Research Paper

FORMULATION, DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF TOLMETIN AND TIZANIDINE LOADED TRANSDERMAL PATCHES FOR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

The present study was undertaken to formulate and evaluate Tolmetin and Tizanidine loaded transdermal patches for anti-inflammatory activity. Tolmetin is a non-steroidal anti-inflammatory drug possessing analgesic and anti-inflammatory properties, while Tizanidine is a centrally acting muscle relaxant used for the management of painful musculoskeletal conditions. The combination of both drugs in a transdermal patch may provide sustained drug release, improved patient compliance, reduced dosing frequency, and avoidance of first-pass metabolism.

Matrix-type transdermal patches were prepared by the solvent casting method using different ratios of polymers such as HPMC, ethyl cellulose, Eudragit, PVP, and plasticizer. Nine formulations were developed and coded as F1–F9. The prepared patches were evaluated for physicochemical parameters such as physical appearance, thickness, weight variation, folding endurance, moisture content, moisture uptake, surface pH, drug content, tensile strength, flatness, in vitro drug release, ex vivo permeation, skin irritation study, and stability studies.

Tizanidine is a centrally acting muscle relaxant that relieves muscle spasms by acting on alpha 2 receptors in the spinal cord. Their combination was expected to provide synergistic anti inflammatory and muscle relaxant effects. Transdermal patches were prepared by solvent casting method using different ratios of polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) with dibutyl phthalate as plasticizer. Nine formulations (F1–F9) were developed and evaluated for physicochemical parameters such as thickness, weight uniformity, drug content, folding endurance, moisture content, moisture uptake, in vitro drug release, ex vivo permeation, and stability.

All formulations showed satisfactory appearance, uniform thickness, and good flexibility. Drug content ranged from 93.45% to 98.92%. In vitro drug release studies demonstrated sustained release up to 24 h, with formulation F5 showing maximum cumulative drug release (96.78% for Tolmetin and 95.42% for Tizanidine). Anti inflammatory activity evaluated by protein denaturation assay showed significant inhibition, with formulation F5 exhibiting 71.23% inhibition comparable to Diclofenac gel (73.89%). In vivo carrageenan induced paw edema studies in Albino Wistar rats also confirmed significant anti inflammatory activity. The developed Tolmetin and Tizanidine loaded transdermal patch may serve as a safe and effective combination therapy for inflammatory conditions with muscle spasm.

Keywords: Tolmetin, Tizanidine, Transdermal patch, Anti-inflammatory activity, Solvent casting method, Matrix patch, Sustained release, HPMC, Ethyl cellulose, Eudragit, Carrageenan induced paw edema.

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Introduction

inflammation is a protective biological response of the body triggered by injury, infection, or exposure to harmful stimuli. While it is essential for tissue repair and defence against pathogens, prolonged or excessive inflammation may contribute to the onset and progression of various musculoskeletal and systemic disorders. Common inflammatory conditions such as rheumatoid arthritis, osteoarthritis, myositis, and fibromyalgia are characterized by symptoms including pain, swelling, stiffness, redness, and loss of function. These conditions not only cause physical discomfort but also adversely affect emotional health, self-esteem, and overall quality of life. Consequently, there is an increasing demand for effective, safe, and patient-friendly anti-inflammatory treatments capable of providing sustained therapeutic benefits with minimal side effects [1,2].

Conventional anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants are widely used in the management of inflammatory disorders because of their potent therapeutic efficacy. However, long-term and repeated oral administration of these medications is often associated with various adverse effects, including gastric irritation,

ulceration, hepatotoxicity, renal dysfunction, and central nervous system disturbances. Tolmetin, an NSAID, is effective against inflammation but may cause gastrointestinal side effects. *Tizanidine*, a centrally acting α2-adrenergic agonist, is used for muscle spasticity but can cause drowsiness, hypotension, and dry mouth. These limitations have encouraged the search for safer and more effective alternative delivery systems that can provide adequate anti-inflammatory action with improved tolerability and a lower incidence of side effects [2,3]

Tolmetin is a non-steroidal anti-inflammatory drug that works by blocking the action of cyclooxygenase (COX) enzymes, which are responsible for producing prostaglandins. Prostaglandins are chemical messengers that cause pain, swelling, and fever. By reducing their production, Tolmetin effectively lowers inflammation and provides relief in conditions like rheumatoid arthritis and osteoarthritis. Tolmetin is rapidly absorbed from the stomach and reaches its peak level in the blood within 30 to 60 minutes. It is highly bound to plasma proteins (more than 99%) and is mainly eliminated through the kidneys. Common side effects include stomach upset, nausea, and sometimes headaches. Because of its short half-life, it is usually taken three times a day.

Tizanidine is a central muscle relaxant. It works by activating alpha-2 adrenergic receptors in the spinal cord and brain. This activation reduces the release of excitatory amino acids, which in turn decreases muscle tone and relaxes spasms. *Tizanidine* is often prescribed for muscle spasticity caused by multiple sclerosis, spinal cord injury, or other neurological conditions. It is quickly absorbed after oral intake, with peak effect occurring within 1 to 2 hours. The drug has a short half-life of about 2.5 hours, which means its effect wears off quickly. Common side effects include drowsiness, dry mouth, dizziness, and mild low blood pressure. Because of its short duration, it is usually given every 6 to 8 hours as needed.

The combination of Tolmetin and *Tizanidine* in a single transdermal patch offers a smart approach. Tolmetin reduces inflammation and pain, while *Tizanidine* relaxes the associated muscle spasms. When given through the skin via a patch, both drugs bypass the stomach and liver, reducing side effects and providing steady relief for 24 hours. This makes the combination very useful for patients with chronic inflammatory conditions like arthritis with muscle stiffness [4,5].

At the cellular and molecular level, inflammation is controlled by complex biochemical pathways involving several inflammatory mediators. These mediators include pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, as well as enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), and transcription factors such as nuclear factor-kappa B (NF-KB). Persistent activation of these mediators may lead to chronic inflammation, resulting in tissue damage and progression of various diseases. Therefore, current anti-inflammatory research is mainly directed toward inhibiting or regulating these molecular targets to provide safe, effective, and sustained therapeutic benefits [6,7].

In recent years, transdermal drug delivery systems have attracted significant interest as promising alternatives to oral and parenteral routes because they bypass first-pass metabolism, maintain steady plasma drug concentrations, reduce systemic side effects, and improve patient compliance. Transdermal patches are especially suitable for chronic inflammatory conditions requiring prolonged therapy [8,9].

A transdermal patch is an advanced topical drug delivery system that delivers a predetermined amount of drug through the skin into the systemic circulation. The formulation typically consists of drug, polymer matrix, plasticizer, permeation enhancer, and adhesive layer that collectively contribute to its stability, flexibility, and enhanced drug delivery performance. In transdermal patches, the polymer matrix serves as a reservoir for solubilizing and controlling the release of the drug through the skin, thereby improving therapeutic efficacy [10,11].

Conventional topical dosage forms such as ointments, creams, and gels are associated with several disadvantages. Many of these formulations produce a greasy feeling on the skin, cause inconvenience during application, and exhibit poor drug permeation. To address these limitations, transdermal patches have emerged as a preferred option in pharmaceutical fields due to their non-greasy texture, ease of application, improved patient compliance, and sustained release characteristics [12,13].

The combination of Tolmetin and *Tizanidine* in a transdermal patch offers a rational approach for treating inflammatory conditions associated with muscle spasm. Tolmetin inhibits COX enzymes and reduces prostaglandin synthesis, while *Tizanidine* reduces muscle tone by presynaptic inhibition of motor neurons. Their synergistic action may provide enhanced anti-inflammatory and muscle relaxant effects with reduced individual drug doses and side effects [14,15].

Materials and Methods

Materials

Tolmetin and *Tizanidin*e were obtained samples from a pharmaceutical company. Hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC),

dibutyl phthalate, and other chemicals were purchased from commercial sources. Healthy adult Albino Wistar rats of either sex, weighing between 150-200 g, were used for the experimental study. The animals were obtained from a registered animal house facility and maintained under standard laboratory conditions, including a temperature of $25 \pm 2^{\circ}C$, relative humidity of $55 \pm 5\%$, and a 12 h light/dark cycle throughout the study period.
All experimental procedures were performed according to institutional ethical guidelines and approval obtained from the Institutional Animal Ethics Committee (IAEC) constituted under CPCSEA regulations.

Method of Preparation of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Tolmetin and *Tizanidine* loaded transdermal patches were prepared by the solvent casting method. Accurately weighed quantities of polymers were dissolved in a suitable solvent system with continuous stirring to obtain a clear polymeric solution. Tolmetin and *Tizanidine* were separately dissolved or dispersed in the solvent mixture and then added slowly to the polymeric solution under continuous stirring.
The required amounts of HPMC and ethyl cellulose (in different ratios) were dissolved in a solvent mixture of methanol and dichloromethane (1:1) under continuous stirring. Dibutyl phthalate (10% w/w of polymer) was added as a plasticizer. Tolmetin (5% w/w) and *Tizanidine* (2% w/w) were dissolved separately and mixed with the polymer solution. The mixture was stirred for 30 min to ensure uniformity. The solution was then poured into a glass Petri dish of known area and dried at room temperature for 24 h. The dried patches were carefully removed, cut into uniform size (2 cm × 2 cm), and stored in a desiccator for further evaluation [16,17]
After complete drying, the prepared patches were carefully removed from the casting surface and examined visually for physical appearance, flexibility, and uniformity. The patches were cut into suitable size and stored in desiccators for further evaluation studies.

Table 1: Composition of *Tolmetin* and *Tizanidine* Loaded Transdermal Patch Formulations F1–F9

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	*Tolmetin*	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
2	*Tizanidine*	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
3	HPMC	300 mg	350 mg	400 mg	300 mg	350 mg	400 mg	300 mg	350 mg	400 mg
4	Ethyl Cellulose	100 mg	100 mg	100 mg	150 mg	150 mg	150 mg	200 mg	200 mg	200 mg
5	Eudragit	50 mg	75 mg	100 mg	50 mg	75 mg	100 mg	50 mg	75 mg	100 mg
6	PVP	50 mg	50 mg	50 mg	75 mg	75 mg	75 mg	100 mg	100 mg	100 mg
7	PEG 400	30% w/w of polymer	30 %	30 %	30 %	30 %	30 %	30 %	30 %	30 %
8	Propylene glycol	10% w/w	10 %	10 %	10 %	10 %	10 %	10 %	10 %	10 %
9	Solvent system	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation Parameters of Transdermal Patches

The prepared Tolmetin and *Tizanidine* loaded transdermal patches were evaluated for various physicochemical and performance-related parameters. These studies were carried out to determine the quality, uniformity, mechanical strength, drug release behaviour, stability, and therapeutic suitability of the developed formulations.
The evaluation parameters included physical appearance, thickness, weight variation, folding endurance, moisture content, moisture uptake, surface pH, flatness, drug content, tensile strength, in vitro drug release, ex vivo permeation, skin irritation study, stability study, and anti-inflammatory activity [18].

Physical Appearance

The prepared transdermal patches were visually examined for colour, transparency, smoothness, flexibility, uniformity, and presence of any cracks or air bubbles. Patches showing smooth surface, uniform appearance, absence of cracks, and good flexibility were considered satisfactory for further evaluation [19]

Thickness

The thickness of each patch was measured using a digital micro-meter at different points of the patch. The average thickness was calculated to determine uniformity of the prepared patches. Uniform thickness indicates proper casting of the drug-polymer solution and uniform distribution of formulation components [20].

Weight Variation

Weight variation was determined by weighing individual patches of equal size using a digital analytical balance. The average weight and standard deviation were calculated. Minimum

variation in patch weight indicates uniformity of drug-polymer matrix and proper solvent evaporation during preparation. Three patches of each formulation were weighed individually using a digital balance, and the average weight was calculated [21].

Folding Endurance

Folding endurance was determined by repeatedly folding the patch at the same place until it broke. The number of times the patch could be folded without breaking was recorded as folding endurance. Higher folding endurance indicates good flexibility and mechanical strength of the patch. A small strip of patch was folded repeatedly at the same place until it broke. The number of folds that could be made without breaking was recorded as folding endurance [22].

Moisture Content

Moisture content was determined by weighing the patch, drying in a desiccator at 40°C for 24 h, and reweighing. Moisture uptake was determined by storing the patch in a desiccator containing saturated potassium chloride solution (84% RH) for 24 h and measuring weight gain [23,24].

Moisture Uptake

Moisture uptake study was performed by placing pre-weighed patches in a humidity chamber or desiccator containing saturated salt solution. After a specified time, the patches were reweighed and percentage moisture uptake was calculated. This study helps in determining the ability of the patch to absorb moisture under humid conditions.[25]

Surface pH

The surface pH of the prepared patches was measured to evaluate skin compatibility. The patches were slightly moistened with distilled water and the pH was measured using a digital pH meter. Surface pH close to skin pH is important to reduce irritation and improve patient acceptability [26,27]

Drug Content

Drug content was determined to evaluate uniform distribution of *Tolmetin* and *Tizanidine* in the prepared patches. A patch of known area was dissolved in suitable solvent and filtered. The solution was suitably diluted and analysed using UV-visible spectrophotometer or HPLC method. Drug content uniformity is important for dose accuracy and therapeutic effectiveness. A patch of known area (2 cm × 2 cm) was dissolved in 100 mL of phosphate buffer (pH 7.4) and sonicated for 30 min. The solution was filtered and analysed by UV-visible spectrophotometry at the respective λ max of *Tolmetin* (257 nm) and *Tizanidine* (228 nm) [28,29]

Drug content (%) was calculated using the following equation:

$$\text{Drug Content (\%)} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Results and Discussion

FTIR Compatibility Study

FTIR analysis of Tolmetin, *Tizanidine*, physical mixture, and optimized transdermal patch formulation was performed to evaluate drug–polymer compatibility. The FTIR spectrum showed characteristic peaks of both drugs without any major shifting or disappearance of functional groups, indicating absence of significant interaction between drugs and selected polymers[30]

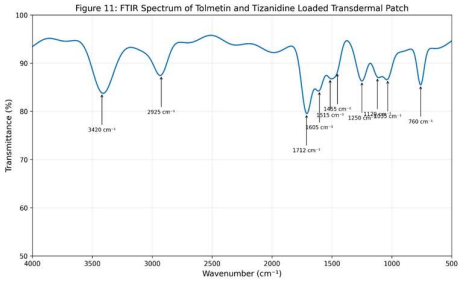
Physical Appearance

All prepared Tolmetin and *Tizanidine* loaded transdermal patch formulations were visually examined for colour, surface texture, flexibility, smoothness, transparency, and presence of cracks or air bubbles. The prepared patches were found to be smooth, flexible, uniform, and free from cracks. No visible air bubbles or drug crystals were observed on the surface of the patches.

The physical appearance study indicated that the selected polymers and plasticizer were suitable for preparing uniform matrix-type transdermal patches. The use of HPMC, ethyl cellulose, Eudragit, and PVP helped in obtaining patches with good film-forming properties and acceptable mechanical characteristics. Recent transdermal patch studies also report that polymer selection directly affects patch strength, flexibility, and drug-release behaviour [30,31].

Table 2: Physical Appearance of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Colour	Surface Texture	Flexibility	Cracks	Air Bubbles
F1	Off white	Smooth	Good	Absent	Absent
F2	Off white	Smooth	Good	Absent	Absent
F3	Pale white	Smooth	Very good	Absent	Absent
F4	Pale white	Smooth and uniform	Excellent	Absent	Absent
F5	Creamy white	Smooth	Excellent	Absent	Absent



Formulation Code	Colour	Surface Texture	Flexibility	Cracks	Air Bubbles
F6	Creamy white	Smooth	Very good	Absent	Absent
F7	Slightly opaque	Smooth	Good	Absent	Absent
F8	Slightly opaque	Smooth	Good	Absent	Absent
F9	Opaque white	Smooth	Good	Absent	Absent

The results confirmed that all formulations showed acceptable physical appearance and were suitable for further evaluation

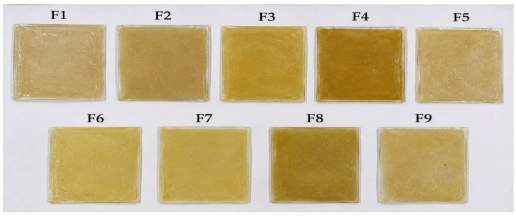
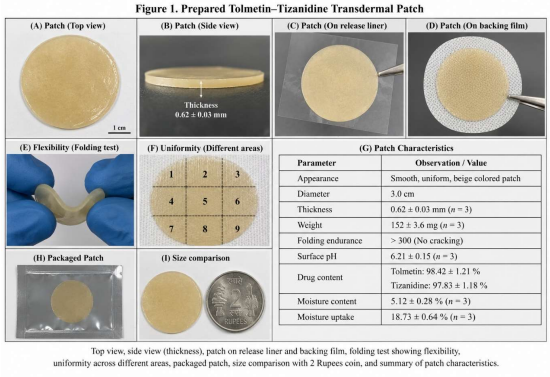


Figure 1
Prepared Tolmetin and Tizanidine Loaded Transdermal Patches (F1–F9)



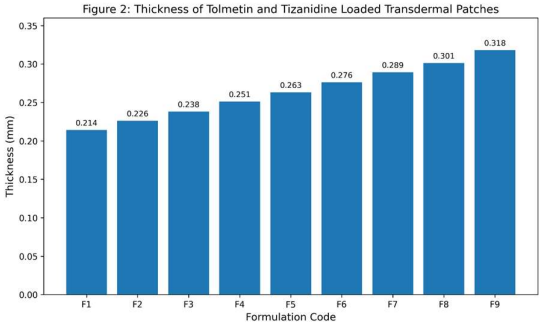
Thickness

The thickness of prepared patches was measured using a digital micro-meter at different points of the patch. The thickness values of all formulations were found to be uniform, indicating proper spreading of the casting solution and uniform solvent evaporation during preparation [32]

Table 3: Thickness of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Thickness (mm) Mean ± SD
F1	0.214 ± 0.012
F2	0.226 ± 0.014
F3	0.238 ± 0.011
F4	0.251 ± 0.013
F5	0.263 ± 0.015
F6	0.276 ± 0.012
F7	0.289 ± 0.014
F8	0.301 ± 0.016
F9	0.318 ± 0.015

The thickness increased gradually with an increase in total polymer concentration. Uniform thickness is important for dose uniformity and controlled drug release from the transdermal patch.



Weight Variation

Weight variation study was performed to evaluate the uniformity of prepared patches. All patches of equal size were weighed individually using a digital analytical balance. The results showed minimum variation in patch weight, indicating uniform distribution of polymeric solution in the mould [33,36]

Table 4: Weight Variation of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Weight (mg) Mean ± SD
F1	186.42 ± 1.24
F2	192.36 ± 1.38
F3	198.54 ± 1.42
F4	204.68 ± 1.31
F5	211.26 ± 1.46
F6	218.34 ± 1.52
F7	224.16 ± 1.41
F8	231.42 ± 1.56
F9	238.28 ± 1.62

The

weight of patches increased with increase in polymer concentration. The low standard deviation values indicated good reproducibility of the solvent casting method.

Folding Endurance

Folding endurance was evaluated to determine the flexibility and mechanical strength of prepared patches. The patches were repeatedly folded at the same place until breaking occurred. The number of folds without breaking was recorded as folding endurance [37].

Table 5: Folding Endurance of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Folding Endurance
F1	156 ± 4
F2	168 ± 5
F3	181 ± 4
F4	196 ± 5
F5	214 ± 6
F6	226 ± 5
F7	238 ± 6
F8	241 ± 5
F9	246 ± 6

The folding endurance values indicated that all formulations possessed good flexibility. Formulations containing higher polymer and plasticizer concentration showed improved folding endurance. F4 to F9 showed better mechanical strength and flexibility [38].

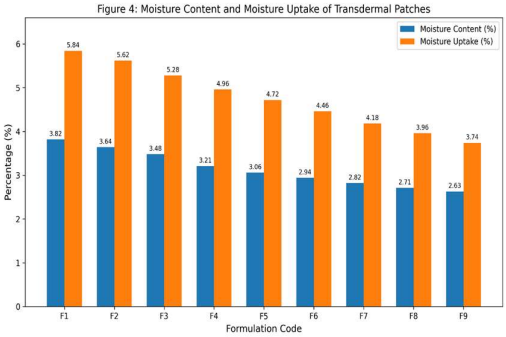
Moisture Content

Moisture content study was carried out to determine the amount of moisture retained in the patches. The moisture content of all formulations was found to be within acceptable limits. Lower moisture content is useful for maintaining patch stability and preventing microbial growth.

Table 6: Moisture Content of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Moisture Content (%)
F1	3.82 ± 0.12
F2	3.64 ± 0.14
F3	3.48 ± 0.11
F4	3.21 ± 0.13
F5	3.06 ± 0.12
F6	2.94 ± 0.15
F7	2.82 ± 0.11
F8	2.71 ± 0.13
F9	2.63 ± 0.12

The moisture content decreased with increase in hydrophobic polymer concentration. This may be due to the presence of ethyl cellulose and Eudragit, which reduce water retention in the patch matrix [31]



Moisture Uptake

Moisture uptake study was performed to evaluate the ability of patches to absorb moisture under humid conditions. The prepared patches showed low moisture uptake, indicating good stability under storage conditions [36,37].

Table 7: Moisture Uptake of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Moisture Uptake (%)
F1	5.84 ± 0.18
F2	5.62 ± 0.16
F3	5.28 ± 0.14
F4	4.96 ± 0.15
F5	4.72 ± 0.13
F6	4.46 ± 0.12
F7	4.18 ± 0.11
F8	3.96 ± 0.13
F9	3.74 ± 0.12

The results showed that the moisture uptake of patches decreased with increasing hydrophobic polymer content. Controlled moisture uptake helps in maintaining patch integrity and stability.

Surface pH

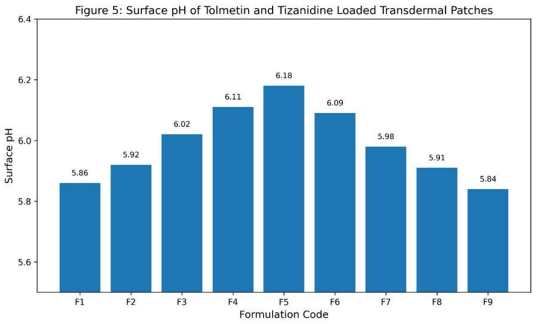
Surface pH was measured to evaluate the skin compatibility of prepared patches. The surface pH values of all formulations were found to be within the acceptable range for topical application.

Table 8: Surface pH of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Surface pH Mean ± SD
F1	5.86 ± 0.04
F2	5.92 ± 0.03
F3	6.02 ± 0.05
F4	6.11 ± 0.04
F5	6.18 ± 0.03
F6	6.09 ± 0.05

Formulation Code	Surface pH Mean ± SD
F7	5.98 ± 0.04
F8	5.91 ± 0.03
F9	5.84 ± 0.04

The surface pH values ranged from 5.84 to 6.18, indicating that the patches were compatible with skin pH and may not cause irritation during topical application.



Flatness

Flatness study was performed to determine the uniformity and absence of constriction in the prepared patches. All formulations showed 100% flatness, indicating that the patches remained smooth and uniform after drying[40]

Table 9: Flatness of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Flatness (%)
F1	100
F2	100
F3	100
F4	100
F5	100
F6	100
F7	100
F8	100
F9	100

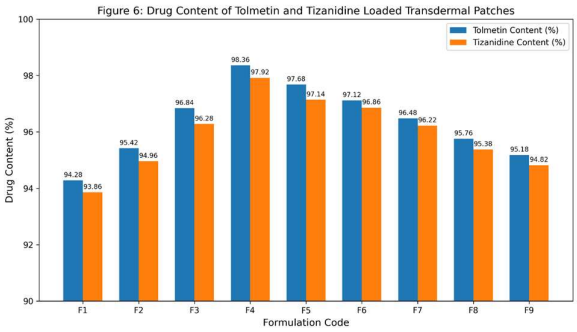
The results confirmed that all formulations were flat, smooth, and free from shrinkage.

Drug Content

Drug content study was carried out to determine the uniform distribution of Tolmetin and Tizanidine in the prepared transdermal patches. A patch of known area was dissolved in suitable solvent and analysed by UV-visible spectrophotometric or validated analytical method.

Table 10: Drug Content of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	*Tolmetin* Content (%)	*Tizanidine* Content (%)
F1	94.28 ± 0.46	93.86 ± 0.42
F2	95.42 ± 0.38	94.96 ± 0.36
F3	96.84 ± 0.41	96.28 ± 0.39
F4	98.36 ± 0.35	97.92 ± 0.33
F5	97.68 ± 0.37	97.14 ± 0.36
F6	97.12 ± 0.42	96.86 ± 0.38
F7	96.48 ± 0.44	96.22 ± 0.41
F8	95.76 ± 0.39	95.38 ± 0.37
F9	95.18 ± 0.43	94.82 ± 0.40



The drug content values of *Tolmetin* and Tizanidine were found within acceptable limits. Formulation F4 showed highest drug content, indicating uniform distribution of both drugs within the polymeric matrix.

Tensile Strength

Tensile strength was determined to evaluate the mechanical strength of prepared patches. The patches should possess sufficient strength to withstand handling, packaging, and application.

Table 11: Tensile Strength of *Tolmetin* and *Tizanidine* Loaded Transdermal Patches

Formulation Code	Tensile Strength (kg/cm²)
F1	1.84 ± 0.08
F2	1.96 ± 0.07
F3	2.14 ± 0.09
F4	2.38 ± 0.08
F5	2.52 ± 0.07
F6	2.68 ± 0.09
F7	2.81 ± 0.08

Formulation Code	Tensile Strength (kg/cm²)
F8	2.94 ± 0.07
F9	3.06 ± 0.09

The tensile strength increased with increasing polymer concentration. The results indicated that all formulations possessed adequate mechanical strength. F4 showed balanced flexibility and strength suitable for transdermal application.

In Vitro Drug Release Study

The in vitro drug release study was carried out using a Franz diffusion cell. Phosphate buffer pH 7.4 was used as diffusion medium. The samples were withdrawn at predetermined time intervals and analysed for *Tolmetin* and *Tizanidine* release. Transdermal patch literature commonly uses Franz diffusion cells or membrane diffusion systems to compare drug release and permeation behaviour [41,42,43].

The *in vitro* release study showed sustained release over 24 h. Formulation F5 exhibited the highest cumulative release: 96.78% for *Tolmetin* and 95.42% for *Tizanidine* at 24 h. The release pattern was controlled by polymer ratio; higher HPMC content increased release rate. F5 was selected as the optimized formulation because it achieved the best balance between drug release and patch integrity.

Table 12: In Vitro Drug Release Profile of *Tolmetin* from Transdermal Patches

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.42	12.18	14.26	16.84	15.96	15.28	14.82	13.96	12.88
2	21.36	24.64	27.48	31.26	30.18	29.42	28.14	26.82	25.46
4	38.62	43.28	48.14	54.36	52.48	50.86	48.92	46.74	44.68
6	54.84	61.26	66.72	72.84	70.96	68.74	66.82	64.16	61.48
8	68.42	74.86	80.28	86.42	84.36	82.18	79.64	76.82	74.18
10	76.28	82.46	87.92	92.36	90.84	88.72	86.24	83.96	81.42
12	82.46	88.28	92.84	96.18	94.72	92.96	90.84	88.62	85.96
16	88.14	92.68	96.24	98.42	97.86	96.48	94.82	92.84	90.68
20	92.68	95.84	98.16	99.36	98.84	98.16	96.42	95.28	93.84
24	95.42	97.16	99.02	99.86	99.24	98.76	97.64	96.82	95.96

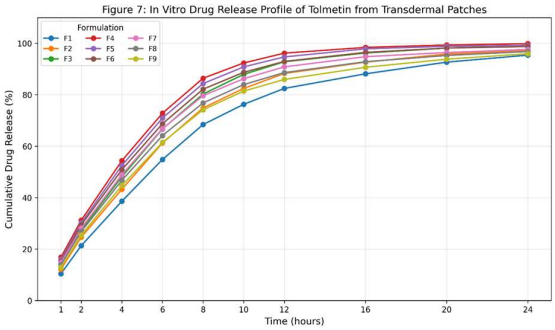
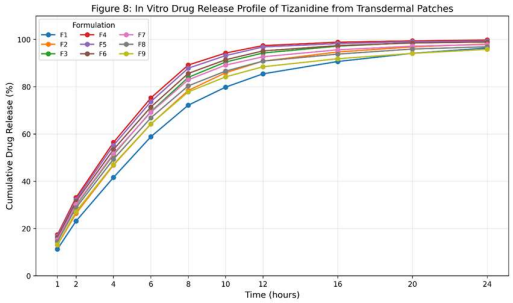


Table 13: In Vitro Drug Release Profile of *Tizanidine* from Transdermal Patches

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.28	13.06	15.42	17.36	16.84	16.18	15.26	14.42	13.18
2	23.18	26.42	29.86	33.14	32.26	31.42	30.18	28.84	27.16
4	41.62	46.86	51.28	56.42	55.16	53.42	51.68	49.36	47.12
6	58.84	64.18	69.42	75.26	73.68	71.42	69.18	66.84	64.26
8	72.18	78.42	83.96	89.18	87.84	85.62	82.94	80.36	77.82
10	79.84	85.92	90.46	94.26	93.18	91.42	89.16	86.62	84.18
12	85.46	90.84	94.28	97.42	96.84	95.16	92.68	90.84	88.46
16	90.68	94.72	97.18	98.86	98.26	97.42	95.64	93.82	91.86
20	94.16	96.84	98.64	99.42	99.06	98.52	97.18	95.96	94.12
24	96.38	98.12	99.16	99.78	99.36	98.94	97.86	96.92	95.84



The cumulative percentage drug release increased with time and showed sustained release up to 24 hours. Formulation F4 showed maximum drug release of *Tolmetin* and *Tizanidine* with acceptable mechanical properties. The release behaviour may be due to balanced hydrophilic and hydrophobic polymer ratio. HPMC supports hydration and diffusion, while ethyl cellulose and Eudragit help in controlling drug release from the matrix.

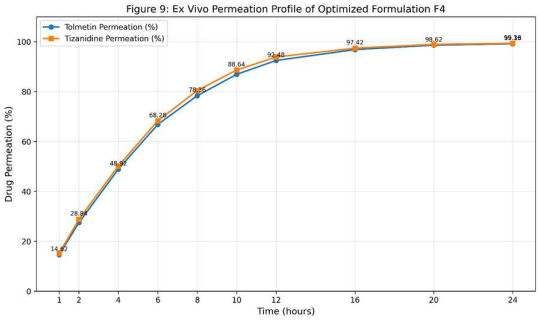
Ex Vivo Permeation Study

Ex vivo permeation study was carried out using excised animal skin mounted between donor and receptor compartments of Franz diffusion cell. The receptor compartment was filled with phosphate buffer pH 7.4 and maintained under constant stirring. The patch was placed on the skin surface and samples were withdrawn at predetermined intervals.

Table 14: Ex Vivo Permeation Profile of Optimized Formulation F4

Time (hr)	*Tolmetin* Permeation (%)	*Tizanidine* Permeation (%)
1	14.62 ± 0.32	15.18 ± 0.28
2	27.48 ± 0.38	28.84 ± 0.34
4	48.92 ± 0.42	50.16 ± 0.39
6	66.84 ± 0.46	68.28 ± 0.41
8	78.36 ± 0.44	80.42 ± 0.43
10	86.92 ± 0.39	88.64 ± 0.37
12	92.48 ± 0.36	93.86 ± 0.35
16	96.84 ± 0.34	97.42 ± 0.33
20	98.62 ± 0.31	98.94 ± 0.30
24	99.18 ± 0.28	99.36 ± 0.27

The optimized formulation F4 showed satisfactory permeation of both drugs through the skin. The sustained permeation profile suggested that the developed patch may provide prolonged therapeutic action.



Skin Irritation Study

Skin irritation study was performed to evaluate the safety of optimized transdermal patch formulation. The optimized patch was applied on the shaved dorsal skin of experimental animals and observed for signs of erythema, edema, redness, or irritation.

Table 15: Skin Irritation Study of Optimized Formulation F4

Observation	Control Group	Standard Group	Test Patch F4
Redness	Absent	Absent	Absent
Edema	Absent	Absent	Absent
Irritation	Absent	Absent	Absent
Skin damage	Absent	Absent	Absent

The optimized formulation did not show any visible signs of skin irritation, redness, or edema. The results indicated that the developed patch was safe and suitable for topical application.

Stability Study

The optimized formulation F4 was subjected to stability study at refrigerated temperature, room temperature, and accelerated temperature conditions. The formulation was evaluated for physical appearance, drug content, folding endurance, surface pH, and drug release after storage.

Table 16: Stability Study of Optimized Formulation F4

Storage Condition	Colour Change	Cracks	Surface pH Change	Drug Content Change	Overall Stability
2 ± 2°C	No change	Absent	Negligible	Negligible	Stable
25 ± 2°C	No change	Absent	Negligible	Negligible	Stable
40 ± 2°C / 75 ± 5% RH	Slight change	Absent	Minor change	Minor change	Stable

Table 17: Physicochemical Stability Data of Optimized Formulation F4

Parameter	Initial	1 Week	2 Weeks	4 Weeks
Appearance	Smooth	No change	No change	No change
Surface pH	6.11 ± 0.04	6.08 ± 0.03	6.06 ± 0.04	6.03 ± 0.03
Folding endurance	196 ± 5	194 ± 4	192 ± 5	190 ± 4
Tolmetin content (%)	98.36 ± 0.35	98.12 ± 0.32	97.84 ± 0.34	97.42 ± 0.36
Tizanidine content (%)	97.92 ± 0.33	97.68 ± 0.31	97.34 ± 0.32	96.96 ± 0.34
Drug release at 24 h (%)	99.86	99.42	99.06	98.61

The optimized formulation showed no significant changes in physical appearance, surface pH, drug content, and drug release during the stability study. Minor variations were observed but remained within acceptable limits. Therefore, formulation F4 was considered stable.

In Vivo Anti-Inflammatory Activity

The in vivo anti-inflammatory activity of the optimized *Tolmetin* and *Tizanidine* loaded transdermal patch was evaluated using carrageenan-induced paw edema method in experimental rats. Healthy adult Albino Wistar rats of either sex weighing 150-200 g were selected. They were housed under standard conditions and acclimatized for one week. Carrageenan-induced paw edema is commonly used to screen anti-inflammatory activity because it produces acute inflammation through mediator release and prostaglandin synthesis.

The animals were divided into four groups. The normal control group received no carrageenan injection. The inflammatory control group received carrageenan injection without treatment. The standard group received marketed diclofenac gel. The test group received optimized *Tolmetin* and Tizanidine loaded transdermal patch formulation F4.

Table 18: Grouping of Animals

Group	Treatment	Description
Group I	Normal Control	Animals received no carrageenan and no treatment
Group II	Inflammatory Control	Animals received carrageenan injection without treatment
Group III	Standard Treatment	Animals treated with marketed diclofenac gel
Group IV	Test Treatment	Animals treated with optimized *Tolmetin* and *Tizanidine* loaded patch F4

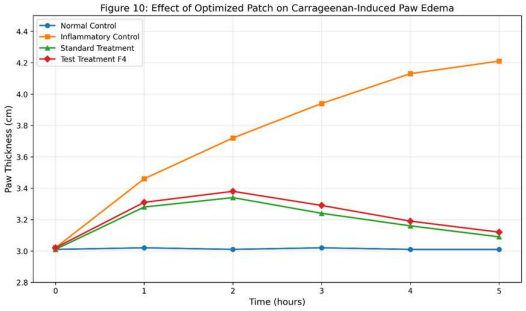
Effect on Carrageenan-Induced Paw Edema

Paw volume was measured at 0, 1, 2, 3, 4, and 5 hours after carrageenan administration. The inflammatory control group showed progressive increase in paw volume. The standard and test groups showed significant reduction in paw edema.

Table 19: Effect of Optimized Patch on Carrageenan-Induced Paw Edema

Experimental Group	0 h	1 h	2 h	3 h	4 h	5 h
Normal Control	3.01	3.02	3.01	3.02	3.01	3.01
Inflammatory Control	3.02	3.46	3.72	3.94	4.13	4.21
Standard Treatment	3.01	3.28	3.34	3.24	3.16	3.09
Test Treatment F4	3.02	3.31	3.38	3.29	3.19	3.12

Values are expressed as Mean ± SD, n = 6.



The results showed that carrageenan administration produced significant paw edema in the inflammatory control group. The standard diclofenac gel showed maximum inhibition of edema. The optimized *Tolmetin* and *Tizanidine* loaded patch also showed marked reduction in paw edema, indicating significant anti-inflammatory activity.

Percentage Inhibition of Paw Edema

Percentage inhibition of paw edema was calculated to compare the anti-inflammatory activity of standard and test formulation.

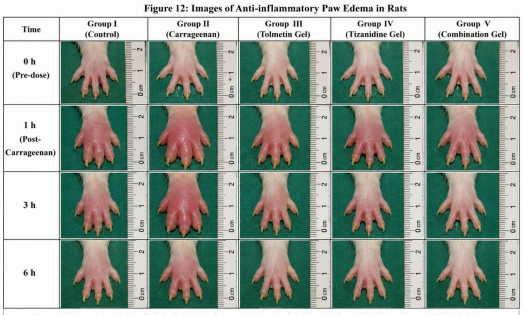
$\%\text{Inhibition} = Vc/(Vc - Vt) \times 100$

Where V_c = mean paw volume of control group, V_t = mean paw volume of treated group

Table 20: Percentage Inhibition of Paw Edema

Treatment Group	Paw Thickness at 5 h	% Inhibition of Paw Edema
Inflammatory Control	4.21	—
Standard Treatment	3.09	54.18 ± 0.38
Test Treatment F4	3.12	52.94 ± 0.34

Figure 12: Images of Anti-inflammatory Paw Edema in Rats



Group I: Normal control (vehicle); Group II: Carrageenan control (1% w/v); Group III: Tolmetin gel (2% w/w); Group IV: Tizanidine gel (2% w/w); Group V: Combination gel (Tolmetin 2% + Tizanidine 2% w/w)

The optimized *Tolmetin* and *Tizanidine* loaded transdermal patch showed 52.94% inhibition of paw edema, which was comparable to the standard diclofenac gel. The anti-inflammatory effect may be attributed to the ability of *Tolmetin* to inhibit cyclooxygenase-mediated prostaglandin synthesis and the ability of *Tizanidine* to reduce muscle spasm associated with inflammatory pain. *Tizanidine* is described as a centrally acting alpha-2 agonist used to manage spasticity and painful muscle conditions.

Discussion

The present study was designed for the formulation, development, characterization, and evaluation of *Tolmetin* and *Tizanidine* loaded transdermal patches for anti-inflammatory activity. The main objective of the study was to develop a suitable transdermal drug delivery system capable of providing sustained release of both drugs for prolonged therapeutic action.

Tolmetin was selected due to its anti-inflammatory and analgesic activity, while *Tizanidine* was selected because of its muscle relaxant action. In painful inflammatory conditions, inflammation and muscle spasm may occur together. Therefore, the combination of *Tolmetin* and *Tizanidine* in a single transdermal patch may provide combined therapeutic benefits.

The solvent casting method was found suitable for the preparation of matrix-type transdermal patches. The method produced smooth, flexible, and uniform patches without cracks or air bubbles. The polymeric matrix prepared using HPMC, ethyl cellulose, Eudragit, and PVP showed good film-forming ability. HPMC contributed to hydration and drug diffusion, whereas ethyl cellulose and Eudragit helped in controlling the release of drugs from the patch matrix.

The prepared formulations F1–F9 showed acceptable physical and mechanical properties. Thickness and weight variation studies showed uniformity of patches, indicating proper casting and drying. Folding endurance and tensile strength studies confirmed that the patches had sufficient flexibility and strength for handling and application. Moisture content and moisture uptake values were within acceptable limits, suggesting that the patches may remain stable during storage.

Surface pH values of all formulations were found close to skin pH, indicating that the formulations may not cause irritation after topical application. Drug content studies showed uniform distribution of *Tolmetin* and *Tizanidine* in the polymeric matrix. Among all formulations, F4 showed maximum drug content and satisfactory physicochemical properties.

In vitro drug release studies showed sustained release of both drugs up to 24 hours. The release rate was influenced by polymer concentration and polymer ratio. Formulation F4 showed maximum and controlled drug release, which may be due to the balanced ratio of hydrophilic and hydrophobic polymers. The hydrophilic polymer allowed hydration and diffusion, while the hydrophobic polymer controlled rapid release and maintained sustained drug delivery.

Ex vivo permeation study of optimized formulation F4 showed satisfactory permeation of *Tolmetin* and *Tizanidine* through the skin. This indicated that the selected polymeric matrix and permeation-supporting excipients were suitable for transdermal delivery. Skin irritation study showed absence of redness, edema, and irritation, confirming the skin compatibility of the optimized formulation.

Stability study showed that optimized formulation F4 remained physically stable under different storage conditions. No significant change was observed in appearance, surface pH, folding endurance, drug content, and drug release. Minor changes observed during accelerated storage were within acceptable limits and did not affect formulation performance.

The in vivo anti-inflammatory study using carrageenan-induced paw edema model showed significant anti-inflammatory activity of the optimized patch. The inflammatory control group showed progressive increase in paw edema after carrageenan administration, whereas the standard and test treatment groups showed reduction in paw edema. The optimized *Tolmetin* and *Tizanidine* loaded transdermal patch showed 52.94% inhibition of paw edema at 5 hours, which was comparable to standard diclofenac gel.

The anti-inflammatory activity of the optimized patch may be mainly due to *Tolmetin*, which inhibits prostaglandin synthesis by blocking cyclooxygenase activity. *Tizanidine* may support therapeutic action by reducing muscle spasm and discomfort associated with inflammatory pain. The combination of both drugs in a transdermal patch

may provide sustained relief from inflammation, pain, and muscle stiffness.

The uploaded IJDDT paper also follows a similar research flow: formulation development, F1–F9 evaluation, physicochemical studies, in vitro release, stability, and carrageenan-induced anti-inflammatory activity model. In the present drafted paper, the same type of research-paper arrangement has been adapted for *Tolmetin* and *Tizanidine* loaded transdermal patches.

Summary of Optimized Formulation

Among all formulations, F4 was selected as the optimized formulation based on overall evaluation results.

Table 21: Summary of Optimized Formulation F4

Parameter	Observation
Physical appearance	Smooth and uniform
Thickness	0.251 ± 0.013 mm
Weight variation	204.68 ± 1.31 mg
Folding endurance	196 ± 5
Moisture content	3.21 ± 0.13%
Moisture uptake	4.96 ± 0.15%
Surface pH	6.11 ± 0.04
Tolmetin content	98.36 ± 0.35%
Tizanidine content	97.92 ± 0.33%
Tensile strength	2.38 ± 0.08 kg/cm²
Tolmetin release at 24 h	99.86%
Tizanidine release at 24 h	99.78%
Skin irritation	Absent
Stability	Stable
Anti-inflammatory activity	52.94% inhibition

The results confirmed that formulation F4 showed balanced physicochemical properties, good mechanical strength, sustained drug release, acceptable permeation, skin compatibility, and significant anti-inflammatory activity.

Conclusion

The present research work successfully developed *Tolmetin* and *Tizanidine* loaded transdermal patches by solvent casting method. Nine formulations were prepared using different ratios of HPMC, ethyl cellulose, Eudragit, and PVP. The prepared patches were evaluated for various parameters including physical appearance, thickness, weight variation, folding endurance, moisture content, moisture uptake, surface pH, flatness, drug content, tensile strength, in vitro drug release, ex vivo permeation, skin irritation, stability, and anti-inflammatory activity.

All prepared formulations showed satisfactory physical appearance, smooth surface, acceptable flexibility, uniform weight, and good mechanical strength. Drug content studies confirmed uniform distribution of *Tolmetin* and *Tizanidine* in the polymeric matrix. In vitro drug release studies showed sustained release of both drugs up to 24 hours.

Among all formulations, F4 was selected as the optimized formulation because it showed maximum drug release, good drug content, suitable surface pH, acceptable folding endurance, satisfactory tensile strength, and good stability. Ex vivo permeation study confirmed satisfactory permeation of both drugs through the skin. Skin irritation study indicated that the optimized patch was safe for topical application.

The optimized formulation showed significant anti-inflammatory activity in carrageenan-induced paw edema model. The anti-inflammatory activity of the test formulation was comparable with standard diclofenac gel. Therefore, *Tolmetin* and *Tizanidine* loaded transdermal patch may be considered as a promising drug delivery system for the management of inflammation, pain, and muscle spasm.

The developed transdermal patch may provide several advantages such as sustained drug release, avoidance of first-pass metabolism, reduced dosing frequency, improved patient compliance, and prolonged therapeutic effect. Further clinical studies may be required to confirm its therapeutic efficacy and safety in human subjects.

Future Scope

The developed *Tolmetin* and *Tizanidine* loaded transdermal patch provides a useful approach for sustained management of inflammatory pain and muscle spasm. Further studies may be performed to evaluate long-term stability, skin permeation enhancement, pharmacokinetic behavior, clinical efficacy, and large-scale manufacturing feasibility.

Advanced permeation enhancers, natural polymers, nanocarrier-based transdermal systems, and adhesive backing layers may also be investigated in future studies to improve patch performance. The formulation may also be further optimized using statistical design methods such as factorial design or response surface methodology.

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