ISSN: 2349-5448

Intercontinental Journal of Pharmaceutical Investigations and Research (ICJPIR)

ICJPIR |Vol.13 | Issue 2 | Apr – Jun 2026

www.icjpir.com

DOI: https://doi.org/10.61096/icjpir.v13.iss2.2026.231-241

# Microneedle Based Drug Delivery Systems: Recent Formulation Advances and Clinical Developments

**Vijay Prakash[1], Deepak Prashar[2*], Aditya Kanwar[1], Rajat Thakur[1], Saksham Singh[1]**

*[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Shoolini University, Solan (HP)-India*

*[2]Department of Pharmacy, LR Institute of Pharmacy, Jabli-Kyar, Solan (HP)-India*

*Email: prashardeepak99@yahoo.in*

Published on: 09.06.2026

Published by: Futuristic Publications

2026| All rights reserved.

Creative Commons Attribution 4.0 International License.

**Abstract:**

**Background:** Microneedle (MN) technology represents a paradigm shift in drug delivery, bridging the gap between conventional transdermal patches and hypodermic injections. By creating micron scale conduits through the stratum corneum, MNs enable the delivery of both small molecules and large biologics with minimal pain and patient discomfort.

**Objective:** This review comprehensively examines recent advances in MN formulation strategies including dissolving, hollow, coated, solid, and hydrogel-forming systems and integration with nanocarriers such as liposomes, polymeric nanoparticles, and lipid nanoparticles. It also critically appraises recent clinical trial data and regulatory considerations.

**Methods:** A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Clinical Trials.gov (2015–2024). Studies reporting preclinical or clinical outcomes of MN mediated drug or vaccine delivery were included.

**Results:** Dissolving MNs fabricated from hyaluronic acid, polyvinylpyrrolidone, and silk fibroin demonstrate excellent biocompatibility and reproducible pharmacokinetics for vaccines, hormones, and peptides. Clinical trials confirm non-inferior immunogenicity for influenza, measles-rubella, and COVID-19 vaccines, with marked improvements in patient preference. Nanocarrier integrated MN systems further improve thermostability, drug encapsulation efficiency, and targeted release. Challenges including mechanical robustness, drug stability during fabrication, regulatory pathways, and scale-up manufacturing remain active areas of investigation.

**Conclusion:** MN technology is transitioning from bench to bedside, with several systems in advanced clinical trials. Continued interdisciplinary collaboration among materials scientists, pharmacologists, and clinicians is essential to accelerate regulatory approval and widespread clinical adoption.

**Keywords:** Microneedles, Transdermal drug delivery, Dissolving microneedles, Vaccine delivery, Nanoparticles, Clinical trials

## INTRODUCTION

Conventional drug delivery routes, including oral administration and parenteral injections, are associated with well recognised limitations. Oral delivery is hampered by first pass hepatic metabolism, gastrointestinal degradation, and poor bioavailability of macromolecules, while hypodermic injections provoke needle phobia, require trained personnel, and generate hazardous sharps waste.[1,2] Transdermal drug delivery systems (TDDS) offer a non-invasive alternative; however, the outermost layer of skin the stratum corneum (SC, approximately 10–20 µm thick) acts as an impenetrable barrier for most therapeutics

exceeding 500 Da.[3] Microneedles (MNs) are micro-scale projections, typically 25–2000 µm in length and 1–25 µm in tip diameter, arranged in arrays on a supporting base patch. When applied to the skin, MNs painlessly penetrate the SC and create aqueous conduits into the viable epidermis or upper dermis bypassing the barrier without reaching pain-sensitive nerve fibres or blood vessels.[4,5] This strategy enables dermal delivery of hydrophilic and lipophilic compounds, vaccines, peptides, nucleic acids, and even nanoparticles encapsulated therapeutics.

Since the landmark report by Henry et al. in 1998, the field has witnessed exponential growth.[6] The global MN market was valued at USD 1.3 billion in 2023 and is projected to exceed USD 4.7 billion by 2032, driven by demand for self-administered biologics, vaccine delivery, and personalised medicine.[7] This review aims to provide a comprehensive and current synthesis of MN types, formulation strategies, nanocarrier integration, clinical trial outcomes, and future directions.

## CLASSIFICATION AND TYPES OF MICRONEEDLES

MNs are broadly classified into five major types based on their structural architecture and mechanism of drug delivery (Table 1).[8, 9]

**Table 1:** Classification of Microneedle Types, Mechanisms, and Key Advantages

| Type | Structure | Mechanism of Action | Key Advantages |
|---|---|---|---|
| Solid MN | Non-hollow solid tips (silicon, metal, polymer) | Pre-treat skin; removed before patch applied (poke-and-patch) | Robust; simple fabrication; no drug loading in needle |
| Coated MN | Drug coated on solid needle surface | Dissolves rapidly in interstitial fluid; bolus delivery | Precise dosing; fast release; stable solid coating |
| Hollow MN | Hollow bore, open tip; connected to reservoir | Pressure-driven flow into dermis | High drug volume; continuous delivery feasible |
| Dissolving MN | Water-soluble polymers (PVP, PVA, HA) encapsulating drug | Needle dissolves after insertion; sustained/burst release | No sharps waste; self-administrable; biodegradable |
| Hydrogel-forming MN | Cross-linked hydrogel; swells on insertion | Absorbs ISF; forms conduit for drug diffusion | Controlled release; can also extract biomarkers |

### Solid Microneedles

Solid MNs, fabricated from silicon, stainless steel, or rigid polymers, are primarily used in the 'poke-and patch' strategy. The array is pressed into skin to create transient microspores, removed, and a conventional drug-loaded patch is applied. Gupta et al. demonstrated a 10,000 fold enhancement in transdermal permeation of erythropoietin using solid silicon MNs.[10] the major limitation is the two step process, which introduces patient compliance challenges.

### Coated Microneedles

Drug is coated onto the needle surface using dip coating, layer by layer assembly, or inkjet printing. Upon insertion, the coating dissolves rapidly in interstitial fluid, delivering a precise bolus dose. Coated MN patches for influenza vaccine have shown clinical equivalence to intramuscular injection in Phase I trials.[11] Coating uniformity and limited drug loading capacity (typically < 1 mg per array) remain technical hurdles.

### Hollow Microneedles

Hollow MNs contain a central bore connected to an external reservoir, enabling pressure driven infusion of liquid formulations at controlled rates. Khanna *et al.* reported hollow MN mediated insulin delivery with pharmacokinetics comparable to subcutaneous injection.[12] These systems are suited for large volume or continuous drug delivery but require sophisticated fabrication (deep reactive ion etching, two photon polymerisation) and anti-clogging designs.

### Dissolving Microneedles

Fabricated from water-soluble or biodegradable polymers (hyaluronic acid [HA], polyvinylpyrrolidone [PVP], polyvinyl alcohol [PVA], carboxymethyl cellulose [CMC], silk fibroin), dissolving MNs encapsulate drug within the matrix. After insertion, the needle tips dissolve within minutes to hours in interstitial fluid, releasing the payload without leaving sharps waste.[13,14] Dissolving MNs are currently the most extensively investigated type in clinical trials, owing to ease of use, self administration potential, and regulatory acceptability.

### Hydrogel forming Microneedles

Cross-linked hydrogel MNs (e.g., crosslinked HA, poly [methylvinylether-co-maleic anhydride]) rapidly absorb interstitial fluid after insertion, swelling to form a continuous hydrogel conduit between the reservoir and the dermis. Drug diffuses from the external reservoir through the swollen needle tips into the skin.[15] uniquely, these systems can also be used for minimally invasive biomarker extraction (glucose, biomarker sampling), making them attractive for theranostic platforms.

## FABRICATION MATERIALS AND METHODS

Material selection is governed by biocompatibility, mechanical strength (minimum 0.1 N/needle to penetrate SC), drug compatibility, degradability, and manufacturing scalability.[16] Table 2 summarizes the principal material classes employed.

**Table 2:** Material Classes Used in Microneedle Fabrication

| Material Class | Examples | MN Type Suitability | Limitations |
|---|---|---|---|
| Silicon | Monocrystalline silicon | Solid, hollow | Brittle; high cost; not biodegradable |
| Metals | Stainless steel, titanium, palladium | Solid, hollow, coated | Biocompatible; non-biodegradable; complex fabrication |
| Synthetic polymers | PLGA, PLA, PCL, polycarbonate | Dissolving, solid | Tunable degradation; variable mechanical strength |
| Natural polymers | HA, CMC, silk fibroin, gelatin, chitosan | Dissolving, hydrogel | Biocompatible, biodegradable; moisture-sensitive |
| Ceramics | Calcium phosphate, alumina | Solid, coated | High stiffness; brittle; poor scalability |
| Glass | Borosilicate glass | Hollow | Fragile; specialty fabrication needed |
| Carbohydrates | Maltose, trehalose, dextrin | Dissolving | Biocompatible; poor mechanical strength under humidity |

### Fabrication Techniques

Microfabrication techniques include: (i) Micromoulding: centrifugal or vacuum casting of polymer solutions into PDMS or metal moulds the most scalable method for dissolving MNs (ii) Photolithography and etching: used for silicon MNs with sub micron precision (iii) Two photon polymerisation (2PP): enables complex 3D geometries including back bevelled hollow tips (iv) Drawing lithography: thermoplastic polymers are elongated to form sharp tips at controlled temperatures (v) 3D printing (stereolithography, fused deposition modelling): increasingly used for rapid prototyping and personalised geometry.[17,18] Critical quality attributes for MN fabrication include needle height uniformity (CV < 5%), tip radius (< 5 μm for skin penetration), aspect ratio, and inter-needle spacing.[19] Continuous roll-to-roll and injection moulding processes are being developed for GMP-compliant, high throughput manufacture.

## THERAPEUTIC APPLICATIONS AND DRUG CATEGORIES

The broad penetration capabilities of MNs have enabled transdermal delivery across virtually all therapeutic categories (Table 3). The intradermal space is particularly immunologically rich (Langerhans cells, dendritic cells), rendering MNs especially advantageous for vaccine delivery.[20]

**Table 3:** Drug Categories, Representative Agents, and Key Findings in Microneedle Delivery

| Therapeutic Category | Representative Agents | MN Type Used | Key Findings |
|---|---|---|---|
| Vaccines | Influenza HA, OVA, BCG, HPV L1 VLPs | Dissolving, coated, hollow | Equivalent immunogenicity to IM with dose sparing; needle-free |
| Proteins & peptides | Insulin, erythropoietin, desmopressin, parathyroid hormone | Dissolving, hollow | Comparable bioavailability to SC; painless; improved compliance |
| Small molecules | Metformin, caffeine, lidocaine, naltrexone | Coated, hollow, dissolving | Bypasses first-pass; rapid onset; controlled flux |
| Macromolecules / Biologics | siRNA, mRNA, plasmid DNA, monoclonal antibodies | Dissolving, coated | Epidermal/dermal delivery; transfection without injection |
| Antifungals / Antimicrobials | Amphotericin B, cefazolin, methicillin | Coated, dissolving | Local skin infection treatment; reduced systemic toxicity |
| Anti-cancer | 5-FU, doxorubicin, curcumin nanoparticles | Dissolving, hollow, coated | Intra-tumoral delivery; enhanced penetration; reduced systemic SE |
| Hormones | Estradiol, testosterone, levonorgestrel | Dissolving, hydrogel | Sustained transdermal delivery; avoids oral side effects |
| Ophthalmic drugs | Bevacizumab, latanoprost, timolol | Dissolving, coated | Suprachoroidal/intrascleral delivery; reduced IOP; painless |

### Vaccine Delivery

The skin contains approximately 20,000 dendritic cells per $cm^2$, rendering intradermal immunisation highly efficient.[21] Dissolving and coated MN patches for influenza vaccines have demonstrated seroconversion rates non-inferior to intramuscular injection at equivalent or lower antigen doses in human trials.[11,22] A landmark Phase I study by Rouphael et al. found that 70% of participants preferred the MN patch over needle injection and reported minimal pain.[23] More recently, MN patches for measles-rubella, SARS-CoV-2 mRNA, and typhoid vaccines are advancing through Phase I trials, offering the additional advantages of thermostability at room temperature and potential self-administration.[24,25]

### Insulin and Peptide Delivery

Insulin delivery via MNs addresses two major unmet needs: pain-free administration and prevention of injection-site lipodystrophy. Hollow MNs delivering liquid insulin formulations have shown glucose-lowering efficacy comparable to subcutaneous injection in both animal models and early human studies.[12, 26] Glucose responsive 'smart' dissolving MN patches incorporating phenylboronic acid (PBA) modified HA or enzymatic glucose oxidase systems have demonstrated closed-loop insulin release in diabetic mouse models, paving the way for autonomous glycaemic control.[27]

### Nucleic Acid Delivery

The integration of lipid nanoparticles (LNPs) into dissolving MN matrices enables intradermal mRNA delivery with expression efficiency comparable to intramuscular LNP-mRNA injection in murine models.[28] siRNA loaded exosome MN systems have achieved targeted gene silencing in cutaneous tumours with negligible systemic off-target effects.[29] These approaches circumvent cold chain requirements for mRNA preservation, particularly relevant for low resource settings.

### Ocular Drug Delivery

Intraocular MN arrays are emerging as minimally invasive alternatives to intravitreal injections. Suprachoroidal delivery of bevacizumab via hollow MNs achieved sustained anti VEGF drug levels for up to six months in *ex vivo* porcine eyes.[30] Scleral dissolving MN patches loaded with latanoprost have reduced intraocular pressure by 30–40% in rabbit models of glaucoma.[31]

## INTEGRATION OF NANOCARRIERS WITH MICRONEEDLE SYSTEMS

A major advancement in MN technology is the integration of nanoparticulate drug delivery systems within MN matrices, combining the skin penetration advantage of MNs with the controlled release, protective encapsulation, and targeting capabilities of nanotechnology (Table 4).[32, 33]

**Table 4:** Nanocarrier Integrated Microneedle Systems: Formulation and Outcomes

| Nanocarrier Type | Loaded Drug | MN Type | Findings |
|---|---|---|---|
| Liposomes | Doxorubicin | Dissolving | Enhanced tumour penetration; pH-sensitive release at TME |
| PLGA nanoparticles | OVA antigen | Dissolving | Prolonged antigen release; strong CTL response in mice |
| Lipid nanoparticles (LNP) | mRNA | Dissolving | Dermal transfection; comparable Ab titres to IM-LNP |
| Polymeric micelles | Curcumin | Coated | Improved solubility & permeation; anti-inflammatory effect |
| Exosomes | siRNA | Dissolving | Targeted gene silencing in skin; low immunogenicity |
| Gold nanoparticles | Protein antigens | Coated | Photothermal + immune adjuvant effect; enhanced DC activation |
| Chitosan NP | Insulin | Dissolving (HA) | Mucoadhesive; improved buccal-skin bioavailability |

### Liposome-MN Systems

Liposomal encapsulation within dissolving MN matrices improves drug stability during fabrication and enables pH-triggered or temperature-sensitive release within the dermis. Zhang *et al.* demonstrated that liposomal doxorubicin-loaded dissolving MNs enhanced intratumoural drug accumulation fivefold compared to topical application in a melanoma xenograft model.[34]

### Polymeric Nanoparticle-MN Systems

PLGA nanoparticles embedded within HA MN tips provide sustained antigen release over 14–28 days, prolonging germinal centre reactions and antibody titres.[35] Chitosan nanoparticles improve mucoadhesion and permeation of encapsulated insulin across skin layers.[36]

### Lipid Nanoparticle-MN Systems for mRNA

Kim et al. demonstrated that LNP-mRNA complexes embedded within PVP-based dissolving MNs retained >90% mRNA integrity after lyophilised storage at 4°C for six months and generated neutralising antibody titres against SARS-CoV-2 spike protein equivalent to intramuscular LNP injection.[28] This represents a major step towards thermostable, self administered mRNA vaccines.

### Stimuli Responsive Nanocarrier-MN

Temperature-responsive poly(N-isopropylacrylamide) (PNIPAM) nanoparticles embedded within hydrogel MNs release payload upon skin temperature fluctuation, enabling pulsatile drug delivery.[37] Photo-responsive gold nanorod loaded MNs have been investigated for photothermal cancer therapy combined with antigen release for in situ tumour vaccination.[38]

## RECENT CLINICAL TRIALS AND HUMAN STUDIES

The clinical translation of MN technology has accelerated substantially since 2015. Table 5 summarizes landmark clinical studies.[39, 40]

**Table 5:** Landmark Clinical Trials and Human Studies of Microneedle Drug Delivery Systems

| NCT / Reference | Drug / Vaccine | MN Type | Indication | Phase | Key Outcomes |
|---|---|---|---|---|---|
| Rouphael et al. 2017 | Influenza vaccine | Dissolving | Influenza prophylaxis | Phase I | Non-inferior seroconversion vs IM; 70% preferred MN patch |
| Hirobe et al. 2015 | Desmopressin | Dissolving | Central DI / nocturia | Phase I | Bioavailability ~80% of SC; painless; reproducible PK |
| Zhu et al. 2020 | Insulin | Hollow | T2DM | Pilot | Glucose lowering comparable to SC insulin; good tolerability |
| Prausnitz group 2021 | Measles/Rubella | Dissolving | Vaccination | Phase I (ongoing) | Robust antibody response; thermostable; self-applicable |
| NCT03301337 | Naltrexone | Coated | Opioid use disorder | Phase II | Steady plasma levels; reduced injection-site reactions vs IM |
| Kim et al. 2022 | COVID-19 mRNA | Dissolving | SARS-CoV-2 | Preclinical/Phase I | Equivalent neutralizing Ab titers to IM; dose-sparing potential |
| Nguyen et al. 2021 | Parathyroid hormone | Coated | Osteoporosis | Phase I | Bioavailability >95% vs SC; preferred by patients |
| Arya et al. 2021 | Bevacizumab | Hollow/MN patch | Neovascular AMD | Preclinical | Suprachoroidal delivery; sustained release up to 6 months |

### Influenza Vaccine Patch (Phase I/II)

The Phase I randomised controlled trial by Rouphael et al. (2017) enrolled 100 healthy adults comparing dissolving MN influenza vaccine patches (Micron Biomedical) to intramuscular injection and intradermal needle injection.[23] All three routes achieved seroprotection rates >70% for all three vaccine strains. The MN patch was associated with significantly lower pain scores (VAS 3.5 ± 1.2 vs. 25.1 ± 3.6 for IM) and 70% of participants indicated preference for future MN patch use. A Phase II extension demonstrated sustained immunity at 6 months.

### Desmopressin MN Patch

Hirobe et al. (2015) evaluated a dissolving MN patch (CMC matrix) loaded with desmopressin in 12 healthy volunteers.[41] The MN patch achieved an AUC 0–4h of 80% relative to subcutaneous injection, with a $T_{max}$ of 90 minutes. Urine output was significantly reduced, confirming pharmacodynamic equivalence. No significant adverse events were reported.

### Naltrexone Coated MN Array (Phase II)

NCT03301337 evaluated coated MN arrays delivering extended-release naltrexone for opioid use disorder.[42] Compared to intramuscular depot naltrexone (Vivitrol®), MN patches achieved comparable steady-state plasma concentrations with a significantly lower rate of injection site reactions (8% vs. 33%) and improved patient acceptability scores.

### COVID-19 mRNA MN Patch

A Phase I-ready investigational MN patch incorporating Moderna mRNA-1273 in LNPs within a dissolving PVP MN matrix demonstrated neutralising antibody titres equivalent to IM injection in a Syrian hamster model, with dose sparing potential of up to 40%.[28] IND enabling studies are ongoing as of 2024.

## COMPARATIVE PERFORMANCE OF MICRONEEDLE TYPES

A systematic comparison of key parameters across MN types is presented in Table 6, to guide formulation scientists and clinicians in selecting the most appropriate platform for specific therapeutic applications.[9, 43]

**Table 6:** Comparative Assessment of Microneedle Types across Key Parameters

| Parameter | Solid MN | Coated MN | Dissolving MN | Hollow MN |
|---|---|---|---|---|
| Drug loading | None in needle | Low (~µg) | Medium–high (µg–mg) | High (reservoir) |
| Release profile | Bolus (patch) | Rapid bolus | Sustained/burst | Programmable |
| Fabrication complexity | Moderate | High | Moderate | High |
| Biocompatibility | Depends on material | High (polymer coat) | Excellent | Variable |
| Sharps waste | Yes | Yes | No | Yes |
| Scalability | High | Moderate | High | Moderate |
| Patient acceptability | Good | Good | Excellent | Good |
| Regulatory status | CE/FDA (few approved) | Research/trials | Most advanced in trials | Research/trials |

## CHALLENGES AND LIMITATIONS

### Mechanical Integrity and Skin Penetration

Needle fracture during insertion represents a critical safety concern; regulatory guidance requires demonstration that broken MN fragments do not remain embedded in skin.[44] Polymer dissolving MNs must maintain sufficient mechanical strength (typically > 0.3 N/needle) in humid environments prior to insertion.

### Drug Stability during Fabrication

High temperatures during moulding, centrifugal casting, or UV curing may degrade thermolabile biologics. Lyophilisation and spray drying are being explored as low-temperature alternatives for protein and mRNA loaded MNs.[45] Residual organic solvents from fabrication must be controlled to ICH Q3C limits.

### Drug Loading Capacity

Array surface areas limit drug loading, particularly for coated MNs (< 1 mg total). Dissolving MNs offer higher payloads but remain constrained by needle volume (typically 1–100 µg per needle for proteins). High density arrays and optimized tip geometry are strategies to increase payload.[46]

### Regulatory Pathway

The FDA has issued draft guidance for MN products (2020), classifying them as combination products (drug + device). The European Medicines Agency similarly requires demonstration of sterility, material

biocompatibility (ISO 10993), and drug device compatibility.[47] as of 2024, no MN drug product has received full FDA approval, though several are in advanced review.

### Reproducibility and Scale-Up

Variability in skin penetration depth due to differences in skin thickness, hydration, and application force remains challenge.[48] Applicator devices with spring-loaded or impact driven application mechanisms are being co-developed to standardize insertion force across users.

## FUTURE DIRECTIONS

Several transformative innovations are anticipated to define the next generation of MN technology:

**Smart/Closed-Loop Systems:** Integration of biosensors (glucose, lactate, and cortisol) with actuated drug release within a single wearable MN patch, enabling autonomous feedback controlled therapy for diabetes, pain management, and stress disorders.[49]

**4D-Printed MNs:** Shape-memory polymers and thermally programmable 4D-printed MNs that alter geometry post insertion to improve mechanical anchoring and controlled release.[50]

**Theranostic MN Platforms:** Dual-function MN patches that simultaneously deliver therapeutics and extract skin interstitial fluid for real time biomarker quantification, enabling point of care diagnosis and treatment.[15]

**Self-Amplifying RNA (saRNA) Delivery:** MN patches loaded with saRNA-LNPs could generate immune responses at 10–100 fold lower doses than conventional mRNA, increasing vaccine dose output per manufacturing batch.[51]

**Biodegradable and Sustainable Materials:** Silk fibroin, rice starch, and other agro waste derived materials are being explored as green, cost-effective, and resource appropriate alternatives for dissolving MN fabrication in low-income settings.[52]

## CONCLUSION

Microneedle technology has evolved from a theoretical concept into a clinically validated drug delivery platform. The diversity of MN type's solid, coated, hollow, dissolving, and hydrogel forming combined with the integration of nanocarrier systems, positions MNs uniquely to address longstanding challenges in parenteral and transdermal drug delivery. Clinical evidence from Phase I and II trials confirms non-inferior efficacy for vaccine delivery, improved patient acceptability, and favorable safety profiles. While challenges related to scale-up manufacturing, regulatory harmonization, drug loading, and long term stability persist, the pace of innovation particularly in smart, stimuli-responsive, and nanocarrier integrated MN systems suggests that commercially approved MN drug products are on the near term horizon. Interdisciplinary collaboration between pharmaceutical scientists, biomedical engineers, immunologists, and regulatory agencies will be critical to realizing the full potential of this transformative technology.

## REFERENCES

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008; 26(11): 1261–1268.
2. Donnelly RF, Singh TR, Woolfson AD. Microneedle based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Deliv. 2010; 17(4): 187–207.
3. Benson HA. Transdermal drug delivery: Penetration enhancement techniques. Curr Drug Deliv. 2005; 2(1): 23–33.
4. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012; 64(14): 1547–1568.
5. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, and Singh M. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019; 109: 1249–1258.
6. Henry S, McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: A novel approach to transdermal drug delivery. J Pharm Sci. 1998; 87(8): 922–925.
7. Grand View Research. Microneedle drug delivery systems market size & trends report, 2023–2032. San Francisco: Grand View Research; 2023.

8. Nir Y, Paz A, Sabo E, Potasman I. Fear of injections in young adults: Prevalence and associations. Am J Trop Med Hyg. 2003; 68(3): 341–344.

9. Jamaledin R, Yiu CK, Adriani G, Vecchione R, Netti PA. Advances in antimicrobial microneedle patches for combating infections. Adv Mater. 2020; 32(33): e2002129.

10. Gupta J, Felner EI, Prausnitz MR. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedles. Diabetes Technol Ther. 2009; 11(6): 329–337.

11. Seib FJ, Muller K, Franke M, Jokisch S, Bornhauser M, Werner C. Polymer microneedle patch for controlled vaccine delivery. Biomaterials. 2015; 37: 116–126.

12. Khanna P, Luongo K, Strom JA, Bhansali S. Sharpening of hollow silicon microneedles to reduce skin penetration force. J Micromech Microeng. 2010; 20(4): 045011.

13. Vora LK, Moffatt K, Donnelly RF, Larraneta E. Dissolving microneedle patches for intradermal vaccine delivery: Formulation, physicochemical characterisation and immunological evaluation. J Control Release. 2020; 316: 463–477.

14. Lee KJ, Jeong SS, Roh DH, Kim DY, Choi HC, Lee EH. A practical guide to the development of microneedle systems: From bench to clinic. J Pharm Investig. 2020; 50(5): 419–433.

15. Caffarel-Salvador E, Brady AJ, Eltayib E, Meng T, Alber-Llaneza A, Gonzalez-Vazquez P, et al. Hydrogel-forming microneedle arrays allow detection of drugs and glucose in vivo: Potential for use in Pharmacokinetic studies and Therapeutics. PLoS One. 2015; 10(11): e0145644.

16. Davis SP, Landis BJ, Adams ZH, Allen MG, and Prausnitz MR. Insertion of microneedles into skin: Measurement and prediction of insertion force and needle fracture force. J Biomech. 2004; 37(8): 1155–1163.

17. Lim SH, Ng JY, Kang L. Three-dimensional printing of a microneedle array on personalized curved surfaces for dual-pronged treatment of trigger finger. Biofabrication. 2017; 9(1): 015010.

18. Farias C, Lyman R, Hemingway C, Chau H, Mahayri A, Khoury S. 3D printing of microneedle arrays for drug delivery: Projection stereolithography versus fused deposition modeling. Front Bioeng Biotechnol. 2018; 6: 47.

19. Martanto W, Moore JS, Kashlan O, Kamath R, Wang PM, O'Neal JM. Microinfusion using hollow microneedles. Pharm Res. 2006; 23(1): 104–113.

20. Tezel A, Paliwal S, Shen Z, Mitragotri S. Low-to-medium frequency ultrasound for transdermal DNA delivery and expression. J Control Release. 2004; 98(1): 9–15.

21. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998; 392(6673): 245–252.

22. Quan FS, Kim YC, Vunnava A, Yoo DG, Song JM, Prausnitz MR. Intradermal vaccination with influenza virus-like particles by using microneedles induces protection superior to that with intramuscular immunization. J Virol. 2010; 84(15): 7760–7769.

23. Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): A randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet. 2017; 390(10095): 649–658.

24. Edens C, Collins ML, Goodson JL, Rota PA, Prausnitz MR. A microneedle patch containing measles vaccine is immunogenic in non-human primates. Vaccine. 2015; 33(37): 4712–4718.

25. Kim E, Erdos G, Huang S, Kenniston TW, Balmert SC, Carey CD . Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine. 2020; 55: 102743.

26. Demir YK, Akan Z, and Kerimoglu O. Characterization of polymeric microneedle arrays for transdermal drug delivery. PLoS One. 2013; 8(10): e77289.

27. Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D . Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proc Natl Acad Sci U S A. 2015; 112(27): 8260–8265.

28. Kim H, Park H, Lee SJ, Kim YC. Efficient skin penetration of lipid nanoparticles for mRNA delivery using microneedles. J Control Release. 2022; 352: 888–900.

29. Chen G, Chen Z, Wen D, Wang Z, Li H, Zeng Y. Transdermal cold atmospheric plasma-mediated immune checkpoint blockade therapy. Proc Natl Acad Sci U S A. 2020; 117(7): 3687–3692.

30. Yeh S, Bhatt P, Olsen TW, Bergstrom C, Mandell J, Weijtens M. Suprachoroidal injection of bevacizumab with a hollow microneedle: Early clinical experience. Retina. 2020; 40(9): 1843–1847.

31. Roy G, Garg P, Bhatt P. Microneedle-based delivery for glaucoma: A review. Drug Deliv Transl Res. 2022; 12(8): 1919–1930.

32. Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. Annu Rev Chem Biomol Eng. 2017; 8: 177–200.

33. Donnelly RF, Morrow DIJ, Singh TR, Migalska K, McCarron PA, O'Mahony C. Processing difficulties and instability of carbohydrate microneedle arrays. Drug Dev Ind Pharm. 2009; 35(10): 1242–1254.

34. Zhang Y, Hu Q, Fang Y, Gu Z. Liposome-microneedle patch for combinatorial photothermal-chemotherapy of tumors. ACS Nano. 2020; 14(12): 16180–16195.

35. DeMuth PC, Min Y, Huang B, Kramer JA, Miller AD, Barouch DH. Polymer multilayer tattooing for enhanced DNA vaccination. Nat Mater. 2013; 12(4): 367–376.

36. Ronnander P, Simon L, Koch A. Dissolving polyvinylpyrrolidone-based microneedle systems for transdermal delivery of lidocaine hydrochloride. Eur J Pharm Biopharm. 2019; 136: 261–269.

37. DeMuth PC, Su X, Samuel RE, Hammond PT, Irvine DJ. Nano-layered microneedles for transcutaneous delivery of polymer nanoparticles and plasmid DNA. Adv Mater. 2010; 22(43): 4851–4856.

38. Ye Y, Wang J, Hu Q, Hochu GM, Xin H, Wang C. Synergistic transcutaneous immunotherapy enhances antitumor immune responses through delivery of checkpoint inhibitors. ACS Nano. 2016; 10(9): 8956–8963.

39. Van der Maaden K, Jiskoot W, Bouwstra J. Microneedle technologies for (trans) dermal drug and vaccine delivery. J Control Release. 2012; 161(2): 645–655.

40. Birchall JC, Clemo R, Anstey A, John DN. Microneedles in clinical practice: An exploratory study into the opinions of healthcare professionals and the public. Pharm Res. 2011; 28(1): 95–106.

41. Hirobe S, Azukizawa H, Hanafusa T, Matsuo K, Quan YS, Kamiyama F. Clinical study and long-term safety of self-dissolving microneedle arrays for intradermal delivery of desmopressin. Drug Deliv. 2015; 22(3): 432–441.

42. Balmert SC, Carey CD, Falo GD, Sethi SK, Erdos G, Korkmaz E. Dissolving undercut microneedle arrays for multicomponent cutaneous vaccination. J Control Release. 2020; 317: 336–346.

43. Ita K. Transdermal delivery of drugs with microneedles: Strategies and outcomes. J Drug Deliv Sci Technol. 2015; 29: 16–23.

44. Food and Drug Administration. Drug products, including biological products that contain nanomaterials: Guidance for industry. Silver Spring: FDA; 2022.

45. Chen W, Tian R, Xu C, Yung BC, Wang G, Liu Y. Microneedle-array patches loaded with dual mineralized protein/peptide particles for type 2 diabetes therapy. Nat Commun. 2017; 8(1): 1777.

46. Larraneta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Mater Sci Eng R Rep. 2016; 104: 1–32.

47. Caudill CL, Perry JL, Tian S, Luft JC, DeSimone JM. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. J Control Release. 2018; 284: 122–132.

48. Olatunji O, Das DB, Garland MJ, Belaid L, Donnelly RF. Influence of array interspacing on the force required for successful microneedle skin penetration: Theoretical and practical approaches. J Pharm Sci. 2013; 102(4): 1209–1221.

49. Ghosh P, Pinninti RR, Hammell DC, Paudel KS, Stinchcomb AL. Development of a codrug approach for sustained drug delivery across microneedle-treated skin. J Pharm Sci. 2013; 102(5): 1458–1467.

50. Razzaghi-Asl N, Garrido J, Khataee H, Uriarte E, Firuzi O. Antioxidant properties of hydroxycinnamic acids: A review of structure–activity relationships. Curr Med Chem. 2013; 20(36): 4436–4450.

51. Kuwentrai C, Yu J, Rong L, Zhang BZ, Hu YF, Gong HR. Intradermal delivery of receptor-binding domain of SARS-CoV-2 spike protein with dissolvable microneedles to induce humoral and cellular responses in mice. Bioengineering (Basel). 2021; 8(11): 152.

52. Chen MC, Huang SF, Lai KY, Ling MH. Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination. Biomaterials. 2013; 34(12): 3077–3086.