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Formulation and evaluation of transdermal patches of Lamotrigine

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Abstract

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Existing approved formulations of lamotrigine present cyclical plasma concentration of drug with peaks occurring after administration followed by troughs occurring before the next administration. The objective of this study was to develop a transdermal patch of lamotrigine for the better management of anti-convulsive therapy, alone or in combination. Transdermal patches were prepared by solvent casting method using HPMC, ethyl cellulose, and eudragit as the polymeric matrix. The patches were evaluated for thickness, folding endurance, % moisture content and uptake, drug content, tensile strength and in vitro permeation study. The thickness of the transdermal patches F1-F6 for different polymer ratios varied from 0.070±0.008 mm to 0.083±0.005 mm. Formulation F4 contain minimum moisture contain 1.85±0.32% and minimum moisture uptake 2.14±0.32% with a folding endurance of 220±12, and 99.94±0.52% drug content.

Keywords: Transdermal, eudragit, HPMC, ethyl cellulose, Lamotrigine, release

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Introduction

Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular intervals, due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing. The limitations of the oral route can be overcome and benefits of intravenous drug infusion such as to bypass hepatic "first pass" hepatic elimination (HEPE) to maintain constant prolonged and therapeutic effective drug levels in the body can be closely duplicated, without its potential hazards, by transdermal drug administration through intact skin[1-3].

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Existing approved formulations of lamotrigine present cyclical plasma concentration of drug with peaks occurring after administration followed by troughs occurring before the next administration[4].

In special population like pregnant women, bioavailability of Lamotrigine is reduced by 50% due to its increased clearance attributed to increased renal blood flow and estradiol induced glucoronidation of Lamotrigine. These problems can be overcome by bypassing the first pass metabolism and sustaining the drug release, both of which can be achieved by formulating drug in a transdermal system. The objective of this study was to develop a transdermal patch of lamotrigine for the better management of anti-convulsive therapy, alone or in combination.

Material and Methods

Lamotrigine was obtained as a generous gift sample form Aurobindo Pharma, Hyderabad. Eudragit L-100, ethyl cellulose and hydroxyl propyl methyl cellulose (HPMC) were purchased from Loba Chemie, Mumbai. All other reagents and chemicals were procured from SD Fine Chemicals, Mumbai and were used as obtained.

Formulation of Transdermal Patches

The casting solution was prepared by dissolving weighed quantities of HPMC (250, 300 and 350mg) and ethyl cellulose, Eudragit RSPO (50, 100 and 150mg) in 10 mL of methanol and chloroform and water mixture in ratio 1:1 (Table 1). To the resulting solution, 0.5% w/w of propylene glycol as plastisizer and 10% w/w penetration enhancer was added in this solution. Then drug (10 mg) was added and mixed thoroughly to form a homogeneous mixture. The casting solution was then poured into glass mould/Petri dish specially designed to seize the contents. The glass mould containing the casting solution was dried at room temperature for 24 hours in vacuum oven. The patch was removed by peeling

and cut into round shape of 1 cm^2. These patches were kept in desiccators for 2 days for further drying and enclose in aluminum foil and then packed in self-sealing cover[5].

Table 1. Composition of transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit (mg)	Ethyl Cellulose (mg)	Propylene glycol (%w/w)	Permeation Enhancer (%w/w)
F1	300	250	-	150	0.5	10
F2	300	300	-	100	0.5	10
F3	300	350	-	50	0.5	10
F4	300	250	150	-	0.5	10
F5	300	300	100	-	0.5	10
F6	300	350	50	-	0.5	10

Evaluation of Patches

The prepared patches were evaluated for thickness, percent moisture content, percent moisture uptake, folding edurance, tensile strength, drug content and *in vitro* skin permeation.

Patch thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated[6].

Percent moisture content

Weighed individually the films (2.5x2.5cm2) and kept them in desiccators containing calcium chloride at room temperature for at least 24 hrs. Film was weighed again; the difference in weight (initial and final weight) gives moisture content[7].

$$\% \text{ Moisture content} = \frac{\text{Intial weight} - \text{final weight}}{\text{Intial weight}} \times 100$$

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 h. Remove the films from desiccators and exposed to 4% relative humidity using saturated solution of potassium chloride in a another desiccator until a constant weight is achieved[8].

$$\% \text{ Moisture uptake} = \frac{\text{final weight} - \text{Intial weight}}{\text{final weight}} \times 100$$

Folding endurance

This was determined by repeatedly folding one film at the same place until it broken. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance[9].

Tensile Strength

The tensile strength of the patch was evaluated by using a tensiometer (Erection and instrumentation, Ahmedabad). It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2×2cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg[10].

$$\text{Tensile Strength } (s) = \frac{\text{Applied force } (m * g)}{\text{Cross sectional area}(b * t)}$$

Where, S = tensile stress in 980 dynes/cm^2; m = mass in grams; g = acceleration due to gravity (980 dynes/cm^2); b = breadth of strip in centimeters; t = thickness of strip in centimeters.

Drug Content

The patches (2.5*2.5 cm (Equivalent to 25mg of drug) were taken into a three separate 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. The solution was centrifuged to separate out any particulate matter. 0.1mL of sample was withdrawn and transferred in volumetric flask (10 mL of capacity). The sample was dilute up to the mark with distilled water and analyzed by UV spectrophotometer at 224.0 nm[11].

In vitro skin permeation study

The in vitro skin permeation study was carried out by using a Franz diffusion cell (receptor compartment capacity: 80 ml: area: 2.5*2.5 cm (Equivalent to 5 mg of drug). The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The patch was firmly pressed onto the centre of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell. The temperature of receptor compartment was maintained at 32±0.5ºC.

The samples were withdrawn at different time intervals and analyzed for drug release using a UV-visible spectrophotometer at 224nm. At the same time receptor phase was replaced with an equal volume of buffer solution at each time interval[12].

Stability Studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months.

Results and Discussion

The identity of the obtained sample was confirmed confirmed by FTIR spectroscopic analysis (Figure 1).

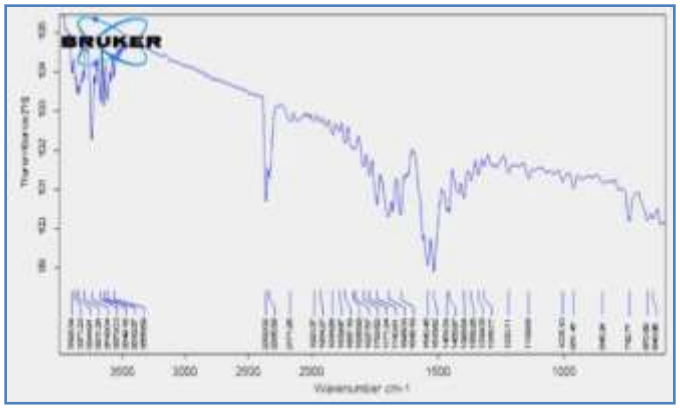

Figure 1. FTIR spectrum of Lamotrigine

The drug-excipient compatibility was determined using differential scanning calorimeter (DSC). DSC thermogram of Lamotrigine exhibited melting point at 215°C. The mixture of drug and excipients which

was kept in accelerated condition of 40°C/ 75% RH for 30 days and subjected to DSC analysis. The characteristic melting point of Lamotrigine does not deviate from 215°C that predicts that there is no interaction between drug and excipients (Figure 2).

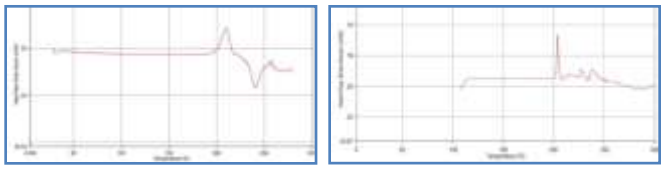

Figure 2. (a) DSC of pure Lamotrigine (b) drug and excipients

Evaluation of patches

The thickness of the transdermal patches **F1-F6** for different polymer ratios varied from 0.070±0.008 mm to 0.083±0.005 mm. The maximum difference between the thicknesses of patches was 0.016 mm, which indicates that all the prepared patches were of nearly uniform thickness (Table 2).

All the formulation show lowest moisture content and moisture uptake i.e. less than 4%. Moisture in this value is required to provide strength and flexibility to the patches. In all formulations formulation **F4** contain minimum moisture contain 1.85±0.32% and minimum moisture uptake 2.14±0.32%.

The folding endurance was found to be in the range of >150. This data revealed that the patches had good mechanical strength along with flexibility the values for all the formulation is tabulated. Maximum folding endurance was found in formulation **F-4** (220±12).

Tensile strength lies in between 372 g/cm^2 and 400 g/cm^2, the difference in values were due to the composition of polymer used. Also, there was an increase in the tensile strength with increasing concentration of polymers. Highest tensile strength was observed in **F4**, and this might be due to the highest concentration of Eudragit.

Table 2. Results of evaluation of patches of Lamotrigine

Formulation Code	Thickness (mm)	% moisture content	% moisture uptake	Folding endurance	Tensile Strength
F1	0.070±0.007	2.36±0.45	3.45±0.21	165±6	0.68±0.05
F2	0.072±0.008	2.85±0.25	3.52±0.25	185±8	0.85±0.08
F3	0.075±0.012	2.56±0.41	3.26±0.42	196±10	0.76±0.06
F4	0.068±0.014	1.85±0.32	2.14±0.32	220±12	0.96±0.07
F5	0.072±0.015	2.45±0.42	3.41±0.45	165±14	0.74±0.06
F6	0.076±0.016	2.65±0.32	3.52±0.32	175±8	0.65±0.07

Drug content of the all formulations was determined by dissolving the transdermal patches in methanol followed by centrifugation and then analyze on UV spectrophotometry. The drug content was found more than 95% in all the formulations with slight fluctuation (Figure 3). The drug content ranged between 97.85±0.48 and 99.94±0.52. The maximum drug content was found in formulation **F4** (99.94±0.52%).

The release of Lamotrigine from **F4** was determined using Franz diffusion cell and it was found that

18.85% of the drug was released in the initial 30 min of patch dissolution while 99.12% drug was released by the end of 12thh. The patch was able to release drug in a steady manner over the entire duration of the study (Figure 4).

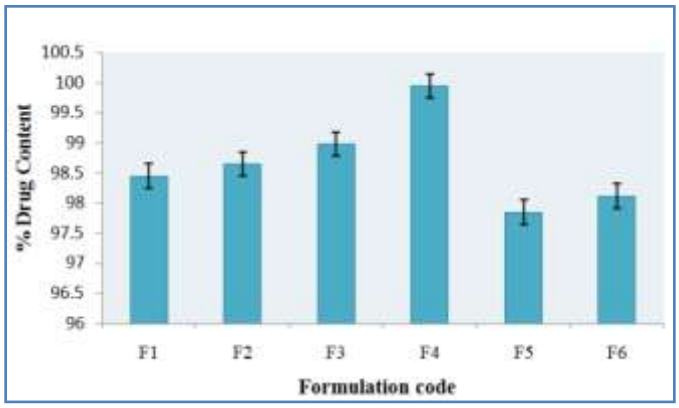

Figure 3. Percent drug content of patches

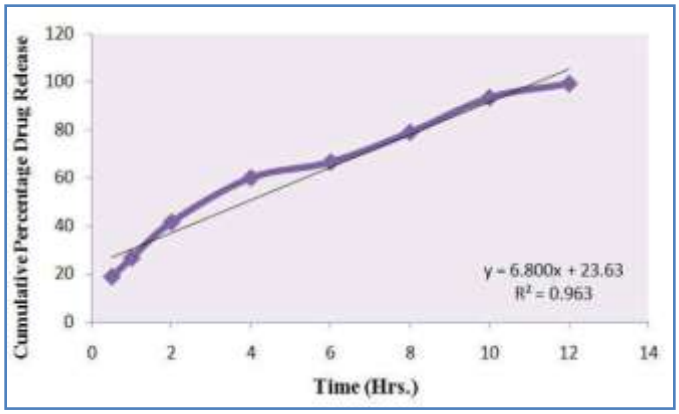

Figure 4. Release of Lamotrigine from F4

Stability Studies

Transdermal patch preparations were observed for any change in appearance or color for the period of 3 weeks. There was no change in appearance in formulation throughout the period of study.

Conclusion

The prepared transdermal drug delivery system of Lamotrigine using HPMC, ethyl celluose and Eudragit had shown good promising results for all the evaluated parameters. It was concluded that HPMC and Eudragit useful for preparation of sustained release matrix transdermal patch formulation.

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