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DEVELOPMENT, EVALUATION AND *IN-VIVO* ASSESSMENT OF FENOPROFEN CALCIUM-LOADED NANOPARTICLE-BASED TRANSDERMAL PATCHES

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ABSTRACT

Background: The objectives of this study were to prepare and test fenoprofen calcium loaded nanoparticles for transdermal patches and to study the preliminary dermal tolerability and in-vivo anti-inflammatory effect of optimized formulation. **Methods:** A total of six formulations (TP1–TP6) were prepared in the solvent-casting method with different amounts of hydroxypropyl methylcellulose (HPMC), Eudragit RLPO, Eudragit RSPO and ethyl cellulose. Physical and Mechanical properties, Drug Content, Moisture content, Water vapour transmission rate (WVTR) and in-vitro drug diffusion were evaluated on the patches. The optimized formulation was subjected to accelerated stability test at 75 ± 5%RH and temperature 40 ± 2°C for six months. The dermal irritation and anti-inflammatory activity were evaluated in the Wistar albino rat skin irritation test and carrageenan-induced paw oedema model, respectively. **Results:** Formulation TP5 exhibited the best overall performance with folding endurance of 245 ± 5.7 folds, tensile strength of 0.86 ± 0.019 kg/cm², elongation of 38.2 ± 1.3%, drug content of 98.2 ± 0.6%, moisture content of 3.9 ± 0.15%, and WVTR of 4.1 ± 0.21 g/m²/24 h. The cumulative drug diffusion was 97.1 ± 0.92% after 24 hours. The drug content in the accelerated stored samples was 95.8 ± 1.1% after 6 months with no change in appearance. The primary irritation index for TP5 was 0.17. At 24 hours, mean paw thickness was 5.72 ± 0.05 mm for TP5, 5.76 ± 0.04 mm for oral nanoparticles, and 5.86 ± 0.03 mm for the oral reference group. There was a significant reduction in paw thickness compared with the reference group in the case of TP5 and oral nanoparticles. **Conclusion:** Further skin permeation, pharmacokinetic, stability and safety studies of TP5 were warranted due to its promising formulation properties and initial in-vivo activity.

KEYWORDS: Fenoprofen calcium; nanoparticles; transdermal patch; drug diffusion; dermal irritation; anti-inflammatory activity.

1. INTRODUCTION

Fenoprofen calcium belongs to a group of medications called non-steroidal anti-inflammatory drugs (NSAIDs) which are used to treat pain and inflammation. Its therapeutic activity relates to the inhibition of the activity of the enzymes involved in the synthesis of prostaglandins, helping to modulate inflammatory responses.[1] Although it is therapeutically beneficial, the traditional method of drug administration can give rise to adverse effects and drug delivery problems at systemic levels. Hence, the development of alternative delivery systems which can deliver controlled drug release is an area of important pharmaceutical formulation research.[2]

The other option is transdermal drug delivery that involves delivering a drug via the skin. This can lead to sustained release of a drug or decrease the frequency of drug administration.[3] The Stratum Corneum, however, is a significant obstacle to the permeation of drugs. Thus, a transdermal formulation must rely on several factors such as drug properties, polymeric matrix formulation, mechanical properties of the patch, and the drug-release behavior.[4]

Transdermal patches using nanoparticles as a formulation method is a combination of the benefits of polymeric nanoparticles and the benefits of a patch delivery system. This is accomplished by embedding drug loaded nanoparticles within a film-forming polymer matrix. The nanoparticles act as drug carriers, the patch offers an appropriate structure to apply to skin.[5] The choice and ratio of film-forming polymers may affect flexibility, strength, moisture properties, drug content and in-vitro drug diffusion of the patches. Therefore, the development and evaluation of a formulation system is required to find a patch that has appropriate pharmaceutical and mechanical properties.[6]

In the present study, fenoprofen calcium loaded Eudragit RL100 nanoparticles were formulated in matrix type transdermal patches using the solvent-casting method, which is a well-known method in the formulation field. Six formulations (TP1-TP6) were prepared by altering the ratio of hydroxypropyl methylcellulose (HPMC), Eudragit RLPO, Eudragit RSPO and ethyl cellulose with the same quantity of the total polymer. The prepared patches were subjected to evaluation of their thickness, moisture content, water vapour transmission rate, folding endurance, tensile strength, percentage elongation, drug content and in-vitro drug diffusion.[7]

The optimized formulation was then evaluated for stability, dermal irritation and in-vivo anti-inflammatory activity in the carrageenan induced paw oedema model in Wistar albino rats. The present work was done to select an appropriate transdermal patch that could be based on nanoparticles and evaluate the formulation properties and the preliminary performance of the selected patch.

2. MATERIALS AND METHODS

2.1 Materials

The transdermal patches were prepared by using fenoprofen calcium loaded polymeric nanoparticles (PNPs) with a polymeric carrier (Eudragit RL100) and stabilizer (polyvinyl alcohol (PVA)) Patch formulation was prepared using hydroxypropyl methylcellulose (HPMC), Eudragit RLPO, Eudragit RSPO, ethyl cellulose, polyethylene glycol 6000 (PEG 6000), methanol and chloroform.

2.2 Preparation of Nanoparticle-Based Transdermal Patches

The solvent-casting technique was used to make six formulations (TP1–TP6). Both formulations consisted of optimized fenoprofen calcium-loaded nanoparticles of 100 mg of fenoprofen calcium per formulation.[8] The content of the

polymer was kept constant at 500 mg and amounts of the film-forming polymers were changed. Plasticizer of PEG 6000 was added at 0.5 wt/wt and 10 mL of methanol–chloroform solvent system was used for casting.[9]

Weighing the required amounts of polymers, a homogeneous polymeric solution was prepared by dissolving the polymers in the solvent system under continuous stirring. PEG 6000 was added and well mixed. Optimized nanoparticles were then dispersed in the polymeric solution and mixed carefully to ensure uniform distribution of the nanoparticles in the polymeric solution.[10]

The resultant dispersion was applied to a clean flat casting surface, and left to dry at room temperature for 24 hours. The actual dried film was delicately removed, examined for homogeneity and defects and cut into patches of appropriate size. The ready patches were put in protective packaging for further evaluation.[11]

2.3 Formulation Composition

The composition of the six transdermal patch formulations is presented in Table 1.

Table 1: Composition of fenoprofen calcium-loaded transdermal patch formulations.

Formulation	HPMC (mg)	Eudragit RLPO (mg)	Eudragit RSPO (mg)	Ethyl cellulose (mg)
TP1	400	100	—	—
TP2	300	150	—	50
TP3	200	200	—	100
TP4	400	—	100	—
TP5	300	—	150	50
TP6	200	—	200	100

Each formulation contained optimized nanoparticles equivalent to 100 mg fenoprofen calcium, 500 mg total polymer, PEG 6000 at 0.5% w/w, and 10 mL methanol–chloroform solvent system.

2.4 Physical and Mechanical Evaluation

2.4.1 Thickness and Weight Variation

A digital Vernier caliper was used for measuring the thickness of the patches at various points and the average was determined. The weights of individual patches were measured on an analytical balance to evaluate the weight variation and uniformity of the prepared formulations.[12]

2.4.2 Folding Endurance

Endurance of folding was determined by folding each patch at the same point over and over until a crack or break was observed. The number of times a fold to cause damage was noted as an indicator of the flexibility and mechanical resistance of the patch.[13]

2.4.3 Tensile Strength and Percentage Elongation

Tensile strength was assessed by stretching a patch specimen until breakage and recording the maximum force required. It was calculated by dividing the breaking force by the cross-sectional area of the specimen. Percentage elongation was determined from the change in length at break relative to the initial length.[14]

2.4.4 Drug Content

Drug content was estimated to determine the amount of fenoprofen calcium in the prepared patches. The results were presented as percentages and drug incorporation within the formulations was compared. The analytical method should be the same as the validated one described in the original experimental protocol.[15]

2.4.5 Moisture Content

The pre-weighed patch was set in a desiccator with activated silica at room temperature for 24 hours and reweighed. The percentage moisture content was determined by the weight loss.[16]

Moisture content (%) = Initial weight- Final weight × 100 / Initial weight

2.4.6 Water Vapour Transmission Rate

The water vapour transmission rate (WVTR) was measured by sealing a patch specimen over a container filled with a hygroscopic material, and measuring the increase in weight at regular intervals in a controlled environment.[17]

WVTR = Weight gain × 100 / Exposed area

The results were expressed as g/m²/24 h.

2.5 In-Vitro Drug Diffusion Study

The in-vitro drug diffusion study was conducted to compare the fenoprofen calcium diffusion from formulation TP1–TP6 for 24 hours. The patch specimen of known area was inserted into the diffusion assembly with samples removed from the diffusion medium at regular time intervals. The amount of fenoprofen calcium was determined by the analytical procedure outlined in the experimental procedure. The values of cumulative drug diffusion were calculated and plotted against time. The obtained profiles were then compared to optimize the patch.[18]

2.6 Selection of the Optimized Formulation

Their physical, mechanical, pharmaceutical and in-vitro drug diffusion properties were compared between the 6 formulations. The formulation TP5 was chosen to be investigated further as showing a favourable overall balance of folding endurance, tensile strength, percentage elongation, drug content, moisture content, water vapour transmission rate and drug diffusion.[19]

2.7 Stability Study

The optimized formulation TP5 was put to accelerated stability test for six months at 40 ± 2°C and 75 ± 5%RH. Samples were evaluated at initial stage and after three and six months. Various physical characteristics, thickness, drug content, folding endurance and other selected formulation parameters were compared to evaluate the change during storage.[20]

2.8 Dermal Irritation Study

The dermal irritation study was carried out in healthy male Wistar albino rats as approved by the Institutional Animal Ethics Committee (IAEC approval number: CCSEA/IAEC/JLS/24/11/25/043). Each of the four groups had 6 animals, and the control was untreated, blank transdermal patch was blank, positive irritation control was patch with a product that irritates the skin, and optimized TP5 was patch with optimized formulation.

The area of skin to be treated dorsally or ventrally was shaved around 24 hours prior to treatment and was examined for obvious damage. The planned treatments were performed as per the approved protocol. After treatment, erythema and

oedema of the skin was assessed by a Draize-type visual grading system. Recorded scores were used to calculate the primary irritation index (PII) that provides an estimate of the observed dermal irritation potential.[21]

2.9 In-Vivo Anti-Inflammatory Study

The anti-inflammatory activity of TP5 was tested in carrageenan induced paw oedema model in healthy male Wistar albino rats. Twenty-four animals with an average weight of 200-250 g were split into 4 groups of 6 animals, each being administered a different treatment: normal control, oral fenoprofen calcium reference formulation, optimized fenoprofen calcium loaded nanoparticles, and optimized TP5 patch.[22]

Oral reference formulation and optimized nanoparticles were given at a 45mg/kg fenoprofen calcium equivalent dose. TP5 patch was applied once at 1-hour prior to inflammation induction in the study design (nominal dose equivalent: 45 mg/kg).[23]

Acute inflammation was induced by injecting 0.1 mL of 1% suspension of carrageenan sub-plantar. The thickness of the paw was measured prior to induction and at 2, 6, 12 and 24 hours post induction. The time-dependent anti-inflammatory response was assessed for changes in paw thickness between groups.[24]

2.10 Statistical Analysis

The ordinal scores for erythema and oedema were compared between the groups in the dermal irritation study using the Kruskal–Wallis test and pairwise Mann–Whitney U tests with Holm correction. For other experimental data, statistical procedures set for the studies have been used. Where appropriate, results were given as mean ± SD and statistical significance was determined using the criteria utilized in the original analysis.[25]

3. RESULTS

3.1. Physical and Mechanical Evaluation of Transdermal Patches

The six formulations of the 6 fenoprofen calcium loaded patches (TP1-TP6) were assessed for thickness, weight difference, folding endurance, tensile strength, % elongation, drug content, moisture content and water vapour transmission rate (WVTR). The data obtained from the experiment is given in tabular form in Table 1.

Table 1: Physical and mechanical evaluation of transdermal patch formulations.

Parameter	TP1	TP2	TP3	TP4	TP5	TP6
Thickness (mm)	0.21 ± 0.008	0.22 ± 0.012	0.24 ± 0.009	0.23 ± 0.014	0.22 ± 0.011	0.25 ± 0.017
Weight (mg)	185 ± 2.7	190 ± 3.4	198 ± 2.9	193 ± 3.8	188 ± 2.5	201 ± 3.2
Folding endurance (folds)	180 ± 5.1	195 ± 3.8	210 ± 6.2	225 ± 4.6	245 ± 5.7	235 ± 4.3
Tensile strength (kg/cm²)	0.58 ± 0.025	0.64 ± 0.018	0.69 ± 0.032	0.74 ± 0.026	0.86 ± 0.019	0.82 ± 0.028
Elongation (%)	30.5 ± 1.4	32.4 ± 0.9	34.2 ± 1.6	35.6 ± 1.1	38.2 ± 1.3	36.5 ± 0.8
Drug content (%)	92.4 ± 1.1	93.8 ± 1.5	95.1 ± 0.7	96.2 ± 1.3	98.2 ± 0.6	97.4 ± 1.0
Moisture content (%)	5.2 ± 0.26	4.9 ± 0.18	4.7 ± 0.31	4.5 ± 0.23	3.9 ± 0.15	4.2 ± 0.27
WVTR (g/m²/24 h)	5.0 ± 0.17	4.8 ± 0.24	4.6 ± 0.13	4.4 ± 0.29	4.1 ± 0.21	4.3 ± 0.16

Values are expressed as mean ± SD (n = 3). WVTR: water vapour transmission rate.

The thickness varied from 0.21 to 0.25 mm; the weight measured varied from 185 to 201 mg. TP5 showed the highest folding endurance (245 ± 5.7 folds), tensile strength (0.86 ± 0.019 kg/cm²), percentage elongation (38.2 ± 1.3%) and drug content (98.2 ± 0.6%). It also showed the lowest moisture content (3.9 ± 0.15%) and WVTR (4.1 ± 0.21 g/m²/24 h).

3.2. In-Vitro Drug Diffusion

All six formulations were tested for cumulative drug diffusion after 24 hours. The following is a summary of the results in Table 2.

Table 2: In-vitro cumulative drug diffusion from transdermal patch formulations.

Time (h)	TP1 (%)	TP2 (%)	TP3 (%)	TP4 (%)	TP5 (%)	TP6 (%)
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	10.5 ± 0.42	12.2 ± 0.31	13.8 ± 0.57	14.6 ± 0.26	15.2 ± 0.48	14.8 ± 0.36
2	20.8 ± 0.63	23.5 ± 0.45	26.1 ± 0.72	28.2 ± 0.39	29.5 ± 0.58	28.8 ± 0.81
4	35.6 ± 0.84	39.8 ± 0.52	43.2 ± 0.91	46.5 ± 0.67	48.2 ± 0.43	47.4 ± 0.76
6	49.2 ± 0.71	53.8 ± 0.93	57.5 ± 0.64	61.4 ± 0.82	63.5 ± 0.55	62.2 ± 0.97
8	61.4 ± 0.96	65.2 ± 0.61	69.8 ± 0.83	73.1 ± 0.49	75.6 ± 0.74	74.2 ± 0.58
12	75.6 ± 0.53	79.1 ± 0.88	83.4 ± 0.69	86.2 ± 0.94	89.1 ± 0.62	87.5 ± 0.79
24	88.2 ± 0.87	91.5 ± 0.54	94.1 ± 0.76	95.2 ± 0.63	97.1 ± 0.92	96.3 ± 0.47

Values are expressed as mean ± SD (n = 3).

Time was found to increase cumulative drug diffusion in all the formulations. At 24 hours, TP5 showed the highest reported diffusion (97.1 ± 0.92%), followed by TP6 (96.3 ± 0.47%), TP4 (95.2 ± 0.63%), TP3 (94.1 ± 0.76%), TP2 (91.5 ± 0.54%) and TP1 (88.2 ± 0.87%).

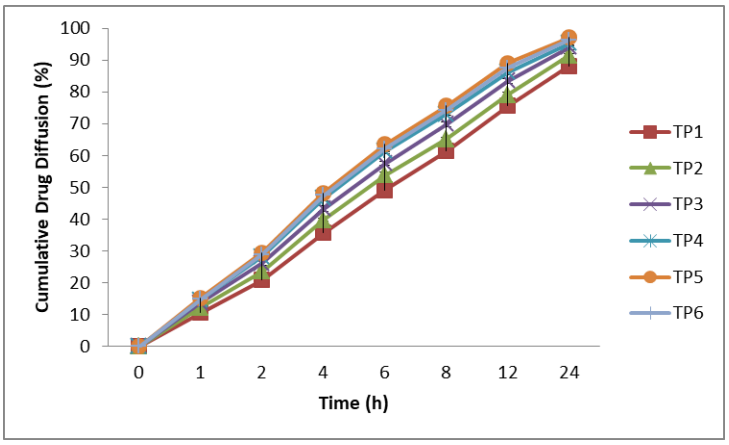


Figure 1: In-vitro cumulative drug diffusion profiles of TP1–TP6 over 24 hours. Plot time (h) on the x-axis and cumulative drug diffusion (%) on the y-axis. Show each formulation as a separate line with SD error bars.

3.3. Accelerated Stability of the Optimized TP5 Patch

The patch for TP5 was optimized and tested at accelerated conditions of 40 ± 2°C and 75 ± 5% relative humidity. The observations recorded are given in Table 3.

Table 3: Accelerated stability evaluation of the optimized TP5 patch.

Parameter	Initial	3 months	6 months
Appearance	Smooth and uniform	No visible change	No visible change
Thickness (mm)	0.22 ± 0.01	0.22 ± 0.02	0.23 ± 0.01
Drug content (%)	98.2 ± 0.8	97.1 ± 0.9	95.8 ± 1.1
Folding endurance (folds)	245 ± 4.6	238 ± 5.3	230 ± 4.7

Storage conditions: 40 ± 2°C/75 ± 5% relative humidity. Values are reproduced from the thesis results.

Changes in appearance were not observed for the 6-month study period. Drug content decreased from 98.2 ± 0.8% initially to 95.8 ± 1.1% at six months. Folding endurance decreased from 245 ± 4.6 to 230 ± 4.7 folds, while thickness changed from 0.22 ± 0.01 to 0.23 ± 0.01 mm.

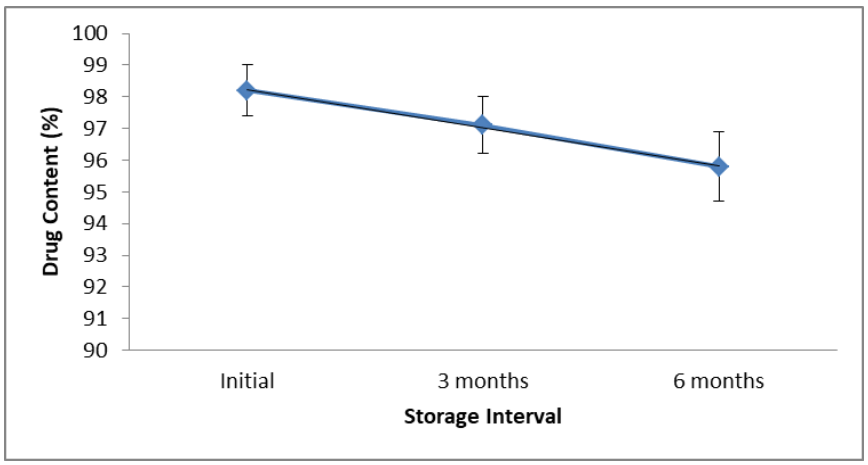
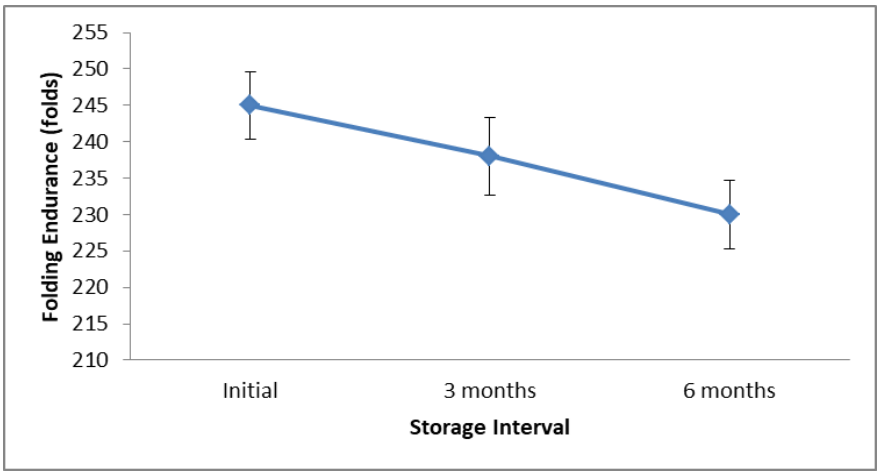


Figure 2: Change in drug content of TP5 during accelerated stability testing at the initial, 3-month and 6-month intervals.



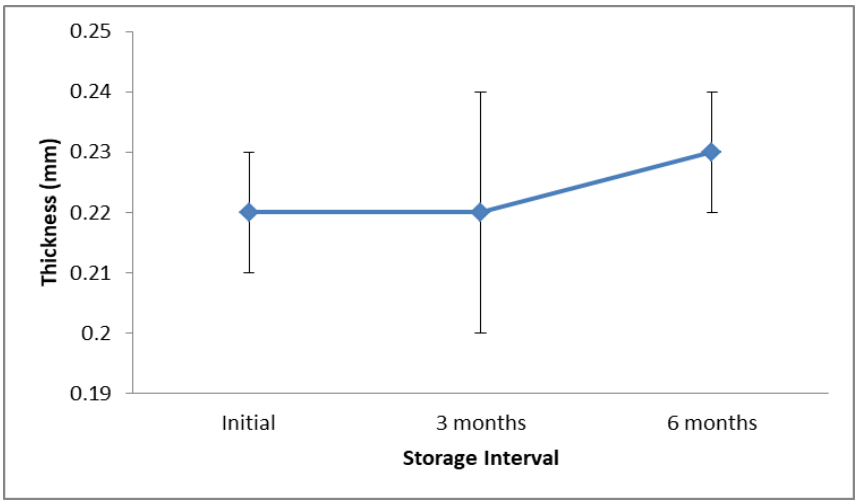


Figure 3: Changes in folding endurance and thickness of TP5 during accelerated stability testing. Use separate panels because the parameters have different units.

3.4. Dermal Irritation Study

The dermal irritation response was assessed in the normal-control, blank-patch, positive-control and optimized TP5 groups. The reported primary irritation index (PII) values are shown in Table 4.

Table 4: Primary irritation index of the experimental groups.

Group	PII
Normal control	0.00
Blank patch	0.33
Positive control (0.8% v/v aqueous formalin)	4.83
Optimized TP5 patch	0.17

The overall Kruskal–Wallis test showed a significant difference among the groups (H = 17.938, df = 3, p = 0.00045). Pairwise Mann–Whitney U tests with Holm adjustment revealed that the positive control group differed significantly from the normal control and blank patch groups as well as the TP5 group (adjusted p = 0.0151, 0.0168 and 0.0168, respectively). There was no significant difference between the normal-control, blank-patch and TP5 groups (adjusted p > 0.05).

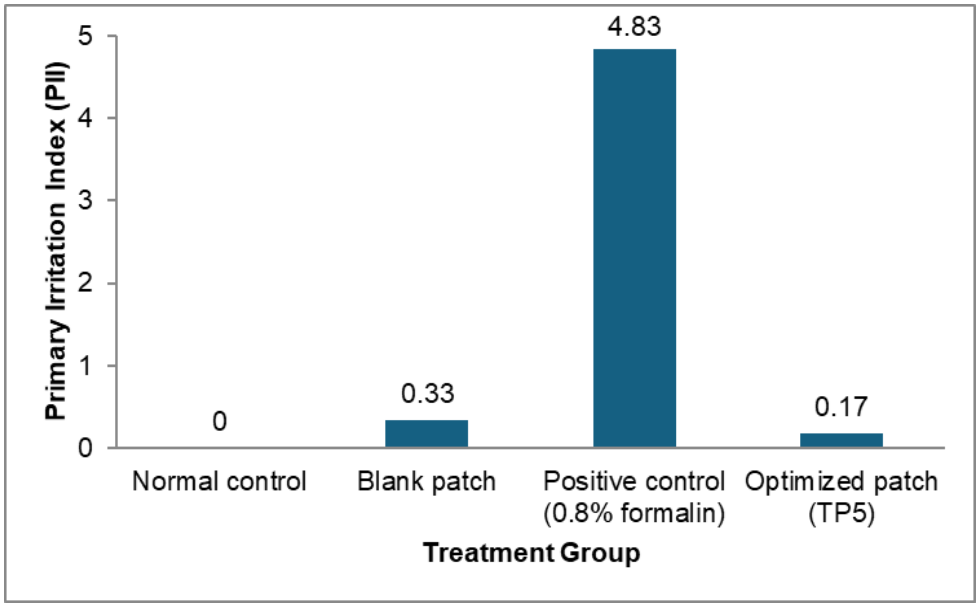


Figure 4: Primary irritation index in the normal-control, blank-patch, positive-control and TP5 groups.

3.5. In-Vivo Anti-Inflammatory Activity.

Anti-inflammatory effect of the optimized TP5 patch was assessed by carrageenan-induced paw edema in rats. The four experimental groups comprised a normal control, oral fenoprofen calcium reference formulation, oral optimized nanoparticles and the TP5 transdermal patch. Paw thickness was determined prior to induction and at 2, 6, 12 and 24 hours following induction. The group summaries are shown in Table 5.

Table 5: Paw thickness across experimental groups during the carrageenan-induced paw-edema study.

Group	0 h (mm)	2 h (mm)	6 h (mm)	12 h (mm)	24 h (mm)
Normal control	5.83 ± 0.03	5.85 ± 0.02	5.84 ± 0.03	5.84 ± 0.02	5.82 ± 0.03
Oral reference formulation	5.82 ± 0.03	6.15 ± 0.04	6.03 ± 0.04	5.92 ± 0.03	5.86 ± 0.03
Optimized nanoparticles (oral)	5.82 ± 0.03	6.19 ± 0.04	5.94 ± 0.04	5.82 ± 0.04	5.76 ± 0.04
TP5 patch (transdermal)	5.83 ± 0.03	6.27 ± 0.05	5.98 ± 0.05	5.82 ± 0.04	5.72 ± 0.05

Values are expressed as mean ± SD (n = 6 animals per group).

There was no significant difference among the groups for baseline paw thickness (F = 0.236, p = 0.870). After administration of carrageenan, paw thickness was found to be increased in the treated groups. The mean thickness of paws was greatest in TP5 (6.27 ± 0.05 mm) at 2 h. The mean paw thickness was lowest in the TP5 group (5.72 ± 0.05 mm) and highest in the oral reference group (5.86 ± 0.03 mm), with the nanoparticle group being in between (5.76 ± 0.04 mm) in 24 hours.

Table 6: One-way ANOVA for paw thickness at different time points.

Time point	df	F-value	p-value	Overall comparison
Baseline (0 h)	3, 20	0.236	0.870	Not significant
2 h	3, 20	122.586	<0.001	Significant
6 h	3, 20	26.751	<0.001	Significant
12 h	3, 20	13.820	<0.001	Significant
24 h	3, 20	17.667	<0.001	Significant

Statistical method: one-way ANOVA at each time point, followed by Tukey's HSD post-hoc test, as reported in the thesis.

The reported post-hoc comparisons showed the following:

- **At 2 h:** The oral reference group (p < 0.001) and nanoparticle group (p = 0.011) had significantly less paw thickness than TP5. The difference between the two groups reference and the group nanoparticle was not significant (p = 0.456).
- **At 6 h:** The paw thickness in the nanoparticle group was significantly lower than that in the oral reference group (p = 0.003). Neither the difference between TP5 and reference group (p = 0.112) nor the difference between TP5 and nanoparticles (p = 0.342) was significant.
- **At 12 h:** Both the nanoparticle and TP5 groups had significantly lower paw thickness than the oral reference group (p < 0.001). No significant difference was found between the nanoparticle group and TP5 group (p = 0.998).
- **At 24 h:** The paw thickness of both the nanoparticle and TP5 groups were significantly lower than the oral reference group (p < 0.001). No significant difference was found when comparing the difference between TP5 and the nanoparticle group (p = 0.198).

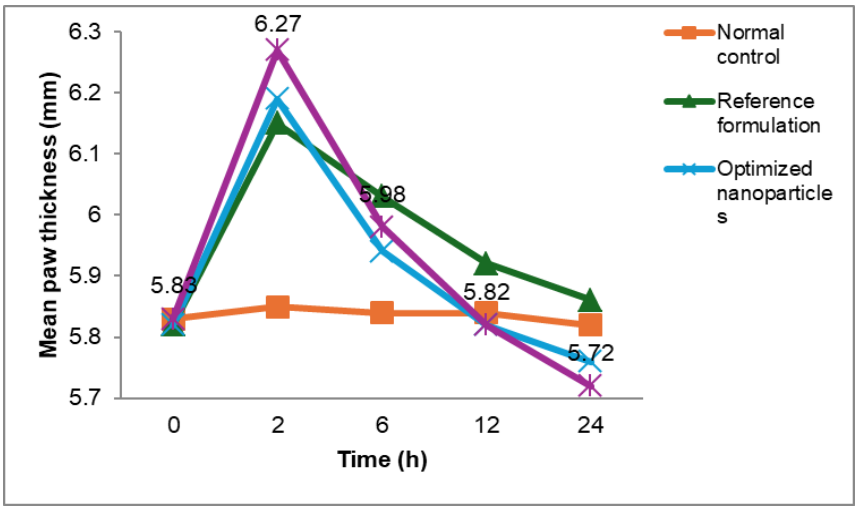


Figure 5: Time-dependent change in mean paw thickness across the normal-control, oral reference, oral nanoparticle and TP5 transdermal groups. Plot time (h) against mean paw thickness (mm) and include SD error bars.

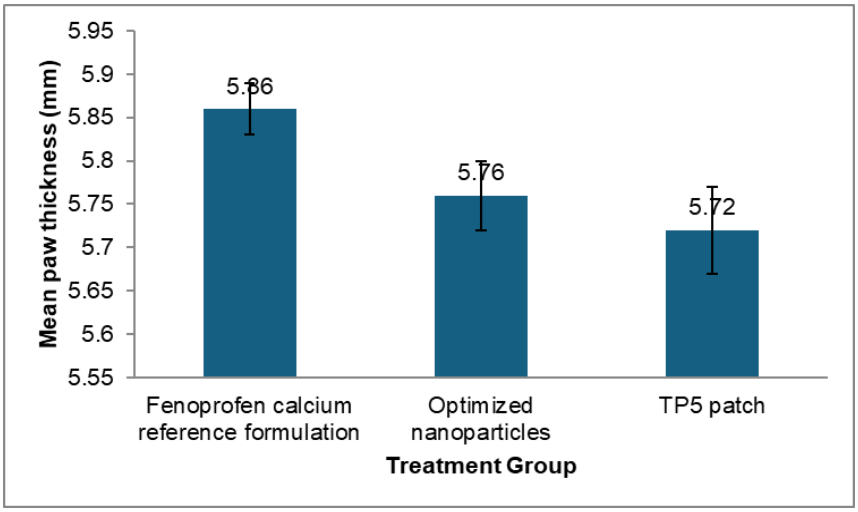


Figure 6: Comparative mean paw thickness at 24 hours for the oral reference formulation, optimized nanoparticles and TP5 patch.

4. DISCUSSION

The physical and mechanical evaluation showed that one of the six patches was a promising formulation, TP5. The tensile strength and elongation were also reported as higher than that of the other materials, indicating that the folding endurance of the material might be greater than other materials under the mechanical stress. The high drug content along with the lower moisture level and WVTR further supported its selection for further investigation.

These results are not the result of the effect of one polymer alone but rather the combined effect of the formulation composition. As several proportions of polymer were used in different formulations, the observed changes cannot be solely attributed to HPMC, Eudragit RSPO and Eudragit RLPO or ethyl cellulose.

Cumulative drug diffusion was found to increase with the test duration for all drug formulations. TP5 recorded the highest final diffusion value with TP6 showing slightly lower value. This pattern backs up the choice of TP5 based on the results of diffusion and physical-evaluation.

The difference could be because of the combination of polymers, and the structure of the matrix containing the nanoparticles. The cumulative diffusion value, however, does not allow for the exact determination of the release mechanism. Before assigning a specific release model, kinetic modelling and goodness-of-fit analysis would need to be carried out further. The in-vitro diffusion should not be used as direct evidence of permeation in vivo through living skin or bioavailability to the systemic circulation.

Accelerated storage showed a smooth and uniform appearance of TP5. The drug content and folding endurance decreased and thickness increased respectively, but decreased in a gradual manner. These results indicate that the formulation maintained its overall physical properties throughout the six-month period, but that the incorporated changes in the measured properties suggest that further studies of both chemical and mechanical properties are warranted.

The results provide no independent indication of shelf life. A formal shelf-life claim would necessitate predefined acceptance criteria, an appropriate stability-indicating analytical method along with supporting long-term stability data.

The PII of TP5 was 0.17 while the blank patch was 0.33 and the positive control was 4.83. Based on the statistical analysis, the positive control group was found to be significantly different from the normal-control, blank-patch and TP5 groups, but no significant difference was observed between the blank-patch and TP5 groups.

This pattern helps to achieve low visible irritation response for the TP5 under the conditions tested. However, the irritation assessment made in the study does not indicate the absence of sensitization, delayed reactions or other skin toxicity reactions from the material(s). Thus, the results must only be used in the context of the experimental protocol.
The paw-edema results exhibited a time dependent response among the treatment groups. The mean paw thickness for TP5 was the greatest at 2 hrs and the post-hoc analysis showed significantly more swelling than the oral reference and the nanoparticle groups at 2 hrs. This suggests that the transdermal preparation was not most effective in the initial model response.

At 12 hours, there was no significant difference among the mean paw thickness of the TP5 and nanoparticle groups, which were both smaller than the oral reference group. TP5 had the thinnest mean numerical paw thickness at 24 hours, which was nearly equal to that of the nanoparticles group. The difference between the optimized delivery systems and the oral group was statistically significant, while the difference between the two optimized delivery systems was not.

The higher early paw thickness may be comparable to the time required for drug release and permeation through the skin in the case of TP5. No measurements of drug concentrations or pharmacokinetic parameters were made in this experiment, however, a transdermal lag time may account for the observations or may be directly demonstrated as a mechanism.

The results indicate that TP5 could be a suitable vehicle for transdermal delivery of fenoprofen calcium and warrants additional study. They have no clinical superiority and the animal findings should not be directly translated to human beings.

5. CONCLUSION

The present research was directed toward the development, evaluation and in-vivo testing of fenoprofen calcium loaded nanoparticle based transdermal patch. Six formulations (TP1 to TP6) were made with different combinations of HPMC, Eudragit RLPO, Eudragit RSPO, and ethyl cellulose, and assessed for their physical, mechanical, pharmaceutical and in-vitro drug diffusion properties. The overall performance of the tested formulations is best for TP5 which shows the following results: folding endurance of 245 ± 5.7 folds, tensile strength of 0.86 ± 0.019 kg/cm², percentage elongation of 38.2 ± 1.3%, drug content of 98.2 ± 0.6% and cumulative drug diffusion of 97.1 ± 0.92% at 24 hours. It also had the least amount of moisture and water vapour transmission rate of the formulations tested.

Accelerated stability testing performed at 40 ± 2°C, 75 ± 5%RH revealed that TP5 remained smooth and uniform for 6 months. The slow down in the drug content and folding endurance was seen, and the thickness showed a slight change. The dermal irritation study showed a primary irritation index of 0.17 for TP5, which indicates a low degree of irritation under experimental conditions. The thickness of the paw in the TP5 group was reduced during the later period of the observation period in the carrageenan induced paw oedema model. The mean paw thickness of the TP5 group was the lowest at 24 h (5.72 ± 0.05 mm) as compared to 5.76 ± 0.04 mm for the oral nanoparticle group and 5.86 ± 0.03 mm for

the oral reference formulation. The difference between TP5 and the optimized nanoparticle group was not statistically significant, but both groups differed significantly from the oral group.

In summary, the results highlight the potential of TP5 as a formulation for the further study of transdermal delivery of fenoprofen calcium using nanoparticles. These results, however, are preliminary and do not mean there is clinical superiority, systemic bioavailability or a definite shelf life. Additional studies of skin permeation, pharmacokinetic evaluation, longer-term stability testing, and skin safety testing will be needed before its potential for therapeutic use can be determined.

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Conflict of Interest

Nil

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