AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Preparation and Evaluation of Mucoadhesive Bilayered Buccal Patches of Lamotrigine

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ABSTRACT

Bilayer mucoadhesive buccal patches of lamotrigine were prepared by solvent casting technique using different polymers like PVA, PVP K30, pullulan, carbopol and HPMC 5cps. These formulations were prepared and evaluated for various parameters like weight variation, visual inspection, content uniformity, surface pH, bioadhesive strength, *in-vitro* and *ex-vivo* diffusion studies. It was found that F3 (PVA 3% and PVP K30 2%) and F4 (PVA 4% and PVP K30 1%) formulations showed good physical, mechanical properties and sustained drug release profile of about 85% and 80% in 8 hours. The formulation was found to follow zero order model dependent kinetics with Fickian diffusion. Ex-vivo diffusion studies were conducted using Franz diffusion cell. Ex vivo diffusion studies were conducted using goat buccal mucosa. The formulations containing PVA and PVP K30 in 3:2 and 4:1 ratio and 10% of PG as a plasticizer was found to be optimized which showed 66% and 60% of drug release in 8 hours. These formulations have shown bioadhesive strength of 0.06N and 0.09N and good bioadhesion time up to 6-7 hours respectively. These formulations were found to be zero order model dependent kinetics with anomalous transport as release mechanism. Lag time, cumulative amount permeated/area, flux and permeability coefficient for optimized formulations were found to be 30 & 40 min, 1336 & 1212 µg/cm², 2.18 & 2.24 µg/cm²/min and $639x10^{-4}$ & $904x10^{-4}$ cm/min respectively.

Key words: Mucoadhesive patches, lamotrigine patches, bilayered patches, diffusion studies.

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Received 24 December 2016, Accepted 05 January 2017

Please cite this article as: Lakshmi PK *et al*., Preparation and Evaluation of Mucoadhesive Bilayered Buccal Patches of Lamotrigine. American Journal of PharmTech Research 2017.

INTRODUCTION

Buccal drug delivery is one of the novel drug delivery systems. It localized the delivery of drug to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease. Buccal drug delivery also a safer mode of drug delivery system and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism. The administration of drug through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism. It is possible bypass of first pass effect and avoidance of pre-systemic elimination within the gastrointestinal tract. Buccal route is preferred the drugs having poor bioavailability because of high first pass metabolism. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively [1]. The work on lamotrigine mucoadhesive buccal patches is an area of our interest.

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. For epilepsy it is used to treat seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Lamotrigine also acts as mood stabilizer. It is the first medication since lithium granted Food and Drug Administration (FDA) approval for the maintenance of bipolar type I. chemically unrelated to other anticonvulsants, lamotrigine has relatively few side effects and does not require blood monitoring and the half life of this drug is 25 hrs.[2,3,4] Bilayered mucoadhesive buccal patches of lamotrigine were prepared by solvent casting technique using different polymers like PVA, PVP K30, pullulan, carbopol and HPMC 5cps and evaluated.

MATERIALS AND METHOD

Lamotrigine was obtained as a gift sample from Dr. Reddy's laboratory. PEG 400 and propylene glycol were obtained from SD fine chemicals, Ltd. All the other materials used were of analytical grade.

Preparation of Mucoadhesive Buccal Patches

Patches were prepared using different polymers like HPMC E5, carbopol, poly vinyl pyrrolidine K30, polyvinyl alcohol, pullulan, HPMC 5cps and their combinations[5]. Polymer solution was prepared by dissolving the polymers in 8ml of water. 15mg of drug was dissolved in 2ml of water and added to the polymer solution which gives a total volume of 10ml. the solution was stirred

until a clear solution was formed and then poured into a Teflon plate containing backing membrane and was kept at 40^0C for 24 hrs.

After 24hrs, the patch was checked for drying by just touching it. The patches that were not dried were kept for another 24hrs.

Table 1: Composition of Various Formulations of lamotrigine buccal patches

Formulation code	PVA (mg)	PVP K30 (mg)	Pullulan (mg)	PG (%)	PEG (%)
F1	100	400	-	10	-
F2	200	300	-	10	-
F3	300	200	-	10	-
F4	400	100	-	10	-
F5	-	-	200	-	10
F6	-	-	300	-	10
F7	-	-	400	-	10
F8	-	-	500	-	10

Note: In all formulations 175mg of drug was added

Evaluation of Buccal Patches

Visual inspection and film formation

The film was evaluated visually for its clarity, transparency, and stickiness. If it was satisfactory, then it was used for further evaluation.

Thickness variation test

The thickness of the films was measured at five different points (centre and four corners) of the patch by digital screw gauge. Mean thickness was calculated from the five points.

Weight variation test

The formulated films were prepared in triplicate. Three films from each batch were weighed individually and the average weight calculated.

Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip o film (2cmχ2cm) at the same place till it broke. The number of times, the film could be folded at the same place without breaking give the value of folding endurance.

Assay

The assay was performed to ensure the loading in each patch. This test was performed by taking $2cm^2$ patch in a 100ml volumetric flask and dissolving it in 10ml of methanol. Then it is made upto the volume by 6.8pH buffer and filter it through Whatmann filter paper. Dilutions were made from the filtrate and the samples were analysed at a wavelength of 305.2nm.

Content uniformity

This test was performed to ensure that every film contains the amount of drug substance intended with little variation among different pieces in a patch. From the whole patch 3 pieces were cut, each of 4cm^2 areas and assayed for its drug content. Uniformity of content was reported by measuring the mean and standard deviation values.

Surface pH

A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1ml of distilled water pH (6.8±0.1) for 2hrs at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute.

In vitro diffusion studies

Diffusion study of the patch was performed using Franz diffusion cell. The cell was locally fabricated and volume of receptor compartment was 25ml. the dialysis membrane was soaked in buffer for 24hrs before conducting the study. Patches were supposed to release the drug from one side only. The dialysis membrane was mounted between the donor and receptor compartments. Patch formulation (2cm*2cm) was applied uniformly on the dialysis membrane and the compartment clamped together. The receptor compartment was filled with 6.8 pH buffer with 0.5% SLS and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead. At predetermined time intervals, 2ml of samples were withdrawn and equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically.

Ex-vivo diffusion studies using goat buccal mucosa

Ex –vivo release profile was employed through goat buccal mucosa and the percentage release profile of the optimized formulation was observed.

Tissue preparation (Isolation)

Goat buccal tissue was obtained from local slaughter house and was used within 2hrs after slaughtering. The tissue was stored in Krebs buffer at 4^0C after collection. The epithelium was removed from the underlying connective tissue with surgical technique and the de-lipidized membrane was allowed to equilibrate for approximately 1hr in receptor buffer to regain the lost elasticity.

Ex –vivo drug permeation studies

The buccal epithelium was mounted carefully in between two compartments of the Franz diffusion cell with internal diameter of 10cm with a receptor compartment volume of 20.0ml. 20ml of 6.8pH

with 0.5% SLS buffer was placed in the receptor compartment and the buccal patch was attached to the dialysis membrane in such a way that the drug layer faces towards the buffer in the receptor compartment. The entire setup was placed on the magnetic stirrer and temperature was maintained at 37^0C. 1ml of sample was collected at predetermined time intervals from the receptor compartment and was replaced with the same amount of buffer. Samples were diluted to 5ml using 6.8pH buffer and were analyzed using spectrophotometer at 305.2nm. All the experiments were conducted in triplicates.

In vitro swelling studies of buccoadhesive patch

The degree of swelling of bioadhesive polymer is an important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The polymeric films cut into 2cmχ2cm were weighed accurately and kept immersed in 50ml of water. The films were taken out carefully at 5, 10, 30, 60 minutes intervals, blotted with filter paper to remove the water present on their surface and weighed accurately and the percent swelling was calculated using the formula,

$$\text{Swelling index} = W_2\text{-}W_1 / W_1$$

Flux (µg/cm^2/hr)

Mass transport of molecules in a solution of molecular transport across a barrier is normally measured by fluxes. The flux of a solute is simply defined as the mass or number of molecules moving through a given cross sectional area during a given period of time. It is obtained by plotting a graph between time and cumulative percentage release per cm^2 area.

Lag time (hrs)

Lag time is the time required for the drug to get released from the matrix system. It is calculated by plotting cumulative amount of drug permeated vs time. The x-intercept value gives the lag time.

Permeability coefficient (cm/hr)

The rate of drug permeation through unit area of the patch per unit time along the concentration gradient gives the value of permeability coefficient. It is obtained by dividing flux with donor concentration.

$$\mathbf{Kp = Jss / C}$$

Jss= steady state flux (µg/cm^2/min)

C_0= drug donor concentration (mg/cm^3)

Bioadhesion time

The ex-vivo mucoadhesion time was determined by using USP dissolution test apparatus II. The ex vivo mucoadhesion time was examined (n=3) after application of the mucoadhesive patch on

freshly cut goat's buccal mucosa. The goat's buccal mucosa was tied to paddle and the drug layer was wetted with 1 drop of 6.8pH buffer and adhered to the mucosal tissue by applying a light force with a fingertip for 30seconds. The paddle was then kept in the beaker which was filled with 900ml buffer and kept at $37^0C \pm 0.5^0C$. After 2minutes, a slow stirring rate (50rpm) was applied to simulate the oral environment and the patch adhesion was monitored. The time for the patch to detach from the goat's buccal mucosa was recorded as bioadhesion time[5].

Bioadhesive strength

Fresh goat buccal mucosa was obtained from a local slaughter house, placed in saline, and used within 2 hrs of slaughter. The mucosal membrane was cleaned and separated by removing the underlying fat and loose tissues. Bioadhesive strength of the patch was measured on a modified physical balance. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by a small plastic cap vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane. The goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a diffusion cell, which was placed and tightly fitted in the center of glass beaker. The phosphate buffer (pH 6.8, 37 ± 2° C) was filled in to the glass beaker in such a way that it makes contact with buccal mucosal surface. The patch was stuck to the lower side of flat surface plastic cap with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 g weight on the right-hand side pan. A weight of 5 g was removed from the right-hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 min contact time, and then slowly the weights were increased on the right-hand side pan till the patch separated from the mucosal surface as shown in the figures. [6]

$$\text{Force of adhesion (N)} = \text{Bioadhesive strength}/1000\chi 9.81$$

Model Dependent Kinetics

In order to understand the mechanism and kinetics of drug release from drug reservoir through rate controlling membrane, the *in-vitro* release data were fitted with the following mathematical models.

Regression coefficients (r^2) were calculated for all the formulations. Release compartment "n" was calculated from Korsemeyer Peppas equation. The release kinetic calculations were carried out using MS-OFFICE EXCEL.

RESULTS AND DISCUSSION

Among all the polymers used in the preliminary screening, the formulations containing the combinations of PVA and PVP K30 have shown good physical and mechanical properties and were further evaluated for percentage release profiles.

Lamotrigine buccal patches were prepared according to the formulas in the table 1

Evaluation of prepared patches

Table 2: Physicochemical evaluations of optimized formulations

Formulation	Weight variation (mg) ±SD	Content uniformity (mg)±SD	Thickness (mm)±SD	Assay (%)	Surface pH	Folding endurance
F1	121.33±3.05	19.36±0.32	0.2±0.1	95.4±1	6.3	>300
F2	127.66±4.9	19.06±0.25	0.32±0.064	98.1±0.5	6.5	>300
F3	125.95±4.5	19±0.45	0.34±0.05	99.2±0.57	6.8	>300
F4	124.53±3.07	18.63±0.05	0.39±0.06	101.2±1.3	7.0	>300

Note: Number of trials n =3

Visual inspection

The patches were clear and transparent when casted on Teflon plate.

Weight variation

The patches have shown percentage weight variation of less than 5%. This slight variation can be due to the Teflon plates not having ideal surface or due to surface of trays in hot air oven where patches were kept for drying. Weight Variation Test The weight of all the films was found to be uniform. It was found to be in a range of 121.3 to 125.9 mg for 2cm^2 area. According to the obtained results it was observed that increase in polymer concentration increases weight of the film. Weight variation is an important parameter to consider as any variation in the weight of film leads to under medication or over medication. Average weight results were shown in Table 2[7].

Content uniformity

The drug was distributed uniformly throughout the patch. The little variation may be due to variation in the thickness.

Thickness

Thickness of each film was measured using Screw gauge at 6 different locations. The average patch thickness was varying for patch to patch from 0.1-0.4mm. According to the obtained results it was observed that increase in polymer concentration increases thickness of the film. All the films prepared showed uniform thickness (Table 2) as it is important factor to consider which ascertains the accuracy and uniform distribution of dose in the strip[7].

Assay

The assay values for all the patches in the formulation were in the range of 95-101%. This shows the dose 25mg per patch was available and nearly maintained to that of theoretical value. The given lower percentage indicates the loss of drug while casting solution on plates as the drug and polymer solution was viscous, the last drops of solution might have not fallen in the plate. The results are given in table 2.

Surface pH

The pH of the formulations should be in compliance with the oral pH i.e., between 6.5 and 7.5 in order to prevent adverse effects like irritation and burning sensation. The surface pH of the patches was determined in order to investigate to possibility of any side effects in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was to keep the surface pH close to the neutral pH. The pH of all the formulations was found to be within this range which was acceptable[8]. The results were found to be close to neutral in all the formulations, and this means that they have less potential to irritate the buccal mucosa[9].

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion [8,9]. Attempts were made to keep the surface pH as close to buccal/salivary pH as possible, by the proper selection of the polymers for developing the buccal films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

Swelling index

Appropriate swelling behavior of buccal films is the essential property for uniform and prolonged release of the drug with effective mucoadhesion. During the swelling studies, it was found that, in the first hr approximately 35% swelling occurred in all the four formulations. This may be due to the hydrophilic nature of the secondary layer polymers, which were PVP and PVA. All the patches showed a negligible increase in weight[4]. Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. When bioadhesive comes in contact with aqueous medium they swell and form a gel. The faster this phenomenon occurs more rapid will be the polymer adherence to the buccal mucosa. The swelling of the patches was observed in phosphate buffer solution (pH 6.8). These results were in agreement with the increase in area due to swelling. The results revealed that all the formulations provide an acceptable swelling index in the range[10].

Folding endurance

The folding endurance gives an idea over the flexibility of films as brittle films gives less value of folding endurance and films with good flexibility gives high value of folding endurance. Folding endurance was measured manually by folding the film repeatedly at a point till they broke. Films did not show any cracks even after folding for more than 300 times and represents good mechanical characteristics. Hence it was taken as the end point. According to the obtained results all the films did not show any crack or cut after 300 times folding and all were having satisfactory flexibility. Also, it was observed that increase in thickness of polymer concentration decreases folding endurance value. The values were found to be optimum to reveal good film properties [9,10].

In vitro diffusion studies

In vitro diffusion studies showed that the formulations with different ratios of drug to polymers has released maximum drug within 480mins as shown in table 4.8. The formulations F3 and F4 were found to release about 85% and 80% respectively within 480mins. Phosphate buffer pH 6.8 was used as medium for the release study of lamotrigine patches containing different ratios of polymer to drug . The drug release was governed by polymer content. An increase in the polymer content was associated with decrease in drug release rates. The patch (F1 and F2) released the drug much faster than the other formulations. This is because the polymer PVP K30 used was of lesser viscosity and unlike the other grade of polymer, PVP K30 dissolves much faster.

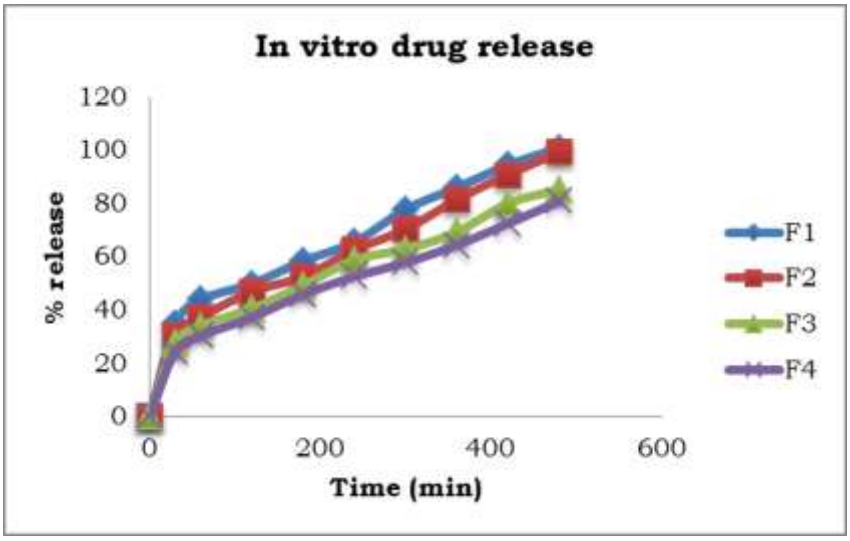


Figure 1: In vitro drug release for optimized formulations

Formulations with PVA polymer content (F3 and F4) showed slower drug release. Increasing the amount of the polymer in the patches produced the water swollen gel like state that could substantially reduce the penetration of the dissolution medium into the patches, and so the drug release was retarded[10]. The results of in vitro permeation studies indicated that the rate of drug

permeation was slow and it was found to be approximately 80% after 8 hr. The slow release of PVA: PVP (4:1) patches may be due to the complex formation between PVP and drug.

Determination of Release Rate From In Vitro Diffusion Studies

In vitro drug release rate was determined by plotting a graph for formulations (F1-F4) between square root of time and the amount of drug release per 4cm² area of patch and it was found to be 28.7 & 28.6 µg/cm²/min.

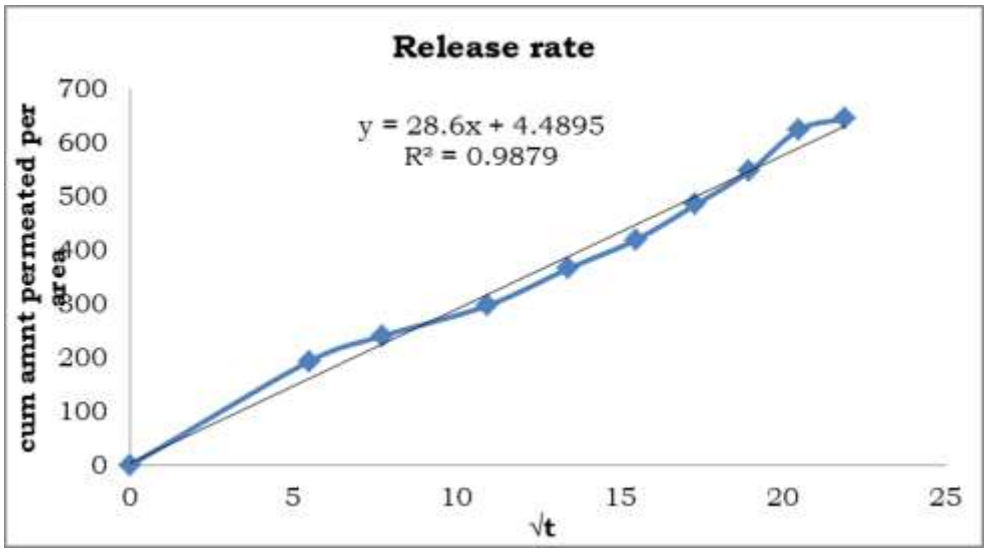


Figure 2: Determination of release rate for in vitro diffusion studies (µg/cm²min½)

MODEL DEPENDENT KINETICS

Model dependent kinetics provides the information related to mechanism of drug release from the dosage form. Four models were plotted based on the data obtained from *in-vitro* drug diffusion studies and their R² values were compared. The model which has the gather R² value indicates that the drug follows such mechanism of drug release. These four formulations shows zero order release with Fickian diffusion as release mechanism.

Table 3: Model dependent kinetics for *in vitro* drug release

Formulation	Zero order R²	First order R²	Higuchi R²	Korsemeyer peppas R²	N	Release mechanism
F1	0.9944	0.894	0.9736	0.9602	0.381	Fickian diffusion
F2	0.9942	0.9012	0.9656	0.9606	0.4311	Fickian diffusion
F3	0.9849	0.974	0.9848	0.987	0.3936	Fickian diffusion
F4	0.995	0.9723	0.9789	0.9735	0.4454	Fickian diffusion

EX-VIVO DRUG DIFFUSION STUDIES THROUGH GOAT BUCCAL MUCOSA

An ex-vivo drug penetration study was conducted using Franz diffusion cell for final optimized formulation (F3 and F4) and cumulative percentage release was noted. It was found that the formulation has released maximum drug i.e., above 20% within 30mins and the complete release

was found to be within 480 mins. In ex vivo study, drug permeation through the porcine buccal mucosa was determined for formulation F3 and F4. The drug permeation was found to be 66 and 60% in 8 h. The drug permeation decreased in ex vivo study in comparison of in vitro release. This decrease in drug diffusion observed from ex vivo study compared to in vitro, may be due to the lesser permeability of porcine mucosa and also the presence of a backing membrane in the ex vivo study, which make the release unidirectional. The backing membrane restricting the contact of the film with the receptor fluid to one side alone slows down the water uptake, swelling and disruption of the matrix in turn releasing lesser amount of drug in specified time, compared to the one without the backing membrane[11,12].

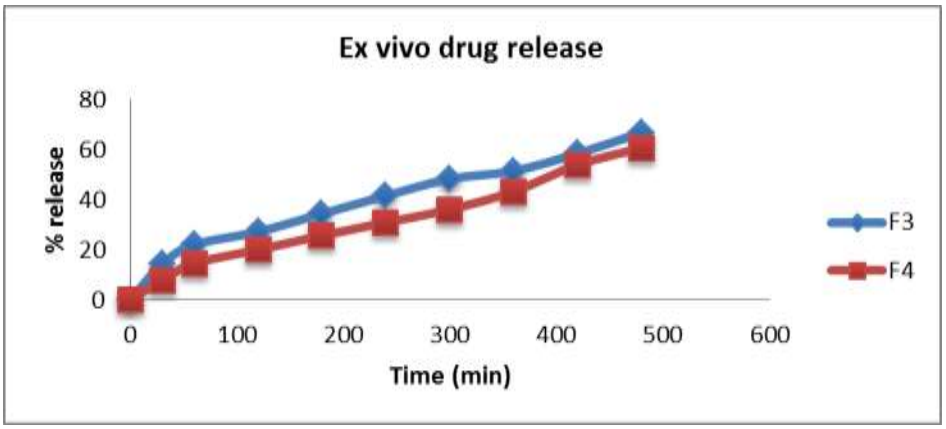
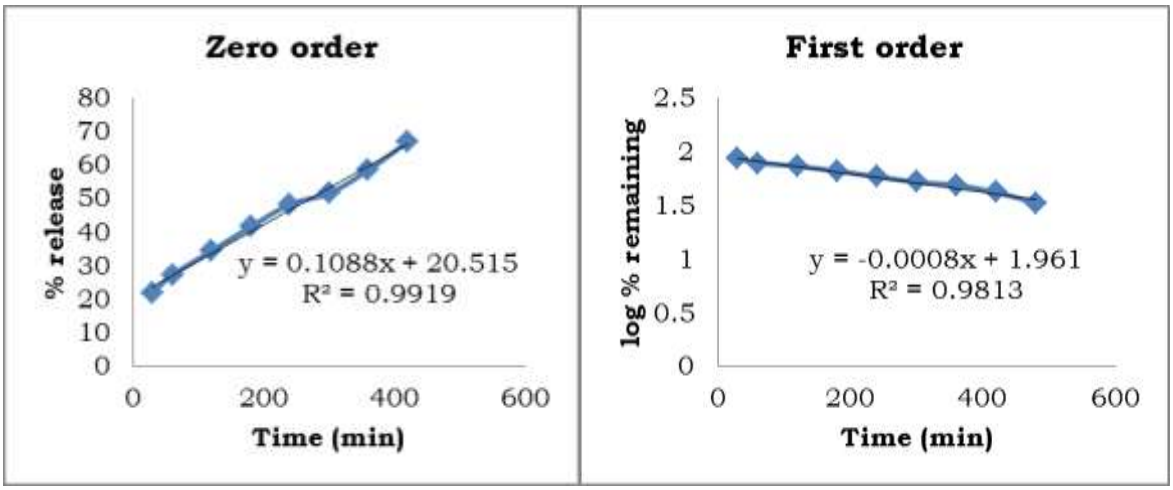


Figure 3: Ex vivo diffusion studies for optimized formulations (F3 & F4)

MODEL DEPENDENT KINETICS

Model dependent kinetics provides the information related to mechanism of drug release from the dosage form. Four models were plotted based on the data obtained from *ex-vivo* drug diffusion studies and their R^2 values were compared. The model which has the gather R^2 value indicates that the drug follows such mechanism of drug release.



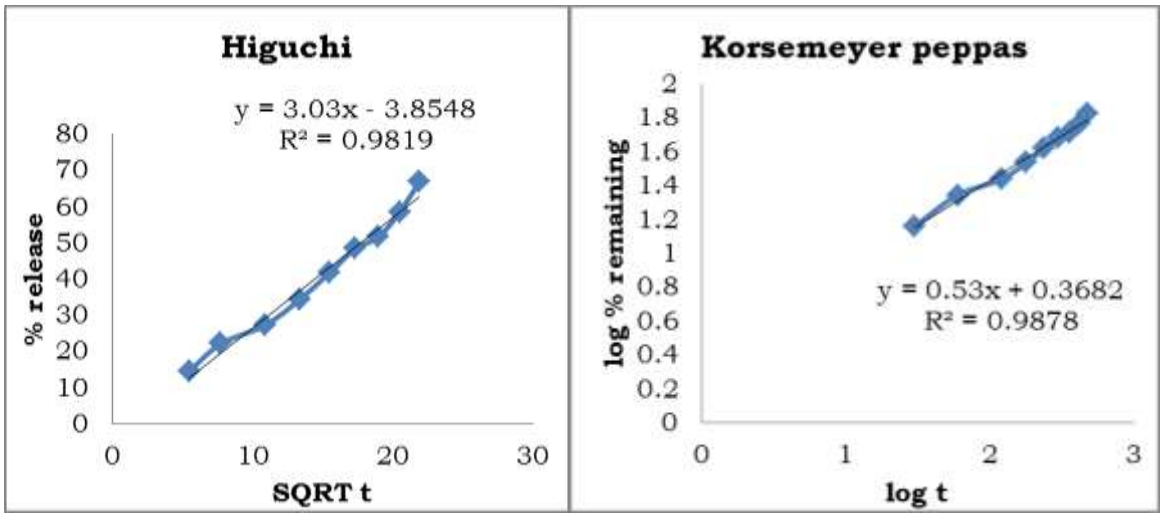


Figure 4: Model dependent kinetics of optimized formulation F3

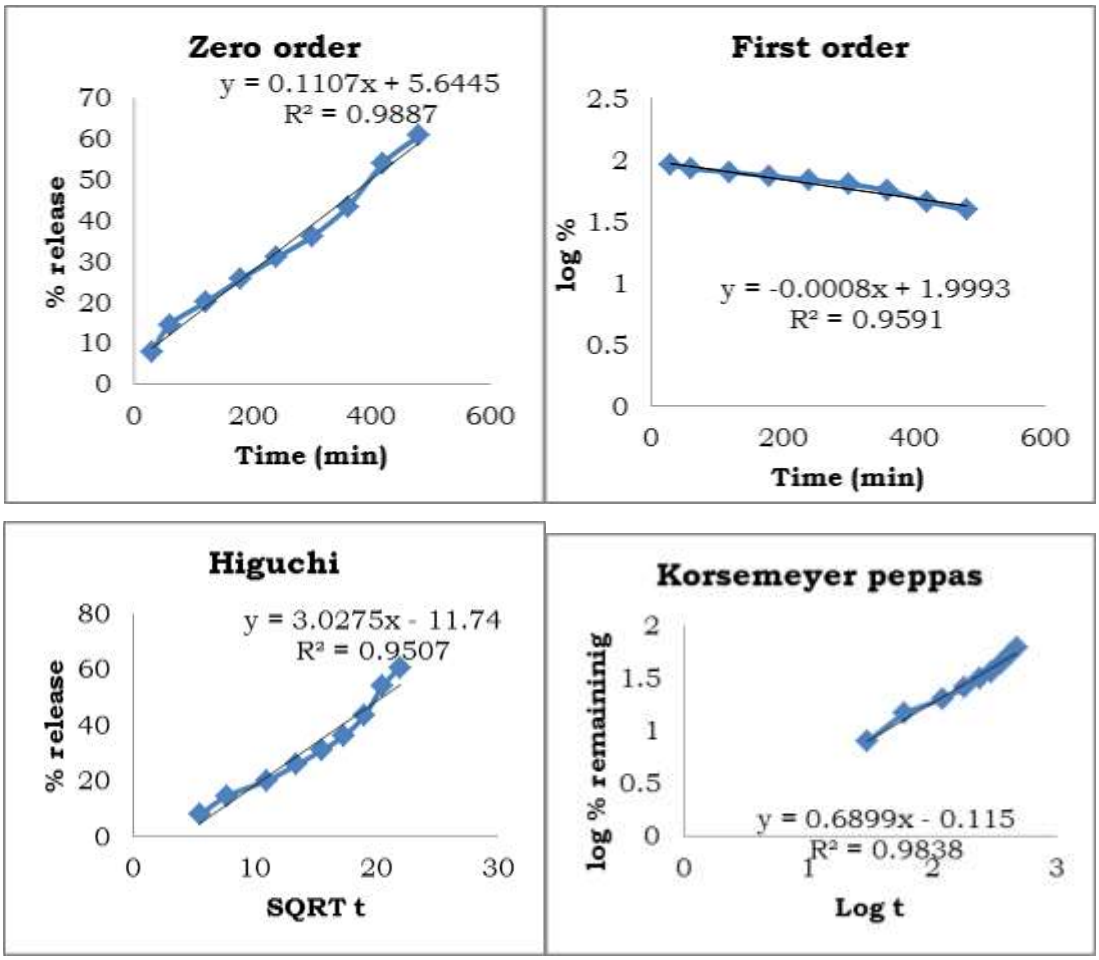


Figure 5: Model dependent kinetics of optimized formulation F4

Table 7: Model dependent kinetic analysis

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsemeyer's peppas R^2	N	Release mechanism

F3	0.9919	0.9813	0.9819	0.9878	0.53	Anomalous transport
F4	0.9887	0.9591	0.9507	0.9838	0.68	Anomalous transport

F3 and F4 formulations shows zero order with anomalous transport as release mechanism.

Flux

A graph is plotted between time and cumulative percentage release per cm² area of the patch.

Slope gives the value of flux and was found to be 2.18 & 2.214 µg/cm²/min.

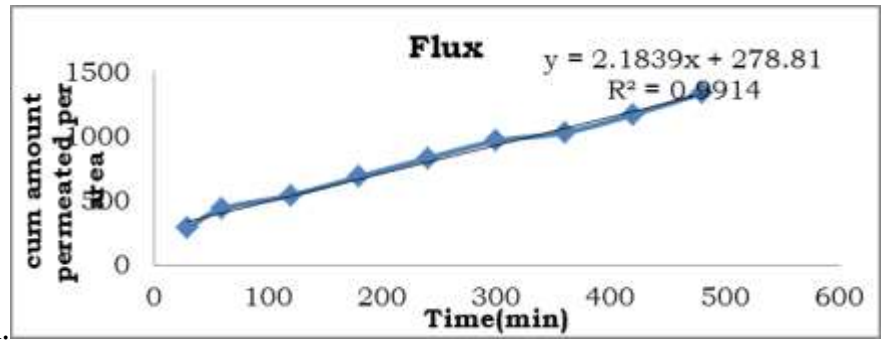


Figure 6 : Ex vivo diffusion study of the optimized formulation (F3)

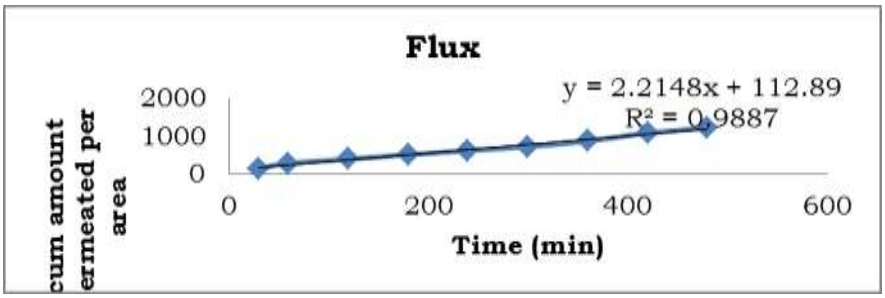


Figure 7 : Ex vivo diffusion study of the optimized formulation (F4)

Permeability coefficient

Permeability coefficient was found to be $639x10^{-4}$ & $904x10^{-4}$ cm/min.

Bioadhesive strength

Mucoadhesion of buccal patches may be defined as the adhesion between buccal patches and buccal mucosa. The strength of mucoadhesion is affected by various factors like biological membrane used in the study, molecular mass, and swelling rate of polymers present in the formulation. In this study, fresh goat buccal mucosa was used as biological membrane. Various mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength exhibited by these patches was satisfactory for maintaining them in oral cavity. Among all these formulated patches, formulation no. F3 and F4 showed maximum mucoadhesive strength[12]. The weight for which the patch got detached was 6.88 and 9.23 gms. The bioadhesive strength were found to be 6.88 and 9.23 gms and force of adhesion was found to be 0.06 and 0.09N.

Table 4: Bioadhesive strength for optimized formulations

Formulation	Bioadhesive strength (gm)	Force of adhesion (N)
F3	6.88	0.06
F4	9.23	0.09

Bioadhesive time

Bioadhesive time was found to be 6.5 to 7 hours for F3 & F4 formulations. Incorporation of PVP K-30 and the drug reduced significantly ex vivo mucoadhesion time of the patches[13]. In addition, increased viscosity led to formation of surface gel that maintained its structural integrity for a longer period of time, thereby resulting in increased residence time.

Table 5: Bioadhesive time for optimized formulations

Formulation	Bioadhesive time (hr)
F3	6.5
F4	7

CONCLUSION

Bilayered mucoadhesive buccal patches of lamotrigine were prepared by solvent casting technique using different polymers like PVA, PVP K30, pullulan, carbopol and HPMC 5cps. Different polymers of buccal patches were screened depending upon their properties and cumulative percentage release profiles. The percentage release was found to be 85% and 80% for F3 (3:2) and F4 (4:1) formulations in 8 hours respectively. Ex vivo diffusion studies were conducted using goat buccal mucosa. The formulations containing PVA and PVP K30 in 3:2 and 4:1 ratio and 10% of PG as a plasticizer was found to be optimized which showed 66% and 60% of drug release within 8 hours. These formulations have shown bioadhesive strength of 0.06N and 0.09N and good bioadhesion time up to 6-7 hours respectively. These formulations were found to be zero order model dependant kinetics with anomalous transport as release mechanism. Lag time, cumulative amount permeated/area, flux and permeability coefficient for optimized formulations were found to be 30 & 40 min, 1336 & 1212 µg/cm², 2.18 & 2.24 µg/cm²/min and $639x10^{-4}$ & $904x10^{-4}$ cm/min respectively. Further study needs to be done on animals for its effect on permeation through skin.

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