Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2026, 15(2):171-180

https://doi.org/10.51847/oVfPO8LWLa

Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Delivered Dose as an Emergent Property of Microneedle Formulations: A Coupled Mechanical–Pharmaceutical Framework for Skin Deformation, Insertion Heterogeneity, and Incomplete Matrix Dissolution

Thomas Mwangi[1]*, Farah Aziz[2], Michael Brenner[3]

[1]Department of Pharmaceutical Sciences, University of Nairobi, Nairobi, Kenya.
[2]Department of Pharmaceutical Technology, Universiti Putra Malaysia, Serdang, Malaysia.
[3]Department of Biomedical Engineering, University of Vienna, Vienna, Austria.

***Email:** thomas.mwangi@uonbi.ac.ke*

ABSTRACT

Dissolving microneedle patches are commonly characterized by the amount of active pharmaceutical ingredient incorporated, the fraction of needles judged to penetrate skin, and the extent of matrix dissolution. These measurements address different physical events and cannot, individually, establish the mass or time course of biologically accessible drug. This mechanism-based theoretical analysis examines how deformation of skin under an applied array, spatially heterogeneous penetration, contact with interstitial fluid, and formulation-dependent release jointly determine drug disposition. Drawing on published microneedle mechanics, polymer dissolution, pharmacokinetic, and carrier-delivery studies, the analysis distinguishes nominal loading, mechanically implanted cargo, dissolved matrix, liberated intact drug, local tissue deposition, and bioavailable exposure. It proposes a position- and time-resolved account in which these states may covary, making simple multiplication of average insertion and dissolution percentages potentially misleading. Rival insertion-limited, dissolution-limited, and post-release transport explanations are specified alongside discriminating measurement requirements. The resulting design principle is to verify pharmaceutical delivery at the anatomical and chemical state relevant to intended therapy, while treating penetration indicators and polymer disappearance as intermediate observations. The account remains a testable nonempirical synthesis; its relationships require formulation- and skin-context-specific validation.

Key words: *Dissolving microneedles, Delivered-dose verification, Skin deformation, Insertion heterogeneity, Polymer dissolution, Intradermal drug deposition*

Received: 21 July 2026; **Revised:** 24 August 2026; **Accepted:** 30 August 2026

INTRODUCTION

Dissolving microneedles offer a means of placing pharmaceutical materials across the stratum corneum without a conventional hypodermic injection. Their translation, however, remains sensitive to limited payload capacity, incomplete release, variable application and difficulty demonstrating the dose that actually becomes available in the target tissue. A recent critical analysis identifies these limitations as formulation-development problems with translational consequences [1]. The unresolved issue is a definition problem as much as an engineering problem: what observation should count as successful dose delivery when the patch enters the skin, loses polymer mass, and distributes cargo through more than one material compartment?

© 2026 The International Journal of Pharmaceutical Research and Allied Sciences (IJPRAS). **Open Access** - This article is under the **CC BY NC SA** license (https://creativecommons.org/licenses/by-nc-sa/4.0).

Regulatory discussion of skin-applied microneedle dosage forms calls for consistent characterization of quality, performance and administration conditions [2]. Mechanical integrity, insertion, drug content and release tests can each be reproducible while describing different attributes. In particular, a mechanically successful patch may leave material in the backing or undissolved needle roots; a chemically depleted patch may transfer carrier-associated drug whose active fraction has not been measured. An adequate account must retain those distinctions when connecting device specifications to pharmaceutical performance.

The importance of the endpoint is illustrated by pharmacokinetic comparisons of intradermal microneedle and subcutaneous administration of protein therapeutics: route and formulation-dependent absorption can modify concentration–time behavior even if equivalent quantities were initially presented [3]. Geometry reviews likewise show that needle dimensions matter for performance, yet there is no single universally optimal array geometry independently of intended cargo, application and testing conditions [4]. These observations motivate a mechanism-based theory in which insertion, hydration, dissolution, liberation, retention and subsequent transport are distinct but interacting processes. Its contribution is an experimentally refutable account of their coupling, not a new clinical efficacy claim or a retrospectively calculated delivered-dose estimate.

Nominal formulation content and the problem of actual dose delivery

The nominal dose, designated here as M_0, is the analytically measured inventory of active pharmaceutical ingredient (API) assigned to an individual patch at a defined pre-application state. This denominator must specify whether the assay includes needles, substrate, backing and carrier-associated drug. Dissolving microneedles span different therapeutic classes, needle geometries and excipient systems [5]; consequently, a manufacturer-declared patch loading should not silently become an estimate of intradermal deposition. The useful question is which fraction of M_0 progresses to each subsequent anatomical or chemical state over a clinically relevant interval.

A first separation concerns mechanically inserted material. Needle penetration requires an appropriate relation between local insertion force, needle failure resistance, array contact and skin deformation; dissolvable polymer systems differ in these attributes [6]. A needle that contacts a folded or compressed skin surface may be partly embedded while a neighboring needle enters more deeply. Total array insertion judged through a binary image or post-removal marker may conceal where the loaded portion of each needle actually crossed the barrier. We therefore distinguish embedded cargo inventory from the count of visibly puncturing needles. This is a proposed measurement distinction, not a published universal calibration.

A second separation concerns matrix loss and API release. The levonorgestrel microneedle literature illustrates that drug incorporation, in-vitro characterization and in-vivo delivery need to be assessed in the context of the actual formulation [7]. For a dissolving array, loss of needle height can result from dissolution, deformation or fracture, and disappearance of a polymer signal need not establish liberation of intact drug. The residual mass on the removed patch, API remaining in undissolved polymer and API present in skin are distinct analytes requiring suitable extraction recovery and chemical-identity assays.

The distinction becomes especially important for peptides. Formulation characterization of therapeutic-peptide dissolving microneedles demonstrates that drug content, matrix selection and material performance must be examined together [8]. Peptides can additionally require stability-indicating analysis: nominal peptide-equivalent mass and pharmacologically intact peptide are not automatically identical. For this analysis, mechanically inserted fraction, dissolved-matrix fraction, intact released mass, tissue-deposited amount and biologically available amount are defined as different observables. They cannot be converted into one another without validated mass accounting, relevant time points and a declared anatomical destination.

Existing evidence on microneedle mechanics and pharmaceutical dissolution

The mechanical literature supplies component mechanisms, although it does not by itself solve the complete delivery problem. A model for pyramid-shaped dissolvable microneedles compares insertion force with buckling or failure resistance and accounts for formulation-sensitive material properties [9]. Its useful theoretical lesson is that predictions of needle penetration depend on both geometry and the actual drug–polymer construct. A model calibrated for an unloaded or differently plasticized needle cannot automatically predict the insertion of a cargo-rich tip.

Finite-element analysis of solid conical microneedle arrays further indicates that skin mechanical behavior and the position of a needle within the array influence local insertion response [10]. This supports distinguishing array-level load from needle-level insertion. It does not prove an identical quantitative pattern for dissolving needles, whose stiffness and tip morphology may change on hydration. Local deformation and force redistribution are

plausible causes of spatially correlated insertion deficits, but the magnitude and distribution must be determined in the target material and skin model.

Geometry is also modified by retention design. Barbed, substrate-free dissolving needles have been investigated to enhance adhesion and delivery efficiency [11]. Their behavior suggests that maintaining contact during wear may influence release opportunities after initial puncture. Adhesion is nevertheless a separate variable from penetration depth or absorbed mass: a retained needle can still face insufficient fluid access, poorly located payload or slow liberation from a secondary carrier. Mechanically favorable architecture cannot alone define pharmaceutical completion.

The dissolution literature supplies a distinct source of variation. Experiments comparing dry, intact and barrier-disrupted skin showed differences in dissolving-needle behavior and polymer expansion under altered skin conditions [12]. These observations make a constant per-needle dissolution rate across patients or anatomical sites scientifically questionable. They do not justify assigning a universal hydration correction factor: water availability, barrier state, tissue preparation, polymer chemistry and contact duration remain intertwined with the observed behavior.

A mechanistic polymer-physics model treats solvent interaction, polymer dynamics and an interfacial fluid region as determinants of release after insertion [13]. The model identifies a plausible transport mechanism, but a fitted or model-predicted release profile is conditional on the chosen polymer, pharmaceutical compound and assumptions about the surrounding medium. Insertion-depth measurements cannot substitute for parameters governing solvent access, polymer disentanglement or diffusion, while release measured in a bath may overstate the fluid supply experienced by needles inside skin.

Manufacturing adds an upstream constraint. Work combining digital-light-processing fabrication with vacuum-compression molding to produce rivastigmine microneedles links fabrication choices to geometry, material characterization and delivery assessment [14]. Manufacturing variability may therefore alter the initial distribution of tip shape and cargo before any biological heterogeneity is encountered. The available evidence establishes that mechanics and dissolution are both important; it does not provide a validated general joint distribution of these processes for a diverse patient population.

Unresolved relationships among skin deformation, insertion, and drug deposition

The first unresolved relation concerns the spatial location of payload. A glucose-responsive insulin microneedle design explicitly addresses restricted loading and incomplete release through specialized architecture and release visualization [15]. This product-specific advance exposes a wider ambiguity: a needle may pierce skin while drug-rich root or basal material remains outside the efficiently wetted zone. Dissolution measurements averaged across a patch can miss a systematically retained, disproportionately loaded region.

Layered systems create further nested states. A trilayer peptide-delivery patch separates functions among structural and drug-carrying regions [16]. A double-layered platform concentrating peptide-bearing poly(lactic-co-glycolic acid) microparticles at microneedle tips illustrates how dissolution of the insertion matrix can establish an intradermal depot without completing release from that depot [17]. Where the therapeutic objective is sustained exposure, delayed release may be intentional; where prompt dosing is needed, identical needle dissolution could represent incomplete pharmaceutical delivery. The endpoint must reflect that intended time course.

Carrier architecture can independently change later release. Mesoporous silica nanoparticles with different pore sizes embedded in dissolving microneedle arrays have been investigated as a tunable sustained-release platform [18]. Similarly, donepezil-bearing microparticle depots extend the analytical sequence beyond the disappearance of the dissolving needle [19]. In both cases, carrier deposition, cargo liberation from carrier, free-drug presence and tissue elimination are distinguishable. A favorable insertion indicator cannot tell which of these states dominates at a subsequent sampling time.

Nor is recovered skin drug automatically equivalent to systemic exposure or pharmacodynamic response. Acyclovir-loaded dissolving microneedles have been evaluated for site-specific skin delivery, illustrating why local deposition may itself be the relevant endpoint [20]. For a local dermatological objective, tissue localization and persistence might matter more than plasma concentration. For a systemically acting protein, access to absorptive pathways and systemic concentration–time behavior are additional requirements. A common label, “delivered dose,” therefore requires a declared destination and measurement interval.

These findings leave a key causal question open: do apparent delivery losses chiefly arise before insertion, during fluid-dependent matrix breakdown, during release from embedded secondary carriers, or after free drug enters tissue? The pathways can produce the same aggregate result. A low drug recovery in receptor fluid, for example,

could reflect shallow insertion, retained undissolved mass, intradermal sequestration or biological clearance. Without position-resolved insertion observations and complementary chemical mass balance, those explanations remain observationally confounded.

The most consequential proposed relationship is covariance among needle position, deformation, wetting and payload distribution. If a loaded tip is less likely to insert at the edge of an array, and the same low-contact region also dissolves more slowly, multiplying a mean insertion proportion by an independently measured mean dissolution proportion will misstate joint delivery. Conversely, repeated uniform wetting may make marginal differences in initial penetration less consequential than later cargo release. This theory predicts conditional interactions; neither direction nor magnitude is established as universal. **Table 1** separates the observable physical states and the rival explanations relevant to this inference. **Figure 1** traces their possible overlap across the skin interface while preserving the distinction between published component mechanisms and relationships proposed here.

Table 1. Distinct locations and pharmaceutical states that can produce apparently similar microneedle delivery results

Physical unit or state	Directly inspectable quantity	Plausible mechanism of incomplete dose	Competing interpretation	Proposed discriminating observation
Loaded needle tip above the skin interface	Pre-use tip API content and post-use remnant	Skin indentation prevents a drug-rich segment from entering tissue	Needle contains less API than nominal specification	Paired tip-content mapping, insertion depth and residual chemical assay
Embedded dissolving polymer	Penetration location, residual matrix and hydration state	Limited local water access delays polymer loss	Slow API liberation occurs despite complete polymer hydration	Co-registered time-resolved polymer imaging and intact API measurement
Carrier-containing intradermal depot	Spatially recovered carrier and released API	Carrier retention outlasts needle-matrix disappearance	Pharmaceutical delay is intentionally sustained release	Separate particulate/depot recovery from free intact API over time
Superficial drug-containing skin compartment	Depth-resolved local intact API	Lateral redistribution or local binding retains cargo	Poor receptor-fluid recovery reflects inadequate insertion	Spatial tissue extraction paired with receptor and residual-patch accounting
Systemically accessible tissue fraction	Free intact API and exposure kinetics	Tissue transport or elimination limits systemic availability	Local delivery is the intended therapeutic endpoint	Prespecified local-versus-systemic endpoint and relevant time course

Note. The rows identify physically distinct candidate states, not a measured ranking of failure frequencies. Experimental support for the individual material states does not validate the complete proposed causal chain. API, active pharmaceutical ingredient.

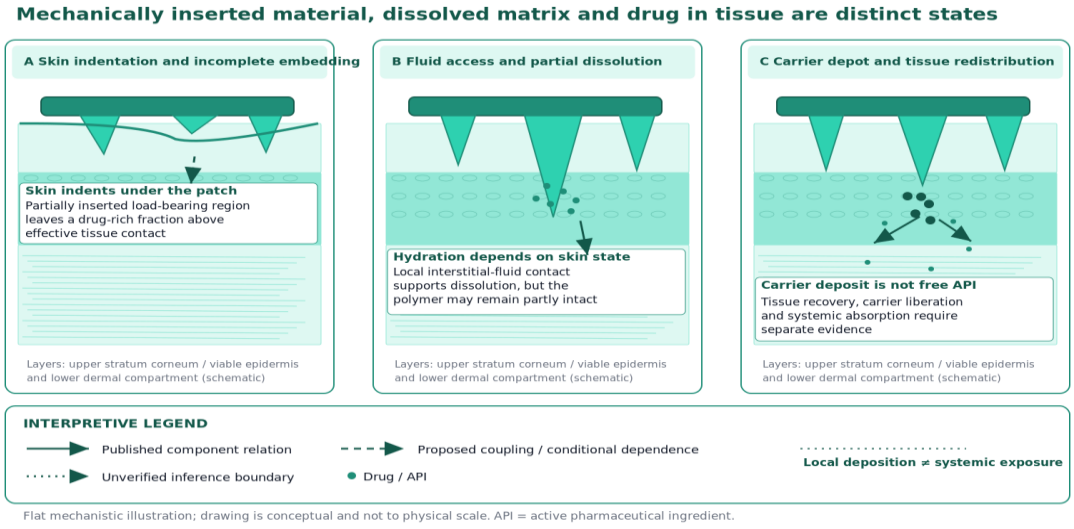


Figure 1. A locally inserted needle can cross the skin barrier without completing intradermal drug liberation

Caption. A layered tissue cross-section shows heterogeneous insertion at neighboring array positions, deformation of the skin surface, alternative wetting zones and the distinction between mechanically embedded material, dissolved needle polymer, cargo still retained in a secondary carrier, free intact drug and redistributed tissue drug. Solid connectors represent component relations supported by the cited mechanics and formulation studies; dashed connectors represent the proposed coupling of indentation, wetting and drug-rich tip placement. Dotted boundaries separate directly observable interface states from subsequently inferred tissue exposure; arrow types are defined in the embedded legend. No arrow asserts a measured population probability, and the local skin pool is not equivalent to systemic bioavailability. API, active pharmaceutical ingredient; ISF, interstitial fluid.

Alt text. Wide layered cross-section read from left to right: compressed stratum corneum over viable epidermis and dermis, with several unequal-depth microneedles; one needle is incompletely inserted and retains API above the surface, another penetrates and encounters an ISF hydration zone, and a third leaves a carrier-containing depot. Solid arrows indicate physical insertion, hydration and release steps documented as component processes; dashed arrows connect skin indentation to uncertain wetting and payload transfer. The legend distinguishes solid process arrows, dashed proposed coupling and dotted inference boundaries; the graphic explicitly states that local deposition is not equivalent to systemic exposure.

Development of a coupled mechanical–pharmaceutical dose-delivery framework

Consider needle position i at time t. Let L_i denote the assayed API inventory at that position; $I_i(t)$ the fraction of its loaded region physically embedded in tissue; $D_i(t)$ the fraction of that embedded needle matrix that has dissolved; $R_i(t)$ the pharmacologically intact API liberated from relevant matrix and carrier compartments; and $A_i(t)$ the amount reaching the prespecified biologically accessible compartment. Each quantity has a distinct denominator and must be defined by an assay. None is presumed to be directly inferable from a neighboring quantity. A patch-level delivery statement would aggregate API in the intended compartment across positions and time while explicitly accounting for residual patch mass, intradermal retention, degradation and removal.

Visual insertion and removal indicators developed for an enfuvirtide microneedle platform may help standardize user action [21]. Their value depends on the indicator's sensitivity to the intended event. A color or contact signal can support the claim that application proceeded as designed; it cannot independently measure intact drug liberated from a polymer or retained tissue concentration. The first constraint is therefore *mechanical observability*: depth or insertion state must be measured at the level where loading and release differ meaningfully, while a user-facing proxy is validated against that measurement.

The second constraint is *chemical and material non-portability*. Multi-material, three-dimensionally printed eutectogel microneedles demonstrate that compositions and fabrication pathways can be designed to control delivery behavior [22]. The relation between penetration and release that holds for one water-soluble polymer matrix will not automatically transfer to an eutectogel, particle-loaded, or multilayer system. A formulation change may simultaneously alter stiffness, contact geometry, partitioning and release kinetics, violating an analysis that varies one averaged factor while fixing the rest.

The third constraint is *state-specific drug availability*. Nanocarrier-integrated microneedle systems involve interactions among carrier, drug and skin that can modify disposition after penetration [23]. For nucleic-acid cargo, analysis must also consider whether the recovered material remains chemically intact and functionally competent; a recent synthesis of dissolving-microneedle nucleic-acid delivery emphasizes modality-dependent formulation and delivery requirements [24]. Recovering analytical mass is consequently an inadequate surrogate for biologically meaningful delivery when molecular integrity, intracellular access or activity is the intended endpoint.

A proposed mechanistic discriminator follows. Under an insertion-only explanation, variation in delivery among matched patches should largely disappear after conditioning on physically embedded intact API mass, even if skin hydration or matrix chemistry varies. Under a dissolution-limited explanation, hydration kinetics and residual intact cargo should retain explanatory power after accounting for insertion. The coupled explanation predicts interaction: at equivalent measured penetration, altered skin fluid access can change polymer fate; at equivalent polymer disappearance, payload location or depot chemistry can change free API recovery. These are competing predictions, not results from a fitted model.

A simple multiplication of average efficiencies is therefore justified only when the dependencies are established or experimentally negligible for the target formulation and patient context. In general, the spatial average of joint

delivery states is not equal to the product of separately averaged states. Individual needle contributions may share application pressure, skin compliance, fluid access and manufacture-related loading variation, creating common rather than independent errors. **Figure 2** treats those covariances as constraints on interpretability and specifies which observations could distinguish mechanical failure, matrix-limited liberation and post-release transport. Successful development requires matching the analytical endpoint to the therapy: tissue exposure for a local active, timed systemic availability for a circulating drug, and intact functional delivery for fragile biological cargo.

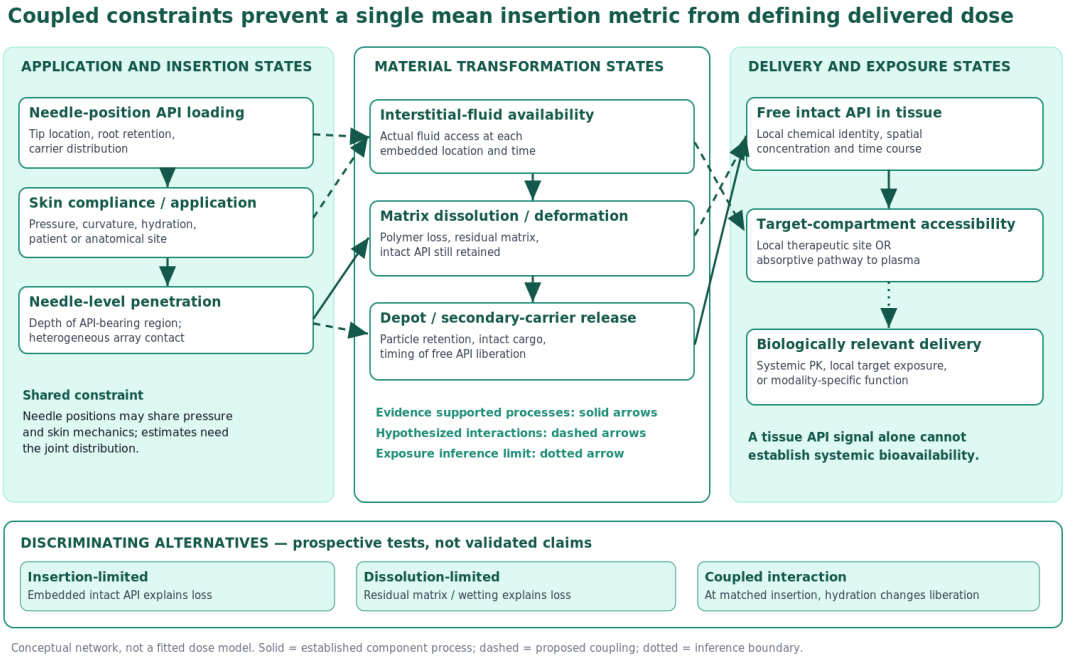


Figure 2. Delivered-dose interpretation is constrained by covariation across insertion, dissolution, payload state and tissue access

Caption. The interdependent network links position-resolved loading and insertion, skin-dependent fluid access, matrix breakdown, secondary-carrier liberation, intact free-drug deposition and intended biological availability. Horizontal strata distinguish initial mechanical states, physicochemical transformation and measurement endpoints. Solid lines identify individual component processes discussed in the published literature; dashed directional lines denote proposed interaction or non-portability hypotheses. Cross-links denote potential shared determinants, including pressure, compliant skin, hydration and matrix chemistry. Blunt endpoints identify conditions that can constrain inference without implying zero transfer. The lower comparison band lists competing mechanistic explanations requiring discriminating tests. A patch-level summary is conditional on the joint distribution of needle-specific states and is not portrayed as a validated universal dose equation. API, active pharmaceutical ingredient; PK, pharmacokinetics.

Alt text. Wide asymmetric network read mainly left to right. An upper band groups initial API location, regional skin indentation and needle-level penetration; a middle band groups local ISF availability, matrix dissolution and depot retention; a right band groups intact free API in tissue and exposure at a prespecified therapeutic destination. Solid arrows connect component processes, dashed arrows show hypothesized interactions between contact, wetting and release, and cross-links identify common skin or formulation determinants. A lower band shows proposed discriminating alternatives: insertion-limited, dissolution-limited and coupled interaction explanations. Distinct line patterns, enclosed levels and textual labels carry meaning independently of turquoise shade.

Implications for formulation optimization and delivered-dose verification

Formulation optimization should start with a declared pharmaceutical destination: free, intact drug at a specified skin depth; a local depot whose release persists over a specified interval; or drug reaching systemic circulation. The optimization target is therefore the amount and time course observed in that compartment under realistic administration, accompanied by a recovery-qualified account of residual patch and tissue-associated material. A

nominally high-loading design may perform poorly if most cargo occupies uninserted roots, whereas a lower-loading design can be more informative when location and release are measurable.

Application variability cannot be relegated to a fixed correction for insertion efficiency. Human-volunteer evaluations of large microneedle patches show why user handling and anatomical application conditions belong in performance assessment [25]. For early design comparisons, the proposed approach is to vary payload distribution, needle stiffness and dissolution chemistry alongside controlled application conditions. Paired measurements of insertion and recovered intact API can identify whether an apparent material benefit persists after mechanical contact is standardized. For particle-loaded systems, residual carrier and free-drug assays must remain distinct. These comparisons prioritize interpretable delivered-dose performance; they do not establish an optimal geometry or formulation for all products. A candidate design should be rejected or redesigned when its measured success depends on an unusually favorable skin preparation, extended contact interval or selective recovery assay. Equally, incomplete short-term release need not constitute failure for an intentionally sustained formulation if the prespecified time-resolved destination remains supported.

Proposed mechanistic tests and measurement requirements

The decisive experiment would cross controlled skin mechanical states and hydration states with formulations having distinguishable matrix-release kinetics, while holding nominal drug inventory and sampling times as consistent as technically possible. Pressure, dwell time, array position and anatomical site should be recorded, and measured skin compliance treated as a covariate rather than inferred from nominal applied force. Within each patch, pre-application tip loading and post-application residual mass would be registered to needle position. Depth-resolved insertion imaging should be paired with spatial extraction of intact drug, carrier-associated cargo and relevant degradation products.

Lateral diffusion in human skin can alter the location where drug is recovered after insertion, as shown by quantitative and qualitative skin-distribution work [26]. Consequently, loss from an insertion track cannot, by itself, identify systemic uptake. Optical approaches for microneedle visualization provide complementary anatomical information, but their contrast and depth limitations require orthogonal chemical analysis [27]. A useful comparison would separately assay removed patch, superficial and deeper skin fractions, receptor phase where applicable, and blood only when systemic exposure is the specified endpoint. Recovery controls, extraction efficiency, analyte stability and sampling delay should be documented for each compartment.

A formulation intended to deliver nucleic acids introduces a further discrimination: analytical RNA mass, intact RNA and functional biological activity can diverge. A dissolving-microneedle mRNA vaccine study links formulation to stability and immunogenicity within its product-specific experimental system [28]. Thus, where appropriate, orthogonal integrity and functional assays should accompany chemical quantification. The coupled theory would be weakened if measured penetration alone explained accessible intact drug across skin and formulation conditions, after suitable error adjustment. Conversely, a persistent interaction between local hydration, insertion position and liberated cargo would support its relevance without proving universality. **Table 2** identifies the observation required before each success claim is licensed.

Table 2. Measurement pairings needed to distinguish microneedle dose states at the intended destination

Dose-state claim	Necessary specimen and spatial registration	Orthogonal readout	Rival explanation that remains	Defensible conclusion
Nominal drug loaded	Pre-application patch; needle, root and backing partitions	Validated API content and chemical identity	Uneven loading within otherwise identical patches	Initial inventory only
Drug-bearing tissue insertion	Needle-resolved penetration map paired with tip inventory	Depth imaging plus post-use tip extraction	Superficial indentation or retained loaded root	Embedded material at defined locations
Matrix dissolution in skin	Embedded region and residual patch sampled over time	Polymer-state imaging plus carrier recovery	Fragmentation, swelling or erosion without liberation	Matrix-state change, not free API dose
Intact API released in tissue	Depth-stratified skin and secondary carrier fractions	Stability-indicating extraction and free/bound separation	Binding, degradation or laterally redistributed API	Accessible intact tissue drug at sampling time

Target-relevant exposure	Prespecified local tissue, systemic or functional compartment	Compartment concentration–time or validated functional assay	Local depot persistence or delayed absorption	Endpoint-specific availability, not automatic clinical effect

Note. These are proposed evidentiary pairings, not a validated assay panel. API, active pharmaceutical ingredient. No universal sensitivity, dose fraction or clinical threshold is claimed.

Discussion and translational development priorities

The practical priority is to decide which causal ambiguity could change a formulation decision. A device failure investigation first needs needle-resolved contact and residual drug mapping; a slow-onset product needs time-resolved intact release; a depot preparation needs carrier-specific disposition. These are different development questions despite sharing a patch format. Standardizing only a penetration indicator risks selecting designs that appear reliable mechanically while remaining heterogeneous pharmacologically.

The therapeutic context also changes what counts as completion. Curcumin nano-formulations combined with dissolving microneedles have been investigated for psoriasis, where local skin exposure is central to interpretation [29]. Comparisons between powder-loaded hollow and dissolving microneedle arrays for tofacitinib demonstrate that delivery modality itself is a relevant comparator, not merely an interchangeable manufacturing choice [30]. Neither study warrants transferring efficacy or a preferred architecture to unrelated actives. Formulation selection should therefore compare clinically meaningful destination, assay observability and realistic application variability before inferring equivalence from nominal payload. Translational programs would benefit from a predefined chain of comparability linking batch specifications, application technique, skin-model selection, chemical recovery and the intended use condition. Batch-to-batch reproducibility of needle geometry should be interpreted alongside reproducibility of loaded-tip distribution. Training or applicator design may reduce administration variance, yet the resulting change in biologically accessible dose still requires direct testing. Selection of a local versus systemic endpoint should occur before analytical validation, because a well-characterized patch remnant is compatible with several incompatible in-vivo exposure histories.

Limitations, patient variability, and framework boundaries

This analysis synthesizes published component mechanisms without fitting parameters to individual-patient dose data. Its principal uncertainty is whether needle-level insertion, hydration and release are sufficiently correlated in a given product to alter a practical decision. Mechanical simulations and ex-vivo skin models cannot by themselves reproduce perfusion, immune response, movement during wear or longitudinal interpatient variability. Skin thickness, hydration, disease state, age, site and technique can modify relevant boundary conditions, but no common adjustment coefficient is justified by the selected evidence [12].

The proposed mass accounting also has limits: apparent nonrecovery may reflect analytical extraction error, chemical transformation, tissue binding or redistribution beyond the sampled volume [27]. Local tissue recovery is not equivalent to systemic exposure; intact nucleic acid is not equivalent to successful intracellular function [24]. Product-specific discrimination and uncertainty reporting are required before any clinical dose-uniformity claim. The framework applies most directly to dissolving drug-bearing arrays and requires substantial re-specification for coated, hollow, solid or implant-forming modalities.

CONCLUSION

Microneedle delivered dose emerges from interdependent anatomical contact, loading position, matrix hydration, drug liberation and subsequent disposition. A mechanically penetrated needle, a disappearing polymer matrix and a chemically detectable skin reservoir each mark different stages of that sequence. The defensible endpoint is the intact, accessible drug—or validated biological activity—at the intended destination and time. Needle-resolved, chemically specific and compartment-aware measurements can test whether insertion, dissolution or their coupling dominates a particular formulation. Until those comparisons are made, nominal loading and convenient surrogate readouts cannot establish reproducible pharmaceutical delivery.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Moawad F, Pouliot R, Brambilla D. Dissolving microneedles in transdermal drug delivery: A critical analysis of limitations and translation challenges. J Control Release. 2025;383:113794. doi:10.1016/j.jconrel.2025.113794
2. Dul M, Alali M, Ameri M, Burke MD, Creelman BP, Dick L, et al. White paper: Understanding, informing and defining the regulatory science of microneedle-based dosage forms that are applied to the skin. J Control Release. 2025;378:402-15. doi:10.1016/j.jconrel.2024.11.056
3. Koenitz L, Crean A, Vucen S. Pharmacokinetic differences between subcutaneous injection and intradermal microneedle delivery of protein therapeutics. Eur J Pharm Biopharm. 2024;204:114517. doi:10.1016/j.ejpb.2024.114517
4. Visscher M, Frijlink HW, Hinrichs WLJ. What is the optimal geometry of dissolving microneedle arrays? A literature review. Pharmaceutics. 2025;17(1):124. doi:10.3390/pharmaceutics17010124
5. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: Applications and growing therapeutic potential. J Control Release. 2022;348:186-205. doi:10.1016/j.jconrel.2022.05.045
6. Ali M, Namjoshi S, Benson HAE, Mohammed Y, Kumeria T. Dissolvable polymer microneedles for drug delivery and diagnostics. J Control Release. 2022;347:561-89. doi:10.1016/j.jconrel.2022.04.043
7. Yao G, Quan G, Lin S, Peng T, Wang Q, Ran H, et al. Novel dissolving microneedles for enhanced transdermal delivery of levonorgestrel: In vitro and in vivo characterization. Int J Pharm. 2017;534(1-2):378-86. doi:10.1016/j.ijpharm.2017.10.035
8. Dillon C, Hughes H, O'Reilly NJ, McLoughlin P. Formulation and characterisation of dissolving microneedles for the transdermal delivery of therapeutic peptides. Int J Pharm. 2017;526(1-2):125-36. doi:10.1016/j.ijpharm.2017.04.066
9. Abbasi A, Kheirieh A, Mousavi Shaegh SA, Lakhi M, Darabifard A, Golmohammadzadeh S, et al. A method to predict insertion of dissolvable microneedles: No need to fabricate. Int J Pharm. 2025;678:125699. doi:10.1016/j.ijpharm.2025.125699
10. Shu W, Heimark H, Bertollo N, Tobin DJ, O'Cearbhaill ED, Ní Annaidh A. Insights into the mechanics of solid conical microneedle array insertion into skin using the finite element method. Acta Biomater. 2021;135:403-13. doi:10.1016/j.actbio.2021.08.045
11. Ren Y, Yang K, Wang Z, Zhang Z, Chen Y, Shi X, et al. Substrate-free dissolving microneedles with barbed shape to increase adhesion and drug-delivery efficiency to skin. J Control Release. 2024;368:199-207. doi:10.1016/j.jconrel.2024.02.009
12. Limcharoen B, Wanichwecharungruang S, Kröger M, Sansureerungsikul T, Schleusener J, Klein AL, et al. Dissolvable microneedles in the skin: Determination the impact of barrier disruption and dry skin on dissolution. Eur J Pharm Biopharm. 2024;199:114303. doi:10.1016/j.ejpb.2024.114303
13. Yadav PR, Hingonia P, Das DB, Pattanayek SK. Modeling of dissolving microneedle-based transdermal drug delivery: Effects of dynamics of polymers in solution. Mol Pharm. 2024;21(10):5104-14. doi:10.1021/acs.molpharmaceut.4c00492
14. Monou PK, Saropoulou E, Junqueira LA, Kolipaka SS, Andriotis EG, Tzimtzimis E, et al. Fabrication and characterization of dissolving microneedles combining digital light processing and vacuum compression molding technique for the transdermal delivery of rivastigmine. Eur J Pharm Biopharm. 2025;210:114687. doi:10.1016/j.ejpb.2025.114687
15. He Y, Chen N, Zang M, Zhang J, Zhang Y, Lu H, et al. Glucose-responsive insulin microneedle patches for long-acting delivery and release visualization. J Control Release. 2024;368:430-43. doi:10.1016/j.jconrel.2024.03.001
16. Pandya AK, Vora LK, Moreno-Castellanos N, Sabri A, Naser YA, Baviskar SM, et al. A trilayer microneedle patch for transdermal delivery of the peptide salmon calcitonin for osteoporosis therapy. J Control Release. 2025;386:114146. doi:10.1016/j.jconrel.2025.114146

17. Xu B, Liu H, Yang G, Zhang S, Zhou Z, Gao Y. Novel double-layered PLGA microparticles-dissolving microneedle (MPs-DMN) system for peptide drugs sustained release by transdermal delivery. Int J Pharm. 2025;670:125128. doi:10.1016/j.ijpharm.2024.125128
18. Paris JL, Vora LK, Pérez-Moreno AM, Martín-Astorga MDC, Naser YA, Anjani QK, et al. Dissolving microneedle array patches containing mesoporous silica nanoparticles of different pore sizes as a tunable sustained release platform. Int J Pharm. 2025;669:125064. doi:10.1016/j.ijpharm.2024.125064
19. Lee JH, Song GJ, Hwang HS, Lee CS. Dissolving microneedle patch integrated with microparticle depots for sustained intradermal delivery of donepezil. Int J Pharm. 2025;678:125653. doi:10.1016/j.ijpharm.2025.125653
20. Pamornpathomkul B, Ngawhirunpat T, Tekko IA, Vora L, McCarthy HO, Donnelly RF. Dissolving polymeric microneedle arrays for enhanced site-specific acyclovir delivery. Eur J Pharm Sci. 2018;121:200-9. doi:10.1016/j.ejps.2018.05.009
21. Li H, Vora L, Li Y, Pandya AK, Wang J, Luo Y, et al. Transdermal delivery of enfuvirtide using dissolving microneedles integrated with novel insertion and removal indicator. J Control Release. 2025;385:113954. doi:10.1016/j.jconrel.2025.113954
22. Liu H, Zhou X, Nail A, Yu H, Yu Z, Sun Y, et al. Multi-material 3d printed eutectogel microneedle patches integrated with fast customization and tunable drug delivery. J Control Release. 2024;368:115-30. doi:10.1016/j.jconrel.2024.02.023
23. Khairnar P, Phatale V, Shukla S, Tijani AO, Hedaoo A, Strauss J, et al. Nanocarrier-integrated microneedles: Divulging the potential of novel frontiers for fostering the management of skin ailments. Mol Pharm. 2024;21(5):2118-47. doi:10.1021/acs.molpharmaceut.4c00144
24. Tobos CI, Woodrow KA. Dissolving microneedles for nucleic acid delivery: A systematic search, review, and data synthesis. Acta Biomater. 2025;200:115-31. doi:10.1016/j.actbio.2025.05.025
25. Ripolin A, Quinn J, Larrañeta E, Vicente-Perez EM, Barry J, Donnelly RF. Successful application of large microneedle patches by human volunteers. Int J Pharm. 2017;521(1-2):92-101. doi:10.1016/j.ijpharm.2017.02.011
26. Nguyen HX, Puri A, Bhattaccharjee SA, Banga AK. Qualitative and quantitative analysis of lateral diffusion of drugs in human skin. Int J Pharm. 2018;544(1):62-74. doi:10.1016/j.ijpharm.2018.04.013
27. Limcharoen B, Wanichwecharungruang S, Banlunara W, Darvin ME. Seeing through the skin: Optical methods for visualizing transdermal drug delivery with microneedles. Adv Drug Deliv Rev. 2025;217:115478. doi:10.1016/j.addr.2024.115478
28. Tang Z, Su T, Jiang T, Hu J, Chen D, Li X, et al. Development of a dissolving microneedle patch for transdermal delivery of SARS-CoV-2 mRNA vaccine with enhanced stability and immunogenicity. J Control Release. 2025;388(Pt 1):114263. doi:10.1016/j.jconrel.2025.114263
29. Xu P, Xu K, Li J, Liu A, Xiao W, Sun L. Screening and preparation of curcumin nano-formulations combined with dissolving microneedles on the application in the effective treatment of psoriasis. Int J Pharm. 2025;675:125528. doi:10.1016/j.ijpharm.2025.125528
30. Cárcamo-Martínez Á, Mallon B, Anjani QK, Domínguez-Robles J, Utomo E, Vora LK, et al. Enhancing intradermal delivery of tofacitinib citrate: Comparison between powder-loaded hollow microneedle arrays and dissolving microneedle arrays. Int J Pharm. 2021;593:120152. doi:10.1016/j.ijpharm.2020.120152