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ORIGINAL ARTICLE

Design of a novel bilayered gastric mucoadhesive system for localized and unidirectional release of lamotrigine

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KEYWORDS

Lamotrigine;
Bilayered gastric mucoadhesive tablets;
2^3 full factorial design;
Methacrylic polymers;

Abstract Lamotrigine is a BCS class II drug with pH dependent solubility. The bilayered gastric mucoadhesive tablets of lamotrigine were designed such that the drug and controlled release polymers were incorporated in the upper layer and the lower layer had the mucoadhesive polymers. The major ingredients selected for the upper layer were the drug and control release polymer (either HPMC K15M or polyox) while the lower MA layer predominantly comprised of Carbopol 974P. A 2^3 full factorial design was constructed for this study and the tablets were optimized for parameters like tablet size, shape, *ex vivo* mucoadhesive properties and unidirectional drug release.

Abbreviations: %, percentage; BCS, biopharmaceutical classification system; API, active pharmaceutical ingredient; cms, centimetres; h, hours; °C, degrees centigrade; Mg, milligrams; G, grams; mL, millilitre; nm, nanometre; mm, millimetre; min, minute; sec, seconds; MDT, mean dissolution time; rpm, revolution per minute; #, sieve number; USP, United States pharmacopoeia; HCl, hydrochloric acid; UV, ultra violet; f_2, similarity factor; f_1, difference factor; ≈, approximately equivalent to; r^2, correlation coefficient; n, release exponent (power law Korsmeyer Peppas equation); MA layer, mucoadhesive layer; CR layer, control release layer; BGMT, bilayered gastric mucoadhesive tablets.

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Modified basket dissolution model;
Zero order release;
Unidirectional drug release

Oval tablets with an average size of 14 mm diameter were set optimum. Maximum mucoadhesive bond strength of 79.3 ± 0.91 * 10^3 dyn/cm^2 was achieved with carbopol when used in combination with a synergistic resin polymer. All the tested formulations presented a mucoadhesion time of greater than 12 h. The incorporation of methacrylic polymers in the lower layer ensured unidirectional drug release from the bilayered tablets. The unidirectional drug release was confirmed after comparing the dissolution results of paddle method with those of a modified basket method. Model independent similarity and dissimilarity factor methods were used for the comparison of dissolution results. Controlled drug release profiles with zero order kinetics were obtained with polyox and HPMC K15M which reported $t_{90\%}$ at 6th and 12th hours, respectively. The "*n*" value with polyox was 0.992 and that with HPMC K15M was 0.946 indicating an approximate case II transport. These two formulations showed the potential for oral administration of lamotrigine as bilayered gastric mucoadhesive tablets by yielding highest similarity factor values, 96.06 and 92.47, respectively, between the paddle and modified basket method dissolution release profiles apart from reporting the best tablet physical properties and maximum mucoadhesive strength.

1. Introduction

Lamotrigine (LM) is an antiepileptic agent used as a monotherapy and as an adjunct with other antiepileptic agents for the treatment of partial seizures and primary and secondary generalized tonic–clonic seizures. It is also used for seizures associated with the Lennox–Gastant syndrome (Brodie, 1992). LM is a 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 first pass metabolism and requires multiple dosing (2–3 times daily) for maintaining the therapeutic effect throughout the day. Existing formulations of LM provide immediate release with t_{max} ranging from 1.4 to 4.8 h and result into a release profile exhibiting cyclic peaks and troughs (Cheng et al., 2005). It is also marketed as an extended release tablet formulation which is manufactured by a special, laborious and expensive process wherein a central orifice is drilled into an enteric coated tablet to form a device called Diff-CORE™ (http://www.biospace.com/news_story.aspx?StoryID=169319 &full=1. Date: 2/1/2010, time: 7:08:36 AM). 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 gastroretentive mucoadhesive formulation of LM as one of the most attractive routes for the oral delivery of LM.

Bilayered and gastric mucoadhesive drug delivery systems offer distinct advantages. The phenomenon of bioadhesion is related to the ability of some synthetic or biologic macromolecules and hydrocolloids adhere to biological tissues. If the biological tissue involved is mucous or mucous membrane, the phenomenon is referred as mucoadhesion (Joao, 2010). Mucoadhesion has the potential to localize the drug delivery by retaining the dosage form at the adhesion site. Gastric mucoadhesive systems can be the best formulations for the administration of drugs with good acid solubility and for those drugs which are rapidly and completely absorbed from gastro intestinal tract (Bardonnet et al., 2006). The concept of bi-layer tablet was explored in the present study to control the release of API from one layer by utilizing the functional property of the other layer since this property finds appreciation in the fabrication of novel drug delivery systems (Sivakumar et al., 2010).

This study aimed to develop a gastric mucoadhesive tablet formulation of LM using Carbopol 974P and polyox as the mucoadhesive polymers. The primary challenge had been to handle the incompatibility problem between carbopol and the amine containing LM (Rowe et al., 2009). Hence, a bilayered tablet formulation containing drug in one layer and mucoadhesive polymers in the other layer has been worked out so as to avoid any contact between carbopol and LM. Literature reported the development of several bilayered tablet formulations for the unidirectional delivery of drugs in the buccal cavity, the concept of which has been applied in the current research work. The size of the resting pylorus aperture, 12.8 ± 7 mm was also considered while designing the tablet size in the present study (Chanda et al., 2010). The unidirectional and controlled release of LM for systemic use in the form of bilayered gastric mucoadhesive tablets (BGMT) was investigated in the present paper. The aim of present study was to ascertain the feasibility of *in vitro* development of BGMT formulation of LM, understand the effect of different excipients on the ex vivo mucoadhesion and release profile of final formulation besides studying and exploring the application of a newly designed dissolution method in combination with model independent methods in characterizing the unidirectional drug release profile.

2. Materials and methods

Lamotrigine (LM), Polyox, HPMC K15M Premium, Carbopol 974P, Eudragit L100, Talc, Aerosil, Magnesium stearate, Lactose monohydrate and MCC 102 were sponsored by RA Chem Pharma Ltd. (Hyderabad, India). All chemical reagents used were of analytical grade. Goat gastric mucosa was obtained from a slaughter house.

2.1. Precompression flow properties and compressibility of bilayered gastric mucoadhesive tablets

All the precompression properties were determined independently for upper "controlled release (CR) drug layer" and

the lower "mucoadhesive (MA) polymer layer". The bulk and tapped densities were determined initially with USP tap density apparatus (Electrolab) from which the Hausner's ratio and compressibility index, I (Carr's index) were further calculated. The angle of repose was determined by fixed funnel method.

2.2. Preparation of bilayered gastric mucoadhesive tablets

A 2^3 full factorial design (FFD) was constructed (Table 1) for which the composition of mucoadhesive polymer in the lower mucoadhesive polymer layer, the type and the concentration of controlled release polymers in the upper controlled release drug layer were taken as the three independent variables or factors. The levels of the three factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variables were kept invariant throughout the study. The dependent variables studied were the bioadhesion force, mean dissolution time (MDT), difference factor (f_1) and similarity factor (f_2).

The two layers of the bilayered tablets were differentiated as the upper "controlled release (CR) drug layer" and the lower "mucoadhesive (MA) polymer layer". The tablets were designed and formulated such that the mucoadhesive polymers were accommodated in the lower MA polymer layer while the drug was incorporated in the upper CR layer. It ensures lack of interaction between drug and carbopol. The functional mucoadhesive property of the MA layer was utilized not only to achieve gastric mucoadhesion but also to modulate the drug release from the upper CR layer. A total of eight runs were formulated; the formulae for which were presented in Table 2.

Mucoadhesive bilayered tablets were prepared by dry granulation procedure involving four consecutive steps which include the slugging and the subsequent compression of each layer. The compression was manual and the tablets were compressed one after the other. Carbopol 974P was roller compacted (CIP Machineries Pvt. Ltd.) to improve its flow properties prior to slugging. The entire mucoadhesive polymer mixture comprising the MA layer was passed through #40, mixed homogeneously and slugged on a 10 station punching machine (Rimek karnavathi) using 14.8 * 7.9 mm punches. The slugs were sieved through #18 and thus obtained MA layer granules were mixed geometrically with magnesium stearate using a polyethylene bag for 10–15 min to ensure homogenous mass. The drug and controlled release polymer mixture comprising the CR layer was treated in the same way as the mucoadhesive polymer mixture to obtain CR layer granules. The mass of MA layer granules equivalent to the MA layer composition of each individual tablet (350 mg) was com-

Table 1 Selection of independent variables for 2^3 full factorial design (FFD).

Factors (independent variables)	Levels[a]	
	−1	+1
Factor A: Type of control drug release polymer (upper CR layer)	Polyox	HPMC K15M
Factor B: Concentration of control drug release polymer (upper CR layer) (%)	13	15
Factor C: Ratio (Carbopol 974P: Polyox) of primary mucoadhesive polymer (Carbopol 974P) to mucoadhesive synergistic polymer (Polyox) (lower MA layer)	50:50	75:25

[a] −1 = lower level and +1 = higher level.

Table 2 FFD experimental runs formulae.

S. no.	Ingredients	2^3 FFD runs (L1–L8) showing % w/w of ingredients used							
		L1	L2	L3	L4	L5	L6	L7	L8
Controlled release (CR) layer									
1	Lamotrigine[a]	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.3
2	Lactose monohydrate	11.7	9.7	11.7	9.7	11.7	9.7	11.7	9.7
3	Polyox	13	15	–	–	13	15	–	–
4	HPMC K15M	–	–	13	15	–	–	13	15
5	MCC 102	7	7	7	7	7	7	7	7
6	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
8	Magnesium stearate	1	1	1	1	1	1	1	1
Mucoadhesive (MA) layer									
9	Carbopol 974P (RC)[b]	20	20	20	20	30	30	30	30
10	Eudragit L100	8	8	8	8	8	8	8	8
11	Polyox	20	20	20	20	10	10	10	10
12	Magnesium stearate	2	2	2	2	2	2	2	2
Total tablet weight (mg)	700	700	700	700	700	700	700	700	

[a] Dose or tablet strength is 100 mg lamotrigine which approximately constitutes 14.3% of the total tablet weight (700 mg).
[b] RC stands for roller compaction.

pressed for a period of half the consolidation time and a loose compact was formed. The upper punch was raised and the slugged CR layer granules (350 mg) were then added on the MA layer compact and the two layers were compressed to form a final bilayered tablet (700 mg).

2.3. Evaluation of bilayered gastric mucoadhesive tablets

2.3.1. In process tests

Weight variation test, tablet thickness, hardness, friability, diametrical fracture (DF)[1], and CSFR (Crushing Strength: Friability ratio)[1] (Sivakumar et al., 2010) were reported for all the formulations. Tablets were evaluated for uniformity in weight using an electronic balance (Sartorius). The thickness and hardness were measured using an electronic hardness tester (Pharmag Tab test) and friability was measured using Roche-type friabilator (Electrolab Pvt. Ltd., India). DF was visually examined and CSFR was calculated from the hardness and friability values.

2.3.2. Measurement of bioadhesion

The *ex vivo* adhesion studies were conducted using a modification of test assembly described by Gupta et al. (1992) and Patel et al. (2007). The goat stomach mucosa was kept frozen in pH 1.2 acid buffer and thawed to room temperature before use. The membrane was excised by removing the underlying connective and adipose tissues and was equilibrated at 37 ± 0.5 °C for 30 min in pH 1.2 acid buffer before the study. The upper CR layer of the tablet was glued to the apparatus assembly while the lower MA layer was exposed to the mucosal surface. The tablet was placed on mucosa under constant weight of 5 g for a total contact period of 1 min. The bioadhesive strength was determined by measuring the strength required for complete breakdown of bioadhesive bond between the dosage form and the surface of mucosa. Each measurement was carried out in triplicate and the results were averaged. The peak force of detachment was calculated for each bioadhesive strength value and finally the corresponding mucoadhesive bond strength was further calculated and reported for each batch.

2.3.3. Ex vivo mucoadhesion time

The *ex vivo* mucoadhesion time was examined ($n = 3$) after adhering the gastric mucoadhesive tablet on freshly cut goat's gastric mucosa (Han et al., 1999; Patel et al., 2007; Raval and Patel, 2011). Goat's fresh gastric mucosa was pasted on the glass slide using a cyanoacrylate adhesive, and the mucoadhesive core side (MA layer) of tablet was wetted with a drop of pH 1.2 acid buffer and adhered to goat's gastric mucosa by applying a light force with fingertip for 30 s. The glass slide was then placed in a beaker, which was filled with 200 mL of the pH 1.2 acid buffer and kept at 37 °C ± 0.5 °C. After 2 min, a slow stirring rate (50 rpm) was applied to simulate the gastric environment, and the tablet mucoadhesion was monitored for 12 h. The time for the tablet to detach from goat's gastric mucosa was recorded as the mucoadhesion time.

2.3.4. Assay and in vitro drug release studies

Ten tablets were weighed and powdered using a mortar and pestle. Powder equivalent to the quantitative mass of one tablet (equivalent to 100 mg of LM) was transferred into a volumetric flask containing 0.1 N HCl. Following sonication, the sample was filtered (Whatmann filter paper, 0.2 μm), suitably diluted and analyzed spectrophotometrically (ELICO-SL 164 double beam spectrophotometer, Hyderabad, India) at λ_{max} of LM at 244 nm. For each batch, the assay procedure was performed in triplicate and the average was recorded. *In vitro* drug release studies were performed on the tablet matrices of all the batch formulations using the USP apparatus II (Electrolab TDT-08L, India) with 900 mL of 0.1 N HCl as the medium at 37 ± 0.5 °C and 50 rpm rotation rate. At the end of predetermined time intervals (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h), aliquots (5 mL) were withdrawn from each dissolution vessel and replaced with an equal volume of drug free medium (5 mL). The samples were filtered and analyzed by ultraviolet spectroscopy at 244 nm with a total of six replicate determinations for each batch to quantify the percentage drug released at each time point. Release kinetics for all the eight batch formulations of 2^3 FFD runs were studied using Microsoft Office Excel 2007 version. The release data was analyzed by fitting the drug release profiles into zero order, first order, Higuchi and Korsmeyer Peppas models. Correlation coefficients (r^2) and rate constants were calculated for each of the models. Further, the release mechanism and the MDT were studied from the power law Peppas model.

2.3.5. Modified basket method

The *in vitro* drug release studies of bilayered tablets were further carried out using the USP dissolution apparatus I (Electrolab TDT-08L, India). In order to mimic the *in vivo* adhesion of the devises (Narendra et al., 2005), the lower MA layer of the bilayered tablet was attached through cyanoacryl adhesive to the bottom end of the stirring rod instead of placing the tablet in the basket fixtures. By this, only drug containing upper CR layer was exposed to the dissolution medium. The rotation rate was 100 rpm and 900 mL of freshly prepared 0.1 N HCl was used as dissolution medium maintained at 37 ± 0.5 °C. At predetermined time intervals samples were withdrawn for UV analysis at 244 nm. The dissolution studies of all the batch formulations were performed in six replicates.

2.3.6. Model independent analysis for the characterization of unidirectional drug release

The dissolution results of the modified basket method were set as reference and the results of the paddle method were considered as the test sample. For each dissolution run, a mean of six determinations was recorded for the reference and test methods both of which were matched for similarity in drug release profiles by calculating the similarity and difference factors. A comparison of the similarity and difference factors was obtained.

The similarity factor (f_2) was calculated as

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

The difference factor (f_1) was calculated as

$$f_1 = \left\{\left[\sum_{t=1}^{n} |R_t - T_t|\right] \Big/ \sum_{t=1}^{n} * [R_t]\right\} * 100$$

R_t and T_t are the cumulative percentage dissolved at each of the selected "n" time points of the reference and test product, respectively.

3. Results and discussions

3.1. Formulation of bilayered gastric mucoadhesive tablets

The current work was undertaken to formulate bilayered gastric mucoadhesive tablets (BGMT) of lamotrigine (LM) by dry granulation method and to perform the *in vitro* evaluation of the formulation. The aim was to confirm the two layers of the bilayered tablet functioned independently such that the MA layer of the tablet which was designed to adhere to the gastric mucosa posses' good bioadhesive strength and CR layer controls the drug release unidirectionally. The dependent variables studied for the 2^3 FFD runs namely the bioadhesion force, MDT, f_1 and f_2 were reported in Table 3.

3.2. Tablet physical properties and characterization

The major excipients selected for the upper CR layer were the drug and control release polymer (either HPMC K15M or polyox). The lower MA layer predominantly comprised Carbopol 974P, polyox and Eudragit L100. The precompression flow properties were studied separately for the upper CR layer and the lower MA layer. Roller compaction solved the poor flow of Carbopol 974P. Slugging excellently improved the flow properties of both the layers. Flow properties were further improved by the addition of silica and the lubricant, magnesium stearate which was added prior to tableting (He et al., 2007). Angle of repose values of the upper CR layer ranged between 25° and 28° while that of the lower MA layer ranged between 22° and 27°. The compressibility index values of the formulation batches ranged between 8% and 13% for both the upper CR layer and the lower MA layer indicating the suitability of the powders for dry granulation. Hausner's ratio ranged between 1 and 1.2 for both the layers.

The addition of different polymers did not affect the tablet physical characteristics. All tablet formulations presented hardness in the range 9–11 kg/cm^2 and passed the diametrical fracture test. The percent friability values reported for the tablet formulations were very low ($< 0.12\%$) with no measurable differences among the between batch results. The CSFR (Crushing Strength: Friability Ratio) of all the batches was

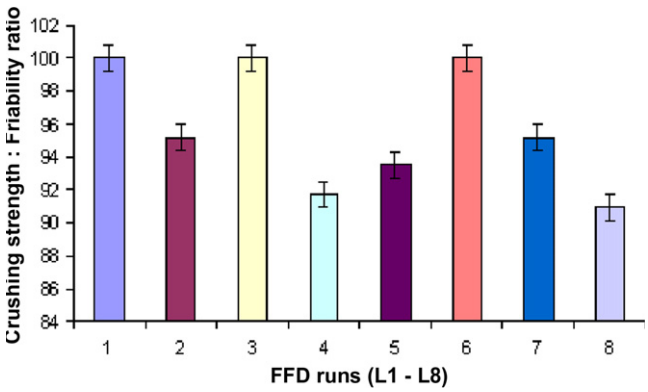

Figure 1 Comparison of the Crushing Strength: Friability Ratio of all the 2^3 FFD experimental runs as mean ± SD, $n = 3$.

> 90 indicating appreciable mechanical strength of the bilayered tablets (Fig. 1). The thickness ranged between 7.11 ± 0.01 mm and 7.18 ± 0.01 mm while the weight of different batch formulations varied between 700 ± 0.82 mg and 700 ± 0.94 mg.

3.3. Effect of formulation variables on bioadhesion force

Carbopol 974P and polyox were used to form the bioadhesive polymer mixture in the lower MA layer. The mucoadhesive effect was studied by varying the ratio of Carbopol 974P to polyox as 50:50 and 75:25. The preliminary trails showed that the bioadhesion of the BGMT increases significantly with increase in carbopol concentration. Higher concentrations of carbopol upon exposure to the moist surfaces lowered the pH of the microenvironment which caused an increase in bioadhesion. The acidic environment favors the presence of excess uncharged COOH groups which form stronger hydrogen bonds with water and strengthen the mucoadhesive bond (Park and Robinson, 1987; Ponchel et al., 1987). The 50:50 ratio of Carbopol 974P to polyox was set as optimal formulation as it recorded the highest mucoadhesive bond strength (Table 3). Such a behavior may be attributed to the synergistic mucoadhesive effect of polox and Carbopol 974P. The formulations had not detached from the mucosa through out the observation period of 12 h thus promising a residence period of not less than 12 h.

Table 3 Dependent variables.

FFD runs	Mucoadhesive bond strength*10^3 dyn/cm^2	MDT (h)[b]	f_1[a]	f_2[a]
L1	78.2	3.348625	3.027494594	84.61878888
L2	79.3	4.350583	1.79981203	91.34875888
L3	78.6	5.562674	2.833691616	86.9944641
L4	77.9	6.197267	2.659747	85.14939911
L5	70.2	3.313689	1.811824539	90.44206798
L6	73.4	4.07946	4.393823437	76.31060377
L7	71.2	5.511291	2.093023256	89.1357774
L8	72.8	6.00934	5.169628433	73.96518287

[a] Similarity and difference factors (f_1 and f_2) for 2^3 FFD runs were calculated by comparing the dissolution profiles derived from paddle method with their corresponding modified basket reference method results.
[b] Mean dissolution time.

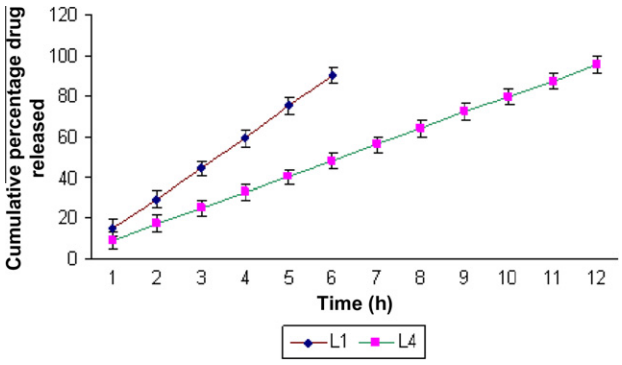

Figure 2 Comparison of drug release profiles modulated by the optimized percentages of controlled release polymers, 13% polyox (L1) and 15% HPMC K15M (L4) as mean ± SD, $n = 6$.

3.4. In vitro drug release profile

In addition to mucoadhesivity, controlled drug release was also a prerequisite for this formulation. The formulations were subjected to *in vitro* dissolution testing to study their drug release profile. A formulation with an appropriate controlled release profile and 90% drug release over a 6–12 h period was desired for the purpose of this study. Since preliminary studies confirmed that the polymers polyox and HPMC K15M had not presented any problem of burst drug release, an attempt was made to study the drug release modulation by these polymers at 13% and 15% concentrations.

It was evident from the dissolution profiles that while the drug release rate was controlled, 90% of LM was released with 13% polyox (L1 and L5) and 15% HPMC K15M (L4 and L8) by the end of 6 and 12 h, respectively. Polyox at both 13% and 15% concentrations retarded the drug release for a lesser duration compared to HPMC K15M which could be due to the difference in their viscosities. The extended retardation of drug release observed with HPMC K15M may be attributed to the three dimensional gel network structure developed by complex formation between the drug and the polymer following penetration of dissolution medium into the tablet matrix. Polyox being a water soluble resin, might have altered the structural properties of the tablet matrix by creating an increased porosity, thus allowing more rapid penetration of the dissolution medium into the tablet which in turn facilitated the faster drug release behavior. Fifteen percent polyox and thirteen percent HPMC K15M presented an unusual drug release blockade after 80% drug release indicating that these percentages are inappropriate for the complete release of LM from the BGMT formulation. Therefore, for the purpose of this study, formulation with 13% polyox or 15% HPMC K15M in the upper CR layer was considered most suitable. Hence, the formulations comprising of 13% polyox or 15% HPMC K15M in the upper CR layer and 50:50 ratio of Carbopol 974P to polyox in the lower MA layer were identified as being capable of providing both optimum mucoadhesion and a controlled drug release profile. Fig. 2 depicts the graphical representation of drug release profiles modulated by the optimized percentages of controlled release polymers, 13% polyox (L1) and 15% HPMC K15M (L4).

3.5. Characterization of the optimal formulation

The formulations were further subjected to a detailed characterization in terms of release kinetics. The study results were presented in Table 4.

3.5.1. Kinetic analysis of drug release profiles and model fitting

The evaluation of the drug release profile kinetics of all the 2^3 FFD experimental runs was based on the correlation coefficient (r^2) values. The results depicted that all the release profiles best fitted into the zero order kinetic model (indicated

Table 4 Model dependent kinetic analysis of the dissolution profiles of 2^3 FFD runs.

FFD runs	Zero order release model parameters		First order release model parameters		Higuchi release model parameters		Korsmeyer–Peppas release model parameters			Release mechanism
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	K_{KP}	n	
L1	0.999	14.96	0.908	0.713	0.98	26.98	0.999	0.151	0.992	≈Case II transport
L2	0.997	12.82	0.951	0.597	0.985	24.8	0.994	0.178	0.743	Anomalous transport
L3	0.999	9.29	0.948	0.526	0.986	20.53	0.999	0.104	0.924	Anomalous transport
L4	0.999	8.2	0.852	0.46	0.976	19.76	0.999	0.09	0.946	≈Case II transport
L5	0.999	15.33	0.906	0.709	0.981	27.53	0.999	0.158	0.967	≈Case II transport
L6	0.985	12.86	0.973	0.59	0.981	25.47	0.989	0.155	0.855	Anomalous transport
L7	0.999	9.69	0.935	0.523	0.982	21.14	0.997	0.118	0.863	Anomalous transport
L8	0.999	8.6	0.808	0.45	0.976	20.56	0.999	0.099	0.913	Anomalous transport

by the highest r^2 values) which signified that all the formulations by kinetics followed zero order.

3.5.2. Release mechanism

In order to understand the complex mechanism of drug release from the BGMT, the *in vitro* LM release data were studied using Korsmeyer Peppas release model. The release exponent (n) values from the power law Peppas equation enlightens in understanding the release mechanism from the dosage form. The n values thus obtained ranged from 0.74 to 0.99. Formulations L2, L3, L6, L7, and L8 exhibited anomalous (non-Fickian transport) diffusion mechanism with n value ranging between 0.74 and 0.92 (Table 4). The anomalous transport refers to a combination of diffusion and erosion controlled drug release from the polymer and it occurs due to the coupling of Fickian diffusion and case II transport. This means while the erosion did occur to some extent, the mechanism of drug release was not purely erosion dominant. The n values suggested that the mechanism of drug release was anomalous and was controlled by a combination of diffusion, polymeric relaxation and erosion. For formulations L1, L4, and L5, the release exponent values were observed between 0.95 and 0.99 confirming the closeness to the attainment of an ideal zero order drug release. The n values (Table 4), indicated the release mechanism of LM from these BGMT as an approximate case II transport, where the drug release is due to polymer dissolution and erosion. Case II generally refers to the erosion of the polymeric chain after swelling where the matrix relaxation holds a predominant role to play. The drug is released as the polymer swells, relaxes and erodes gradually. The zero order drug release behavior here may suggest that the release of LM was controlled by a combination of polymer matrix erosion and the three dimensional network structure which was produced by polymer complex formation following liquid penetration into the tablet (Peppas, 1985). Hence the results signified that polyox at 13% and HPMC K15M at 15% concentrations predominantly modulated the drug release in a controlled fashion. Since these formulations reported highest r^2 values for zero order kinetic model, it was remarked that the LM release from these BGMT not only followed zero order kinetics but also zero order controlled release mechanism. Therefore the runs L1 and L4 were considered as optimal formulations on account of their reproducible and promising drug release profiles.

3.5.3. Mean dissolution time

Mean dissolution time (MDT) value is generally used to characterize the drug release rate from a dosage form and it indicates the drug release retarding efficiency of a polymer. The results showed that the MDT values were approximately constant for a given controlled release polymer at a given concentration irrespective of the lower MA layer composition (Table 3). The MDT values of Run L1 $\approx$ Run L5, similarly that of Run L2 $\approx$ Run L6, Run L3 $\approx$ Run L7 and Run L4 $\approx$ Run L8. This indicates that the lower MA layer composition does not interfere with the drug release modulation facilitated by the upper CR layer. The drug release retarding efficiency of polymers was in the order polyox 13% < polyox 15% < HPMC K15M 13% < HPMC K15M 15%. This finding can be related to the ascending order of polymer viscosities (Mockel and Lippold, 1993).

3.6. Unidirectional drug release studies

3.6.1. In vitro release studies by modified basket method

The *in vitro* drug release studies of gastric mucoadhesive compacts were additionally carried out using the USP dissolution apparatus I. By this modified basket method design, only the peripheral/upper CR drug layer of the gastric mucoadhesive compact was exposed to the dissolution medium which ensures the study of *in vitro* unidirectional drug release. All the tablet batches run were incorporated with a rigidizing polymer, Eudragit L100 in the lower mucoadhesive layer. This ingredient is insoluble in gastric pH and hence expected to prevent any deformation of tablet all through the course of its gastric residence time. The purpose was served as none of the tablets showed deformation during the *in vitro* dissolution studies carried out by both the paddle method and modified basket method.

3.6.2. Characterization of unidirectional drug release

Model independent methods (similarity factor, f_2 and difference factor, f_1) were used for the characterization and optimization of 2^3 FFD experimental runs with respect to their unidirectional release profile. The dissolution results of the modified basket method were set as reference and the results of the paddle method were considered as the test sample. The *similarity factor* denoted as f_2 directly compares the similarity in the percentage drug dissolved per unit time between the test and reference products. The f_2 is a logarithmic transformation of the sum squared error of differences between the test and reference products over all time points (Thomas et al., 1998; Costa and Jose, 2001; Costa, 2001; Ruben et al., 2008). The comparison of the similarity and difference factors obtained for all the eight formulations was presented in Table 3. The tabulated values signified that the paddle method dissolution profiles of all the formulations showed significant similarity with their respective modified basket method dissolution profiles. In general, f_2 values higher than 50 (50–100) signifies similarity of the dissolution profiles. The 2^3 FFD formulation runs L1, L2, L4 and L5 showed exceptionally high (>90) f_2 values. The formulations, L1 with polyox 13% and L4 with 15% HPMC K15M were optimized attributing to their highest f_2 values. Higher similarity factor implies predominant and ensured unidirectional drug release.

Based on the results obtained from various tests namely precompression analyses, tablet physical tests, *ex vivo* mucoadhesion studies, dissolution studies and unidirectional drug release studies, the precise polymeric combinations comprising of 13% polyox or 15% HPMC K15M in the upper CR layer and 50:50 ratio of Carbopol 974P to polyox in the lower MA layer were identified as the most potent formulations providing both enhanced mucoadhesion and unidirectional controlled drug release.

4. Conclusion

The results signified that the *in vitro* development of bilayered gastric mucoadhesive tablets with optimal mucoadhesion and ensured unidirectional controlled drug release profile for lamotrigine was feasible. The study of drug release kinetics and the mechanism indicated zero order drug release from the

optimized formulations. While the combined use of polyox and Carbopol 974P demonstrated maximum mucoadhesive strength, the addition of Eudrgit L100 ensured unidirectional drug release profile. The newly designed modified basket dissolution method in combination with model independent methods proved successful in characterizing the unidirectional drug release profile from the formulation. Therefore, for a drug like lamotrigine, a BCS class II drug with pH dependent solubility and incompatibility with the most promising mucoadhesive polymer, carbopol, a novel bilayered gastric mucoadhesive tablet may serve as the best possible rationale, potential, economic and industrially applicable formulation for the delivery of lamotrigine for an extended period of time from 6 to 12 h.

References

Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F., 2006. Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. J. Control Release 111, 1–18.

Brodie, M.J., 1992. Lamotrigine. Lancet 339, 1397–1400.

Chanda, R., Roy, A., Bahadur, S., Saha, S., Das, S., Choudhury, A., 2010. Floating drug delivery: a potential alternative to conventional therapy. Int. J. Pharm. Tech. Res. 2 (1), 49–59.

Cheng, C.L., Chou, C.H., Hu, O.Y., 2005. Determination of lamotrigine in small volumes of plasma by high-performance liquid chromatography. J. Chromatogr. B 817 (2), 199–206.

Costa, P., Jose, M.S.L., 2001. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Costa, P., 2001. An alternative method to the evaluation of similarity factor in dissolution testing. Int. J. Pharm. 220, 77–83.

Gupta, A., Garg, S., Khar, R.K., 1992. Measurement of bioadhesive strength of muco-adhesive buccal tablets: design of an in vitro assembly. Indian Drugs 30, 152–155.

Han, R.Y., Fang, J.Y., Sung, K.C., Hu, O.Y.P., 1999. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Int. J. Pharm. 177, 201–209.

He, X., Secreast, P.J., Amidon, G.E., 2007. Mechanistic study of the effect of roller compaction and lubricant on tablet mechanical strength. J. Pharm. Sci. 96, 1342–1355.

Joao, F.P., 2010. Site-specific drug delivery systems within the gastrointestinal tract: from the mouth to the colon. Int. J. Pharm. 395, 44–52.

Mockel, J.E., Lippold, B.C., 1993. Zero order release from hydrocolloid matrices. Pharm. Res. 10, 1066–1070.

Narendra, C., Srinath, M.S., Rao, B.P., 2005. Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique. Int. J. Pharm. 304, 102–114.

Park, H., Robinson, J.R., 1987. Mechanisms of bioadhesion of poly (acrylic acid) hydrogels. Pharm. Res. 4, 457–464.

Patel, V.M., Prajapati, B.G., Patel, M.M., 2007. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS PharmSciTech 8 (1), E1–E8 (Article 22).

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Ponchel, G., Touchard, F., Duchene, D., Peppas, N.A., 1987. Bioadhesive analysis of controlled release systems. I. Fracture and interpenetration analysis in poly(acrylic-acid) containing systems. J. Control Release 5, 129–141.

Raval, J.A., Patel, M.M., 2011. Formulation and characterization of gastroretentive discs containing famotidine. Braz. Arch. Biol. Technol. 54 (2), 293–300.

Rowe, R.C., Sheskey, P.J., Quinn, M.E., 2009. Handbook of Pharmaceutical Excipients, sixth ed. Pharmaceutical Press, London, UK, American Pharmacists Association, Chicago, USA, pp. 110–114.

Ruben, M.M., Patrico, M.C., Teodoo, S.K., 2008. A new principal component analysis-based approach for testing "similarity" of drug dissolution profiles. Eur. J. Pharm. Sci. 34, 66–77.

Sivakumar, R., Vaithiyalingam, Vilayat, Sayeed, A., 2010. Critical factors in manufacturing multi-layer tablets — assessing material attributes, in-process controls, manufacturing process and product performance. Int. J. Pharm. 398, 9–13.

Thomas, O.H., Adrian, D., Jackie, D., John, D., 1998. A review of methods used to compare dissolution profile data. Pharm. Sci. Technol. Today 1 (5), 214–223.

http://www.biospace.com/news_story.aspx?StoryID=169319&full=1. Date: 2/1/2010, time: 7:08:36 AM. FDA approves Glaxo SmithKline (GSK)'s once-a-day Lamictal(R)XR(TM) as add-on epilepsy therapy for primary generalized tonic–clonic seizures.