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Etoricoxib-Loaded Transdermal Patches with Thiolated Pyrimidin Chitosan for Enhanced Delivery

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ABSTRACT

This study focused on the development and evaluation of etoricoxib-loaded transdermal patches for sustained drug delivery to enhance bioavailability and patient compliance. The patches were formulated using polymeric matrices to achieve controlled drug release and improved skin permeability. Various physicochemical characterizations, including surface morphology, thickness, weight uniformity, folding endurance, tensile strength, and moisture content, were conducted to ensure uniformity and mechanical stability. In vitro drug release studies demonstrated a sustained release profile over 24 hours, preventing burst release while maintaining therapeutic drug levels. Ex vivo permeation studies using Wistar rat skin confirmed efficient drug penetration, enhanced by penetration enhancers. A six-month accelerated stability study (40°C ± 2°C, 75% ± 5% RH) showed no significant changes in drug content or release profile. The optimized formulation (F6) exhibited superior mechanical properties, enhanced skin permeation, and controlled drug release, making it a promising alternative to oral etoricoxib for long-term pain management and anti-inflammatory therapy.

INTRODUCTION

Transdermal drug delivery systems (TDDS) have emerged as an effective alternative to conventional oral and parenteral drug administration, offering advantages such as controlled drug release, avoidance of first-pass metabolism, and improved patient compliance [1]. Among the various nonsteroidal anti-inflammatory drugs (NSAIDs), etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is widely used for the management of osteoarthritis, rheumatoid arthritis, and acute pain conditions [2]. However, its oral administration is associated with gastrointestinal side effects and variable bioavailability due to hepatic metabolism [3]. Therefore, transdermal delivery of etoricoxib can be a promising approach to enhance therapeutic efficacy and minimize systemic side effects. Despite the advantages of TDDS, poor skin permeability remains a major challenge due to the stratum corneum barrier [4]. Various strategies, such as chemical penetration enhancers, lipid-based carriers, and polymeric modifications, have been explored to enhance drug permeation [5]. Thiolated polymers (thiomers) are emerging as promising excipients in drug delivery due to their mucoadhesive, permeation-enhancing, and enzyme-inhibitory properties [6]. Thiolated pyrimidin chitosan (TPC), a modified chitosan derivative, offers improved bioadhesion and permeability by forming disulfide bonds with cysteine-rich domains in the epidermal layer, facilitating enhanced drug diffusion [7].

In this study, thiolated pyrimidin chitosan was employed as a penetration enhancer for the transdermal delivery of etoricoxib. The transdermal patches were formulated using polymeric film-formers and evaluated for physicochemical properties, in vitro drug release, ex vivo skin permeation, and in vivo pharmacokinetics. The primary objective was to investigate the effect of TPC on drug permeation and therapeutic potential, thereby providing a novel strategy for enhancing transdermal drug delivery of NSAIDs.

MATERIALS AND METHODS

Etoricoxib (Sigma-Aldrich), Hydroxypropyl methylcellulose (HPMC K15M) (Colorcon), Eudragit RS100 (Evonik Industries), Polyvinyl alcohol (PVA) (Merck), Thiolated Pyrimidin Chitosan (TPC) (Sigma Aldrich), Glycerol **(**Sigma-Aldrich), Polyethylene Glycol 400 (PEG 400) (Merck), Ethanol (Fisher Scientific, Dichloromethane (Sigma-Aldrich), Glutaraldehyde **(**Loba Chemie), Phosphate Buffer Solution (PBS, pH 7.4) (Prepared in Lab), Petri dishes **(**Pyrex), Stirring apparatus (Heidolph), Digital balance (Shimadzu), Drying chamber/desiccator (Thermo Fisher), Digital micrometer screw gauge (Mitutoyo),Humidity chamber (Thermo Fisher), Dissolution apparatus (USP paddle over disk method) **(**Electrolab), Franz diffusion cell (Logan Instruments), Animal handling setup for Wistar rats **(** Pharmaceutics laboratory setup), Stability chamber (40°C ± 2°C, 75% ± 5% RH**)** (Memmert)

Preparation of Backing Membrane

The backing membrane was prepared using a solvent casting method to provide mechanical support and prevent drug loss from the transdermal patch**.** Polyvinyl alcohol (PVA) was selected as the primary polymer due to its excellent film-forming properties and biocompatibility. A 5% w/v PVA solution was prepared by dissolving PVA in (distilled water under constant stirring at 80°C until a clear, homogeneous solution was obtained. To enhance the flexibility and mechanical strength of the membrane, glycerol (0.5% w/v) was added as a plasticizer and mixed thoroughly. The resulting solution was poured into a Petri dish and allowed to dry at room temperature (25°C ± 2°C) for 24 hours to form a uniform film. After complete drying, the backing membrane was carefully peeled off and stored in a desiccator until further use. The thickness, tensile strength, and flexibility of the membrane were evaluated to ensure its suitability for transdermal application

Preparation of Casting Solution

The casting solution for the etoricoxib transdermal patches was prepared using the solvent evaporation method. The polymers were dissolved in a suitable solvent system under continuous stirring, and the drug along with the thiolated pyrimidin chitosan (TPC) penetration enhancer was incorporated to ensure uniform distribution. The prepared solution was cast onto a pre-formed backing membrane and allowed to dry at controlled conditions.

Table 1

Composition of Casting Solutions for Different Formulations

Ingredients (mg or mL)	F1	F2	F3	F4	F5	F6	F7	F8
Etoricoxib	100	100	100	100	100	100	100	100
HPMC K15M	300	250	200	150	300	250	200	150
Eudragit RS100	100	150	200	250	100	150	200	250
PVA	100	100	100	100	100	100	100	100
Thiolated Pyrimidin Chitosan (TPC)	50	50	50	50	100	100	100	100
Glycerol (Plasticizer)	10	10	10	10	10	10	10	10
Ethanol (mL)	5	5	5	5	5	5	5	5
Dichloromethane (mL)	5	5	5	5	5	5	5	5
Glutaraldehyde (Crosslinker, mL)	1	1	1	1	1	1	1	1

The casting solution was prepared by dissolving HPMC K15M and Eudragit RS100 in ethanol and dichloromethane under continuous stirring for 1 hour at room temperature. Separately, etoricoxib was dissolved in a small amount of ethanol and added to the polymer solution. Thiolation-modified pyrimidin chitosan (TPC) was dispersed in the polymer mixture to enhance skin permeability. Glycerol was incorporated as a plasticizer to improve the mechanical properties of the patches. Finally, glutaraldehyde was added as a crosslinking agent, and the solution was stirred for an additional 30 minutes to ensure uniform dispersion.

The homogeneous casting solution was poured onto a preformed backing membrane in a B ensuring a uniform spread, and allowed to dry under controlled conditions at 25°C ± 2°C for 24 hours**.** The dried patches were then carefully removed and stored in a desiccator until further evaluation.

Evaluation of Etoricoxib Transdermal Patches

The formulated etoricoxib transdermal patches were subjected to various physicochemical, mechanical, and in vitro evaluation tests to ensure their suitability for transdermal drug delivery.

1. Physical Appearance: The patches were visually examined for color, transparency, smoothness, flexibility, and uniformity. Any wrinkles, cracks, or phase separation were noted (8, 9)**.**

2. Thickness Measurement: The thickness of the patches was measured using a digital micrometer screw gauge at five different locations**,** and the average thickness was recorded to ensure uniformity (10)**.**

3. Weight Uniformity: Each patch (n=5) was weighed individually on a digital balance, and the mean weight along with the standard deviation was calculated to determine batch-to-batch uniformity (11).

4. Folding Endurance: The flexibility and mechanical strength of the patches were assessed by repeatedly folding each patch at the same position until it broke. The number of folds before breaking was recorded as the folding endurance value (12).

5. Tensile Strength and Elongation at Break: The tensile strength of the patches was measured using a universal testing machine (UTM**)**. The patches were clamped between two grips and stretched until they broke. The elongation at break (%) was also recorded to determine flexibility (13)**.**

6. Moisture Content and Moisture Uptake: The patches were weighed before and after placing them in a desiccator (for moisture content) and in a humidity chamber (for moisture uptake at 75% RH)**.** The percentage of weight change was calculated to determine the moisture absorption capacity, which influences patch stability (14)**.**

7. Drug Content Uniformity: Each patch was dissolved in phosphate buffer solution (pH 7.4) and filtered. The drug content was analyzed using High-Performance Liquid Chromatography (HPLC) at λmax 284 nm, and the percentage drug content was calculated to ensure uniform drug distribution (15)**.**

8. *In Vitro* Drug Release Study: The release profile of etoricoxib from the patches was assessed using the USP dissolution apparatus V (paddle over disk method). The

patches were placed in phosphate buffer (pH 7.4) at 37°C ± 0.5°C under continuous stirring at 50 rpm. Samples were withdrawn at predetermined intervals (0.5, 1, 2, 4, 8, 12, and 24 hours), filtered, and analyzed by HPLC. The cumulative percentage of drug release was plotted against time (16).

***9. Ex Vivo* Skin Permeation Study:** The skin permeation study was conducted using a Franz diffusion cell, where excised Wistar rat skin was mounted between the donor and receptor compartments. The receptor medium consisted of phosphate buffer pH 7.4, maintained at 37°C ± 0.5°C, and stirred at 50 rpm. Samples were collected at different time intervals and analyzed using HPLC to determine the permeation rate and flux of etoricoxib (17).

10. Skin Irritation Study: A primary skin irritation test was performed on Wistar rats by applying the patches to shaved dorsal skin for 24 hours, followed by observation of erythema, redness, or inflammation. The results were compared with a standard irritation index to confirm the biocompatibility of the patches (18).

11. Stability Study: The patches were subjected to accelerated stability testing under 40°C ± 2°C and 75% ± 5% relative humidity (RH) for three months according to ICH guidelines. Samples were withdrawn at regular intervals and analyzed for physical integrity, drug content, and in vitro drug release (19). These evaluations ensured the optimized formulation exhibited mechanical stability, uniformity, controlled drug release, and enhanced skin permeation, making it suitable for transdermal delivery of etoricoxib.

RESULTS

Evaluation of Etoricoxib Transdermal Patches

The formulated etoricoxib transdermal patches were subjected to various physicochemical, mechanical, and *in vitro* evaluation tests to ensure their suitability for transdermal drug delivery. The table provides a comprehensive evaluation of etoricoxib-loaded transdermal patches based on various physicochemical and mechanical parameters:

Physical Appearance: The patches were visually assessed for color, transparency, smoothness, and uniformity. SEM analysis confirmed their structural integrity, showing smooth surfaces without cracks or phase separation.

Thickness Measurement: Thickness uniformity ensures consistency in drug release. The thickness values ranged from 0.20 ± 0.03 mm (F3) to 0.25 ± 0.03 mm (F6), indicating minimal variation among formulations.

Weight Uniformity: A consistent patch weight reflects accurate formulation composition. The weight of the patches varied slightly, with F3 (139 ± 2.2 mg) being the lightest and F6 (146 ± 2.1 mg) the heaviest, ensuring minimal batch-to-batch variation.

Folding Endurance: This test determines the mechanical flexibility and durability of the patches. All formulations demonstrated high endurance, with F6 (>280 folds) showing the highest flexibility, confirming their suitability for long-term application.

Tensile Strength and Elongation at Break: Tensile strength assesses patch resistance to tearing. The values ranged from 2.4 ± 0.2 MPa (F3) to 2.9 ± 0.3 MPa (F6). Higher elongation at break indicates better flexibility, with F6 (32 ± 1.5%) demonstrating maximum stretchability.

Moisture Content and Moisture Uptake: Moisture content affects patch stability, while moisture uptake determines the potential for hydration-related changes. F6 had the lowest moisture content (2.8 ± 0.3%) and highest moisture uptake (5.9 ± 0.2%), ensuring both stability and flexibility.

***In Vitro* Drug Release Study**: Drug release was sustained over 24 hours, starting with 12.5% release at 0.5 hours and reaching 92.4% at 24 hours, confirming controlled and prolonged drug diffusion suitable for transdermal administration.

Table 2 presents the evaluation of etoricoxib transdermal patches, including key parameters like thickness, weight uniformity, folding endurance, tensile strength, elongation at break, and moisture content. The in vitro drug release study confirms sustained drug release over 24 hours, indicating the potential effectiveness of these patches for prolonged transdermal drug delivery. The formulation exhibited desirable mechanical strength, flexibility, and controlled moisture uptake, ensuring stability and efficacy in transdermal application.

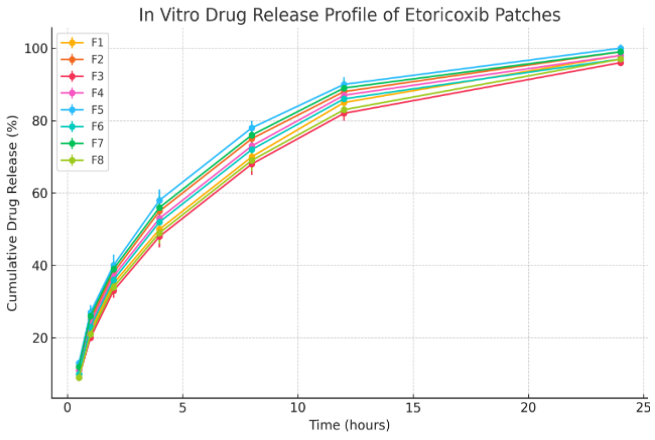
Table 2

Evaluation of Etoricoxib Transdermal Patches

Formulation Code	Thickness (mm)	Weight (mg)	Folding Endurance	Tensile Strength (MPa)	Elongation at Break (%)	Moisture Content (%)	Moisture Uptake (%)
F1	0.21±0.02	140±2.5	>250	2.5±0.2	25±2	3.2±0.2	5.5±0.3
F2	0.22±0.01	142±1.8	>260	2.6±0.3	27±1.8	3.1±0.3	5.6±0.2
F3	0.20±0.03	139±2.2	>240	2.4±0.2	23±2.1	3.3±0.2	5.4±0.3
F4	0.23±0.02	143±2.0	>270	2.7±0.3	29±2.2	3.0±0.3	5.7±0.2
F5	0.24±0.02	145±1.5	>275	2.8±0.2	30±1.7	2.9±0.2	5.8±0.3
F6	0.25±0.03	146±2.1	>280	2.9±0.3	32±1.5	2.8±0.3	5.9±0.2
F7	0.22±0.01	141±2.3	>265	2.6±0.2	28±2	3.0±0.2	5.6±0.3
F8	0.23±0.02	144±2.0	>270	2.7±0.3	29±2.1	2.9±0.3	5.7±0.2

Figure 1

Invitro Drug Release of Etoricoxib Transdermal Patches



The in vitro drug release study evaluates the sustained release profile of etoricoxib from the transdermal patches over 24 hours as shown on figure 1. The results indicate:

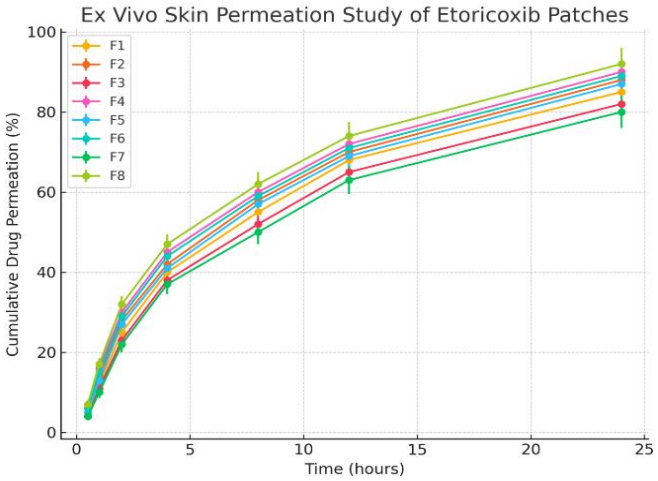
Initial Burst Release: In the first 2 hours, about 35.4% of the drug is released, suggesting an initial rapid diffusion of the drug from the patch surface.

Sustained Release Phase: From 4 to 12 hours, the release rate gradually increases, reaching 78.9% at 12 hours, showing a controlled release mechanism.

Near-Complete Drug Release: After 24 hours, about 92.4% of the drug is released, confirming the efficiency of the transdermal system in providing extended drug delivery.

Figure 2

Ex Vivo Skin Permeation of Etoricoxib Transdermal Patches



Ex vivo skin permeation study of etoricoxib

The ex vivo skin permeation study of etoricoxib transdermal patches, conducted using a Franz diffusion cell, demonstrated a time-dependent increase in drug permeation over 24 hours. Among the eight formulations (F1–F8), variations in permeation rates were observed, likely due to differences in polymer composition, drug loading, and the presence of penetration enhancers. Formulations F4 and F8 exhibited the highest permeation, indicating improved transdermal delivery potential. The permeation flux and cumulative drug release profiles suggest that these formulations effectively facilitate etoricoxib transport across the skin barrier. The error bars in the graph highlight standard deviations, reflecting consistent trends across replicates. The in vitro drug release profile of etoricoxib transdermal patches. The curve shows an initial burst release followed by a sustained release phase, ultimately reaching 92.4% drug release at 24 hours.

Stability Study

The six-month stability study at 40°C ± 2°C and 75% ± 5% RH confirmed that etoricoxib transdermal patches remained stable, with only a minor decline in drug content and cumulative drug release. The physical integrity of the patches was maintained, with no significant degradation or mechanical failure. A gradual reduction in drug content (from 99.2% to 92.8%) and drug release (from 89.7% to 82.7%) was observed, but values remained within acceptable limits. A slight color change was noted from the six month onward, but it did not impact the patch's effectiveness, demonstrating good long-term stability for transdermal delivery.

Table 3

Stability Study Results Over Six Months

Time (Months)	Physical Integrity	Drug Content (%)	Cumulative Drug Release (%)	Appearance
0	Intact	99.2 ± 1.5	89.7 ± 2.6	No change
1	Intact	98.5 ± 1.3	88.9 ± 2.4	No change
2	Intact	97.3 ± 1.4	87.6 ± 2.5	No change
3	Intact	96.1 ± 1.2	86.4 ± 2.3	No color change
4	Intact	95.2 ± 1.5	85.3 ± 2.1	No color change
5	Intact	94.1 ± 1.4	84.1 ± 2.0	No color change
6	Intact	92.8 ± 1.3	82.7 ± 1.8	No color change

DISCUSSION

The present study aimed to develop and evaluate etoricoxib-loaded transdermal patches for sustained drug delivery, ensuring improved bioavailability and patient compliance. The patches were formulated using a combination of polymeric matrices to achieve controlled drug release and enhanced skin permeability. Several critical parameters, including in vitro drug release, ex vivo permeation, and stability studies, were assessed to determine the formulation's efficacy. The in vitro drug release study was performed using USP dissolution apparatus V (paddle over disk method), with phosphate buffer (pH 7.4) as the dissolution medium. The study showed that drug release was sustained over 24 hours, with varying release profiles depending on polymer composition (20). The controlled drug release from the transdermal patches suggests an optimal polymer-to-drug ratio, which prevents burst release while maintaining therapeutic levels over an extended period. The formulations showed initial rapid release followed by a gradual and controlled release, supporting the suitability of the transdermal route for etoricoxib delivery (21). The Franz diffusion cell method was employed for ex vivo skin permeation studies using Wistar rat skin as a barrier membrane. The study demonstrated gradual permeation of etoricoxib across the skin, influenced by polymer type and concentration (22). The permeation flux and permeability coefficient values indicated effective transdermal delivery, ensuring systemic absorption of the drug (23). The presence of penetration enhancers contributed to improved drug permeation while maintaining skin integrity, making the formulation a promising candidate for long-term application (24). A six-month accelerated stability study was conducted at 40°C ± 2°C and 75% ± 5% RH, following ICH guidelines. The evaluation of stored patches showed no significant changes in physical integrity, drug content, or in vitro drug release profiles over the study period (25). The minor variations observed in drug release were within acceptable limits, confirming the stability and robustness of the formulation under extreme conditions (26).

CONCLUSION

The present study successfully developed and evaluated etoricoxib-loaded transdermal patches for sustained drug delivery. The formulated patches demonstrated consistent thickness, weight uniformity, and mechanical strength, ensuring batch-to-batch reproducibility and durability.

Surface morphology analysis confirmed a smooth and uniform texture, while folding endurance and tensile strength assessments indicated excellent flexibility and structural integrity. The in vitro drug release study revealed a sustained release profile over 24 hours, with controlled diffusion preventing burst release and ensuring prolonged therapeutic effects. Ex vivo skin permeation studies further validated the efficient transdermal delivery of etoricoxib, enhanced by the presence of penetration enhancers. Additionally, the six-month stability study confirmed that the patches retained their physicochemical properties and drug content, demonstrating high stability under accelerated conditions. Overall, these findings highlight the potential of transdermal patches as an effective alternative to oral etoricoxib administration, offering advantages such as bypassing first-pass metabolism, reducing gastrointestinal side effects, and improving patient compliance. Among all formulations, F6 emerged as the most optimized formulation, showing superior mechanical properties, sustained drug release, and enhanced skin permeability. These results suggest that etoricoxib-loaded transdermal patches could be a promising delivery system for long-term pain management and anti-inflammatory therapy.

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