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Formulation And Characterization Of Lacidipine Containing Transdermal Patches

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Abstract
The aim of this study was to formulate and characterize lacidipine-containing transdermal patches using various polymers and excipients, focusing on optimizing the drug release profile and mechanical properties. Lacidipine, a calcium channel blocker, was incorporated into transdermal patches made with a combination of Eudragit L-100, ethyl cellulose, and HPMC as the main polymer matrix. The patches were evaluated for their physical properties such as thickness, moisture content, folding endurance, tensile strength, and drug content. In vitro drug release studies showed that the optimized formulation (F4) exhibited a steady, controlled release of lacidipine over a 12-hour period, with a cumulative drug release of 98.98%. The in vitro diffusion release kinetics followed a zero-order release model ($R^2 = 0.985$), suggesting a constant rate of drug release. These findings indicate that the lacidipine transdermal patch provides an effective, controlled release system, making it a promising candidate for improving patient compliance in hypertension management.

Keywords: *Lacidipine, Transdermal Patches, Drug Release, Eudragit L-100, Ethyl Cellulose, HPMC, Zero-order Kinetics, Controlled Release, Polymer Matrix, Hypertension.*

INTRODUCTION

Lacidipine, a third-generation calcium channel blocker, is widely used in the treatment of hypertension and cardiovascular diseases. However, it exhibits poor bioavailability (approximately 10-15%) due to extensive first-pass metabolism in the liver when administered orally. To overcome these challenges, transdermal drug delivery systems (TDDS) have gained attention as a promising alternative, allowing for controlled and sustained release of drugs, bypassing the gastrointestinal tract and liver. Transdermal patches provide several advantages over conventional oral dosage forms, including avoidance of the first-pass effect, improved patient compliance, and controlled drug release, offering a steady therapeutic effect **(Vyas & Khar, 2002)**. Transdermal patches are designed to deliver drugs through the skin, utilizing the skin as a route of administration. The stratum corneum, being the outermost layer of the skin, presents a major barrier to drug penetration. Thus, enhancing the permeation of drugs through the skin is a critical challenge in the development of transdermal systems. Various methods, such as the use of permeation enhancers, microneedles, and iontophoresis, have been explored to improve drug absorption through the skin **(Mishra & Jain, 2008)**. The formulation of transdermal patches involves the selection of suitable polymers for the matrix, drug, permeation enhancers, and plasticizers. The polymers used in the formulation provide the patch with its mechanical strength and flexibility, while the plasticizers help in ensuring the patch remains pliable. Common polymers for transdermal patches include hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and polyvinyl alcohol (PVA) **(Chien, 2008).** The incorporation of permeation enhancers such as DMSO (dimethyl sulfoxide) or menthol can further improve the drug's ability to cross the skin barrier **(Rajbongshi & Rajkhowa, 2014; Shweta & Manpreet, 2012).** In this study, lacidipine-containing transdermal patches are developed and characterized for their physicochemical properties, drug release, and in vitro skin permeation. The aim is to formulate a system that provides a controlled and sustained release of lacidipine, ensuring continuous blood pressure regulation over an extended period, thereby improving patient compliance and minimizing side effects associated with oral formulations.

Material and Methods

Material

The materials used for the formulation development of lacidipine-containing transdermal patches include lacidipine (procured from Aurobindo Pharmaceuticals), which serves as the active pharmaceutical ingredient. The polymers used in the patch matrix include Eudragit L-100, ethyl cellulose, and

hydroxypropyl methylcellulose (HPMC), all sourced from Loba Chemie Pvt. Ltd., Mumbai. These polymers provide structural support and control the drug release rate. Propylene glycol 400, obtained from Thomas Baker (Chemicals) Pvt. Ltd., Mumbai, is used as a plasticizer to enhance the flexibility of the patch. Disodium hydrogen phosphate, methanol, ethanol, chloroform, and hydrochloric acid, all sourced from S.D. Fine Chem. Ltd., Mumbai, are used as solvents, buffer agents, and for other formulation requirements.

Methods

Determination of λ_{max} of Lacidipine

The λ_{max} of Lacidipine was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. Accurately weighed 10 mg of drug was dissolved in 10 ml of methanol in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with Phosphate buffer pH 7.4 solution prepare suitable dilution to make it to a concentration range of 2-10 µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+) **(Moorthi and Sumithira; 2011).** The spectrum peak point graph of absorbance of Lacidipine versus wave length was shown in figure 1.

Preparation and characterization of transdermal patches

Lacidipine containing transdermal patch was prepared utilizing method given by **Touitou et al., (2000)** with slight modification. The casting solution was prepared by dissolving weighed quantities of HPMC (350, 400 and 450mg) and ethyl cellulose, Eudragit L-100 (50, 100 and 150mg) in 10 mL of methanol and dichloromethane mixture in ratio 1:2. 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 (48mg) 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.

Table 1: Different Formulation used for transdermal patches

Formulation Code	Drug (mg)	HPMC (mg)	Eudragit L-100 (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Propylene glycol (Plasticizer) % w/w	Permeation Enhancer % w/w
F1	48	450	-	50	500	0.5	10
F2	48	425	-	75	500	0.5	10
F3	48	400	-	100	500	0.5	10
F4	48	450	50	-	500	0.5	10
F5	48	425	75	-	500	0.5	10
F6	48	400	100	-	500	0.5	10

Dose calculations

- Width of the plate (mould) = 5 cm
- Length of the plate (mould) = 12 cm
- No. of 2.5 x 2.5 cm patch present whole(mould) = 12
- Each film contains 4 mg of drug.
- 12 no. of films contains mg of drug = 4×12 = 48mg
- The amount of drug added in each plate was approximately equal to 48 mg.

Characterization of transdermal patches

The prepared transdermal patches were evaluated for the following parameters:

Microscopic pictures of transdermal patches

Microscopic pictures of all the formulations were observed using an electronic microscope with digital camera to determine the surface of the films formed and uniform dispersion of drug and polymer. In addition to microscopic study, transdermal patches were evaluated for their physicochemical characteristics **(Kumar et al., 2013).**

Thickness

Patch thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated **(Santosh et al., 2009).**

Percent moisture content

Weighed individually the films ($1cm^2$) 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 **(Murthy et al., 2001; Saxena et al., 2006).**

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

Percent moisture uptake

Weighed individually the films and kept them in desiccator containing calcium chloride at room temperature for at least 24 hrs. 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 **(Darwhekar et al., 2011).**

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

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 **(Prabhakar et al., 2011).**

Tensile Strength

The tensile strength of the patch was evaluated by using the tensiometer **(Jadhav et al., 2009).** 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.

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

Where, S = tensile stress
m = mass in grams
g = acceleration due to gravity
b = breadth of strip in centimeters
t = thickness of strip in centimeters

Drug Content

The patches (2.5*2.5 cm (Equivalent to 4 mg 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. 1mL of sample was withdrawn and transferred in volumetric flask (10 mL of capacity). The sample was dilute upto the mark with methanol and dilute suitably and analyzed by UV spectrophotometer at 285.0 nm **(Prajapati et al., 2011).**

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). Drug permeation studies were carried out using the skin of male Wistar rats. The skin samples were cut, removed, and washed with normal saline. Adhering fat and connective tissue were removed using blunt-ended forceps. The skin was kept in normal saline solution for 6 h. The hairs from the skin of the rat were shaved carefully to avoid peripheral damage. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal 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 37±0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content **(Gibaldi and Feldman: 1967; Cilurzo et al., 2018).**

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RESULTS AND DISCUSSION

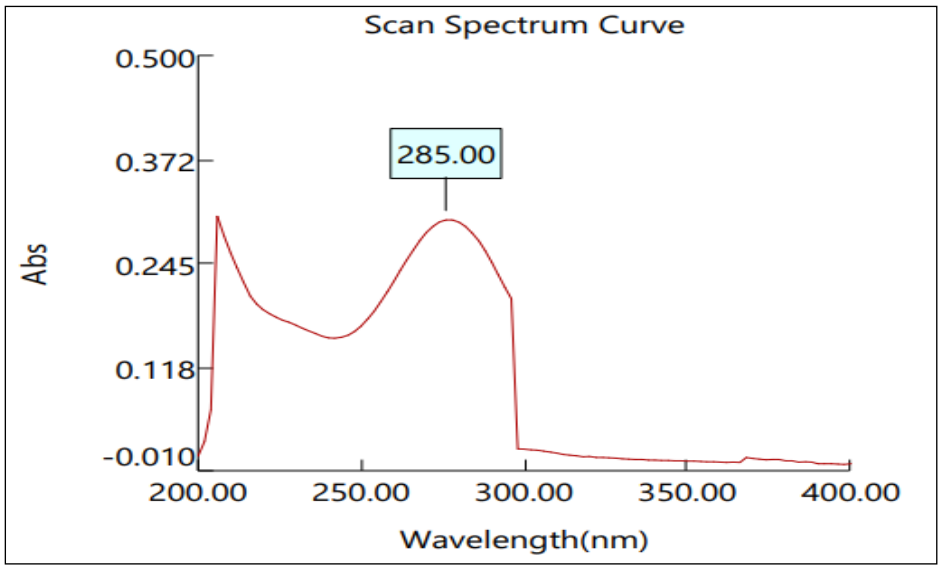

Figure 1: Determination of λ_{max} of Lacidipine

The determination of the maximum absorbance wavelength (λmax) is an essential step in the UV-visible spectrophotometric analysis of drug molecules, as it ensures accurate and reproducible quantification. In the present study, Lacidipine was scanned in the UV range of 200–400 nm using phosphate buffer (pH 7.4) as the solvent medium. The λmax was found to be 285 nm (Figure 1), which corresponds to the characteristic absorption peak of Lacidipine, likely due to its conjugated aromatic structure. A calibration curve was constructed for Lacidipine in the concentration range of 2–10 µg/ml. The choice of phosphate buffer at physiological pH (7.4) simulates in-vivo conditions, making it highly relevant for formulations intended for biological applications such as transdermal or oral delivery systems. The linearity of absorbance within this concentration range confirms the suitability of the method for quantitative analysis. The solvent system did not show any significant absorbance interference at 285 nm, indicating the buffer's compatibility and absence of overlapping absorbance. This further supports its selection as the medium for subsequent analytical or in-vitro release studies involving Lacidipine.

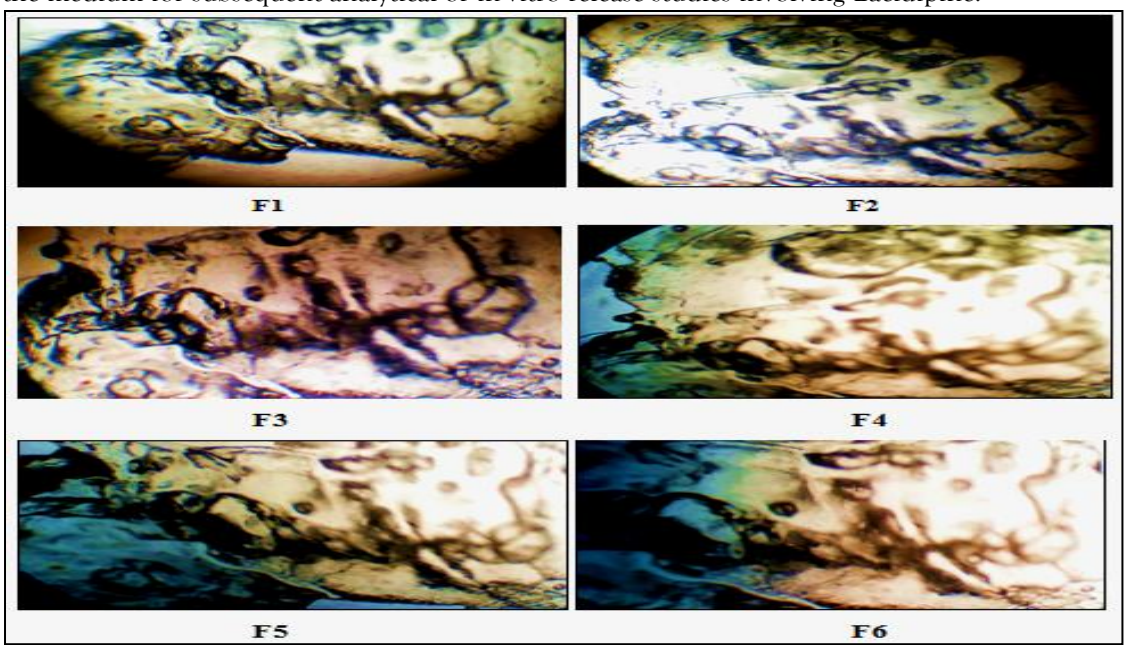

Figure 2: Microscopic pictures of transdermal patches

Microscopic evaluation is a useful technique to examine the surface morphology and uniformity of transdermal patches. In the present study, microscopic images of formulations F1 to F6 were captured and are presented in Figure 2. The images reveal that all patches exhibited a relatively smooth and

homogeneous surface, indicating uniform distribution of the drug and excipients within the polymer matrix. No visible cracks, air bubbles, or phase separation were observed in any of the formulations, suggesting good compatibility of components and an efficient casting process.

Table 2: Results of Thickness

S. No.	Formulation Code	Thickness* (mm)	% Moisture Content	% Moisture Uptake	Folding Endurance (Number of fold)	Tensile Strength (kg/cm)	% Drug Content
1.	F1	0.204±0.002	0.65±0.05	1.85±0.25	135±15	0.885±0.005	98.85±0.65
2.	F2	0.209±0.005	0.56±0.04	1.23±0.36	140±20	0.658±0.003	98.69±0.56
3.	F3	0.207±0.003	0.45±0.06	1.65±0.45	154±16	0.745±0.006	99.12±0.21
4.	F4	0.208±0.002	0.35±0.03	0.89±0.65	165±20	0.712±0.004	99.65±0.45
5.	F5	0.203±0.004	0.45±0.05	1.32±0.32	130±15	0.865±0.002	98.98±078
6.	F6	0.204±0.006	0.39±0.04	1.45±0.47	135±14	0.652±0.004	98.74±041

(Mean± SD, n=3)

The physicochemical evaluation of transdermal patches is essential to ensure their mechanical strength, uniformity, and stability. In the present study, various parameters including thickness, moisture content, moisture uptake, folding endurance, tensile strength, and drug content were evaluated for formulations F1 to F6. Thickness of all patches ranged from 0.203 ± 0.004 mm (F5) to 0.209 ± 0.005 mm (F2), indicating a uniform casting process with minimal variability. Uniform thickness ensures consistent drug release and structural integrity. The % moisture content was found to be lowest in F4 (0.35 ± 0.03%), suggesting better stability against microbial growth and less chance of patch deformation during storage. On the other hand, F1 exhibited the highest moisture content (0.65 ± 0.05%), which might affect its mechanical properties and shelf life. Moisture uptake was highest for F1 (1.85 ± 0.25%) and lowest for F4 (0.89 ± 0.65%). Lower moisture uptake is desirable as it indicates reduced hygroscopicity, contributing to better stability under humid conditions. Folding endurance reflects the flexibility and durability of the patch. F4 showed the highest folding endurance (165 ± 20 folds), demonstrating superior mechanical resilience, which is fundamental for patient comfort and adherence. In contrast, F5 showed the lowest value (130 ± 15 folds), which may affect its performance during long-term application. Tensile strength indicates the mechanical robustness of the patches. F1 had the highest tensile strength (0.885 ± 0.005 kg/cm), suggesting strong film-forming properties. F6 had the lowest tensile strength (0.652 ± 0.004 kg/cm), which may limit its practical use if not supported by other parameters. The % drug content was found to be within the acceptable range for all formulations, indicating uniform drug distribution. F4 had the highest drug content (99.65 ± 0.45%), making it the most promising formulation in terms of drug loading efficiency and uniformity (table 2).

Table 3: Percentage drug content of all the formulations

S. No	Time (Hrs.)	F1	F2	F3	F4	F5	F6
1	0.5	33.65±0.25	26.65±0.42	23.36±0.10	15.56±0.85	13.25±0.16	11.45±0.12
2	1	46.65±0.36	39.98±0.32	35.45±0.32	23.32±0.32	20.25±0.36	16.65±0.36
3	2	59.98±0.45	48.85±0.25	41.12±0.42	36.65±0.45	30.36±0.25	28.87±0.55
4	4	76.65±0.12	56.65±0.36	50.36±0.33	42.25±0.65	39.98±0.36	35.65±0.14
5	6	98.78±0.33	69.98±0.14	65.58±0.15	56.65±058	55.45±0.14	45.65±0.33
6	8	-	98.85±0.25	76.65±0.36	69.98±0.42	68.98±0.36	60.32±0.47
7	10	-	-	99.12±0.25	79.85±0.15	76.65±0.41	74.45±0.33
8	12	-	-	-	98.98±0.78	83.32±0.25	82.25±0.18

(Mean± SD, n=3)

The in-vitro drug release study of transdermal patches (F1–F6) was conducted to evaluate the sustained release characteristics of Lacidipine over a 12-hour period. The results are summarized in Table 3, and they demonstrate significant differences in release behavior among the formulations. Formulation F1

exhibited a rapid release, with 98.78 ± 0.33% of the drug released within 6 hours, indicating a burst release pattern. Similarly, F2 and F3 reached complete or near-complete drug release by 8–10 hours, suggesting a moderately sustained profile but with a faster initial release rate. In contrast, F4 displayed a more controlled and sustained release pattern, with only 15.56 ± 0.85% released at 0.5 hours, gradually increasing to 98.98 ± 0.78% over 12 hours. This extended release is likely due to the optimal polymer composition and matrix structure in F4, which regulated the diffusion of Lacidipine over time. The consistent and slower release observed in F4 reduces the risk of dose dumping and supports prolonged therapeutic action. Formulations F5 and F6 also demonstrated sustained release but did not reach complete drug release within 12 hours, with final values of 83.32 ± 0.25% and 82.25 ± 0.18%, respectively. This may indicate slower drug diffusion possibly due to higher polymer concentration or lower permeability. Based on the release profile, formulation F4 was identified as the optimized formulation, as it achieved a controlled, gradual, and complete drug release over the intended duration, aligning well with the objectives of transdermal drug delivery. Its performance also correlates well with favorable mechanical properties and uniform drug content, further supporting its selection as the most promising formulation for transdermal application.

Table 4: In vitro skin permeation study from optimized batch of transdermal patches F4

S. No.	Time (Hrs.)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	15.56±0.85	1.192	84.44	1.927
2	1	1	0	23.32±0.32	1.368	76.68	1.885
3	2	1.414	0.301	36.65±0.45	1.564	63.35	1.802
4	4	2	0.602	42.25±0.65	1.626	57.75	1.762
5	6	2.449	0.778	56.65±058	1.753	43.35	1.637
6	8	2.828	0.903	69.98±0.42	1.845	30.02	1.477
7	10	3.162	1	79.85±0.15	1.902	20.15	1.304
8	12	3.464	1.079	98.98±0.78	1.996	1.02	0.009

Values are represented as mean ±SD (n=3)

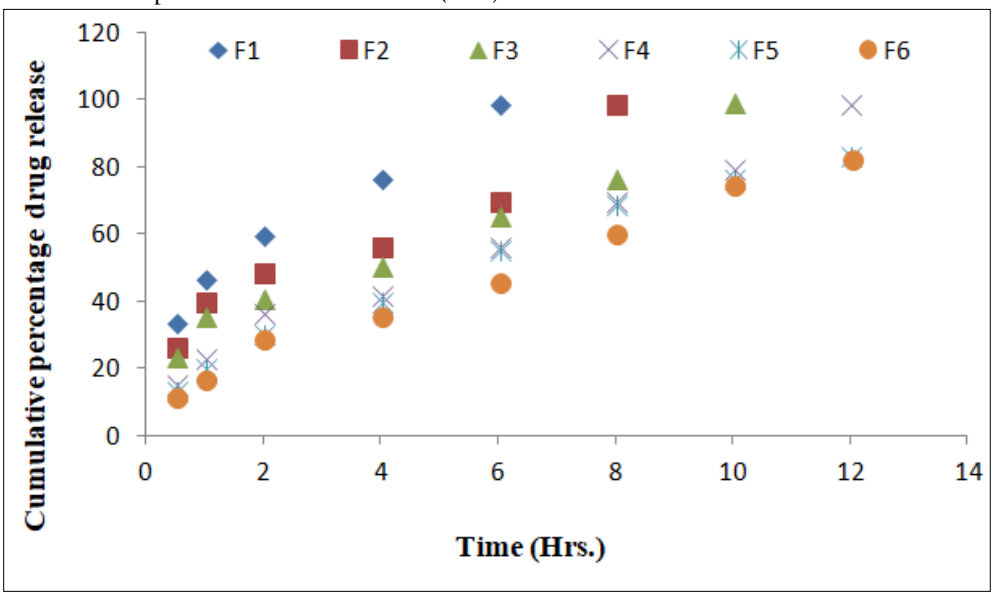

Figure 3: Graph of Cumulative Percentage Drug Release of formulation F1 to F6

Table 5: Regression analysis data of formulation F4

Formulation	Zero order	First order	Higuchi	Pappas plot

F4	R^2 = 0.985	R^2 = 0.709	R^2 = 0.977	R^2 = 0.986

The in-vitro skin permeation study of the optimized transdermal patch formulation F4 was conducted to evaluate the rate and extent of drug permeation through the skin over a 12-hour period. The results demonstrated a steady and controlled release pattern, with the cumulative percentage drug release gradually increasing from 15.56 ± 0.85% at 0.5 hours to 98.98 ± 0.78% at 12 hours. This sustained release behavior indicates that the drug was uniformly distributed in the polymer matrix, and there was minimal burst release effect. The smooth increase in permeation with time reflects the formulation's ability to provide consistent therapeutic levels over an extended duration. To elucidate the drug release mechanism, the data were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The regression coefficient (R^2) values obtained for these models were 0.985 (Zero-order), 0.709 (First-order), 0.977 (Higuchi), and 0.986 (Korsmeyer–Peppas). Among these, the Korsmeyer–Peppas model showed the highest correlation, indicating that the release of Lacidipine from formulation F4 follows anomalous (non-Fickian) diffusion, which is governed by both drug diffusion and polymer matrix relaxation or erosion. The close correlation with the zero-order model further confirms that the formulation is capable of delivering the drug at a relatively constant rate, which is a key advantage for transdermal systems aimed at maintaining steady plasma concentrations.

CONCLUSION

In conclusion, the lacidipine-containing transdermal patches formulated in this study demonstrated successful drug incorporation and controlled release properties. The combination of Eudragit L-100, ethyl cellulose, and HPMC as polymers proved effective in achieving a steady and sustained drug release over a 12-hour period. The optimized formulation (F4) exhibited desirable physical properties, including appropriate thickness, moisture content, and tensile strength. The in vitro drug release studies revealed that the release followed a zero-order kinetic model, ensuring a constant release rate, which is crucial for maintaining consistent therapeutic levels of lacidipine. These results suggest that transdermal patches of lacidipine have the potential to offer an efficient alternative to oral administration, providing prolonged drug delivery, improving patient compliance, and reducing side effects associated with fluctuating plasma concentrations. The transdermal patch formulation could be a promising strategy for the management of hypertension and potentially other cardiovascular conditions, offering the advantage of non-invasive, controlled drug delivery.

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