PLGA Nanoparticle-Embedded Dissolving Microneedle Systems for Transdermal Ibuprofen Delivery: Formulation Design, Characterization, and Skin Permeation—A Structured Review

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***Abstract*—Transdermal drug delivery has attracted considerable clinical interest as a non-invasive administration route, chiefly because it circumvents hepatic first-pass metabolism and sidesteps gastrointestinal exposure—two factors that collectively limit the tolerability and bioavailability of many orally administered drugs. Despite these advantages, the outermost barrier of the skin, the stratum corneum, continues to frustrate efforts to deliver most therapeutic molecules in pharmacologically relevant quantities. The convergence of nanotechnology and microneedle (MN) platforms has emerged as a practically viable approach to address this limitation, yielding new opportunities to engineer around the skin barrier without sacrificing clinical acceptability. Ibuprofen (IBU), a Biopharmaceutics Classification System (BCS) Class II nonsteroidal anti-inflammatory drug (NSAID), presents well-recognized formulation challenges. Its poor aqueous solubility and the gastrointestinal complications commonly associated with oral use make it a compelling candidate for alternative delivery strategies. Encapsulating IBU within poly(lactic-co-glycolic acid) (PLGA) nanoparticles has demonstrated tangible benefits in terms of drug stabilization and prolonged, predictable release. Embedding these drug-loaded nanoparticles into dissolving microneedle arrays extends the concept further by mechanically bypassing the stratum corneum and substantially improving transdermal drug flux. This review critically examines IBU-PLGA microneedle systems across multiple dimensions—nanoparticle preparation methods, physicochemical characterization, microneedle fabrication strategies, and in vitro permeation testing conducted with Franz diffusion cells. Relevant advances reported in 2024 are highlighted, including improvements in skin permeation, drug release duration, and anti-inflammatory efficacy. Areas where significant scientific and technical gaps persist are discussed honestly, and practical pathways toward clinical translation are considered.**

***Index Terms*—Ibuprofen; PLGA nanoparticles; dissolving microneedles; transdermal drug delivery; Franz diffusion cell; controlled release; skin permeation**

I. INTRODUCTION

Of the several pathways available for systemic drug administration, the transdermal route occupies a distinctive position. It is well-tolerated, requires no needles or swallowing of tablets, and provides drug input at a relatively steady rate—eliminating the plasma concentration peaks and valleys that accompany intermittent oral dosing. For chronic conditions that demand maintained drug levels over extended periods, and where long-term patient adherence is often a clinical problem, this pharmacokinetic profile translates into meaningful practical value. The complete avoidance of hepatic first-pass metabolism is an additional benefit, particularly for compounds whose oral bioavailability is meaningfully reduced by enzymatic extraction in the gut wall and liver.

The fundamental obstacle to transdermal delivery is structural. The stratum corneum—comprising layers of flattened, keratin-filled corneocytes embedded within a complex lipid lamellar matrix—functions with remarkable efficiency as a permeability barrier. Passive diffusion across it is realistically available only to a restricted subset of drugs: those with modest molecular weights, adequate lipophilicity, and sufficient pharmacological potency to achieve therapeutic tissue concentrations at the low fluxes that passive permeation allows. The vast majority of clinically useful drugs fall outside these parameters.

Microneedle arrays have matured into one of the more practical and clinically translatable answers to this problem. Applied to the skin surface with modest

manual pressure, the sharp needle tips puncture through the stratum corneum and create transient microchannels extending into the viable epidermis—without reaching dermal nerve fibers or capillaries, making the process essentially painless. Among the various microneedle types, dissolving formulations are particularly attractive. The needle matrix is itself composed of water-soluble or hydrolysable polymers; once inserted, it absorbs interstitial fluid and progressively breaks down, releasing the drug payload directly within the skin and leaving no residual material requiring removal.

Coupling PLGA nanoparticles with dissolving microneedle platforms addresses two distinct barriers simultaneously: the skin barrier and the challenge of controlled drug release. This review focuses on IBU-PLGA microneedle systems specifically, covering how they are designed and manufactured, how their performance is evaluated, and what would realistically be required to move them from laboratory investigation toward clinical use.

II. SCIENTIFIC RATIONALE FOR IBU-PLGA MICRONEEDLE SYSTEMS

A. Pharmacokinetic and Safety Limitations of Oral Ibuprofen

Despite its widespread clinical use and well-established efficacy, oral ibuprofen carries documented pharmacokinetic and tolerability shortcomings that limit its suitability for long-term administration. These include:

- Erosion of the gastrointestinal mucosa with potential for peptic ulceration, particularly with chronic use
- A relatively short plasma elimination half-life that necessitates multiple daily doses to sustain therapeutic concentrations
- Difficulty in maintaining drug levels consistently within the therapeutic window throughout the dosing interval
- Reduced adherence to prescribed regimens, most notably in elderly patients and in pediatric populations for whom the tablet formulation presents practical challenges

B. Therapeutic Utility of PLGA as a Nanoparticle Carrier

PLGA is a synthetic, biodegradable, and biocompatible copolymer with an established regulatory history in pharmaceutical applications, having received approval from multiple international health authorities. Its utility as a nanoparticle drug carrier derives from several distinctive properties:

- Drug release can be programmed through the kinetics of hydrolytic polymer degradation, enabling true sustained-release behavior
- The nanoparticle matrix physically shields the encapsulated drug from environmental degradation, improving stability in biological fluids
- Systemic bioavailability of poorly soluble drugs is enhanced relative to free-drug formulations, partly through particle size-dependent absorption mechanisms
- Release kinetics can be finely adjusted by modifying the lactide-to-glycolide molar ratio and the polymer molecular weight

C. Mechanistic Advantages of Dissolving Microneedle Integration

Incorporating PLGA nanoparticles into dissolving microneedle arrays introduces several mechanistic and therapeutic advantages that neither platform achieves independently:

- Drug-laden nanoparticles are deposited directly in the viable epidermis—effectively circumventing the stratum corneum without pharmacological enhancers
- Drug flux across the skin is substantially greater than that achievable through passive topical preparations such as gels or conventional patches
- Systemic side effects are potentially minimized because drug release occurs locally, as a depot, rather than through systemic recirculation
- Overall therapeutic yield is improved, and dose precision is enhanced relative to topical formulations where surface application variables affect delivery

III. FORMULATION DESIGN OF IBU-LOADED PLGA NANOPARTICLES

A. Nanoparticle Preparation Approaches

Several preparation strategies have been employed for the manufacture of IBU-PLGA nanoparticles. Each approach carries distinct process characteristics that make it more or less suited to particular requirements of particle size, drug loading, scalability, and compatibility with downstream processing.

(i) Emulsification–Solvent Evaporation

Principle

Emulsification–solvent evaporation is the most widely adopted method for preparing IBU-PLGA nanoparticles, a position it has earned through its reproducibility, reasonable scalability, and favorable compatibility with hydrophobic drugs. The underlying principle is straightforward: PLGA and ibuprofen are co-dissolved in a volatile organic solvent to form the dispersed phase, which is emulsified into an aqueous stabilizer solution. Progressive evaporation of the organic solvent causes the polymer to precipitate and consolidate around the drug, yielding discrete nanoparticles.

Methodology

Step 1 — Organic Phase Preparation: Ibuprofen and PLGA are dissolved together in a water-immiscible volatile organic solvent—typically dichloromethane, chloroform, or ethyl acetate—chosen for its ability to dissolve both the polymer and the hydrophobic drug efficiently.

Step 2 — Aqueous Phase Preparation: An aqueous stabilizer solution is prepared separately, commonly incorporating polyvinyl alcohol (PVA), Tween 80, or poloxamer. The stabilizer functions by adsorbing at the oil–water interface, reducing interfacial tension, and preventing droplet coalescence.

Step 3 — Emulsification: The organic phase is introduced dropwise into the aqueous phase with continuous agitation, probe sonication, or high-shear homogenization to form an oil-in-water emulsion. The energy input at this stage determines the droplet size distribution, and therefore the final nanoparticle dimensions.

Step 4 — Solvent Evaporation: The emulsion is subjected to sustained stirring under atmospheric or reduced pressure conditions, allowing the organic solvent to evaporate. As solvent is lost, PLGA precipitates progressively to form solid nanoparticles enclosing the drug.

Step 5 — Collection and Purification: Nanoparticles are recovered by centrifugation and washed repeatedly with purified water to remove residual surfactant and unentrapped drug. Freeze-drying with a cryoprotectant such as mannitol or trehalose is typically performed to yield a stable dry powder for storage.

Advantages

- Consistently high encapsulation efficiency for hydrophobic drug molecules
- Reproducible process parameters amenable to scale-up
- Controllable particle size through modulation of emulsification conditions
- Compatible with standard pharmaceutical manufacturing infrastructure

Limitations

- Risk of residual organic solvent requiring validation of removal
- Drug partitioning into the external aqueous phase may limit loading efficiency
- Particle aggregation may occur during freeze-drying or storage
- Homogenization conditions require careful process optimization

Fig. 1. Schematic of Polymeric Nanoparticle Preparation by Solvent Evaporation Method

(ii) Solvent Displacement (Nanoprecipitation)

Principle

Nanoprecipitation exploits spontaneous polymer precipitation at the interface between a water-miscible organic solvent and an aqueous receiving phase. When the organic solution of PLGA and ibuprofen is injected into water, rapid solvent diffusion reduces polymer solubility at the phase boundary, triggering instantaneous nanoparticle formation without the need for high-energy emulsification.

Methodology

Step 1 — Organic Phase: PLGA and IBU are dissolved in a semi-polar, water-miscible solvent such as acetone, ethanol, or acetonitrile.

Step 2 — Aqueous Phase: A stabilizer solution (PVA or poloxamer) is prepared and stirred gently.

Step 3 — Nanoparticle Formation: The organic solution is injected slowly and dropwise into the aqueous phase under moderate magnetic stirring. Solvent diffusion is spontaneous and rapid, triggering immediate polymer precipitation and nanoparticle formation.

Step 4 — Solvent Removal: Residual organic solvent is eliminated by evaporation under reduced pressure or by dialysis.

Step 5 — Purification: Nanoparticles are isolated by centrifugation and washed to remove free drug and stabilizer residues.

Advantages

- Operationally simple, requiring minimal specialized equipment
- Low energy input—no sonication or high-speed homogenization required
- Produces narrow particle size distributions
- Suitable for heat-sensitive compounds

Limitations

- Encapsulation efficiency may be lower than emulsification methods for some drugs
- Polymer concentration is constrained by solubility in water-miscible solvents
- Storage stability can be challenging without additional excipient optimization

Fig. 2. Nanoprecipitation Method for PLGA Nanoparticle Preparation (doi: 10.3390/nano12030576)

(iii) Spray Drying

Principle

Spray drying is a continuous, single-step manufacturing process that converts a liquid feed—here, a solution or suspension of PLGA and ibuprofen—into a dry powder by atomizing the feed through a nozzle into a heated drying chamber. Rapid solvent evaporation from the airborne droplets yields solid particles with well-defined physicochemical properties.

Methodology

Step 1: IBU and PLGA are dissolved or homogeneously dispersed in a volatile solvent system appropriate for spray drying.

Step 2: The feed solution is pumped through an atomizing nozzle, generating a fine aerosol of droplets.

Step 3: Droplets contact heated drying air within the chamber; solvent evaporates rapidly, yielding solid particles.

Step 4: The resulting nanoparticle powder is collected by cyclone separation and stored under controlled temperature and humidity.

Advantages

- Continuous, industrially scalable process
- Produces dry powders with improved stability and flowability
- Easily integrated into tablets, capsules, or microneedle formulations
- Reduces microbial contamination risk associated with aqueous processing

Limitations

- Thermal exposure during drying may compromise thermolabile actives
- Product yield may be reduced by wall deposition within the drying chamber
- Requires access to specialized spray drying equipment

Fig. 3. Spray Drying Process for PLGA Nanoparticle Manufacture (doi: 10.1016/j.jafr.2020.100085)

B. Formulation Variables Governing Nanoparticle Quality

The physicochemical attributes and biological performance of IBU-PLGA nanoparticles are shaped by both compositional choices and process parameters. A coherent understanding of how each variable influences particle size, encapsulation efficiency, drug release profile, and colloidal stability is essential for rational formulation development.

A. Drug-to-Polymer Ratio

The proportion of ibuprofen relative to PLGA is perhaps the most fundamental compositional variable. Higher polymer concentrations increase the viscosity of the organic phase and generally yield larger particles, because polymer chains entangle more extensively before precipitation is complete. Adequate polymer content improves encapsulation efficiency by providing a sufficiently dense matrix to retain the drug. Conversely, an excess of drug relative to polymer may lead to surface crystallization and pronounced burst release—both undesirable for sustained-release applications. In practice, optimizing this ratio involves balancing encapsulation efficiency against the desired release kinetics.

B. Surfactant Type and Concentration

Surfactants stabilize the emulsion by adsorbing at the oil–water interface and reducing interfacial tension. PVA remains the most widely used stabilizer for PLGA nanoparticle systems, though Tween 80, poloxamers, and sodium cholate are also employed. Increasing stabilizer concentration generally decreases particle size by reducing droplet coalescence, but excessive stabilizer can impair encapsulation efficiency through drug leakage into the external aqueous phase and may complicate downstream purification. The choice and concentration of surfactant also influence zeta potential and, consequently, the long-term physical stability of the dispersion.

C. Organic Solvent Selection

The organic solvent governs polymer solubility, drug partitioning behavior, and the rate of solvent evaporation or diffusion—all of which directly affect nanoparticle formation and properties. Highly volatile solvents accelerate polymer hardening and may produce smaller, more uniformly formed particles. Water-miscible solvents employed in nanoprecipitation tend to generate smaller particles through rapid solvent exchange. Solvent polarity influences the drug partition coefficient between

organic and aqueous phases, which in turn determines encapsulation efficiency. Residual solvent content must be controlled within pharmacopoeial limits, making solvent selection a safety consideration as well as a formulation one.

D. Homogenization Rate and Emulsification Energy
The energy imparted during emulsification is a primary determinant of droplet and final particle size. Higher homogenization speeds and longer sonication durations produce smaller emulsion droplets and, therefore, smaller nanoparticles. Excessive energy input, however, can destabilize the emulsion or cause local heating that affects drug integrity. Optimizing sonication amplitude, processing duration, and temperature together typically achieves the target particle size range with minimal polydispersity.

C. Physicochemical Characterization of IBU-PLGA Nanoparticles
Thorough physicochemical characterization is both a quality assurance requirement and a scientific necessity in nanoparticle development. For IBU-PLGA systems, it provides the evidence base needed to relate formulation decisions to observed performance, to demonstrate batch reproducibility, and to satisfy regulatory expectations for pharmaceutical nanoparticle products. A coordinated set of analytical tools is routinely deployed to characterize these systems.
Particle Size and Polydispersity Index
Particle size is among the most consequential physicochemical attributes of a nanoparticle formulation, with downstream effects on drug release rate, membrane permeability, cellular uptake, and tissue distribution. IBU-PLGA systems intended for transdermal delivery via microneedles generally target hydrodynamic diameters in the 100–300 nm range. Dynamic light scattering (DLS) is the standard technique for measuring hydrodynamic diameter and polydispersity index (PDI) in aqueous suspensions. The method quantifies fluctuations in scattered laser intensity arising from the Brownian motion of suspended particles, and extracts size information through autocorrelation analysis. A PDI below 0.3 is generally accepted as indicating a homogeneous size distribution. Reported mean particle sizes for IBU-PLGA nanoparticles typically fall in the range of 120–250 nm, with PDI values between 0.12 and 0.28.
Zeta Potential
Zeta potential—the electrokinetic potential at the hydrodynamic shear plane surrounding a particle—is a widely used indicator of colloidal stability. Particles with absolute zeta potential values exceeding ±30 mV generate sufficient electrostatic repulsion to resist aggregation, maintaining a stable dispersion over time. IBU-PLGA nanoparticles typically exhibit negative zeta potential values, attributable to the terminal carboxylic acid groups generated by PLGA hydrolysis. Reported values in the literature generally span −18 to −38 mV. Beyond stability, zeta potential influences biological interactions at membrane surfaces, affecting transdermal permeation behavior and potential for cellular internalization.

Morphological Analysis by Electron Microscopy
While DLS provides hydrodynamic size data, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) yield direct visual information about particle shape, surface texture, degree of aggregation, and internal architecture. SEM produces surface-resolved images showing whether particles are spherical, whether their surfaces are smooth or irregular, and whether they remain discretely separated or form aggregates. IBU-PLGA nanoparticles characteristically appear as well-rounded, smooth spheres in SEM images—morphological features consistent with uniform polymer solidification and homogeneous drug distribution. TEM extends the analysis to the particle interior, enabling visualization of core–shell architecture and confirming that structural integrity is maintained after preparation.

Drug Entrapment Efficiency and Loading Capacity
Entrapment efficiency (EE%) and drug loading capacity (DL%) are operationally critical parameters that quantify, respectively, what proportion of the initial drug input was successfully captured within the nanoparticles, and what mass fraction of the recovered nanoparticles consists of drug. Both are determined by measuring unentrapped drug in the supernatant following centrifugation, typically by UV–visible spectrophotometry or HPLC. HPLC is generally preferred for complex matrices because of its superior selectivity and sensitivity. For IBU-PLGA systems prepared by emulsification–solvent evaporation, EE values of 65–90% and DL values of 8–20% are commonly reported. High EE% reflects the efficiency of drug retention within the polymer matrix and is favored by appropriate drug-to-polymer ratios and surfactant concentrations that minimize drug partitioning into the external phase.

IV. ENGINEERING OF DISSOLVING MICRONEEDLE ARRAYS

A. Matrix Polymer Selection

The mechanical and release properties of dissolving microneedles are largely determined by the water-soluble polymer selected as the needle matrix. The chosen material must satisfy two potentially competing requirements: it must be rigid enough at room humidity to penetrate the stratum corneum reliably upon application, yet dissolve within the skin at a rate appropriate for the intended drug release profile. Polymers in routine use include:

- Polyvinyl alcohol (PVA)—confers mechanical strength and dissolution characteristics that can be modulated by degree of hydrolysis and molecular weight
- Polyvinylpyrrolidone (PVP)—dissolves rapidly on contact with interstitial fluid, suited to formulations where prompt drug release is desired
- Hyaluronic acid—a naturally occurring polysaccharide with excellent biocompatibility, native affinity for skin tissue, and useful viscoelastic properties

B. Microneedle Fabrication Methods

The physical form and dimensional accuracy of dissolving microneedle arrays are achieved through precision fabrication, with the following techniques most commonly employed:

- Micromolding using PDMS (polydimethylsiloxane) master molds—the standard approach, capable of producing arrays with well-defined needle tip geometry, tip-to-tip spacing, and height
- Centrifugation-assisted casting—facilitates complete filling of narrow mold cavities and expels entrapped air bubbles that would otherwise compromise needle integrity
- Vacuum-assisted filling—particularly suited to loading viscous suspensions of nanoparticles in polymer solutions, ensuring uniform distribution of PLGA nanoparticles throughout the needle matrix

C. Mechanism of Skin Penetration and Drug Release

The therapeutic function of these systems unfolds through a mechanically and biochemically sequential series of events. Understanding each stage is helpful for relating formulation design choices to observed in vitro and in vivo performance.

Stage 1: Microneedle Penetration

Application of the patch delivers localized mechanical stress to the skin surface. The sharp microneedle tips concentrate this force at the point of contact, generating a stress sufficient to breach the stratum corneum. The needles advance into the viable epidermis, creating discrete microchannels without penetrating to nerve-rich or vascularized dermal tissue, which accounts for the essentially painless character of the procedure.

Stage 2: Matrix Dissolution

Once the tips are seated in the tissue, the water-soluble polymer matrix comes into contact with interstitial fluid. Hydration causes the hydrophilic polymer to swell and undergo progressive dissolution, beginning at the needle tips where surface area-to-volume ratio is highest. The rate of dissolution is determined by the polymer's water absorption characteristics and molecular weight, both of which can be selected to match the intended release profile.

Fig. 4. Mechanism of Dissolving Microneedle Drug Delivery (doi: 10.3389/fchem.2023.1181159)

Stage 3: Nanoparticle Deposition

As the matrix dissolves, the embedded PLGA nanoparticles are released from their polymer scaffold and deposited directly within the viable epidermis and uppermost dermis. These particles disperse within intercellular spaces, establishing a localized drug reservoir in the tissue immediately accessible to cutaneous circulation and lymphatics.

Stage 4: Sustained Ibuprofen Release

The PLGA nanoparticles, now resident in the skin, begin to degrade hydrolytically. Water diffuses into the polymer matrix and cleaves ester linkages, progressively eroding the particle structure and releasing ibuprofen into the surrounding tissue. Release proceeds in characteristic phases: an initial phase driven largely by diffusion of surface-associated or loosely entrapped drug; a middle phase governed by diffusion through the intact polymer matrix; and a terminal phase dominated by polymer bulk erosion. This triphasic profile, which is dictated by PLGA composition and molecular weight, can be tuned to match the therapeutic duration requirements.

V. IN VITRO PERMEATION ASSESSMENT USING FRANZ DIFFUSION CELLS

A. Rationale and Scientific Basis

The Franz diffusion cell (FDC) has been the standard in vitro model for transdermal permeation

measurement for several decades, and retains that position today because it provides controlled, reproducible conditions that reasonably replicate the thermodynamic and hydrodynamic environment of the skin surface in vivo. Data generated in FDC studies are routinely used to rank formulations, estimate in vivo flux, and design subsequent ex vivo and animal studies on a rational basis.

B. Experimental Setup

The configuration employed in MN-based permeation studies typically comprises:

- A donor compartment housing the applied microneedle patch on the membrane surface, which may be left open or occluded depending on the study design
- A receptor compartment filled with phosphate buffered saline (PBS, pH 7.4) to simulate physiological interstitial fluid composition and ionic strength
- A biological membrane—most commonly excised porcine ear skin (a widely accepted surrogate for human skin) or rat dorsal skin; human cadaver skin is used where the highest clinical relevance is required
- Temperature control at 32°C to reflect the normal skin surface temperature and maintain physiologically relevant lipid and membrane fluidity

C. Permeation Parameters Evaluated

Quantitative characterization of drug permeation in FDC studies typically focuses on the following parameters:

- Cumulative amount of drug permeated per unit membrane area as a function of time—the primary data set
- Steady-state flux (Jss)—calculated from the linear portion of the cumulative permeation versus time curve; represents drug transport rate per unit area
- Apparent permeability coefficient (Kp)—derived by normalizing flux to donor concentration; allows comparison across formulations regardless of loading differences
- Lag time—the intercept of the extrapolated linear region with the time axis; reflects membrane tortuosity and nanoparticle uptake kinetics

D. Reported Experimental Outcomes

FDC studies on IBU-PLGA microneedle systems reported in recent literature have consistently identified the following advantages over conventional topical formulations:

- Drug permeation substantially exceeding that of equivalent topical gels or passive patches, attributed to microneedle-mediated disruption of the stratum corneum barrier
- Extended drug release profiles sustaining measurable permeation beyond 24 hours, reflecting the controlled degradation kinetics of the PLGA matrix
- Enhanced apparent tissue bioavailability at the target site
- Shortened lag times relative to passive delivery systems, reflecting the reduced diffusion pathway length for drugs delivered subsuperficially by the microneedles

VI. DRUG RELEASE KINETICS AND MATHEMATICAL MODELING

Fitting in vitro release data to kinetic models provides mechanistic insight into how ibuprofen exits the PLGA matrix and diffuses through the skin, and offers a principled basis for predicting and optimizing formulation behavior. Analysis of IBU-PLGA MN systems in the literature has most consistently identified two models as providing the best fit:

- The Higuchi square-root model—indicating that drug release is predominantly governed by diffusion from a matrix system, with the cumulative amount released proportional to the square root of time
- The Korsmeyer–Peppas power law model—which describes anomalous, non-Fickian transport when the diffusional exponent (n) falls between 0.45 and 0.89, indicating that both molecular diffusion and polymer relaxation or erosion contribute to release

Key formulation variables that shape the release profile include the molecular weight and lactide-to-glycolide ratio of PLGA, mean nanoparticle diameter, the composition and crosslinking degree of the microneedle matrix polymer, and the drug-to-polymer mass ratio within the nanoparticles. These parameters are interdependent, and their judicious selection allows formulation scientists to shift the release behavior along a spectrum from an early pronounced burst toward a more gradual, sustained depot-type profile extending over multiple days.

VII. THERAPEUTIC BENEFITS OF THE COMBINED PLATFORM

The functional advantages of the integrated PLGA nanoparticle–dissolving microneedle system, relative to both oral ibuprofen and conventional topical formulations, can be summarized as follows:

- Administration is non-invasive and essentially free of pain, improving acceptability across patient populations including those with needle aversion
- Drug release is programmable and sustained at the intended anatomical site, avoiding the systemic exposure associated with oral dosing
- Systemic and local bioavailability are meaningfully improved relative to passive topical preparations, where drug absorption is limited by intact stratum corneum
- The sustained release profile reduces dosing frequency, which in turn supports better long-term adherence, particularly in elderly or pediatric patients
- Gastrointestinal adverse events characteristic of oral NSAID use are substantially reduced or avoided, since the systemic exposure pathway is different
- Anti-inflammatory and analgesic outcomes at the target site can be improved through higher and more consistent local drug concentrations

VIII. CURRENT CHALLENGES AND LIMITATIONS

Several substantive obstacles must be addressed before IBU-PLGA microneedle systems can realistically be advanced to the clinic:

- Manufacturing complexity and cost: scaling nanoparticle preparation and precision microneedle fabrication from laboratory batches to commercial volumes requires process engineering investment and significant capital expenditure
- Long-term physical and chemical stability: maintaining the structural integrity of drug-loaded nanoparticles within a solid polymer microneedle matrix over a clinically relevant shelf life remains technically demanding and requires formulation-specific stability strategies
- Regulatory pathway complexity: these are drug–device combination products, subject to overlapping regulatory requirements that vary across jurisdictions and introduce additional preclinical and clinical data requirements
- Local tolerability: although microneedle insertion is generally well-tolerated, repeated application or individual skin sensitivity can give rise to localized erythema, transient discomfort, or sensitization reactions that require monitoring
- Skin permeation variability: differences in skin thickness, hydration status, and barrier function across anatomical sites, age groups, and individual patients introduce variability in drug flux that is not yet fully characterized

IX. RECENT ADVANCES IN 2024

The past year has produced several advances that reflect the growing technical maturity of this field:

- Stimuli-responsive microneedle architectures have been developed that enable on-demand drug release triggered by local temperature changes, pH shifts, or enzymatic activity—allowing drug delivery to be coupled to the physiological state of the target tissue
- Multi-component nanoparticle formulations incorporating combinations of NSAIDs or co-loading with anti-inflammatory biologics have been explored for synergistic therapeutic effects
- Use of full-thickness human skin in Franz diffusion cell studies, rather than animal skin surrogates, has improved the clinical translatability of in vitro permeation data
- Conceptual integration of microneedle patches with wearable sensor platforms has been proposed, enabling real-time monitoring of drug delivery and potentially supporting closed-loop therapeutic adjustment

X. FUTURE RESEARCH DIRECTIONS

Several research priorities emerge from the current state of the field:

- Controlled clinical studies examining pharmacokinetics, local tolerability, and therapeutic efficacy in human subjects are essential to bridge the gap between encouraging preclinical data and regulatory approval
- Personalized microneedle platforms that can be tailored to individual pharmacokinetic profiles—whether through adjustable drug loading, modular polymer composition, or patient-specific design—represent a longer-term but scientifically plausible goal
- Machine learning tools offer potential for high-throughput formulation screening and

optimization, reducing the experimental burden associated with identifying optimal formulation compositions

- Continuous, cost-effective manufacturing technologies such as microfluidics-based nanoparticle production and roll-to-roll microneedle fabrication could substantially reduce the unit cost of these systems
- Development of bioresponsive PLGA copolymers that modulate degradation and release kinetics in response to local biochemical signals could enable more intelligent, condition-responsive drug delivery

XI. CONCLUSION

The convergence of PLGA nanoparticle technology with dissolving microneedle platforms represents a coherent, scientifically grounded advance in transdermal drug delivery. The logic is straightforward: PLGA nanoparticles address the drug solubility and sustained release problem, while the microneedle array addresses the skin barrier problem. Together, the two technologies produce a system capable of delivering ibuprofen in controlled quantities into the viable skin, sustaining therapeutic concentrations over pharmacologically meaningful durations, and doing so without the gastrointestinal burden that accompanies oral NSAID administration.

In vitro evidence from Franz diffusion cell studies is consistent and encouraging: IBU-PLGA microneedle formulations have repeatedly outperformed both passive topical preparations and, in comparative studies, oral dosing equivalents in terms of skin permeation, release duration, and local tissue bioavailability. These findings are not artifacts of a single laboratory—they represent a pattern across multiple independent investigations using varied formulation compositions and membrane models.

The path to clinical translation, however, is not without real obstacles. Manufacturing at scale, long-term product stability, and the regulatory complexity of drug–device combination products are all solvable problems, but solving them requires sustained investment, collaboration between pharmaceutical scientists and engineers, and proactive engagement with regulatory agencies. Future platforms that incorporate personalized dosing, AI-assisted formulation design, and integration with digital health monitoring tools could substantially accelerate this journey—and make these systems genuinely accessible as therapeutic options for the patients who stand to benefit from them.

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