Ind. J. Pharm. Edu. Res., 2026; Krupapharmacon:84-99.
https://www.ijper.org

Original Article

Formulation Development and Characterization of Oxaprozin Transdermal Patch in A Quality by Design Paradigm

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ABSTRACT

Objectives: Oxaprozin is a propionic acid derivative belonging to the Non-Steroidal Ant-Inflammatory Drug (NSAID) class, used to treat inflammation and pain in musculoskeletal conditions. Oral administration of Oxaprozin is associated with limited solubility, gastrointestinal irritation, hepatotoxicity, and extensive first-pass metabolism. The present study was focused on reducing gastric side effects and bypasses first pass metabolism by developing oxaprozin transdermal patch using natural skin permeation enhancers by applying Quality by Design (QBD). **Materials and Methods:** Oxaprozin transdermal patches were prepared using Eudragit RS 100 as the polymer and solvent evaporation method. A custom experimental design was employed to assess the effect of natural skin permeation enhancers, namely *Rosemary oil*, limonene, oleic acid. 13 formulations were developed and systematically evaluated for physicochemical properties, drug content uniformity, *Ex vivo* skin permeation, *in vitro* drug release, skin irritation, and stability. **Results:** The optimized formulation exhibited a global desirability value of 0.8352 and contained 700 mg of Eudragit RS 100 with 0.1 mL of *Rosemary oil*. The optimized patch showed 88.68% *ex vivo* permeation and 94.56% *in vitro* drug release over 24 hr. Drug release followed a non-Fickian diffusion mechanism, indicating controlled and sustained release. The Draize skin irritation test confirmed that the formulation was not causing skin irritation. **Conclusion:** The developed oxaprozin transdermal patch shows promising potential as an alternative to oral treatment. By minimizing gastrointestinal irritation and avoiding first-pass metabolism, the formulation offers enhanced patient adherence and enhanced management of musculoskeletal disorders.

Keywords: Custom design, Oxaprozin, QbD, *Rosemary oil*, Transdermal patch.

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INTRODUCTION

Arthritis has become a serious global health issue that affects people's quality of life as the population ages. Arthritis is a long-term disorder that affects the joints and adjacent tissues. It is characterized by pain, swelling, and inflammation.[1,2] In the 2022 National Health Interview Survey (NHIS) it was reported that 3.6% of adults aged 18-34 have arthritis, increasing to 53.9% of those aged 75 and above, and women are more likely than men to experience arthritis. Rheumatoid arthritis, a common inflammatory form, is managed with Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) like oxaprozin to control these symptoms.[3]

Oxaprozin is an orally administered, non-selective NSAID used to relieve mild to moderate pain and manage arthritis symptoms by inhibiting cyclooxygenase and reducing prostaglandin synthesis. It is categorized as BCS class II (high permeability and low solubility), with peak plasma concentration achieved 2-6 hr after oral administration and a half-life of 40-60 hr.[4] Oxaprozin is commercially available as tablets (600 mg) and is used to reduce the swelling, inflammation, joint pain, and stiffness. However, oral administration is associated with adverse effects such as difficulty in breathing, gastrointestinal irritation, and hematuria. The drug is well absorbed after oral administration and undergoes metabolism.[5] According to the National Centre for Biotechnology Information (NCBI), approximately 15% of long-term users were found to have elevated liver enzymes.[5] Oxaprozin is considered a suitable candidate for transdermal delivery due to its low molecular weight, high lipophilicity, prolonged half-life, and potent anti-inflammatory activity. These properties support sustained drug permeation across the skin and prolonged therapeutic action.

To minimize the complications associated with the oral route, an attempt has been made to deliver the oxaprozin through

DOI: 10.5530/ijper.krupapharmacon.26

transdermal route. It offers a promising alternative by avoiding first-pass metabolism, enhancing patient compliance and reducing the hepatic exposure.[6] Transdermal patches have emerged as an effective means of delivering drugs through the skin. When oxaprozin is applied through transdermal, it permeates through the stratum corneum, epidermis and dermis layers to reach the tiny blood vessels called capillaries. In this study, natural permeation enhancers, namely oleic acid, limonene and *Rosemary oil*, were employed to facilitate drug penetration through the skin.[7] These natural permeation enhancers offer several advantages over synthetic enhancers such as DMSO, propylene glycol and pyrrolidone, including lower skin irritation potential, better biocompatibility, rapid metabolism and non-accumulation in the body.[8] The transdermal patch of oxaprozin was developed using QbD, which methodically optimized the formulation by assessing the impact of each ingredient and process parameter on ultimate performance.[9]

The present study explores the development of an oxaprozin transdermal patch using natural permeation enhancers (oleic acid, *Rosemary oil* and limonene) combined with a Quality by Design approach using Custom Experimental Design. Unlike previous studies that employed synthetic enhancers such as DMSO and propylene glycol, the present work utilizes safer, naturally derived enhancers with Eudragit RS 100 as the matrix polymer, offering a novel, biocompatible and statistically optimized formulation for sustained transdermal delivery of oxaprozin.[10]

MATERIALS AND METHODS

Materials

Oxaprozin (gift sample, Dhamtec Pharma, Mumbai), Eudragit RS 100 (Ultra-Pure LAB CHEM Industries LLP, Palghar), *Rosemary oil* (Intimify, Haryana), Limonene (Suyash Ayurveda, Gujarat), Ethanol (CDH Fine Chem Limited, Bengaluru), Oleic acid (Central Drug House (P) Ltd., New Delhi), Polyethylene glycol 400(S D Fine Chem Ltd., Mumbai), Potassium dihydrogen phosphate (Central Drug House (P) Ltd., New Delhi), and Sodium hydroxide (Central Drug House(P) Ltd., New Delhi).

Methods

Quality by Design

QbD is a systematic pharmaceutical development approach used to optimize transdermal patches for oxaprozin, an NSAID for pain and inflammation. It involves determining Critical Quality Attributes (CQAs) like patch adhesion and drug release rate, and defining Quality Target Product Profiles (QTPP), and evaluating Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) using Design of Experiment (DOE).[11]

Quality Target Product Profile (QTPP)

The QTPP is a fundamental element in the development of transdermal drug delivery systems, outlines the essential quality attributes that a product must meet for its safety, efficacy, and performance. The QTPP was designed for the oxaprozin transdermal patch, including dosage form, dosage strength, route of administration and drug product quality attributes like pH, patch size, skin irritation and stability.[12] Table 1 represents the QTPP justification.

Critical Quality Attributes (CQAs)

The CQAs are those that have an impact on the products' performances. The CQAs for the formulation of oxaprozin transdermal patch include the following: thickness, folding endurance, drug moisture, drug content, drug release, and permeability.[13] The potential CQAs affecting the performance of the oxaprozin transdermal patch and their justifications are listed in the Table 2.

Quality Risk Management (QRM)

QRM is a structured approach used to evaluate, identify and manage potential risks across the entire product lifecycle, ensuring both product quality and patient safety. In transdermal patch development, the process starts with recognizing possible risks, which may include insufficient drug release, weak adhesion to the skin, potential irritation at the application site, or formulation instability. Risk assessment involves analysing the severity, detectability, and probability of each identified risk to prioritize the most critical factors.[14] The RPN score was evaluated and predicted for the chosen factors against the responses using the QbD add-ins version of JMP 18.0.2. The variables are assigned according to their risk priority, such as low, medium, and high levels, with 1, 3, and 9. The RPN score was computed to obtain the clarity to screen out the potential factors against responses. The RPN score was studied through the pareto charts based on that the factors and the responses were screened. The factors and replies were selected based on the RPN score, which was examined using Pareto charts. The QbD add-ins version of JMP 18.0.2 was used to estimate the RPN score. In comparison to the replies, the RPN was evaluated and projected for the chosen parameters. The factors are numbered 1, 3, and 9 in accordance with their risk priority, such as low, medium, and high levels.

Ishikawa Diagram

The Ishikawa diagram, sometimes referred to as the cause-and-effect diagram or fishbone diagram, is a visual aid utilized in QRM to methodically find and examine the sources of a risk or issue. This diagram helps in the development of transdermal patches by outlining every possible factor that could have an impact on the formulation's performance, safety and quality.[15] Figure 1 represents the Ishikawa diagram explaining the factors affecting the cause of the formulation.

Risk Estimation Matrix (REM)

A REM is a tool used in QRM to evaluate and prioritize risks on the basis of their severity, probability, and detectability. This structured approach helps in deciding which risks need strict control and which can be managed with routine monitoring. Each risk is assigned a score for severity, probability, and detectability, and then combined to classify the risk as Low (Green), Medium (Yellow), or High (Red)[16] as illustrated in Table 3.

The Risk Priority Number (RPN) was calculated using the formula:

$$RPN = Occurrence \times Severity \times Detectabilit$$

A scale of 1 to 5 was used to score each parameter, with 1 denoting minimal risk and 5 denoting high risk.

CQA VS CPP heat map

The heatmap (Figure 2) gives a visual representation of the impact of different CPPs on the identified CQAs of the transdermal patch. The RPN values were calculated and mapped, with darker regions signifying higher risk scores and light regions indicating minimal impact. The heatmap makes it easier to identify key variables, which helped in design space development in QbD and support better decision making to achieve stable and reproducible patch formulation.

CQA Pareto chart and CPP overall Pareto chart

The risk assessment showed how CQAs, CMAs, and CPPs affect the final product of the transdermal patch. As shown in Figure 3, thickness (2244), drug release (1874), and folding endurance (1742) showed the highest risk, indicating a strong influence on the patch's mechanical strength and release behavior Figures 4 illustrated that the factors such as polymer, i.e., Eudragit RS 100 and skin permeation enhancer had a high impact, affecting the process parameters like stirring speed (171), drying time (33) and temperature (29). Overall, RPN-based assessment helped to identify the critical variables and supported the design of an effective control strategy, ensuring the final formulation meets pre-defined quality, safety, efficacy and stability.

Formulation and development of oxaprozin

Transdermal patch (custom design)

Custom designs

The factors and responses were systematically selected using risk assessment and heatmap analysis. Parameters with higher Risk Priority Numbers (RPN) were identified, as they pose a greater potential impact on product quality. The heat map provided a clear visualization of the degree of influence of each factor, enabling easier identification of significant variables. Based on this approach, formulation factors such as polymer concentration and permeation enhancers, while responses were selected as Critical Quality Attributes (CQAs), including thickness, folding endurance and *in vitro* drug release. The selected responses and factor limits are mentioned in Tables 4, 5.

Formulation of transdermal patch

In solvent casting evaporation method using Eudragit RS 100 as the polymer to create transdermal patches filled with oxaprozin (12 mg). The polymer (700 mg) was weighed and dissolved in 15

Table 1: QTPP of Oxaprozin Transdermal Patch.

Elements	Target	Justification
Dosage form	Transdermal patch	Systematic distribution of medicine over a long period through skin penetration.
Dosage strength	12 mg	Delivers the required drug amount to achieve the desired therapeutic effect.
Route of administration	Transdermal	Bypasses first-pass metabolism, improve the patient convenience.
Drug product Quality attributes		
pH	Between 5-8	Maintain skin compatibility, ensure the drug stability and reduce the irritation.
Patch size	2×2 cm	Ensures adequate surface area for drug absorption and patient comfort.
Skin irritation	Should be minimal	Transdermal drugs and adhesives are applied to the skin, causing minimal or no irritation, while effectively providing their therapeutic action.
Stability	6 -12 months	Assures the safety and quality of the product.
Packaging	Sealed laminated pouches	Prevents moisture loss, contamination and maintain drug stability.

Table 2: CQAs of Oxaprozin Transdermal Patch.

Quality attributes of the product	Target	CQAs	Justification
Thickness	Uniform thickness 0.1 -0.5mm.[14]	Yes	Impacts the drug release and mechanical strength
Drug content	95% -100%.[15]	Yes	Ensures the therapeutic efficiency
Moisture content	Within acceptable limits (<5%).[16]	Yes	It can lead to product damage and microbial growth, which may affect the stability of the product.
Folding endurance	150-250 folds without Breaking.[17]	Yes	Reflects mechanical strength, flexibility and may cause brittleness
Permeability	Adequate drug permeation across the skin to achieve therapeutic levels	Yes	It controls the release of the drug through the skin layers, ensures the therapeutic levels.
Drug release	≥ 85%.[18]	Yes	It determines how quickly and effectively, the drug reaches the body

mL of ethanol. Using magnetic stirrer, the polymeric dispersion was stirred at 500 rpm for 30 min to produce an opaque solution. Oxaprozin drug was added to the polymeric solution and stirred to enhance even distribution. PEG 400 was added at a concentration of 30%w/w to the aforesaid solution to improve the flexibility of the patch. Oleic acid, D-limonene, and *Rosemary oil* were added individually to different batches and blended until a homogenous solution was generated in order to assess the impact of different natural skin permeation enhancers. After that, it was put into a petri dish with an inverted funnel to keep the evaporation constant and stop the patch from splitting. For full drying, the set was left undisturbed for the entire night. Drying was done at room temperature (25±2°C) with regulated humidity. The patch was carefully taken out of the petri dish when it had dried, sliced into 2 x 2 cm squares, and kept in a desiccator for additional assessment research.[17]

Checking CQA's

Folding endurance, thickness, and *in vitro* drug release were all effectively generated and assessed in all 13 formulation studies.

Determination of Thickness

Patch thickness was measured at 5 different points using a screw gauge, and the average thickness was calculated.[18]

Determination of Folding endurance

The Folding endurance was calculated manually by repeatedly folding a 2×2 cm patch at the same point until breakage was observed. The patch's ability to withstand folds without splitting was recorded. To calculate average this procedure was repeated three times, and the standard deviation was calculated.[19]

In vitro drug release

The *in vitro* drug release from the oxaprozin transdermal patch was evaluated by using a Franz diffusion cell containing a donor and a 50 mL receptor compartment with a 2×2 cm oxaprozin patch placed over 70-micron cellulose membrane**.** The receptor compartment was filled with pH 7.4 phosphate buffer and kept at 32±0.5°C. Then the solution was stirred continuously at 50 rpm using a magnetic stirrer. Sample 1 mL was withdrawn at the specific time intervals of 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 22 and 24 hr, then replaced with fresh buffer solution, and samples were analysed using UV-visible spectroscopy at 286nm, and the drug release was calculated.[20]

Design evaluation

The efficiency of the Custom Design was assessed using design diagnostics, primarily expressed as percentage design efficiency. The Evaluate Design platform generated results consistent with standard DOE design evaluation outlines. Key diagnostics include a Colour Map on Correlations, which visually represents absolute correlations between effects using an intensity scale, and Design Diagnostics, which summarize the overall efficiency of the design.[21]

Model fit

The response data for *in vitro* drug release, folding endurance and thickness obtained from all 13 Oxaprozin transdermal patch formulations were incorporated into the design software to evaluate the model fit. Multiple regression models were fitted with the intercept fixed at zero in order to conduct statistical analysis. Statistically significant models were identified for the responses, with variables showing *p*-values below 0.05. The model fit was determined by comparing the real and predicted plots.[22] The derived models demonstrated no significant lack of fit and were

statistically significant with $p<0.05$, indicating the suitability of the chosen model.

Statistical optimization of selected responses of oxaprozin transdermal patch

The desirability function approach is the most often used numerical and graphical method for simultaneous optimization of the formulation. While the optimization is carried out by obtaining individual desire functions for the corresponding responses, the desirability function approach makes use of a prediction profiler. A number between 0 and 1 is assigned to the derived global desirability function value. The maximization of desirability is indicated by a value around one. In the custom design, cube plots were selected to represent the design space as they clearly illustrate the effect of three factors and their interactions on the chosen responses. Each axis in the cube corresponds to a factor, while the vertices indicate different combinations of factor levels. This graphical approach makes it easier to understand how critical parameters influence formulation performance and helps in identifying the optimal region within the design space for achieving consistent and reliable product quality.

Characterization of optimized oxaprozin transdermal patch

The findings are shown as mean±standard deviation, and each experiment was conducted in triplicate (n=3).

Surface pH

A pH meter was used to measure the transdermal patch's surface pH. Each patch was soaked in 1 mL of distilled water for 2 hr at room temperature. The pH was then measured and recorded by placing an electrode on the patch surface for 1 min. This process was repeated three times, and the average and standard deviation were computed. 1 mL of distilled water was used to soak each patch for 2 hr at room temperature. An electrode was placed on the patch surface for 1 min to measure the pH after soaking. The pH was then noticed and recorded. The average and standard deviation were computed after the process was repeated three times.[23]

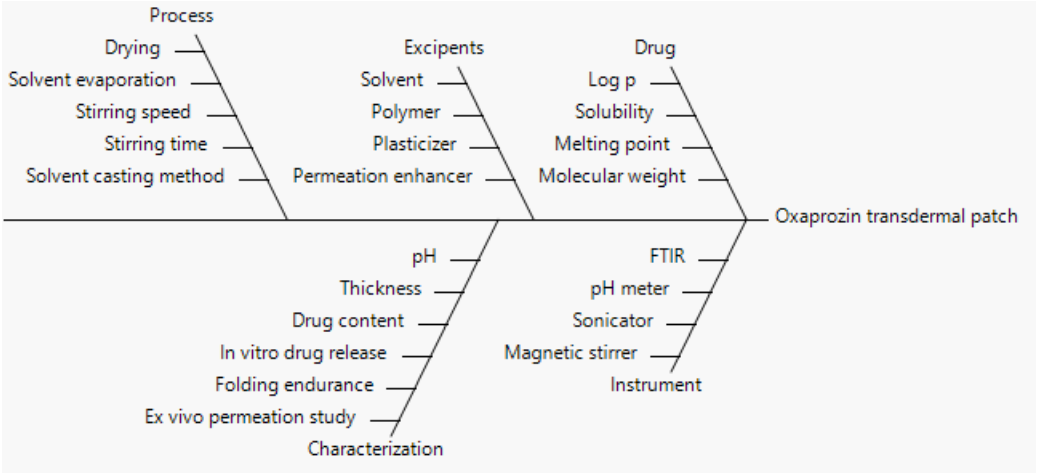

Figure 1: Ishikawa diagram.

Table 3: CMA, CPP vs CQA Table of REM.

CQAs	Drug [Mixing]	Polymer [Mixing]	Solvent [Mixing]	Skin permeation enhancer [Mixing]	Stirring time [Mixing]	Stirring speed [Mixing]	Drying time [Drying]	Drying temperature [Drying]
Appearance	Low	Medium	Medium	Low	Low	Low	Low	Medium
Thickness	Low	High	High	Low	Medium	Medium	High	High
Drug content	High	Medium	Medium	Medium	High	Medium	Medium	Medium
Folding endurance	Medium	High	Medium	Medium	Medium	Low	Low	Medium
Moisture content	Low	Low	Low	High	Low	Low	Low	Low
Permeability	High	Medium	Low	High	Low	Low	Low	Medium
Drug release	High	High	Medium	High	Low	High	High	Medium

Weight variation

A digital weighing balance was used to weigh the transdermal patch in order to evaluate the weight variation. Each of the three patches was weighed separately, and an average was recorded.[24]

Percentage moisture content

The oxaprozin transdermal patches were initially weighed and then stored in a desiccator containing calcium chloride at room temperature for 24 hr. The calcium chloride helps to keep the surrounding region dry to stop the patches from absorbing moisture. The patches were weighed again after a day, and the moisture content was determined using the difference between the initial and end weights.[25]

$$\text{Moisture Content (\%)} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Final weight}} \times 100$$

Percentage moisture uptake

The moisture uptake patch is weighed and kept in a desiccator with a saturated KCl solution for a whole day at an 84% relative humidity.[25] After that, the patch is weighed again, Thus the moisture uptake is calculated using the formula below:

$$\text{Moisture Uptake (\%)} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

Swellability

The swellability of a transdermal patch was evaluated by placing the sample on a previously weighed cover slip and immersing it in a petri dish containing 50 mL of pH 7.4 phosphate buffer. Then the petri dish was kept undisturbed for 30 min, to allow the patch to absorb fluid. After the specific time, the cover slip with the patch was removed, then washed with distilled water and dried. After then, the cover slip is weighed again, and the rise in mass indicates how much water the patch has absorbed.[26]

$$\text{Swellability (\%)} = \frac{(\text{Swollen weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

Determination of folding endurance

Folding endurance was evaluated as mentioned earlier.

Determination of thickness

Thickness was determined as mentioned earlier.

In vitro drug release

As previously noted, *in vitro* drug release investigations were carried out.

Drug release kinetics

To clarify the release mechanism and rate from the dosage form, the drug release data from the transdermal patch were fitted into a number of models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models.[27]

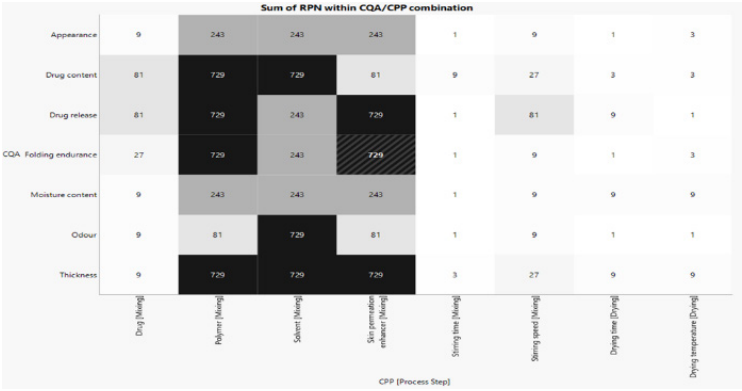

Figure 2: CQA vs. CPP heatmap.

Table 4: Variables and their limits of Custom Design.

Factors	Role	Upper limit	Lower limit	
Eudragit RS 100	Continuous	750 mg	650 mg	
Skin permeation enhancer	Categorical	*Rosemary oil* (0.1 mL)	Oleic acid (0.1 mL)	Limonene (0.1 mL)

Table 5: Responses, goals and their limits in Custom Design.

Responses	Goal	Upper limit	Lower limit
Folding endurance	Target	250	150
Thickness	Target	0.45 mm	0.11 mm
% drug release	Maximize	90	75

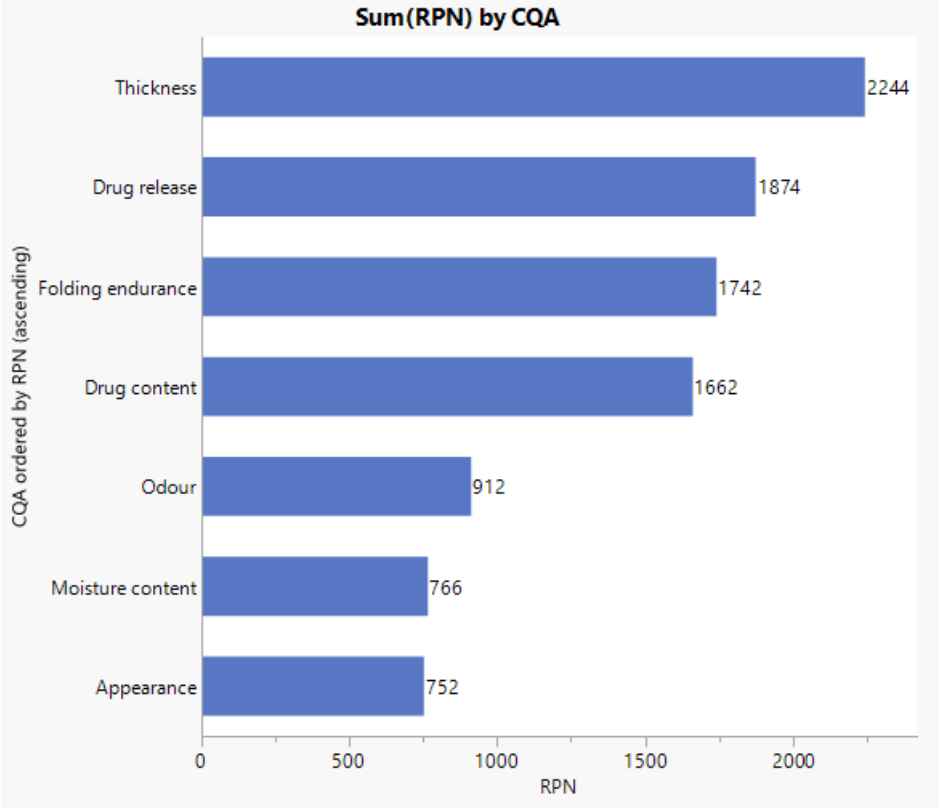

Figure 3: CQA Pareto.

Ex vivo permeation study

The oxaprozin transdermal patches *Ex vivo* penetration was investigated using pig ear skin as the membrane. A nearby slaughterhouse provided the *porcine ear skin*. An electric clipper was used to precisely remove the hair, and a scalpel was used to remove the subcutaneous fat. Before being used, the cleansed skin was rinsed with phosphate buffer (pH 7.4). The skin was placed between the donor and receptor compartments with the stratum corneum facing the donor side. The receptor compartments were filled with phosphate buffer (pH 7.4) and fitted with a magnetic stirrer bar. The entire assembly was maintained at 37±1°C on a magnetic stirrer. The optimized 2×2 cm patch was placed on the surface of the excised *porcine ear skin* membrane. At pre-arranged intervals, 1 mL of receptor medium was withdrawn from the receptor compartment, and the same volume of new receptor medium was promptly added. Similarly, permeation study was performed for the control group, i.e. pure drug repeated the same procedure. The amount of Oxaprozin permeated through the excised *porcine ear skin*, both in transdermal patch and pure drug, was assayed by UV-visible spectrophotometer at 286 nm wavelength (λ_{max}) against a blank.[28]

Stability studies

Following ICH recommendations, accelerated stability testing of the improved transdermal patch was carried out for nine months at 40±2°C and 75±5% relative humidity. Samples were collected and analyzed for drug content, surface pH, and *in vitro* release profile at predefined intervals of three, six, and nine months. Samples were taken and examined for drug concentration, surface pH, and *in vitro* release profile at prearranged intervals of three, six, and nine months.[29]

Statistical analysis

JMP 18.0.2 was used to analyze the collected data. The findings are shown as mean±Standard Deviation (SD). At $p<0.05$, statistical significance was assessed.

RESULTS AND DISCUSSION

Quality By Design

Checking and confirming the CQAs of Oxaprozin transdermal patch

The identified CQAs were evaluated (Table 6), such as folding endurance, thickness and *in vitro* drug release of all 13 formulations indicated that all the formulations met their basic quality standards. Specific excipient ratios provided a better combination of mechanical strength, uniformity and controlled drug release, making them more suitable for identifying optimized transdermal patch formulation. Overall, the CQAs ensure the optimized transdermal patch has good mechanical strength and effective control of drug release.

Effect of polymer (Eudragit RS 100)

Thickness

The critical quality attributes of the Oxaprozin transdermal patch were significantly influenced by the concentration of Eudragit RS 100. The findings showed that all thirteen formulations had patch thicknesses ranging from 0.14 mm to 0.25 mm. All trial patches exhibited thickness values within the acceptable standard limits, confirming uniform film formation. The transdermal patch thickness was found to be significantly influenced by the polymer content, according to the CQA analysis. These results show that the transdermal patch thickness is directly and significantly impacted by the concentration of Eudragit RS100.

Folding endurance

The result showed that the folding endurance of the transdermal patches ranged from 175 to 230 across all thirteen formulations. All trial patches exhibited folding endurance values within the acceptable standard limits, confirming adequate mechanical strength and uniform film formation. CQA analysis revealed that polymer concentration had a significant influence on folding endurance. These findings demonstrate that the concentration of Eudragit RS 100 directly and significantly affects the folding endurance of the oxaprozin transdermal patch.

In vitro drug release

The polymer concentration showed an inverse association with the *in vitro* drug release. The *in vitro* drug release of the Oxaprozin transdermal patches ranged from 76.48% to 95.92% across all thirteen formulations. Most formulations exhibited drug release values within acceptable limits, indicating satisfactory and consistent release characteristics. CQA analysis revealed that polymer concentration significantly influenced drug release behaviour. These findings confirm that the concentration of Eudragit RS 100 has a direct and significant effect on the *in vitro* drug release of the Oxaprozin transdermal patch.

The polymer matrix became more compact at higher Eudragit RS 100 levels, lengthening Oxaprozin diffusional path and limiting its release from the patch. Similar observations were reported by (Ozcan Bulbul *et al.*, 2022), where increasing polymer concentration reduced drug diffusion due to formation of a dense polymeric matrix. Eudragit RS 100's quaternary ammonium groups permit limited permeability; however, an excessive polymer concentration slowed the rate of drug diffusion, leading to a controlled release profile. As demonstrated by the greatest log worth value (4.275) and a highly significant *p*-value (0.00005), statistical analysis validated Eudragit RS 100's dominant influence on CQAs. The effect summary is mentioned in Table 7.

Table 6: DoE of Transdermal Patch Matrix.

Formulation	Eudragit RS 100 (Polymer)	Skin permeation enhancer (0.1 mL)	Folding endurance	Thickness	*In vitro* drug release
1	650	Rosemary oil	183±2.76	0.18±0.121	79.93±0.22
2	700	Rosemary oil	193±3.76	0.22±0.004	90.53±0.09
3	650	Oleic acid	181±1.09	0.14±0.875	81.31±0.03
4	750	Rosemary oil	223±2.34	0.25±0.0023	85.79±0.21
5	700	Rosemary oil	203±1.97	0.22±0.092	80.53±0.23
6	650	Limonene	177±2.76	0.15±0.002	81.83±0.34
7	708	Limonene	193±3.12	0.19±0.034	95.97±0.19
8	650	Limonene	175±1.80	0.17±0.076	84.81±0.01
9	708	Limonene	199±3.87	0.2±0.092	79.45±0.12
10	700	Oleic acid	195±2.10	0.21±0.024	83.47±0.05
11	750	Limonene	230±4.09	0.23±0.012	76.48±0.24
12	750	Oleic acid	212±2.87	0.22±0.020	82.31±0.10
13	700	Oleic acid	186±1.98	0.18±0.001	95.92±0.03

Table 7: Effect Summary.

Source	Log worth		*p* Value
Eudragit RS 100 (650,750)	4.275		0.00005
Skin permeation enhancer	1.538		0.02900
Eudragit RS 100*Eudragit RS 100	1.437		0.03652
Eudragit RS 100*Skin permeation enhancer	1.262		0.05470

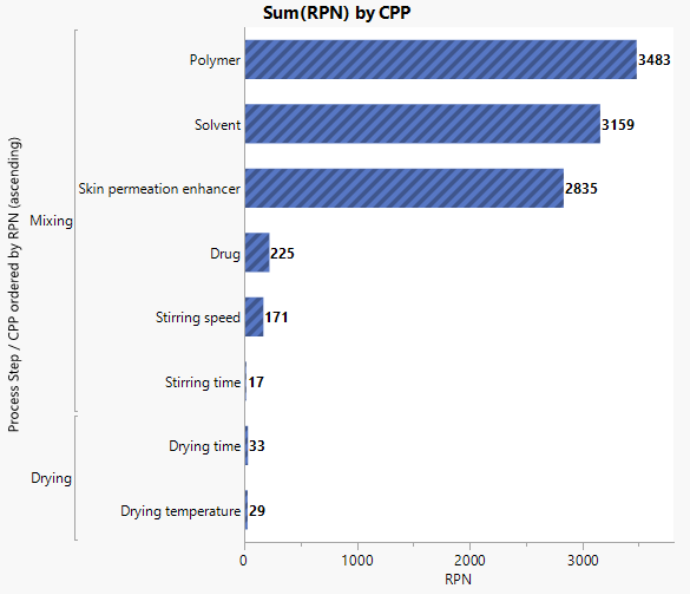

Figure 4: CPP overall Pareto.

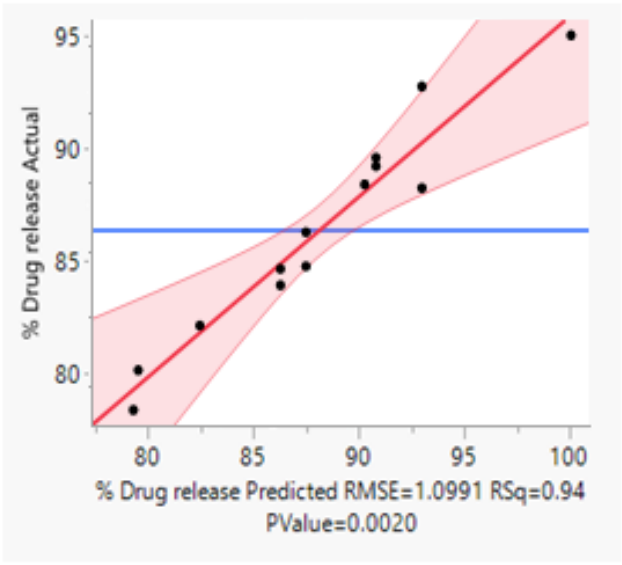

Figure 5: Leverage plots of % drug release.

Effect of permeation enhancer

The transdermal patch's drug release and permeation behaviour were significantly impacted by permeation enhancers such as oleic acid, limonene, and *Rosemary oil*. while having a minimal impact on mechanical properties such as thickness and folding endurance. The incorporation of permeation enhancers notably improved *in vitro* drug release. Among the enhancers studied, *Rosemary oil* produced the highest drug release, followed by limonene and oleic acid. The enhanced release can be explained by the presence of terpenes in *Rosemary oil*, which increase drug solubility within the polymeric matrix and reduce drug-polymer interactions, thereby facilitating improved diffusion of Oxaprozin. Similar findings were reported in previous transdermal studies where terpene-based natural permeation enhancers improved drug permeation via upsetting the stratum corneum's lipid composition.

Actual vs predicted plot of selected responses

Regression analysis between the actual and predicted values for *in vitro* drug release, thickness and folding endurance showed good accuracy with the R^2 values of 0.94, 0.93, and 0.95, respectively, as represented in Figures 5-7. The high R^2 value and $p<0.005$ confirmed that the model showed good fit and reliability for predicting the CQAs. The obtained models were statistically significant with $p<0.05$ and showed no significant lack of fit, confirming the adequacy of the selected model. The red line indicates the best-fit line showing the relationship between the actual and predicted values of each response.

Statistical optimization of the selected response of the oxaprozin transdermal patch

Prediction profile of optimized formulation

Optimization of the oxaprozin transdermal patch formulation was achieved through the application of the global desirability function. According to the prediction profiler, Figure 8 illustrates that increasing Eudragit RS 100 concentration showed slight impact on thickness and higher folding endurance improved the flexibility of the patch. The optimized formulation found at 700mg Eudragit RS 100 and 0.1 mL *Rosemary oil* with the global desirability of 0.835, it indicates that the selected responses and factors were statistically significant.

CHARACTERIZATION OF OPTIMIZED TRANSDERMAL PATCH

Surface pH

The surface pH of the optimized oxaprozin transdermal patch was determined using a digital pH meter and was found to be 6.60±0.05, which is within a limit, indicating the patch has minimal irritation.

Weight variation

Weight variation of the formulated patches was evaluated and the results showed 147±2.00 mg. The minimal variation in weight indicates uniform distribution of the drug and excipients, as it ensures dose accuracy and therapeutic efficacy.

Table 8: Characterization of Optimized Formulation.

Sl. No.	Parameters	Observation			
		Trial 1	Trail 2	Trail 3	Average±SD
1.	Surface pH	6.65	6.58	6.56	6.60±0.05
2.	Weight variation (mg)	147	149	145	147±2.00
3.	% of moisture content	6.09	5.87	5.91	5.95±0.117
4.	% of moisture loss	7.24	7.29	7.43	7.32±0.098
5.	% drug content	95.34	94.98	95.62	95.31±0.321
6.	Thickness (mm)	0.23	0.25	0.22	0.223±0.002
7.	Folding endurance	195	198	194	195.66±2.08
8.	Swellability	8.16	6.04	6.89	7.03±1.067

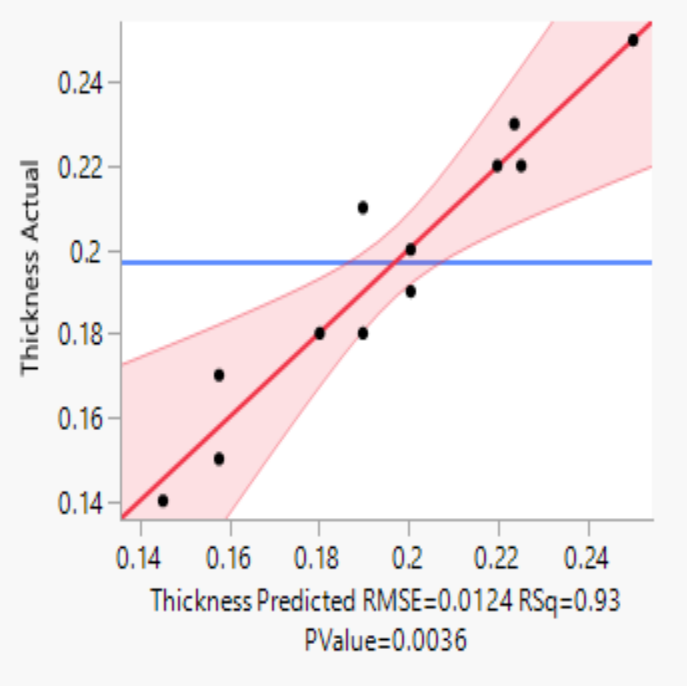

Figure 6: Leverage plots of thickness.

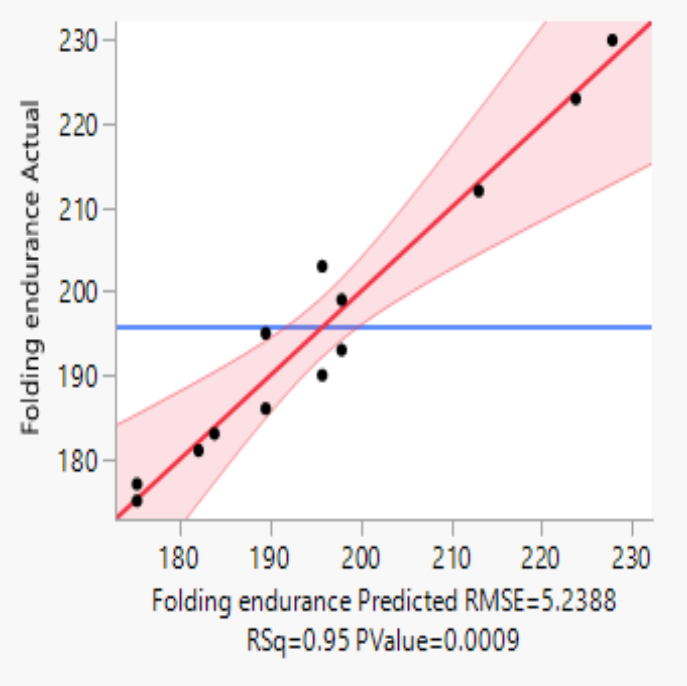

Figure 7: Leverage plots of Folding endurance.

Percentage of moisture content

The percentage of moisture content loss was found to be 7.32±0.098. This moderate loss ensures that the patch remains stable and flexible without becoming brittle, also it minimizes the risk of microbial growth.

Thickness

The thickness of the formulated patch was found to be 0.223±0.002 mm, and there is no significant variation in mm, which indicates the uniformity and precision of the patch. The obtained thickness falls within the range for transdermal patches, which generally vary from 0.12 to 0.25 mm.

Folding endurance

The folding endurance of the patch was found to be 195.66±2.08, which shows the strong mechanical strength and good flexibility. The result confirms the ability of a patch to sustain repeated bending without breaking or losing integrity.

Percentage drug content

The prepared transdermal patch showed a drug content of 95.31%, indicating that the drug was evenly and efficiently incorporated into the formulation. This high drug content ensures accurate dosing and effective delivery, confirming that the patch is stable and reliable for further studies.

Swellability

The swellability of the patch was found to be 7.03% as mentioned in Table 8, which indicated that the Eudragit RS 100 polymer had a capacity to absorb fluid and swell. Thus, the obtained swellability reflects a stable formulation with balanced water

Table 9: *In vitro* drug release (%) of transdermal patch release.

Time (hours)	Average±SD
0.5	7.023±0.345
1	16.53±1.073
2	21.72±1.803
3	28.44±0.935
4	33.98 ±1.131
5	40.08±0.750
6	46.75±1.880
8	54.78±0.881
10	65.99±0.982
12	74.83±1.252
14	79.36±0.656
16	83.74±0.938
18	87.52±1.858
20	90.22±0.452
22	92.59±0.946
24	94.56±0.836

uptake properties, ensuring both flexibility and effective drug release.

In vitro drug release study

The *in vitro* drug release from the oxaprozin transdermal patch was carried out for 24 hr, the results are shown in Table 9 and Figure 9. The drug release showed a gradual increase in drug diffusion over a time period of 24 hr. At 0.5 hr the release was 7.023% which increased to 91.59% at 24 hr. This result demonstrates that the formulation effectively maintains a prolonged release profile. Comparable sustained release behaviour has been reported in previously developed NSAID transdermal patches prepared using acrylic polymer matrices.

Drug release kinetics

The optimized oxaprozin transdermal patches *in vitro* release profile was fitted to a number of kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas, in order to examine the drug release mechanism. The fit accuracy was evaluated using the R^2 value, and the rate constants were computed from the slopes of the corresponding plots. The

Table 10: *In vitro* release kinetics data of Optimized Transdermal Patch.

Release kinetics				
Zero order kinetics R^2	First order kinetics R^2	Higuchi R^2	Korsmeyer-Peppas	
			R^2	N
0.9975	0.96529	0.9947	0.9937	0.529

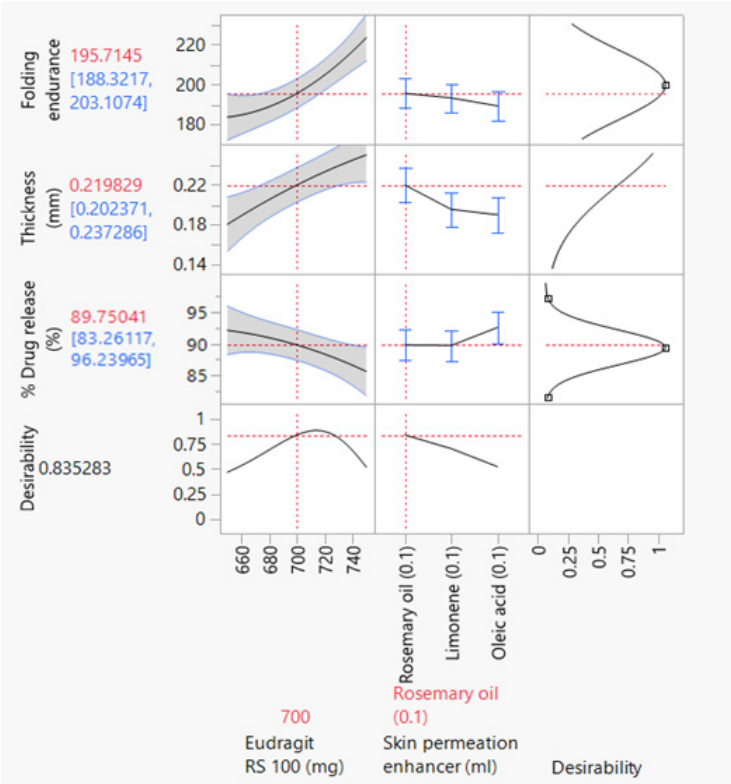

Figure 8: Prediction profiler of optimized formulation.

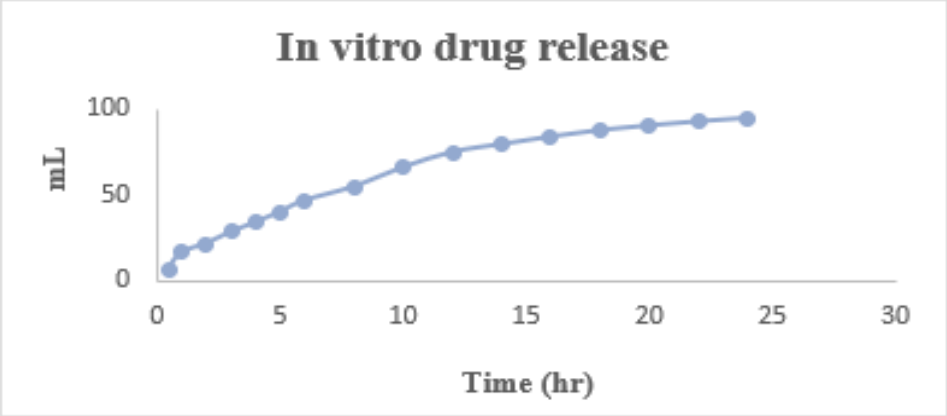

Figure 9: *In vitro* drug release (%) of Transdermal.

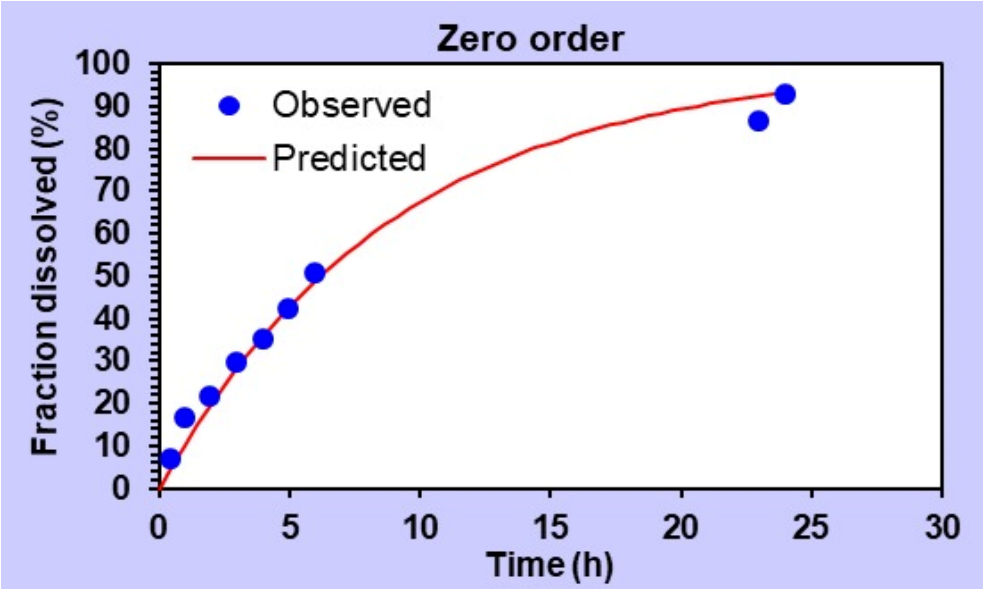

Figure 10: Zero-order kinetics.

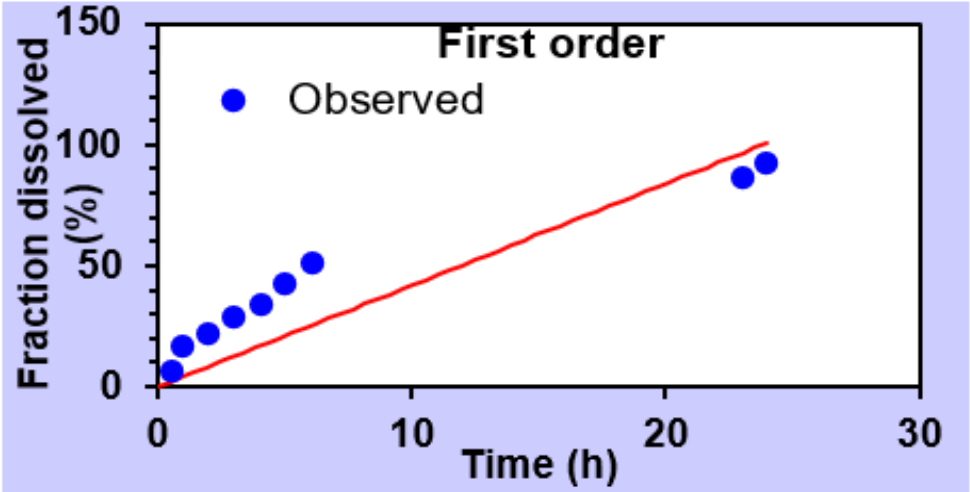

Figure 11: First-order kinetics model.

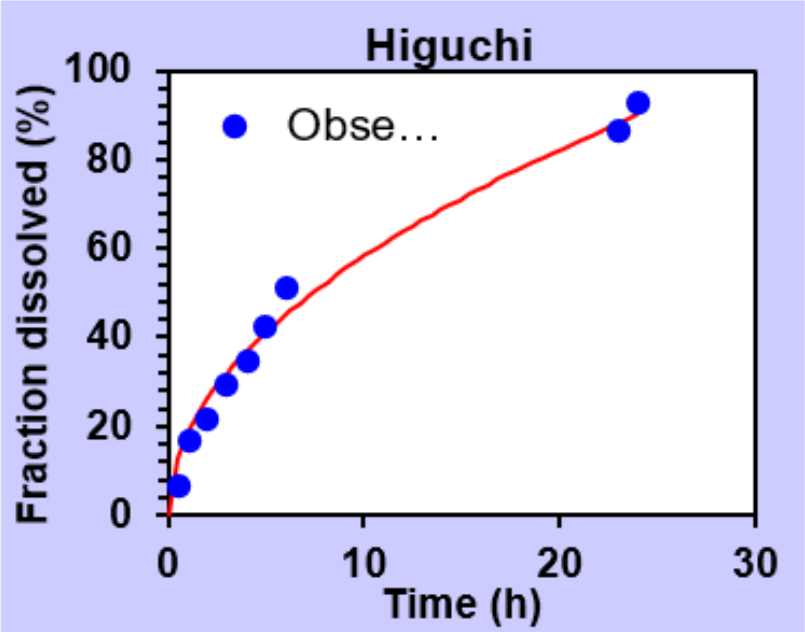

Figure 12: Higuchi model.

Table 11: ***Ex vivo*** **Skin permeation (%) of Transdermal Patch.**

Time (hr)	The average cumulative amount of the drug permeated per cm² (µg/mL/cm²)	
	Oxaprozin (control)	Oxaprozin transdermal patch
0.5	1.39±0.0325	6.87±0.01
1	4.57±0.012	13.34±0.151
2	7.74±0.098	17.57±0.01
3	10.94±0.023	21.53±0.043
4	13.36±0.032	26.98±0.003
5	15.61±0.011	31.76±0.023
6	18.22±0.121	39.32±0.01
8	20.96±0.136	47.38±0.648
10	23.22±0.145	55.36 ±0.345
12	25.98±0.452	62.47±0.88
14	29.02±0.131	69.54±0.01
16	32.62±0.043	75.85±0.146
18	33.86±0.001	82.85±0.131
20	36.59±0.024	88.68±0.235
22	38.54±0.258	92.66±0.074
24	39.85±0.017	98.56±0.01
Flux (mg/cm²/hour)	0.0575	0.486

slopes of the corresponding plots were used to calculate the rate constants, and the fit accuracy was evaluated using the R^2 value. As presented in Figures 10-13, the zero-order/*in vitro* drug release showed a higher correlation (R^2 =0.9975) compared to the first-order kinetics (R^2 =0.9652) and Higuchi's plot (R^2 =0.9947). Thus, a slow and controlled release of the formulated transdermal patch was represented by a non-Fickian model, as indicated by the release exponent 'n' calculated from the Korsmeyer-Peppas equation, which ranged between 0.5 and 0.85. Anomalous or non-Fickian diffusion is indicated by a "*n*" value between 0.5 and 0.85, which implies that drug release happens via a mix of diffusion and polymer relaxation mechanisms Table 10 contains information on the Optimized Transdermal Patch's *in vitro* release kinetics.

Ex vivo skin permeation of transdermal patch

Ex vivo skin permeation study was performed using *porcine ear skin*, the Oxaprozin transdermal patch showed cumulative drug permeation of 88.68% at the end of 24 hr, which was significantly higher than the pure drug (control) which showed 36.86%. As shown in Table 11 and Figure 14, the patch's steady state flux was determined to be 0.486 mg/cm2/hour. The presence of *Rosemary oil* disrupts the lipid structure of the stratum corneum by increasing lipid fluidity and breaking hydrogen bonds, thereby enhancing drug diffusion through the skin barrier. The significantly higher cumulative drug permeation observed with *Rosemary oil* confirms its efficacy as a natural enhancer, demonstrating its valuable role in improving transdermal drug delivery. The optimized transdermal patch exhibited significantly higher permeation compared to the pure drug control, indicating the effectiveness of *Rosemary oil* as a permeation enhancer.

Skin irritation study

The skin irritation study was employed to evaluate safety and biocompatibility of the transdermal patch. The study was conducted on three *Wistar rats* for 72 hr, and erythema/oedema

Table 12: Skin Irritation Study.

Group	Treatment		Draize scoring
1	Standard	0.8%v/v formalin solution	3
2	Control	Placebo transdermal patch	0
3	Test	Oxaprozin transdermal patch	0

Table 13: Stability study.

Parameters	3 months	6 months	9 months
pH	6.45	6.35	6.34
% Drug content	94.64	93.84	93.54
Folding endurance	193	192	195

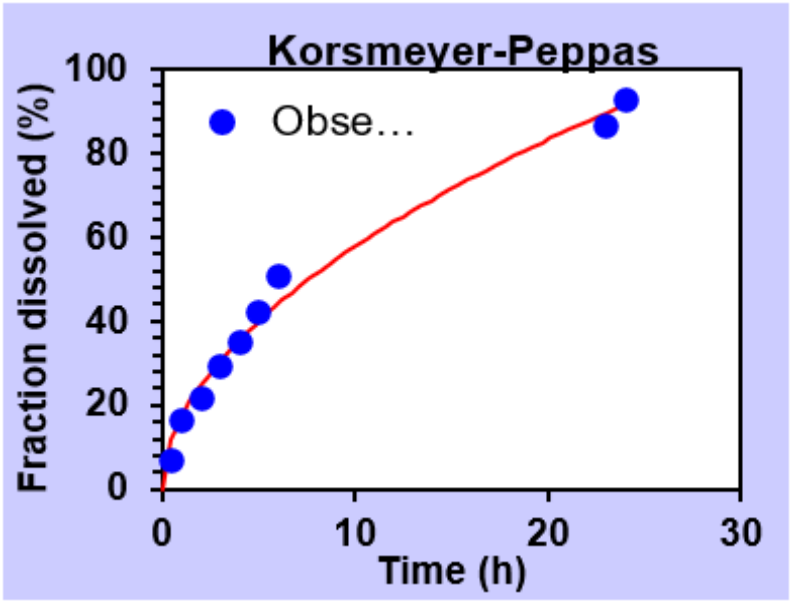

Figure 13: Korsmeyer-Peppas model.

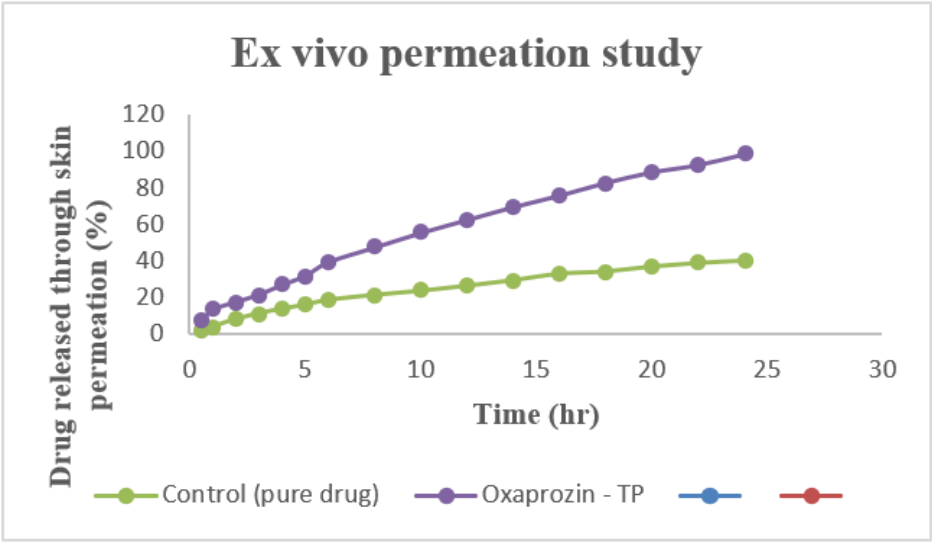

Figure 14: Graphical representation of *Ex vivo* skin permeation study.

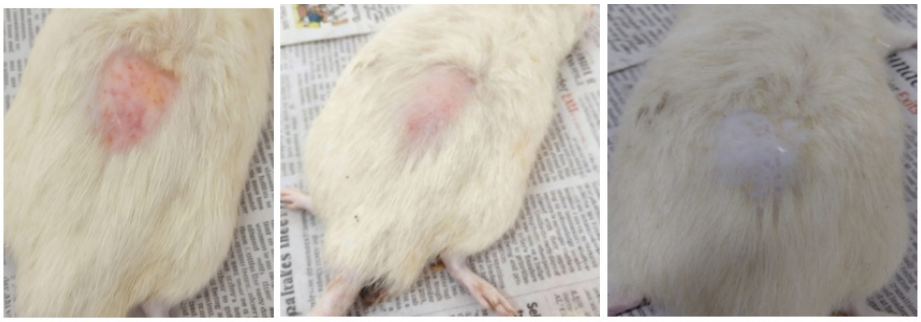

Figure 15: Skin irritation on *Wistar rats*. a) Standard group. b) Control group. c) Test group.

scores were recorded according to Draize scoring criteria. The erythema, oedema, and other signs of irritation were observed during the study period (Figure 15 and Table 12). The results indicated that the formulation caused minimal to no irritation, suggesting good skin compatibility. The study suggests that the developed transdermal patch possesses good skin compatibility for topical application.

Stability study

The stability study was conducted over a period of 9 months Table 13 shows that the patch maintained consistent pH, retained drug content, and preserved folding endurance, indicating good chemical and mechanical stability under the tested conditions. No significant changes in drug content, pH, or folding endurance were observed during 9 months of storage, indicating formulation stability.

CONCLUSION

The present study successfully designed, developed and optimized an Oxaprozin transdermal patch by employing a QbD approach using different natural skin permeation enhancers. Arthritis treatment often requires long term medication, and oral administration of Oxaprozin is associated with several adverse effects. Hence, TDDS was pursued as an alternative route to improve the patient compliance and minimize the risk factors. The Custom Design was constructed using JMP 18.0.2 software. Each formulation was systematically evaluated to CPPs such as *in vitro* drug release, thickness, folding endurance then the data were analyzed using model fit and prediction profiler showed maximum desirability. *Rosemary oil* showed good results in improving drug release. The optimized transdermal patch showed good flexibility and uniform drug distribution. *In vitro* studies confirmed that the patch provides controlled drug release and it follows the zero-order kinetics and non-Fickian diffusion. *Rosemary oil* enhanced drug flux, and no noticeable skin irritation occurred. Overall, the developed Oxaprozin transdermal patch showed promising potential as an alternative to oral therapy by reducing gastrointestinal exposure and providing sustained drug release.

ACKNOWLEDGEMENT

The authors thank Dhamtec Pharma, Mumbai, India for their assistance in providing Oxaprozin.

ABBREVIATIONS

BCS: Biopharmaceutics Classification System; **CPP:** Critical Process Parameters; **CQA:** Critical Quality Attributes; **DOE:** Design of Experiments; **QRM:** Quality Risk Management; **QTPP:** Quality Target Product Profile; **RPN:** Risk Priority Number; **TDDS:** Transdermal Drug Delivery System; **ICH:** International Council for Harmonisation; **NCBI:** National Center for Biotechnology Information; **NHIS:** National Health Interview Survey; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **DMSO:** Dimethyl Sulfoxide; **KCl:** Potassium Chloride; **PEG:** Polyethylene Glycol; **RH:** Relative Humidity; **RS:** Reference Standard; **UV:** Ultraviolet; **JMP:** JMP Statistical Software; **CDH:** Central Drug House.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

The animal study protocol was reviewed and approved by the institutional Animal Ethics Committee (IAEC), Krupanidhi College of Pharmacy, Bangalore, Karnataka, India (Approval No: KCP/IAEC/PCOL/QA/173/APR-2025, dated: 05/04/2025). All animal experiments were performed in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

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Cite this article: Murali G, Narayanappa S, Samy MP, Govindarajan S. Formulation Development and Characterization of Oxaprozin Transdermal Patch in A Quality by Design Paradigm. Indian J of Pharmaceutical Education and Research. Krupapharmacon 2026:84-99.