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Formulation and Characterization of Transdermal Patches of Venlafaxine HCl

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ABSTRACT

***Background**: Oral venlafaxine hydrochloride is widely used for depressive and anxiety disorders but is associated with dose-related adverse effects and peak–trough plasma fluctuations, and undergoes hepatic first-pass metabolism, which may contribute to tolerability limitations. **Objective**: To formulate venlafaxine HCl transdermal matrix patches using HPMC K15 and to evaluate the effect of polymer ratio and triethyl citrate concentration on physicomechanical properties, compatibility, dermal safety, and in-vitro release behavior. **Methods**: Six matrix patch formulations were prepared by solvent casting using an ethanol: dichloromethane (1:1) system with three drug-to-polymer ratios (0.5:0.7, 0.5:0.85, 0.5:1.0) and two plasticizer levels (triethyl citrate 0.05 or 0.15 mL). Patches were evaluated for weight variation, thickness, drug content, folding endurance, moisture loss/absorption, tensile strength, and related quality parameters. Drug–polymer compatibility was assessed by FTIR. Dermal irritation was tested in rabbits using Draize scoring. In-vitro release was assessed using USP apparatus II in phosphate buffer pH 7.4 at 32°C, with kinetic modeling using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. **Results:** Increasing HPMC ratio was associated with increased physicomechanical parameter values and slower in-vitro drug release, whereas higher triethyl citrate content was associated with improved flexibility and faster release. FTIR indicated no significant drug–polymer incompatibility, and rabbit testing showed no significant irritation. **Conclusion:** HPMC ratio and triethyl citrate concentration are key formulation determinants governing matrix patch quality and in-vitro release of venlafaxine HCl; further work should include quantitative statistical comparison and membrane-based permeation flux testing.*

Keywords
Venlafaxine hydrochloride; transdermal matrix patch; HPMC K15; triethyl citrate; solvent casting; in-vitro release; FTIR; Draize irritation.

INTRODUCTION

Depression and anxiety disorders remain major contributors to disability worldwide, with substantial personal, societal, and economic consequences, and the long-term nature of treatment frequently demands sustained symptom control with acceptable tolerability and adherence (1). Venlafaxine hydrochloride, a serotonin–norepinephrine reuptake inhibitor, is widely used across depressive and anxiety-spectrum disorders; however, oral administration is associated with dose-related adverse effects including nausea, headache, dizziness, fatigue, dry mouth, cardiovascular effects such as tachycardia and elevated blood pressure, and sexual dysfunction, which can compromise adherence and functional outcomes (2). Moreover, oral dosing is characterized by peak–trough fluctuations and is subject to hepatic first-pass metabolism, which may contribute to variable systemic exposure and accentuate transient high plasma concentrations linked with intolerance, particularly during dose escalation (3). These limitations have driven continued interest in alternative delivery approaches that can provide controlled systemic exposure while improving patient acceptability.

Transdermal drug delivery systems (TDDS) offer a clinically valuable platform for sustained and controlled drug administration by bypassing gastrointestinal degradation and hepatic first-pass metabolism, reducing dosing frequency, and limiting systemic concentration peaks that contribute to side effects (1,4). In addition to improving adherence, TDDS can provide stable plasma concentrations over extended periods and facilitate therapy discontinuation when needed by rapid patch removal. Despite these advantages, successful transdermal delivery requires that drug physicochemical properties and formulation architecture overcome the barrier function of the stratum corneum, and many antidepressants pose challenges due to variability in lipophilicity, ionization, and molecular interactions with polymer matrices (2,4). The feasibility of antidepressant TDDS has been demonstrated for drugs spanning hydrophilic to hydrophobic profiles, supporting the plausibility of transdermal strategies for centrally acting agents when formulation parameters are optimized (2).

Venlafaxine hydrochloride has been explored for transdermal delivery using passive diffusion and iontophoresis approaches, underscoring both the opportunity and complexity of delivering this molecule through skin and the importance of formulation factors that influence drug release and membrane transport (3). However, there remains limited systematically reported evidence on optimized hydrophilic polymer-based matrix patches for venlafaxine HCl, particularly with respect to how polymer loading and plasticizer modulation jointly influence film formation, mechanical

integrity, moisture behavior, and controlled in-vitro release performance. Hydrophilic cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) are widely used as film-forming polymers for matrix-type transdermal patches because they can provide uniform films with adjustable swelling and diffusional characteristics, while plasticizers such as triethyl citrate can improve flexibility, reduce brittleness, and modulate polymer chain mobility—thereby influencing both mechanical performance and release kinetics (5). A formulation-focused evaluation that integrates physicochemical characterization, mechanical assessment, compatibility analysis, and controlled release testing is therefore necessary to establish a reproducible and clinically relevant design space for venlafaxine HCl matrix patches.

Accordingly, the objective of the present work was to develop venlafaxine hydrochloride transdermal matrix patches using HPMC K15 as the film-forming polymer at three drug-to-polymer ratios and triethyl citrate at two plasticizer levels via solvent casting, and to evaluate how these formulation factors affect patch physicomechanical properties, drug content uniformity, moisture-related behavior, polymer–drug compatibility, skin irritation potential, and in-vitro drug release kinetics. We hypothesized that increasing HPMC K15 content would enhance mechanical strength and moisture uptake while slowing drug release through formation of a denser swollen matrix, whereas increasing triethyl citrate would improve flexibility and accelerate release by increasing polymer free volume and diffusional mobility (5).

MATERIALS AND METHODS

This experimental formulation development and characterization study employed a comparative 2×3 design to evaluate the effect of polymer loading and plasticizer content on venlafaxine hydrochloride transdermal matrix patches. Venlafaxine HCl was formulated with hydroxypropyl methylcellulose (HPMC K15) at three drug-to-polymer ratios (0.5:0.7, 0.5:0.85, and 0.5:1) and triethyl citrate at two levels (0.05 mL and 0.15 mL), yielding six formulations (AF1–FF6). Venlafaxine HCl was provided as a gift sample from Hamaz Pharma (Pvt.) Ltd. (Pakistan). HPMC K15 and triethyl citrate were obtained from Merck (Germany). Ethyl alcohol (Analar grade), methanol, sodium hydroxide, and potassium dihydrogen phosphate were obtained from Merck (Germany). Dichloromethane was obtained from Allied Signal, Riedel-de Haën. Potassium chloride was obtained from AppliChem. Distilled water was sourced from Bahauddin Zakariya University, Multan. Apparatus used included a hot plate magnetic stirrer (Lab Tech), pH meter (OHAUS®), screw gauge, digital balance (OHAUS®), dissolution apparatus (DIGITEK), tensile strength apparatus, and UV spectrophotometer (1720 Yoke Golvano), along with standard glassware and consumables.

A preparatory solvency assessment of venlafaxine hydrochloride was performed to evaluate solubility behavior in water–methanol mixtures. Solutions tested included 100% methanol and water:methanol mixtures of 8:2, 6:4, 4:6, and 2:8. Approximately 100 mg of venlafaxine HCl was added to each of five 100 mL conical flasks, volumes were adjusted using the respective solvent systems, and each flask was stirred for at least 1 min. Solutions were filtered and absorbance was determined at 224 nm using a UV spectrophotometer, and drug dissolved was calculated as concentration multiplied by dilution factor.

Phosphate buffer solution (pH 7.4) was prepared using two stock solutions. Solution A consisted of 0.2 M sodium hydroxide prepared by dissolving 8.0 g NaOH in 1000 mL distilled water. Solution B consisted of 0.2 M monobasic potassium dihydrogen phosphate prepared by dissolving 27.2 g KH_2PO_4 in 1000 mL distilled water. For buffer preparation, 39.1 mL of 0.2 M NaOH and 50 mL of 0.2 M KH_2PO_4 were combined in a 200 mL volumetric flask and brought to volume with distilled water to obtain pH 7.4 buffer.

A UV spectrophotometric calibration curve for venlafaxine hydrochloride was prepared at 224 nm. A stock solution was prepared by dissolving 100 mg venlafaxine HCl in 100 mL distilled water. Aliquots ranging from 1.0 mL to 10.0 mL of stock were transferred into separate volumetric flasks and diluted to 100 mL with distilled water to obtain concentrations within 10–100 µg/mL. Absorbance of each standard solution was measured at 224 nm and a calibration plot of concentration versus absorbance was constructed for quantitative analysis.

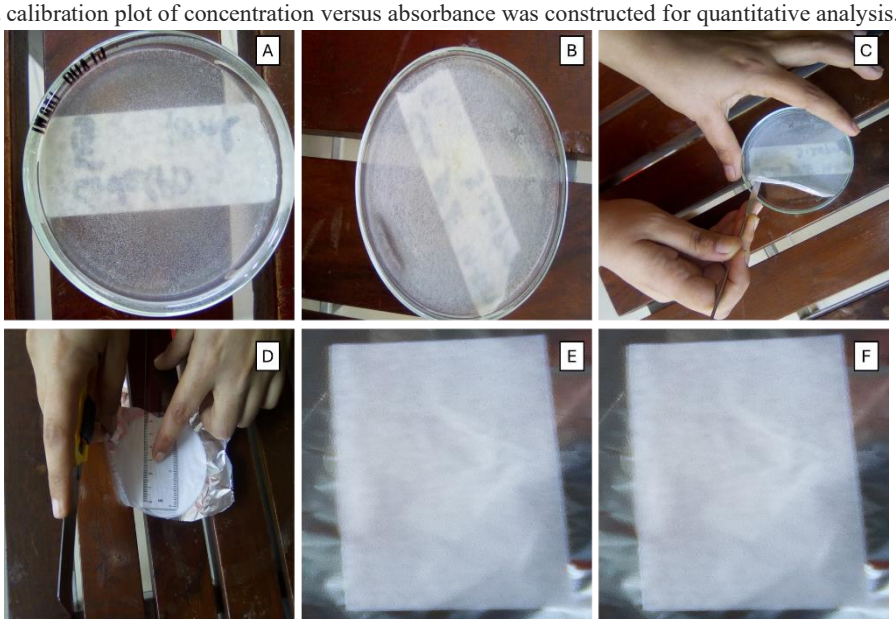

Figure 1 Preparation and processing of venlafaxine hydrochloride transdermal matrix patches by solvent casting. (A–B) Polymer–drug casting solution poured into Petri dishes and allowed to dry at room temperature to form uniform films. (C) Dried transdermal film carefully peeled from the Petri dish using a sharp blade to avoid tearing. (D) Films cut into patches of the required size and packed in aluminum foil for storage. (E–F) Representative dried venlafaxine HCl transdermal patches showing smooth surface and uniform appearance.

Transdermal matrix patches of venlafaxine hydrochloride were prepared using the solvent casting technique. The required amount of HPMC K15 for each formulation was weighed according to the formulation matrix. A solvent system was prepared by mixing ethanol and dichloromethane in a 1:1 ratio and stored in a closed container to minimize evaporation. Approximately 15–20 mL of the solvent system was transferred into a 50 mL beaker, the weighed polymer was added gradually, and the beaker was covered with aluminum foil. The mixture was stirred on a magnetic stirrer

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at low revolutions until the polymer was completely dissolved. Venlafaxine hydrochloride was then added with continuous stirring until a clear solution was obtained. The specified volume of triethyl citrate was incorporated and stirring was continued, with speed increased for 30–35 min to ensure homogeneity. The casting solution was poured into Petri dishes, covered with inverted funnels to minimize cracking, and dried at room temperature for 24 h. Dried films were carefully removed using a sharp blade, cut into patches as required, wrapped in aluminum foil, and stored in desiccators.

Physicochemical and mechanical evaluation of the prepared patches was conducted using standard tests. Weight variation was assessed by weighing three randomly selected patches per formulation and calculating mean weight. Thickness was measured at three points on each patch using a screw gauge and mean thickness was recorded. Drug content was determined by placing a patch in a 100 mL volumetric flask containing phosphate buffer pH 6.8, sonication, filtration, and UV analysis at 224 nm. Folding endurance was assessed by repeatedly folding each patch at the same location until breakage occurred, and the number of folds sustained without breaking was recorded. Percentage moisture loss was determined by placing patches in a desiccator containing calcium chloride at room temperature for 24 h and recording weights before and after drying, using the equation: % Moisture Loss = [(Initial weight − Final weight) / Final weight] × 100. Percentage moisture absorption was evaluated by placing accurately weighed patches in a desiccator containing 100 mL saturated aluminum chloride solution (84% relative humidity) for 64 h and calculating moisture uptake using: % Moisture uptake = [(Final weight − Initial weight) / Initial weight] × 100.

Tensile strength was determined using a pulley-based tensile strength apparatus with film strips of approximately 2.0 cm width. Incremental weights were applied until the film strip broke, and the force required to break the patch was recorded. Tensile strength was calculated using: Tensile strength = Applied force / Area, where applied force was recorded in kg and area in mm², yielding kg/mm². Three patches from each formulation were tested and mean ± standard deviation were intended for reporting. Visual inspection was performed to evaluate clarity, smoothness, flexibility, and overall appearance, categorized qualitatively as good (+), great (++), or excellent (+++).

Figure 2 Application of the venlafaxine HCl transdermal patch to the shaved dorsal skin of a rabbit for dermal irritation assessment (Draize method).

Water vapor transmission rate (WVTR) was measured using dried 5 mL glass vials filled with 1.00 g fused calcium chloride. A film of known area (3.83 cm²) was secured to the vial mouth using adhesive tape, and vials were weighed and stored in a humidity chamber (80–90% relative humidity) for up to 4 days. Vials were reweighed at defined intervals, and WVTR was calculated as: WVTR = (Final weight − Initial weight) / (Exposure period × Surface area of film) × 100. Swelling behavior was assessed by cutting patches of area 2 cm², drying in desiccators for 24 h, and exposing them to 75% relative humidity (saturated NaCl solution) until constant weight. Flatness was evaluated by cutting longitudinal strips, measuring initial and final lengths, and assessing constriction to describe percent flatness, where 100% flatness corresponded to zero constriction.

Compatibility between venlafaxine hydrochloride and HPMC K15 was assessed using Fourier-transform infrared spectroscopy (FTIR). FTIR spectra of pure drug, polymer, and formulated films were recorded, and characteristic peaks were compared to evaluate possible drug–polymer interactions. In-vitro drug release from the patches was studied using USP apparatus II (paddle method) with phosphate buffer pH 7.4 as dissolution medium. Each vessel contained 900 mL buffer and temperature was maintained at 32°C. Patches were placed at the vessel bottom and secured with gauze to prevent floating. The apparatus was operated at 50 rpm, and 5 mL samples were withdrawn at predefined intervals, with immediate replacement by equal volumes of fresh buffer. Samples were diluted as required and analyzed by UV spectrophotometry at 224 nm. Release experiments were intended to be performed on three patches per formulation, with mean values reported.

Skin irritation potential was assessed in healthy male rabbits (approximately 1.8 ± 0.2 kg) using an in-vivo Draize method with minor adjustments. Hair was removed from the left dorsal region using adhesive tape followed by careful shaving to remove residual hair, and the area was cleaned with an alcohol swab. A patch of 5 cm² was applied and secured with tape. After 24 h, the patch was removed and the application site was examined for erythema and edema using Draize scoring criteria on a 0–4 scale. Ethical conduct for animal experimentation was maintained in accordance with institutional standards; no ethical approval identifier was provided in the source manuscript.

Results

Table 1. Formulation Composition of Venlafaxine HCl Transdermal Matrix Patches

Formulation	Composition (Drug:Polymer)	Polymer	Casting Solvent	Plasticizer (Triethyl citrate)
AF1	0.5 : 0.7	HPMC K15	DCM : Ethanol (1:1)	0.05 mL
BF2	0.5 : 0.85	HPMC K15	DCM : Ethanol (1:1)	0.05 mL
CF3	0.5 : 1.0	HPMC K15	DCM : Ethanol (1:1)	0.05 mL
DF4	0.5 : 0.7	HPMC K15	DCM : Ethanol (1:1)	0.15 mL
EF5	0.5 : 0.85	HPMC K15	DCM : Ethanol (1:1)	0.15 mL
FF6	0.5 : 1.0	HPMC K15	DCM : Ethanol (1:1)	0.15 mL

Release kinetics were analyzed using standard models: zero-order (Qt = K0t), first-order (log Qt = log Q0 − Kt/2.303, where Qt is amount remaining at time t), Higuchi (Qt = KH t^1/2), and Korsmeyer–Peppas (Mt/M∞ = Kt^n), where Mt/M∞ is the fraction released at time t, K is the kinetic constant, and n is the diffusional exponent. Statistical analysis was planned to compare formulation effects using two-way ANOVA to assess the main and interaction effects of polymer ratio and plasticizer level for physicomechanical outcomes and repeated measures ANOVA for release

profiles, with post-hoc multiple comparison procedures as appropriate; statistical significance was defined at $p < 0.05$. Citations supporting general TDDS methodologies and evaluation approaches are consistent with established transdermal patch literature (6,7).

Patch formation and formulation feasibility

All six venlafaxine hydrochloride matrix patches (AF1–FF6) were successfully prepared by the solvent casting method using HPMC K15 as the film-forming polymer and triethyl citrate as plasticizer. Films were cast using a dichloromethane–ethanol solvent system (1:1) and dried at room temperature for 24 hours before removal, cutting, and storage in desiccators. The formulation design enabled systematic evaluation of polymer loading (0.7, 0.85, and 1.0 relative to drug) and plasticizer concentration (0.05 mL vs 0.15 mL) on patch properties (Table 1).
Physicochemical and mechanical characterization (qualitative results available)
The manuscript reports that physicochemical evaluations—including weight variation, thickness, drug content, folding endurance, percentage moisture loss, percentage moisture absorption, and tensile strength—were performed across all formulations. Although numerical results are not presented, the study states a consistent directional trend: as the polymer ratio increased, the values of these evaluated parameters increased, and similarly, higher plasticizer concentration was associated with higher values for these parameters. This implies that increased HPMC K15 content and increased triethyl citrate likely enhanced film mass, thickness, and mechanical robustness, consistent with expected behavior in hydrophilic polymer matrices where polymer fraction drives film structure and tensile integrity, and plasticizer improves flexibility and mechanical handling.

Drug–polymer compatibility (FTIR)

Compatibility assessment using FTIR was performed for the pure drug, polymer, and patch formulations. The manuscript reports that no drug–polymer interaction was observed, suggesting that venlafaxine hydrochloride remained chemically compatible with HPMC K15 under the formulation conditions. However, the manuscript does not provide a spectral overlay figure or a table of peak positions; therefore, the conclusion remains qualitative in the current draft.

Skin irritation outcomes (Draize test, qualitative result available)

A skin irritation test in rabbits was conducted using the Draize method. The manuscript states that no significant irritation was observed, indicating an acceptable short-term dermal tolerability profile of the patches. However, the scoring outputs (erythema and edema grades) are not shown as a results table, so the irritation conclusion cannot be quantitatively verified by the reader at present.

In-vitro drug release (USP apparatus II; qualitative trends available)

In-vitro release testing was conducted using USP apparatus II (paddle method) in phosphate buffer (pH 7.4) at 32°C over a 4–5 hour window. The manuscript reports that as HPMC K15 ratio increased, drug release slowed, consistent with formation of a denser hydrated matrix and increased diffusional path length. It also reports that formulations with higher triethyl citrate (0.15 mL) released the drug more rapidly than those containing 0.05 mL plasticizer, consistent with plasticizer-mediated increases in polymer chain mobility and free volume, facilitating drug diffusion. These statements support a controlled release pattern governed by matrix composition, but release percentages at each time point are not provided.

DISCUSSION

The present experimental formulation study demonstrates that venlafaxine hydrochloride can be incorporated into HPMC K15-based matrix transdermal patches prepared by solvent casting, and that systematic modulation of polymer ratio and triethyl citrate concentration produces predictable directional effects on physicomechanical properties and in-vitro release behavior. The reported trends—namely increased patch thickness, mechanical strength, and moisture-related parameters with increasing HPMC content—are consistent with the fundamental behavior of hydrophilic cellulose matrices, in which polymer fraction governs film-forming capacity, cohesive strength, and the development of a hydrated gel layer that increases diffusional path length and restricts drug mobility. Such matrix-controlled mechanisms have been widely described in transdermal and topical polymeric systems and are frequently associated with release slowing as polymer density and hydration-mediated barrier formation increase (8). Within this framework, higher HPMC K15 likely contributed to a more continuous polymer network and greater water uptake, yielding a swollen diffusion barrier that reduced venlafaxine diffusion from the patch into the medium during the 4–5 h release window, which aligns with classical diffusion-controlled release concepts (8).
Conversely, the observed trend of faster release from formulations containing higher triethyl citrate is mechanistically plausible and consistent with the role of plasticizers in polymeric films. Triethyl citrate is expected to reduce intermolecular forces and increase free volume, resulting in enhanced polymer chain mobility, improved film flexibility, and increased diffusivity of dissolved drug molecules through the matrix. Plasticizer-mediated enhancement of drug release has been repeatedly documented in transdermal film systems, where increased plasticizer concentration can accelerate solvent penetration and reduce matrix tortuosity, thereby facilitating diffusion-driven release while also improving mechanical handling and reducing brittleness (5,8). In the context of venlafaxine hydrochloride, which has been explored for transdermal delivery using enhancer strategies and permeation optimization approaches, such formulation-controlled release modulation is particularly relevant because venlafaxine's transdermal feasibility is strongly influenced by both drug mobility within the matrix and its subsequent movement across barrier membranes (9). Although the present work assessed in-vitro release using USP apparatus II rather than a diffusion-cell permeation configuration, the reported trends provide a preliminary formulation basis for selecting compositions that balance mechanical integrity with adequate release rates, which is essential before moving to flux-based permeation studies (7,11).
The FTIR findings indicating no evidence of significant drug–polymer interaction suggest that venlafaxine hydrochloride remained chemically compatible with HPMC K15 under the processing conditions, supporting a stable formulation environment and reducing concern for chemical incompatibility that could compromise potency or release performance. In pharmaceutics formulation science, "no interaction" in FTIR typically implies preservation of characteristic functional group peaks without meaningful shifts, disappearance, or new peak emergence, indicating that the drug is predominantly physically dispersed within the polymer network and that bonding interactions are not strong enough to alter chemical structure (8,14). While such compatibility is supportive of formulation stability, the evidentiary strength would be substantially improved by

presenting representative FTIR spectra overlays and a table of key peak positions for the drug, polymer, and optimized patch formulation, particularly if the work is intended for a Q1 pharmaceutics audience (14).

Dermal tolerability is an essential early requirement for transdermal patch development, and the Draize rabbit irritation outcomes reported as "no significant irritation" are consistent with the expected safety profile of HPMC-based hydrophilic matrices and citrate plasticizers used at conventional levels. However, a Q1-level interpretation requires full reporting of erythema and edema scores, their time course, and a clear irritation index calculation where applicable, because the regulatory and translational value of irritation testing depends on transparent scoring and reproducibility (7,11). If the irritation profile remains consistently non-irritant across all formulations, this would support further optimization steps, including the addition of permeation enhancers or adhesive layers, which are commonly required in real-world transdermal systems and may influence irritation risk (4,7,13).

A key practical output of formulation development studies is the identification of an optimal formulation based on a performance balance rather than any single endpoint. In this work, the optimal formulation would be the one demonstrating acceptable mechanical integrity (adequate tensile strength, folding endurance, uniform thickness, and minimal brittleness), reliable drug content uniformity, and a controlled—but sufficiently rapid—release profile across the test window. Based on the qualitative trends described, formulations with higher HPMC content likely offer superior structural robustness but slower release, whereas higher triethyl citrate formulations likely offer improved flexibility and faster release. Therefore, the optimal candidate would plausibly emerge from the intermediate-to-high polymer ratio group combined with the higher plasticizer level, though this conclusion must remain provisional until the quantitative dataset is presented in full and statistically compared across the 2×3 formulation matrix (5,8).

Several limitations should be acknowledged. First, the in-vitro release method used (USP apparatus II) assesses drug liberation into the dissolution medium but does not quantify transdermal permeation across a biological membrane, and therefore cannot directly support claims of controlled permeation through skin. A Franz diffusion cell study using excised animal or human skin is required to calculate permeation flux (J), permeability coefficient (Kp), lag time, and to confirm whether release-limiting behavior persists under skin barrier conditions (9,13). Second, the release duration evaluated (4–5 h) is short relative to conventional transdermal patch objectives, which often target prolonged delivery, and the manuscript should clarify whether the intended product concept is short-duration controlled release or whether the experimental window was limited by study constraints (4,11). Third, critical transdermal performance attributes—including adhesive strength, tack, peel force, stability under ICH-like conditions, and long-term moisture protection—were not reported, limiting translational readiness (7,11). Future work should integrate permeation enhancement strategies documented for venlafaxine and other drugs with similar delivery challenges and confirm safety and efficacy through expanded irritation evaluation and permeation/retention profiling (9,13).

Overall, within the constraints of the available qualitative dataset, this work supports the formulation principle that polymer ratio and plasticizer concentration are dominant controllable determinants of venlafaxine hydrochloride matrix film properties and release behavior. With complete quantitative reporting, rigorous statistical comparison, and follow-up permeation flux testing using diffusion-cell methodology, these findings could provide a reproducible design foundation for venlafaxine transdermal patch development and contribute useful formulation evidence to the antidepressant TDDS literature (16-18).

CONCLUSION

Venlafaxine hydrochloride transdermal matrix patches prepared by solvent casting using HPMC K15 and triethyl citrate exhibited formulation-dependent physicomechanical performance and in-vitro release behavior, with increasing polymer ratio reported to enhance patch structural characteristics while slowing drug release, and higher triethyl citrate concentration reported to improve flexibility and accelerate release relative to lower plasticizer content. FTIR compatibility assessment suggested absence of major drug–polymer incompatibility, and short-term rabbit irritation testing indicated acceptable dermal tolerability under the study conditions. Although the present work establishes a rational formulation framework and directional trends for optimizing venlafaxine HCl matrix patches, definitive selection of an optimal formulation and translation toward a clinically relevant transdermal system requires complete quantitative reporting, statistical comparison across the 2×3 formulation matrix, and confirmatory membrane-based permeation testing (e.g., Franz diffusion cell) with flux and permeability metrics.

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