Original Research Article

Comparative evaluation of single and bilayered lamotrigine floating tablets

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Abstract

Aim: The purpose of this study was to prepare lamotrigine (LM) bilayered and single layered floating tablets and to compare their release profiles. **Materials and Methods:** LM floating tablets were prepared by direct compression method. Drug, hydroxy propyl methyl cellulose K4M, lactose monohydrate and polyvinylpyrrolidone K30 constitute controlled release layer components and floating layer components includes polymers and sodium bicarbonate. The prepared tablets were evaluated for physicochemical parameters such as hardness, friability, weight variation, thickness, floating lag time (FLT), floating time, *in vitro* buoyancy study, *in vitro* release studies. The drug-polymer interaction was studied by fourier transform infrared and differential scanning calorimetry. **Results and Discussion:** The FLT of all the formulations were within the prescribed limits (<3 min). When ethyl cellulose was used as floating layer component, tablets showed good buoyancy effect but eroded within 6-8 h. Hence it was replaced with hydroxypropyl cellulose -M hydrophilic polymer, which showed good FLT and floating duration for 16 h. Formulation LFC4 was found to be optimized with dissolution profile of zero order kinetics showing fickian diffusion. A comparative study of bilayered and single layered tablets of LM showed a highest similarity factor of 83.03, difference factor of 2.74 and *t*-test ($P < 0.05$) indicates that there is no significant difference between them. **Conclusion:** Though bilayered tablet possess many advantages, single layered tablet would be economical, cost-effective and reproducible for large scale production in the industry. However, the results of present study demonstrated that the *in vitro* development of bilayered gastro retentive floating tablets with controlled drug release profile for LM is feasible.

Key words: Epilepsy, gastro retentive drug delivery system, hydroxy propyl methyl cellulose

INTRODUCTION

Epilepsy (sometimes referred to as a seizure disorder) is a common chronic neurological condition that is characterized by recurrent unprovoked epileptic seizures. Epileptic seizures result from abnormal, excessive or hyper synchronous neuronal activity in the brain.[1] About 50 million people world-wide have epilepsy and nearly 80% of epilepsy occurs in developing countries.[2] Epilepsy is usually controlled, but not cured, with medication.

Lamotrigine (LM) is an antiepileptic agent used as a monotherapy and as an adjunct with other antiepileptic agents for the treatment of partial seizures, primary and secondary generalized tonic — clonic seizures.[3] LM is a biopharmaceutical classification system (BCS) class II drug with pH dependent solubility (solubility in water is 0.17 mg/mL at 25°C while that in 0.1 M HCl 4.1 mg/mL at 25°C). LM is an amine containing compound with a good solubility in the acidic or the gastric media and its solubility decreases with increasing pH. Gastric retention of such a drug facilitates better absorption on account of its higher solubility at stomach's acidic pH. It is rapidly and completely absorbed after oral administration with negligible frst pass metabolism and requires multiple dosing (2-3 times daily) for maintaining the therapeutic effect throughout the day.[4,5]

Existing formulations of LM 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.[6] LM requires an extended release delivery system with differential control mechanisms in the gastric and intestinal regions to overcome its pH-dependent solubility. Glaxo Smithklime (GSK) manufactures Lamictal extended release (XR) tablets using conventional pharmaceutical excipients typical of those used for extended release tablets. Lamictal XR extended release tablets use the differential control release (DiffCORE) technology in combination with an enteric coat and a polymer system that swells and erodes to control the release rate of LM. Lamictal XR tablets are drilled on two sides

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of the tablets and this modified release system is designed to deliver drug for 12-15 h.

Side-effects of the drug such as drug rash eosinophilia and systemic symptoms syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis caused by unregulated plasma concentrations of LM and the method of manufacturing using DiffCORE technology is highly laborious and expensive. In order to overcome the limitations of the available formulations, it was proposed to develop a less laborious, economic and an industrially applicable method for the delivery of LM with improved solubility and plasma concentrations within the therapeutic window over an extended period of time. Therefore, we consider gastro retentive mucoadhesive formulation of LM as one of the most attractive routes for the oral delivery of LM.

Gastro retentive drug delivery system is the technique in which the formulation is retained in the stomach for longer duration of time and hence the bioavailability of the drugs is improved preferentially absorbed from proximal gastro intestinal tract.[5] Gastro retentive dosage forms are of four main classes: (i) Floating systems, (ii) expandable systems, (iii) bio adhesive systems and (iv) high density systems.

Floating systems are of two types: Effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids and non-effervescent systems. The latter systems can be further divided into four sub-types, including hydro dynamically balanced systems,[7] micro porous compartment systems.[8] Alginate beads[9] and hollow microspheres/ microballoons.[10]

Floating drug delivery is of particular interest for drugs which:
- act locally in the stomach;
- are primarily absorbed in the stomach;
- are poorly soluble at an alkaline pH;
- have a narrow window of absorption and
- are unstable in the intestinal or colonic environment.[11]

In the present work bilayered effervescent floating tablets of LM were developed using excipients such as hydroxy propyl methyl cellulose (HPMC) grades (K100M, K15M, K4M, HPMC K100, HPMC E50 LV), hydroxypropyl cellulose (HPC)-M, Sodium bicarbonate, Ethyl cellulose E1415, polyvinyl pyrrolidine (PVP) K30, Xanthan gum, Eudragit RS100. Sodium bicarbonate on contact with gastric fluid releases CO_2, which makes the tablet buoyant and improve the residence time at gastric pH.

MATERIALS AND METHODS

Materials

LM was a gift from RA Chem Pharma Ltd. (Hyderabad), HPMC-K100M Premium, HPMC-K15M Premium, HPMC-K4M Premium, HPMC-K100 Premium were purchased from Colorcon, HPMC-E50 LV (Lubrizol), Eudragit-RS100 were purchased from Corel Pharma Chem (Ahmadabad), Xanthan gum was purchased from Yarrow chem Products (Mumbai), Sodium bicarbonate and Magnesium stearate were purchased from SD fine chemicals (Mumbai), Talc from Accord labs (Hyderabad) and PVP K-30 from Burgoyne Burbidge's & co (Mumbai).

Methods

Drug excipient compatibility

FTIR study

Fourier transform infrared (FTIR) study was performed to verify any physical or chemical interaction between the pure drug and the excipients. It was performed by potassium bromide (KBr) pellet method. The pure drug was triturated with KBr and pellet was prepared by setting the pressure to 100 kg/cm^2 for 2 min. The obtained pellet was analyzed in FTIR 8400 S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedure was repeated for the analysis of drug-excipient physical mixture (drug and HPMC K100M) [Figure 1].

Differential scanning calorimetric study

Differential scanning calorimetry (DSC) study was performed to verify any physical or chemical interaction between the pure drug and the excipients.

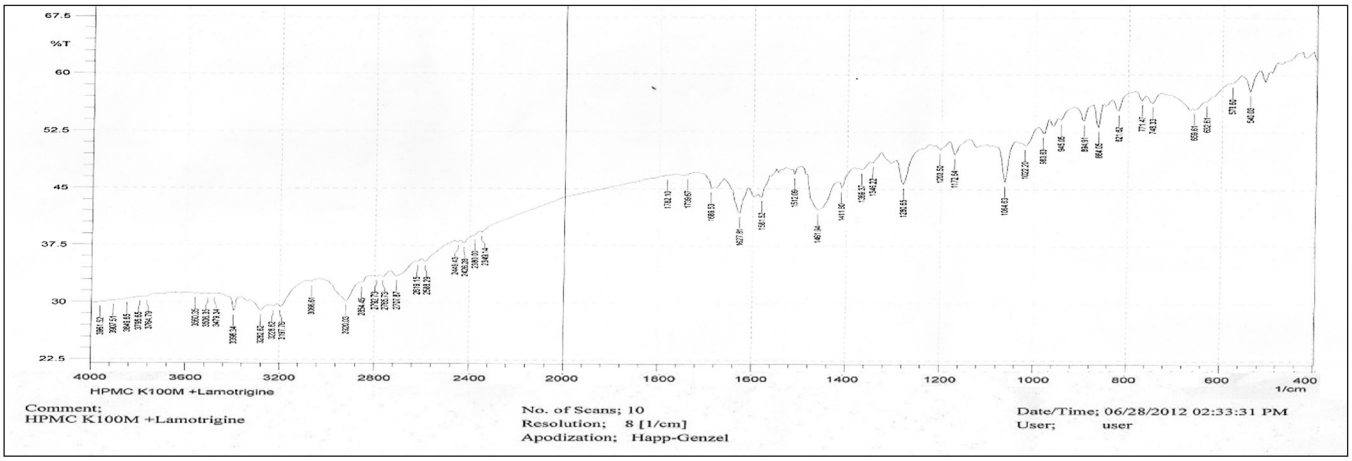

Figure 1: Fourier transform infrared (FTIR) graph of pure drug and hydroxy propyl methyl cellulose (HPMC) K100M mixture

Preparation of tablets

Preparation of bilayered tablets

Bilayered tablets were prepared by direct compression procedure involving the following three consecutive steps:

- Step 1 (controlled release [CR] layer preparation): Accurately weighed quantities of drug and all other excipients were passed through #40 to get uniform sized particles and then they were mixed geometrically using a mortar and pestle for 10-15 min to ensure homogenous mixing. Magnesium stearate was added as a lubricant; talc was added as a glidant to the blended material and mixed. The amount of this CR polymer mixture sufficient for individual tablet weight was weighed separately and accurately [Table 1].
- Step 2 (floating layer preparation): Accurately weighed quantities of polymers, sodium bicarbonate and all other necessary excipients were mixed geometrically using a mortar and pestle for 10-15 min to ensure homogenous mixing. Magnesium stearate was added as a lubricant; talc was added as a glidant to the blended material and mixed. The amount of this floating polymer mixture sufficient for individual tablet weight was weighed separately and accurately [Tables 2 and 3].
- Step 3 (final tablet compression): Tablets were prepared by manually feeding each layer composition into the die and compressing the entire die content together in a 10 station punching machine using 11.1 mm concave shaped punch.

Irrespective of the composition of the CR drug layer and the floating layer, all the tablets formulated at each stage were prepared by the above mentioned procedure.

Preparation of single layered tablets

Single layered tablets were prepared from LFC4 formulation using direct compression method. Accurately weighed quantities of drug and all other excipients (used in bilayered tablet preparation) were passed through #40 to get uniform size particles and

Table 1: Optimized formulations of controlled release drug layer and floating layer

Ingredients (mg)	Batches			
	LFC1	LFC2	LFC3	LFC4
Controlled release layer				
Lamotrigine	25	25	25	25
HPMC K100M	25	50	100	150
PVP K30	30	30	30	30
Floating layer				
Sodium bi carbonate	40	40	40	40
HPC-M	100	100	100	100
PVP K30	20	20	20	20
Total tablet weight in mg	280	305	355	405

All ingredients were lubricated with 0.3% (w/w) magnesium stearate, talc prior to compression, HPMC: Hydroxy propyl methyl cellulose, PVP: Polyvinyl pyrrolidine, HPC-M: Hydroxypropyl cellulose-M

Table 2: Optimization of polymers for floating layer

Batches	HPMC K15M	HPC-M	HPMC K100	Sodium bicarbonate	PVP K30
LF1	140	0	—	40	20
LF2	120	20	—	40	20
LF3	100	40	—	40	20
LF4	80	60	—	40	20
LF5	60	80	—	40	20
LF6	40	100	—	40	20
LF7	20	120	—	40	20
LF8	0	140	—	40	20
LF9	—	0	140	40	20
LF10	—	20	120	40	20
LF11	—	40	100	40	20
LF12	—	60	80	40	20
LF13	—	80	60	40	20
LF14	—	100	40	40	20
LF15	—	120	20	40	20
LF16	—	140	0	40	20

All ingredients were lubricated with 0.3% (w/w) magnesium stearate, talc prior to compression, HPMC: Hydroxy propyl methyl cellulose, PVP: Polyvinyl pyrrolidine, HPC-M: Hydroxypropyl cellulose-M

Table 3: Optimization of polymer quantity in floating layer

Ingredients (mg)	Batches							
	LP1	LP2	LP3	LP4	LP5	LP6	LP7	LP8
Controlled release layer								
HPMC K100	150	150	150	150	150	150	150	150
Lactose monohydrate	25	25	25	25	25	25	25	25
PVP K30	30	30	30	30	30	30	30	30
Floating layer								
Sodium bi carbonate	40	40	40	40	40	40	40	40
HPMC K15M	40	40						
HPMC K4M			40	40				
HPMC K100					40	40		
HPMC E50LV							40	40
EC 1415	100		100		100		100	
HPC-M		100		100		100		100
PVP K30	20	20	20	20	20	20	20	20
Total tablet weight in mg	405	405	405	405	405	405	405	405

All ingredients were lubricated with 0.3% (w/w) magnesium stearate, talc prior to compression, HPMC: Hydroxypropyl methyl cellulose, PVP: Polyvinyl Pyrrolidine, HPC-M: Hydroxypropyl cellulose-M, EC: Ethyl cellulose

mixed geometrically using a mortar and pestle for 10-15 min to ensure homogenous mixing. Magnesium stearate was added as a lubricant and talc was added as a glidant to the blended material. Tablets were prepared by manually feeding the composition into the die and compressed using 11.1 mm concave shaped punch.

Evaluation

Weight variation

A total of 20 tablets were selected randomly from each batch and weighed using analytical balance. The average weight and standard deviation were calculated and not more than two tablets should deviate from the average weight by more than 7.5%.

Hardness

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and their average hardness with standard deviation was calculated.

Friability

A total of 20 tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 min (100 rotations) using Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets. Conventional compressed tablets that lose < 0.5-1% of their weight were considered acceptable.

Diametrical fracture

It is a qualitative attribute concerned with the breaking of the tablet diametrically as opposed to de-laminating or capping and was tested by simple visual inspection.

Thickness

The thickness in millimetres (mm) was measured individually for 10 pre-weighed tablets using screw gauge and their average thickness with standard deviation were calculated.

In vitro buoyancy studies

In vitro buoyancy was determined by observing floating lag time (FLT) and floating time. The tablets were placed in a beaker containing 100 ml of 0.1N HCl. The time taken for the dosage form to emerge to the surface of the medium is called FLT or buoyancy lag time and the total duration of time up to which the dosage form remain buoyant is called total floating time (TFT).

In vitro release studies

The *in vitro* release studies of LM bilayered and single layered tablets were conducted using USP apparatus – II, fitted with paddle (50 rpm) at 37 ± 0.5°C using 900 ml of 0.1 NHCl as dissolution medium. Samples of 5 ml were withdrawn at 1, 2, 3, 4 and 5 up to 18 h at regular 1 h intervals and replaced with same volume of fresh medium. The samples were analyzed by ultraviolet spectrophotometry at 244 nm and the cumulative percentage release was calculated using the standard calibration curve.[11]

Drug release kinetics

Drug release kinetics was studied by plotting zero order, first order, Higuchi and Korsmeyer-Peppas equations. Regression coefficients (r^2) were calculated for all the formulations and the release component "*n*" was calculated from Korsmeyer-Peppas equation. Based on the "*n*" value release mechanism was characterized.

Calculation of similarity and difference factors

The dissolution results obtained from the single layered formulation was set as reference (R_j) and the results of the optimized bilayered formulation (T_j) was compared using difference factor (f_1) and similarity factor (f_2).[12,13]

The similarity factor was calculated with the formula

$$f_2 = 50 \times \log \left\{ \left[1 + (1/n) \sum_{j=1}^{n} w_j \left| R_j - T_j \right|^2 \right]^{-0.5} \times 100 \right\}$$

The difference factor was calculated with the formula:

$$f_t = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} R_j} \times 100$$

Accelerated stability studies for the optimized formulations

Accelerated stability studies were conducted for the optimized formulations as per ICH guidelines. The studies were carried out at 40°C/75% RH for 3 months. The samples were withdrawn for every 1 month and evaluated for physical properties such as appearance, hardness, floating property, dissolution and assay.

RESULTS AND DISCUSSION

Drug excipient compatibility

FTIR study

The principal peaks of LM were observed at 1631.67 indicating the presence of N-H bending, 1583.45 for C=C of an aromatic ring, 1064.63 for C-N stretch of an aromatic amine and 962.41 cm^{-1} for C-Cl of an aromatic halide. The characteristic peaks for drug and excipients mixture also appeared at 1631.67, 1583.45, 1064.63 and 962.41 cm^{-1}. No peaks were found at these wave numbers for excipients indicating no interaction between drug and the polymers therein.

DSC

Pure drug showed an endothermic peak at 250.9°C, exothermic peak at 283°C and pure HPMC K100M polymer showed an endothermic peak at 99.9°C. The drug-excipient mixture showed endothermic peaks at 103.7°C, 247.2°C, which indicates no interaction between drug and the polymers therein and the pure drug was not altered functionally.

Physical properties of the floating tablets

All the eight preliminary batches formulated as placebo tablets were evaluated for pre-compression flow property, angle of repose independently for both the layers and for in-process parameters such as hardness, thickness, friability, diametrical fracture. When hardness is in the range of 6-8 kg/cm^2 tablets did not float. So their hardness was adjusted to 4-5 kg/cm^2 for better FLT. Percentage friability ranging from 0.34% to 0.88% and thickness within 4.90-4.98 mm range were obtained. All the formulations LP1-LP8 passed the test for diametrical fracture, which reflects good adhesion between the two layers of the bilayered tablets and in turn their physical integrity. From the formulations, LP1-LP8 only LP2, LP6 were optimized for the further development of bilayered tablets, which consists of HPMC K15M, HPMC K100 respectively. Though LP1, LP3, LP5, LP7 batches containing ethyl cellulose showed good buoyancy effect but eroded within 6-8 h. Hence ethyl cellulose was replaced with HPC-M hydrophilic polymer which showed good FLT and total floating duration for 16 h and above in LP2 and LP6 formulations. They were further optimized for final formulation.

In vitro buoyancy studies

In vitro lag time measurement

Floating layer polymers HPMC K15M, HPMC K100 were used at different ratios in combination with HPC-M for the preparation of tablets and all the formulations showed a FLT <1 min.

Effect of sodium bicarbonate on floating lag

From the results, it was evident that sodium bicarbonate has significant effect on lag time. FLT decreased with the increase in sodium bicarbonate concentration.

TFT measurement

TFT for the optimized formulation was found to be >18 h.

In vitro release studies

When *in vitro* drug release studies of LM using different polymers were compared then the formulation LC4 with HPMC K100 showed maximum amount of drug release for prolonged period of time i.e., 97.2 ± 0.39 for 16 h. Then formulations LFC1-LFC4 were prepared using different proportions of HPMC K100. Among those formulations LFC4 was found to release maximum amount of drug for long period of time i.e., 99.14 ± 6.23% for 18 h. The dissolution profile of bilayered and single layer tablets were compared and were found to show similar results. Marketed Lamictal XR extended release tablet is designed to deliver the drug for 12-15 h by varying the aperture size and surface area [Figures 2-4].[14,15]

Drug release kinetics

The final optimized formulation of bilayered tablets was found to follow zero order kinetics with fickian diffusion and single layer tablets followed higuchi release with fickian diffusion [Table 4 and Figure 1].

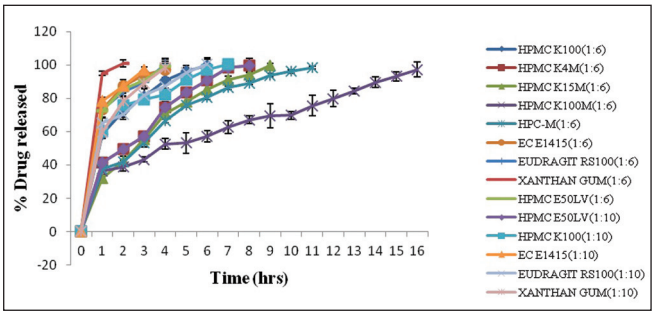

Figure 2: Comparative *in vitro* release profile of lamotrigine using different polymers

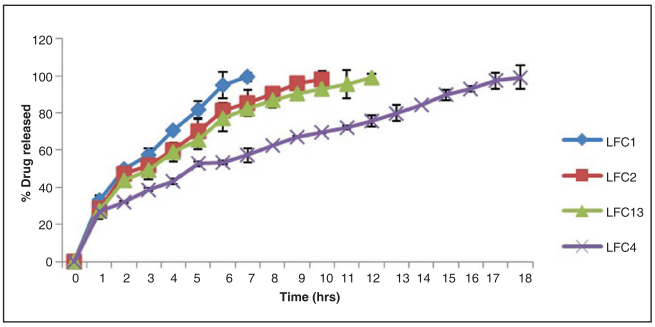

Figure 3: Comparative *in vitro* release profile of lamotrigine using hydroxy propyl methyl cellulose K100M in different proportions

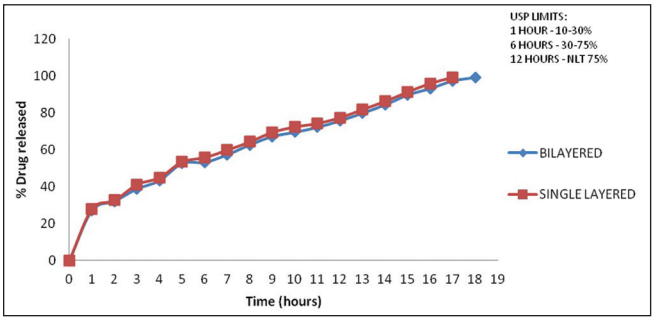

Figure 4: Comparative *in vitro* release profile of lamotrigine in bilayered and single layered tablet formulation

Table 4: Model dependent kinetic study for bilayered and single layered tablet

Formulation	Zero order release model parameters	First order release model parameter	Higuchi release model parameters	Korsmeyer-Peppas release model parameters		Release mechanism
	r^2	r^2	r^2	r^2	n	
Bilayered tablet	0.9901	0.9879	0.9311	0.9836	0.4728	Fickian diffusion
Single layered tablet	0.9881	0.926	0.9896	0.9859	0.4649	Fickian diffusion

Accelerated stability studies

The accelerated stability studies signify that the results comply with the specifications. The optimized formulation ensured physical integrity, reproducible floating property, promising drug release profiles and assay values after accelerated stability studies.

CONCLUSION

To conclude, an attempt has been made to achieve unidirectional, zero order release from a bilayered tablet which was successful, economical compared to expensive marketed LM (DIFFCORE™) tablets. The parameters such as FLT, TFT and controlled drug release were optimized in the study. The formulation was developed in 4 stages, the design of deformation resistant, pleasant appearing bilayered tablets, development of placebo bilayered tablets with maximum floating property, modulating controlled drug release profile and finally the comparison of release profiles between single layered and bilayered tablets.

Controlled drug release profile with zero order kinetics was obtained with LFC4 formulation. The formulations were stable under storage conditions and showed the potential for oral administration as bilayered gastro retentive floating tablets. Though bilayered tablet possess many advantages, single layered tablet would be economical, cost-effective and reproducible for large scale production in the industry. These results demonstrate that the *in vitro* development of bilayered gastro retentive floating tablets with controlled drug release profile for LM is feasible.

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