DESIGN, DEVELOPMENT AND EVALUATION OF ANTI-INFLAMMATORY PATCHES OF ECLIPTA ALBA LEAF EXTRACT

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ABSTRACT

Transdermal patches are a convenient drug delivery system that can provide a constant therapeutic effect over a prolonged period. The use of natural plant extracts in transdermal patches has been gaining attention due to their potential therapeutic benefits and fewer side effects. This study aims to formulate, optimize, and evaluate transdermal patches of Eclipta alba leaf extract. The Eclipta alba leaf extract was prepared by maceration using ethanol as a solvent. The extract was then incorporated into the transdermal patch matrix, which consisted of a mixture of HPMC K4, HPMC K15 and polyethylene glycol 400. The patches were prepared by the solvent evaporation method, and the patch thickness was optimized using a 3^2 factorial design. The optimized patches were evaluated for physicochemical characteristics, in vitro release, and skin irritation potential. The optimized transdermal patches had a thickness between 0.112±0.01 and 0.154±0.01mm, and the weights ranged between 7.10±0.75mg to 7.96±0.75mg. The release of the Eclipta alba leaf extract was sustained over 24 hours. The patches showed good skin irritation potential, as evidenced by the absence of erythema or edema on the skin. The physicochemical characteristics of the patches, such as weight variation, drug content, and moisture content, were within the acceptable limits. The study successfully formulated, optimized, and evaluated transdermal patches of Eclipta alba leaf extract. Transdermal patch (F5) didn't cause any noticeable signs of irritation or edema on rat skin. Transdermal patch (F5) shown a good anti-inflammatory activity comparative to the marketed formulation in carrageenan-induced paw edema model.

KEY WORDS: Eclipta Alba, anti-inflammatory, transdermal patch, factorial design, HPMC K4, polyethylene glycol 400.

INTRODUCTION

Topical application of medicines to healthy, undamaged skin for local treatment of tissues under the surface or for systemic therapy is commonly referred to as transdermal drug administration [1]. Transdermal drug delivery also has the potential to reduce systemic side effects compared to other routes of administration. However, transdermal drug delivery has its limitations, including the limited permeability of the skin barrier and the need for a drug molecule to have the appropriate physicochemicalproperties to facilitate transdermal absorption. Additionally, transdermal drug deliverymay not be suitable for drugs with a narrow therapeutic window, as the rate of absorption can vary depending on factors such as skin hydration, temperature, and individual variations in skin thickness and integrity [2]. Transdermal drug delivery offers several advantages over other routes of administration, but careful consideration of drug properties, formulation design, and patient factors is necessaryto ensure successful transdermal delivery and optimal therapeutic outcomes.

The use of Eclipta alba leaf extract in transdermal patches offers a promising approach to deliver these active compounds for the treatment of various skin disorders,such as psoriasis, atopic dermatitis, and acne, as well as for systemic therapies such as cancer treatment [3]. In addition to these activities, wedelolactone an active constituent of Eclipta alba has been reported to have anti-cancer properties, including inhibition of tumor growth, induction of apoptosis (programmed cell death), and inhibition of angiogenesis (the formation of new blood vessels to supply tumors) [4]. The furanocoumarins in Eclipta alba have also been shown to have anti-tumor effects in preclinical studies [5]. The sustained release of the active compounds from the transdermal patch of Eclipta alba leaves extract may improve therapeutic efficacy and reduce potential side effects associated with other routes of administration. However, further studies are necessary to determine the safety and efficacy of Eclipta alba transdermal patches in clinical settings [6].

The present investigation aimed to design, develop and evaluate transdermal patches of Eclipta alba leaf extract using hydrophilic polymers. The specific objectives wereas follows: a) To prepare and characterize the Eclipta alba leaf extract using maceration with ethanol as a solvent. b) To formulate transdermal patches using hydrophilic polymers, namely HPMC K4, HPMC K15, and polyethylene glycol 400.

c) To optimize the transdermal patch formulation using a 3^2 full factorial design to determine the effect of the independent variables, including the polymer ratio, drug loading, and plasticizer concentration, on the dependent variables, including patch thickness, drug content, and in vitro drug release. d) To study the in vitro diffusion behavior of the prepared transdermal patch formulations in the presence and absence of a penetration enhancer.

These objectives aimed to evaluate the feasibility and potential of Eclipta alba leaf extract transdermal patches as a novel drug delivery system for anti-inflammatory activity. The findings of the study may provide insights into the optimal formulation and performance of the transdermal patches for future clinical trials and applications.

MATERIALS AND METHODS

Materials

The Eclipta alba leaves were purchased from Shobhasavi Ayurvedics and agros,Bhopal, India. Department of Botany, Shri Krishna University, Chhatarpur, Madhya Pradesh, India, identified and Authenticated the plant. HPMC K4 and K15 were purchased from SD Fine Ltd., Indore, India. From Sigma Chemicals Ltd., Mumbai, India, we obtained Oleic acid (OA), polyethylene glycol (PEG) 400 LR, and Di-n- butyl phthalate (DBP). Additional materials employed in the investigation were of analytical quality (chloroform, methanol, dichloromethane, glycerol, potassium dihydrogen phosphate, etc.). Milli-Q water was used for during all investigations.

Preparation of Eclipta Alba leaf extract

The preparation of Eclipta alba leaf extract was carried out using the maceration method with ethanol as a solvent. The leaves of Eclipta alba were collected, washed, and dried in the shade. The dried leaves were then ground into a fine powder using a mechanical grinder. A weighed amount of Eclipta alba leaf powder was macerated with ethanol (70% v/v) in a sealed container for 72 hours with occasional stirring. After 72 hours, the mixture was filtered using filter paper, and the filtrate was collected. The filtrate was then concentrated using a rotary evaporator under reduced pressure to obtain a thick, dark greenish-brown residue. The residue was then dried in a vacuum oven at 40°C until a constant weight was achieved. The dried extract was stored in an airtight container at room temperature until further use. The dried extract was characterized for its phytochemical constituents, including total phenolic and flavonoid contents, using established methods. The characterized extract was then used to formulate transdermal patches [7].

Preparation of transdermal patch

The transdermal patches were prepared by solvent casting method using the prepared Eclipta alba leaf extract and hydrophilic polymers, HPMC K4, HPMC K4, and polyethylene glycol 400. The Eclipta alba leaf extract was first dissolved in ethanol to obtain a uniform solution [8]. The hydrophilic polymers HPMC K4, and HPMC K4 were separately dissolved in distilled water with polyethylene glycol 400 to obtain a uniform solution. The solutions were then mixed in different ratios, and a plasticizer, such as propylene glycol or glycerol, was added to the solution to improve theflexibility and elasticity of the patches (Table 1). The drug-polymer-plasticizer solution was poured onto a flat glass surface and spread uniformly using a knife. The solution was then allowed to dry in a hot air oven at 40°C for 24 hours. The dried filmwas then cut into small circular patches of appropriate size using a punch.

The prepared transdermal patches were evaluated for various physicochemical properties, including thickness, weight, drug content, folding endurance, and tensile strength. The patches were also evaluated for their in vitro drug release behavior using a Franz diffusion cell apparatus. The optimized transdermal patch formulation was

selected based on the desired physicochemical properties and in vitro drug release behavior [9].

Table 1. Composition of transdermal patches

Ingredients	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Extract	10mg	10mg	10mg	10mg	10mg	10mg
HPMC K4	2%	3%	4%	-	-	-
HPMC K15	-	-	-	2%	3%	4%
Oleic acid	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL
PEG 400	30 % w/v	30 % w/v	30 % w/v	30 % w/v	30 % w/v	30 % w/v
PVA (backing membrane)	2%	2%	2%	2%	2%	2%
Di-butyl phthalate	30 % w/v	30 % w/v	30 % w/v	30 % w/v	30 % w/v	30 % w/v
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Physicochemical characterization of transdermal patch

Thickness

The thickness of the transdermal patch is an important physicochemical parameter that influences drug release and skin permeation. The thickness of patches was measured at three different places using a micrometer (India Tools & Instruments Co.,Mumbai), and mean values were calculated. To measure the thickness of the transdermal patch, the patch is placed on a flat surface, and the thickness gauge is applied perpendicular to the surface of the patch. The thickness of the patch ismeasured at different locations to obtain an average value [10].

Weight variation

Weight variation is a critical parameter in the quality control of transdermal patches. It ensures that each patch contains a consistent amount of drug and excipients, which is important for ensuring the efficacy and safety of the product. To measure the weight variation of the transdermal patches, each patch was weighed individually using a calibrated balance [11]. The weight of each patch is recorded, and the average weight is calculated. The weight of each patch should be within a specified range, andthe weight variation between patches should not exceed a certain limit.

Drug content

The drug content of transdermal patches is a critical parameter that ensures the consistency and potency of the product. It refers to the amount of active ingredient present in each patch, which should be within a specified range [12]. To determine the drug content transdermal patches of a specified area (1 cm^2) were dissolved in 5 mL of Phosphate buffer pH 7.4, and the volume was made up to 10 mL with the same buffer. A blank was prepared using a drug-free patch treated similarly. The solutions

were filtered through a 0.45 µm membrane, diluted suitably, and absorbance was read at 382nm in a double-beam UV-Visible spectrophotometer (UV-1800 Shimadzu, Japan).

Folding endurance

Folding endurance is a measure of the flexibility and strength of transdermal patches. It refers to the number of times a patch can be folded back and forth without breaking or cracking. To determine the folding endurance of transdermal patches, a sample of patches was selected, and each patch is cut into a rectangular shape of a standard size. One end of the patch is clamped, and the other end is folded back and forth repeatedly until it breaks or cracks. The number of folds required to cause failure is recorded as the folding endurance value [13].

***In-vitro* skin permeation studies**

In-vitro skin permeation studies are conducted to evaluate the ability of transdermal patches to deliver the active ingredient through the skin into the bloodstream. *In-vitro* skin permeation studies were performed using a Diffusion Cell Apparatus with a receptor compartment. The donor compartment was placed on the surface of the rat skin, and the receptor compartment was filled with phosphate buffer pH 7.4 (PBS). The solution in the receptor compartment was constantly stirred using magnetic beadsat 50 rpm; the temperature was maintained at 37±0.5°C. Samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically [14].The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimeter of patches were plotted against time [15].

Full factorial design

Randomized full factorial design is a statistical experimental design method that is used to investigate the effect of two or more factors on a response variable. In this design, all possible combinations of the selected factors and their levels are tested in a randomized manner [16]. Randomized full factorial design is used to determine the main and interaction effects of the selected factors on the response variable. The amounts of isopropyl myristate (X1) and oleic acid (X2) were chosen as the independent variables in a 3^2 randomized full factorial design. The drug release after 10 hours was chosen as tdependent variable.

***In vivo* studies of optimized transdermal patches**

Pharmacological examination of optimized transdermal formulations was done to evaluate the pharmacological potential of the prepared formulation. Acute skin toxicity studies and anti-inflammatory activity was performed. In vivo studies were conducted at the Adina Institute of Pharmaceutical Sciences, Sagar as per CPCSEA guidelines (Approval number: 1546/PO/E/S/11/CPCSEA).

Acute dermal toxicity study:

Young albino rats were utilized as test subjects and were acclimated to laboratory settings in accordance with CPCSEA requirements. Prior to testing, animals were randomized to treatment groups by random selection. The hair on the dorsal trunk surface of animals was shaved off one day before to the test. Care has been made to

avoid skin abrasion. As a test material, various transdermal patch formulations were put to the skin [17]. The patch was put to the skin for four hours before being removed. No clinical indicators of dermal toxicity were identified.

Anti-Inflammatory Activity by Carrageenan Rat Paw Edema (Winter et al.,1962).

Albino rats (200-250 g) were divided in three groups. Each group contain six animals Group I received a suspension of 0.5% of CMC (control), group II applied a transdermal patch of optimized formulation, in the abdominal region after the hair removal. Group-III standard group applied NU patch (Diclofenac Diethylamine BP 200 mg) (Nilufer Ercan, et al 2013). The animals were applied patches and subsequently 1 hour after treatment. 0.1 ml suspension was injected 1% carrageenan into physiological saline in the subplantar of the left hind leg to induce edema [18]. The volume of paw was measured at 0, 1, 2, 3 and 4 hours after carrageenan injection using a digital leg edema meter.

$$\% \text{ inhibition} = 100\ (1\text{-}Vt/Vc),$$

Where 'Vc' is control edema volume and 'Vt' edema volume of groups

RESULTS AND DISCUSSION

Phytochemical analysis of Eclipta alba leaf extract

Phytochemical analysis of Eclipta alba leaf extract can help to identify the presence of various bioactive compounds that are responsible for the plant's therapeutic properties. The extractive qualities of ethanolic extract were high, and it was soluble in the solvents necessary for its biological assessment. Eclipta alba plant extracts were extracted using maceration in accordance with the British Pharmaceutical Codex. Alkaloids, saponins, tannins, phenolic chemicals, flavonoids, and sterols were discovered by phytochemical analysis (Table 2). Overall, the phytochemical analysis of Eclipta alba leaf extract reveals the presence of various bioactive compounds that can contribute to its therapeutic properties. These compounds have been shown to have antioxidant, anti-inflammatory, and hepatoprotective activities, among others.

Table 2. Phytochemical characterization of Eclipta alba leaf extract

Chemical Constituent	Extract
Alkaloid	Present
Saponin	Present
Tannins	Present
Phenolic compounds	Present
Flavonoids	Present
Sterol	Present
Glycosides	Present
Amino acids	Absent
Reducing sugar	Absent
Terpenoids	Absent

Physicochemical characterization of transdermal patch

The physical properties of a transdermal patch include its thickness, weight variation, drug content and folding endurance. These properties are important as they can affect the rate and extent of drug delivery. The range of thickness was between 0.112±0.01 and 0.154±0.01, suggesting uniformity. The weights ranged between 7.10±0.75mg to 7.96±0.75mg, indicating that patch weights were comparable between batches. All formulations exhibited batch-to-batch consistency in drug concentration ranging from 9.4±0.62 to 10.4±0.24 μg/cm^2. The findings of this investigation show that the method used to create patches might yield patches with consistent medication content and little patch variability. The findings of the folding endurance tests suggested that the patches would not break and would keep their integrity when applied to normal skin folding (Table 3).

Table 3. Evaluation of transdermal patch formulations of Eclipta alba leaf extract

Formulation code	Thickness uniformity (mm)	Weight variation test (mg)	Drug content (μg/cm^2)	Folding endurance
F1	0.118±0.011	7.13±0.73	9.8±0.42	182±6
F2	0.112±0.01	7.10±0.75	9.4±0.62	208±4
F3	0.119±0.005	7.14±0.45	9.6±0.44	86±10
F4	0.142±0.015	7.53±0.95	10.2±0.43	134±8
F5	0.124±0.01	7.42±0.95	9.8±0.52	194±4
F6	0.154±0.01	7.96±0.70	10.4±0.24	98±2

*** mean ± SD (n = 3).**

***In-vitro* skin permeation**

The *in-vitro* release profile is an important tool that predicts a drug's behavior in-vivo. The results of *in-vitro* skin permeation studies of extract from transdermal patches are shown in Figure 1. The present study used hydrophilic polymers (HPMC K4 and HPMC K15) to prepare patches. Formulation F5 exhibited the greatest, 92.02%, drug release in 10h, while formulation F1 exhibited the lowest, 95.34%, drug release in 6 h.The cumulative amount of drug released from formulations containing hydrophilic polymer HPMC K4 released the drug faster than HPMC K15. The cumulative amountof drug released from formulations F1, F2, and F4 was much higher than other formulations. The transdermal drug delivery system F6 (4% HPMC K 15) showed drug release (88.92%) and lasted only 8h. However, the transdermal drug delivery system F5 (3% HPMC K15) showed the highest prolonged drug release successfully for 10h (92.02%). F5 achieved a high cumulative drug permeation at the end of 10 h. Based on physicochemical and *in-vitro* release experiments, F5 was chosen for furtherstudies.

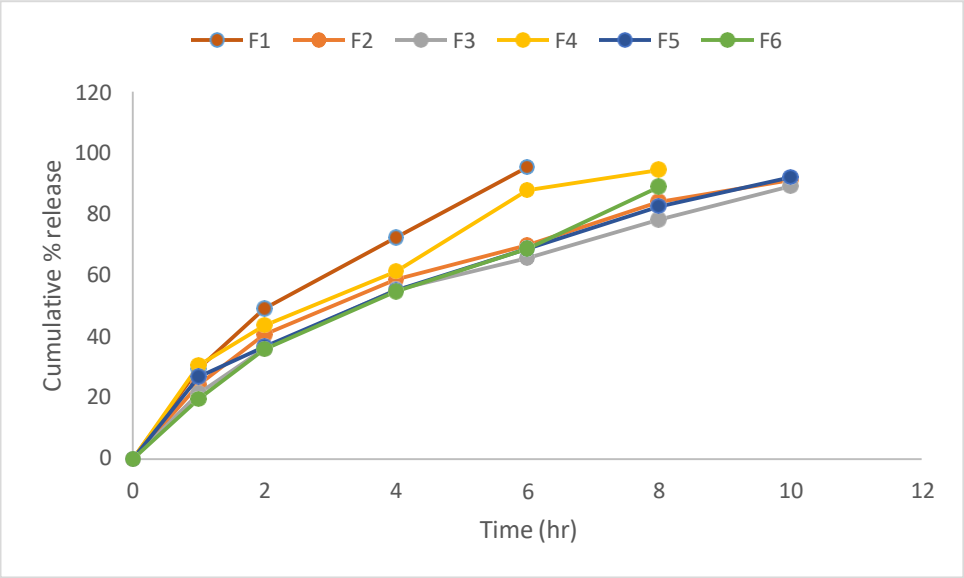

Figure 1. Release profiles of extract from patches containing different concentrations of HPMC K4 and HPMC K15

Full factorial design

Transdermal patch (F5) was used to optimize the concentration of plasticizer oleic acid and isopropyl myristate. The cumulative percentage of drug that penetratedthrough the epidermis of rats wearing patches with varying dosages of penetration enhancer was investigated. Because the coefficient b1 has a positive sign, a rise in oleic acid content results in an increase in Q10h. The Q10h value increased when the content of oleic acid and isopropyl myristate concentration rose from 5% to 10%. In this case, the coefficient of interaction terms was negative. Q10h was not substantially impacted by the combination of two penetration enhancers, as shown by the interaction term. This suggests that modifying two variables simultaneously had no effect on Q10h. The largest quantity of extract (Q10h) that penetrated over the 10- hour research period was 93.14% from formulation E8. The flow was estimated by dividing the total amount of medication that penetrated per cm^2 of skin over time by the area of the skin. The associated flow values varied between 208.50 and 292.03 gcm^{-2} h^{-1}. From formulation E8, the equivalent flow of extract was 296.04 gcm^{-2} h^{-1}. Several quantities of penetration enhancers put into the patch exhibited a pronounced impact on extract permeation. The cumulative percentage of extract that penetrated over a period of 10 hours rose, ranging from 68.45% to 93.14% for patches. Formulation E8 demonstrates the greatest flux across all formulations. This findings suggested that the formulation comprising 10% oleic acid and 10% isopropyl myristate enhanced extract penetration through the skin of rats (Table 4 and Table 5).

Table 4. 3^2 full factorial design layouts for transdermal patches

Batch No.	X1	X2	Q10h release (%)	Flux (J) ($\mu g \cdot cm^{-2} \cdot h^{-1}$)
E 1	-1	-1	68.45	219.50
E 2	1	1	88.01	262.12
E 3	0	1	88.78	268.74
E 4	1	-1	69.48	216.20
E 5	1	0	83.12	254.60
E 6	0	0	82.65	254.27
E 7	0	-1	69.18	216.50
E 8	-1	0	93.14	296.04
E 9	-1	1	92.26	280.63

Table 5: Translation of coded levels in actual units

Variables level	Low (-1)	Medium (0)	High (+1)
Amount of isopropyl myristate (% W/W of drug) X1	0	5	10
Amount of oleic acid (% W/W of drug) X2	0	10	15

Kinetic modeling of drug release

The cumulative amount of drug penetrated per square centimeter of patches (E1 to E9) via rat skin was fitted to zero, first, and Higuchi kinetic models when plotted against time. In various formulations, the release profile of H followed a mixed zero-order and first-order kinetics. Higuchi's equation was utilized to examine the release profile of patches E1 through E9. The penetration of the drug from the patches was regulated by a diffusion mechanism, as demonstrated by the release profile of the optimized formulation E8 (r^2 = 0.9964 for Higuchi).

Skin irritation studies

Skin irritation studies are conducted to evaluate the potential of a substance or product to cause irritation or damage to the skin. These studies are typically conducted using in vitro or in vivo models and can be performed for various reasons, such as regulatory compliance, product development, and safety assessment. In vivo skin irritation studies involve the application of the test substance to the skin of animals to evaluate its potential to cause skin irritation. These studies can provide more detailed information on the extent and severity of skin irritation, as well as any systemic

effects of the substance.The skin irritation study reveals that the drug loaded and blank patches didn't cause any noticeable signs of irritation or edema on albino rat's skin, indicating the skin compatibility of drug as well as polymer matrix.

Anti inflammatory activity

The carrageenan-induced paw edema method is a widely used method for evaluating the anti-inflammatory effect of various substances, including drugs and natural compounds. The method involves inducing inflammation in the paw of an animal, typically a rat or a mouse, using an injection of carrageenan, which is a natural polysaccharide derived from red seaweed. The degree of inflammation is measured by the increase in paw volume or paw thickness. The paw volume in the control group prominently increased after intraplantar injection of carrageenan. F5 formulations of transdermal patch showed significant decrease in paw edema volume to 0.25±0.023 in 4th h, which was found to be highly significant when compared to control 0.68±0.054 and standard Nu Patch 200 mg i.e 0.20±0.016. In our experiment, Q3 caused a potent inhibition of the inflammation at the fourth hour.

Table 6. Anti-Inflammatory Activity of Transdermal Patch

Group	**No. of animals**	**Treated**	**Paw edema volume (ml)**			
			1h	2h	3h	4h
Group I	6	Control	0.68±0.065	0.68±0.062	0.68±0.058	0.68±0.054
Group II	6	F5	0.68±0.064	0.63±0.058	0.46±0.072	0.25±0.023
Group III	6	Nu Patch 200 mg	0.68±0.064	0.60±0.055	0.40±0.034	0.20±0.016

Values are expressed as mean ±SEM, n = 6

CONCLUSION

The results suggests that the objectives of formulating a transdermal patch of Eclipta Alba leaf extract have been achieved successfully. The use of different polymers in the formulation has resulted in good physicochemical properties such as thickness, weight variation, drug content, folding endurance, and tensile strength. The study alsoconfirms that the drug release from the patch formulation followed mixed zero-order and first-order kinetics of diffusion. Furthermore, the study evaluated the effect of polymer types and concentrations on drug release from the patch formulation. The in- vitro release data indicated that the polymer types and concentrations affected the drug release from the patch formulation. Transdermal patch (F5) didn't cause any noticeable signs of irritation or edema on rat skin. Transdermal patch (F5) shown a good anti-inflammatory activity comparative to the marketed formulation incarrageenan-induced paw edema model. Overall, the results suggest that the formulated transdermal patch of Eclipta Alba leaf extractcan be successfully used topically to reduce inflammation.

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