

Chapter: 6 Microneedle Drug Delivery System: A Painless Revolution

Shreya Patel, Dhara Patel, Grishma Patel, Dhananjay Meshram

Department of Pharmaceutical Quality Assurance, Pioneer Pharmacy College, Nr. Ajwa crossing, Sayajipura, Vadodara-390019, Gujarat, India.

Abstract:

Abstract: This manuscript explores the forefront of innovator in microneedle-based drug delivery system. Microneedle arrays (MNA) are considered as a one of the most promising resource to achieve systemic effect boy transdermal delivery of drug. They are designed as a minimally invasive painless System which a bypass the stratum corneum, overcoming the potential drawbacks of subcutaneous injections of other transdermal delivery systems, such as chemical enhancers, nano p micro particles or physical treatments. The present work mainly emphasizes all the case studies reported from the past ten years that utilize MNS Containing therapeutics in the treatment -of chronic pain - associated disease like rheumatoid arthritis, neuropathic Pain, osteoarthritis, psoriatic arthritis of atopic dermatitis. This review intends to offer a general overview of current state of MNA research, focusing on strategies, applications, op types of molecules delivered recently by these systems. In addition, some Information about the fabrication technique., of mechanism of drug delivery, applications of advantages over traditional methods are in discussed. of challenges of limitations are discussed.

Keywords: Microneedle, Transdermal delivery, MNS- Micro Needle System, MNA- Micro Needle Array, Micro Fabrication, Close-Looped delivery.

6.1 Introduction

The oral route is the most frequently used for drug administration, due to its simplicity and low cost (specialized staff is not required). In addition, oral solid pharmaceutical forms (tablets, capsules) generally have good physicochemical stability and easy dosing. However, these formulations also face certain obstacles that may impair the bioavailability of the drug such as hepatic first pass effect, complex formation,

References

- 1. Aldawood FK, Andar A, Desai S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications. Polymers. 2021 Aug 22;13(16):2815.
- 2. Kaur R, Arora V. Advancements in microneedle-based drug delivery systems: A painless revolution in transdermal medicine. E3S Web of Conferences. 2024 Jan 1;509:02002–2.
- 3. Shi J, Votruba AR, Farokhzad OC, Langer R. Nanotechnology in Drug Delivery and Tissue Engineering: From Discovery to Applications. Nano Letters [Internet]. 2010 Sep 8 [cited 2020 Jan 4];10(9):3223–30.
- 4. Lim DJ, Kim HJ. Microneedles in Action: Microneedling and Microneedles-Assisted Transdermal Delivery. Polymers. 2022 Apr 15;14(8):1608.
- 5. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Advanced Drug Delivery Reviews [Internet]. 2012 Nov;64(14):1547–68.
- 6. Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug delivery system. Journal of Pharmacy and Pharmacology. 2011 Nov 4;64(1):11–29.
- 7. Larrañeta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Materials Science and Engineering: R: Reports. 2016 Jun;104:1–32.
- 8. Kumbhar PS, Jadhav TP, Chopade SS, Gavade TT, Sorate RC, Shinde TU, et al. Microneedles: An advanced approach for transdermal delivery of biologics. Asian Journal of Pharmaceutical Research. 2021 Jan 1;11(1):46–54.
- 9. Mahmood Razzaghi, Akbari M. The Effect of 3D Printing Tilt Angle on the Penetration of 3D-Printed Microneedle Arrays. Micromachines. 2023 May 30;14(6):1157–7.
- 10. Li Z, Li Y, Liu M, Cui L, Yu Y. Microneedle Electrode Array for Electrical Impedance Myography to Characterize Neurogenic Myopathy. Annals of Biomedical Engineering. 2015 Sep 25;44(5):1566–75.
- 11. Li YC, Feng SJ, Chen HX, Chen ZL, Zhang DM. Random vibration of train-track-ground system with a poroelastic interlayer in the subsoil. Soil Dynamics and Earthquake Engineering. 2019 May;120:1–11.
- 12. Alkilani A, McCrudden MT, Donnelly R. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. Pharmaceutics. 2015 Oct 22;7(4):438–70.
- 13. Wilke N, Mulcahy A, Ye SR ., Morrissey A. Process optimization and characterization of silicon microneedles fabricated by wet etch technology. Microelectronics Journal. 2005 Jul;36(7):650–6.

- 14. Wilke N, Hibert C, O'Brien J, Morrissey A. Silicon microneedle electrode array with temperature monitoring for electroporation. Sensors and Actuators A: Physical. 2005 Sep;123-124:319–25.
- 15. Lyu S, Dong Z, Xu X, Bei HP, Yuen HY, James Cheung CW, et al. Going below and beyond the surface: Microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration. Bioactive Materials [Internet]. 2023 Sep 1;27:303–26.
- 16. Chen Z, He J, Qi J, Zhu Q, Wu W, Lu Y. Long-acting microneedles: a progress report of the state-of-the-art techniques. Drug Discovery Today. 2020 Aug;25(8):1462–8.
- 17. Ita K. Ceramic microneedles and hollow microneedles for transdermal drug delivery: Two decades of research. Journal of Drug Delivery Science and Technology. 2018 Apr;44:314–22.
- 18. Chang H, Cui Y. Image Classification Algorithm Based on Big Data and Multilabel Learning of Improved Convolutional Neural Network. Wireless Communications and Mobile Computing. 2021 Jan 1;2021(1).
- 19. Boks MA, Wendy W.J. Unger, Engels S, Ambrosini M, Yvette van Kooyk, Luttge R. Controlled release of a model vaccine by nanoporous ceramic microneedle arrays. International Journal of Pharmaceutics. 2015 Aug 1;491(1-2):375–83.
- 20. Bystrova S, Luttge R. Micromolding for ceramic microneedle arrays. Microelectronic Engineering. 2011 Aug;88(8):1681–4.
- 21. Chen YT, Liao Y, Chen TT. Fabrication of arrayed microneedles by laser LIGA process(Laser processing). Proceedings of International Conference on Leading Edge Manufacturing in 21st century: LEM21. 2005;2005.1(0):285–90.
- 22. Yuan W, Sixing Yang, Yan Feng, Lijun Zhang, Nixiang Chen, Tuo Jin. A scalable fabrication process of polymer microneedles. International Journal of Nanomedicine. 2012 Mar;1415.
- 23. Zhang Y, Jiang G, Yu W, Liu D, Xu B. Microneedles fabricated from alginate and maltose for transdermal delivery of insulin on diabetic rats. Materials Science and Engineering: C. 2018 Apr;85:18–26.
- 24. Prausnitz MR. Microneedles for transdermal drug delivery. Advanced Drug Delivery Reviews. 2004 Mar;56(5):581–7.
- 25. Ji Yong Lee, Dae Hyun Kim, Lee K, Il Ho Seo, Seung Hyun Park, Eui Hwa Jang, et al. Transfer-molded wrappable microneedle meshes for perivascular drug delivery. Journal of Controlled Release. 2017 Dec 1;268:237–46.
- 26. Moga KA, Bickford LR, Geil RD, Dunn SS, Pandya AA, Wang Y, et al. Rapidly-Dissolvable Microneedle Patches Via a Highly Scalable and Reproducible Soft Lithography Approach. Advanced Materials. 2013 Jul 29;25(36):5060–6.
- 27. Lee MT, Lee I, Tsai SW, Chen C, Wu M, Juang Y. Spin coating of polymer solution on polydimethylsiloxane mold for fabrication of microneedle patch. Journal of The Taiwan Institute of Chemical Engineers. 2017 Jan 1;70:42–8.

- 28. McGrath MG, Vucen S, Vrdoljak A, Kelly A, O'Mahony C, Crean AM, et al. Production of dissolvable microneedles using an atomised spray process: Effect of microneedle composition on skin penetration. European Journal of Pharmaceutics and Biopharmaceutics. 2014 Feb;86(2):200–11.
- 29. Anto Vrdoljak, Allen EA, Ferrara F, Temperton NJ, Crean AM, Moore AC. Induction of broad immunity by thermostabilised vaccines incorporated in dissolvable microneedles using novel fabrication methods. Journal of controlled release. 2016 Mar 1;225:192–204.
- 30. Kim MJ, Park SC, Rizal B, Guanes G, Baek SK, Park JH, et al. Fabrication of Circular Obelisk-Type Multilayer Microneedles Using Micro-Milling and Spray Deposition. Frontiers in Bioengineering and Biotechnology. 2018 May 11;6.
- 31. Muzzalupo R, Tavano L. Niosomal drug delivery for transdermal targeting: recent advances. Research and Reports in Transdermal Drug Delivery. 2015 Jul;23.
- 32. Donnelly RF, Singh TRR, Woolfson AD. Microneedle-based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Delivery. 2010 Mar 18;17(4):187–207.
- 33. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Advanced Drug Delivery Reviews [Internet]. 2012 Nov;64(14):1547–68.
- 34. Nasiri MI, Vora LK, Ershaid JA, Peng K, Tekko IA, Donnelly RF. Nanoemulsion-based dissolving microneedle arrays for enhanced intradermal and transdermal delivery. Drug Delivery and Translational Research. 2021 Dec 22.
- 35. Prausnitz MR. Engineering Microneedle Patches for Vaccination and Drug Delivery to Skin. Annual Review of Chemical and Biomolecular Engineering. 2017 Jun 7;8(1):177–200.
- 36. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, et al. Microneedles: a Smart Approach and Increasing Potential for Transdermal Drug Delivery System. Biomedicine & Pharmacotherapy [Internet]. 2019 Jan;109:1249–58.
- 37. Ita K. Transdermal Delivery of Drugs with Microneedles—Potential and Challenges. Pharmaceutics [Internet]. 2015 Jun 29;7(3):90–105.
- 38. Sudhakar B, NagaJyothi K, Murthy KV. Nanosuspensions as a Versatile Carrier based Drug Delivery System An Overview. Current Drug Delivery. 2014 May 4;11(3):299–305.
- 39. Guillot AJ, Cordeiro AS, Donnelly RF, Montesinos MC, Garrigues TM, Melero A. Microneedle-Based Delivery: An Overview of Current Applications and Trends. Pharmaceutics. 2020 Jun 19;12(6):569.
- 40. Mahadevan G, Sheardown H, Ponnambalam Selvaganapathy. PDMS embedded microneedles as a controlled release system for the eye. Journal of Biomaterials Applications. 2012 Jan 19;28(1):20–7.
- 41. Patel S, Berezovsky DE, McCarey BE, Vladimir Zarnitsyn, Edelhauser HF, Prausnitz MR. Targeted Administration into the Suprachoroidal Space Using a

- Microneedle for Drug Delivery to the Posterior Segment of the Eye. Investigative Ophthalmology & Visual Science. 2012 Jul 1;53(8):4433–3.
- 42. Miquel-Clopés A, Bentley EG, Stewart JP, Carding SR. Mucosal vaccines and technology. Clinical and Experimental Immunology [Internet]. 2019 May 1 [cited 2021 Jan 6];196(2):205–14.
- 43. Belyakov IM, Derby MA, Ahlers JD, Kelsall BL, Earl PL, Moss B, et al. Mucosal immunization with HIV-1 peptide vaccine induces mucosal and systemic cytotoxic T lymphocytes and protective immunity in mice against intrarectal recombinant HIV-vaccinia challenge. 1998 Feb 17;95(4):1709–14.
- 44. Lee SE, Kim SY, Jeong BC, Kim YR, Bae SJ, Ahn OS, et al. A Bacterial Flagellin, Vibrio vulnificus FlaB, Has a Strong Mucosal Adjuvant Activity To Induce Protective Immunity. Infection and Immunity [Internet]. 2006 Jan [cited 2023 Jan 12];74(1):694–702.
- 45. B. Hasséus, M. Jontell, G. Bergenholtz, Dahlgren UI. T-cell costimulatory capacity of oral and skin epithelial cells in vitro: presence of suppressive activity in supernatants from skin epithelial cell cultures. European Journal Of Oral Sciences. 2004 Feb 1;112(1):48–54.
- 46. Creighton RL, Woodrow KA. Microneedle-Mediated Vaccine Delivery to the Oral Mucosa. Advanced Healthcare Materials. 2018 Dec 10;1801180.
- 47. Ma Y, Tao W, Krebs SJ, Sutton WF, Haigwood NL, Gill HS. Vaccine Delivery to the Oral Cavity Using Coated Microneedles Induces Systemic and Mucosal Immunity. Pharmaceutical research. 2014 Mar 13;31(9):2393–403.
- 48. Hye-Seung Seon-Woo, Kim HJ, Roh JY, Park JH. Dissolving Microneedle Systems for the Oral Mucosal Delivery of Triamcinolone Acetonide to Treat Aphthous Stomatitis. Macromolecular Research. 2018 Nov 9;27(3):282–9.
- 49. Duong HTT, Kim NW, Thambi T, Giang Phan VH, Lee MS, Yin Y, et al. Microneedle arrays coated with charge reversal pH-sensitive copolymers improve antigen presenting cells-homing DNA vaccine delivery and immune responses. Journal of Controlled Release. 2018 Jan;269:225–34.
- 50. Heathman TR, Nienow AW, McCall MJ, Coopman K, Kara B, Hewitt CJ. The translation of cell-based therapies: clinical landscape and manufacturing challenges. Regenerative Medicine. 2015 Jan;10(1):49–64.
- Ghaznavi A, Xu J, Lee CU, Hara SA. 3D-Printed Hollow Microneedles Array with Luer Lock Connection for Facile and Painless Intradermal Injection: A Proof of Concept. Advanced Materials Technologies. 2024 Jun 14;
- 52. King JN, Simpson BS, Overall KL, Appleby D, Pageat P, Ross C, et al. Treatment of separation anxiety in dogs with clomipramine: results from a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. Applied Animal Behaviour Science. 2000 Apr;67(4):255–75.

- 53. Kim E, Erdos G, Huang S, Kenniston TW, Balmert SC, Carey CD, et al. Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine. 2020 Apr;55(102743):102743.
- 54. Arya J, Prausnitz MR. Microneedle patches for vaccination in developing countries. Journal of Controlled Release [Internet]. 2016 Oct;240:135–41.
- 55. Gupta J, Felner EI, Prausnitz MR. Minimally Invasive Insulin Delivery in Subjects with Type 1 Diabetes Using Hollow Microneedles. Diabetes Technology & Therapeutics. 2009 Jun;11(6):329–37.
- 56. Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, et al. Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proceedings of the National Academy of Sciences [Internet]. 2015 Jun 22;112(27):8260–5.
- 57. Li W, Tang J, Terry RN, Li S, Brunie A, Callahan RL, et al. Long-acting reversible contraception by effervescent microneedle patch. Science Advances [Internet]. 2019 Nov 1 [cited 2021 May 5];5(11):eaaw8145.
- 58. Wang C, Ye Y, Hochu GM, Sadeghifar H, Gu Z. Enhanced Cancer Immunotherapy by Microneedle Patch-Assisted Delivery of Anti-PD1 Antibody. Nano Letters. 2016 Mar 24;16(4):2334–40.
- 59. Park Y, Park J, Chu GS, Kim KS, Sung JH, Kim B. Transdermal delivery of cosmetic ingredients using dissolving polymer microneedle arrays. Biotechnology and Bioprocess Engineering. 2015 Jun;20(3):543–9.
- 60. Marwah H, Garg T, Goyal AK, Rath G. Permeation enhancer strategies in transdermal drug delivery. Drug Delivery. 2014 Jul 9;23(2):564–78.
- 61. Kaushik S, Hord AH, Denson DD, McAllister DV, Smitra S, Allen MG, et al. Lack of Pain Associated with Microfabricated Microneedles. Anesthesia and Analgesia. 2001 Feb;502–4.
- 62. Seetharam AA, Choudhry H, Bakhrebah MA, Abdulaal WH, Gupta MS, Rizvi SMD, et al. Microneedles Drug Delivery Systems for Treatment of Cancer: A Recent Update. Pharmaceutics [Internet]. 2020 Nov 17 [cited 2022 Jan 26];12(11):1101.
- 63. Donnelly R, Douroumis D. Microneedles for drug and vaccine delivery and patient monitoring. Drug Delivery and Translational Research. 2015 Jul 30;5(4):311–2.
- 64. van der Maaden K, Jiskoot W, Bouwstra J. Microneedle technologies for (trans)dermal drug and vaccine delivery. Journal of Controlled Release. 2012 Jul;161(2):645–55.

- 65. Swain S, Pratap Singh A, Yadav RK. A review on polymer hydrogel and polymer microneedle based transdermal drug delivery system. Materials Today: Proceedings. 2021 Nov
- 66. Aich K, Singh T, Dang S. Advances in microneedle-based transdermal delivery for drugs and peptides. Drug Delivery and Translational Research. 2021 Sep 26
- 67. Alkilani A, McCrudden MT, Donnelly R. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. Pharmaceutics. 2015 Oct 22;7(4):438–70.
- 68. 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. Journal of controlled release. 2024 Apr 1;368:430–43.
- 69. Liu Y, Yang L, Cui Y. A wearable, rapidly manufacturable, stability-enhancing microneedle patch for closed-loop diabetes management. Microsystems & Nanoengineering [Internet]. 2024 Aug 19 [cited 2024 Oct 12];10(1).
- 70. Ikechukwu Adigweme, Yisa M, Ooko M, Edem Akpalu, Bruce A, Donkor S, et al. A measles and rubella vaccine microneedle patch in The Gambia: a phase 1/2, double-blind, double-dummy, randomised, active-controlled, age de-escalation trial. Lancet. 2024 Apr 1;403(10439).
- 71. Kohlhepp P, Harb H, Wolisz H, Waczowicz S, Müller D, Hagenmeyer V. Large-scale grid integration of residential thermal energy storages as demand-side flexibility resource: A review of international field studies. Renewable and Sustainable Energy Reviews. 2019 Mar;101:527–47.
- 72. Pollard AJ, Bijker EM. A Guide to vaccinology: from Basic Principles to New Developments. Nature Reviews Immunology [Internet]. 2020;21(21):1–18.
- 73. Nadeem AY, Adeeb Shehzad, Mazhar Ul-Islam, khan S, Al-Suhaimi EA, Noor A. Transdermal Glucose Responsive Composite Polymeric Microneedle Patches for Personalized Diabetes Treatment: A Novel Approach to Precision Medicine. 2025 Jan 1
- 74. García-Guzmán JJ, Pérez-Ràfols C, Cuartero M, Crespo GA. Microneedle based electrochemical (Bio)Sensing: Towards decentralized and continuous health status monitoring. TrAC Trends in Analytical Chemistry. 2021 Feb;135:116148.
- 75. Indermun S, Luttge R, Choonara YE, Kumar P, du Toit LC, Modi G, et al. Current advances in the fabrication of microneedles for transdermal delivery. Journal of Controlled Release. 2014 Jul;185:130–8.
- 76. Ates HC, Nguyen PQ, Gonzalez-Macia L, Morales-Narváez E, Güder F, Collins JJ, et al. End-to-end design of wearable sensors. Nature Reviews Materials. 2022 Jul 22;7.
- 77. Yetisen AK, Martinez-Hurtado JL, Ünal B, Khademhosseini A, Butt H. Wearables in Medicine. Advanced Materials. 2018 Jun 11;30(33):1706910.

- 78. Li W, Tang J, Terry RN, Li S, Brunie A, Callahan RL, et al. Long-acting reversible contraception by effervescent microneedle patch. Science Advances [Internet]. 2019 Nov 1;5(11):eaaw8145
- 79. Wei M, Gao Y, Li X, Serpe MJ. Stimuli-responsive polymers and their applications. Polymer Chemistry [Internet]. 2016 Dec 20 [cited 2020 May 20];8(1):127–43.
- 80. Zhang X, Chen G, Yu Y, Sun L, Zhao Y. Bioinspired Adhesive and Antibacterial Microneedles for Versatile Transdermal Drug Delivery. 2020 May 8;2020.
- 81. Vora LK, Moffatt K, Tekko IA, Paredes AJ, Volpe-Zanutto F, Mishra D, et al. Microneedle array systems for long-acting drug delivery. European Journal of Pharmaceutics and Biopharmaceutics [Internet]. 2021 Feb 1 [cited 2022 May 4];159:44–76.
- 82. Sargioti N, Levingstone TJ, O'Cearbhaill ED, McCarthy HO, Dunne NJ. Metallic Microneedles for Transdermal Drug Delivery: Applications, Fabrication Techniques and the Effect of Geometrical Characteristics. Bioengineering. 2022 Dec 23;10(1):24.
- 83. Fonseca DFS, Costa PC, Almeida IF, Dias-Pereira P, Correia-Sá I, Bastos V, et al. Swellable Gelatin Methacryloyl Microneedles for Extraction of Interstitial Skin Fluid toward Minimally Invasive Monitoring of Urea. Macromolecular Bioscience. 2020 Aug 17;20(10):2000195.
- 84. Tuan-Mahmood TM, McCrudden MTC, Torrisi BM, McAlister E, Garland MJ, Singh TRR, et al. Microneedles for intradermal and transdermal delivery. European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences [Internet]. 2013 Dec 18 [cited 2020 Aug 23];50(5):623–37.
- 85. Jiang X, Lillehoj PB. Microneedle-based skin patch for blood-free rapid diagnostic testing. Microsystems & Nanoengineering [Internet]. 2020 Nov 2 [cited 2021 Jun 1];6(1):1–11.