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THE ROLE OF ARTIFICIAL INTELLIGENCE IN ADVANCING TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Transdermal drug delivery systems (TDDS) are gaining significant attention in pharmaceutical science for their ability to deliver drugs in a controlled, non-invasive manner, improving bioavailability and patient adherence while avoiding first-pass metabolism. However, TDDS are limited by challenges such as the skin's permeability barrier, particularly the stratum corneum, and the need for optimized formulations. Factors such as skin type, hydration levels, and age further complicate the development of effective systems. Designing efficient TDDS is complex and requires careful consideration of drug–skin interactions, excipient selection, and formulation stability. Artificial intelligence (AI) is emerging as a powerful tool to address these challenges. By utilizing techniques such as machine learning and predictive modeling, AI can accurately forecast drug permeation, optimize formulation parameters, and assist in designing novel carriers with enhanced performance. Personalized transdermal drug delivery systems are increasingly being developed to align with individual patient profiles, thereby enhancing therapeutic precision and efficacy. Innovations such as sensor-integrated patches enable dynamic modulation of drug release in response to real-time physiological feedback, ensuring optimal therapeutic outcomes. AI also streamlines the pharmaceutical workflow—from disease diagnosis to predicting drug penetration and distribution within skin layers—thus facilitating the development of efficient and targeted formulations. This review highlights the impact of AI in TDDS and discusses applications of advanced computational models including Deep Neural Networks (DNN), Artificial Neural Networks (ANN), BIOSIM, COMSOL Multiphysics, K-Nearest Neighbours (KNN), and Support Vector Machines (SVM). These technologies have the potential to overcome current limitations in transdermal delivery, offering innovative solutions for both dermatological and systemic conditions, and ultimately improving patient care through advanced drug delivery strategies.

KEYWORDS: Transdermal Drug Delivery Systems (TDDS), Artificial Intelligence (AI), Machine Learning, Deep Learning, BIOSIM, COMSOL Multiphysics.

1. INTRODUCTION

Transdermal drug delivery systems offer a compelling alternative to oral or injectable administration by enabling non- invasive delivery of drugs through the skin. Among the key advantages are the ability to bypass first pass metabolism, offer a controlled and sustained release, maintain steady therapeutic plasma levels, and improve patient compliance particularly for chronic therapies. Despite these benefits, the widespread adoption of TDDS remains limited by the formidable barrier imposed by the skin, especially by the outermost layer -the stratum corneum which restricts the permeation of many drugs, particularly hydrophilic molecules, and macromolecules. Variability in skin physiology (e.g., skin type, hydration level, age)adds further complexity, making it hard to develop universal transdermal formulations.[1] To overcome these obstacles researchers have traditionally employed chemical penetration enhancers, lipid- based carriers (like liposomes, nanoemulsions), physical enhancement

techniques (microneedles, iontophoresis, sonophoresis), or combination thereof.[2] Indeed microneedles have received particular attention because they can physically bypass the stratum corneum and deliver even macromolecules or hydrophilic drugs into viable skin layers without pain or invasiveness compared to injections.[3] However, the design and optimization of effective TDDS- whether, patches microneedles, or nano carrier-based remains challenging because there are many interacting parameters (molecular weight, lipophilicity, solubility), excipient/enhancer choice, carrier systems, skin variables, and device geometry or physical parameter.[4] Traditional development has often relied on trial-and-error experiments or incremental modifications, which are time-consuming, resource-intensive and may still fail to achieve ideal outcome.[5]

In recent years, Artificial Intelligence (AI) and Machine learning (ML)-along with computational modeling- have emerged as a powerful tool to address these challenges in TDDS design and development. A recent review demonstrated that ML models trained on a large and curated molecular dataset can predict skin permeability and prioritize drug candidates suitable for transdermal delivery, thereby greatly reducing the experimental burden of screening. Moreover, AI-driven algorithms are now being applied to optimize formulations (e.g. Selection and concentration of penetration enhancers, lipid-or polymer-based carriers), to design advanced delivery technologies such as microneedles and nanocarriers, and even to tailor TDDS according to individual characteristics (skin type, age, hydration).[1]

In addition, AI enables novel "smart "transdermal systems; patches or nanocarriers integrated with sensors and feedback mechanisms for real time monitoring and adapting drug release-a step towards personalized and precision medicine in dermal pharmacotherapy.[6] Given this rapidly evolving landscape, there is a need for comprehensive synthesis: summarizing how AI and computational tools are currently being applied in TDDS, what successes have been achieved, what limitations remain (data limitations, variability, regulatory issues, interpretability), and what future directions might be promising.

This review aims to provide an in-depth analysis of the role of artificial intelligence in transdermal drug delivery systems. It highlights key AI methodologies, summarizes major applications in permeability prediction, formulation optimization, and device engineering, presents recent case studies, and discusses emerging opportunities for personalized and adaptive TDDS. By synthesizing current knowledge, this article underscores the potential of AI to accelerate and refine transdermal drug delivery research, ultimately contributing to more efficient and patient-tailored therapeutic solutions.

2. Overview – AI technologies relevant to TDDS

Artificial intelligence (AI) increasingly used in pharmaceutical formulation development, including TDDS to optimize formulation variables, predict permeation profiles, and design smarter delivery systems. The major AI approaches include machine learning, deep learning, expert systems, optimization algorithms, and computational modeling.

1. Machine learning (ML) for TDDS Optimization

Machine learning models can predict skin permeability based on physiochemical properties. Optimize formulation variables (polymer content, permeation enhancers, plasticizer). Screen drugs suitable for transdermal delivery. Model drug release kinetics and in vitro permeation. Algorithms such as Random Forest (RF), XG boost, SVM and linear/ elastic net regressions, ANN,K- Nearest Neighbours (KNN).Learn relationships between molecular/formulation descriptors and outcomes (e.g., skin permeability, kp, flux, particle size) These models are fast to train, perform well on moderate-sized datasets, and are widely used for ranking candidate molecules or formulation experiments.[7]

2. Deep Learning (DL) Approaches

Deep Learning provides superior predictive accuracy for skin permeation prediction, image-based analysis of microneedle insertion depth, intelligent design of nanocarriers for TDDS. Techniques used are Deep Neural Networks (DNN), Convolutional Neural Networks (CNN) for imaging, Recurrent Neural Networks (RNN) for time-dependent release prediction.[7]

3. Graph Neural Networks (GNN) for molecules

GNNS represent molecules as graphs (atoms=nodes, bonds=edges) and learn features that are intrinsically structure aware. They often improve prediction of molecular properties relevant to transdermal deliver (log p, polar surface area surrogates, permeability predictors) compared with hand-crafted descriptors.[7]

4. Hybrid Mechanistic-data models (PBPK+ML: Physics -informed NN)

These combine mechanistic models(Ficks law, compartmental PBPK) with ML to learn parameters or correct residuals (physics-informed neural networks, surrogate models). Hybrid models bring physiological interpretability and allow extrapolation to new dosing/regimen/subject scenarios with fewer training samples.[8]

5. Computer vision & image analysis (CNNs)

CNNs are used to analyze skin photos, histology, and sensor images to assess skin condition (eczema, hydration, vascularization) or to QC manufactured devices image-based classifiers support personalized dosing decisions (e.g., identify skin that will absorb more) and automated quality checksfor microneedle arrays.[9]

Furthermore, AI- driven systems enable the development of smart transdermal devices that monitor physiological parameters in real time and adjust drug release dynamically to ensure consistent therapeutic outcomes. This convergence of AI in TDDS holds the potential to overcome traditional barriers and pave the way for innovative, personalized, and efficient drug delivery solutions.[1]

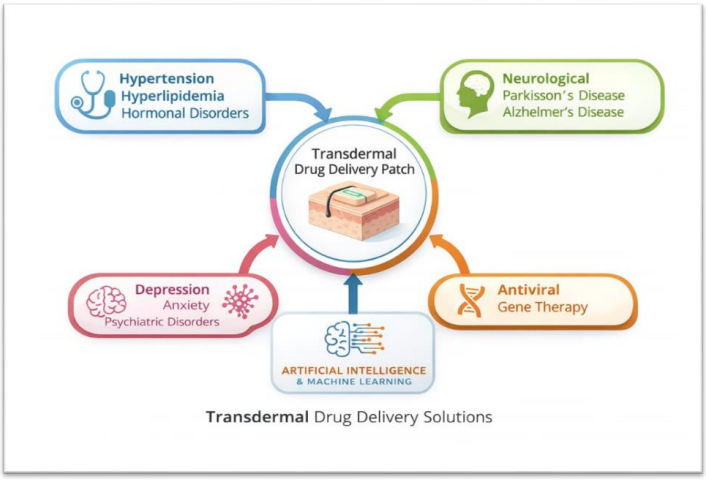

Figure 1: Integration of AI and ML in TDDS based therapies.

3. Emerging TDDS for the treatment of Viral Infections

3. 1 TDDS for the treatment of Viral Infections

Transdermal drug delivery systems (TDDS) have gained increasing attention as an emerging strategy for the treatment and prevention of viral infections. TDDS offer several advantages over conventional delivery routes, such as the ability to bypass hepatic first-pass metabolism, maintain steady-state plasma concentrations, reduce dosing frequency, and improve patient compliance—particularly for chronic or long-term antiviral therapy. In addition, advanced TDDS platforms, including microneedles, nano-formulations, and polymeric patches, have expanded the scope of transdermal delivery beyond small molecules, enabling the delivery of antiviral agents with poor oral bioavailability or short half-lives.

A growing body of research highlights the potential of TDDS for combating both cutaneous viral infections (e.g., herpes simplex virus, human papillomavirus) and systemic viral diseases (e.g., influenza, measles, HIV, and emerging viral pathogens). Wang et al. (2021) reported that microneedles, nano emulsions, iontophoretic systems, and polymeric films show significant promise for enhancing the permeation of antiviral molecules and immunogens across the skin barrier, making them suitable platforms for both therapeutic and preventive applications.[10]

One of the well-established applications is in the management of herpes simplex virus (HSV) infections. Conventional topical acyclovir therapy shows limited clinical efficacy due to poor penetration across the stratum corneum. Recent advances using hydrogel microneedle arrays have demonstrated remarkable improvements in dermal and transdermal permeation. A study published in 2022 reported that acyclovir-loaded hydrogel microneedle arrays increased skin permeation by nearly 39-fold compared with conventional film formulations, while also achieving sustained drug release for up to 24 hours. Such performance improvements may reduce dosing frequency, shorten healing time, and enhance therapy adherence for HSV infections[11] Beyond cutaneous infections, TDDS is gaining traction for systemic viral pathogens owing to the increasing sophistication of microneedle patches for vaccine and antiviral drug delivery. Microneedle vaccination has shown strong potential for influenza, measles, polio, and COVID-19 immunization. These patches can deliver viral antigens to the abundant immune cells in the dermal and epidermal layers, eliciting robust immune responses comparable to injectable vaccines. Moreover, microneedle patches eliminate the need for cold-chain storage, reduce biohazardous sharps waste, and allow painless self-administration, making them highly attractive for mass vaccination in resource-limited settings. Several animal studies have shown superior stability and immunogenicity of microneedle-based influenza and COVID-19vaccines compared with intra muscular injections.[10]

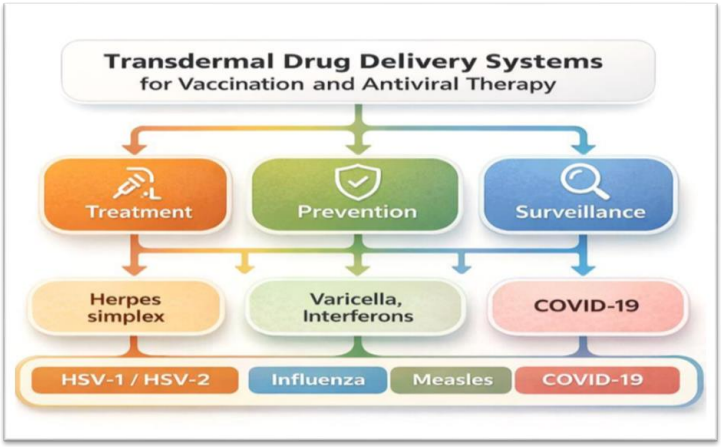

Figure 2: TDDS for the treatment of common Viral Infectious diseases.

Emerging antiviral agents, including nucleoside analogues, small interfering RNAs (siRNA), and long-acting antiviral formulations, are also being investigated for microneedle-assisted transdermal delivery. For example, polymeric microneedles have been used to deliver tenofovir and lamivudine for potential HIV prophylaxis and therapy. These findings indicate that TDDS can serve not only for acute viral infections but also for managing chronic viral diseases.[12] A list of Viral Infections treated using TDDS is presented in Table below.

Table 1: Transdermal Drug Delivery Systems (TDDS) for Viral Infections.[1]

Disease	Virus	Type of TDDS	Purpose/Role of TDDS
Herpes simplex infections	HSV-1 / HSV-2	Water-in-oil microemulsion with acyclovir Binary ethosomal system Acyclovir gel patch with sponge-spicules (AGP-SS)	Improves cutaneous permeation and enhances dermal acyclovir levels Enhances transdermal transport of acyclovir sodium by improving vesicle penetration Creates microchannels to promote deeper skin absorption
Influenza	Influenza virus	Hydrogel nano emulsion with penciclovir Influenza vaccine–loaded egg microneedles Microneedle patch with zanamivir	Boosts skin permeation and sustain antiviral release Minimally invasive vaccination without cold-chain requirements Provides targeted dermal delivery and enhanced systemic levels
Warts	HPV	Solid microneedle system	Enhances penetration of 5-fluorouracil (5-FU) into wart tissue
COVID-19	SARS-CoV-2	Fluorocarbon-modified chitosan vaccine patch Dissolving microneedles with S1 subunit	Transdermal antigen delivery with immune response comparable to injections Thermostable, self-administered vaccination with strong antibody response

3.2 TDDS for the treatment of cardiovascular diseases

Cardiovascular diseases, particularly heart failure (HF), often lead to substantial alterations in drug pharmacokinetics (PK) and pharmacodynamics (PD). In HF, reduced cardiac output causes systemic hypoperfusion, which in turn affects drug absorption and distribution. Renal dysfunction further contributes to impaired drug clearance, while conditions such as hypoalbuminemia and hepatic congestion can significantly influence drug metabolism and overall therapeutic response. Because of these complex physiological changes, transdermal drug delivery systems (TDDS) offer an advantageous route, providing sustained drug release while avoiding first-pass metabolism, gastrointestinal variability, and fluctuations in plasma concentration.

Transdermal Propranolol

Propranolol, a nonselective β-adrenergic blocker, undergoes extensive hepatic first-pass metabolism when administered orally, resulting in low systemic bioavailability (~23%). In an animal study involving rabbits, oral propranolol reached a peak concentration (C_{max}) of 56.4 ng/mL at approximately 13 minutes, but only 12.3% of the dose eventually became systemically available due to significant hepatic extraction. When delivered through a transdermal patch, propranolol achieved a steady-state plasma concentration (CSS) of 9.3 ng/mL after an initial lag phase of about 8 hours,

offering a 74.8% increase in bioavailability compared to the oral formulation. These findings indicate that TDDS can effectively improve systemic exposure for drugs with high first-pass metabolism.

Transdermal Nitroglycerin

Nitroglycerin is widely used in the management of angina pectoris, and its therapeutic role has been understood for more than a century. Early clinical observations documented tolerance following repeated dosing. Later research by Ferid Murad elucidated that nitroglycerin exerts its vasodilatory effect through nitric-oxide-mediated activation of the cyclic guanosine monophosphate (cGMP) pathway in vascular smooth muscle.A two-way crossover study in healthy volunteers comparing two nitroglycerin patch formulations—Nitro-Dur® and Nitro-Dur II®—reported C_{max} values of 0.383 ng/mL and 0.432 ng/mL, respectively. These patches provide controlled release of nitroglycerin and help maintain consistent anti-anginal activity throughout the dosing period.

Bisoprolol Transdermal Patch (Bisono® Tape)

Bisono® Tape is a bisoprolol-containing transdermal patch used for conditions such as aortic dissection, premature ventricular contractions, orthostatic hypotension associated with HF, and atrial fibrillation. A clinical comparison between edematous and non-edematous patients using the 4 mg Bisono® Tape showed slight differences in C_{max} (13.3 vs. 17 ng/mL), but these variations were not clinically significant. Importantly, systemic edema did not alter bisoprolol absorption or its heart-rate-lowering effects following patch application. This suggests that TDDS can maintain reliable therapeutic action even in critically ill patients with fluid-balance abnormalities.

Transdermal Clonidine

Clonidine, an α2-adrenergic agonist originally developed for hypertension, has also been used for attention-deficit hyperactivity disorder (ADHD) and withdrawal symptom management. The transdermal clonidine system, approved by the FDA in 1984, offers smoother plasma levels and improved patient adherence. A comparative study of oral and transdermal clonidine found similar C_{max} values (0.39 ng/mL vs. 0.3 ng/mL), yet the half-life of the transdermal system (31.9 h) was substantially longer than the oral form (10.8 h), with comparable antihypertensive efficacy.

Transdermal Losartan

Losartan, an angiotensin II receptor blocker (ARB), has also been investigated for transdermal delivery. In a study using a proniosomal formulation on rat skin, transdermally delivered losartan achieved a C_{max} of 141 ng/mL, comparable to the oral dose (152ng/mL). Notably, the transdermal formulation exhibited 1.93-fold higher bioavailability than oral losartan. These outcomes highlight the potential of TDDS to enhance the therapeutic profile of cardiovascular agents that undergo significant first-pass metabolism.[1] A list of cardiovascular diseases treated using TDDS is presented in Table below.

Table 2: Transdermal Drug Delivery Systems (TDDS) for cardiovascular diseases.[1]

Drug/system	Therapeutic use	TDDS	Purpose of TDDS
Propranolol transdermal patch	Hypertension, arrythmias.	Propranolol delivered via polymeric transdermal matrix	Avoids first- pass metabolism, achieved steady -stateconcentration (CSS) of 9.3ng/ml after~8h:~75% higher bioavailability than oral propranolol
Oral vs transdermal propranolol	Hypertension	Comparative PK evaluation in animalsBisono® Tape (bisoprolol patch)	Oral propranolol: C_{max} 56.4 ng/mL, bioavailability 12.3%; transdermal route significantly improved systemic exposure
Nitro-Dur® / Nitro-Dur II® nitroglycerin patches	Angina pectoris	Transdermal nitrate patches for sustained vasodilation	Clinical crossover study: C_{max} values 0.383 ng/mL and 0.432 ng/mL; provides controlled nitrate delivery and reduced tolerance risk
Bisono® Tape (bisoprolol patch)	HF, arrhythmias, PVCs, orthostatic hypotension	β1-selective blocker in adhesive transdermal drug reservoir	C^{max}: 13.3 ng/mL (edema) vs. 17 ng/mL (non-edema); edema did not affect absorption or HR reduction
Clonidine transdermal patch	Hypertension, ADHD, withdrawal syndromes	α2-agonist transdermal system approved in 1984	Oral vs. TDDS comparison: Similar C_{max} (~0.3–0.39 ng/mL); TDDS half-life significantly longer (31.9 h vs. 10.8 h), supporting stable BP control
Proniosomal losartan TDDS	Hypertension, HF	Losartan embedded in proniosomal transdermal formulation	Transdermal losartan: C_{max} 141 ng/mL vs. 152 ng/mL orally; 1.93× higher bioavailability than oral solution

3.3 TDDS for the treatment of Central Nervous System (CNS) disorders

Transdermal drug delivery systems (TDDS) have emerged as an important approach for managing various central nervous system (CNS) disorders due to their ability to bypass hepatic first-pass metabolism, provide controlled release, and improve patient adherence. Significant advancements have been made in formulating transdermal therapies for conditions ranging from nicotine dependence to neurodegenerative and psychiatric disorders.

Nicotine and Nicotinic Agonists; Nicotine patches are among the most established CNS-targeted TDDS. They are widely used to assist smoking cessation, helping to mitigate withdrawal symptoms and reduce dependence. Clinical findings also suggest that transdermal nicotine may offer benefits in conditions associated with cognitive dysfunction, including schizophrenia, Alzheimer's disease, and attention-related disorders. Notably, nicotine patches have shown symptom improvement in ADHD, likely due to enhanced dopamine release, a mechanism shared with stimulant medications such as methylphenidate and amphetamine.[13]

Transdermal Methylphenidate Patch for ADHD;A long-acting methylphenidate transdermal system has been developed to allow personalized ADHD therapy. By adjusting patch size and wear-time, clinicians can modify dosage without altering formulation. This model provides consistent drug delivery over extended periods and offers an alternative for patients with difficulty swallowing oral medications.

Buprenorphine Transdermal System for Chronic Pain; Chronic pain associated with cancer and neurological conditions can be effectively managed with transdermal buprenorphine patches. The system provides steady opioid delivery, reduces the need for frequent oral dosing, and has been shown to enhance sleep quality while maintaining tolerable side-effect profiles. It is also being explored for specialized uses, including sickle cell disease–related pain.

Selegiline Transdermal System (MAO Inhibitor Patch); A notable CNS-targeted TDDS is the selegiline transdermal patch, approved for major depressive disorder. It inhibits MAO-A and MAO-B enzymes in the brain and avoids extensive gastrointestinal and hepatic metabolism, reducing dietary restrictions required with oral MAO inhibitors.

AChE Inhibitors Delivered via TDDS; Early clinical investigations with transdermal physostigmine and tacrine did not demonstrate strong therapeutic benefits compared to placebo.

However, transdermal rivastigmine, approved for Alzheimer's disease, has shown meaningful improvement in both cognitive function and daily living performance while reducing gastrointestinal side effects compared with oral dosing.[1] A list of Central Nervous System diseases treated using TDDS is presented in Table below.

Table 3: Transdermal Drug Delivery Systems (TDDS) for Central Nervous Systems.

Drug/system	Disease	TDDS	Purpose of TDDS	Reference
Nicotine TDDS (Nicotinell®, Nicoderm®	Smoking cessation, cognitive disorders	Matrix-type nicotine patch	Reduces withdrawal symptoms; improves cognitive performance; potential benefit in ADHD and schizophrenia	[14]
Transdermal nicotine for ADHD	ADHD symptom control	Nicotine patch used off-label	Dopamine-enhancing effect improves attention and reduces hyperactivity	[13]
Methylphenidate TDDS (Daytrana®)	ADHD	Adhesive patch with drug reservoir	Allows adjustable dosing via patch size/wear time; sustained release over 8–12 hrs	[15]
Selegiline TDDS (Emsam®)	Major depressive disorder	MAO-A/B inhibitor patch	Avoids GI & hepatic metabolism; fewer dietary restrictions; modest antidepressant effect	[1]
Fentanyl TDDS (Duragesic®, Matrifen®)	Chronic severe pain	Opioid patch with reservoir or matrix	Strong analgesic effect for cancer & neuropathic pain; long-acting	[1]
Rivastigmine TDDS (Exelon® Patch)	Alzheimer's disease, dementia	Matrix-based AChE inhibitor patch	Demonstrated improved cognition & daily functioning; fewer GI side effects than oral form	[1]
Rotigotine TDDS (Neupro®)	Parkinson's disease, RLS	dopamine agonist transdermal system	Provides stable dopaminergic stimulation; improves motor function	[13]

4. Currently Approved Transdermally Delivered Drugs

The TDD market has had a considerable impact on the delivery of numerous drugs, primarily in the fields of pain management, hormonal applications, central nervous system disorders, cardiovascular diseases, and other applications, such as smoking cessation. The global TDD market is anticipated to be quite large. Factors such as the prevalence of chronic diseases and technological improvements in TDD methods are leading this market forward. In 1979, the first transdermal patch for systemic delivery was approved in the United States (Transderm Scop™; Novartis, Basel, Switzerland)—a three-day patch that delivered scopolamine to treat motion sickness. The most recently approved patch for severe pain is buprenorphine (Burtans; Purdue Pharma L.P, Stamford, CT, USA), approved by the FDA for the management of chronic pain that is non-responsive to other medications. In addition, several over-the-counter (OTC) products are also available, including nicotine, capsaicin, and menthol patches.

In 2018, the first anti-histamine transdermal patch, emedastine Di fumarate (Allesaga™ TAPE, Hisamitsu Pharmaceutical, Tosu, Japan), indicated to treat allergic rhinitis, was approved in the Japanese market. It has a dose-dependent anti-histaminic action and a long-lasting effect that lasts up to 24 h after administration. In 2007, the first Parkinson's patch containing rotigotine (Neupro™, UCB, Brussels, Belgium) was approved by the FDA—a once-daily patch that comes in four dose strengths: 2 mg, 4 mg, 6 mg, and 8 mg. Rivastigmine is currently FDA-approved for administration via a transdermal patch (Exelon™, Novartis) for the treatment of Alzheimer's disease; the patch overcomes gastrointestinal (GI) adverse effects associated with oral rivastigmine. Ortho Evra™ is an FDA-approved transdermal ethinyl oestradiol and norelgestromin contraceptive patch. The patch is applied once-a-week for three weeks (21 days), with one patch-free week included in the cycle. Apleek™ is a transdermal contraceptive patch containing 550 micrograms of ethinylestradiol and 2.10 mg of gestodene as active ingredients; it is applied once a week for three weeks, followed by a seven-day patch-free period.[16]

5. Applications ofAI in Various stages of TDDS

5.1 Drug Selection &Skin permeability prediction.

The success of TDDS depends largely on whether a drug possesses suitable physicochemical properties to pass through the skin barrier, particularly the stratum corneum. AI-based models accelerate drug selection by analysing large datasets of molecular descriptors—such as molecular weight, lipophilicity (logP), melting point, solubility, and hydrogen-bonding potential—and predicting their compatibility with transdermal administration.ML models trained on curated permeability datasets can rapidly rank candidate molecules for transdermal delivery and estimate permeability coefficients, reducing wet-lab screening. Recent studies show strong predictive performance using ensemble models and deep networks when good descriptor sets are available.[7]

A comprehensive dataset on FDA-approved drugs was analysed using advanced machine learning techniques such as ensemble methods (e.g., Random Forest, XGBoost) and artificial neural networks (ANNs). These models predicted skin permeability (LogKp values) and demonstrated enhanced accuracy for drug diffusion properties in transdermal systems.[1]

5.2 Formulation design & Optimization

Formulation development for patches, nano emulsions, SLNs, NLCs, and microneedle systems typically involves extensive trial-and-error. AI simplifies this by predicting the influence of formulation variables—such as polymer concentration, backing membrane material, surfactant level, plasticizer amount, permeation enhancers, and drug loading—on product performance. Artificial intelligence (AI) plays a transformative role in improving the design, engineering, and performance of transdermal drug delivery systems. By analysing large datasets and identifying complex nonlinear relationships, AI enables researchers to optimize multiple patch parameters simultaneously—including geometry, adhesive properties, polymer composition, and matrix architecture. Machine learning models can efficiently predict how changes in these design variables influence drug release kinetics, enabling the development of patches with consistent and controlled delivery profiles. Through these predictive tools, AI helps determine the ideal combination of adhesive layers, backing films, and drug-loaded matrices to maintain a balance between strong adhesion, patient comfort, and sustained diffusion.AI also facilitates the creation of personalized transdermal patches tailored to individual patient characteristics such as skin hydration, age, ethnicity, and permeation behaviour. Advanced simulation-based approaches allow scientists to model patch performance under different temperature, humidity, and activity conditions, helping ensure reliability in real-world environments. These capabilities significantly reduce experimental workload, accelerate formulation development, and improve clinical performance.

The field of microneedle (MN) technology benefits even more profoundly from AI integration. Machine learning algorithms refine essential microneedle parameters—such as needle length, tip radius, shape, density, and material type—to achieve optimal skin penetration with minimal discomfort. AI-based mechanical models simulate the interaction between microneedles and different skin types, predicting insertion efficiency, potential breakage risk, and drug diffusion patterns. These insights allow researchers to design microneedles that penetrate deep enough to be effective, yet remain painless and safe. Furthermore, AI supports the development of biodegradable microneedles, ensuring complete dissolution after insertion and avoiding needle

waste. Simulation-driven prototyping also accelerates the creation and evaluation of microneedle arrays, reducing both time and material consumption during development. Such advancements have broadened the clinical utility of microneedles, making them suitable for diverse applications including vaccination, peptide and protein delivery, hormone therapy, and chronic disease management.[7]

5.3 Screening of Drug molecules and Optimizing formula

Artificial intelligence (AI) has become a powerful tool for identifying drug molecules that possess suitable physicochemical characteristics—such as solubility, lipophilicity, molecular weight, and pKa—for effective transdermal delivery. By analysing large chemical datasets, AI systems can rapidly filter and prioritize compounds that are most likely to achieve adequate skin permeation, significantly reducing the time and cost associated with early-stage drug screening. Machine learning (ML) models further strengthen this process by predicting how formulation components, such as polymers, permeation enhancers, and solvents, influence drug release and absorption through the skin. Advanced computational techniques, including quantitative structure–activity relationship (QSAR) modelling and deep learning algorithms, allow researchers to forecast molecular behaviourand drug–excipient interactions with high accuracy. These predictive tools help in selecting the most promising drug candidates for TDDS while guiding the rational design of optimized formulations. By integrating experimental data with AI-driven predictions, formulating transdermal systems becomes more efficient, systematic, and scientifically grounded.[1]

5.4 Personalized Medicine

Smart transdermal patches equipped with AI-driven sensors represent a major advancement in modern drugdelivery. These intelligent systems continuously monitor physiological parameters and drug levels in real time, allowing the patch to automatically adjust the release rate based on the patient's needs. Such adaptive feedback mechanisms help maintain stabletherapeutic concentrations, reducing the likelihood of underdosing or overdosing and improving overall treatment outcomes.

AI-enabled smart patches also support personalized therapy by analysing individual patient characteristics, including skin type, hydration status, age, genetic factors, and medical history. By incorporating this data into predictive algorithms, AI can recommend customized dosing schedules and optimize drug release based on each patient's unique skin permeability and health condition. This level of personalization enhances treatment precision, improves patient adherence, and reduces the complexity typically associated with chronic medication regimens. As a result, AI-integrated smart patches are poised to significantly improve the safety, efficiency, and convenience of transdermal drug delivery.[1]

5.5 Process Optimization & Quality-by-Design (QbD)

AI enables prediction of critical quality attributes and process parameters for patch manufacturing, allowing real-time control and reduced batch failure. Integration with PAT (process analytical technology) can create smart manufacturing pipelines.[17]

5.6 Efficiency in Clinical Trials

Artificial intelligence (AI) has greatly improved the efficiency and reliability of clinical trials, particularly those involving transdermal drug delivery systems (TDDS). One of the most significant contributions of AI lies in patient recruitment. By analyzing extensive datasets—including electronic health records (EHRs), medical databases, social media patterns, and even genetic information—AI can quickly identify individuals who closely match the inclusion criteria. This targeted approach not only accelerates recruitment but also increases the likelihood of enrolling participants who will respond favourably to the investigational therapy, thereby improving the overall quality of the study population. AI technologies also play a critical role in supporting patient retention. Predictive algorithms can identify participants at risk of discontinuing trials by evaluating adherence patterns, communication frequency, and health parameters. Automated systems, such as reminder alerts and digital engagement tools, help encourage continued participation and ensure that subjects follow trial protocols consistently.

Data management is another area where AI offers substantial benefits. Automated data capture from electronic medical records, wearable sensors, and digital monitoring devices reduces manual entry errors and ensures uniform, high-quality datasets. AI-driven analytics enable rapid interpretation of large volumes of clinical data, making it possible to detect trends, anomalies, or safety signals earlier in the trial process.

Moreover, AI supports predictive modeling to estimate trial outcomes and optimize study design. These models help researchers modify protocols based on early results, reducing the risk of trial failure due to ineffective dosing strategies or unforeseen complications.

Collectively, these AI-enabled improvements shorten clinical trial timelines, lower operational costs, and enhance the likelihood of successful trial outcomes by optimizing recruitment, improving adherence, ensuring data accuracy, and enabling real-time outcome prediction.[1]

6. Advantages

Reduces experimental burden and accelerates candidate selection.[7]

Handles complex, nonlinear interactions between formulation variables and skin response.[18]

Enables personalization via sensors and patient data—potential to improve therapeutic outcomes.[19]

7. Limitations and Challenges of AI in TDDS

Data Scarcity & Heterogeneity

Limited or poor-quality data sources: Many AI models depend on large, high-quality datasets. In TDDS research, such datasets are often small, fragmented, or inconsistent. For example, data may come from different skin sources (human vs porcine vs artificial membranes), in vitro vs in vivo studies, or varied permeation protocols — making it difficult to aggregate data for robust model training.[20]

Under-representation of rare conditions or demographic groups: For many diseases or specific skin types (e.g., paediatric, geriatric, ethnic variants), data are scarce. Lack of representative data undermines the generalizability of AI predictions across populations.[21]

Generalizability & Interpretability (Black-Box Problem)

Overfitting and poor external validity: Many ML/deep learning models perform very well on training or test data but fail to generalize to new, unseen data — particularly when formulation protocols or skin models differ.[1] Lack of mechanistic insight: Deep models often act as "black boxes," i.e., they provide predictions without clear explanation of why a given formulation or parameter set works. This opacity limits their usefulness in hypothesis-driven drug delivery research and reduces trust among regulators and clinicians. Difficulty updating or validating models: Once trained, some AI models struggle to incorporate new data or adapt to updated experimental protocols. This rigidity can make them obsolete when formulations or skin models evolve.[20]

Regulatory & Ethical Challenges

Regulatory uncertainty and lack of standard guidelines: Traditional drug development and delivery systems follow well-defined regulatory pathways. In contrast, AI-driven models (for permeability prediction, formulation optimization, smart patches) currently lack clear, universally accepted regulatory frameworks. This regulatory gap complicates validation, approval, and real-world deployment.[21] Data privacy and security risks: Many AI/ML systems rely on sensitive patient data — especially in personalized TDDS or wearable patches. Ensuring compliance with data protection laws (e.g., HIPAA, GDPR) and safeguarding against breaches is a major challenge.[22] Bias, fairness, and representativeness: If training data is biased or unrepresentative (e.g., skewed toward a particular age group, ethnicity, or skin type), AI models may produce biased outcomes — limiting their reliability across diverse patient populations.

Transparency and accountability in decision-making: Because many AI-based predictions are not easily interpretable, assigning responsibility when something goes wrong (e.g., unexpected side-effects, dosing errors) becomes difficult. Regulators and clinicians are often reluctant to adopt AI-based decisions without explainability.[20]

8. Future potential of AI in overcoming obstacles in Transdermal Drug Delivery Systems

The integration of artificial intelligence (AI) into transdermal drug delivery systems (TDDS) is expected to revolutionize the field by addressing long-standing challenges related to drug selection, skin permeability, formulation design, and patient-specific variability. As AI technologies continue to evolve, TDDS will become more intelligent, efficient, and adaptable, enabling transformative advances in drug delivery science.

One of the most promising future directions is the convergence of AI and nanotechnology. By combining predictive algorithms with nanocarrier engineering, researchers can design advanced transdermal platforms capable of delivering drugs with exceptional precision. AI can model how nanoparticles—such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nano emulsions, and polymeric nanocarriers—interact with the skin barrier, predict their permeation behaviour, and optimize surface properties for enhanced targeting. This may enable the development of nano-enabled TDDS that deliver drugs to specific tissues, immune cells, or disease sites with unprecedented accuracy, significantly improving therapeutic outcomes for complex disorders such as cancer, neurodegenerative diseases, and chronic inflammatory conditions. AI also holds the potential to advance personalized and adaptive TDDS. By integrating patient-specific biological data—including genetic profiles, metabolic rates, skin hydration, age, and disease state—AI algorithms can design individualized dosing regimens and tailor drug release patterns. Future smart patches could dynamically adjust drug output in real time based on biological signals measured through embedded sensors, allowing precise, closed-loop feedback control. Such adaptive systems could transform chronic disease management by offering continuous monitoring, automated dosage adjustment, and improved adherence.

Overall, the future of TDDS lies in intelligent systems that combine nanotechnology, advanced biomaterials, biosensing platforms, and AI-driven modeling to create delivery systems that are highly precise, adaptive, and patient-centered. As these technologies continue to mature, AI-empowered TDDS will play a transformative role in personalized medicine and next-generation therapeutics.[1]

9. CONCLUSION

AI is rapidly advancing the development of transdermal drug delivery systems by improving drug screening, formulation optimization, and patch design. Emerging AI-driven tools, combined with sensors and smart wearable technologies, are paving the way for

personalized and adaptive TDDS that can adjust drug release based on individual patient needs.

However, challenges such as limited high-quality datasets, the need for robust model validation, and evolving regulatory requirements must be addressed to ensure safe and effective clinical translation. Despite these hurdles, AI holds strong potential to transform TDDS into more precise, efficient, and patient-centered therapies in the near future.

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