

## Trans(Dermal) Microneedles in Diabetes Therapy

Md Jasim Uddin\*

Department of Pharmacy, Southern University Bangladesh, Chittagong 4000, Bangladesh

### ABSTRACT

Microneedle (MN) is the latest generation of transdermal drug delivery system composed of micron-sized needles for the delivery of a wide range of biopharmaceuticals. In the recent era, MN provides a great flexibility toward the development of non-invasive insulin therapy by enhancing the transport of drug across the barrier stratum corneum. MN-mediated insulin delivery is not only overcome the limitations of conventional injections also provide steady-state plasma concentration for diabetes therapy. This editorial discusses the possibility of insulin-loaded MN product for the future diabetes therapy in relation to their patient acceptability.

**Key words:** Diabetes, insulin, microneedle

Protein and peptides delivery have been introduced in different chronic disease conditions. Most of these drugs are still introduced by the parenteral routes for their rapid bioavailability than other routes. Among these proteins and peptides, insulin is one of the major concentrations for therapy, isolated from bovine pancreas in 1922 by Frederick Banting and Charles Best (Nobel Prize for Medicine with John McLeod in 1923).<sup>[1]</sup>

Microneedle (MN)-mediated insulin delivery is a familiar method that has been studied by many researchers in recent time. For the first time, Martanto *et al.*<sup>[2]</sup> designed and fabricated arrays of metallic MN array for the delivery of insulin in diabetic hairless rats. In this experiment, it was indicated that MN could improve skin delivery of insulin at a required amounts for 4 h. The results suggested that shorter insertion was beneficial to avoid local damage to the skin by multiple insertions. This might defend the large molecules to enter into the deeper tissue by passive diffusion. In the next year similar research group,<sup>[3]</sup> designed, fabricated, and tested persistent and constant delivery of insulin *in vivo* using hollow MN array. They figured out three challenges related to this research works: (1) MN geometry and material should penetrate into the skin without break it off; (2) It should support rapid scale-up for continuous manufacturing; and (3) MN should capable of delivering reasonable amounts of insulin into the body. It was also noted that biocompatibility and lack of pain during administration were also taken into consideration for the development of MN-loaded insulin product. The study suggested that urethane might have

lessened the blood glucose level. The improved delivery was explained by a stronger pharmacodynamic response to insulin delivered from MNs near the capillary loops at the dermal-epidermal junction compared to insulin injected with a hypodermic needle into the subcutaneous space.

In another approach, a piezoelectric attached to a silicon MN array was designed by Ma *et al.*<sup>[4]</sup> for the delivery of insulin. This device was recommended as it did not damage pharmaceutical active ingredient and release of toxic material. This system was small, precise, and accurate than mechanical pump for fluid sampling. As a novel approach, Nordquist *et al.*<sup>[5]</sup> designed to confirm painless intradermal delivery by attaching a drug dispenser with insulin pump. Unfortunately, this therapy did not meet the patients' demands as a painless, discreet, and easy-to-use treatment regimen.

As a new technology, Zhou *et al.*<sup>[6]</sup> performed a study on the delivery efficiency of insulin using commercially available MN rollers (250, 500, and 1000  $\mu\text{m}$  in length) into diabetic rats. It was observed that different MN length showed slight differences in blood glucose regulation due to the insulin is hydrophilic, but stratum corneum has a phospholipid bilayer. Nevertheless, the researchers suggested that the 250 and 500  $\mu\text{m}$  MN rollers can pierce the skin during manual application and are the most promising tools for *in vivo* delivery of insulin.

2 years later McVey *et al.*<sup>[7]</sup> managed to improve insulin pharmacokinetics through intradermal route. Basically, this research group compared the pharmacokinetic and pharmacodynamic effects of insulin lispro administered prior two daily meals, employing MN-based intradermal or subcutaneous delivery. The results recommended that there is three-fold increase in insulin delivery, would be beneficial to patient and future scientist.

\*Corresponding author:

Email: dr.jasim@southern.edu.bd

<http://dx.doi.org/10.20530/IJPRI427>  
ISSN 2046-5114 © 2017

Recently, Liu *et al.*<sup>[8]</sup> developed a novel insulin-loaded MN arrays prepared from hyaluronic acid that possesses some advantages such as biocompatible, strong mechanical strength, hydrophilic material, and did not change the stability of insulin. *In vivo* findings indicated that insulin was quickly released (1 h) from MN overcoming the biocompatibility issues of silicon and metal MN. However, the overall conclusion suggested that the degree of the glucose regulation could be maintained by optimizing the amount of insulin-loaded in the novel MNs. Further, Qiu *et al.*<sup>[9]</sup> developed a lyophilized hydrogel system for MN-mediated insulin delivery. Hydrogel could be a better option for insulin delivery as it improved contact with skin. The results revealed that lyophilized system helped to maintain a sustained and steady-state insulin release for 8 h.

As a different approach, Qiu *et al.*<sup>[10]</sup> compared the immunogenicity of insulin between the MN-mediated delivery and subcutaneous injection. MN supported the increased immunogenicity of insulin delivery due to the rich number of immune cells in epidermal region. The investigation also suggested that MN can be an excellent technology to evaluate the immunogenicity of biological macromolecules like insulin. Clinical studies for hollow MN have been tested by Norman *et al.*<sup>[11]</sup> in children and adolescents with type 1 diabetes mellitus. MN-mediated insulin delivery achieved rapid onset of action that might result in ultrafast insulin uptake. This study was limited by small sample size with limited demographic and single injection timeframe. However, additional studies were suggested for improving the matters related to long-term safety, tolerability, compliance, and glycemia control.

In 2013, Ling and Chen<sup>[12]</sup> stated that the insulin-loaded starch/gelatin MN patches fabricated to determine the delivery efficiency *in vivo*. Insulin-loaded MN confirms a peak plasma concentration at 2 h after administration. A remarkable finding concluded that insulin can be encapsulated in the polymeric MNs to serve as a solid-state formulation. It was strongly recommended that the dissolving MN system will reduce the cost for cold chain storage and transportation provide more flexibility and convenience in use and packaging. A novel inkjet printing technology<sup>[13]</sup> was employed by Ross *et al.*<sup>[14]</sup> for the delivery of insulin on metallic MN. The coatings were more accurate and precise those overcome the limitations of conventional coating techniques for MN. The experimental findings suggested that solid-state delivery through inkjet-printed MN can be possible for diabetic therapy.

In 2017, Lee *et al.*<sup>[15]</sup> have presented a dissolvable polyvinylpyrrolidone (PVP)-based MN for the rapid delivery of encapsulated insulin. MN composed of PVP extended the half-life of the drug by binding to plasma proteins and helped in blood glucose level control.

Nevertheless, PVP had the longest circulation time with restricted tissue distribution.

Moreover, there is a rapid increasing in number of MN-mediated transdermal products for commercial development. Ultimately, MN-mediated insulin delivery can be an excellent alternative to hypodermic injections to deliver drugs across the skin. However, there are diverse challenges for the development of MN products but can be overcome by pre-formulation approaches and selection of appropriate analytical techniques can drive to successful MN product for personalized medicine.

## REFERENCES

1. Khafagy el-S, Morishita M, Onuki Y, Takayama K. Current challenges in non-invasive insulin delivery systems: A comparative review. *Adv Drug Deliv Rev* 2007;59:1521-46.
2. Martanto W, Davis SP, Holiday NR, Wang J, Gill HS, Prausnitz MR, *et al.* Transdermal delivery of insulin using microneedles *in vivo*. *Pharm Res* 2004;21:947-52.
3. Davis SP, Martanto W, Allen MG, Prausnitz MR. Hollow metal microneedles for insulin delivery to diabetic rats. *IEEE Trans Biomed Eng* 2005;52:909-15.
4. Ma B, Liu S, Gan Z, Liu G, Cai X, Zhang H, *et al.* A PZT insulin pump integrated with a silicon microneedle array for transdermal drug delivery. *Microfluid Nanofluidics* 2006;2:417-23.
5. Nordquist L, Roxhed N, Griss P, Stemme G. Novel microneedle patches for active insulin delivery are efficient in maintaining glycaemic control: An initial comparison with subcutaneous administration. *Pharm Res* 2007;24:1381-8.
6. Zhou CP, Liu YL, Wang HL, Zhang PX, Zhang JL. Transdermal delivery of insulin using microneedle rollers *in vivo*. *Int J Pharm* 2010;392:127-33.
7. McVey E, Hirsch L, Sutter DE, Kapitza C, Dellweg S, Clair J, *et al.* Pharmacokinetics and Postprandial Glycemic Excursions following Insulin Lispro Delivered by Intradermal Microneedle or Subcutaneous Infusion. *J Diabetes Sci Technol* 2012;6:743-54.
8. Liu S, Jin MN, Quan YS, Kamiyama F, Katsumi H, Sakane T, *et al.* The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. *J Control Release* 2012;161:933-41.
9. Qiu Y, Qin G, Zhang S, Wu Y, Xu B, Gao Y, *et al.* Novel lyophilized hydrogel patches for convenient and effective administration of microneedle-mediated insulin delivery. *Int J Pharm* 2012;437:51-6.
10. Qiu Y, Gao Y, Zhang S, Guo L, Chen J, Xu B, *et al.* Immunological effects of microneedle-mediated insulin delivery: Preliminary rat studies. *Int J Pharm* 2013;444:103-5.
11. Norman JJ, Brown MR, Raviele NA, Prausnitz MR, Felner EI. Faster pharmacokinetics and increased patient acceptance of intradermal insulin delivery using a single hollow microneedle in children and adolescents with Type 1 diabetes. *Pediatr Diabetes* 2013;14:459-65.
12. Ling MH, Chen MC. Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. *Acta Biomater* 2013;9:8952-61.

13. Uddin MJ, Scoutaris N, Klepetsanis P, Chowdhry B, Prausnitz MR, Douroumis D, *et al.* Inkjet printing of transdermal microneedles for the delivery of anticancer agents. *Int J Pharm* 2015;494:593-602.
14. Ross S, Scoutaris N, Lamprou D, Mallinson D, Douroumis D. Inkjet printing of insulin microneedles for transdermal delivery. *Drug Deliv Transl Res* 2015;5:451-61.
15. Lee IC, Wu YC, Tsai SW, Chen CH, Wu MH. Fabrication of two-layer dissolving polyvinylpyrrolidone microneedles with different molecular weights for *in vivo* insulin transdermal delivery. *RSC Adv* 2017;7:5067-75.