International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 16s,2025
https://theaspd.com/index.php

Development And Evaluation Of Felbinac-Loaded Nanoparticle-Based Transdermal Patches For Sustained Anti-Inflammatory Therapy

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Abstract
The present study aimed to develop and evaluate felbinac-loaded transdermal patches using a nanoparticle-based drug delivery system for sustained anti-inflammatory action. Various formulations (F1–F6) were prepared using different polymers and plasticizers, with F4 identified as the optimized formulation. The patches were evaluated for physicochemical properties including thickness, folding endurance, moisture content, tensile strength, and drug content. Formulation F4 exhibited the highest tensile strength (0.889 kg/cm²), excellent folding endurance (289±4), and drug content (98.85±0.45%). In vitro drug release studies revealed a sustained release of 89.98% over 12 hours, following Higuchi kinetics (R^2 = 0.991) with non-Fickian diffusion behavior. Stability studies confirmed F4's physical and chemical stability under accelerated conditions. Skin irritation testing showed no signs of dermal toxicity. Pharmacodynamic evaluation using the carrageenan-induced paw edema model demonstrated significant anti-inflammatory activity of F4 compared to control. Overall, the results suggest that felbinac-loaded nanoparticle-based transdermal patches offer a promising and effective approach for sustained drug delivery and improved patient compliance.

Keywords: *Felbinac, Transdermal patch, Nanoparticles, Sustained release, Higuchi model, Skin irritation, Anti-inflammatory activity, Carrageenan-induced paw edema, Eudragit, Drug delivery system*

INTRODUCTION

Transdermal drug delivery systems (TDDS) have emerged as an attractive alternative to conventional drug administration routes due to their ability to provide controlled and sustained drug release, bypass hepatic first-pass metabolism, and enhance patient compliance (Prausnitz et al., 2008). Among various therapeutic classes, non-steroidal anti-inflammatory drugs (NSAIDs) such as felbinac are well-suited for transdermal application due to their potent anti-inflammatory effects and the need for localized drug delivery in conditions such as arthritis and muscle pain (Yano et al., 1994).Despite its efficacy, felbinac is limited by a relatively short half-life and frequent dosing requirements, which can lead to reduced patient adherence and inconsistent therapeutic outcomes (Kasting et al., 2001). To address these limitations, nanoparticle-based drug delivery systems have been explored to enhance skin permeation, improve drug solubility, and provide sustained drug release (Prow et al., 2011).Incorporation of felbinac-loaded nanoparticles into transdermal patches can improve the drug's pharmacokinetic profile and therapeutic efficacy. Among the various polymers employed, Eudragit RLPO and RSPO are widely used for controlled-release transdermal systems due to their film-forming capacity, permeability-controlling properties, and biocompatibility (Bharkatiya et al., 2010). The use of plasticizers such as PEG 600 further enhances the flexibility and mechanical properties of the patches (Raghvendra et al., 2013).The present study aims to develop and evaluate felbinac-loaded nanoparticle-based transdermal patches using Eudragit polymers and PEG 600. The formulations were characterized for their physicochemical parameters, drug content, in vitro release kinetics, stability, skin irritation potential, and in vivo anti-inflammatory efficacy using a carrageenan-induced paw edema model in rats.

MATERIAL AND METHODS

Material

Felbinac was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Eudragit RLPO and RSPO were purchased from Evonik Industries (Mumbai, India). Polyethylene glycol 600 (PEG 600) and glycerin were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Chloroform and methanol of analytical grade were supplied by Merck Ltd. (India). All other chemicals and reagents used were of analytical grade and used as received.

METHODS

Development of transdermal patches of nanoparticles loaded with felbinac

Transdermal patches composed of different polymers HPMC, ethyl cellulose, Eudragit RLPO and Eudragit RSPO (Sadhasivam et al., 2015). The polymers were dissolved in chloroform and methanol along with plasticizer. Then the solution was poured into a glass moulds containing Glycerin. The solvent was allowed to evaporate under room temperature for 24 hrs. The polymers and drug (30 mg per film) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After vortex then the solution was poured on glycerin placed in a glass Petri dish and dried at room temperature for 24 hrs.

Table 1: Preparation of matrix type transdermal patches of felbinac

F. Code	Drug (Nanoparticles eq. to) (mg)	HPMC (mg)	RLPO (mg)	RSPO (mg)	Ethyl cellulose (mg)	Total polymer weight (mg)	Plasticizer % w/w of total polymer PEG 600 ml	Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml
F1	360	800	100	-	100	1000	0.5	10
F2	360	700	150	-	150	1000	0.5	10
F3	360	600	200	-	200	1000	0.5	10
F4	360	800	-	100	100	1000	0.5	10
F5	360	700	-	150	150	1000	0.5	10
F6	360	600	-	200	200	1000	0.5	10

*360mg drug for 12 patches (Formulation for 12 patches)

Evaluation parameters

The prepared transdermal patches were evaluated for the following parameters:

Thickness

The thickness of patches was measured by Vernier calipers.The thickness of patches were measured at three different places and average of three readings was taken with standard deviation (Madhulatha and Ravikiran, 2013).

Folding endurance

This was determined by repeatedly folding one patch at the same place until it broken. The number of times the patch could be folded at the same place without breaking / cracking gave the value of folding endurance (Patel et al., 2009).

Tensile strength

Cut the patch at the centre having 2cm length and 2cm breadth (Patel et al., 2012). Patch was hanged on top and lower side of instrument, then start the switch and note the reading on screen. The thickness and breadth of strips were noted at three sites and average value was taken for calculation.

$$\text{Tensile stress (s)} = \frac{\text{Applied force}}{\text{Cross Sectional Area}}$$

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 centimetres

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual patches were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to initial weight (Suryani et al., 2019).

Percentage of moisture uptake

Firstly weighed the patches and then kept in a desiccators at room temperature for 24 hrs and then it's exposed to 84% RH (A saturated solution of potassium chloride) in a desiccators. The % of moisture uptake was calculated by difference between final and initial weight with respect to initial weight (Sowjanya et al., 2013).

Drug content analysis

The patches (n = 3) of specified area (6.16cm^2) were taken into a 10 ml volumetric flask and dissolved in methanol (10ml) with the help of shaker. After the vortex the solution was filtered and prepared subsequent dilutions and analyzed by UV spectrophotometer.

In vitro skin permeation study

The in vitro skin permeation study was done by using a Franz diffusion cell (receptor compartment capacity: 80 ml: surface area: 3.14 cm^2. The egg membrane was separated and used for in vitro study (Jhawat et al., 2013). The receiver compartment was filled with 50ml of phosphate buffer, pH 7.2. 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. The whole assembly was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of receptor compartment was maintained at 37± 0.5^{o}C. The samples were withdrawn at different time intervals up to 12 hrs and analyzed for drug content. Receptor phase was replaced with an equal volume of buffer solution at each time interval.

Release Kinetics Studies

Zero order kinetics- Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$Q_t = Q_o + k_o t$

Where, Q_t= amount of drug released in time 't', Q_o= initial amount of drug in the solution, k_t= zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

First order kinetics - The application of this model to drug dissolution studies was first proposed by Gibaldi and Perrier, (1982). The following relation can express this model:

$\text{Log } Q_t = \text{Log } Q_o + k_t t/2.303$

Where, Q_t= amount of drug released in time't', Q_o= initial amount of drug in the solution, k_t= first order release constant. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model – Higuchi, (1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$f_t = k_H t^{1/2}$

Where, k_H= Higuchi diffusion constant, f_t= fraction of drug dissolved in time 't'.
Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

Korsmeyer-Peppas model - Korsmeyer et al., (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t);

$$f_t = at^n$$

Where, a = constant incorporating structural and geometric characteristics of the drug dosage form, n = release exponent, $f_t = M_t/M_\infty$ = fraction release of drug.

Stability studies

The short term stability studies of the formulated transdermal patches were carried out on prepared patches at different temperature and humidity according to ICH guidelines.

Transdermal patches of nanoparticles loaded with felbinac for anti-inflammatory activity

Animals

Wistar rats (180±20 g) were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2 °C, 55–65%). Mice received standard rodent chow and water ad libitum.
Animas were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of mice was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

Acute toxicity study

An acute toxicity study of Felbinac nanoparticles was performed as per OECD-423 guidelines (https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd_gl423.pdf). According to OECD guideline no. 423, an acute toxicity study was conducted. Throughout the next 14 days, the rats were monitored for signs of toxicity. A number of clinical symptoms were noted, such as behavioral, vision, weight, skin, and fur changes. However, no adverse effects, behavioral changes, or pathological abnormalities were observed. The animals maintained normal body weight, food, and water intake, and necropsy findings were unremarkable.

Assessment of carrageenan-induced paw edema

A carrageenan-induced rat paw edema assay was used to measure the anti-inflammatory effect. The rats were randomly divided into 3 groups of 6 animals each. Group I served as a carrageenan control (0.1 ml of 1% (w/v) of carrageenan in saline in the sub plantar region of the right hind paw), Group II was Felbinac nanoparticle loaded transdermal patch (0.5%). Group III was Felbinac nanoparticle loaded transdermal patch (1.0%). Group IV was Felbinac nanoparticle loaded transdermal patch (1%). %). Group V was Felbinac nanoparticle loaded transdermal patch (1%). Oedema was induced by injecting 0.1 ml. of a 1% solution of carrageenan in saline into the sub-plantar region of the right hind paw of the rats. The volumes of oedema of the injected and the contralateral paws were measured after the induction of inflammation using a plethysomgraph (Nagakura et al., 2008).

Experimental Groups

It consisted of 3 groups (n=6) of six animals each.

Group I: Rats were administered carrageenan control (0.1 ml of 1% (w/v) of carrageenan in saline in the subplantar region of the right hind paw) without patch

Group II: Inflammation rats were treated with felbinac transdermal patch (4 cm^2)

Group III: Inflammation rats were treated with plain gel (1%)

Paw volume was initially measured using a plethysmometer before inducing inflammation by injecting 0.1 ml of 1% carrageenan into the right hind paw of rats, with the left paw receiving saline as a control (Nagakura et al., 2008). Rats were divided into groups, including a carrageenan control and others treated with felbinac nanoparticle-loaded transdermal patches. Edema progression was then assessed at various

time points using a plethysmometer and caliper, alongside observations of inflammation parameters like erythema, hyperalgesia, and leukocyte infiltration, with the percent inhibition of edema calculated to determine treatment efficacy.

$$\text{Percentage Inhibition} = \frac{Vc - Vt}{Vc} x100$$

Where, Vc- Edema volume of control group
Vt- Edema volume of test group

RESULTS AND DISCUSSION

The transdermal patches developed using various formulations (F1–F6) were evaluated for physicochemical properties, drug content, in vitro release, stability, and pharmacodynamic effects. Among the formulations, F4 consistently demonstrated superior performance, making it the optimized formulation.From Table 2, the thickness of patches ranged from 89 µm (F6) to 99 µm (F1), with all values within acceptable limits indicating uniform formulation. Folding endurance, a key parameter reflecting mechanical strength, was highest for F4 (289±4), suggesting excellent flexibility and durability.

Moisture content and uptake (Table 3) influence patch stability and integrity. F4 showed the lowest moisture content (5.16±0.25%) and uptake (2.45±0.36%), reducing microbial contamination risk and maintaining structural integrity over time.In Table 4, tensile strength—indicative of mechanical resistance—was maximum for F4 (0.889 kg/cm²), further confirming its superior mechanical properties.

Drug content (Table 5) ranged from 92.25% (F5) to 98.85% (F4), with F4 showing the highest and most uniform drug distribution, suggesting good formulation reproducibility.

The in vitro drug release profile (Table 6) revealed a sustained and controlled release for F4, with 89.98% of felbinac released over 12 hours. This sustained release supports a once or twice-daily application regime, improving patient compliance.Based on regression analysis (Table 8), drug release from F4 followed Higuchi kinetics (R^2 = 0.991), indicating diffusion-controlled release. The Korsmeyer-Peppas model (R^2 = 0.9746) further suggests anomalous (non-Fickian) transport, implying both diffusion and polymer relaxation mechanisms contribute to drug release.

The stability data (Table 9) show minimal degradation over 60 days under different temperature and humidity conditions. Drug content remained above 97%, confirming the chemical and physical stability of the patch.The skin irritation study (Table 10) showed no adverse skin reactions (all A scores), confirming that both the blank and drug-loaded patches are dermatologically safe for transdermal use.

The anti-inflammatory effect of felbinac-loaded patches was evaluated using the carrageenan-induced paw edema model in rats (Table 11, Figure 1). Group II (treated with F4) showed a significant reduction in paw edema, especially at *2 hr (1.15 ± 0.45, $p<0.05$) and 4 hr (0.85 ± 0.4) compared to the control group (Group I). This suggests effective transdermal absorption and therapeutic action of felbinac from the patch.

Table 2: Thicknesses and Folding Endurance of Different Formulations of transdermal patch

S. No.	Formulation Code	Thickness (µm)*	Folding Endurance*
1.	F1	99±5	245±8
2.	F2	95±3	265±6
3.	F3	93±7	253±7
4.	F4	97±4	289±4
5.	F5	93±6	265±5
6.	F6	89±2	247±3

Table 3: % Moisture Content and Moisture Uptake of Different formulations of transdermal patches

S. No.	Formulation Code	% Moisture Content	% Moisture Uptake
1.	F1	6.95±0.25	3.66±0.44
2.	F2	7.12±0.32	4.87±0.32
3.	F3	6.22±0.14	3.95±0.14
4.	F4	5.16±0.25	2.45±0.36

5.	F5	6.98±0.36	4.36±0.22
6.	F6	7.05±0.21	4.85±0.18

Table 4: Tensile Strength of Different formulation

S. No.	Formulation code	Tensile Strength (kg/cm^2)
1.	F1	0.662
2.	F2	0.715
3.	F3	0.667
4.	F4	0.889
5.	F5	0.744
6.	F6	0.658

Table 5: Percentage drug content of all the transdermal patch

S. No	Formulation Code	% Drug Content
1	F1	93.32±0.22
2	F2	96.65±0.35
3	F3	94.45±0.14
4	F4	98.85±0.45
5	F5	92.25±0.32
6	F6	95.44±0.77

Table 6: In vitro % Permeation Profile of Nanoparticles loaded with Felbinac in Formulation F4

S. No.	Time (hr)	% of Drug Release
1	0.5	12.25
2	1.0	26.65
3	2.0	33.15
4	4.0	46.65
5	6.0	59.98
6	8.0	68.85
7	10.0	76.65
8	12.0	89.98

Table 7: In-vitro drug release data for optimized formulation F4

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	12.25	1.088	87.75	1.943
1	1	0	26.65	1.426	73.35	1.865
2	1.414	0.301	33.15	1.520	66.85	1.825
4	2	0.602	46.65	1.669	53.35	1.727
6	2.449	0.778	59.98	1.778	40.02	1.602
8	2.828	0.903	68.85	1.838	31.15	1.493
10	3.162	1	76.65	1.885	23.35	1.368
12	3.464	1.079	89.98	1.954	10.02	1.001

Table 8: Regression analysis data of nanoparticles loaded with Felbinac loaded Transdermal patches

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F4	0.9705	0.9453	0.991	0.9746

Table 9: Results of stability study of optimized formulation F4

F. Code	Initial Drug Content	25±2^{0}C (60±5% RH)			40±2^{0}C (75±5% RH)		
		15 days	30 days	60 days	15 days	30 days	60 days
F4	98.85±	98.45±	98.32±	98.10±	98.12±	97.32±	97.45±

Table 10: Results of skin irritation study

	After 12 hrs	After 24 hrs	After 36 hrs	After 48 hrs
Blank Patch	A	A	A	A
F4	A	A	A	A

A – No reaction, B – Slight patchy erythema, C-Slight but Confluent or Moderate but patchy erythema, D-Moderate erythema, E-Severe erythema with or without edema.

Table 11: Effect of Transdermal patches of nanoparticles loaded with felbinac on paw oedema induced by carrageenan in rats

Group	0 hr (Mean ± SEM)	30 min (Mean ± SEM)	1 hr (Mean ± SEM)	2 hr (Mean ± SEM)	4 hr (Mean ± SEM)
Group-I	0.8 ± 0.3	2.6 ± 0.5	3.0 ± 0.6	3.1 ± 0.6	3.3 ± 0.6
Group-II	0.73 ± 0.38	2.3 ± 0.5	1.4 ± 0.48	1.15 ± 0.45*	0.85 ± 0.4
Group-III	0.75 ± 0.35	2.8 ± 0.55	1.8 ± 0.5	1.30 ± 0.45*	1.15 ± 0.42

Values are expressed as mean ± S.E.M. (n = 6). Values are statistically significant at *** $p<0.001$, ** $p<0.01$, and *$p<0.05$ (One-way ANOVA followed by Tukey's test).

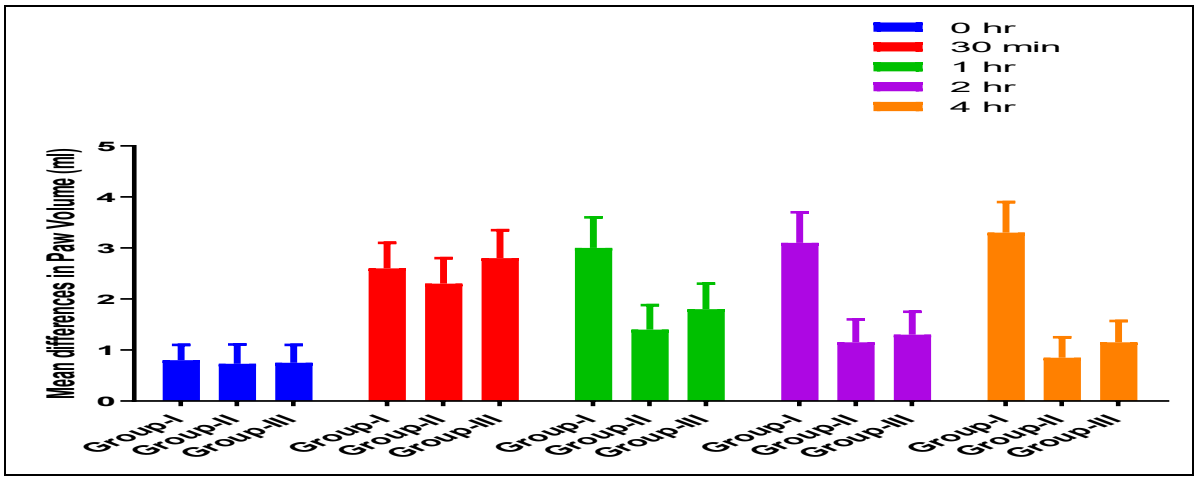

Figure 1: Effect of Transdermal patches of nanoparticles loaded with felbinac on paw oedema induced by carrageenan in rats

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