RESEARCH ARTICLE

Formulation of Transdermal Drug Delivery System of Piper Nigrum

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Received: 1st May, 2021; Revised: 19th May, 2021; Accepted: 21st July, 2021; Available Online: 25th September, 2021

ABSTRACT

Objective: In this study an attempt was made to formulate transdermal patches using *Piper nigrum* to treat pain associated with rheumatoid arthritis. *P. nigrum* contains piperine, an alkaloid which is known for its anti-inflammatory properties from long time and RA is a chronic, inflammatory autoimmune disease characterized by the presence of inflammatory mediators such as TNF α (Tumor necrosis factor-alpha), IL-1, (Interleukin) IL-6, which are known to aggravate the inflammation and bone destruction. Piperine is found to have Disease-modifying anti-rheumatic drugs (DMARDs) activity similar to NSAIDS. The activity has been attributed to inhibition of TNF α secretion and prevention of proliferation of synovial fibroblasts. The main objective of the present work was to find an alternative to the existing NSAIDs and minimize the side effects caused by them.

Methods: *P. nigrum* was extracted with dichloromethane, and Piperine alkaloid was separated and purified. The two methods of transdermal patches of *P. nigrum* were developed using two polymers of hydroxypropyl methylcellulose (HPMC) and Ethylcellulose (EC) and evaluated for various physicochemical factors like weight variation, moisture uptake, thickness, moisture content, and folding endurance.

Results: Transdermal patches prepared using HPMC by solvent evaporation method showed better results in all parameters comparatively with EC. The folding endurance of the formulation F2 (prepared with EC) was less than F1 (prepared with HPMC), as F2 was brittle. The drug content of both formulations was above 90%w/w. Thickness, weight variation, percentage moisture absorption, and loss were within the specifications for both formulations.

Conclusion: Piperine can be formulated as transdermal patches with HPMC as polymer by solvent evaporation method and can be selected for further studies like pharmacokinetic and pharmacodynamic in the future.

Keywords: Auto-immune disease, Interleukin, Piperine, Rheumatoid arthritis, Transdermal patch, Tumor necrosis factor.

International Journal of Drug Delivery Technology (2021); DOI: 10.25258/ijddt.11.3.23

How to cite this article: Rajalakshmi G, Sundhararajan R, Jeevitha A. Formulation of Transdermal Drug Delivery System of Piper Nigrum. International Journal of Drug Delivery Technology. 2021;11(2):793-796.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Recent innovations in the drug delivery system have enabled the successful implementations of many of these novel pharmaceuticals and created space for the development of new medical treatments with existing drugs. A shift from conventional to novel drug delivery is noticed as conventional drug delivery suffers from various drawbacks, like pulsating blood levels, frequent dosing, patient noncompliance, more side effects, whereas a novel drug delivery system is a tailor-made system. These innovations offer substantial clinical advantages, including reduced dosing frequency, improved patient compliance, minimized concentration fluctuation, and maintenance of dose in desired levels. The invention of the transdermal drug delivery system has been one of the most important innovations, providing several advantages over the oral route. Drugs that cannot be tolerated by the oral route drugs undergoing the first metabolism can be given by this method.[1]

A transdermal drug delivery device, which may be of an active or a passive design, is a device that provides an alternative way for administrating medication. Transdermal patches offer various advantages over other dosage forms. Unlike conventional dosage forms like ointments, creams, Transdermal patches are user-friendly. It improves bioavailability, reduces dosing interval, is convenient, painless, and non-invasive. The system helps increase the therapeutic value of many drugs by helping patients stick to the therapy. This device allowed for pharmaceuticals to be delivered across the skin barrier. Diffusion is the driving phenomenon in pushing the drugs from the higher concentration, i.e., the patch, to reach the skin. These devices allow pharmaceuticals to be delivered across the skin barrier.[2] The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects, thereby maintain consistent plasma levels of drug [3-4]

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Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease characterized by the presence of inflammatory mediators such as TNF α, IL-1, IL-6, which aggravate the inflammation and bone destruction.[5-7] Disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) form the mainstay of RA treatment.[8] Piperine is a naturally occurring alkaloid obtained from *P. nigrum*, Linn belonging to the family Piperaceae. It has many medicinal properties, a well-known spice in cooking. It is used as an anti-inflammatory, anti-malarial, anticonvulsant, bioavailability enhancer, stomach disorders, anti Leukemia, fever prevention, etc. The anticonvulsant effects of piperine are possibly mediated via GABAergic pathways. Many phytoconstituent of piperine is found to have DMARD activity. The activity has been attributed to inhibition of TNF α secretion and prevention of proliferation of synovial fibroblasts.[9-10] Therefore, the current work aims at transdermal delivery of piperine for the treatment of rheumatoid arthritis, thereby reducing the side effects of conventional NSAID dosage forms.

MATERIALS AND METHODS

Black pepper powder was purchased from India Mart, HPMC from Loba chemie, Ethyl cellulose, and PVP k30 from Sisco chemicals. All other chemicals used were of analytical grade.

Pharmacognostic Evaluation

The powder was tested for various physical and chemical tests. Physical tests consist of the evaluation of organoleptic characters like color, odor, and taste. The chemical test involves a test for alkaloids. Powder microscopy was performed for authentication.[11]

Isolation of Piperine from Back Pepper Powder[12-14]

A 50 g of ground pepper powder was refluxed with 100 mL of dichloromethane for 1-hour in a round bottom flask. The condenser was attached, and water was allowed to run through to condense dichloromethane vapors. Later on, the flask was cooled and filtered through Buchner funnel. The extract was treated with acetone and hexane.

Purification

The filtrate was transferred to 50 mL round bottom flask, and using a sand bath, excess dichloromethane was removed till a dark brown oil remained. The oil was cooled in an ice bath, and 6 mL cold ether was added. After stirring for 5 minutes, the solvent was removed again by heating on the sand bath. The procedure was repeated till piperine was precipitated out and recrystallized using acetone. Yellow rod-shaped crystals were recrystallized after 24 hours.

Calibration Cure[11] 100 mg piperine was dissolved in methanol, and volume was made up to 100 mL with methanol. Then 1, 2, 3, 4, 5 mL taken and diluted to 100 mL to get 10 to 50 µg/mL concentration. The absorbance of the solution was measured by UV spectrophotometer 342.5 nm against blank.

Figure 1: Black pepper

Methods for Preparation of Patches[15]

- *Method 1:* Ethylcellulose, PVP, was used as the skeletal material of preparation—propylene glycol as a penetration enhancer. PVP (1 g) and ethyl cellulose (1 g) were weighed in requisite ratios, mixed in 10 mL distilled water, and stirred mixture over a hot water bath until dissolved. After the mixture was cooled down to 25ºC, drug 500 mg, propylene glycol (0.5 mL), glycerol (0.5 mL) were added. The mixture was then poured into glass molds and dried at room temperature for 24 hours. The patches were removed by peeling and cut into the required size.
- *Method 2:* The polymer (HPMC) and drug were weighed. PEG, which acts as a plasticizer and permeation enhancer, was used. Ethanol was used as a solvent. PEG 2.68 mL (30% weight of polymer) was dissolved in ethanol with stirring. The calculated amount of HPMC (500 mg) was dispersed in solvent ethanol. Piperine was dissolved in ethanol; this solution was then added to the polymer base and stirred continuously to get a uniform solution. This solution was poured into Petri plate coated with liquid paraffin and then dried a room temperature. After drying, patches were removed and cut into required sizes, and used for further studies. The composition is shown in Table 1.

EVALAUATION[16-17]

- *Organoleptic Characteristics:* The prepared patch were physically examined for its color, clearness, flatness, and smoothness.
- *Weight variation:* Ten patches from each batch were randomly selected and individually weighed on a digital balance. The average weight was calculated.

Table 1: Composition of transdermal patches of *P. nigrum*

S. No.	*Ingredients*	*F1*	*F2*
1	Pepper (mg)	500	500
2	HPMC E3 (mg)	500	-
3	Ethyl cellulose (mg)	-	1000
4	PEG K 30 (mg)	500	-
5	PVP (mg)	-	1000
6	Glycerol (mL)	0.5	0.5
7	Propylene glycol (mL)	0.5	0.5
8	Water (mL)	10	-
9	Ethanol (mL)	-	10

- *Thickness:* The thickness of the films was measured using a screw gauge and mean values were calculated at three different places.
- *Folding Endurance:* Developed patch was taken and subjected to repetitive folding at the same point until it gets severe. Instances of time when patch folded without breaking were noted down.
- *Moisture Content:* Developed patch after weighing was placed in desiccators consisting of compounded calcium chloride at room temperature for 24 hours. After taking out from desiccators, patches were weighed. The below mentioned formula was used to compute % moisture content:

$$\text{Percentage of moisture content} = \frac{[\text{Initial weight} \quad \text{Final weight}]}{\text{final weight}}$$

- *Uniformity of Drug Content in the Patch:* The uniformity of drug distribution was evaluated by determining the drug content of the film by a spectrophotometric method. A known weight of film (2×2 cm) was dissolved and diluted subsequently with methanol, and the concentration of the drug was spectrophotometrically measured at 342.5 nm against the blank ethyl alcohol solution containing the same amount of polymer and plasticizer without drug.
- P*ercentage of Moisture Content Uptake:* A weighed film kept in a desiccator at room temperature for 24 hours was taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight concerning initial weight.

$$\%\text{Moisture content} = \frac{[\text{Initial weight - Final weight}]}{\text{Initial weight}}$$

RESULTS

The pepper powder was tested for authentication. Various pharmacognostic evaluations, including morphological observation, chemical tests, and powder characteristics tests, were found. The results are shown in Tables 2 and 3.

Table 2: Morphological characters of *P. nigrum* powder

Character	*Observation*
Colour	Blackish grey
Odour	Aromatic
Taste	Pungent

Table 3: Chemical tests for isolated piperine

Reagent	*Inference*	*Presence*
Dragendroff's reagent	Orange red color	Alkaloids
Wagners reagent	Reddish brown	Alkaloids
Mayers test	Cream color ppt	Alkaloids
Hager's test	Yellow color ppt	Alkaloids

Powder Microscopy

Powder stained with safranin shows isodiametric or slightly elongated stone cells, interspersed with thin-walled polygonal hypodermal cells, beaker-shaped stone cells from endocarp and abundant polyhedral.

Calibration Curve

The piperine calibration in transdermal patches was done by UV spectrophotometer at 342.5 nm with methanol as blank. The results are shown in Figure 2.

Physical Evaluation

These studies were conducted manually by visual inspection. All the films were good in physical appearance.

Evaluation of the Transdermal Patches:

The prepared formulation was evaluated for different Physico-chemical characteristics such as Thickness, Folding endurance, Percent moisture content, and Weight uniformity.

Folding Endurance

The folding endurance was found to be in the range of 10-20. The values for all four formulations are given in the table no: 4. This data revealed that the films had good mechanical strength along with flexibility.

Surface pH

A combined pH electrode was used for this purpose. The patches were slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the film.

Percentage Moisture Absorption and Moisture Loss

The amount of moisture in the film could be crucial as it affects the mechanical strength, adhesive properties, and friability of film. The results of percentage moisture absorption and loss are shown in Table 4.

Drug Content

This test performed to found uniform drug distribution. The drug content of both the formulations was 90% to 92%.

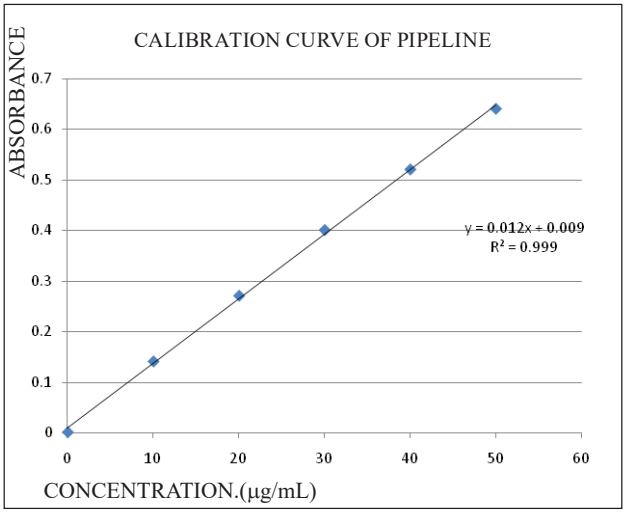

Figure 2: Calibration curve of piperine

Table 4: Physico-chemical characteristics of *P. nigrum* Transdermal patches

Parameters	*F1*	*F2*
Weight uniformity (g)	0.015	0.012
Thickness (mm)	0.32	0.34
Moisture absorption (%)	2.1	2.4
Moisture loss (%)	1	1.3
Folding Endurance	50	38
pH	5	5.8
Drug Content (%)	90	92

DISCUSSIONS

The physical appearance of the film revealed that all the films were without imperfections, slight brownish due to the drug, F_2 was slightly gritty than F_1. The thickness of various patches was found to be uniform. The folding endurance reveals that the film has good mechanical strength along with flexibility. The folding endurance was consistent, and the weight uniformity was good and within the range. The results show that as the concentration of polymer increases, the folding endurance also increases. Folding endurance test results indicated that the patches would remain intact and integrity with general skin folding when applied. Folding endurance of F_1 showed 20 and F_2 10. It shows that F_2 with ethylcellulose was brittle and gritty in appearance. The amount of moisture in the film could be crucial as it affects the film's mechanical strength, adhesive properties, and friability. Studies on percentage moisture absorption and moisture loss revealed that films are within specifications. All the formulations have good drug content, more than 90%. The surface pH of all the formulations was near to the skin pH.

Among the two formulations, the film-forming ability was good for HPMC polymer. The plasticity and appearance also hold good for formulation F1 than F2. F2 formulations were slightly brittle and gritty in appearance. So the formulation F1 containing HPMC can be selected for further studies like an in-vivo and in-vitro release in the future. Comparing the formulations, a formulation containing HPMC has an excellent film-forming capacity than ethyl cellulose. The Polymer HPMC has good clarity; the film had good mechanical strength, flexibility.

CONCLUSION

Conventional dosage forms have their advantages and disadvantages. Transdermal drug delivery overcomes this by easy handling, dose accuracy, sustained action, improved compliance, etc. They are patient-friendly—the Transdermal patches using *P. nigrum* as an analgesic to treat RA. The components present in *P. nigrum* are used from the olden days as analgesics based on the literature review. This research highlights that piperine may be incorporated into the transdermal drug delivery system using HPMC as the polymer system for suitable and convenient use. Studies have shown promising results. Hence there is a scope for further pharmacodynamics and pharmacokinetic evaluation

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