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Novel core in cup (In-lay) tablets of lamotrigine for mucoadhesive drug delivery system

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ABSTRACT

Lamotrigine a BCS class II drug used in treatment of epilepsy has several disadvantages when taken orally (first pass metabolism and increased C_{max}). The aim of the study is to design core in cup (In lay) buccoadhesive tablets which aims for controlled, unidirectional release, increased patient compliance and decreased side effects. The present study involves the preparation of core in cup tablets containing release retarding polymers like sodium alginate, xanthan gum and HPMC E 15LV in core and HPMC K 15M in cup for mucoadhesion. L9 orthogonal array Taguchi design was constructed for the study. The dependent variable studied for L9 orthogonal array Taguchi runs include % drug release from which the formulation with highest S/N ratio was optimized. All the runs were evaluated for physical parameters, drug release, mucoadhesive studies and assay. L1, L2, L4 and L8 formulations showed controlled release for up-to 8 hours with good assay values. The model dependent kinetics showed zero order kinetics with super case II transport and Hixson Crowell mechanism which indicates unidirectional drug release.

Abbreviations: %, percentage; BCS, biopharmaceutical classification system; h, hours; °C, degrees Celsius; Mg, milligrams; MDT, mean dissolution time; rpm, revolution per minute; #, sieve number; USP, United States pharmacopoeia; UV, ultra violet; r^2, correlation coefficient; *n*, release exponent (power law Korsmeyer Peppas equation), S/N, signal to noise.

Key Words: Core in cup (In-lay) tablets, Lamotrigine, L9 orthogonal array Taguchi design, zero order kinetics, unidirectional release.

INTRODUCTION

The oral cavity is the attractive site for the delivery of drugs due to high patient compliance, ease in administration, direct access to systemic circulation, avoids first pass metabolism and also degradation in GIT. Oral cavity delivers the drug through sublingually from the floor of the mouth, locally for local delivery into oral cavity and buccal delivery through buccal mucosa. Buccal drug delivery system is only responsible for administration of retentive dosage form (Mujoriya *et al.*, 2011). It is advantageous over transdermal delivery due to increased permeation, *i.e.*, 4-4000 times greater than transdermal delivery (Patel *et al.*, 2011).

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, had several disadvantageous when given orally. Immediate release formulations of lamotrigine lead to high first pass metabolism (Mashru *et al.*, 2005) cyclical observations of peak plasma concentration, severe side-effects, rashes due to rapid increase in blood plasma levels after each dosing (Werz, 2008), increased glucoronidation during menopause and oral contraceptive therapy due to increased cytochrome p450 enzyme (Gaffield *et al.*, 2011), changes in lamotrigine clearance during pregnancy (Harden, 2002). To ameliorate the drawbacks associated with immediate release formulations, lamotrigine is formulated into buccal mucoadhesive controlled release dosage form.

Solubility of lamotrigine is pH dependent. Studies revealed that as the pH increases the solubility of drug gets decreased but with buccal pH (6.8) though the solubility of lamotrigine is low the partition coefficient and permeability coefficient of drug made it possible for the transport of drug through buccal mucosa. This is due to availability of drug in unionized form (98%) due to which the drug transport occurs through transcellular route, which forms basis for the buccal drug delivery (Patel *et al.*, 2011).

The core in cup (In-lay) buccal tablets offers several advantages like availability of active ingredient for modified release, ability to release drugs at a zero-order rate and maintenance of plasma concentration with in therapeutic window (Modi *et al.*, 2013).

The present study involves the preparation of core in cup (In-lay) buccoadhesive tablets of lamotrigine. The core and cup are different from each other in which the core consists of lamotrigine with other control release polymers like sodium alginate, xanthan gum and HPMC E 15 LV and cup consists of mucoadhesive polymer (HPMC K 15M).

Buccal route is one such alternative and buccal route has not been explored for the administration of this drug. The drug is available in the market as conventional tablet and the buccal permeation forms the basis for the drug to formulate as buccal tablet and the core in cup tablets were responsible for the controlled release and maintenance of drug concentration in the plasma.

L9 orthogonal array Taguchi design was constructed to minimizes the experimental trials. All the runs were evaluated for the *in vitro* drug release, swelling index, surface pH, assay, MDT, *ex-vivo* mucoadhesion strength and time. The dependent variable studied for L9 orthogonal array Taguchi runs include % drug release.

MATERIALS AND METHODS

Lamotrigine, eudragit L100, eudragit S 100, are obtained from Evonik Roehm Pharma polymers. Sodium alginate, Xanthan gum, HPMC E 15LV and HPMC K 15M are obtained from Yarrow Chem. products, Mumbai. Talc, magnesium stearate and lactose monohydrate are

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obtained from SD fine chemicals. All chemical reagents used were of analytical grade. Goat buccal mucosa was obtained from a slaughter house.

Preparation of 6.8 pH Mcilvaine buffer: 772.5ml of 0.2M disodium hydrogen phosphate solution was transferred into a 1000ml volumetric flask and volume was made up to 1000ml with 0.1M citric acid solution.

Preparation of 0.2M disodium hydrogen phosphate solution: 35.5 gm of disodium hydrogen phosphate was taken into 1000ml volumetric flask and dissolved in small quantity of distilled water. Finally, volume was made up to 1000ml with distilled water.

Preparation of 0.1M citric acid: 20.01 gm citric acid was taken into 1000ml volumetric flask and dissolved in small quantity of distilled water. Finally, volume was made up to 1000ml with distilled water.

Pre-compression flow properties and compressibility of buccal core in cup tablets

All the pre-compression properties were determined independently for core tablet as well as for the coat/cup. The bulk and tapped densities were determined with USP tap density apparatus (Electrolab) from which Hausner's ratio and compressibility index (% Carrs's index) were calculated. Fixed funnel method was used for the angle of repose determination.

Preparation of core in cup buccoadhesive tablets

The core in cup buccal tablets was prepared by direct compression method. All the ingredients for the core tablet were screened through #60. Lamotrigine was mixed with polymers, talc and lactose monohydrate as diluent for 10 min. Then blends were lubricated with magnesium stearate for 3-5min. The core mixture is compressed using 10 station rotary tablet compression machine by 6 mm punches. Then upper punch was raised and the pre-compressed core tablet was removed from 6 mm punch and placed onto 8 mm punch then turret was allowed to move to an extent and the mucoadhesive layer (HPMC K 15M) was added to the die containing core tablet and compressed again to attain core in cup buccal tablets.

Experimental design

The effect of different parameters on the mean and variance of the process performance was investigated by Taguchi experimental design (Sharma *et al.*, 2005; Maghsoodloo and Ozdemir, 2004). In this design, orthogonal arrays arrange the affecting parameters and their levels in the way, most likely to affect the process. Unlike factorial design, in which all possible combinations are tested, Taguchi employs a minimal number of trials by testing pairs of combinations. This saves both time and resources. The optimal parameters obtained from these trials are not sensitive to environmental changes and other noise factors. "Minitab 15" was the software employed to carry out Taguchi experimental design.

Optimization of formulation

In the present study, the following three process parameters were selected: type of controlled release polymer, drug: concentration of polymer and concentration of binder. Each of these parameters was at three different levels, as stated in table 1. Three parameters, at three levels each, would give 27 experiments in full factorial design but only nine experimental runs by 3X3 designs

using L9 orthogonal array Taguchi design, as shown in table 2. The sequence of the experimental runs was randomized to prevent any bias.

Total weight of tablet is 150 mg and core tablet weighs about 75mg which consists of drug (25mg), magnesium stearate (2%), talc (2%), lactose monohydrate as diluent (qs) in constant along with the polymer and binder as mentioned in table 2. The outer coat/cup consists of 75 mg of HPMC K 15M.

Evaluation of core in cup (In-lay) buccal tablets
In-process tests

Weight variation, hardness and friability tests were carried out for all the formulations (Raju *et al.*, 2012). Tablets were evaluated for the weight variation using electronic balance. Thickness and hardness were measured by screw gauge and Monsanto hardness tester and friability by Roche friabilator.

Assay

Ten tablets were taken and grounded into fine powder. Powder equivalent to 25 mg of drug was weighed and transferred to 50 ml volumetric flask containing 25 ml of methanol and finally made the volume to 50 ml with methanol. The volumetric flask was sonicated for 15 minutes. To 50 ml of volumetric flask add 2ml of above solution, add 25 ml 6.8pH Mcilvaine buffer and make up the volume to 50ml with buffer (Raju *et al.*, 2012; Patel *et al.*, 2012) and checked for the absorbance at 304.5nm in UV spectrophotometer.

In Vitro drug Release

USP type I apparatus was used to carry out dissolution using 500ml Mcilvaine buffer for 8 hours, during which the aliquots (5ml) were withdrawn for every one hour and replaced with fresh media (Raju *et al.*, 2012; Patel *et al.*, 2012). The absorbance was checked at 304.5nm in UV spectrophotometer (Chemito Instruments Pvt. Ltd., Mumbai, India) and the concentration of drug released was calculated using calibration curve.

Table 1: Selection of independent variables for L9 orthogonal array Taguchi design.

Factors (independent variables)	Levels		
	Low	Medium	High
Factor A: Type of controlled release polymer	Sodium alginate	Xanthan gum	HPMC E 15LV
Factor B: Drug: Concentration of polymer (%)	1:0.5	1:0.75	1:1
Factor C: Concentration of binder (%)	0	3	5

Table 2: Various trials to be carried out according to L9 orthogonal array.

Run	Factor A (Type of control release polymer)	Factor B (drug: concentration of polymer)	Factor C (% of binder)
1	Sodium alginate	1:0.50	0
2	Sodium alginate	1:0.75	3
3	Sodium alginate	1:1	5
4	Xanthan gum	1:0.50	3
5	Xanthan gum	1:0.75	5
6	Xanthan gum	1:1	0
7	HPMC E 15 LV	1:0.50	5
8	HPMC E 15 LV	1:0.75	0
9	HPMC E 15 LV	1:1	3

Swelling Study

Buccal tablets were weighed individually (W_1) and placed separately in 2% agar gel plates with core facing the gel surface and incubated at 37±1°C. After 8 hours the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W_2) and the swelling index (SI) were calculated using the formula (Patel *et al.,* 2012).

$$\%SI = \frac{W2-W1}{W1} \times 100$$

Ex-vivo mucoadhesion time

The tablet was placed over excised goat mucosa which is secured on glass slide and pressed for 30 sec and was immersed in a basket of the dissolution apparatus containing about 750 ml of pH 6.8 Mcilvaine buffer, at 37°C. The paddle of the dissolution apparatus was adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment from the mucosa was recorded (Raju *et al.,* 2012; Patel *et al.,* 2012).

Ex-Vivo Mucoadhesive Strength

A modified balance method was used to study the *ex vivo* mucoadhesive strength (Raju *et al.,* 2012). Fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 hours. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with Mcilvaine buffer pH 6.8 solutions at 37°C. A piece of buccal mucosa was tied to the cork and was fitted into a glass beaker (filled with Mcilvaine buffer pH 6.8, at 37±1°C) so that it just touches the mucosal surface. The buccal tablet was placed to the lower side of a glass stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa (Raju *et al.,* 2012; Patel *et al.,* 2012). The balance was kept in this position for 5 minutes. Different weight was put slowly to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

RESULTS AND DISCUSSION

Formulation of buccal core in cup tables

The S/N ratio for larger-the-better characteristic was chosen for % drug release in 6.8 pH Mcilvaine buffer. The S/N ratio for the response is given in table 3. The mean of these S/N ratios at each level of process variable is summarized in table 4 and figure 1. The ranks obtained for each factor determine its effect on the drug release pattern. Table 3 shows that the ratio between drug and concentration of polymer plays primary role in drug release from the tablet. The characteristic for optimization of tablets is the largest S/N ratio. Based on this, as depicted in table 3, it can be concluded that the tablets would be optimized for % drug release when the processing conditions are A1B2C2 which represents sodium alginate as the controlled release polymer in 0.75:1 ratios with drug and PVP K 30 in 3% as binder. Similarly, from table 4 the highest value was observed for experiment run 2, *i.e.,* L2 formulation. Hence L2 formulation was optimized.

Table 3: Response table for S/N ratio.

Level	A	B	C
1	38.07	37.51	36.39
2	36.14	38.01	37.51
3	36.61	35.3	36.94
Delta	1.93	2.71	1.12
Rank	2	1	3

Table 4: Signal to noise ratio of response for all experimental runs.

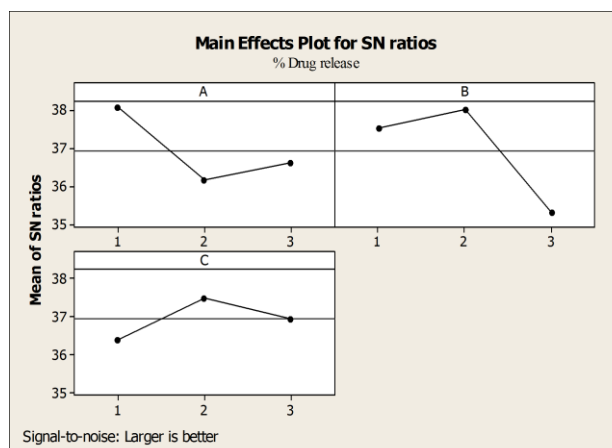| Experimental run	S/N ratio of response (% drug release)
1	38.0815
2	39.7
3	36.4248
4	37.2759
5	37.2094
6	33.949
7	37.1764
8	37.1292
9	35.539

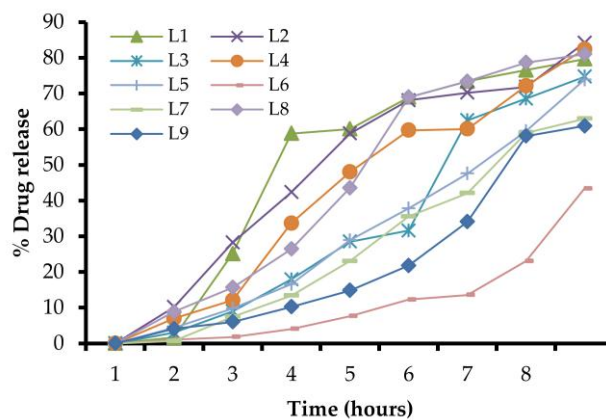**Figure 1: Main effects plot for S/N ratio of % drug release.**

Figure 2: Comparative dissolution profiles of L9 orthogonal array experimental runs.

Table 5: Model dependent kinetic analysis of the dissolution profiles of L9 orthogonal array Taguchi runs.

Runs	Zero order release model parameters	First order release model parameters	Higuchi release model parameters	Korsmeyer-Peppas release model parameters			Release mechanism	Hixson Crowell release model parameter
	r^2	r^2	r^2	r^2	K_{kp}	n		r^2
L1	0.82	0.55	0.91	0.8	0.613	1.68	super case II	0.9
L2	0.92	0.76	0.97	0.95	0.98	1.1	super case II	0.96
L3	0.95	0.9	0.91	0.98	0.483	1.58	super case II	0.93
L4	0.96	0.84	0.97	0.96	0.83	1.26	super case II	0.97
L5	0.98	0.93	0.94	0.99	0.61	1.37	super case II	0.97
L6	0.81	0.97	0.71	0.95	0.13	1.75	super case II	0.95
L7	0.98	0.92	0.94	0.99	0.41	1.57	super case II	0.911
L8	0.94	0.97	0.95	0.97	0.911	1.18	super case II	0.98
L9	0.9	0.98	0.82	0.93	0.456	1.37	super case II	0.86

Tablet physical properties and characterization

The major excipients selected for the core tablet were the drug and control release polymer (sodium alginate, xanthan gum and HPMC E 15LV). The outer coat/cup predominantly comprised of HPMC K 15M. The pre-compression flow properties were studied separately for both core and coat/cup. Flow properties were further improved by the addition of lubricant, magnesium stearate which was added prior to tableting. Angle of repose values of the core ranged between 15° and 34° while that of the coat/cup was 32°. The compressibility index values of the formulation batches ranged between 14% and 21% for both core and coat/cup indicating the suitability of the powders for dry granulation. Hausner's ratio ranged between 1.16 and 1.27 for both core and coat/cup.

The addition of different polymers did not affect the tablet physical characteristics. All the tablet formulations presented hardness in the range 4-6 kg/cm². The percent friability values reported for the tablet formulations were very low (<0.55%) with no measurable differences among the between batch results. The thickness ranged between 1.70 ± 0.02 mm and 1.82 ± 0.02 mm while the weight of different batch formulations varied between 150 ± 0.78 mg and 150 ± 0.94 mg.

Assay

The drug content of each batch of all the formulations (L1-L9) was evaluated as per the standard protocol. The results indicate that the percentage of drug content was found to be 90.41 to 96.5%.

In-vitro drug release profile

Formulations containing sodium alginate (F1-F3) showed drug release as 81.65%, 84.19% and 74.7%, respectively. The formulation with 1: 0.75 ratios of drug: polymer and PVP K 30 of 3% showed increased drug release in 8 hours.

Formulations containing xanthan gum (F4-F6) showed decreased drug release with increase in the concentration of the polymer. The initial burst release was seen with xanthan gum because it can hydrate rapidly even in cold water. It is highly swellable and showed sustained release (Mughal *et al.*, 2011; Singh *et al.*, 2011).

Xanthan gum provides time-independent release kinetics and establishes constant drug plasma levels as observed during *in vivo* drug release behaviour (Singh *et al.*, 2011).

Formulations containing HPMC E 15LV with PVP K 30 (F7, F8 and F9) showed to have drug release as 62.93, 81.01 and 60.93%, respectively. The results concluded that the drug release was influenced by PVP K 30 in which the 0% PVP K 30 showed increased drug release, *i.e.*, 81.01%

(F8) when compared to F7 and F9 formulations with PVP K 30 of 3% and 5%, respectively. The decreased drug release is due to increased retarding efficiency of HPMC E 15LV and PVP K 30 in combination, *i.e.*, synergistic effect was observed. It has been reported that HPMC with low viscosity grades also shows maximum release retarding efficiency in tablets containing 20-50% (Mughal *et al.*, 2011).

Swelling index

The swelling index studies were conducted for all the nine formulations using 2% agar gel. All the tablets were hydrated for 8 hours and % SI was calculated. The highest swelling index (70.39% for 8 hours) was seen with HPMC E 15LV and PVP K30 in 5%. The reason for increased swelling index of HPMC E 15LV is due to high degree of erosion and low viscosity which makes the tablet to swell (Mughal *et al.*, 2011; Singh *et al.*, 2011).

Ex-vivo mucoadhesion time

Ex-vivo mucoadhesion studies were carried out for the all L9 Taguchi runs. The formulations containing sodium alginate and xanthan gum showed promising results than formulations with HPMC E 15 LV. The mucoadhesion time for sodium alginate and xanthan gum are more than 15 hours and for that of HPMC E 15 LV, where it is only about 8 hours. The reason for the decreased contact time or mucoadhesion time is due to swelling nature of polymer which makes tablet unable to withstand in contact position for longer durations.

Characterization of the optimal formulation

The formulations were further subjected to a detailed characterization in terms of release kinetics. The study results are presented in table 5.

Table 6: Evaluation parameters.

Code	% Swelling index	MDT (hours)	Mucoadhesive time (hours)
F1	34.8	0.832	>15
F2	48.6	0.528	>15
F3	49.35	0.966	>15
F4	49.7	0.644	>15
F5	50	0.826	>15
F6	55.2	1.97	>15
F7	63.1	1.07	>8
F8	68.8	0.58	>8
F9	70.39	1	>8

Kinetic analysis of drug release profiles and model fitting

The evaluation of the drug release profile kinetics of the entire L9 orthogonal array Taguchi 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 models (indicated by the highest r^2 values) which signified that all the formulations by kinetics followed zero order which indicates controlled drug release except L6, L8 and L9 which showed first order kinetics.

Release mechanism

In order to understand the complex mechanism of drug release from the core in cup mucoadhesive tablet, the *in vitro* LM release data were studied using Korsmeyer Peppas release model. The release exponent (*n*) values from the power law Peppas equation enlighten the release mechanism from the dosage form. The *n* values thus obtained ranged from 1.1 to 1.75 which indicates super case II transport mechanism, *i.e.*, drug release by both diffusion and relaxation of polymer chain (Bose *et al.*, 2011; Kumar *et al.*, 2012).

Unidirectional drug release studies

The regression coefficient was calculated from the Hixson Crowell equation and found that the r^2 value of L2 was approximately equal to the r^2 values of Higuchi kinetics which indicates unidirectional drug release.

Mean dissolution time (MDT)

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 (Kumar *et al.*, 2012). The results showed that the MDT values were found to be increased with increase in the concentration of the polymers. No effect was observed with the cup/coat of the tablet. The drug release retarding efficiency of polymers was in the order Xanthan gum>HPMC E 15 LV> sodium alginate.

Ex vivo mucoadhesive strength

The weight for which tablet got detached was 15.58 grams. The bioadhesive strength was found to be 15.58 grams and force of bioadhesion was found to be 0.152 N for L2 optimized formulation.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of pure lamotrigine and the optimized tablet formulation were recorded with a FTIR spectrophotometer (FTIR-Shimadzu 8400 S, Japan) from 4000–400 cm^{-1} using KBr press pellet method. The pellets were prepared using a mixture of lamotrigine, sodium alginate and KBr by applying a pressure of 100 kg/cm^2 for 2 min. The FTIR of optimized formulation showed no extra peaks with pure drug indicating no interaction between drug and the polymers therein.

CONCLUSION

The results signified that the *in vitro* development of core in cup mucoadhesive tablets with optimal mucoadhesion and ensured unidirectional controlled drug release profile for lamotrigine was feasible. From S/N ratio it can be concluded that the concentration of the polymers plays an important role on the release of drug and formulation with sodium alginate: drug in 0.75:1 ratios and PVP K 30 in 3% was found to be optimized. The study of drug release kinetics and the mechanism indicated zero order drug release from the optimized formulation. Therefore, for a drug like lamotrigine, a BCS class II drug with pH dependent solubility and with high first pass metabolism the buccal drug delivery is feasible with controlled release up to 8 hours.

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