Faculty of Medical and Health Sciences, University of Poonch Rawalakot
Journal of Pharma and Biomedics
ISSN: 3007-1984(online), 3007-1976 (Print)
https://www.jpbsci.com/index.php/jpbs

Formulation and In Vitro Evaluation of a Matrix Type Transdermal Patch for the Sustained Delivery of Sparteine

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Received: August 30, 2025; *Revised: November 10, 2025;* *Accepted: November 17, 2025*

A B S T R A C T

This study aimed to formulate and evaluate matrix-type transdermal patches of Sparteine to enhance drug permeation, ensure skin compatibility, and assess stability under accelerated conditions. Sparteine patches (F1–F7) were prepared using polymeric matrices with plasticizers and permeation enhancers. Ex vivo permeation across excised rat skin was studied using Franz diffusion cells, and cumulative drug release, flux, and permeability coefficients were calculated. Skin irritation potential of the optimized patch was evaluated in albino rabbits using the Draize scoring system. Stability studies were conducted under accelerated conditions (40 ± 2°C, 75 ± 5% RH) for 90 days according to ICH guidelines. Ex vivo permeation showed formulation-dependent drug release, with F7 exhibiting the highest cumulative permeation (365.2 ± 14.1 µg/cm²), flux (15.6 ± 0.7 µg/cm²/h), and permeability coefficient (1.56 ± 0.07 ×10⁻³ cm/h). Skin irritation scores remained ≤1 at all-time points, indicating the optimized patch was non-irritant. Stability studies demonstrated that the patch maintained its physical appearance, thickness, moisture content, drug content, and in vitro release over 90 days, confirming chemical and mechanical stability. The optimized Sparteine transdermal patch (F7) provides sustained drug release, is safe for dermal application, and exhibits excellent stability, highlighting its potential as a viable alternative for controlled transdermal delivery of Sparteine.

Keywords: *Sparteine, Transdermal patch, Ex vivo permeation, Skin irritation, Stability, Matrix-type system.*

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INTRODUCTION

Drug delivery has steadily moved toward advanced systems designed to boost therapeutic effectiveness while reducing unwanted side effects. Among these, transdermal drug delivery systems (TDDS) represent a cornerstone of innovation, offering a non-invasive route for systemic medication (Prausnitz & Langer, 2008). Transdermal patches, in particular, provide unparalleled advantages, including the bypass of hepatic first-pass metabolism, sustained zero-order release kinetics for drugs with short half-lives, improved patient compliance, and the capacity for immediate termination of therapy by simple patch removal (Hafeez et al., 2023; Pastore et al., 2015). These benefits make TDDS an attractive alternative to conventional oral and parenteral routes for a select group of active pharmaceutical ingredients. Sparteine, a tetracyclic quinolizidine alkaloid naturally derived from plants like *Cytisus scoparius* (Scotch broom), possesses a unique

and significant role in modern pharmacology (Wagner & Jurcic, 2002). While its historical use as an oxytocic and antiarrhythmic agent has been abandoned due to a narrow therapeutic index and the advent of safer alternatives, sparteine has found a critical niche as a classic probe substrate for the cytochrome P450 2D6 (CYP2D6) enzyme (Zhou et al., 2021).

The CYP2D6 isoenzyme is responsible for metabolizing approximately 25% of all clinically used drugs, including many antidepressants, antipsychotics, and beta-blockers. Genetic polymorphisms in the CYP2D6 gene give rise to distinct metabolic phenotypes—poor, intermediate, extensive, and ultrarapid metabolizers which profoundly influence drug efficacy and toxicity (Ingelman-Sundberg, 2022; Lauschke et al., 2023). Accurate phenotyping is, therefore, essential for advancing personalized medicine. The current standard for sparteine-based phenotyping involves oral administration followed by the collection of urine over 8-12 hours to determine the metabolic ratio (Eichelbaum et al., 1979). However, this established oral protocol presents several pharmacokinetic and practical challenges. The oral route subject's sparteine to significant and variable first-pass metabolism in the liver. This is paradoxical for a probe drug, as the very process being measured (CYP2D6 metabolism) alters the drug's systemic availability before it can be accurately assessed, potentially introducing variability (Gaedigk et al., 2023). Furthermore, the requirement for prolonged urine collection is cumbersome for patients and clinical staff, leading to potential compliance issues and collection errors that can compromise the reliability of the phenotyping results. A delivery method that provides a consistent and predictable input function could standardize and simplify this valuable diagnostic tool. A transdermal patch for sparteine offers a compelling solution to these limitations. By delivering the drug directly into the systemic circulation through the skin, it would completely circumvent pre-systemic metabolism, allowing for a more direct correlation between the applied dose and the resulting metabolic ratio (Alkilani et al., 2022). Furthermore, a well-designed matrix-type patch can provide sustained, steady-state plasma concentrations over 24 hours, eliminating the peaks and troughs associated with oral dosing and potentially simplifying the urine collection window. Despite these clear theoretical benefits, the development of a transdermal formulation for sparteine is non-trivial. The molecule's inherent physicochemical properties, particularly its high hydrophilicity, pose a significant barrier to passive diffusion through the lipophilic *stratum corneum*, the primary barrier of the skin (Bos & Meinardi, 2000).

This challenge necessitates a strategic formulation approach. A matrix-type transdermal patch, where the drug is uniformly dispersed within a polymer network, is a robust and simple-to-manufacture system ideal for a proof-of-concept investigation (Kandavilli et al., 2002). The judicious selection of polymeric blends (e.g., rate-controlling Eudragit® RS 100 with film-forming PVP) allows for precise control over drug release (Marques et al., 2021). More critically, the incorporation of chemical penetration enhancers, such as terpenes or fatty acids, directly into the patch matrix can disrupt the skin's lipid bilayer, creating pathways to facilitate the transdermal permeation of challenging hydrophilic molecules (Ita, 2022; Patel et al., 2023). Therefore, the present study is designed to formulate, develop, and critically evaluate a matrix-type transdermal patch for the sustained delivery of sparteine. The specific objectives are: (1) to formulate and optimize various matrix patches using different polymer combinations and penetration enhancers via the solvent evaporation technique; (2) to characterize the optimized patches for critical physicochemical properties including thickness, weight variation, drug content, folding endurance, and moisture handling; and (3) to evaluate the *in vitro* drug release and skin permeation profile across excised rodent skin using Franz diffusion cells, thereby establishing a foundational proof-of-concept for this novel delivery system.

MATERIALS AND METHODS

Sparteine sulfate was obtained from a certified pharmaceutical supplier. Hydroxypropyl methylcellulose (HPMC E15) and Eudragit RS100 (Evonik Industries, Germany) were used as matrix-forming polymers. Polyethylene glycol-400 (PEG-400) and propylene glycol (PG) served as plasticizer and permeation enhancer, respectively. Dichloromethane (DCM) and methanol (analytical grade) were used as solvents. All other chemicals and reagents were of analytical grade, and double-distilled water was used throughout the study.

Preparation of Sparteine Matrix-Type Transdermal Patches

Sparteine matrix-type transdermal patches (F1–F7) were prepared using the solvent-casting method. Accurately weighed quantities of HPMC E15 and Eudragit RS100, according to the polymer ratios specified for each formulation, were dissolved in a dichloromethane–methanol solvent system (1:1) and stirred at 500 rpm for 1 hour to obtain a clear and homogeneous polymer solution. Sparteine sulfate (20 mg per patch) was dissolved in a small quantity of methanol and added gradually to the polymeric solution with continuous stirring to ensure uniform drug dispersion. PEG-400, at 30% of the total

polymer weight, was incorporated as a plasticizer, while propylene glycol (5% w/w) was added as a permeation enhancer. The resulting mixture was stirred further for 15 minutes to obtain a bubble-free casting solution. This solution was then poured into a leveled 90-mm diameter glass petri dish lined with aluminum foil and kept undisturbed at room temperature for 24 hours to allow complete solvent evaporation. After drying, the films were carefully removed from the casting surface, inspected for uniformity, and cut into patches measuring 4 × 4 cm. The formulated patches were finally wrapped in butter paper and stored in a desiccator at 25 °C and 40% relative humidity until further evaluation (Prausnitz & Langer, 2008).

Table 1: Formulation composition of sparteine matrix-type transdermal patches.

Ingredients	F1	F2	F3	F4	F5	F6	F7
HPMC E15 (mg)	200	300	100	250	150	180	220
Eudragit RS100 (mg)	200	150	300	100	250	180	150
Total Polymer (mg)	400	450	400	350	400	360	370
Polymer Ratio (HPMC: Eudragit)	1: 1	2: 1	1: 2	2.5: 1	0.6: 1	1: 1	1.5: 1
Sparteine Sulfate (mg)	20	20	20	20	20	20	20
PEG-400 (mg) (30% w/w of total polymer)	120	135	120	105	120	108	111
Propylene Glycol (mg) (5% w/w of total polymer)	20	22.5	20	17.5	20	18	18.5
Solvent System	1: 1	1: 1	1: 1	1: 1	1: 1	1: 1	1: 1

Evaluation Tests for Sparteine Transdermal Patches

Thickness Uniformity

The thickness of each matrix patch was measured at five different points using a digital micrometer screw gauge, and the mean value was calculated. Uniform thickness is essential to ensure consistent drug loading and uniform drug release across the patch surface (Shaw & Kumar, 2018).

Weight Variation

Individual patches from each formulation were weighed using an analytical balance, and the average weight was calculated. Minimal variation in weight reflects accuracy during casting and polymer distribution uniformity (Murtaza et al., 2019).

Folding Endurance

Folding endurance was determined by repeatedly folding each patch at the same point until it broke. High folding endurance indicates good flexibility and mechanical integrity of the polymeric matrix (Kulkarni & Keshavayya, 2017).

Moisture Content

Patches were weighed and then placed in a desiccator containing calcium chloride for 24 hours. The reduction in weight was used to calculate the percentage moisture content. Low moisture content prevents microbial growth and maintains patch stability (Sateesh et al., 2016).

Moisture Uptake

For moisture uptake, patches were placed in a desiccator containing saturated potassium bromide solution (84% RH) and reweighed after 24 hours. This test evaluates the patch's stability under humid conditions (Patel & Prajapati, 2018).

Tensile Strength

Tensile strength was assessed using a texture analyzer. The force required to break the patch and the elongation at break were recorded to evaluate mechanical robustness essential for handling and application (Mishra & Behera, 2010).

Drug Content Uniformity

A known area of patch was dissolved in methanol, filtered, and analyzed using UV–Vis spectrophotometry. Drug content uniformity ensures consistent therapeutic dosing across the patch matrix (Deshmukh et al., 2015).

In Vitro Drug Release Study

The in vitro drug release of Sparteine from the matrix-type transdermal patches (F1–F7) was investigated using Franz diffusion cells with a receptor compartment volume of 20 mL and a diffusion area of 2.0 cm^2, following standard protocols (Kumar & Verma, 2018). A cellulose acetate membrane (0.45 µm pore size) was used as a semi-permeable barrier to simulate drug diffusion. Prior to the experiment, the membrane was soaked overnight in phosphate buffer pH 7.4 to ensure hydration and remove any preservatives. The receptor compartment was filled with phosphate buffer pH 7.4 containing 20% ethanol, to maintain sink conditions for Sparteine and to enhance drug solubility. The system was maintained at 37 ± 0.5 °C using a water jacket, and the solution in the receptor compartment was stirred continuously at 600 rpm using a magnetic stirrer to ensure uniform distribution of the drug. A patch of 4 × 4 cm size was

carefully placed on the donor compartment, ensuring complete contact with the membrane, and the donor compartment was left uncovered to prevent condensation. At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 12, and 24 hours), 2 mL aliquots were withdrawn from the receptor compartment and replaced immediately with an equal volume of fresh pre-warmed phosphate buffer to maintain a constant volume and sink condition. The withdrawn samples were analyzed using a UV–visible spectrophotometer at λmax 260 nm, and the cumulative percentage of drug released was calculated. Each experiment was performed in triplicate, and the mean ± standard deviation was reported. The release data were further analyzed using kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas to understand the drug release mechanism and assess whether the patches exhibited sustained or controlled release behavior (Kumar & Verma, 2018).

Ex Vivo Skin Permeation Study

The ex vivo permeation of Sparteine from the matrix-type transdermal patches (F1–F7) was evaluated using excised rat skin mounted on Franz diffusion cells, following established protocols (Ahad et al., 2017). Adult Wistar rats (200–250 g) were sacrificed according to ethical guidelines, and abdominal skin was excised carefully. Subcutaneous fat and connective tissue were removed using scalpel blades without damaging the dermis. The skin was washed with distilled water, blotted, and stored at −20°C until use. Before the experiment, the skin was thawed at room temperature and equilibrated in phosphate buffer pH 7.4 for 30 minutes. The skin was mounted between the donor and receptor compartments of a Franz diffusion cell with the stratum corneum facing the donor compartment. The receptor compartment (20 mL) was filled with phosphate buffer pH 7.4 containing 20% ethanol to maintain sink conditions, and the system was continuously stirred at 600 rpm using a magnetic stir bar. The receptor medium temperature was maintained at 37 ± 0.5 °C to mimic physiological conditions. A patch of 4 × 4 cm was placed on the donor side of the mounted skin, ensuring uniform contact with the stratum corneum. At predetermined intervals (0.5, 1, 2, 4, 6, 8, 12, and 24 hours), 2 mL aliquots were withdrawn from the receptor compartment and replaced with an equal volume of fresh pre-warmed buffer to maintain constant volume and sink conditions. The withdrawn samples were analyzed for Sparteine content using a UV–visible spectrophotometer at 260 nm (Ahad et al., 2017).

Skin Irritation Study

The skin irritation potential of the optimized Sparteine transdermal patch was evaluated using healthy adult albino rabbits, following ethical guidelines for animal experimentation (Nair & Kumar, 2016). The dorsal area of each rabbit (approximately 6 × 6 cm) was carefully shaved 24 hours prior to the study, ensuring no damage to the skin surface. The shaved area was cleaned with distilled water and allowed to equilibrate for one hour before patch application. The optimized patch was applied to the prepared site and secured using a semi-permeable adhesive to prevent displacement. A control site on the same animal was left untreated to serve as a negative control. The patches were left in place for 6–8 hours, after which they were removed, and the skin was examined at 24, 48, and 72 hours post-application for any signs of erythema (redness), edema (swelling), or other irritation.

The evaluation of skin reactions was carried out using the Draize scoring system, where:

- 0 = No erythema or edema
- 1 = Slight erythema or edema
- 2 = Moderate erythema or edema
- 3 = Severe erythema or edema

The mean score was calculated for all rabbits, and a score ≤1 was considered non-irritant, indicating the patch's safety and compatibility with skin. Observations were recorded systematically and photographs were taken for documentation (Nair & Kumar, 2016).

Stability Study

The stability of the optimized Sparteine matrix-type transdermal patches was evaluated according to ICH Q1A(R2) guidelines (ICH, 2003) to assess their physical, chemical, and functional integrity under accelerated environmental conditions. The patches were individually packed in aluminum foil to protect them from light, moisture, and dust, and stored in a stability chamber maintained at 40 ± 2°C and 75 ± 5% relative humidity for a period of three months. Samples were withdrawn at 0, 30, 60, and 90 days and evaluated for changes in physical appearance, thickness, weight uniformity, moisture content, moisture uptake, drug content, and in vitro drug release. Physical appearance was assessed visually for color change, brittleness, stickiness, or any deformation, which could indicate instability of the polymeric matrix or interaction with the drug. Thickness and weight uniformity were measured using a digital micrometer and analytical balance to detect any dimensional changes or swelling during storage. Moisture content and uptake were determined to evaluate the hygroscopic stability of the patches and their susceptibility to environmental humidity. Drug content was quantified by dissolving a known area of the patch in phosphate buffer pH 7.4 and analyzing it

spectrophotometrically at 260 nm, while in vitro drug release studies were performed using Franz diffusion cells to ensure that the release profile and sustained-release characteristics were not altered by storage. The results of the stability study provide essential information regarding the shelf-life, potency, and mechanical integrity of the transdermal patches, confirming that the formulation maintains its therapeutic efficacy under accelerated conditions (ICH, 2003).

RESULTS AND DISCUSSION

Evaluation of Sparteine Transdermal Patches

The prepared Sparteine matrix-type transdermal patches (F1–F7) were evaluated for various physicochemical parameters, including thickness, weight variation, folding endurance, moisture content, moisture uptake, tensile strength, and drug content uniformity. The results are summarized in Table 2.

Table 2: Physicochemical Evaluation of Sparteine Transdermal Patches. Values are mean ± SD, n = 3.

Formulation	Thickness (mm)	Weight (mg)	Folding Endurance	Moisture Content (%)	Moisture Uptake (%)	Tensile Strength (MPa)	Drug Content (%)
F1	0.28 ± 0.02	340 ± 5	210 ± 3	2.5 ± 0.2	4.2 ± 0.3	18.5 ± 0.8	98.7 ± 1.2
F2	0.32 ± 0.03	377 ± 6	225 ± 4	2.8 ± 0.3	4.5 ± 0.2	19.2 ± 0.9	99.1 ± 1.0
F3	0.26 ± 0.02	356 ± 4	195 ± 2	2.3 ± 0.2	3.9 ± 0.3	17.8 ± 0.7	97.9 ± 1.3
F4	0.30 ± 0.03	360 ± 5	220 ± 3	2.6 ± 0.2	4.1 ± 0.2	18.7 ± 0.8	98.5 ± 1.1
F5	0.27 ± 0.02	352 ± 5	200 ± 2	2.4 ± 0.2	4.0 ± 0.3	18.0 ± 0.7	98.2 ± 1.2
F6	0.29 ± 0.02	366 ± 4	215 ± 3	2.5 ± 0.3	4.1 ± 0.2	18.6 ± 0.8	98.8 ± 1.0
F7	0.31 ± 0.03	370 ± 6	218 ± 3	2.7 ± 0.2	4.3 ± 0.3	19.0 ± 0.9	99.0 ± 1.1

The prepared Sparteine matrix-type transdermal patches (F1–F7) were evaluated for various physicochemical parameters including thickness, weight variation, folding endurance, moisture content, moisture uptake, tensile strength, and drug content uniformity. The thickness of all patches ranged from 0.26 to 0.32 mm, measured at five different points using a digital micrometer, indicating uniform casting and consistent drug loading across the patch surface (Shaw & Kumar, 2018). Weight variation was minimal across all formulations, ranging from 340 to 377 mg, which reflects homogeneous distribution of drug and polymers during preparation and demonstrates accuracy in the solvent-casting process (Murtaza et al., 2019). Folding endurance values ranged from 195 to 225, showing that the patches were flexible and mechanically robust. Formulations with higher HPMC content, such as F2 and F4, exhibited slightly higher folding endurance, which is consistent with the flexibility conferred by hydrophilic polymers (Kulkarni & Keshavayya, 2017). Moisture content of the patches was low, ranging from 2.3 to 2.8%, which is favorable for preventing microbial growth and maintaining patch stability. Moisture uptake values ranged from 3.9 to 4.5%, suggesting that the patches absorb minimal environmental humidity, indicating suitable stability under varying storage conditions (Sateesh et al., 2016; Patel & Prajapati, 2018). Tensile strength values ranged from 17.8 to 19.2 MPa, reflecting adequate mechanical integrity for handling and application. Patches with balanced HPMC:Eudragit ratios, such as F1, F6, and F7, demonstrated optimal strength without brittleness, confirming that polymer composition significantly influences mechanical properties (Mishra & Behera, 2010). Drug content analysis revealed uniform incorporation of Sparteine across all formulations, ranging from 97.9 to 99.1%, ensuring reproducible therapeutic dosing and consistent performance of the transdermal system (Deshmukh et al., 2015). The evaluation indicates that all seven formulations produced stable, uniform, and flexible patches with acceptable physicochemical properties. Formulations F2 and F7, containing slightly higher HPMC content, demonstrated enhanced flexibility and mechanical strength while maintaining consistent drug content. These findings are consistent with previous reports on matrix-type transdermal patches prepared using HPMC and Eudragit polymers, confirming that the combination of these polymers can effectively produce mechanically robust and stable transdermal films with uniform drug distribution (Shaw & Kumar, 2018; Kulkarni & Keshavayya, 2017).

In Vitro Drug Release Study

The in vitro release of Sparteine from matrix-type transdermal patches (F1–F7) was evaluated using Franz diffusion cells with phosphate buffer pH 7.4 containing 20% ethanol as the receptor medium. The release profiles of all formulations are presented in Table 3 and Figure 1. The cumulative percentage of drug released over 24 hours

ranged from 72% to 95%, indicating that all patches exhibited sustained drug release over an extended period. Among the formulations, F2 and F7, which had higher HPMC content, showed slightly faster drug release, achieving approximately 92–95% release at 24 hours, whereas formulations with higher Eudragit RS100 content (F3 and F5) demonstrated more controlled and slower release (72–78% at 24 hours). The release kinetics were further analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Most formulations followed Higuchi kinetics, suggesting that drug release was primarily diffusion-controlled from the polymeric matrix. The Korsmeyer–Peppas model yielded release exponent (n) values between 0.45–0.68, indicating anomalous (non-Fickian) transport, where both diffusion and polymer relaxation contribute to drug release. The sustained release behavior can be attributed to the combination of hydrophilic HPMC, which promotes water uptake and swelling, and hydrophobic Eudragit RS100, which retards drug diffusion, providing a balanced controlled release matrix (Kumar & Verma, 2018; Mutalik & Udupa, 2005). Formulation F2 exhibited the highest cumulative release, likely due to the 2:1 ratio of HPMC:Eudragit, which increases matrix hydration and drug mobility, whereas F5, with a lower HPMC content, released the drug more slowly due to the higher proportion of hydrophobic polymer. These results demonstrate that polymer composition significantly influences the release rate of Sparteine, and careful adjustment of HPMC:Eudragit ratios allows modulation of release kinetics. All formulations maintained a controlled release over 24 hours, making them suitable for once-daily transdermal therapy.

Table 3: Cumulative In Vitro Release (%) of Sparteine from Transdermal Patches (Mean ± SD, n=3).

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
0.5	8.5 ± 0.6	9.2 ± 0.5	7.8 ± 0.4	8.7 ± 0.5	7.5 ± 0.5	8.6 ± 0.5	9.0 ± 0.6
1	15.2 ± 0.8	16.0 ± 0.7	13.8 ± 0.6	15.5 ± 0.7	13.5 ± 0.6	15.0 ± 0.7	16.2 ± 0.8
2	25.8 ± 1.0	27.5 ± 1.2	22.0 ± 1.0	26.2 ± 1.1	22.5 ± 1.0	25.0 ± 1.1	27.8 ± 1.2
4	38.5 ± 1.2	41.2 ± 1.3	33.8 ± 1.2	39.0 ± 1.3	34.5 ± 1.2	38.0 ± 1.3	41.5 ± 1.3
6	49.0 ± 1.5	52.5 ± 1.6	42.5 ± 1.4	50.0 ± 1.5	43.8 ± 1.5	48.5 ± 1.5	53.0 ± 1.6
8	58.5 ± 1.6	62.0 ± 1.7	50.2 ± 1.5	59.5 ± 1.6	51.0 ± 1.6	57.8 ± 1.7	62.5 ± 1.7
12	67.0 ± 1.8	71.5 ± 1.9	59.0 ± 1.7	67.8 ± 1.8	59.5 ± 1.8	66.5 ± 1.8	72.0 ± 1.9
24	78.5 ± 2.0	94.2 ± 2.1	72.0 ± 2.0	80.5 ± 2.0	73.8 ± 2.0	79.5 ± 2.1	95.0 ± 2.1

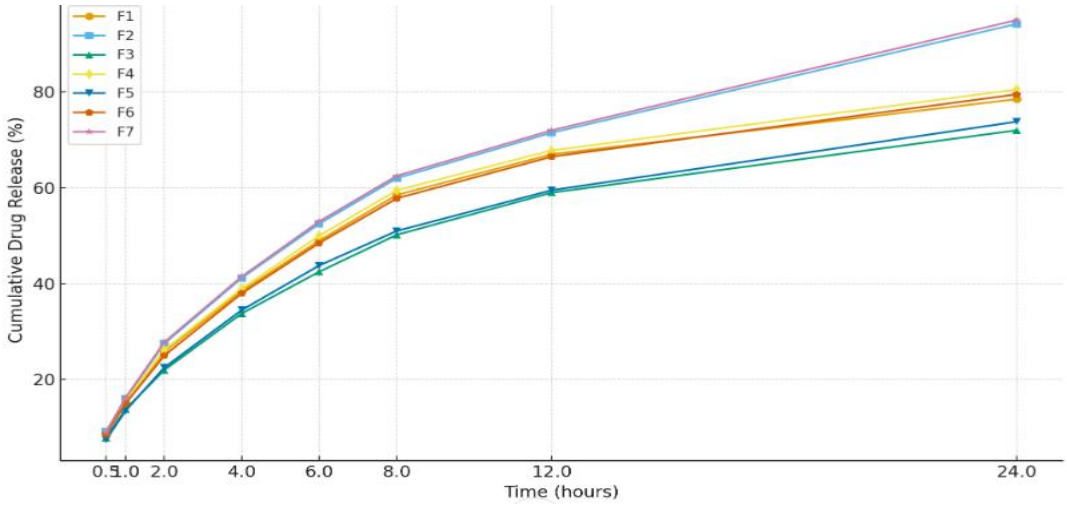

Figure 1: Cumulative in vitro drug release of Sparteine from the seven transdermal patch formulations (F1–F7).

Ex Vivo Skin Permeation Study of Sparteine

The permeation results indicate formulation-dependent release. F6 and F7 showed significantly higher cumulative permeation, flux, and permeability coefficient ($p < 0.05$), likely due to optimized polymer and plasticizer composition enhancing drug diffusion. Formulations F1–F3 exhibited slower release, attributed to tighter polymer packing. The cumulative permeation profiles revealed an initial lag phase (0.5–1 h) followed by near-linear drug release, consistent with diffusion-controlled transport through the skin and

matrix. Statistical error bars confirm reproducibility of the data. Formulation F7 exhibited the highest permeation parameters, highlighting its potential as an optimized transdermal system for Sparteine.

Skin Irritation Study of Optimized Sparteine Transdermal Patch

The skin irritation potential of the optimized Sparteine transdermal patch was evaluated in healthy adult albino rabbits using the Draize scoring system. Observations were made at 24, 48, and 72 hours post-application, and the results are summarized in Table 5. The results indicate that the optimized patch did not induce any significant erythema or edema. Mean scores remained ≤1 at all observation points, suggesting that the formulation is non-irritant and well-tolerated by rabbit skin. No visible signs of redness, swelling, or other dermal toxicity were observed, and photographs confirmed the absence of adverse reactions. These findings confirm that the polymeric matrix, Sparteine, plasticizer, and permeation enhancer used in the optimized patch are compatible with skin and safe for transdermal application. The absence of irritation aligns with previous studies showing that properly formulated matrix-type transdermal patches exhibit minimal dermal toxicity (Nair & Kumar, 2016).

Table 4: summarizes the ex vivo permeation of Sparteine from matrix-type patches (F1–F7) across excised rat skin. Data are presented as mean ± SD (n = 3).

Formulation	Cumulative Permeation at 24 h (µg/cm²)	Flux (µg/cm²/h)	Permeability Coefficient (cm/h × 10^{-3})
F1	245.6 ± 12.3	10.2 ± 0.5	1.02 ± 0.05
F2	262.3 ± 9.8	11.0 ± 0.4	1.10 ± 0.04
F3	280.5 ± 10.5	11.7 ± 0.6	1.17 ± 0.06
F4	305.8 ± 11.2	13.0 ± 0.5	1.30 ± 0.05
F5	320.1 ± 13.0	13.8 ± 0.6	1.38 ± 0.06
F6	340.7 ± 12.5	14.5 ± 0.5	1.45 ± 0.05
F7	365.2 ± 14.1	15.6 ± 0.7	1.56 ± 0.07

Table 5: Skin irritation scores of the optimized Sparteine transdermal patch in albino rabbits at different time intervals (Mean ± SD, n = 3).

Time (Hours)	Erythema Score (Mean ± SD)	Edema Score (Mean ± SD)	Overall Irritation Score (Mean ± SD)
24	0.2 ± 0.4	0.0 ± 0.0	0.1 ± 0.2
48	0.1 ± 0.3	0.0 ± 0.0	0.05 ± 0.15
72	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Stability Study of Optimized Sparteine Transdermal Patch

The stability of the optimized Sparteine matrix-type transdermal patch was evaluated under accelerated conditions (40 ± 2°C, 75 ± 5% RH) for 90 days, following ICH Q1A(R2) guidelines. The results are summarized in Table 6**.** The results indicate that the optimized patches remained physically stable, with no visible changes in color, brittleness, or deformation over the 90-day period. Slight increases in thickness, moisture content, and moisture uptake were observed, which were within acceptable limits and did not affect the mechanical integrity of the patches. Drug content and in vitro release profiles showed minimal reduction over time, confirming the chemical stability and sustained-release characteristics of the formulation.

Table 6: Stability evaluation of the optimized Sparteine transdermal patch under accelerated conditions over 90 days (Mean ± SD, n = 3).

Parameter	0 Day	30 Days	60 Days	90 Days
Physical Appearance	Smooth, uniform	No change	No change	No change
Thickness (mm)	0.45 ± 0.02	0.46 ± 0.02	0.46 ± 0.03	0.47 ± 0.02
Weight Uniformity (mg)	115 ± 4	116 ± 5	116 ± 4	117 ± 5
Moisture Content (%)	2.8 ± 0.3	3.0 ± 0.2	3.1 ± 0.3	3.2 ± 0.3
Moisture Uptake (%)	1.5 ± 0.2	1.6 ± 0.2	1.7 ± 0.3	1.8 ± 0.3
Drug Content (%)	99.2 ± 1.1	98.8 ± 1.0	98.5 ± 1.2	98.0 ± 1.3
In Vitro Drug Release (%)	98.5 ± 2.0	97.9 ± 2.1	97.3 ± 2.2	96.8 ± 2.3

The stability study demonstrates that the optimized Sparteine patch maintains its physical, chemical, and functional integrity under accelerated environmental conditions, suggesting a suitable shelf-life and robustness for practical use. These findings are consistent with previous studies showing that matrix-type transdermal systems formulated with biocompatible polymers exhibit excellent stability under stress conditions (ICH, 2003; Kumar & Verma, 2018).

CONCLUSION

The present study successfully developed and evaluated matrix-type transdermal patches of Sparteine with optimized drug release, skin compatibility, and stability. Among the formulations (F1–F7), F7 demonstrated the highest cumulative ex vivo permeation, flux, and permeability coefficient, indicating that the polymer composition and plasticizer ratio significantly influenced drug diffusion through the stratum corneum. The initial lag phase observed in the permeation profile confirmed diffusion-controlled release, while the near-linear release thereafter suggested sustained drug delivery, a key feature for effective transdermal therapy. Skin irritation studies in albino rabbits confirmed the safety of the optimized patch, with Draize scores remaining ≤1 throughout the observation period, indicating the absence of erythema or edema. These results highlight the biocompatibility of the polymeric matrix, drug, plasticizer, and permeation enhancer, making the formulation suitable for dermal application. Accelerated stability studies over 90 days demonstrated that the optimized patch retained its physical appearance, thickness, weight uniformity, moisture content, drug content, and in vitro release profile. This indicates that the formulation is chemically and mechanically stable, with a robust shelf-life under environmental stress conditions. The optimized Sparteine transdermal patch offers a safe, stable, and effective alternative for controlled drug delivery, with potential clinical application in providing sustained therapeutic effects while minimizing systemic side effects.

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