratio (<

1.25) value indicates better flow properties of blend [18, 19]. It was calculated by the following Eq. (5).

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

2.3 Preparation of lamotrigine floating tablets

The floating tablets of lamotrigine were prepared by direct compression (Karnavati, GMP MiniTab) using 8.25 mm punches on 12 station multi-tooling tablet compression machine. The F1 to F4 formulations were designed using Curdlan gum and F5 to F8 formulations were designed using HPMC K100M polymer [20].

2.4 Evaluation of lamotrigine tablets

2.4.1 Diameter and thickness

Randomly selected three tablets from each formulation and their diameter and thickness were measured using digital vernier caliper (Mitutoyo Products, Japan) [21].

2.4.2 Hardness

Randomly selected three tablets from each formulation were taken and their hardness was determined using Monsanto hardness tester (Rolex, India) [21].

2.4.3 Weight variation test

Randomly selected 20 tablets were weighed and their average weight was determined (Electronic balance Adventure Ohaus, USA) [21].

2.4.4 Friability

Percent friability of the tablets was determined using Roche friabilator (Rolex, India). Previously weighed 20 tablets were placed in a plastic chamber and the plastic chamber was rotated at the speed of 25 rpm for 4 min. The tablets were removed, dedusted and reweighed [21]. The percent friability was calculated using Eq. (6)

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (6)$$

2.4.5 Drug content

Randomly selected twenty tablets from each formulation were accurately weighed and powdered. The powder equivalent to

100 mg of drug was weighed and added into 100 ml volumetric flask. The volume of solution was made up to 100 ml with 0.1N hydrochloric acid (HCL). Then the solution was sonicated for about 30 min and filtered from 0.45 μ membrane filter. The drug content was estimated by recording the absorbance at 270 nm by using UV-Visible spectrophotometer (Shimadzu Pharmaspec UV1700, Japan) [22].

2.4.6 *In-vitro* buoyancy/ floating test

In-vitro buoyancy study of tablets was determined in USP dissolution test apparatus (type II) containing 900 ml of 0.1 N HCL in dissolution vessel maintained at $37 \pm 0.5^\circ\text{C}$ temperature and 50 rpm paddle speed. The floating lag time (FLT) and total floating time (TFT) were determined visually [23].

2.4.7 Swelling studies

The swelling nature of the tablets was estimated by placing the tablets in beaker containing 200 ml of 0.1 N HCL which was maintained at $37 \pm 0.5^\circ\text{C}$. Tablets were withdrawn from the beaker at predetermined intervals and weighed. The measurement was carried out in triplicate [24]. Percentage swelling ability of the tablet was determined using Eq. (7).

$$\text{Swelling ability (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (7)$$

2.4.8 *In-vitro* dissolution studies

The *in-vitro* dissolution studies of prepared tablets were conducted in USP dissolution test apparatus type II (TDT 08 L, Electrolab, India) using 900 ml of 0.1 N HCL at $37 \pm 0.5^\circ\text{C}$ temperature and 50 rpm paddle speed for 12 hr. The tablets were placed into the dissolution vessel when temperature reached to the mark. At predetermined time interval 5 ml of samples was withdrawn from the dissolution medium and replaced with fresh medium to maintain the constant volume. After filtration of sample from 0.45 μ membrane filter and appropriate dilution, each sample was analyzed at 270 nm using UV-Visible spectrophotometer using 0.1N HCL as a

blank. A linear correlation (0.997) was observed over the concentration range 0.5–3.5 $\mu\text{g/ml}$. The dissolution data obtained was plotted between percent cumulative drug dissolved and time [25].

2.4.9 Kinetic analysis of dissolution

Various kinetic models namely zero order, first order, Higuchi matrix and Hixon-Crowell models were applied to determine the release from the tablet formulations and Korsmeyer-Peppas model was used to describe the drug release mechanism using Eq. (8) [26].

$$M^t/M^\infty = K.t^n \quad (8)$$

2.4.10 Stability study

The tablets of optimized formulation of lamotrigine were placed in amber colored bottles. The bottles were wrapped with aluminum foils and stored at the temperature of $40 \pm 2^\circ\text{C}$ and relative humidity (RH) $75 \pm 5\%$ for 3 months in the stability chamber (Remi Laboratory Instrument CHM-6S [GMP]). The tablets were evaluated for any changes in physicochemical, floating ability and *in-vitro* drug release properties after 3 months. The result obtained was compared with data obtained on the day of preparation and room temperature ($28 \pm 2^\circ\text{C}$) and RH ($42 \pm 2\%$). The plot of percentage drug release against time (hr) on the day of preparation of tablets and after 3 months for stability study was plotted [27].

3. Results and discussion

3.1 Micromeritic properties of powder blends

The micromeritic properties like angle of repose, bulk density, tapped density, Carr's index and Hausner ratio were recorded [Table 2]. The values of angle of repose, bulk density, tapped density, Carr's index and Hausner ratio of powder blend were found to be in the range of 22.18 ± 0.85 to 24.57 ± 1.66 , 0.34 ± 0.02 to 0.42 ± 0.06 , 0.39 ± 0.02 to 0.48 ± 0.08 , 10.81 ± 0.81 to 14.46 ± 0.56 and 1.12 ± 0.01 to 1.17 ± 0.01 respectively. The values of angle of repose, Carr's index and Hausner ratio were shows that the powder blends have good flow property.

Table 2: Micromeritic properties of powder blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose ($^\circ$)
F1	0.41 ± 0.04	0.48 ± 0.05	14.46 ± 0.56	1.17 ± 0.01	22.92 ± 1.29
F2	0.40 ± 0.07	0.46 ± 0.08	13.64 ± 1.77	1.16 ± 0.02	23.29 ± 1.27
F3	0.42 ± 0.06	0.48 ± 0.07	11.76 ± 0.59	1.13 ± 0.00	22.18 ± 0.85
F4	0.37 ± 0.04	0.42 ± 0.05	13.31 ± 0.90	1.15 ± 0.01	23.29 ± 1.39
F5	0.34 ± 0.02	0.39 ± 0.02	13.47 ± 1.55	1.16 ± 0.02	24.18 ± 0.55
F6	0.38 ± 0.04	0.43 ± 0.05	11.55 ± 0.98	1.13 ± 0.01	24.57 ± 1.66
F7	0.35 ± 0.02	0.40 ± 0.03	10.81 ± 0.81	1.12 ± 0.01	23.47 ± 1.68
F8	0.42 ± 0.06	0.48 ± 0.08	12.26 ± 2.15	1.14 ± 0.03	23.29 ± 1.15

Where, All the values were expressed in (Mean \pm SD) for triplicate determination (n=3).

3.2 Physicochemical evaluation of tablets

The tablets were evaluated for physicochemical characterizations and their observations were recorded in [Table 3].

Table 3: Physicochemical characteristics of tablets

Formulation	Diameter ^a (mm)	Thickness ^a (mm)	Weight ^b (mg)	Hardness ^a (kg)	Friability ^b (%)	Drug content ^b (%)
F1	8.23 ± 0.00	4.56 ± 0.32	252.12 ± 1.26	4.33 ± 0.28	0.74 ± 0.07	96.40 ± 0.91
F2	8.23 ± 0.00	4.61 ± 0.20	251.06 ± 0.83	4.50 ± 0.50	0.76 ± 0.04	98.03 ± 0.45
F3	8.24 ± 0.01	4.63 ± 0.15	250.17 ± 2.62	4.50 ± 0.21	0.79 ± 0.05	98.10 ± 1.30
F4	8.23 ± 0.00	4.53 ± 0.30	252.26 ± 1.34	4.83 ± 0.57	0.73 ± 0.09	99.23 ± 0.85
F5	8.24 ± 0.01	4.63 ± 0.05	249.73 ± 0.57	5.16 ± 0.76	0.80 ± 0.11	96.56 ± 1.18

F6	8.23±0.00	4.46±0.20	250.96±1.48	5.00±0.50	0.71±0.06	98.76±0.60
F7	8.23±0.00	4.63±0.15	251.03±1.73	5.33±0.28	0.87±0.03	96.70±0.45
F8	8.24±0.00	4.60±0.10	249.36±2.19	6.00±0.50	0.80±0.04	98.56±0.90
F4S	8.23±0.00	4.58±0.03	252.57±1.53	4.87±0.06	0.71±0.02	99.01±0.29

Where, F4S indicates stability batch. All values were expressed in (Mean ± SD) and ^a indicate sample size (n=3) and ^b indicate sample size (n=20).

The diameter of lamotrigine tablets was ranging from 8.23±0.00 to 8.24±0.00 mm. The thickness of lamotrigine tablets was ranging from 4.53±0.30 to 4.6±0.10 mm. The hardness of tablets was found ranging from 4.33±0.28 to 5.33±0.28 kg/cm². The average weight of lamotrigine tablets was ranging from 249.36±2.19 to 252.26±1.34 mg. The % friability of lamotrigine tablets was found in the range of 0.71±0.06 to 0.87±0.03%. The drug content in the lamotrigine tablets was ranging from 96.4±0.91 to 99.23±0.85. All tablet formulations passes the pharmacopoeial tests according to Indian Pharmacopoeia.

3.3 In-vitro buoyancy/ floating test

Floating ability of tablets was expressed by FLT and TFT. Sodium bicarbonate liberates carbon dioxide in the presence of HCL and the generated gas was trapped and protected within the polymeric structure formed by curdlan gum or HPMC K100M. Thus, decreasing the density of the tablets below 1 g/mL and the tablets become buoyant. The optimized concentration of sodium bicarbonate was used for all the lamotrigine floating tablets. All floating tablets had low floating lag time in the range of 88.33 ± 1.15 to 175 ± 0.57 sec. The floating time of tablets was found to be in the range of 8.16 ± 0.76 to 12.16 ± 0.28 hr, indicating the ability of both the polymers to entrap the carbon dioxide for a longer time. The results of the FLT and TFT for the various floating tablets are shown in [Table 4].

Table 4: Floating ability of tablets

Formulation	Floating lag time (sec)	Floating time (hr)
F1	088.33 ± 1.15	08.16 ± 0.76
F2	099.00 ± 1.00	08.83 ± 0.28
F3	137.00 ± 0.57	09.50 ± 0.50
F4	163.00 ± 1.52	12.16 ± 0.28
F5	093.00 ± 1.73	08.83 ± 0.50
F6	112.00 ± 1.15	09.50 ± 0.50
F7	147.00 ± 1.52	10.50 ± 0.50
F8	175.00 ± 0.57	11.16 ± 0.28
F4S	161.67 ± 1.53	12.33 ± 0.58

Where, F4S indicates stability batch. All the values were expressed in (Mean ± SD) for triplicate determination (n=3).

3.4 In-vitro dissolution studies: Fig. 1 and 2 indicates that the drug dissolution from lamotrigine tablets prepared from

curdlan gum and HPMC K100M was dependent upon amount of curdlan gum and HPMC K100M individually.

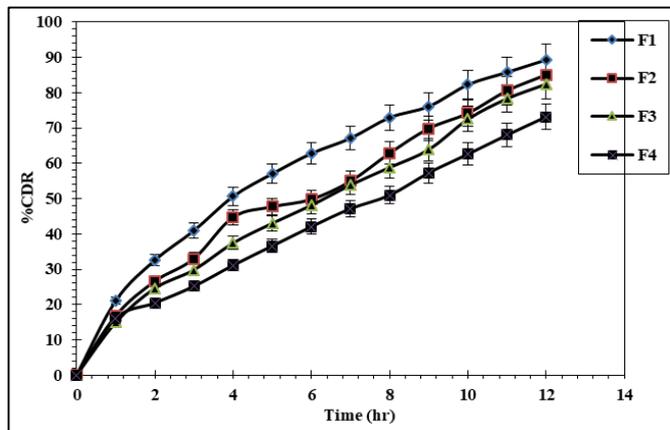


Fig 1: In-vitro dissolution of lamotrigine tablets prepared by using curdlan gum.

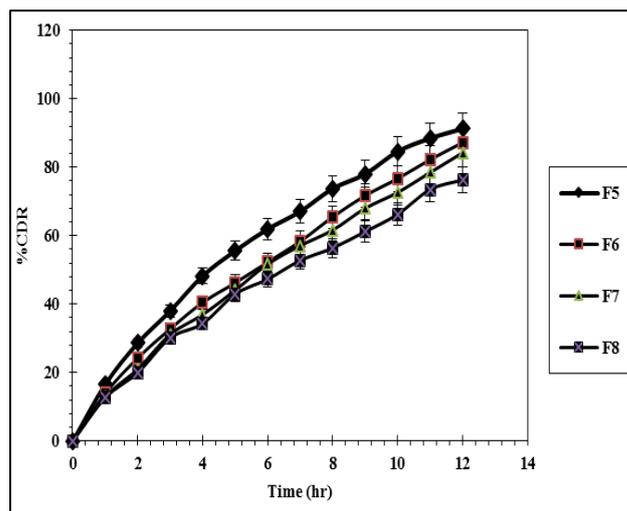


Fig 2: In-vitro dissolution of lamotrigine tablets prepared by using HPMC K100M.

3.5 Kinetic analysis

Dissolution study data were fitted in various mathematical models [Table 5].

Table 5: Kinetic analysis of data

Formulation	Zero order	First order	Hixon- Crowell	Higuchi	Korsmeyer-Peppas	
	R ²	n				
F1	0.937	0.522	0.908	0.996*	0.943	0.724
F2	0.969	0.575	0.941	0.978*	0.923	0.745
F3	0.983*	0.605	0.974	0.971	0.916	0.764
F4	0.986*	0.611	0.983	0.964	0.888	0.741
F5	0.957	0.571	0.902	0.988*	0.972	0.796
F6	0.982*	0.612	0.936	0.975	0.885	0.723
F7	0.983*	0.629	0.933	0.972	0.942	0.802
F8	0.977*	0.621	0.929	0.976	0.944	0.795

Release profiles of formulation F1 and F2 fit in Higuchi model, whereas release profiles of formulation F3 and F4

were fits into zero-order model. Release profiles of formulation F5 fits in Higuchi model, whereas release profiles

of formulation F6, F7 and F8 were fits into zero-order model. The “*n*” values of Korsmeyer–Peppas model were between 0.5 and 1 for the all lamotrigine tablets indicate non-fickian diffusion drug release mechanism.

3.6 Stability studies

The optimized formulation was stored for stability study and evaluated for their physicochemical, floating, and drug release properties [Tables 3], [Table 4] and [Fig. 3].

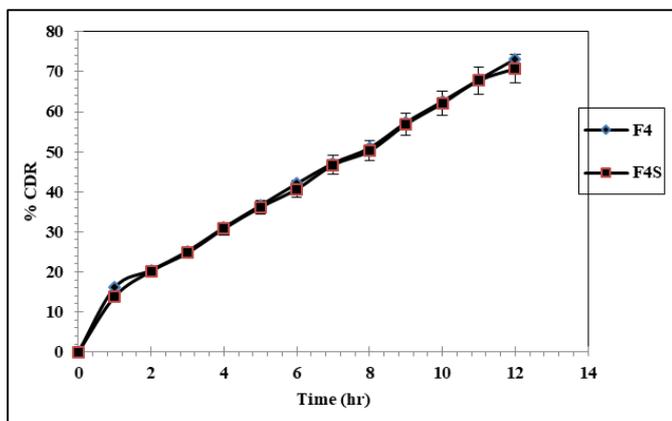


Fig 3: Comparison of release profile of optimized formulation with stability batch.

4. Conclusions

The gastroretentive tablets of lamotrigine were successfully designed using curdlan gum and HPMC K100M individually as retarding polymers. The prepared tablets pass all the pharmacopoeial tests as per Indian Pharmacopoeia and showed desirable *in-vitro* release kinetic properties. The optimized formulation (F4) released the drug in a zero-order fashion demonstrated a short buoyancy lag time and floating time of at least 12 hr. The F4 formulation could maintain the drug release for 12 hr and hence it can be act as a suitable alternative formulation dosing strategy compared to the twice-daily administration of a conventional release product. And also curdlan gum was successfully explored in the design of regioselective drug delivery system in comparison with HPMC K100M.

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