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REVIEW

Review on transdermal patches: optimization in drug administration

Revisión sobre parches transdérmicos: optimización en la administración de fármacos

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Abstract

Aim:

To synthesize technical, clinical, and regulatory knowledge on transdermal patches and identify persistent gaps that impact their safe and effective use.

Methods:

Data sources and selection criteria were defined as follows. Sources consulted included PubMed, Scopus, ScienceDirect, and Google Scholar; regulatory agency websites (FDA, EMA, ANVISA, INVIMA); and official pharmacopeial and methodological documents (USP-NF, European Pharmacopoeia, OECD). English, Spanish, and Portuguese sources were considered, with no predefined time limits. The last search update was performed on September 9, 2025. Regarding study selection, narrative approach including published reviews, relevant primary studies, official regulatory guidances/Q&A, and pharmacopoeia standards related to design, release/permeation, bioavailability/bioequivalence, adhesion, and regulatory frameworks. Non-authoritative or commercial webpages and duplicates were excluded, with priority given to official and peer-reviewed sources. This review was appraised against the SANRA criteria, covering: justification of the article's importance, statement of aims, description of the literature search, referencing, scientific reasoning, and appropriate presentation of data.

Results:

Transdermal systems may offer sustained drug delivery and adherence advantages, but their real-world performance is constrained by biological variability, patient misuse, and fragmented regulatory requirements. Adhesion remains a critical quality attribute, yet test methods are heterogeneous and alignment between in vitro metrics and clinical outcomes is limited.

Conclusions:

Stronger harmonization of adhesion and bioequivalence standards, together with improved patient education and testing under real-life stress conditions, is needed to ensure the quality, safety, and interchangeability of innovator and generic transdermal products.

Conflict of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the content of this manuscript. The funding entity had no influence on the design of the article, the selection of the literature, the analysis of the information, or the conclusions presented. The authors are solely responsible for the views and content expressed in this work. All the authors declared there is no conflict of interest.

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CRediT authorship contribution statement

JGO: Funding acquisition, Project administration, Supervision, Conceptualization, Methodology, Formal analysis, Writing - review & editing. **JJSG:** Investigation, Writing - original draft, Data curation, Formal analysis. **FM:** Investigation, Methodology. **AMC:** Investigation, Methodology.

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Resumen

Objetivos:

Sintetizar el conocimiento técnico, clínico y regulatorio sobre los parches transdérmicos e identificar vacíos persistentes que afectan su uso seguro y eficaz.

Métodos:

Se realizó una búsqueda bibliográfica exhaustiva en múltiples bases de datos y fuentes oficiales, aplicando los siguientes criterios de fuentes y selección. Las fuentes consultadas incluyeron PubMed, Scopus, ScienceDirect y Google Scholar; sitios web de agencias regulatorias (FDA, EMA, ANVISA, INVIMA); y fuentes oficiales farmacopéicas y metodológicas (USP-NF, Farmacopea Europea, OECD). Se consideraron fuentes en inglés, español y portugués, sin restricción temporal a priori. Última actualización: 9 de septiembre de 2025. La selección de estudios siguió un enfoque narrativo que incluyó revisiones publicadas, estudios primarios relevantes, guías regulatorias oficiales y documentos de preguntas y respuestas, así como estándares farmacopéicos relacionados con el diseño, la liberación/permeación, la biodisponibilidad/bioequivalencia, la adhesión y los marcos regulatorios. Se excluyeron páginas web no autorizadas o de carácter comercial y duplicados, priorizando fuentes oficiales y revisadas por pares.

Resultados:

Los sistemas transdérmicos ofrecen liberación sostenida y beneficios en la adherencia terapéutica; sin embargo, su desempeño se ve limitado por la variabilidad biológica, el uso inadecuado por parte de los pacientes y la fragmentación de los requisitos regulatorios. La adhesión continúa siendo un atributo crítico de calidad, con métodos de evaluación heterogéneos y una alineación limitada entre las métricas in vitro y los resultados clínicos.

Conclusiones:

Se requiere una mayor armonización de los estándares de adhesión y bioequivalencia, junto con estrategias de educación al paciente y la realización de ensayos bajo condiciones reales de estrés, para garantizar la calidad, seguridad e intercambiabilidad de los productos transdérmicos innovadores y genéricos.

Remark

1) Why was this study conducted?

Transdermal patches provide a practical alternative for drug delivery; however, their effectiveness in real-world use is limited by patient misuse, variability in clinical performance, and fragmented regulatory requirements

2) What were the most relevant results of the study?

This review integrates technical, clinical, and regulatory perspectives and identifies adhesion as a critical quality attribute that is still evaluated using heterogeneous methods across different settings

3) What do these results contribute?

By highlighting these gaps, this review emphasizes the need to harmonize standards and improve patient education to ensure the safety, consistency, and assessment of real-world outcomes of transdermal systems in clinical practice

Introduction

Pharmaceutical products containing identical active ingredients are often available in multiple routes of administration, each offering specific advantages depending on therapeutic goals, the patient's clinical condition, and preferences. Among these options, transdermal therapeutic systems -commonly known as transdermal patches- represent a non-invasive alternative to oral, subcutaneous, or intravenous delivery. These systems can provide controlled drug release, reduced dosing frequency, and improved patient adherence in selected cases. In addition, they facilitate drug absorption through the skin, allowing either localized or systemic therapeutic effects, as required [1]. Transdermal systems are specifically engineered for sustained and controlled drug release, with designs focused on dose precision and ease of use, particularly in chronic treatments requiring stable plasma concentrations [2].

Transdermal delivery offers several advantages over oral and parenteral routes. It circumvents first-pass hepatic metabolism, reduces the risk of gastrointestinal irritation, and avoids degradation by digestive enzymes or acidic environments [3]. The visible nature of the patch may also act as an adherence aid, making it particularly beneficial for older adults, individuals with cognitive impairment, or caregivers responsible for medication management. Importantly, transdermal patches can be removed promptly in the event of an adverse reaction or overdose, adding a safety margin not present in many systemic formulations [4].

Over the last two decades, the use of transdermal patches has expanded to a wide range of clinical indications, including chronic pain management, hormonal therapies, Alzheimer's disease, smoking cessation, menopause, and contraception [4]. Despite their growing use, transdermal patches are not without limitations. Some of the challenges include local skin irritation, inconsistent absorption due to variability in skin permeability, and formulation constraints when dealing with molecules that are either highly lipophilic, unstable, or high molecular weight [5]. In recent years, concerns have emerged regarding the risk of inconsistent adhesion performance in generic transdermal products. Even a partial lifting of the patch or its complete detachment, can severely compromise drug delivery, therapeutic safety, and quality [6]. These concerns highlight the need for robust regulatory oversight and standardized evaluation criteria to ensure therapeutic equivalence and consistent product adhesive performance.

This review aims to provide an integrative overview of the technological principles, classifications, clinical applications, and regulatory frameworks associated with transdermal patches. Particular attention is given to domains in which current regulations may be insufficient, especially the evaluation of adhesive performance in generic products, a dimension increasingly recognized as critical for ensuring patient safety and therapeutic efficacy. Our aim was to integrate technical, clinical, and regulatory perspectives on transdermal patches and identify persistent gaps in pharmacopoeial and regulatory provisions, particularly adhesion and bioequivalence/bioperformance domains.

Methods

Review type and rationale

This is a narrative review appraised against the SANRA criteria [7]. The methodology followed the instrument's domains: 1) justification of the article's importance, 2) statement of aims, 3) description of the literature search, 4) referencing, 5) scientific reasoning, and 6) appropriate presentation of data. The topic was selected for its clinical and regulatory relevance to transdermal patches, with emphasis on gaps affecting safe and effective use in Colombia.

Literature search and source selection (narrative approach)

A purposive, non-systematic search was conducted in PubMed, Scopus, ScienceDirect, and Google Scholar, complemented by authoritative regulatory/pharmacopoeial websites (FDA,

EMA, ANVISA, INVIMA, OECD, USP, Ph. Eur., BP, JP). Evidence was interpreted according to its nature (regulatory guidance, clinical data, *in vitro* studies, and observational reports), with priority given to primary regulatory documents and peer-reviewed literature. No a priori time limits; last update: 9 September 2025. Priority was given to official guidances, pharmacopeial standards, peer-reviewed reviews and pertinent primary studies addressing design, release/permeation, BA/BE, adhesion, and regulatory frameworks; commercial or non-authoritative webpages and duplicates were excluded.

Referencing policy and appraisal

Key statements are supported by official or peer-reviewed sources. SANRA items guided the appraisal of importance, aims, search description, and referencing.

Data presentation

Findings are presented narratively and summarized in comparative tables when useful (e.g., pharmacopoeial provisions, regulatory requirements, CQAs).

Results

Fundamentals and key aspects of transdermal patches

Evolution. Over the decades, numerous formulations have been developed to improve drug bioavailability, patch wearability, and patient adherence [8]. In this context, transdermal patch technologies have evolved through generations: first-generation systems focused on optimizing the physicochemical properties of small-molecule drugs for passive diffusion; second-generation approaches introduced chemical penetration enhancers and emulsion-based or nanocarrier systems; third-generation technologies rely on physical methods to transiently disrupt the epidermal barrier (e.g., radiofrequency, ultrasound, laser microperforation); and a proposed fourth generation aims to enable personalized therapy through bioelectronic wearable systems [9].

Transdermal patch development. The development of a novel transdermal patch involves a series of interrelated stages, each contributing to the final performance and regulatory viability of the product. The process typically begins with preformulation studies aimed at characterizing the physicochemical properties of the drug, including solubility, stability, and compatibility with potential excipients. This is followed by formulation development, in which excipients, drug loading, and polymer systems are selected and optimized to ensure consistent performance. Patch prototypes are then designed and evaluated for key functional parameters such as adhesion, flexibility, and release kinetics [10].

Subsequently, *in vivo* studies are conducted, initially in animal models, to evaluate pharmacokinetics and pharmacodynamics and to characterize absorption, distribution, metabolism, and excretion. Clinical development involves human trials across successive phases to assess safety, therapeutic efficacy, and pharmacokinetics, thereby supporting regulatory approval. Following successful clinical evaluation, a regulatory submission is prepared for agencies such as the FDA or EMA, demonstrating compliance with quality, safety, and efficacy requirements. After approval, scale-up and manufacturing are carried out under Good Manufacturing Practices to ensure batch-to-batch consistency and commercial viability. In the case of generic transdermal patches, regulatory pathways may allow waivers of clinical efficacy trials when bioequivalence is adequately demonstrated. Nevertheless, complementary assessments of adhesion and local tolerability, including irritation and sensitization studies, remain mandatory, as they are recognized as critical quality attributes by major regulatory agencies [11,12].

Basic components. Formulations integrate various excipients designed to optimize delivery, retention, and stability of the active ingredient. The selection and arrangement of components vary by drug and system type [13], but the essential elements are summarized below and illustrated in Figure 1.

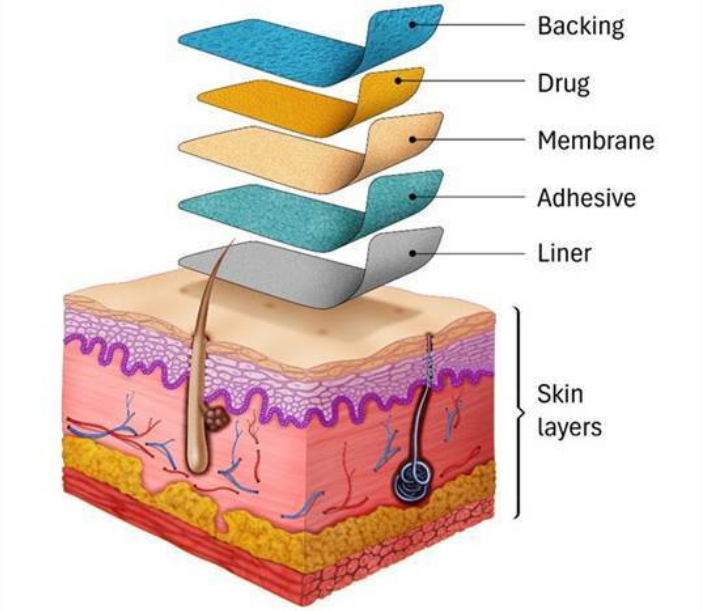

Figure 1. Main structural components of a transdermal patch. Compositions may vary by drug and system type

- **Adhesives**: Secures the patch to the skin and maintains its position throughout wear time [13]. Most systems use pressure-sensitive adhesives such as polyacrylates, polyisobutylenes, or silicone-based compounds [14].
- **Backing layer**: Serves as a protective barrier against external factors while also providing mechanical support, flexibility, and cosmetic appearance [15]. Interaction with internal excipients should be minimized, as prolonged contact may lead to migration or degradation. Materials commonly used include vinyl, polyethylene, polyester, aluminum, and polyolefin films [14].
- **Release liners**: These are part of the primary packaging and are removed before use. They protect the adhesive and matrix, preserving drug content and preventing premature exposure [15]. Typical materials include silicone-coated or polyethylene-coated papers [10].
- **Membrane:** In reservoir or controlled-release systems, semi-permeable membranes regulate drug diffusion into the skin [13]. Materials such as ethylene vinyl acetate, silicone rubber, and polyurethane are commonly employed due to their ability to maintain controlled delivery profiles [14].

Classification

Transdermal patches are commonly classified according to the location and distribution of the drug within the system, resulting in the categories illustrated in Figure 2 A-D [16].

- **Single-layer drug-in-adhesive**: The drug is embedded directly in the adhesive, positioned between a release liner and a backing layer [16]. (Figure 2A)
- **Multi-layer drug-in-adhesive**: Contains two distinct adhesive layers, each capable of carrying drug, often separated by a membrane, which enables combination therapies or controlled dual-release [16]. (Figure 2B)
- **Reservoir system**: Features a separate drug reservoir, liquid, gel, or suspension, contained by a membrane that controls the release rate. These membranes can be microporous or non-porous depending on the formulation [17]. (Figure 2C)
- Matrix system: The drug is dispersed within a polymeric matrix in direct contact with the skin, with an outer adhesive layer ensuring patch placement [17]. (Figure 2D)

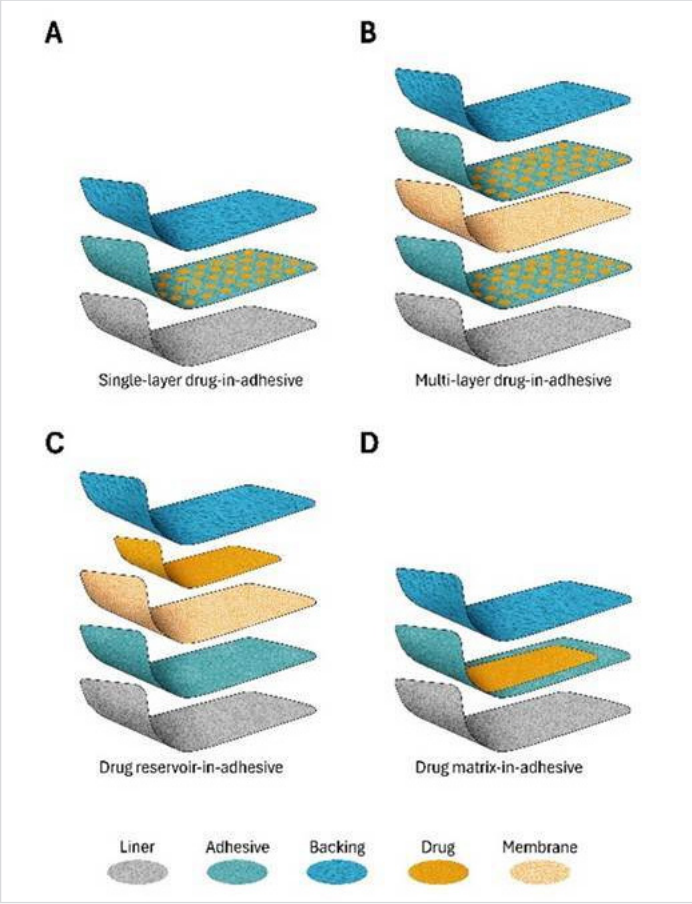

Figure 2. A-D. Classification of transdermal patches based on drug placement: (A) single-layer drug-in-adhesive, (B) multi-layer drug-in-adhesive, (C) reservoir system, and (D) matrix system.

Mechanism of drug release

Drug release from controlled delivery systems, such as transdermal patches, can occur through different mechanisms depending on system design and material characteristics. Reported processes include[18]:

- Diffusion (dominant): The drug moves along a concentration gradient through the polymer.
- Polymer swelling: Hydrophilic polymers absorb water, expand, and promote drug diffusion; in some systems, swelling itself controls the release rate.
- Polymer erosion and degradation: Biodegradable polymers (e.g., PLA, PLGA, chitosan) undergo hydrolysis or enzymatic breakdown, releasing the drug at a rate influenced by surface or bulk erosion
- Externally activated release: Smart polymers respond to stimuli such as pH, temperature, electric fields, or light, altering their structure to trigger drug release.
- Osmosis (rare in patches): Water penetrates a semi-permeable membrane, generating pressure that drives drug solution, enabling controlled release.

In practice, some systems may involve more than one process. However, traditional passive transdermal patches rely primarily on diffusion-controlled release from the patch, followed by partitioning into and diffusion across the stratum corneum. In matrix/drug-in-adhesive designs, the drug is uniformly dispersed within the polymer, which serves as both depot and rate-controlling medium. By contrast, reservoir systems employ a rate-controlling polymeric membrane to regulate drug release, enabling a more constant flux as long as the reservoir remains saturated and largely independent of polymer swelling [17,18].

Permeation

Pathways of transdermal drug permeation. Drug permeation across the skin occurs through two primary pathways: the trans-epidermal route and the trans-appendageal route.

The trans-epidermal route involves passage through the stratum corneum, either directly across corneocytes (transcellular) or through the lipid matrix between them (intercellular). Among these, the intercellular route is generally considered the dominant pathway, requiring a balance of lipophilicity and hydrophilicity for effective absorption [19].

The trans-appendageal route, also referred to as the shunt route, enables penetration through hair follicles and sweat or sebaceous glands. However, its contribution is limited by the small surface area involved (~0.1% of the total skin surface), though follicular density and opening size may significantly influence drug uptake [19,20].

Characteristics of drugs for transdermal permeation. Due to the barrier function of the skin, molecules with certain physicochemical properties are generally more suitable for passive, systemically acting transdermal delivery. The following ranges are practical design guidelines rather than rigid cut-offs [21]:

- Molecular weight under 500 Da.
- Log P between 1 and 3.
- Non-ionized form at physiological pH.
- Aqueous solubility greater than 1 mg/mL.
- Melting point below 200 °C.
- Daily dose of 20 mg or less.

These parameters optimize both solubility and partitioning into the stratum corneum while allowing sufficient flux to achieve therapeutic plasma levels.

Methods to enhance molecular permeation. Given the limited number of drug candidates that naturally meet the criteria for effective passive skin permeation, numerous enhancement strategies have been developed to improve transdermal drug delivery.

Chemical penetration enhancers increase drug permeability by temporarily disrupting the lipid architecture of the stratum corneum or by improving drug solubility and partitioning. Common examples include fatty acids, terpenes, sulfoxides, and surfactants, including anionic, cationic, and non-ionic compounds [22,23]. Another widely used approach involves the design of prodrugs, in which the parent molecule is chemically modified into a bioreversible derivative to optimize pharmacokinetic and physicochemical properties [24].

Lipid-based vesicular systems represent another enhancement strategy by mimicking biological membranes and encapsulating the drug within vesicles, thereby facilitating permeation across the skin. These systems can improve the bioavailability of poorly soluble drugs and protect them from degradation [25].

Microneedle arrays consist of microscale projections arranged on a patch that create transient micropores in the skin, enabling the delivery of large, hydrophilic, or high-molecular-weight drugs. Their length is sufficient to breach the stratum corneum without stimulating pain receptors, minimizing discomfort and infection risk. This approach has demonstrated highly reproducible delivery and low inter-subject variability in bioavailability [26-29].

Additional enhancement techniques include ultrasound, laser, radiofrequency, electrothermal methods, and magnetophoresis. Although effective, these approaches are less commonly used due to their invasiveness, higher cost, or the need for specialized equipment.

Bioavailability and biological factors that influence bioavailability. Bioavailability is commonly defined as "the rate and extent to which the active drug is absorbed from a dosage form and becomes available in the systemic circulation." It is typically assessed by calculating the area under the curve (AUC) from a concentration-time plot, which reflects the total exposure of the body to the unchanged drug [30]. As highlighted in general bioavailability studies, insufficient systemic exposure can reduce treatment efficacy or even result in therapeutic failure [31]. Bioavailability in transdermal patches is shaped not only by formulation aspects or delivery system design, but also by biological variability, which can markedly alter absorption profiles. Several biological factors could contribute to this variability, including skin age, hydration level, lipid composition, temperature, blood flow, cutaneous metabolism, skin barrier integrity, pathologies, ethnicity, gender, and site of application [32,33].

To mitigate these inconsistencies, prescribers and manufacturers must avoid generalizations in dosing and usage instructions. Patient information leaflets and summary of product characteristics should clearly state the recommended application site, duration of use, and dosing schedule, while accounting for the diversity of patient profiles. Furthermore, transdermal formulations should strive to minimize absorption variability by stabilizing parameters such as skin hydration and temperature, either through formulation strategies or usage guidelines [33].

Regulatory standards

To ensure the quality, safety, and therapeutic efficacy of transdermal patches, compliance with regulatory standards is essential. These standards encompass the evaluation of specific attributes that directly influence clinical performance and patient safety. Yet, the mandatory nature and scope of these requirements vary across regions, as each jurisdiction follows its own authority, such as the FDA (United States), EMA (European Union), and INVIMA (Colombia). While many core evaluation principles are broadly aligned, regulatory environments differ in their level of detail and in the specific design of required tests [34,35].

Authorities often rely on pharmacopoeias such as the USP, Ph. Eur., BP, and JP, which are widely referenced internationally, to establish standardized analytical methods for finished product testing, thereby supporting a partial degree of regulatory convergence. For example, in Colombia, Article 22, literal (k), of Decree 677 of 1995 requires that the analytical methodology for finished products correspond to one of the pharmacopoeias officially accepted in the country (USP, BP, French Codex, DAB, Ph. Eur, Ph. Int.). The manufacturer must indicate the selected pharmacopoeia, its edition, and the relevant section; if no method is available in these compendia, complete validation data must be submitted [36].

Nevertheless, evaluating transdermal patches remains challenging, because not all measurable attributes correlate directly with safety or therapeutic effectiveness. To address this, the concept of *Critical Quality Attributes* (CQAs) has been adopted. CQAs are defined as product characteristics that must be controlled within specified limits to ensure safety and efficacy [35,37]. Table 1 presents a comparative overview of CQAs, *in vitro* performance tests, adhesion-related evaluations and their regulatory status across major pharmacopoeias (USP, Ph. Eur., BP, JP).

Table 1. Quality control parameters and testing approaches for transdermal drug delivery systems.,

Critical Quality Attribute (CQA)	Pharmacopeial mention/coverage
Assay	BP, EP, JP, USP
Content Uniformity	BP, EP, JP, USP
Moisture content	EP, USP, JP
Thickness	-
Tensile strength	-
Elongation	-
Flatness test	-
Folding endurance	-
Microbial test	USP, EP, JP
In vitro tests	
Drug release	USP, EP
Drug permeation	EP
Adhesive properties tests	
Tack test	USP (descriptive, not mandatory)
Peel adhesion test	USP (descriptive, not mandatory)
Shear adhesion test	USP (descriptive, not mandatory)
Cold flow test	-
Leak test	USP (case-by-case / reservoir systems / CCI when applicable)
Patch integrity	-
Impurities and degradation	
Impurities and Degradation test/stability	BP, EP, JP, USP
Skin irritation	
Skin irritation and Sensitization test	-

Adapted from Kim et al. [35] and complemented with FDA quality considerations for transdermal delivery systems and EMA quality guidelines[12,72]. BP: British Pharmacopoeia; EP: European Pharmacopoeia; JP: Japanese Pharmacopoeia; USP: United States Pharmacopeia; CQA: Critical Quality Attribute; FDA: Food and Drug Administration; EMA: European Medicines Agency; CCI: Container Closure Integrity. (-): not covered or not explicitly addressed in the consulted pharmacopeias.

Additionally, Table 2 provides an overview of selected international regulatory guidelines. These guidelines, which include both finalized and draft documents, are used by agencies such as the FDA and EMA to assess marketing authorization applications; although generally non-binding, compliance or a scientific justification for deviations is typically expected. For example, *in vitro* release of transdermal patches is assessed according to Ph. Eur. 2.9.4 and the EMA Guideline on the Quality of Transdermal Patches (2014), while bioequivalence is addressed through pharmacokinetic guidance, including FDA product-specific guidance and the EMA Guideline on the Investigation of Bioequivalence (2010). Each guidance addresses a specific parameter and cannot substitute for another, as regulatory agencies expect applicants to provide evidence according to the corresponding requirement.

Adapted from Engelhardt et al. [34] and complemented with international regulatory documents: FDA (*Transdermal and Topical Delivery Systems - Product Development & Quality Considerations*, 2019 draft; *Assessing Adhesion*, rev. draft 2023; *Assessing Irritation/Sensitization*, rev. draft 2023) [11,72,73]; EMA (*Guideline on quality of transdermal patches*, 2014) [12]; pharmacopeias- Ph. Eur. 2.9.4 (EP 11th, 2023) [45], USP <724> (drug release) and USP <1207> (container closure integrity) [44,74]; OECD dermal absorption/irritation methods (TG 427, TG 428, TG 439; GD 28; Guidance Notes 156) [75-78]; and ANVISA Guide No. 20/2019 (v2, 2021) [79].

In contrast, Table 3 summarizes the Colombian regulatory framework. Unlike other regions, Colombia does not have Transdermal Delivery Systems -specific technical guidance; instead, evaluation is based on general pharmaceutical regulations, acceptance of international pharmacopeias, and broad requirements for bioequivalence and stability.

Adapted from Engelhardt et al. [34]. Sources: Decree 677/1995 (art. 22) [36]; Resolution 1124/2016 [80]; INVIMA GU061 [81]; INVIMA GU055 [82]. International compendia as applicable: Ph. Eur. 2.9.4; USP <1207> [45,74].

Evaluation of efficacy, quality, and safety

As previously discussed, various parameters must be assessed to ensure quality, safety, and therapeutic efficacy of transdermal patches. The following overview presents key evaluation criteria, along with their significance in determining the product's overall performance.

Table 2. Regulatory tools applied to transdermal drug delivery systems.

Assay/Country	USA	Europe	Brazil	OECD
Performance test (In vitro release)	USP-NF <724> Drug Release; FDA Transdermal and Topical Delivery Systems - Product Development & Quality Considerations (2019 draft)	Ph. Eur. 2.9.4 (EP 11.x): dissolution test for patches; EMA Guideline on quality of transdermal patches (2014).	ANVISA Guide No. 20/2019 (v2, 2021): dissolution/ permeation methods (applied case by case).	OECD GD 28 and Guidance Notes 156: Franz cell diffusion approach
Bioequivalence Test	PK BE according to PSGs and ANDA; supported by FDA TDS PD&Q (2019 draft), Adhesion (rev. draft 2023), and Irritation/ Sensitization (rev. draft 2023).	Bioequivalence assessed under EMA Guideline on the Investigation of Bioequivalence; the EMA transdermal patch quality guideline (2014) addresses quality/CMC and does not substitute BE guidance	Not specified / No explicit requirement	Not specified / No explicit requirement
Irritation/ sensitization assays	FDA draft guidance on irritation/sensitization (2018; rev. draft 2023): cumulative irritation & sensitization study	EMA Quality Guideline (2014, Appendix I): 21-day cumulative irritation and sensitization	ANVISA Guide No. 20/2019 (v2, 2021): evaluation of cutaneous tolerability	OECD TG 439: in vitro reconstructed human epidermis
Quality attributes evaluation	USP-NF (2024): description, assay, uniformity, microbial limits, adhesive property tests	EP 11th (2023): uniformity of content/dosage units; EMA Quality Guideline (dissolution, microbial limits, and antimicrobial preservative content 2014),	ANVISA Guide No. 20/2019 (2021): description, assay, impurities, physicochemical tests properties, polymorphism, uniformity of dosage units, water content, pH, apparent viscosity, microbial limits, antimicrobial preservative content and antioxidant content.	Not specified / No explicit requirement
Permeation assay in the development stage	FDA guidance (2019): IVPT (and IVIVC where justified) using Franz cells	EMA Quality Guideline (2014): IVPT/IVIVC recommended	ANVISA Guide No. 20/2019: Franz cell or dissolution apparatus	OECD TG 427 (in vivo), TG 428 (in vitro), GD 28/Notes 156
Leak test	USP <1207> Package Integrity-Sterile Products (applies to sterile/CCI, not universal for all TDS) (Case-by-case)	EP 11th (2023): general integrity requirements. (case-by-case)	ANVISA Guide No. 20/2019: leak test for reservoir systems	Not specified / No explicit requirement
Adhesion tests	FDA draft guidance on adhesion (2019; revised 2023): clinical adhesion study with temporal resolution	EMA Guideline (2014, Appendix II): in vivo adhesion evaluation.	ANVISA 20/2019: primarily in vitro peel/tack; in vivo if required)	Not specified / No explicit requirement

Adapted from Engelhardt et al. 34 and complemented with international regulatory documents: FDA (Transdermal and Topical Delivery Systems - Product Development & Quality Considerations, 2019 draft; Assessing Adhesion, rev. draft 2023; Assessing Irritation/Sensitization, rev. draft 2023) 11,72,73; EMA (Guideline on quality of transdermal patches, 2014) 12; pharmacopeias- Ph. Eur. 2.9.4 (EP 11th, 2023) 45, USP <724> (drug release) and USP <1207> (container closure integrity) 44,74; OECD dermal absorption/irritation methods (TG 427, TG 428, TG 439; GD 28; Guidance Notes 156) 75-78; and ANVISA Guide No. 20/2019 (v2, 2021) 79.

Table 3. Regulatory tools applied to transdermal drug delivery systems in Colombia (INVIMA/MSPS).

Assay/Country	Colombia
Performance test (In vitro release)	No national TDS-specific guideline. Relies on pharmacopeias accepted by Decree 677/1995.
Bioequivalence Test	No TDS-specific criteria. Applies general framework: Resolution 1124/2016 + INVIMA Guideline GU061 (protocols).
Irritation / sensitization assays	No specific TDS guidance. Safety evidence expected; international methods accepted.
Quality attributes evaluation	No national chapter on TDS adhesion or mechanical properties. Control based on accepted pharmacopeias (Decree 677/1995).
Permeation assay (IVPT/IVIVC)	No TDS-specific guidance. International methodologies (IVPT/IVIVC with Franz cells) may be used case by case.
Leak test	No explicit national requirement: container-closure integrity testing may be provided if scientifically justified using suitable compendial/validated methods (note: USP <1207> is primarily for sterile products)
Adhesion tests	No Colombian guidance. In vivo adhesion not standardized; case-by-case assessment.

Adapted from Engelhardt et al. 34. Sources: Decree 677/1995 (art. 22) 36; Resolution 1124/2016 80; INVIMA GU061 81; INVIMA GU055 82. International compendia as applicable: Ph. Eur. 2.9.4; USP <1207> 45,74.

Quality evaluation

Physicochemical evaluation. Typically includes the assessment of thickness, weight variation, hardness, drug content uniformity, swellability, moisture content, and surface pH. Patch thickness is measured at multiple points using instruments such as microscopes, dial gauges, or micrometers, as consistent thickness is essential to ensure uniform drug release [38]. Weight variation is evaluated by weighing individual patches from the same batch and comparing the values to the mean to confirm consistency [39]. Hardness is assessed using a hardness tester and reflects the patch's ability to withstand mechanical stress during storage, handling, and application [40]. Drug content uniformity is determined by dissolving and analyzing portions of the patch to verify homogeneous drug distribution within the matrix [41]. Swellability is assessed by immersing the patch in distilled water and measuring dimensional changes, providing insight into matrix-moisture interactions that may influence release kinetics [40]. Moisture content is determined by weighing patches before and after desiccation, as moisture levels directly affect stability and shelf life [42]. Finally, surface pH is measured after exposing patches to distilled water using a calibrated pH meter, as inappropriate pH values may increase the risk of skin irritation [32].

Mechanical properties evaluation. Mechanical properties are evaluated to ensure adequate flexibility, strength, and adhesive performance during use. Folding endurance is assessed by determining the number of times a patch can be folded at the same location without breaking, providing an indication of flexibility [38]. Tensile strength is measured using a tensiometer to quantify the force and elongation at break, reflecting the mechanical durability of the patch [40]. Shear strength represents the cohesive strength of the adhesive and is evaluated by measuring resistance to sliding or detachment under load; adequate shear strength is essential to prevent patch slippage and minimize adhesive residue upon removal [32].

Stability evaluation. Stability is evaluated through accelerated studies as per ICH Q1A(R2) guidelines, which define conditions and climatic zones for pharmaceutical products [43]. Although this guidance is general, its principles are applied to transdermal patches to establish shelf life and ensure product quality. Polymer-drug interactions and structural changes are detected using differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FT-IR) [40]. Additional studies may include photostability, pH stability, and thermostability, depending on the drug's degradation profile.

Efficacy evaluation. *In vitro* evaluation

Transdermal patches are typically subjected to three main *in vitro* tests: drug release, skin permeation, and adhesion assessments:

- ***In vitro* drug release:** Drug release from the finished patch should be measured using compendial apparatus for TDS (e.g. USP <724> apparatus 5/6/7; Ph. Eur. 2.9.4), under controlled hydrodynamics, temperature, and sink conditions [44,45].
- ***In vitro* skin permeation studies**: Provide insight into the thermodynamic activity of the drug within the matrix, although they do not always correlate with *in vivo* release [46]. These studies use animal or synthetic membranes in vertical diffusion cells, with samples collected and analyzed over time [32].
- ***In vitro* adhesion tests**: Three methods are commonly used [47]: Peel adhesion test measures the force required to detach the patch, influenced by angle, speed, substrate, and adhesive thickness. Probe tack test assesses initial stickiness after brief contact, affected by pressure, contact time, and area. Shear adhesion test evaluates internal cohesion of the adhesive by measuring resistance to sliding or detachment under load.

In Vivo evaluation

In vivo studies are conducted in animal models or human volunteers, depending on the development phase and regulatory requirements. Animal models are useful for preliminary *in vivo* assessment of transdermal delivery and for toxicology/irritation work; commonly used species include hairless mice or rats, rabbits and guinea pigs. However, interspecies differences in skin structure and barrier function limit quantitative translation to humans, and ethical considerations also apply [48]. For systemic transdermal products, pharmacokinetic studies in healthy human volunteers are the primary standard to evaluate exposure and support bioequivalence, as they provide the most reliable assessment of real-world patch performance (including adhesion, wear, and tolerability) [49].

Safety evaluation.

Irritation

An ideal transdermal patch system must ensure controlled drug release while minimizing skin irritation. Evaluation of irritation potential is typically performed using *in vivo* models such as rabbits or rats, or through clinical observations in human volunteers. However, *in vitro* assays using reconstructed human epidermis have become a reliable alternative, due to their biochemical and physiological similarity to human skin [35,41]

The irritation potential of transdermal patches can be assessed through visual inspection for signs such as erythema and edema, often using the Primary Irritation Index (PII) test [3,41].

Bioequivalence

Bioequivalence extends the concept of bioavailability by comparing the rate and extent of absorption between a generic and its reference product. In transdermal systems, demonstrating bioequivalence ensures that a generic delivers the drug at the same rate and in the same amount as the reference, confirming comparable efficacy and safety. Regulatory agencies such as FDA and EMA accept bioequivalence data in place of full-scale clinical trials, and frameworks such as the EU Directive 2001/83/EC support regulatory approval and potential interchangeability, depending on national policies [50,51].

For transdermal patches, the type of bioequivalence study required depends on whether the product is intended to exert a systemic or local therapeutic effect [52].

Systemically acting transdermal patches are designed to deliver the drug into systemic circulation, and bioequivalence is therefore often evaluated using approaches similar to those applied to oral formulations, primarily through *in vivo* pharmacokinetic studies. The EMA recommends both single- and multiple-dose studies, as the skin may act as a drug reservoir and steady-state conditions may be required. Because absorption can vary between anatomical sites, standardization of the application site is critical. Furthermore, differences in patch release mechanisms may influence bioequivalence, making replication of studies essential [52].

In contrast, for locally acting transdermal patches not intended to reach systemic circulation, plasma concentrations may not adequately reflect therapeutic performance. In such cases, alternative methods such as pharmacodynamic assessments or clinical endpoint trials are considered more appropriate [48,52-55]:

- *In vitro* studies: Techniques such as *in vitro* permeation tests (IVPT) using excised human skin may provide predictive value for local performance, particularly when *in vitro-in vivo* correlation is demonstrated.

- Pharmacodynamic studies: Methods that assess pharmacological effects or measure drug concentrations at or near the site of action may be employed. For example, the vasoconstrictor assay is commonly used with topical corticosteroids, while dermal microdialysis or open flow microperfusion enables monitoring of local drug concentrations in the skin over time

- Clinical endpoint studies: Although basic and *in vitro* research provide foundational knowledge for transdermal patches development, clinical endpoint studies represent the most decisive step in evidence-based decision making. The ability to properly analyze clinical trial results is essential, as these studies ultimately guide therapeutic decisions.

While these methodologies are valuable, transdermal delivery systems introduce challenges beyond pharmacokinetics. For instance, EMA guidelines recommend evaluating adhesion, irritation, sensitization, phototoxicity, and adverse events when establishing bioequivalence between transdermal formulations [52].

Adhesion as a Critical Determinant of Transdermal Patch Performance.

The adhesive performance of transdermal patches directly impacts their safety, therapeutic efficacy, and overall product quality. Poor adhesion can result in inadequate drug absorption, potentially causing subtherapeutic exposure or erratic dosing. If a patch lifts or partially detaches from the skin, the rate and extent of absorption may vary unpredictably, compromising the intended clinical outcome [56].

Adhesion depends not only on the formulation and type of adhesive used, but also on application site, skin condition, skin thickness, temperature, cleanliness, hydration, pH, and other physiological and environmental factors [57]. As such, formulation strategies are often focused on developing stable systems capable of delivering maximum drug flux while maintaining reliable skin adhesion [57].

A critical element in adhesion performance is the use of pressure-sensitive adhesives (PSAs). These materials adhere upon light pressure. PSAs must: maintain adhesion throughout wear time, not cause irritation or itching, be comfortable to wear, allow painless removal without trauma leave no residue on the skin, and be chemically and physically compatible with a variety of drugs and excipients [57].

Consistent with the failure-mode nomenclature described by Cilurzo et al. and Banerjee et al. [56,57], detachment can occur as follows:

- Case I (Ideal): Patch detaches cleanly with no residue.
- Case II: Complete adhesive transfer to the skin.
- Case III: Cohesive failure with residue on both the patch and the skin.
- Case IV: Mixed failure, with partial transfer and adhesive splitting.

These categories describe mechanical failure modes at the skin-patch interface [56,57]. By contrast, clinical adhesion in volunteers is quantified with regulatory scoring of percentage area adhered over time (e.g., FDA 0-4), not by failure mechanism [11,12]; any association of Case II/III with residue or incomplete wear must be demonstrated using those endpoints, and pharmacopoeial standards remain non-explicit on such defects [35,44,45].

Clinical performance and Real-World Evidence (RWE): from efficacy to adherence

The evaluation of the clinical performance of transdermal drug delivery systems requires distinguishing between efficacy and effectiveness. Efficacy refers to an intervention's ability to produce intended results under controlled experimental conditions, whereas effectiveness reflects outcomes in real-world settings [58]. As discussed earlier, efficacy is evaluated via *in vitro* and *in vivo* studies prior to market approval, but these may not fully capture performance in routine clinical use. As previously noted, factors like interindividual absorption variability, patch adhesion issues, and patient application practices, hard to replicate in trials, can lead to suboptimal outcomes. Thus, real-world effectiveness demands integrating controlled study evidence with actual-use data.

Real-world studies demonstrate the clinical effectiveness and tolerability of transdermal therapies across multiple indications. For example, an 18-month multicenter study of rivastigmine patches in mild-to-moderate Alzheimer's disease reported sustained cognitive outcomes, good tolerability, and strong caregiver preference compared with oral formulations (88.2%) [59]. Similarly, a randomized study comparing transdermal oestradiol with luteinising hormone-releasing hormone agonists for androgen-deprivation therapy in prostate cancer patients reported improved quality-of-life outcomes at six months with transdermal patches, including lower fatigue and fewer hot flushes, although gynaecomastia occurred more frequently [60].

In addition, a prospective observational study in routine clinical practice found that transdermal buprenorphine patches for chronic pain were well tolerated and associated with high patient satisfaction and adherence, with adverse events such as skin irritation rarely leading to discontinuation [61]. Likewise, a meta-analysis of 35 nicotine patch trials found no significant increase in major cardiovascular events compared with placebo, although mild effects such as localized skin irritation and sleep disturbances were more frequent [62].

As previously discussed, patient-related physiological variables influence transdermal drug delivery variability. However, despite age-related skin changes, absorption differences between younger and older individuals remain minimal. Thus, elderly dose adjustments stem primarily from systemic pharmacokinetic/pharmacodynamic factors rather than cutaneous absorption [63].

Safety reports and observational data

A variety of medication and administration errors with transdermal patches have been documented, including cutting the patch, premature removal, applying multiple patches, incorrect anatomical placement, exposure to heat, application on irritated skin, and improper storage or disposal in environments accessible to children or vulnerable individuals. Such errors may result in overdose, treatment failure, local irritation, and, in rare cases, fatal

Table 4. Summary of FDA-recorded complaints for transdermal patch adhesion failure, adapted from Brooks et al. 6.

No	Complaint Description
1	Patches do not adhere properly due to heat, cold, sweating, or showering, often detaching within a day.
2	Frequent replacement is needed, requiring daily applications.
3	Patches fall off during bathing, sleeping, walking, or sweating, forcing users to rely on medical or adhesive tape.
4	Compared to previous brands, some patches are thicker, preventing sweat evaporation and causing them to lift off.
5	Various adhesives and bandages have been tried, but none effectively keep the patch in place.
6	Patients report patches curling, wrinkling, or detaching within 24 hours, particularly around the edges.
7	Adhesion problems lead to increased refills, adding financial burden.
8	Some patches are excessively sticky, causing skin irritation, redness, swelling, and even tearing upon removal.
9	Patches may adhere too strongly to the release liner, tearing when removed from packaging.
10	Some patches are too stiff and do not conform to the skin, leading to detachment.
11	A patient with poor vision accidentally swallowed a patch that had detached and fallen into their food.
12	Some patches show manufacturing inconsistencies, such as different textures, small crystals, or excessive adhesive.
13	Patients feel the product is not as effective as advertised due to unreliable adhesion.

outcomes [64]. Reports submitted to the FDA highlight practical challenges in patch use, summarized in Table 4 [6]. Safety issues outside controlled environments can be categorized into medication and administration errors, patient-related risk factors, and device-related failures.

Medication and administration errors are among the most frequently documented problems. In Colombia, 66.3% of 415 revised prescriptions failed minimum standards and 7% contained dosage errors [65]. Similarly, in Denmark, analysis of 386 harmful incidents with transdermal opioids identified dose omission as the most common administration error, primarily occurring in primary care and nursing home settings [66]. These findings underscore the need for improved prescribing practices, safety systems, and professional training.

Misuse via alternative exposure routes presents a severe risk. Chewing or ingesting fentanyl patches has been associated with fatal respiratory depression [67]. NPDS data from 2005-2016 recorded 6,746 adult and 1,917 pediatric exposures; pediatric cases were mostly accidental, while adult exposures were often intentional. Patch ingestion was the most lethal route, accounting for all 97 reported deaths, all involving fentanyl systems [68].

Even correct use can carry risk in certain populations. Fatal outcomes have been reported with fentanyl patches in patients with COPD, low opioid tolerance, or concomitant interacting drugs. A case series also described severe poisonings following on-skin misuse or ingestion, with postmortem blood levels far above therapeutic ranges [67].

Transdermal drug delivery systems are often theoretically associated with improved adherence compared to oral formulations, as discussed in this review, primarily due to reduced dosing frequency, avoidance of gastrointestinal administration, and more stable plasma drug levels. However, clinical evidence does not consistently support this assumption. For instance, in contraceptive therapy, available data do not demonstrate a clear improvement in long-term adherence with transdermal patches compared to oral formulations. Some studies even report considerable discontinuation rates, highlighting a discrepancy between expected benefits and real-world outcomes [69].

Guidelines for the administration of transdermal patches

For transdermal patches to achieve their intended therapeutic effect, correct application is essential. Best practices for safe and effective use include selecting a clean and dry application site, removing any previously applied patch before placement of a new one, and avoiding cutting or damaging the patch, as this may compromise the drug release system and alter dosing. Patches should be applied only to the recommended anatomical site, handled carefully to avoid unintended dermal exposure by the person applying them, and firmly pressed onto the skin to ensure adequate adhesion. During wear, exposure to external heat sources, such as heating pads, saunas, prolonged sun exposure, or UV lamps, should be avoided, as heat may increase drug absorption and the risk of adverse effects. Application sites should be rotated with each use to minimize skin irritation, sensitization, or allergic reactions. After use, patches should be disposed of safely and responsibly, preferably through authorized medication collection points, to prevent accidental exposure or environmental contamination [52].

Discussion

Transdermal patches offer an innovative alternative to conventional dosage forms, with distinct advantages such as bypassing hepatic first-pass metabolism, reducing systemic side effects, and improving patient adherence. However, this pharmaceutical form faces several challenges that directly impact its effectiveness and safety.

A commonly cited limitation has been the restricted number of drugs capable of penetrating the skin barrier. Nevertheless, advances in formulation strategies, such as lipid-based vesicular systems, chemical enhancers, and the use of prodrugs, have expanded the range of compounds suitable for transdermal delivery. A major challenge, however, remains the misuse of patches by end users. As shown in Table 4, common errors include improper application, failure to remove the previous patch, or simultaneous application of multiple patches.

Similar patterns have been systematically documented in the literature: Lampert et al. [64], identified frequent errors in transdermal opioid administration. More recent regulatory communications confirm that misuse continues to be a clinically relevant concern. For example, the FDA [70] warned that accidental exposure to fentanyl patches remains fatal in children, and the NHS [71] issued updated guidance emphasizing recurrent user errors such as cutting patches or delayed application. Taken together, these findings show that misuse is not a historical issue but an ongoing safety challenge that requires sustained educational and preventive strategies.

Another highly relevant issue concerns patch adhesion failure. As shown in Table 4, many user complaints submitted to the FDA involve partial or complete detachment of patches during use. Such failures can interrupt drug delivery and, when adhesive residue or transfer occurs, may raise safety concerns. These failures not only raise cosmetic or tolerability issues but may also alter systemic exposure; for instance, premature detachment of fentanyl patches has been associated with reduced plasma concentrations and treatment failure, while misperceived detachment may prompt application of additional patches, increasing overdose risk [11,42]. Operationally, extensive adhesive transfer or cohesive failure may be associated with residue on the skin or incomplete wear; however, their clinical impact should be confirmed using the regulatory adhesion endpoints described above. This evidence-practice gap is precisely what recent regulatory guidance aim to manage by complementing bench tests with in-use (*in vivo*) assessments.

Current regulations often lack this level of specificity. As summarized in Table 2, the FDA and EMA require *in vivo* adhesion evaluations using standardized scoring systems, whereas ANVISA relies primarily on in-vitro peel/tack testing and requests *in vivo* studies only on a case-by-case basis; the OECD, meanwhile, provides standardized methodologies for dermal absorption and skin irritation testing, but does not issue adhesion or bioequivalence guidelines specific to transdermal drug delivery systems).

As shown in Table 1, pharmacopoeias provide uneven coverage of attributes relevant to transdermal patches. While drug content (assay), content uniformity, microbial quality, and drug release are consistently addressed, parameters such as mechanical properties (tensile strength, elongation, folding endurance) or drug permeation remain without compendial standards. Adhesion tests, tack, peel, shear, and cold flow, are described in the USP, but these are analytical procedures rather than explicit recognition of adhesion as a critical quality attribute. Indeed, adhesion is not consistently defined as a CQA in pharmacopoeias, even though regulatory agencies such as the FDA and EMA regard it as essential because it directly influences clinical performance. This discrepancy highlights the persistent gap between compendial provisions and regulatory expectations (Table 1; Table 2).

Against this backdrop, Table 3 shows that Colombia lacks a national TDS-specific guideline; consequently, evaluations rely on pharmacopeias (Table 1) and general frameworks (e.g., bioequivalence and stability) rather than standardized requirements for adhesion or permeation.

As shown in Table 3, while the FDA, EMA, and ANVISA expect clinical adhesion data or case-by-case *in vivo* evaluation, in Colombia the absence of standardized national requirements for adhesion studies means that regulatory decisions are made on a case-by-case basis by the national authority. In this context, a marketing authorization dossier may, in some cases, rely primarily on compendial release tests. This regulatory gap increases the risk of heterogeneous evaluations and approval of patches without robust evidence of clinical adhesion (Colombia: Decree 677/1995; Resolution 1124/2016; INVIMA GU061; Table 3 legend).

Moreover, Tables 1, ,22 and and33 together show that requirements and methodologies differ across jurisdictions, including in the definition and measurement of critical quality attributes. In this context, regulatory frameworks should evolve by adopting more specific testing protocols, updating pharmacopoeias, or issuing complementary guidance documents to harmonize the evaluation of key parameters across regions. The lack of alignment can hinder the demonstration of interchangeability, particularly for complex drugs such as transdermal opioids, so a product approved in one region may not meet the standards of another (Table 1 and Table 2; Table 3 legend).

Taken together, these findings highlight that while international agencies have advanced toward greater specificity in adhesion and bioequivalence requirements, Colombia still relies on general provisions. This regulatory asymmetry creates variability in expectations, may compromise therapeutic equivalence, and underscores the urgent need for harmonized, TDS-specific guidelines that ensure patient safety and product reliability.

Evidence from clinical studies and real-world observational data further supports the view that the main limitations of transdermal therapy often arise from system performance rather than from the pharmacological properties of the drug itself. As discussed in the clinical performance section, several transdermal therapies such as rivastigmine, oestradiol, buprenorphine, and nicotine patches demonstrate sustained efficacy, favorable tolerability, and high patient satisfaction under routine clinical conditions. However, safety reports and pharmacovigilance data reveal that variability in real-world outcomes frequently results from device-related factors and handling practices, including premature patch detachment, incorrect application, exposure to heat, or accidental ingestion. These findings suggest that optimizing transdermal systems requires not only improving drug permeation or pharmacokinetics but also strengthening patch engineering, adhesive reliability, and human-factor design to ensure consistent drug delivery outside controlled clinical environments.

Limitations

This work was based on a narrative review and pharmacovigilance data, which may limit the breadth of findings compared with a systematic approach. Nevertheless, by prioritizing primary regulatory documents, pharmacopeial standards, and peer-reviewed literature, this review minimizes bias from non-authoritative sources.

Conclusions

Transdermal patches are increasingly recognized as a valuable therapeutic alternative; however, their real-world performance remains constrained by inadequate handling, biological variability, and fragmented regulatory requirements. These limitations are not inherent to the technology itself but rather reflect persistent gaps in education, evaluation methodologies, and regulatory harmonization across jurisdictions. Addressing these challenges requires a multifaceted approach.

First, targeted education and training programs for both patients and healthcare professionals are essential to reduce common errors of use, including patch stacking, premature removal, and application under inappropriate conditions.

Second, greater regulatory harmonization is needed through internationally aligned frameworks that integrate *in vivo* and *in vitro* assessments, explicitly account for biological variability, and provide clear guidance on the management of stress factors such as heat, humidity, and physical activity.

Third, adhesion performance under real-life conditions must be more rigorously addressed by mandating standardized testing protocols that incorporate biomechanical and environmental challenges, such as movement, sweating, and water exposure, and by linking adhesion outcomes to clinically meaningful endpoints.

Finally, continued innovation and standardization are required to promote the development of advanced adhesive materials capable of adapting to diverse physiological and environmental conditions, alongside the harmonization of methods for drug release, skin permeation, and adhesion testing to avoid the approval of suboptimal products. Implementing these measures will not only raise the quality and safety standards of transdermal patches but also consolidate their role as a reliable, evidence-based therapeutic option.

Ultimately, patients will benefit from safer and more consistent treatments, while healthcare systems will gain greater confidence in both innovator and generic transdermal products.

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