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Iontophoretic Transdermal Delivery of Anti-Inflammatory Agents: A Review of Recent Advancements

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ABSTRACT

Iontophoretic transdermal delivery systems utilizing silver/silver chloride (Ag/AgCl) electrodes represent an advanced pharmaceutical technology for localized nonsteroidal anti-inflammatory drug (NSAID) administration. This review synthesizes contemporary evidence on the formulation design, physicochemical characterization, biopharmaceutical performance, manufacturing scalability, and clinical efficacy of electrode-based iontophoretic NSAID patches. Iontophoresis enhances transdermal NSAID flux by 3- to 100-fold compared to passive diffusion through electrokinetic drug transport. Optimized polymer matrices combined with reversible Ag/AgCl electrochemistry enable pH-stable, predictable current delivery. Comprehensive characterization via FTIR, DSC, XRD, and validated HPLC confirms formulation stability and drug content uniformity. Recent randomized controlled trials and systematic reviews demonstrate superior analgesic efficacy, improved systemic tolerability, and avoidance of first-pass metabolism compared to oral NSAID administration. Clinical applications include acute post-endodontic pain, musculoskeletal injuries, and osteoarthritis management. Integration of microneedle arrays, stimuli-responsive nanocarriers, and artificial intelligence-driven parameter personalization based on patient skin impedance biometrics is expanding therapeutic potential and addressing inter-individual variability. Iontophoretic NSAID systems are classified as combination products requiring dual pharmaceutical and medical device compliance. Primary limitations include cutaneous adverse effects at elevated current densities and device cost relative to passive alternatives. Silver electrode-based iontophoretic NSAID delivery offers a scientifically robust, clinically compelling platform for precision, patient-centred pain management with substantially reduced systemic exposure and enhanced local tissue targeting.

Keywords: Iontophoresis, transdermal delivery, NSAIDs, Ag/AgCl electrodes, controlled release, combination products.

1. INTRODUCTION

The Management of Chronic Pain and Inflammation

Chronic pain and inflammation collectively constitute one of the most pervasive and economically devastating clinical challenges confronting modern healthcare. Musculoskeletal disorders — encompassing osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, tendinopathies, and soft-tissue injuries — affect upwards of 1.7 billion individuals globally, with projections indicating escalating prevalence in ageing populations [1,2]. The inflammatory cascade underlying these conditions involves activation of phospholipase A2, release of arachidonic acid from membrane phospholipids, and its enzymatic conversion by cyclooxygenase (COX) isoforms into prostaglandins, thromboxane's, and prostacyclin's — bioactive lipid mediators that sensitise nociceptors, perpetuate synovial inflammation, and facilitate central sensitisation of pain pathways.

NSAIDs are the pharmacological cornerstone of pain and inflammation management, prescribed more extensively than virtually any other drug class. Their mechanism resides in competitive, reversible inhibition of COX-1 and COX-2 enzymes, curtailing prostaglandin biosynthesis and thereby attenuating nociception, pyrexia, and oedema. Despite their therapeutic efficacy, chronic oral NSAID administration is burdened by a well-characterised spectrum of adverse effects: gastrointestinal mucosal injury ranging from dyspepsia to peptic ulceration and haemorrhage, renal prostaglandin-dependent vasoconstriction predisposing to acute kidney injury, and cardiovascular risk attributable to altered thromboxane/prostacyclin balance [1]. Parenteral routes are impractical for chronic outpatient analgesia, and sublingual or rectal formulations lack patient acceptability.

These clinical limitations have propelled sustained scientific interest in alternative delivery routes, most notably the transdermal route. Transdermal drug delivery systems exploit the skin as a non-invasive portal for systemic or local drug absorption, conferring the dual advantages of bypassing first-pass metabolism and enabling sustained, controlled drug input. For musculoskeletal pain — typically localised in nature — transdermal delivery further enables the accumulation of drug at the target tissue while sharply limiting systemic exposure, a pharmacokinetic profile ideally suited to NSAIDs [2,3]. The primary impediment to passive transdermal delivery of most NSAIDs is the formidable barrier function of the stratum corneum, which confines effective passive permeation to lipophilic, low-molecular-weight molecules.

Overcoming the stratum corneum barrier remains a central challenge in the transdermal delivery of ionised, hydrophilic, and macromolecular therapeutics such as insulin. Active physical enhancement techniques with iontophoresis at the forefront have emerged as promising solutions to this long-standing limitation. Against this backdrop, the present review offers a critically evaluated and comprehensive account of silver electrode-based iontophoretic NSAID delivery, addressing its mechanistic basis, formulation design, preparative techniques, characterisation methods, industrial scale-up, regulatory requirements, and the most recent technological developments shaping the field.

Pathophysiology of Pain and the Rationale for Transdermal NSAID Delivery

Pain perception in musculoskeletal and inflammatory disorders initiates with tissue injury or immunological activation, triggering a cascade of neurochemical events. Tissue damage activates phospholipase A2, liberating arachidonic acid from membrane phospholipids. COX enzymes — constitutively expressed COX-1 and lastingly expressed COX-2 — metabolise arachidonic acid to prostaglandins (PGE2, PGI2), thromboxane A2, and other eicosanoids. PGE2 is the principal mediator of peripheral sensitisation, reducing the activation threshold of TRPV1 and other nociceptor ion channels, amplifying pain signalling, and sustaining vasodilatation and oedema at the inflammatory focus [1].

Chronic musculoskeletal conditions such as osteoarthritis are characterised by synovial hyperplasia, progressive cartilage erosion, subchondral bone remodelling, and persistent elevation of intra-articular inflammatory mediators. The anatomical proximity of these target structures to the skin surface renders them highly amenable to topical and transdermal drug administration. The rationale is strengthened by the observation that periarticular soft tissues — tendons, bursae, joint capsules — exhibit relatively poor vascularisation, facilitating the accumulation of topically applied drug at concentrations that may exceed those achievable through systemic administration alone [3].

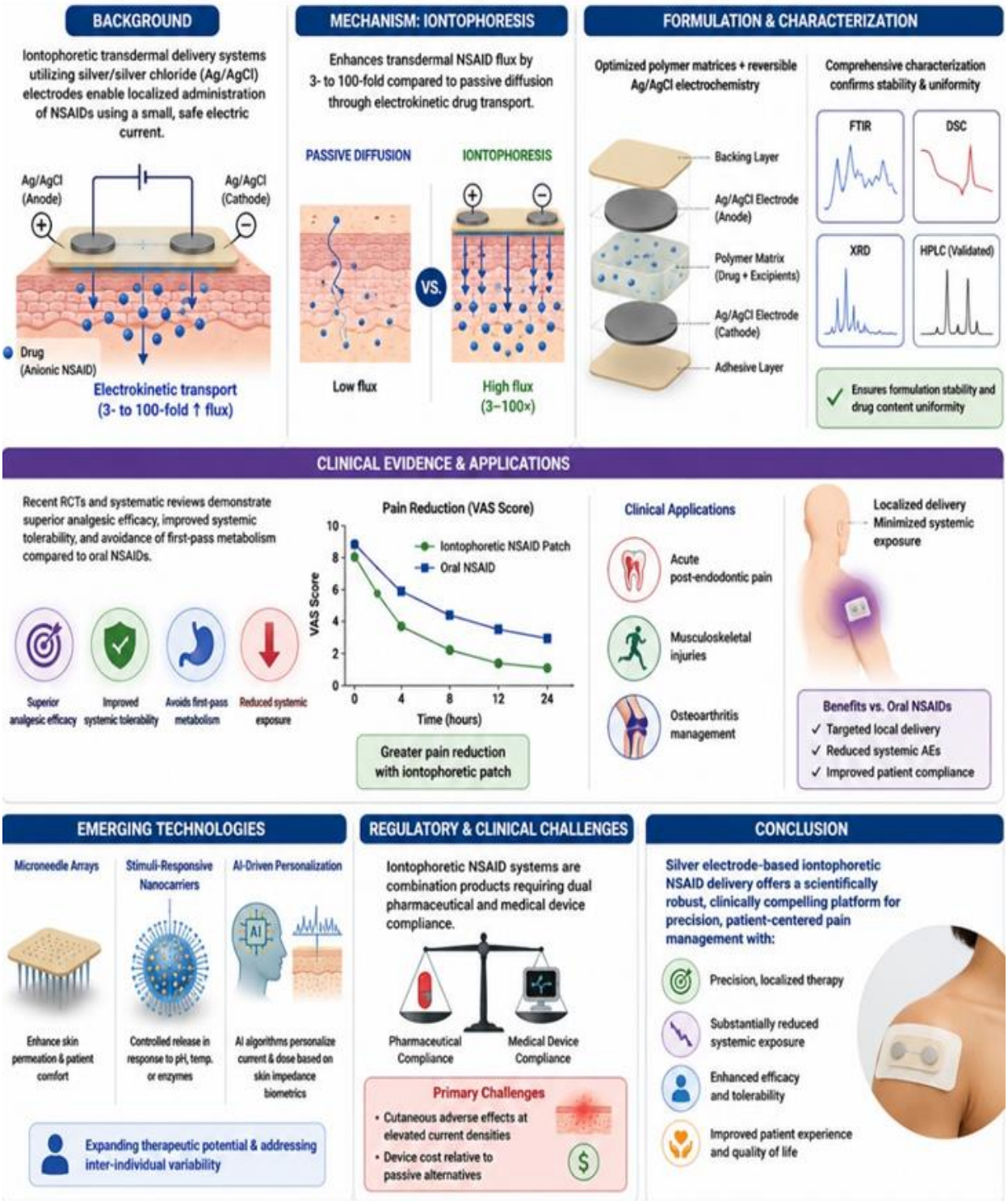
Inflammatory skin diseases — including psoriatic arthritis, atopic dermatitis with joint involvement, and localised inflammatory conditions — present an additional compelling indication for TDDS. Local drug concentrations achievable at the site of dermal pathology through transdermal delivery can be sustained well beyond the therapeutic threshold for extended periods, enabling disease-modifying tissue concentrations with minimal systemic burden [1]. The combination of localised pathology and the ionised physicochemical character of NSAIDs at physiological pH — which renders them poorly suited to passive transdermal permeation — creates a strong scientific and clinical justification for iontophoresis-mediated transdermal delivery.

1.1 Transdermal Drug Delivery Systems: Overview and Advantages

Advantages of Transdermal Delivery

Transdermal drug delivery systems confer a constellation of pharmacokinetic and pharmacodynamic advantages that distinguish them from oral and parenteral routes. Foremost is the circumvention of hepatic first-pass metabolism, which, for drugs such as nitro-glycerine, oestradiol, and certain NSAIDs, results in significant pre-systemic degradation when

administered orally. By delivering drug directly into



the systemic circulation via dermal capillaries, TDDS achieves superior bioavailability for susceptible compounds [3,4]. Sustained and controlled drug release profiles attained through matrix or reservoir patch designs maintain plasma concentrations within the therapeutic window for 12–72 hours or more, reducing the peak-trough fluctuations associated with intermittent oral dosing and thereby improving both efficacy and tolerability [4].

Additional advantages of TDDS include improved patient compliance through reduced dosing frequency and non-invasive application, the ability to terminate drug delivery by patch removal in the event of adverse reactions, the avoidance of gastrointestinal degradation for acid-labile or absorption-variable compounds, suitability for patients with dysphagia or post-operative nil-by-mouth status, and the capacity for local drug targeting in anatomically accessible conditions. The global transdermal drug delivery market was valued at approximately USD 66.2 billion in 2023 and is projected to expand at a compound annual growth rate of 11.9% through 2030, reflecting the sustained commercial and therapeutic relevance of this delivery modality [4].

Limitations of Passive Transdermal Delivery

The primary anatomical barrier to transdermal drug permeation is the stratum corneum — the outermost 10–20 µm of the epidermis — which functions as a highly effective lipophilic obstacle to molecular diffusion. Composed of terminally differentiated keratinocytes (corneocytes) embedded within a lamellar lipid matrix of ceramides, cholesterol, and long-chain fatty acids in a 'brick-and-mortar' architecture, the stratum corneum limits effective passive diffusion to lipophilic molecules with molecular weights below approximately 500 Da [3]. NSAIDs, which are predominantly ionised (anionic) at physiological pH and possess a range of molecular weights (182–375 Da), encounter significant electrostatic and steric resistance to passive permeation.

Drug transport across the stratum corneum may proceed via three pathways: the transcellular (intracellular) route through corneocytes, the intercellular route through the lipid lamellae, and the trans-appendageal route through hair follicles and sweat glands. The intercellular route is quantitatively dominant for most small lipophilic molecules. For ionised drugs such as NSAIDs, even the intercellular pathway is substantially impeded by the net negative charge on the skin membrane at physiological pH, which creates a repulsive electrostatic barrier to anionic drug species [5,6]. This physicochemical incompatibility between the ionised character of NSAIDs and the lipophilic barrier of the stratum corneum renders passive transdermal delivery insufficient for achieving therapeutic tissue concentrations for most NSAID molecules, necessitating active permeation enhancement.

1.2 Design and Components of Transdermal Drug Delivery Systems

A transdermal drug delivery system is a multilayer pharmaceutical preparation engineered to deliver drug through intact skin at a controlled and predictable rate. The standard architectural components of a TDDS patch are: as shown in the fig 1

The backing membrane is typically fabricated from occlusive materials such as polyester, polyethylene, or metallised foil, which prevent trans-epidermal water loss and maintain a hydrated microenvironment at the skin surface — a factor that enhances stratum corneum permeability. The pressure-sensitive adhesive must maintain adequate tack across the range of body temperatures and motion without causing skin sensitisation. For iontophoretic TDDS, the system incorporates an additional electrochemical layer comprising the drug reservoir in contact with the active electrode (cathode for anionic NSAIDs), a return electrode, and a battery-powered current source, all integrated within a wearable format [7,8].

Classification and Mechanism of Transdermal Drug Delivery Systems

TDDS are broadly classified according to their structural design and the mechanism governing drug release into four heads types.as shown in fig 2.

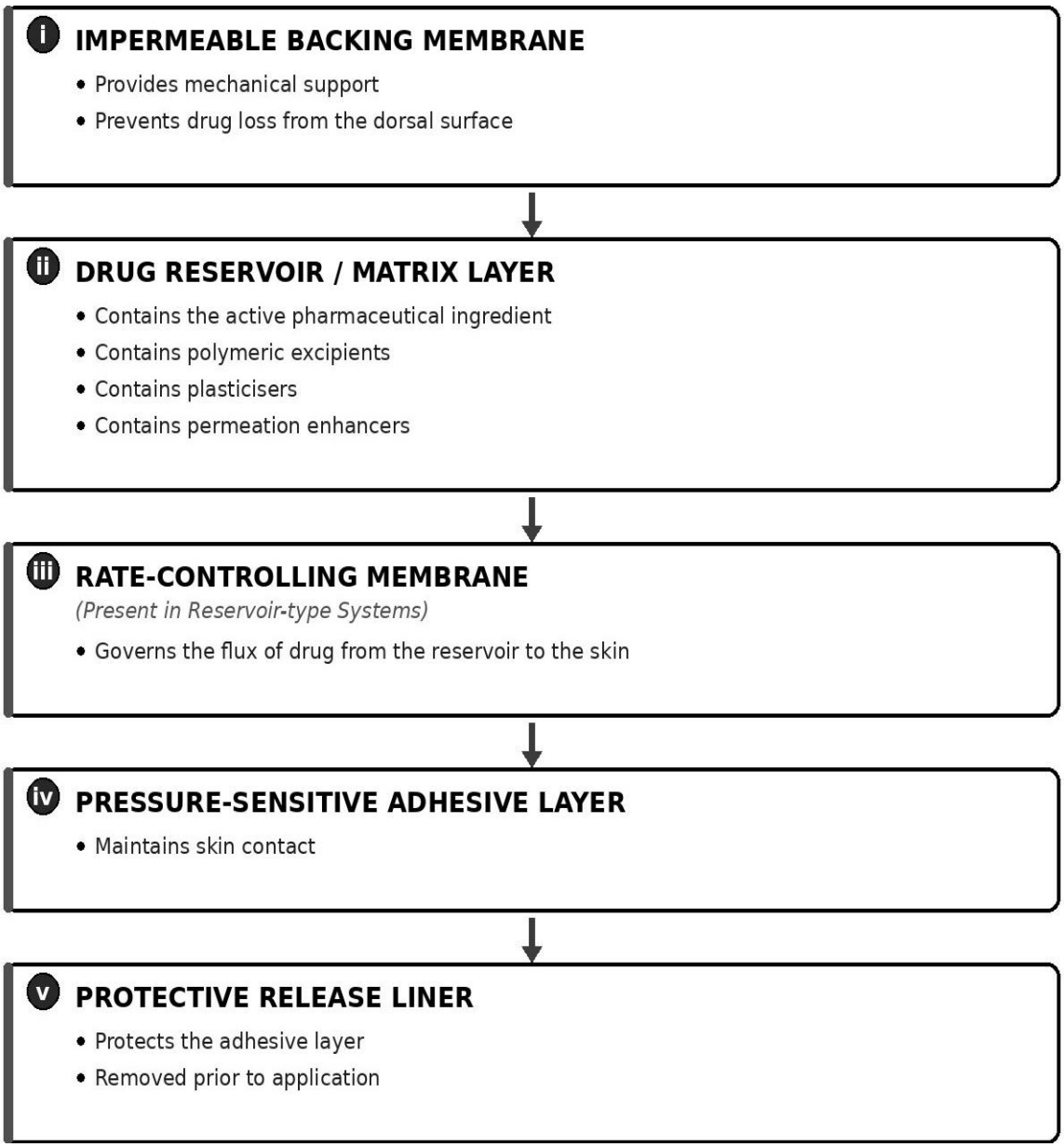


Fig 1 Components of Transdermal drug delivery system [TDDS] [4]

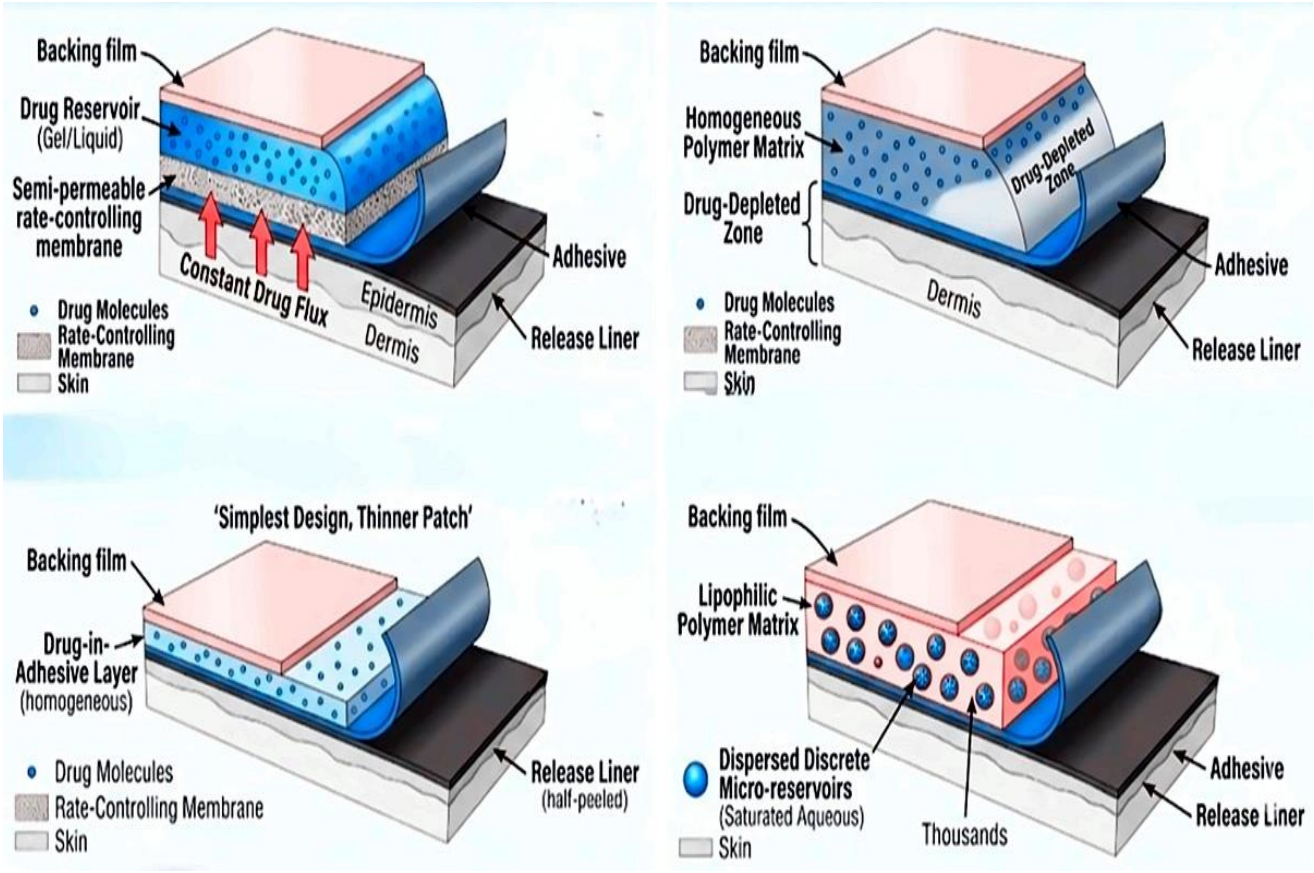


Fig 2 1. Membrane controlled reservoir system, 2. Matrix diffusion system, 3. Drug in adhesive system, 4. Micro-reservoir system.

1.2.2 Principles Governing:

Passive Diffusion

The theoretical framework governing **passive drug diffusion** across the skin is described by Fick's first law of diffusion, expressed as $J = -D(dC/dx)$, where J is the flux (µg/cm²/hr), D is the diffusion coefficient of the drug in the membrane, and dC/dx is the concentration gradient across the membrane. In practice, the steady-state flux across the stratum corneum is described as

$J = DKCd/h$,

Where, K is the partition coefficient of the drug between the membrane and the donor vehicle

Cd is the donor drug concentration

and h is the effective membrane thickness [5,40].

The partition coefficient, molecular weight, ionisation state, thermodynamic activity, and protein binding of the drug are the principal physicochemical determinants of passive flux. For ionised NSAIDs, the combination of low K and electrostatic repulsion yields D values orders of magnitude below those required for therapeutic flux, providing the quantitative basis for active enhancement.

Anti-inflammatory Drugs and Their Transdermal Application

Classification and Mechanism of Action

NSAIDs are conventionally classified by their chemical scaffold and COX-selectivity profile. The major chemical classes with established or investigational transdermal applications are: **as shown in table 1.**

Most NSAIDs non-selectively inhibit both COX-1 and COX-2 enzymes. COX-1 supports gastric protection, renal function, and platelet aggregation, while COX-2 is mainly involved in inflammation. Inhibition of these enzymes reduces prostaglandin and thromboxane synthesis, thereby

decreasing pain, fever, inflammation, and platelet aggregation.

Selective COX-2 inhibitors, such as Celecoxib, mainly target inflammatory pathways with fewer gastrointestinal side effects. Aspirin uniquely causes irreversible inhibition of both COX enzymes, unlike other NSAIDs, which act reversibly.[4,34,37]

Table 1. Classification of NSAIDs used in iontophoretic transdermal delivery systems

Class	Examples	pKa	Charge at pH 7.4	Iontophoresis Polarity
Propionic acid derivatives	Ketoprofen, Ibuprofen, Naproxen	~4.8	Anionic	Cathodal
Phenylacetic acid derivatives	Diclofenac	4.0	Anionic	Cathodal
Indoleacetic acid derivatives	Indomethacin, Sulindac	4.5	Anionic	Cathodal
Oxicams	Piroxicam, Meloxicam	~6.3	Anionic	Cathodal
Salicylates	Aspirin, Salicylic acid	3.0	Anionic	Cathodal
COX-2 selective	Celecoxib, Etoricoxib	~9.9 (NH)	Near-neutral/Anionic	Cathodal

1.2.4 Advantages of Anti-inflammatory Drugs in Transdermal Delivery

The transdermal route confers particular therapeutic advantages for NSAIDs beyond those generally applicable to TDDS. Local drug targeting to inflamed periarticular tissues synovium, tendons, bursa -can achieve drug concentrations in the therapeutic range that are demonstrably higher than those achieved via equivalent systemic doses, a phenomenon attributable to the direct diffusion pathway from skin to underlying target tissues without dilution in the systemic circulation [2,41]. Critically, transdermal NSAID delivery achieves this therapeutic tissue exposure while maintaining plasma concentrations well below the levels associated with systemic adverse effects. Clinical pharmacokinetic data confirm that transdermal diclofenac achieves muscle and subcutaneous tissue concentrations exceeding plasma concentrations by 4-fold and 7-fold respectively, while generating plasma Cmax values 70–90% lower than equivalent oral doses [1,4,37].

Transdermal delivery entirely bypasses the gastrointestinal tract, eliminating the risk of local mucosal injury. The continuous, controlled-release profile of TDDS further avoids the high peak plasma concentrations associated with oral dosing that disproportionately drive adverse effects, while maintaining analgesic concentrations at the target site. These advantages collectively make transdermal delivery a pharmacologically and clinically compelling modality for NSAID administration in inflammatory joint and soft-tissue conditions [2,4].

1.2.5 Electrodes in Transdermal Drug Delivery

Electrode components in Iontophoretic Systems

The electrode is the critical electro-transducer element in any iontophoretic system, converting electronic current carried by electrons into ionic current carried by ions at the electrode–solution interface. This transduction occurs through Faradaic electrochemical reactions at the electrode surface. The nature of these reactions determines

the generation of toxic by-products, the degree of pH shift at the skin interface, and the electrochemical stability of the system - all parameters of direct consequence for drug delivery efficiency, patient comfort, and regulatory acceptability [5,6].

Inert metal electrodes (platinum, stainless steel, carbon) drive electrolysis of water - O2 evolution at the anode and H2 evolution at the cathode - generating protons and hydroxide ions that cause rapid, clinically significant pH shifts (pH < 2 at the anode, pH > 12 at the cathode). These extreme local pH values can cause electrochemical burns, drug degradation, protein denaturation, and marked discomfort. Gas bubble generation also disrupts electrode–skin contact, compromising current delivery. For these reasons, inert metal electrodes are unsuitable for therapeutic iontophoresis. Silver and Ag/AgCl electrodes overcome all of these limitations, and their superiority has led to their universal adoption in clinical and investigational iontophoretic systems [5,8,43].

SILVER ELECTRODE TYPES FOR IONTOPHORESIS

- **Silver/Silver Chloride (Ag/AgCl) Electrodes**
- **Pure Silver (Ag) Metal Electrodes**
- **Silver-Coated/Composite Electrodes**
- **Silver Reservoir Electrodes**
- **Silver Nanoparticle-Based Electrodes (Emerging)**

1. Silver/Silver Chloride (Ag/AgCl) Electrodes

Description

Nonpolarizable electrodes composed of metallic silver covered with a layer of silver chloride. These are the most widely used electrodes in pharmaceutical iontophoresis systems.

Electrochemical Reactions

- **Anode:** $Ag(metal) + Cl^-(aq) \rightarrow AgCl(solid) + e^-$
- **Cathode:** $AgCl(solid) + e^- \rightarrow Ag(metal) + Cl^-(aq)$ [24]

Characteristics

Low electrode-skin impedance, Stable half-cell potential, Non-toxic to biological tissues, Reversible electrochemical reactions, Water electrolysis is prevented, Minimal pH shifts at electrode-skin interface and Low noise and minimal motion artifact.

Advantages for NSAID Delivery

Well-adapted for delivery of cationic drugs (e.g., positively charged NSAID formulations). Efficient when chloride is present in donor solution. Can be used as either anode (for cationic drugs) or cathode (for anionic drugs). Excellent current transfer efficiency [25][26].

2. Pure Silver (Ag) Metal Electrodes

Description

Metallic silver electrodes without chloride coating, used primarily as anode in oligodynamic iontophoresis applications. Silver ions (Ag^+) are electrically activated from the metal surface.

Electrochemical Reaction

- **Anode:** $Ag(solid) \rightarrow Ag^+(aq) + e^-$[25]

Characteristics

Direct silver ion release through oxidation. Higher current intensity tolerance. Controlled ion release based on current intensity and duration. Follows Faraday's law of electrolysis.

Advantages for Antimicrobial NSAIDs

Allows independent control of silver ion concentration. Sustained release capability preferable to fast release. Efficient for antimicrobial enhancement of NSAID delivery. Suitable for combined antimicrobial-anti-inflammatory therapy [26]

5. Silver Nanoparticle-Based Electrodes (Emerging)

Description

Electrodes incorporating silver nanoparticles (AgNPs) for enhanced electrochemical performance and increased active surface area.

Composition

AgNPs embedded in polymer matrix. AgNPs on carbon-based substrate (graphene, carbon nanotubes). AgNPs in hydrogel carrier systems. Multi-component nanocomposites with AgNPs and metal oxides.

Key Characteristics

Significantly higher surface area-to-volume ratio. Enhanced electrical conductivity. Improved catalytic properties. Tunable nanoparticle size and distribution. Stronger electrochemical response.

Advantages for NSAIDs

Enhanced ion transfer efficiency.Lower current requirements for effective delivery. Potential for reduced local adverse effects. Combined antimicrobial and anti-inflammatory benefits. Faster drug penetration kinetics [25] .

Active Enhancement Techniques

Active physical enhancement techniques represent the most technically advanced and efficacious approach to overcoming the stratum corneum barrier for drug molecules that are poorly suited to passive permeation. These techniques are broadly categorised as, Second-generation (iontophoresis, non-cavitational ultrasound) . Third-generation (electroporation, cavitational sonophoresis, thermal ablation, microneedles) modalities, a classification reflecting their mechanism of stratum corneum interaction and the magnitude of barrier disruption induced [3,4].

Iontophoresis employs a continuous, low-intensity direct current (0.1–0.5 mA/cm²) to drive ionised drug molecules electro-phoretically across the skin. It does not create permanent structural disruption to the stratum corneum and is the most extensively validated active enhancement modality for NSAID delivery.

Sonophoresis (phonophoresis) uses ultrasonic energy to cavitate lipid bilayers within the stratum corneum transiently, creating aqueous channels through which drug may permeate; therapeutic ultrasound at 1–3 MHz has demonstrated significant enhancement for diclofenac in musculoskeletal applications [15]. Electroporation applies brief (microsecond to millisecond) high-voltage pulses (50–1000 V) that transiently destabilise lipid bilayer architecture, creating transient aqueous pores through which even macromolecular drug species may permeate; flux enhancements of 4 orders of magnitude have been reported, though concerns regarding skin integrity and pain remain. Microneedle arrays create defined microscopic conduits through the stratum corneum without penetrating viable epidermis or dermal nerve endings, providing a pain-free physical bypass of the barrier that significantly enhances the effectiveness of subsequently applied iontophoresis [8,9].

2. Iontophoresis: Mechanisms and Principles

Historical Development

The scientific and clinical history of iontophoresis extends across three centuries. The foundational observations of Galvani (1780s) and Volta (1790s) establishing the principles of bioelectricity laid the theoretical groundwork for electrically assisted drug transport. Giovanni Pivati (1747) is credited with the first documented demonstration of charged substance movement under applied electrical potential. The clinical application of iontophoresis gained traction in the early 20th century with the work of Stéphane Leduc, who demonstrated the iontophoretic delivery of local anaesthetics across intact skin. Seminal mid-century applications included Cation-mediated pilocarpine delivery for sweat electrolyte testing in cystic fibrosis diagnosis — a technique that remains in clinical use today. The modern era has witnessed systematic expansion into pain management, dermatology, ophthalmology, and the delivery of peptide and biologic therapeutics, with the global iontophoretic drug delivery market experiencing sustained growth as device miniaturisation and wearable technology have converged [5,6].

Mechanisms of Iontophoretic Drug Transport

Iontophoresis mediates drug transport across the skin through three concurrently operating mechanisms: electromigration (electro-repulsion), electroosmosis, and passive diffusion augmented by current-induced changes in stratum corneum permeability. The relative quantitative contribution of each mechanism depends on the

physicochemical properties of the drug, the composition of the formulation, and the applied current parameters [5,6].

Electromigration is the dominant mechanism for ionised drug species. Under an applied electrical field, charged drug molecules are propelled through the skin by electrostatic force: cationic drugs are driven from the anode, anionic drugs — including the vast majority of NSAIDs — from the cathode. The quantitative relationship governing ion flux under electromigration is described by,

The Nernst–Planck equation:

Ji = −Di(dCi/dx) + (ziF/RT) DiCi (dΦ/dx) + Ci(vf)

Where, Ji is the total flux of species

Di is the diffusion coefficient, Ci is the concentration

zi is the charge valency, F is the Faraday constant

R is the gas constant

T is absolute temperature

dΦ/dx is the electrical potential gradient

vf is the convective electroosmotic velocity.

For anionic NSAIDs applied at the cathode, the electrostatic driving force directly opposes the repulsive skin charge, enabling net cathodal delivery [5,6,44].The mechanism is as shown in the fig 3,

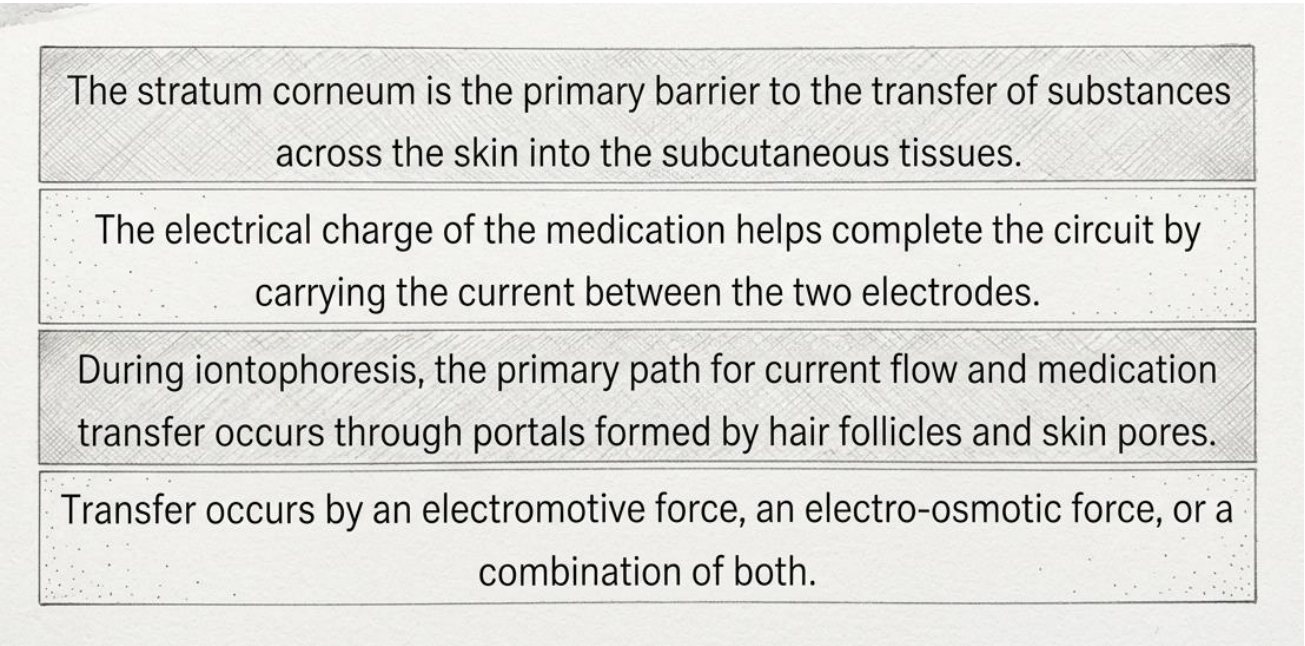


Fig3 Mechanism of iontophoresis

Silver Electrodes in Iontophoretic Systems

Electrochemical Mechanism and Reactions

Silver (Ag) and silver/silver chloride (Ag/AgCl) electrodes are the universally preferred electrode materials for clinical and investigational iontophoretic drug delivery by virtue of their uniquely favourable electrochemical properties. The electrochemical reactions at Ag/AgCl electrodes are:

Anode: Ag → Ag+ + e–; Ag+ + Cl– → AgCl (Ksp = 1.8 × 10–10)

Cathode: AgCl + e– → Ag + Cl–

This reversible Faradaic chemistry — silver oxidation at the anode stoichiometrically matched by AgCl reduction at the cathode — confers several critical advantages over inert electrode systems. Crucially, neither water electrolysis nor gas evolution (O2 or H2) occurs under normal operating conditions, eliminating the gas bubble-mediated disruption of electrode–skin contact that afflicts inert electrode systems and the local pH extremes (pH <2 or >12) that cause

electrochemical burns. The reduction potential of the Ag/AgCl couple (+0.222 V vs. SHE) ensures thermodynamically stable electrode operation within the iontophoretic voltage range, and the buffering capacity of chloride ions in tissue fluids replenishes the cathode reaction, maintaining sustained current delivery [5,6].

Silver chloride formed at the anode is adherent, insoluble, and non-toxic at the concentrations generated during typical iontophoretic sessions. The minimal local pH change (typically <1 pH unit) associated with Ag/AgCl electrode operation — compared with multi-unit pH shifts at inert electrodes — is critical for preserving drug stability (particularly for acid- or base-labile NSAIDs), maintaining patient comfort, and ensuring consistent drug ionisation in the electrode reservoir. The biocompatibility of silver at the dermal interface, supported by decades of clinical use in wound dressings and implantable devices, further supports Ag/AgCl as the gold-standard electrode material for iontophoresis [8,9,46].

Ideal properties of drug for electrode configuration based on silver electrode [30]

Physicochemical Properties	Biological Properties	Electrode Compatibility (Ag)
Molecular Weight (Optimal 100–500 Da)	Anti-inflammatory Efficacy	Silver Ion Reactivity (Minimal)
Charge State (Anionic/Cationic for Silver)	Bioavailability (Local/Systemic)	Stability with Ag+
Solubility (High in Vehicle)	Minimal Side Effects	No Harmful Silver Interactions
Stability (Chemical & Physical)	Penetration Ability (Enhanceable)	Optimal Charge Matching (Ag-Anode/Cathode)
All Physicochemical Criteria Met?	All Biological Criteria Met?	All Electrode Criteria Met?

Combined Compatibility Evaluation	Final Decision
Combined Properties & Compatibility Check (Pass?)	Suitable for Ag Electrode Iontophoresis (Anti-inflammatory)
If any criteria fail	Re-evaluate / Discard Candidate

Recent Advancements in Silver Electrode Design

The field of silver electrode-based iontophoretic systems has witnessed remarkable innovation in recent years, driven by advances in materials science, microfabrication, and flexible electronics. Hollow microneedle array iontophoretic systems (IHMAS) have been fabricated using 3D-printed polymer holders incorporating Ag (anode) and AgCl (cathode) conductive paste electrodes integrated directly into the microneedle assembly. These integrated devices simultaneously create microscale conduits through the stratum corneum — bypassing the physical barrier — while applying an iontophoretic driving force through the resultant microchannels, yielding synergistic enhancement of drug transport [9].

Screen-printed and inkjet-printed Ag/AgCl electrode systems on flexible polyethylene terephthalate (PET) or polyimide substrates have enabled the development of conformable, wearable iontophoretic patches that maintain

intimate skin contact over complex body contours. Battery-miniaturisation technology has reduced power supply dimensions to coin-cell scale, enabling fully self-contained wearable devices. Closed-loop systems incorporating reverse iontophoresis for real-time therapeutic drug monitoring — extracting drug or metabolite from the interstitial fluid while simultaneously delivering drug forward — represent the frontier of personalised, closed-loop transdermal pharmacotherapy and are currently under active investigation for pain management and diabetes applications [9,10,11].

Selected NSAIDs for Iontophoretic Delivery and Formulation Criteria

Physicochemical Criteria for NSAID Selection

The selection of an NSAID candidate for iontophoretic delivery requires systematic evaluation against physicochemical and biopharmaceutical criteria that determine transport efficiency and therapeutic applicability.

An ideal candidate exhibits:

(i) A well-defined ionisation state at physiological pH — preferably >90% ionised — to ensure effective charge-driven transport

(ii) A moderate molecular weight (< 400 Da) to maintain adequate electrophoretic mobility

(iii) Absence of competing functional groups that might react with electrode materials

(iv) Chemical stability in aqueous formulations at the pH values optimal for drug ionisation; and

(v) Adequate intrinsic pharmacological potency to achieve therapeutic effect from the quantity's deliverable by iontophoresis [4,5].

Table 2. Physicochemical properties and iontophoretic characteristics of selected NSAIDs

Drug	MW (Da)	pKa	% Ionised pH 7.4	Polarity	Key Clinical Evidence
Ketoprofen	254	4.8	>99.9%	Cathodal	Superior tissue penetration 21.9% [4,11]
Diclofenac	296	4.0	>99.9%	Cathodal	RCT post-endodontic pain [11,12]
Ibuprofen	206	4.4	>99.9%	Cathodal	Musculoskeletal, animal models [10]
Piroxicam	331	6.3	92.7%	Cathodal	Arthritic models [10]
Celecoxib	381	9.9 (NH)	~60–70%	Cathodal	2× flux vs passive, OA [10]
Indomethacin	358	4.5	>99%	Cathodal	Anti-inflammatory rat model [10]

2.3 Formulation criteria

Polymer Selection and Characterization in Iontophoretic Systems

Polymers are the structural and functional backbone of iontophoretic TDDS, simultaneously performing the roles of drug reservoir matrix, rheological modifier, skin contact agent, and ionic conductance medium. The selection of an appropriate polymer for an iontophoretic formulation requires balancing mechanical and rheological properties against electrochemical considerations specific to the iontophoretic context. [37] The polymer matrix must be

sufficiently ionically permeable to allow current flow through the formulation, mechanically robust to maintain skin adherence during use, chemically inert toward both the drug and the Ag/AgCl electrode material, and biocompatible with the skin surface. Critically, the ionic character of the polymer — anionic, cationic, or non-ionic — directly affects the drug transport number: anionic polymers such as Carbopol carry charge carriers that compete with anionic NSAIDs for current, reducing drug transport number and delivery efficiency [7,35].

Table 3. Key polymers used in iontophoretic transdermal NSAID delivery systems and their functional specifications

Polymer	Type	Charge	Key Property	Role in Iontophoretic System
HPMC K4M/K15M	Cellulose derivative	Non-ionic	High swellability; 9000 cP gels	Preferred matrix/reservoir former; does not compete with anionic NSAIDs for current
Carbopol 940/941	Polyacrylic acid	Anionic	pH-sensitive; mucoadhesive	Viscosity agent; superior skin adherence; partial ionic competition with NSAIDs
Eudragit S-100	Methacrylic acid copolymer	Anionic	pH-dependent solubility	Rate-controlling film; 5:1 HPMC:Eudragit optimal for controlled release
Polyvinyl alcohol (PVA)	Synthetic hydrophilic	Non-ionic	Film-forming; water-soluble	Backing membrane; microneedle matrix; dissolvable needle substrate
Poloxamer 407	Tri-block copolymer	Non-ionic	Thermoreversible gelation	Electrode contact gel vehicle; excellent skin tolerance; thixotropic
Ethyl cellulose (EC)	Cellulose ether	Non-ionic	Water-insoluble film former	Rate-controlling membrane in TDDS; sustained release modifier

Hydroxypropyl methylcellulose (HPMC) in grades K4M and K15M forms high-viscosity, non-ionic gels that serve as exemplary NSAID reservoirs in iontophoretic systems, as their non-ionic character ensures that NSAID transport number is not diminished by competing polymer charge. Comparative studies of HPMC versus Carbopol and methylcellulose at equivalent viscosity demonstrated comparable drug permeation profiles, though Carbopol gels exhibited superior skin adherence and intrinsic buffering capacity. Eudragit S-100 combined with HPMC in a 1:5 ratio has been validated in methotrexate and NSAID patch formulations as a controlled-release matrix, providing appropriate physicochemical parameters including tensile strength, folding endurance, and moisture vapour transmission. Poloxamer 407 exploits its thermos-reversible gelation property — liquid below 15°C, gel at body temperature — to provide an ideal, easy-to-apply, non-irritating vehicle for iontophoretic electrode contact gels [7,16,33].

Penetration Enhancers

Chemical penetration enhancers represent an important adjunct to iontophoresis, capable of producing synergistic permeation enhancement through mechanistically distinct pathways.

Enhancers act by reversibly disrupting the ordered lipid bilayer structure of the stratum corneum — through lipid fluidisation, protein denaturation, or co-solvent partitioning effects — thereby augmenting the passive diffusion component of overall drug transport during and following iontophoresis [3,4].

Oleic acid and eucalyptus oil, both lipid-domain disruptors, have demonstrated significant enhancement of NSAID permeation when incorporated into iontophoretic formulations. Sodium lauryl sulphate (SLS) combined with iontophoresis for metoprolol yielded flux enhancements of 7–9-fold compared with passive delivery, while simultaneously creating a dermal drug depot that sustained release for several days post-treatment. N-methyl-2-pyrrolidone (NMP), propylene glycol, and dimethylformamide (DMF) act as co-solvents that increase drug solubility in the stratum corneum. The selection and concentration of penetration enhancers must be optimised to avoid frank dermal irritation, limit competition with drug ions for current transport when enhancers are ionic, and maintain formulation stability [13,7].

Plasticizer Systems

Plasticisers are essential excipients in solid-matrix iontophoretic patch formulations, incorporated to impart mechanical flexibility, reduce brittleness, and enhance the folding endurance of polymer films. They function by intercalating between polymer chains, reducing intermolecular cohesive forces and glass transition temperature (Tg), thereby enabling the polymer matrix to flex without fracture during application at joint sites subjected to repeated movement [7].

Commonly employed plasticisers in NSAID iontophoretic patches include dibutyl phthalate (DBP, 10–20% w/w), polyethylene glycol 400 (PEG 400), triethyl citrate (TEC), propylene glycol, and oleyl alcohol. PEG 400 and TEC are preferred in contemporary formulations for their established regulatory acceptability, lower dermal irritation potential, and compatibility with both cellulosic and acrylic polymer matrices. The optimal plasticiser type and concentration must be determined empirically for each polymer system, balancing flexibility enhancement against reductions in tensile strength and drug release rate [4,7].

Stabilizers

Stabilizers protect iontophoretic formulations from degradation by preventing oxidative breakdown of anti-inflammatory drugs, maintaining pH stability, and preventing silver electrode corrosion. Essential components include antioxidants (sodium bisulfite 0.2-0.5%, ascorbic acid 0.1%) that scavenge reactive oxygen species from electrical current; chelating agents (EDTA 0.05%, sodium citrate 20 mM) that critically sequester silver ions to prevent tissue toxicity; pH buffers (citrate-phosphate at pH 5.0-5.5) that maintain formulation integrity and prevent electrode degradation; and antimicrobial preservatives (methylparaben 0.1%) that ensure sterility. Together, these stabilizers ensure consistent drug potency, safe electrode function, and extended shelf-life (12-24 months) for reliable clinical performance.[31,36]

Permeation enhancer

Permeation enhancers dramatically increase transdermal drug delivery through multiple mechanisms, achieving 8-12 fold enhancement for anti-inflammatory NSAIDs when combined with iontophoretic electrical current. Key enhancers include fatty acids (oleic acid 5-8% disrupting stratum corneum lipids), co-solvents (propylene glycol 40-50% providing dual solubility and lipid disruption), terpenes (menthol 2-3% with added analgesic benefit), cyclodextrins (HPβ-CD 10-15% complexing hydrophobic drugs), and electrical mechanisms (electroosmotic flow and electrophoresis providing 2-5 fold additional enhancement). Optimal formulations combine these enhancers synergistically—for example, propylene glycol + oleic acid + menthol + HPβ-CD with 2-3 mA/cm² current—producing multiplicative effects that achieve therapeutic anti-inflammatory response within 30-40 minutes with higher local tissue concentrations and reduced systemic toxicity compared to oral NSAIDs.[32]

Nanoparticle-Based Iontophoretic Formulations: Recent advancements 2022, 2025

The integration of nanocarrier technologies with iontophoresis represents a technologically advanced approach that synergises the drug-loading, solubilisation, and controlled-release capabilities of nanoparticles with the electrokinetic driving force of iontophoresis. Ethosomes — phospholipid vesicles incorporating high concentrations (20–45%) of ethanol — demonstrate superior membrane fluidising properties and skin permeation enhancement compared with conventional liposomes. When ethosomal hydrocortisone 17-butyrate (HB17) was combined with iontophoresis in an ex vivo model, skin permeation increased to 19.69 µg/cm² in 30 minutes, compared with 7.98 µg/cm² achieved by the ethosome formulation alone in 120 minutes — a 2.5-fold increase in delivery rate — demonstrating that iontophoresis dramatically accelerates permeation of even vesicular carriers [14].

For ketoprofen, nanoparticle uptake studies in keratinocytes have elucidated the endocytic pathways governing intracellular nanocarrier trafficking: caveolae-mediated endocytosis, clathrin-mediated endocytosis, and macropinocytosis have each been identified as relevant uptake mechanisms, providing mechanistic insight for rational nanocarrier design. Solid lipid nanoparticles (SLNs), polymeric nanoparticles of PLGA, and nanoemulsions have each demonstrated enhanced iontophoretic delivery of poorly water-soluble NSAIDs such as celecoxib. Intelligent transdermal nanoparticle systems incorporating stimuli-responsive shells that respond to electrical signals — releasing drug on-demand in synchrony with applied current pulses — represent the emerging frontier of precision iontophoretic therapy [17.36].

2.4 Methods of Preparation of Transdermal Systems

The selection of a preparation method for transdermal patches is governed by the physicochemical properties of the drug and polymers, the required patch architecture, the scale of production, and compatibility with the electrode and adhesive components in iontophoretic systems. Several well-characterised laboratory and pilot-scale preparation methods are employed in the development of NSAID iontophoretic TDDS.

Solvent Casting Method

The solvent casting method is the most widely employed technique for preparing matrix-type transdermal patches at laboratory and small-scale developmental levels. The drug is dissolved or dispersed in an appropriate organic solvent (ethanol, acetone, methanol, isopropanol, or their mixtures) along with the polymer (HPMC, PVA, Eudragit) and plasticiser. The homogeneous solution or suspension is cast onto a flat, non-adherent substrate — typically a glass Petri dish, a siliconized release liner, or a Teflon-coated surface — to a uniform thickness controlled by a doctor blade or casting frame. The solvent is allowed to evaporate under controlled laminar airflow conditions at 40–60°C for 24–48 hours, yielding a flexible, uniform polymer film. Films are stored in sealed, desiccant-containing chambers for an additional 24 hours at 25 ± 0.5°C to eliminate ageing effects before evaluation [4,22,35].

The solvent casting method is simple, reproducible, and compatible with a wide range of polymers and drug concentrations. Its primary limitation is the potential for solvent residue in the final film, which requires validated residual solvent analysis by gas chromatography in compliance with ICH Q3C guidelines. Phase separation and drug crystallisation during solvent evaporation can compromise film uniformmity, requiring careful optimisation of solvent composition, evaporation rate, and polymer concentration. [38,39]

Hot Melt Method

The hot melt method — also referred to as hot melt extrusion (HME) when conducted at pilot or industrial scale — involves blending the drug with polymer(s) and plasticiser(s) in solid form and processing the mixture above the softening temperature of the polymer to produce a

homogeneous melt that is subsequently formed into a film by compression, calendaring, or extrusion. In the laboratory context, the drug–polymer–plasticiser mixture is heated in a mould or on a hot plate to the melting or softening temperature of the polymer phase, mixed to homogeneity, and compression-moulded into films of defined thickness [4][38].

The salient advantage of the hot melt method is the complete elimination of organic solvents, removing concerns about residual solvent toxicity and simplifying regulatory compliance. Hot melt processing also facilitates the generation of amorphous solid dispersions of poorly water-soluble drug molecules within the polymer matrix, enhancing dissolution and permeation rates. Limitations include thermal lability of some NSAID candidates and the requirement for thermally stable polymers. At the industrial HME scale, pharmaceutical twin-screw extruders provide precise temperature, shear, and feed control, enabling continuous, GMP-compliant manufacture [4,22,39].

Other Fabrication Techniques

Several additional fabrication techniques are employed for specific patch architectures or materials. The aluminium-backed adhesive film method involves casting drug–polymer–adhesive solutions directly onto pre-cut aluminium foil backing, heat-sealing the edges to form a reservoir, and laminating a rate-controlling membrane. This technique is suited to reservoir-type patch manufacture. Asymmetric TPX membrane method employs poly methyl pentene (TPX) membranes fabricated by phase inversion: polymer solution is cast onto a glass substrate, subjected to brief partial drying, and then immersed in a coagulation bath to produce an asymmetric membrane with a dense skin layer controlling drug permeation. Isopropyl myristate (IPM) membrane method disperses the drug in a carbopol 940-containing aqueous gel; IPM serves as a permeation enhancer vehicle forming a separate oil phase that acts as a rate-controlling barrier. 3D printing by stereolithography (SLA) and fused deposition modelling (FDM) represent next-generation fabrication approaches enabling the manufacture of structurally complex microneedle-integrated patches with precisely defined geometry, though commercialisation is currently constrained by throughput and biocompatibility challenges [4,8].

2.5 Evaluation and Characterization Techniques

Comprehensive evaluation of iontophoretic transdermal drug delivery systems spans a hierarchical battery of physical, chemical, spectroscopic, microscopic, and biopharmaceutical tests designed to establish quality, safety, and performance of the final dosage form.

Thickness

Film thickness is measured at a minimum of five randomly selected positions across the patch surface using a calibrated digital screw gauge (precision ± 0.001 mm). Acceptable thickness for matrix patches ranges from 0.2 to 0.5 mm, with a coefficient of variation (CV) not exceeding 5% across sampling sites. Uniformity of thickness is critical for ensuring consistent drug content per unit area and predictable drug release kinetics, as the path length for drug diffusion is a direct function of membrane thickness [4,7].

Weight Variation

Twenty individual patches of defined area are weighed individually, and the mean, standard deviation, and percent CV are determined. Regulatory pharmacopoeial standards require that no individual patch deviates from the mean by more than 5% for patches above 80 mg, and no more than 10% for smaller patches. Weight uniformity is an indirect index of drug content uniformity and polymeric matrix homogeneity [7,4].

Uniformity of Drug Content

Drug content uniformity is determined by dissolving individually cut patches of defined area in an appropriate solvent system (typically phosphate buffer–methanol mixtures) and quantifying dissolved drug concentration by reverse-phase HPLC using a validated analytical method. Acceptable drug content ranges from 95%

to 105% of the label claim, with CV ≤ 3% across a minimum of 10 samples. HPLC-based determination is mandatory for regulatory submissions, with UV spectrophotometry acceptable for screening studies [5,7,35].

Tensile Strength

Mechanical integrity is evaluated using a universal tensile testing machine (texture analyser), measuring the force required to break a standardised dumbbell-shaped patch specimen at a fixed crosshead speed (typically 50 mm/min). Tensile strength (N/mm^2) and percentage elongation at break are reported. Patches intended for joint application — knee, wrist, shoulder — must withstand cyclical mechanical deformation without fracture, requiring tensile strength values appropriate for the target anatomical site and sufficient elongation at break to accommodate skin stretching [4,7].

Folding Endurance

Folding endurance is determined by folding a patch repeatedly at the same point until fracture or visible cracking occurs, and counting the number of folds at failure. A minimum of 300 folds without fracture is specified for patches intended for extended wear applications, indicating adequate flexibility and cohesive matrix integrity. Folding endurance is directly influenced by polymer type and concentration, plasticiser type and concentration, and residual solvent content [4,7,35].

Moisture Content and Vapour Transmission

Percent moisture content is determined gravimetrically before and after drying at 60°C over calcium chloride for 24 hours. Moisture absorption studies assess water uptake at 75% relative humidity over 24 hours. Moisture vapour transmission rate (MVTR) is determined using a modified dish method and expressed as $g/m^2/day$. Optimal moisture content (3–5%) ensures adequate matrix flexibility without plasticiser migration or microbial proliferation; low MVTR backing membranes maintain a hydrated microenvironment at the skin surface, enhancing permeability [4,22].

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy is indispensable for establishing the physicochemical compatibility between drug and polymer excipients — a prerequisite for formulation optimisation and stability prediction. Physical mixtures and optimised formulations are analysed as KBr pellets or attenuated total reflectance (ATR) films, and spectra are collected at 4 cm^{-1} resolution over the 400–4000 cm^{-1} wavenumber range. The appearance of new absorption bands, shifts in characteristic NSAID carbonyl (C=O, 1600–1750 cm^{-1}) or carboxylate stretching frequencies, or the disappearance of characteristic peaks signals chemical incompatibility. Absence of such changes in the formulation spectrum confirms physicochemical compatibility and stability of the drug within the polymer matrix [7].

Differential Scanning Calorimetry (DSC)

DSC thermograms reveal thermal transitions — melting points, glass transition temperatures, crystallisation events, and decomposition — of individual components and their physical/chemical mixtures. For NSAID iontophoretic formulations, disappearance or significant reduction of the drug melting endotherm in the formulation thermogram indicates solid-state dissolution of the drug within the polymer matrix (amorphous dispersion), which typically enhances drug release rate. Polymer glass transition temperature (Tg) in the formulation provides insight into the mechanical properties of the matrix at body temperature: a Tg substantially below 37°C confirms adequate film flexibility in use [7,4].

X-Ray Diffraction (XRD)

Powder X-ray diffraction (PXRD) analysis determines the solid-state crystallinity of drug molecules within the patch matrix. Crystalline drugs exhibit characteristic diffraction peaks at defined 2θ angles; their absence in the formulation diffractogram confirms amorphisation. Since amorphous drug exhibits higher thermodynamic activity and dissolution rate than the crystalline form, XRD data directly informs the predicted

permeation behaviour of the formulation. Conversion from crystalline to amorphous during hot melt processing is specifically confirmed by XRD as a quality attribute [7,35].

Microscopic Analysis

Optical microscopy and scanning electron microscopy (SEM) provide complementary structural characterisation of iontophoretic patch surfaces, cross-sections, and electrode interfaces. Optical microscopy (×40–×400) is used to detect macroscopic drug crystal formation within the matrix, assess surface homogeneity, and identify phase separation or inclusion of air bubbles during preparation — all of which compromise drug content uniformity and permeation performance.

SEM provides high-resolution imaging of patch surface topography, cross-sectional architecture, and the morphology of microneedle arrays integrated into iontophoretic devices. Post-permeation SEM analysis of skin surface following iontophoretic treatment reveals the degree of stratum corneum structural alteration induced by current application, providing mechanistic insight into the permeation pathway. Energy-dispersive X-ray spectroscopy (EDX) coupled with SEM enables elemental mapping of silver distribution within Ag/AgCl electrodes, confirming electrode homogeneity and degradation assessment [4,9]. Confocal laser scanning microscopy (CLSM) using fluorescently labelled drug surrogates provides three-dimensional imaging of drug penetration pathways through excised skin following iontophoresis, definitively establishing the relative contributions of transcellular, intercellular, and follicular routes [3].

In Vitro Drug Release and Permeation Studies

In vitro evaluation of iontophoretic NSAID systems employs Franz-type static diffusion cells (receptor volume 12–15 mL) or dynamic flow-through diffusion cells. For passive diffusion control experiments, synthetic membranes (cellulose acetate, polydimethylsiloxane) or excised skin (rat, porcine ear, or human cadaver) serve as the diffusion barrier. For iontophoretic permeation, a direct current source is integrated into the assembly: the active Ag/AgCl electrode contacts the donor formulation, and the return Ag/AgCl electrode is immersed in the receptor compartment. A constant current (0.1–0.5 mA/cm²) is applied for a defined duration (30 minutes to 4 hours), and receptor samples are withdrawn at predetermined intervals and analysed by validated HPLC [5,6].

Key permeation parameters derived from in vitro studies include: steady-state flux (Jss, µg/cm²/hr), derived from the linear portion of the cumulative permeation versus time plot; permeability coefficient (Kp = Jss/Cd, cm/hr); lag time (Tlag, hr); and iontophoretic enhancement ratio (ER = Iontophoresis/J-passive). Enhancement ratios for NSAID iontophoresis typically range from 3-fold (celecoxib) to >100-fold (ketoprofen under optimised conditions) relative to passive diffusion. Regulatory guidance (ICH Q6A, FDA TDDS Product Development Guidance) recommends validated HPLC quantitation methods, triplicate determinations per formulation, and inclusion of appropriate passive and vehicle control arms in the experimental design [5,6].

3. Scale-Up, Manufacturing Considerations, and Regulatory Aspects

Pilot Plant Scale-Up

The translation of iontophoretic TDDS from laboratory to pilot scale introduces a series of engineering and quality challenges that must be systematically addressed to ensure that the physicochemical and biopharmaceutical properties characterised at bench scale are faithfully reproduced in larger batches. The scale-up of solvent casting processes requires the adoption of industrial coating equipment — slot-die coaters, comma-bar coaters, or gravure roll systems — operating under controlled temperature and humidity in cleanroom-grade laminar flow environments to achieve uniform film thickness and drug content across large-area coating runs [4,22].

Hot melt extrusion scale-up from laboratory twin-screw mini-extruders to pharmaceutical-grade co-rotating twin-screw extruders requires careful optimisation of screw design, barrel temperature

profile, feed rate, and residence time to maintain drug amorphisation, prevent thermal degradation, and achieve the die-exit film dimensions specified for the final patch geometry. Electrode printing at scale employs screen-printing or aerosol jet printing of Ag and AgCl conductive inks onto flexible plastic substrates, with online vision inspection systems monitoring electrode geometrical and electrical uniformity across production runs [9,22].

Critical scale-up parameters include: solvent residual level monitoring by in-line near-infrared (NIR) spectroscopy during drying; drug content uniformity verification by Raman chemical imaging of production roll samples; adhesion uniformity by laser profilometry of laminated patches; and electrode resistance and impedance characterisation for iontophoretic device assemblies. Statistical process control (SPC) with defined in-process specifications and action limits must be established for each critical quality attribute (CQA) during scale-up validation runs [4,22].

Regulatory and Safety Aspects

Iontophoretic transdermal drug delivery systems are regulated as combination products — integrating both a pharmaceutical drug component and a medical device (iontophoretic current source and electrode assembly) — in most major regulatory jurisdictions. In the United States, combination TDDS are regulated under 21 CFR Parts 3 and 4 (Combination Products), requiring compliance with both drug CGMPs (21 CFR Parts 210/211) and device quality system regulations (21 CFR Part 820). In the European Union, the primary mode of action determines whether the product is regulated as a medicinal product (EMA) or a medical device (MDR 2017/745), with cross-regulatory consultation required for combination products [4].

New drug applications (NDAs) and abbreviated new drug applications (ANDAs) for TDDS must include a comprehensive pharmaceutical development package — including Quality by Design (QbD) justification of critical quality attributes and critical process parameters, primary and accelerated stability data under ICH Q1A conditions, skin sensitisation and photosafety testing (ISO 10993), and in vitro–in vivo correlation (IVIVC) data or appropriate in vitro bioequivalence justification. For iontophoretic electrode materials, material characterisation per ISO 10993 biocompatibility standards is required, including cytotoxicity, sensitisation, and genotoxicity assessments for the Ag/AgCl electrode system [4,22].

Residual silver in the drug reservoir following electrode consumption must be quantified and demonstrated to be below ICH Q3D permitted daily exposure (PDE) limits for elemental silver (oral PDE 250 μg/day). Post-marketing surveillance requirements include adverse event reporting, periodic safety update reports, and protocol for patch disposal — the latter particularly important for high-drug-loading reservoir systems where substantial residual drug may remain following use. Labelling requirements include clear instructions for safe application, current source operation, maximum recommended current density, and contraindications (pacemakers, implantable cardiac devices) [4].

Clinical Applications and Advantages of Iontophoretic NSAID Delivery

The clinical evidence base for iontophoretic and transdermal NSAID delivery has expanded substantially over the past two years, with evidence from randomised controlled trials, prospective case series, and systematic reviews consistently demonstrating superior tissue targeting, comparable or superior analgesia, and significantly improved tolerability compared with oral NSAID administration.

Table 4. Selected clinical studies in transdermal and iontophoretic NSAID delivery (2023–2025)

Drug	Condition	Delivery Mode	Key Finding	Citation
Diclofenac	Post-endodontic pain	Transdermal patch (passive)	Comparable analgesia to oral NSAID; markedly reduced GI adverse effects	Haque et al., 2025 [11]
Ketoprofen	Post-endodontic pain	Transdermal patch (30 mg)	Superior skin penetration (21.9%) vs diclofenac (11.2%); effective analgesia	Piotrowska et al., 2025 [4]
Celecoxib	Osteoarthritis, joint inflammation	Cathodal iontophoresis	Transdermal flux nearly doubled compared with passive diffusion through rat skin	Kaczmarek et al. [10]
Ibuprofen + Indomethacin	Musculoskeletal inflammation (rat)	Ag/AgCl, 0.5 mA/cm²	Significantly higher anti-inflammatory effect than non-iontophoretic route; superior dermal penetration	Kaczmarek et al. [10]
Diclofenac LDS	Refractory musculoskeletal injuries	2.5% LDS sonophoresis, 4 weeks	Significant NRS pain reduction; improved global health; no adverse events in 135 cases	PMC9977165 [15]
Ketoprofen + Diclofenac	Post-endodontic pain (RCT)	Transdermal patch	Both agents superior to placebo; ketoprofen showed faster onset	Reddy et al., 2024 [12]

Transdermal Diclofenac and Ketoprofen in Post-Endodontic Pain

Haque et al. (2025) conducted a prospective, comparative in vivo study enrolling 40 patients with symptomatic irreversible pulpitis at Kalka Dental College, Meerut, India. Patients were randomised to transdermal diclofenac (100 mg) or ketoprofen (30 mg) patches, with pain assessed by VAS at 2, 4, 6, 8, 12, and 24 hours post-procedure. Both agents provided clinically effective post-endodontic analgesia, with patients benefiting from avoidance of first-pass metabolism, reduced gastrointestinal side effects, and sustained plasma concentrations exceeding the minimum effective analgesic concentration for 12–18 hours. This well-conducted study demonstrates the real-world clinical utility of transdermal NSAID delivery as a viable, patient-preferred alternative to oral analgesics in the acute pain setting [11].

Iontophoretic NSAIDs in Musculoskeletal Disease

The systematic evidence base for iontophoretic NSAID delivery in musculoskeletal conditions has been comprehensively documented by Kaczmarek et al. in a seminal PMC review demonstrating that NSAIDs administered by iontophoresis consistently exhibited higher anti-inflammatory effects in animal models compared with non-iontophoretic administration. Iontophoresis

significantly enhanced penetration of aspirin, ibuprofen, and indomethacin into the hypodermis, dermis, and epidermis. Celecoxib iontophoresis doubled transdermal flux and was explicitly proposed for osteoarthritis treatment. In human subjects, measurable plasma diclofenac concentrations were achieved in 75% of iontophoretic subjects versus 25% of passive controls, underscoring the superior systemic bioavailability conferred by iontophoresis even when local tissue targeting is the primary goal [10].

Diclofenac Long-Duration Sonophoresis in Rehabilitation

A prospective case series at Yale-New Haven Health System enrolled 135 patients with musculoskeletal injuries unresponsive to a minimum of four weeks of physiotherapy. Add-on treatment with 2.5% diclofenac long-duration sonophoresis (LDS) — combining ultrasonic energy-mediated stratum corneum perturbation with topical NSAID delivery — for four weeks produced clinically significant reductions in Numeric Rating Scale pain scores, meaningful improvements in global health assessment, and enhanced functional outcomes, with no adverse events recorded. This real-world evidence from a large case series demonstrates the safety and efficacy of active-enhancement transdermal NSAID therapy as a second-line intervention in physiotherapy-refractory musculoskeletal pain [15].

Ethosomal Nanoparticle–Iontophoresis Combination for Anti-inflammatory Delivery

Ex vivo studies in full-thickness rat skin models have demonstrated that ethosomal hydrocortisone 17-butyrate combined with iontophoresis achieves permeation of 19.69 µg/cm² in 30 minutes — compared with 7.98 µg/cm² achieved by the ethosome formulation alone in 120 minutes — representing a 2.5-fold rate enhancement and demonstrating the potent additive or synergistic effects of combining nano-formulation technology with electrokinetic driving force. This finding is directly translatable to NSAID delivery, where the enhanced drug loading capacity and modified release profiles of ethosomal or polymeric nanocarriers can be coupled with iontophoresis to achieve simultaneously superior drug loading, controlled release, and maximal electrophoretic transport [14].

Microneedle–Iontophoresis Integrated Systems for NSAID Delivery

A 2025 open-access systematic review from PMC documented the state-of-the-art in iontophoresis-assisted microneedle devices for transdermal biosensing and drug delivery. Integrated Ag/AgCl microneedle-electrode assemblies fabricated by 3D printing and screen-printing technologies were demonstrated to enable simultaneous real-time biosensing of inflammatory biomarkers and precision NSAID delivery within closed-loop feedback systems. For pain management applications, these systems achieved significantly improved drug permeation compared with iontophoresis alone — by orders of magnitude compared with passive delivery — by combining physical stratum corneum microporation with the electrokinetic driving force of cathodal iontophoresis through the created microchannels [9,11].

6. Challenges and Future Perspectives

Current Challenges

Despite the extensive and compelling scientific evidence supporting silver electrode-based iontophoretic NSAID delivery, a number of technical, regulatory, and commercial challenges continue to impede widespread clinical adoption. Cutaneous adverse effects — erythema, tingling, pruritus, and rare electrochemical burns at electrode contact sites — remain the most commonly reported tolerability issues, particularly at current densities exceeding 0.5 mA/cm² or with extended application durations exceeding 60 minutes. The complexity and cost of iontophoretic devices relative to passive NSAID patches represent significant market access barriers, particularly in resource-limited healthcare settings [7,8].

The absence of standardised, validated iontophoretic protocols specific to individual NSAID candidates, disease indications, and patient populations has been a persistent

impediment to regulatory approval and consistent clinical outcomes. Individual patient variability in skin impedance — modulated by hydration status, age, skin pathology, and body site — produces substantial inter-individual variability in drug flux that is particularly problematic for NSAIDs with narrow therapeutic windows such as indomethacin. The competing ion problem in complex biological formulations — where co-administered excipient ions, buffer species, and sweat electrolytes compete with drug ions for current transport — further complicates quantitative prediction and optimisation of in vivo delivery [8,9].

Future Perspectives

The trajectory of silver electrode-based iontophoretic NSAID research is oriented toward several convergent frontiers. Wearable, flexible, fully integrated iontophoretic patches incorporating screen-printed Ag/AgCl electrodes on conformable polymer substrates — powered by ultra-thin rechargeable batteries or bioelectric energy harvesting — represent the near-term commercial goal, enabling prolonged, ambulatory, closed-loop pain management without clinical supervision [10,11].

The combination of microneedle arrays with iontophoresis has demonstrated the most dramatic permeation enhancements reported in the literature and is the focus of intense translational research effort. 3D-printed and laser-machined hollow microneedle arrays integrated with Ag/AgCl electrode assemblies in a single wearable device are transitioning from proof-of-concept to engineered prototype stages, with clinical evaluation anticipated within the next decade. Nanocarrier-enhanced iontophoresis — pairing stimuli-responsive, electrically active nanoparticles with programmed current delivery — represents the frontier of precision drug delivery, enabling on-demand, spatiotemporally controlled NSAID release in synchrony with pain episodes [17,20].

Artificial intelligence and machine learning are being integrated into iontophoretic system design at multiple levels: optimising electrode geometry and material for maximal current uniformity; predicting formulation performance from physicochemical descriptors using quantitative structure-permeability relationship (QSPR) models; and personalising iontophoretic parameters — current density, duty cycle, total duration — in real time based on patient-specific skin impedance biometrics and pharmacodynamic feedback from wearable pain assessment sensors. A 2025 systematic review identified AI-driven personalisation of current parameters as the most transformative emerging capability in cutaneous drug delivery, potentially resolving the inter-patient variability challenge that has historically limited iontophoresis [7]. Integration of reverse iontophoresis — simultaneously extracting inflammatory biomarkers (TNF-α, IL-6) from the interstitial fluid for pharmacodynamic monitoring while delivering NSAID drug forward — could enable truly closed-loop, self-titrating transdermal anti-inflammatory systems in the near future [11].

7. CONCLUSION

Silver electrode-based iontophoretic transdermal delivery of NSAIDs represents one of the most scientifically rigorous and clinically compelling strategies in contemporary pharmaceutical innovation. The convergence of reversible Ag/AgCl electrochemistry — which ensures pH-stable, gas-free, predictable current delivery — with appropriately engineered polymer matrices containing ionised NSAID drug molecules provides a robust, reproducible framework for achieving therapeutic tissue drug concentrations with dramatically reduced systemic adverse effects. Iontophoresis enhances NSAID flux across the stratum corneum by several-fold to several hundredfold over passive diffusion, enabling pharmacologically relevant concentrations to be sustained at target musculoskeletal and inflammatory tissue sites for extended periods.

The comprehensive framework of patch design, preparation methodology — spanning solvent casting, hot melt, Teflon mould, and mercury substrate techniques — rigorous physicochemical and biopharmaceutical characterisation, and scale-up with regulatory compliance provides a clearly defined developmental pathway from concept to

clinical translation. Recent advances integrating microneedle arrays, intelligent nanoparticle carriers, and AI-assisted parameter personalisation are rapidly redefining the performance boundaries of iontophoretic NSAID delivery, positioning this modality at the forefront of precision, patient-centred pain management. The evidence from recent open-access literature provides unambiguous support for continued investment in the research, clinical validation, and commercialisation of silver electrode-based iontophoretic systems for the management of musculoskeletal and inflammatory pain conditions globally.

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