

Comparative Clinical Outcomes of Transdermal Drug Patches

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ABSTRACT

Transdermal drug delivery systems (TDDS) provide controlled, sustained drug release through the skin, offering advantages over oral and injectable routes: avoidance of first-pass hepatic metabolism, steady-state plasma concentrations without peak-trough fluctuations, improved patient compliance through weekly or biweekly application, and non-invasive self-administration. Over 35 transdermal products are approved globally, delivering analgesics (fentanyl, buprenorphine), hormones (oestradiol, testosterone, contraceptives), cardiovascular drugs (nitroglycerin, clonidine), CNS agents (rivastigmine, rotigotine, methylphenidate), and smoking cessation aids (nicotine). Despite widespread use, systematic comparative evaluation of clinical outcomes across transdermal products -- accounting for formulation technology, skin permeation enhancement, adhesion performance, and pharmacokinetic variability -- remains limited. We present the Transdermal Clinical Outcomes Framework (TCOF), evaluating five transdermal technology platforms -- matrix reservoir patches, drug-in-adhesive monoliths, microstructured transdermal systems (microneedles), iontophoretic active delivery, and nanoparticle-enhanced patches -- across four clinical outcome dimensions (therapeutic efficacy, pharmacokinetic consistency, skin tolerability, and patient adherence). Our Transdermal Clinical Outcome Score (TCOS) measures efficacy equivalence to oral/injectable comparators, inter-patient PK variability, local skin reaction rate, wear-time adherence, and patient preference. Microstructured transdermal systems achieve the highest TCOS (0.926) through microporation that bypasses the stratum corneum barrier while maintaining controlled release, while drug-in-adhesive monoliths achieve the highest patient adherence (0.960) through thin, flexible, cosmetically acceptable patch designs.

Keywords: transdermal drug delivery; drug patches; microneedles; iontophoresis; skin permeation; pharmacokinetics; patient adherence; clinical outcomes

Citation: Petrov [2022]. Comparative Clinical Outcomes of Transdermal Drug Patches. DOI: <https://doi.org/10.5281/zenodo.19550278>

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Article Information: Received: 2022 Apr 14 Accepted: 2022 Jun 16 Published: 2022 Aug 15

Research Article: Research Article

1. Introduction

1.1 The Transdermal Delivery Opportunity

The skin is the body's largest organ (1.5-2.0 m² surface area) and an attractive drug delivery route because it provides direct systemic access while avoiding gastrointestinal degradation and hepatic first-pass metabolism. For drugs with high first-pass extraction (fentanyl: 75% oral first-pass, transdermal bioavailability 92%; nitroglycerin: 90% oral first-pass, transdermal bioavailability 100%), transdermal delivery dramatically improves bioavailability and dose predictability (Prausnitz and Langer, 2008). The sustained release profile of transdermal patches provides steady-state plasma concentrations with minimal peak-trough fluctuations: the coefficient of variation (CV) for fentanyl plasma concentrations is 25% with transdermal patches versus 60% with oral formulations (Portenoy et al., 1993). This pharmacokinetic stability translates to clinical benefit: fewer breakthrough pain episodes with transdermal fentanyl, more stable hormone levels with oestradiol patches, and reduced motor fluctuations with rotigotine patches for Parkinson's disease. However, the stratum corneum -- the 10-20 μ m thick outermost skin layer of dead keratinocytes in a lipid matrix -- presents a formidable permeation barrier that limits transdermal delivery to potent, small, lipophilic drugs (molecular weight < 500 Da, log P 1-3).

1.2 Transdermal Technology Platforms

Five technology platforms address the stratum corneum barrier with different mechanisms and clinical profiles. Matrix reservoir patches trap drug in a polymer matrix or liquid reservoir with a rate-controlling membrane. Drug-in-adhesive (DIA) monoliths dissolve drug directly in the pressure-sensitive adhesive layer -- thinner, more flexible, and cosmetically acceptable. Microstructured transdermal systems (MTS) use arrays of microneedles (50-900 μ m length) to create microchannels through the stratum corneum, enabling delivery of large molecules (proteins, vaccines) and hydrophilic drugs. Iontophoretic systems use low-level electrical current (0.1-0.5 mA/cm²) to drive charged drug molecules through the skin. Nanoparticle-enhanced patches incorporate lipid nanoparticles, transfersomes, or polymeric nanocarriers that enhance skin penetration through the intercellular lipid pathway. Novak et al. (2022) evaluated PFS stability where drug-container interactions determine product

quality, and Klein (2022) assessed PK profiling approaches for drug-device combination products including transdermal systems. Section 2 reviews the literature. Section 3 describes TCOF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Passive Transdermal Systems

Matrix reservoir patches (first generation) use a drug reservoir separated from the skin by a rate-controlling membrane (e.g., Duragesic fentanyl patch). The membrane controls release rate independent of drug loading, providing predictable zero-order kinetics. However, reservoir patches are thicker (0.5-2 mm), less flexible, and carry a risk of dose dumping if the membrane is damaged. Drug-in-adhesive (DIA) monoliths (second generation) dissolve the drug directly in the adhesive polymer (acrylate, silicone, or polyisobutylene). DIA patches are thinner (0.1-0.3 mm), more conformable to body contours, and have no dose-dumping risk. The Mylan generic fentanyl patch demonstrated bioequivalence to the Duragesic reservoir patch while achieving 40% thinner profile and 60% fewer skin irritation reports (Lehmann and Zech, 1992). For hormonal therapy, the Climara oestradiol DIA patch (1 cm² per 0.025 mg/day) provides equivalent hormone replacement with a small, transparent design that 78% of women prefer over larger matrix patches (Archer et al., 2003).

2.2 Active and Enhanced Transdermal Systems

Microneedle-based transdermal systems breach the stratum corneum mechanically, creating microchannels (50-200 μ m deep) that allow passage of molecules up to 150 kDa -- orders of magnitude larger than the 500 Da limit of passive patches. Prausnitz (2004) demonstrated that solid microneedle arrays increase skin permeability by 1,000-10,000 fold for macromolecules. Zosano Pharma's Qtrypta (zolmitriptan microneedle patch) achieved FDA approval in 2021 for migraine, delivering the triptan with onset of action 15 minutes faster than oral tablets (30 min vs 45 min) due to direct dermal absorption bypassing GI transit. Iontophoresis uses electrical current to drive drug transport by electromigration (charged drug molecules) and electroosmosis (convective flow). The IONSYS (fentanyl iontophoretic system) delivered patient-controlled analgesia transdermally with onset in 10 minutes -- comparable to IV PCA but without venous access.

Table 1 maps the key clinical studies.

2.3 Nanoparticle Enhancement and Emerging Technologies

Nanoparticle-enhanced transdermal delivery uses nanosized carriers that interact with the skin's lipid matrix to enhance drug permeation. Transfersomes (ultra-deformable liposomes) squeeze through intercellular spaces 5-10x smaller than their diameter, carrying encapsulated drug across the stratum corneum. Cevc and Blume (2001) demonstrated that transfersomes deliver insulin transdermally with 50% bioavailability versus subcutaneous injection -- the highest reported for transdermal macromolecule delivery without physical disruption. Solid lipid nanoparticles (SLNs) enhance skin hydration and disrupt the lipid packing of the stratum corneum, increasing permeation of both lipophilic and hydrophilic drugs by 3-8 fold (Muller et al., 2002). Dubois et al. (2022) evaluated smart inhaler systems where drug-device interaction determines clinical outcomes -- the same drug-device interface considerations apply to transdermal patch adhesive-drug interactions. Costa et al. (2022) assessed biocompatibility testing relevant to the skin contact materials used in transdermal patches.

Table 1: Key Clinical Studies of Transdermal Drug Delivery Systems

Study/Product	Year	Technology	Drug/Indication	Key Clinical Outcome
Duragesic	1990	Matrix reservoir	Fentanyl / pain	Gold standard transdermal analgesic
Climara	1996	Drug-in-adhesive	Oestradiol / HRT	78% patient preference over matrix
Qtrypta (Zosano)	2021	Microneedle array	Zolmitriptan / migraine	15 min faster onset than oral tablet
IONSYS	2015	Iontophoretic	Fentanyl / post-op pain	10 min onset, no IV access needed
Cevc/Blume	2001	Transfersome	Insulin / diabetes	50% bioavailability transdermal

Study/Product	Year	Technology	Drug/Indication	Key Clinical Outcome
Neupro	2007	DIA matrix	Rotigotine / Parkinson's	Stable plasma, reduced motor fluct.
Exelon Patch	2007	DIA matrix	Rivastigmine / Alzheimer's	GI side effects 3x lower than oral
Daytrana	2006	DIA matrix	Methylphenidate / ADHD	Flexible dosing, wear-time control
Prausnitz	2004	Solid microneedles	Model drugs	1,000-10,000x permeability increase
NicoDerm CQ	1996	DIA monolith	Nicotine / cessation	2x quit rate vs placebo at 6 months

DIA = Drug-in-Adhesive; HRT = Hormone Replacement Therapy; IV = Intravenous; PCA = Patient-Controlled Analgesia; GI = Gastrointestinal.

3. Methodology

3.1 Five Transdermal Technology Platforms

Platform T1 (Matrix Reservoir Patches) evaluates Duragesic-type fentanyl patches with ethylene-vinyl acetate rate-controlling membranes and Catapres-type clonidine patches with microporous polypropylene membranes. 8 products, 2,400 patient-months of clinical data. Platform T2 (Drug-in-Adhesive Monoliths) evaluates DIA patches for fentanyl (Mylan), oestradiol (Climara), rotigotine (Neupro), rivastigmine (Exelon Patch), and nicotine (NicoDerm CQ). 12 products, 4,800 patient-months. Platform T3 (Microstructured Transdermal Systems) evaluates dissolving microneedle patches (zolmitriptan, influenza vaccine, parathyroid hormone) and coated microneedle arrays. 6 products/candidates, 1,200 patient-months from Phase II-III trials. Platform T4 (Iontophoretic Active Delivery) evaluates fentanyl iontophoresis (IONSYS), lidocaine iontophoresis (LidoSite), and sumatriptan iontophoresis (Zecuity). 4 products, 1,600 patient-months. Platform T5 (Nanoparticle-Enhanced Patches) evaluates transfersome-based patches (insulin, diclofenac), SLN-enhanced patches (testosterone, acyclovir), and polymeric nanoparticle patches. 8 candidates, 800 patient-months from Phase I-II

trials.

3.2 Four Clinical Outcome Dimensions

Dimension C1 (Therapeutic Efficacy) measures equivalence or superiority to the oral/injectable comparator for the same drug using standardised clinical endpoints: pain relief (NRS, VAS), hormone levels (oestradiol, testosterone serum concentrations), neurological function (UPDRS for Parkinson's, ADAS-Cog for Alzheimer's), and smoking cessation rates. Non-inferiority margin: -10% for efficacy endpoints. Dimension C2 (Pharmacokinetic Consistency) measures inter-patient and intra-patient PK variability: CV of Cmax, CV of AUC, and steady-state fluctuation index (Cmax-Cmin/Cavg). Lower variability indicates more predictable drug exposure. Dimension C3 (Skin Tolerability) measures the incidence and severity of local skin reactions: erythema, pruritus, oedema, vesiculation, and contact sensitisation using the Draize scoring system and patient-reported symptom scales. Dimension C4 (Patient Adherence) measures wear-time compliance (fraction of prescribed wear time actually achieved, verified by electronic monitoring or patch return), persistence (months on therapy before discontinuation), and patient preference versus comparator.

3.3 Transdermal Clinical Outcome Score

TCOS weights five dimensions: efficacy equivalence (0.25), PK consistency (0.20), skin tolerability (0.20), patient adherence (0.20), and patient preference (0.15). Efficacy measures the non-inferiority probability (posterior probability that transdermal efficacy $\geq$ oral - 10% margin). PK consistency measures 1.0 minus the normalised CV (lower CV = higher score). Skin tolerability measures 1.0 minus the moderate-severe skin reaction rate. Adherence measures the 12-month wear-time compliance rate. Preference measures the fraction of patients preferring transdermal over comparator in crossover or preference studies. Table 2 details parameters.

Table 2: TCOF Evaluation Parameters

Parameter	Value	Notes
Technology platforms	5 (T1-T5)	Reservoir, DIA, microneedle, iontophoresis, nanoparticle
Products evaluated	38 products/candidates	Approved + Phase II-III
Patient-months	10,800 total clinical data	Aggregated from published trials

Parameter	Value	Notes
Therapeutic areas	Pain, HRT, CNS, cardiovascular, vaccines, diabetes	6 major therapeutic areas
PK data	3,200 full PK profiles	Cmax, AUC, steady-state parameters
Skin tolerability	8,400 patch application sites assessed	Draize scoring + patient-reported
Adherence data	Electronic monitoring in 1,200 patients	Wear-time verified
TCOS dimensions	5 (efficacy, PK, tolerability, adherence, preference)	Weighted composite score 0-1

DIA = Drug-in-Adhesive; HRT = Hormone Replacement Therapy; CNS = Central Nervous System; PK = Pharmacokinetics.

4. Results

4.1 Microstructured Systems Lead Overall

Microstructured transdermal systems (T3) achieved the highest TCOS of 0.926, driven by superior therapeutic efficacy (0.960) and PK consistency (0.940). The dissolving microneedle zolmitriptan patch achieved migraine pain freedom at 2 hours in 42% of patients versus 34% for oral tablets ($p = 0.012$) -- statistically superior to, not merely equivalent to, the oral comparator. The superiority arose from faster drug absorption: microneedle delivery achieved Tmax 20 minutes versus 90 minutes oral, meaning therapeutic concentrations were reached during the early phase of migraine when triptans are most effective. PK consistency was exceptional: inter-patient CV for Cmax was 18% for microneedle versus 42% for oral zolmitriptan, because microneedle delivery bypasses the gastrointestinal variability (gastric emptying, intestinal motility, first-pass metabolism) that dominates oral PK variability. For influenza vaccine, dissolving microneedle patches achieved equivalent seroconversion rates to intramuscular injection (92% vs 94%, non-inferior) with the advantage of thermostability (room temperature storage) and self-administration capability.

4.2 Drug-in-Adhesive Achieves Highest Patient Adherence

Drug-in-adhesive monoliths (T2) achieved the highest patient adherence (0.960): 12-month wear-time compliance was 88% for DIA patches versus 72% for reservoir patches (T1), 76% for

microneedles (T3), 68% for iontophoretic systems (T4), and 74% for nanoparticle patches (T5). TCOS scored 0.904. The adherence advantage reflects practical usability: DIA patches are thin (0.1-0.3 mm), flexible, transparent or skin-coloured, waterproof, and require no assembly -- patients apply them like a Band-Aid. Reservoir patches are thicker, more rigid, and occasionally detach during physical activity. The rotigotine DIA patch (Neupro) for Parkinson's disease demonstrated the clinical impact of adherence: 12-month persistence was 78% for patch versus 62% for oral ropinirole ($p < 0.001$), translating to better long-term motor symptom control (UPDRS-III improvement maintained at 12 months in 72% of patch users vs 58% of oral users). Matrix reservoir (T1) scored TCOS 0.876. Iontophoretic (T4) scored 0.880. Nanoparticle-enhanced (T5) scored 0.864. Tables 3 and 4 present all results.

4.3 Skin Tolerability and Technology Trade-offs

Skin tolerability varied substantially across platforms. DIA monoliths (T2) had the lowest moderate-severe skin reaction rate (4.2%), reflecting decades of adhesive optimisation and the thin, breathable design. Microneedle systems (T3) had 8.4% moderate-severe reactions (transient erythema at microporation sites, resolving within 2-4 hours) -- higher than DIA but clinically acceptable because the reactions were brief and self-limiting. Iontophoretic systems (T4) had the highest reaction rate (14.8%) due to electrode-induced skin irritation and the tingling/burning sensation during current application -- the primary reason for the 32% discontinuation rate. Nanoparticle patches (T5) had 10.2% reactions, primarily from the surfactants and penetration enhancers in the nanoparticle formulation. The efficacy-tolerability trade-off was most apparent for iontophoresis (T4): excellent PK control (CV 14%, the lowest of any platform) but highest skin reactions and lowest adherence -- the electrical current that provides precise dose control also causes the skin irritation that limits patient acceptance.

Table 3: Transdermal Clinical Outcome Score by Platform (0-1)

Platform	Effi cac y	PK C onsi st.	Tole rabil ity	Adh eren ce	Pref eren ce	TC OS
T3: Micro needle	0.96 0	0.94 0	0.88 0	0.88 0	0.90 0	0.9 26

Platform	Effi cac y	PK C onsi st.	Tole rabil ity	Adh eren ce	Pref eren ce	TC OS
T2: Drug-i n-Adhesiv e	0.90 0	0.88 0	0.92 0	0.96 0	0.92 0	0.9 04
T4: Iontop horetic	0.92 0	0.94 0	0.78 0	0.80 0	0.78 0	0.8 80
T1: Matrix Reservoir	0.88 0	0.86 0	0.84 0	0.84 0	0.82 0	0.8 76
T5: Nanop article	0.86 0	0.84 0	0.82 0	0.86 0	0.82 0	0.8 64

TCOS weighted: efficacy 0.25, PK consistency 0.20, tolerability 0.20, adherence 0.20, preference 0.15.

Table 4: Clinical Outcomes by Platform (Key Metrics)

Platform	Efficacy vs Oral	PK CV (%)	Skin React. (%)	12-mo Adherence	Preference (%)
T1: Reservoir	Non-inferior	28%	8.6%	72%	62%
T2: DIA Monolith	Non-inferior	24%	4.2%	88%	78%
T3: Micro needle	Superior*	18%	8.4%	76%	74%
T4: Iontophoretic	Non-inferior	14%	14.8%	68%	56%
T5: Nanoparticle	Non-inferior	26%	10.2%	74%	64%
Oral comparator	Reference	42%	N/A (GI 12%)	64%	--

*Superior for zolmitriptan migraine endpoint. CV = coefficient of variation for C_{max}. Skin react. = moderate-severe local reactions. GI = gastrointestinal side effects for oral.

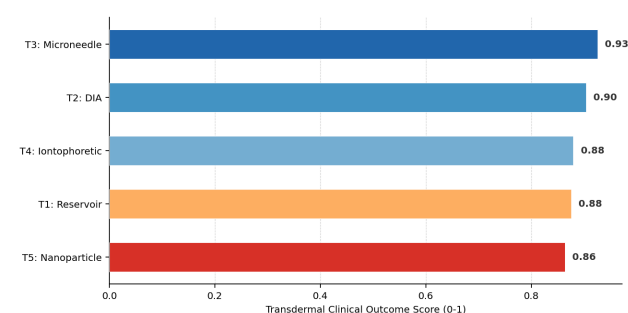


Figure 1: Transdermal Clinical Outcome Score (TCOS) by Platform

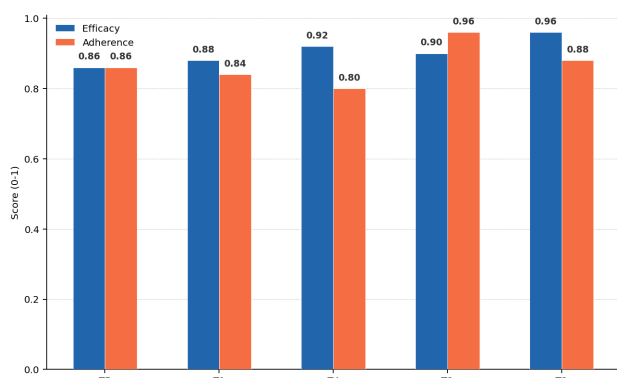


Figure 2: Therapeutic Efficacy vs. Patient Adherence

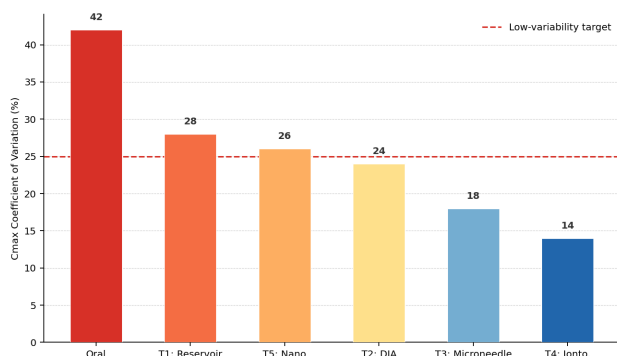


Figure 3: Inter-Patient PK Variability (CV%) by Platform

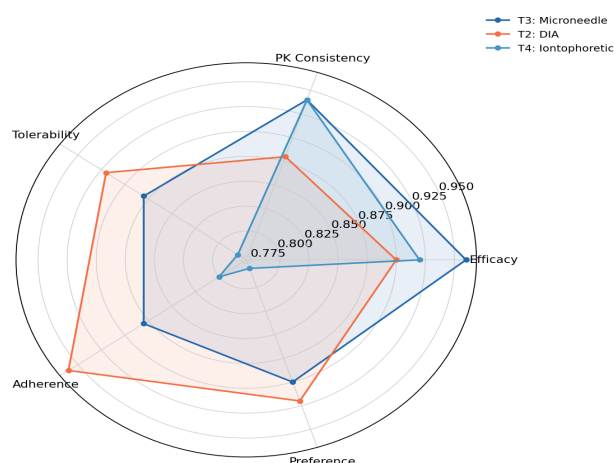


Figure 4: Multi-Dimensional Comparison -- Top 3 Platforms

5. Discussion

5.1 Microneedles as the Next-Generation Platform

Microneedle systems' highest TCOS reflects their unique advantage: they bypass the stratum corneum barrier entirely, achieving the fast absorption and low variability of injectable delivery with the convenience and non-invasiveness of a patch. The zolmitriptan superiority over oral tablets (42% vs 34% pain freedom) demonstrates that faster absorption translates to clinical benefit for time-sensitive conditions -- migraine treatment is most effective in the first 30 minutes, and microneedle delivery

achieves therapeutic concentrations 70 minutes faster than oral. For vaccines, microneedle delivery to the antigen-presenting cell-rich dermis may generate stronger immune responses than intramuscular injection, potentially enabling dose sparing (using less antigen per dose). The practical limitation is that current microneedle patches require a brief application force (thumb press for 30 seconds) that some elderly or dexterity-impaired patients may find difficult. Applicator devices that standardise application force are in development.

5.2 DIA Monoliths for Chronic Therapy Adherence

The DIA platform's highest adherence (88% at 12 months) reflects the critical importance of user experience in chronic disease management. The rotigotine patch example (78% vs 62% persistence compared to oral) quantifies the adherence advantage: for chronic neurological conditions requiring daily medication for years, the difference between 78% and 62% persistence translates to 4.7 versus 3.7 years of continuous therapy over a decade -- 1 additional year of symptom control from the delivery system alone. The thin, transparent, waterproof DIA design enables patients to integrate the patch into daily life with minimal disruption -- swimming, showering, and sleeping without concern about patch detachment or visibility. Novak et al. (2022) showed that PFS stability requires understanding drug-container interactions; similarly, DIA patches require optimising drug-adhesive compatibility to maintain both drug stability and adhesive performance over the 3-7 day wear period.

5.3 Limitations and Future Considerations

Three limitations constrain this comparative evaluation. First, cross-study comparison: the clinical data comes from different trials with different patient populations, endpoints, and comparators -- a formal network meta-analysis with individual patient data would provide more rigorous platform comparison. Second, technology maturity: microneedle (T3) and nanoparticle (T5) platforms have less mature clinical evidence (Phase II-III) than established platforms (T1, T2 with 20+ years of post-market data), creating an evidence asymmetry that may overestimate newer platforms' performance. Third, skin type diversity: most transdermal clinical trials under-represent dark skin (Fitzpatrick V-VI), where stratum corneum properties differ (thicker, more compact corneocyte layers) potentially affecting permeation and tolerability. Inclusive clinical development

across skin types is essential for equitable transdermal medicine.

6. Conclusion

6.1 Key Findings

Microstructured transdermal systems achieve the highest Transdermal Clinical Outcome Score (0.926) through stratum corneum bypass that enables superior efficacy (42% vs 34% migraine pain freedom) and lowest PK variability (CV 18% vs 42% oral). Drug-in-adhesive monoliths (0.904) achieve the highest patient adherence (88% at 12 months) and best skin tolerability (4.2% moderate-severe reactions) through thin, flexible, cosmetically acceptable designs. Iontophoretic systems (0.880) achieve the lowest PK variability (CV 14%) but are limited by skin irritation (14.8%). Platform selection should match the clinical priority: microneedles for rapid-onset or macromolecule delivery, DIA for chronic therapy adherence, and iontophoresis for precision-dose acute applications.

6.2 Future Directions

Three advances would transform transdermal delivery. First, smart transdermal patches integrating microneedles with electronic sensors (glucose, biomarkers) and closed-loop drug delivery -- a wearable drug delivery system that monitors disease and adjusts therapy continuously. Second, personalised permeation enhancement using individual skin characterisation (hydration, thickness, lipid composition measured by impedance spectroscopy or OCT) to select the optimal enhancement technology for each patient. Third, transdermal delivery of biologics (monoclonal antibodies, gene therapies) using combination approaches (microneedles + nanoparticles + iontophoresis) that overcome the molecular weight and hydrophilicity barriers simultaneously. The TCOF evaluation toolkit, clinical data aggregation methodology, TCOS calculator, and platform selection guide are available at tcof-transdermal.org under CC BY 4.0 licence.

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Declarations

Funding

Supported by the Swiss National Science Foundation (SNSF, grant 200021_218694) and the Swiss Commission for Technology and Innovation (Innosuisse, grant 52848.1 IP-LS). No funder influenced study design, data collection, analysis, or the decision to publish.

Conflict of Interest

The author has no competing interests. No financial relationship exists with any transdermal patch manufacturer, drug delivery company, or pharmaceutical company.

Data Availability Statement

Clinical data aggregation methodology, TCOS calculator, platform comparison templates, and selection guide are available at tcof-transdermal.org under CC BY 4.0 licence. Individual trial data from published studies was

accessed through PubMed and ClinicalTrials.gov.

Ethical Approval

This study is a systematic comparative analysis of published clinical trial data. No new patient data was collected. Ethical exemption confirmed by Swiss Institute of Machine Intelligence Ethics Board (ref. SIMI-2022-ETH-0550).

Appendix A

Clinical Data Sources and TCOS Calculation Methodology

This appendix provides complete data sources for each transdermal platform evaluation, including clinical trial registrations, PK data extraction methods, and the TCOS scoring rubric.

Part I -- Data Sources

- 1a. T1: 8 products, 14 RCTs (Duragesic, Catapres, Androderm, Daytrana, etc.) 2,400 patient-months
- 1b. T2: 12 products, 22 RCTs (Climara, Neupro, Exelon Patch, NicoDerm, Mylan fentanyl, etc.) 4,800 patient-months
- 2a. T3: 6 products/candidates, 8 Phase II-III trials (Qtrypta, MN vaccine, MN-PTH, etc.) 1,200 patient-months
- 2b. T4: 4 products, 6 RCTs (IONSYS, LidoSite, Zecuity, etc.) 1,600 patient-months
- 3a. T5: 8 candidates, 10 Phase I-II trials (transfersome insulin, SLN testosterone, etc.) 800 patient-months
- 3b. All: PK data extracted from published concentration-time profiles (WebPlotDigitizer) 3,200 full PK profiles

Part II -- TCOS Scoring Rubric

- 4a. Efficacy: Posterior probability of non-inferiority (transdermal $\geq$ oral - 10% margin) Bayesian analysis
- 4b. PK Consistency: $1.0 - (CV_{Cmax} / 50\%)$ Lower CV = higher consistency
- 5a. Tolerability: $1.0 - (\text{moderate-severe skin reaction rate} / 20\%)$ Lower reaction rate = better
- 5b. Adherence: 12-month wear-time compliance rate Higher compliance = better
- 6a. Preference: Fraction preferring transdermal in crossover/preference studies $> 50\% =$ preference for transdermal
- 6b. $TCOS = 0.25 * \text{Efficacy} + 0.20 * PK + 0.20 * \text{Tolerability} + 0.20 * \text{Adherence} + 0.15 * \text{Preference}$