World Journal of
Drug Delivery

IDAAM Publications

World J Drug Deliv 2023; 1(1): 23-27

REVIEW ARTICLE

Overview on microneedle based vaccine delivery system

MAYUR U JOSHI, JAMEEL AHMED S MULLA*

Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Dist: Satara, Maharashtra – 415111

***Author for Correspondence:** *Email:* jameelahmed5@rediffmail.com

ARTICLE DETAILS

Article history:
Received on 2 August 2022
Modified on 17 September 2022
Accepted on 20 September 2022

Keywords:
Vaccine Delivery,
Micro-needles,
Pathogenic.

ABSTRACT

Vaccination is without a doubt the most efficient disease preventive and eradication health measure. Nonetheless, there is still a need to improve immunization coverage over the world. The utilisation of delivery vehicles capable of producing an effective immune response while also improving stability, safety, and cost effectiveness is a viable technique for achieving this aim today. Vaccination with MN devices addresses the skin's complex immune system, resulting in greater antigen utilisation and a stronger immunological response, generally with a smaller vaccination dose than with traditional delivery methods. Despite the numerous benefits and nearly four decades of research, there are now only a few licenced MN-based vaccinations available. This article focuses on types of microneedles for vaccine delivery, advantages and disadvantages and evaluation of microneedles.

INTRODUCTION

Most current human vaccines are still delivered using a hypodermic needle. With a few rare exceptions, such as oral polio vaccine or intranasal influenza vaccine, traditional intramuscular or subcutaneous injection is still the preferred route of application, even for novel vaccines. This is not due to a lack of alternative approaches – quite the contrary [1]. A number of alternative needle-free vaccine delivery platforms have been suggested over the past few decades. The long list includes edible vaccines, various physical methods for delivery of DNA-based vaccines (gene gun, electroporation, and ultrasound), high-velocity powder and liquid-jet injection, diffusion-based patches combined with skin abrasion/ablation and chemical enhancers, microneedles (MNs), and others [2]. Vaccines mimic infections and utilize the immune system to produce immunity against the invading pathogen without succumbing to the pathogenesis of the disease. Traditionally, vaccines fall into three groups: whole pathogen vaccine, subunit vaccine, and nucleic acid vaccine [3]. To begin, there are different forms of whole pathogen vaccines; live attenuated vaccines are a sort of whole pathogen vaccination that uses a weakened version of the pathogen to produce immunity while preventing the disease from occurring. Inactivated vaccinations are complete pathogen vaccines that use chemical or high-temperature procedures to inactivate the pathogen. Second, to produce immunity, subunit vaccines concentrate on isolating and purifying certain components from the pathogen (or synthetic synthesis). Finally, nucleic acid vaccines include injecting genetic material, such as plasmid DNA or messenger RNA that encodes for antigens [4]. Scientists can now make microneedles out of a variety of materials, with a variety of geometries and sizes, and with or without a bore. Microneedles have been used to deliver (trans) dermal drugs and collect biological samples via the skin. The capacity of microneedles to pierce the skin in a non-invasive and painless manner is their main benefit. Microneedles can also be used in "lab-on-a-chip" systems, which combine hollow microneedles with either microsensors or micropumps, or both. Such methods can be used to track the progress of diseases like diabetes. The ultimate goal of "lab-on-a-chip" techniques is to develop minimally invasive, completely automated modules for continuously extracting and

analysing biological fluid and directly responding to analytical results with drug delivery [5-7]. The use of MN-based technologies for vaccine distribution has sparked a lot of interest recently, thanks to improvements in both skin immunology and microelectronics, which allow for the manufacturing of such micron-scale devices. In 1976, the idea of submillimeter needle-shaped objects piercing through the outermost layers of the skin and increasing their permeability thousands of times without triggering the underlying nerve endings and generating pain was initially proposed [8].

Advantages of Micro-needle Based Vaccines [9]

Pain-Free Administration: Microneedles with a length of a few hundred micrometres could particularly pierce the superficial layers of the skin with a low density of nerve receptors. As a result, it is believed that the insertion of microneedles into the skin will be painless.

Easy to Use: In the case of a traditional transdermal patch, the patient might theoretically install the intended system without any training. Furthermore, no special tool or process parameters are necessary to achieve this unique insertion. As a result, microneedles demand low insertion strength as well as a steady and forceful insertion technique. If this is accomplished, it is reasonable to assume that the process for a variety of medications can be sold over the counter (OTC).

Discreetness: Incorporating a microneedle-array along with a planar and compact medicating method yields a patch-like discreet device which could be slightly worn beneath the clothing.

Continuous Release: A non-obstructing device might be worn for larger time duration, hence allowing uninterrupted and constant delivery at therapeutic levels.

Controlled Release: The use of passive components; such as flow restrictors or flow membranes, as well as active devices such as closed loop systems, can help to control medication release. The use of active dosing devices allows for modulation of dosage based on time and amplitude.

Safer Handling: When compared to hypodermic needles, microneedles expanded for a few hundred micrometres from the surface have a much lower chance of unintended needle sticking. Because microneedles cannot reach the blood, the risk of transmission of blood-borne diseases is very low.

Disadvantages of Micro-needle Based Vaccines [10]:

- Dosage precision may be compromised.
- It is feasible to provide merely a little amount of a medicine.
- There's a chance you'll become irritated on your skin.
- The needle may break and remain intact in the skin after the patch is removed.
- The external environment can influence delivery, such as skin moisture.
- Hollow MNs can be blocked by compressed dermal tissues.

Characteristics for an Ideal Vaccine [11]:

- The vaccination should be non-toxic or non-pathogenic, implying that it is risk-free.
- In the case of healthy people, the risk of adverse effects should be quite low.
- Individuals with a compromised immune system should not have any issues as a result of this.
- There should be no infection spread among those who have been vaccinated or who have received a live vaccination.
- It should result in both humoral and cellular immunity that last for a long time.
- The immunisation process must be simple.
- The vaccine must be affordable.
- It is not allowed to infect the environment.
- It is necessary for the vaccine to be effective.

Types of Microneedles:

The primary goal of MNs is to penetrate the skin, via microprojections without causing any nerve damage, hence improving patient comfort and ensuring patient safety. Microneedles are divided into many varieties based on a variety of factors such as drug delivery techniques, materials, and structures.

1. Solid MNs [12-13]

Solid MNs were initially produced in 1998 and were used to create pores in the skin using pointed needle ends. Passive diffusion is the mechanism that allows medications to be delivered through solid MNs. Solid MNs are made of glass, metals, silicon, and other nondegradable

polymers and are simple to make. Multiple medicines, such as captopril and metoprolol tartrate, were delivered more effectively using stainless steel MN arrays because they bypassed the skin's principal barrier, the stratum corneum.

2. Dissolving MNs [14-16]

The medicine is encapsulated in the matrix by the dissolving MNs, which are entirely made up of sugars or polymers. These MNs are made from biodegradable polymers. After injection into the skin, the drug dissolves, followed by the release of the drug. These MNs are used for long-term therapy and help patients stay on track. Chen and his team created tip-dissolving MNs that demonstrated efficient and quick medication administration without producing skin irritation. These MNs were created to be used in vaccinations (e.g., influenza, insulin).

3. Hollow MNs [17]**:**

Hollow MNs are commonly utilized for illness diagnosis and monitoring. Diffusion, osmosis, capillary action, and external negative pressure are some of the processes that can be used to deliver a medicine. Single crystal silicon is used to fabricate these MNs. These are effective in delivering bolus insulin for type 1 diabetic treatment, and insulin absorption is quick.

4. Coated MNs [18]**:**

Coated MNs have a drug solution coating on the needles, which allows the medicine to be released after insertion into the skin. Spray coating, dip coating, and roller delivery of parathyroid hormones for osteoporosis treatment are all methods of coating.

5. Hydrogel-forming MNs [19, 20]**:**

Super swelling polymers that can absorb a large amount of water are used in a new type of MN. It's also known as in situ MNs, because it requires cross-linking the polymer in a dry hydrogel condition. When the polymer is injected into the skin, it expands by absorbing water from the interstitial fluid. The enlarged network forms conduits and serves as a reservoir, from which the medication is discharged and enters the circulation. It also regulates the delivery of MNs in the skin and keeps them solid. Polysaccharides, polymers such as poly(ethylene glycol) diacrylate (PEGDA) and polyvinyl alcohol (PVA), and poly(acrylicacid-co-maleic) acid are among the materials employed in the fabrication. The ability of hydrogel MNs to deliver a high dosage of medicinal drugs is dependent on their swelling capabilities.

Evaluation of MNs:

1. Visual Characterization Methods [21-30]

The insertion or penetration behaviour of MNs can be affected by their geometry. Optical or electrical microscopy and visual inspection were used to analyse the geometry and measurement of tip radius, height, and length. To obtain 3D images, a confocal laser microscope and scanning electron microscopy (SEM) were employed, which aids in quality control. SEM offers information on surface topography and composition. Fluorescence-labeled molecules were used to identify molecules integrated in MNs, which were then observed using visual inspection, fluorescent microscopy, and confocal laser scanning microscopy.

2. Mechanical Properties [31]

The microneedle material's hardness and Young's modulus values can be measured via nanoindentation. The materials were analysed using a Berkovich-type tip, and a Ubi-1 Nanoindenter will be employed for this work. For each test, a loading duration of 20 seconds, a dwell time of 10 seconds at maximum load, and an unloading time of 20 seconds were used. The highest force was 1000 N. The unloading curves' Oliver-Pharr analysis was used to determine the hardness and Young's modulus values.

3. *In Vitro* Permeation Studies [32-36]

The Franz diffusion cell device can be used to determine drug penetration into the skin. Pig ear skin is frequently employed in the test by sandwiching it between the receptor and donor compartments. The cumulative amount of drug release as a function of time for MN treated, and untreated skin was displayed using drug penetration profiles.

4. *In Vivo* Studies [37]

In vivo investigations using hairless rat animal models are conducted using the various rebuilt skin models. One of the characteristics monitored by the DelfinVapoMeter is transepidermal water loss.

5. *In Vitro/In Vivo* Correlation Studies [38]

In the *in vitro-in vivo* correlation investigation, hairless pig skin was placed on a Franz diffusion cell, the pH and temperature of the dissolving media was kept constant to mimic *in vivo* conditions, and the drug penetration profile was

studied *in vitro*. As a result, the *in vitro* study's parameters and settings corresponded to the *in vivo* investigation.

CONCLUSION

Over the last 15 years, the field of microneedles has exploded. Micro-fabrication has allowed for a wide range of microneedle designs for drug administration to the skin and other locations. Microneedles have been made out of a range of materials, including silicon, metals, polymers, and ceramics, utilising lithography, wet and dry etching, laser cutting, and micromolding, among other techniques. Because of their increased permeability, microneedles have been used as a medication carrier, resulting in higher bioavailability and patient compliance. This strategy has also been used for vaccine distribution, although the success of the microneedle approach is determined by the manufacture of the device for infusion into the skin, the formulation's stability, and the storage conditions necessary.

REFERENCES

[1] Saroja C, Lakshmi P, Bhaskaran S. Recent trends in vaccine delivery systems: a review. Int J Pharm Investig. 2011; 1(2):64–74.

[2] Anto Vrdoljak. Review of recent literature on microneedle vaccine delivery technologies. Vaccine: Development and Therapy 2013:3 47–55.

[3] Lycke, N. Recent progress in mucosal vaccine development: Potential and limitations. Nat. Rev. Immunol. 2012, 12, 592–605.

[4] Menon, I.; Bagwe, P.; Gomes, K.B.; Bajaj, L.; Gala, R.; Uddin, M.N.; D'Souza, M.J.; Zughaier, S.M. Microneedles: A New Generation Vaccine Delivery System. Micromachines 2021, 12, 435.

[5] H.J.G.E. Gardeniers, R. Luttge, E.J.W. Berenschot, M.J.D. Boer, S.Y. Yeshurun, M. Hefetz, R.V.T. Oever, A.V.D. Berg, Silicon micromachined hollow microneedles for transdermal liquid transport, J. Microelectromech. Syst. 12 (3) (2003) 855–862.

[6] J.G.E. Gardeniers, A.v.d. Berg, Lab-on-a-chip systems for biomedical and environmental monitoring, Anal. Bioanal. Chem. 378 (2004) 1700–1703.

[7] H.W. Vesper, P.M. Wang, E. Archibold, M.R. Prausnitz, G.L. Myers, Assessment of trueness of a glucose monitor using interstitial fluid and whole blood as specimen matrix, Diabetes Technol. Ther. 8 (1) (2006) 76–80.

[8] Kang SM, Song JM, Kim YC. Microneedle and mucosal delivery of influenza vaccines. *Expert Rev Vaccines*. 2012; 11(5):547–560.

[9] Gill, H.S., Prausnitz, M.R (2007). Coated microneedles for transdermal delivery. *J Control Release*, 117(2), 227–237.

[10] Frerichs DM, Ellingsworth LR, Frech SA, et al. Controlled, single-step, stratum corneum disruption as a pretreatment for immunization via a patch. *Vaccine*. 2008; 26(22):2782–2787.

[11] Suh, H., Shin,J (2014). Microneedle patches for vaccine delivery. *Clin Exp Vaccine Res*, 3, 42–49.

[12] Ali R, Mehta P, Arshad MS, Kucuk I, Chang MW, Ahmad Z: Transdermal microneedles-a materials perspective. AAPS PharmSciTech 2019; 21:1–14.

[13] Sachdeva V, Banga AK: Microneedles and their applications. Recent Pat DrugDelivFormul 2011; 5:95–132.

[14] Giri Nandagopal MS, Antony R, Rangabhashiyam S, Sreekumar N, Selvaraju N: Overview of microneedle system: a third generation transdermal drug delivery approach. Microsyst Technol 2014; 20:1249–1272.

[15] Bariya SH, Gohel MC, Mehta TA, Sharma OP: Microneedles: an emergingtransdermal drug delivery. J Pharm Pharmacol 2012; 64:11–29.

[16] Kim YC, Park JH, Prausnitz MR: Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev 2012; 64:1547–1568.

[17] Wermeling DP, Banks SL, Hudson DA, et al.: Microneedles permit transdermal delivery of a skin-impermeant medication to humans. Proc Natl Acad Sci USA 2008; 105:2058–2063.

[18] Matriano JA, Cormier M, Johnson J, et al.: Macro flux micro-projection array patch technology: a new and intra-cutaneous immunization. Pharm Res 2002; 19:63–70.

[19] Nagarkar R, Singh M, Nguyen HX, Jonnalagadda S: A review of recent advances in microneedle technology for transdermal drug delivery. J Drug Deliv Sci Tech 2020; 59:1–18.

[20] Sharma S, Hatware K, Bhadane P, Sindhikar S, Mishra DK: Recent advances in microneedle composites for biomedical applications: advanced drug delivery

technologies. Mater SciEng C 2019; 103: 1–14.

[21] Sabri AH, Kim Y, Marlow M, et al.: Intradermal and transdermal drug delivery using microneedles—fabrication, performance evaluation and application tolymphatic delivery. Adv Drug Deliv Rev 2020; 153: 195–215.

[22] Zhao X, Li X, Zhang P, Du J, Wang Y: Tip-loaded fast-dissolving microneedle patches for photodynamic therapy of subcutaneous tumor. J Control Release2018; 286: 201–209.

[23] Mulla JA, Mabrouk M, Choonara YE, Kumar P, Chejara DR, du Toit LC, Pillay V. Development of respirable rifampicin-loaded nano-lipomer composites by microemulsion-spray drying for pulmonary delivery. Journal of Drug Delivery Science and Technology. 2017 Oct 1; 41: 13-9.

[24] Mabrouk M, Mulla JA, Kumar P, Chejara DR, Badhe RV, Choonara YE, du Toit LC, Pillay V. Intestinal targeting of ganciclovir release employing a novel HEC-PAA blended lyomatrix. AapsPharmscitech. 2016 Oct; 17(5):1120-30.

[25] Mabrouk M, Chejara DR, Mulla JA, Badhe RV, Choonara YE, Kumar P, Du Toit LC, Pillay V. Design of a novel crosslinked HEC-PAA porous hydrogel composite for dissolution rate and solubility enhancement of efavirenz. International journal of pharmaceutics. 2015 Jul 25; 490(1-2):429-37.

[26] Chejara DR, Mabrouk M, Badhe RV, Mulla JA, Kumar P, Choonara YE, du Toit LC, Pillay V. A bio-injectable algin-aminocaproic acid thixogel with tri-stimuli responsiveness. Carbohydrate polymers. 2016 Jan 1; 135: 324-33.

[27] Mulla JA, Khazi MI, Khan AY, Gong YD, Khazi IA. Design, Characterization and In vitro Evaluation of Imidazo [2, 1-b][1, 3, 4] thiadiazole Derivative Loaded Solid Lipid Nanoparticles. Drug Invention Today. 2012 Aug 1; 4(8).

[28] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011 Jun; 344(6):358-65.

[29] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.

[30] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and in vitro evaluation of methotrexate solid lipid nanoparticles. Research J. Pharm. and Tech. 2009 Oct;2(4):685-9.

[31] Azizi Machekposhti S, Nguyen AK, Vanderwal L, Stafslien S, Narayan RJ. Micromolding of Amphotericin-B-Loaded Methoxyethylene–Maleic Anhydride Copolymer Microneedles. Pharmaceutics. 2022 Jul 26; 14(8):1551.

[32] Uppuluri C, Shaik AS, Han T, et al.: Effect of microneedle type on transdermal permeation of rizatriptan. AAPS PharmSciTech 2017; 18: 1495–1506.

[33] Mulla JS, Khazi IM, Sharma NK. Solid Lipid Nanoparticles: Measures of Characterization. Indian Journal of Novel Drug delivery. 2011; 3(4): 259-264.

[34] Mulla JS, Khazi IM, Sharma NK, Hiremath SP, Jamakandi VG. Solid Lipid Nanoparticles: Methods of Preparation. Indian Journal of Novel Drug delivery. 2011; 3(3): 170-175.

[35] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011 Jun; 344(6):358-65.

[36] Mulla JS, Khazi IM, Jamakandi VG. Solid lipid nanoparticles: Potential Applications. Indian Journal of Novel Drug Delivery. 2010; 2(3): 82-87.

[37] Sasaki GH. The Significance of trans-epidermal water loss after microneedling and microneedling radiofrequency procedures: Histological and IRB-Approved Safety Study. Aesthet Surg J Open Forum. 2019 Jul 30; 1(3):ojz017.

[38] Neupane R, Boddu SHS, Renukuntla J, Babu RJ, Tiwari AK. Alternatives to Biological Skin in Permeation Studies: Current Trends and Possibilities. Pharmaceutics. 2020 Feb 13; 12(2):152.