



# MICRONEEDLES AS A TRANSFORMATIVE TECHNOLOGY IN DRUG DELIVERY

Here, Kris Hansen, PhD, MTS Technology & Product Development Manager, 3M Drug Delivery Systems Division, makes the case for microneedles as a potentially transformative drug delivery system, with applications across a variety of therapeutic areas and in multiple types of drug molecule. Dr Hansen highlights particular potential applications in: enhancing the efficacy of vaccines, increasing the efficiency of biotherapeutics and, as a more acceptable alternative to needle-based delivery systems, improving patient adherence and outcomes.

The potential for intradermal delivery to improve the efficacy of certain drugs was recognised in the early 1930s when Tuft *et al* documented results of a series of experiments demonstrating that a partial dose of typhoid vaccine, administered intradermally, elicited an antibody response equal to or better than that achieved following a full dose of vaccine administered subcutaneously or intramuscularly.<sup>1</sup> Since that time, much effort has been devoted to understanding both why drugs deposited in the skin can provide more effica-

or systemic delivery.<sup>4-8</sup> These studies demonstrate that intradermal delivery may offer faster absorption,<sup>6-8</sup> higher peak blood levels<sup>5</sup> and higher bioavailability of certain therapies<sup>9</sup> versus what can be achieved via conventional delivery routes.

## MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS

In an effort to leverage the benefits of intradermal delivery, many different delivery methods have been considered.<sup>3</sup> Perhaps the most active area of development is in the use of microneedles to deposit drugs or vaccines into the dermis and/or epidermis. Many variations of microneedles have been developed, including solid, drug-coated microneedles, drug-impregnated dissolvable microneedles and hollow microneedles for delivery of liquid drug formulations.<sup>10</sup> Microneedles are made from

many different materials including silicon, metal, glass and plastic (see Figure 1).

Microneedle-based drug delivery systems can be applied to the delivery of microgram levels of highly potent small molecules or peptides<sup>8,11-13</sup> through to delivery of hundreds of milligrams of high value formulations of proteins.<sup>5,9,14</sup>

**"MICRONEEDLE-BASED DRUG DELIVERY SYSTEMS CAN BE APPLIED TO THE DELIVERY OF MICROGRAM LEVELS OF SMALL MOLECULES OR PEPTIDE THROUGH TO DELIVERY OF HUNDREDS OF MILLIGRAMS OF HIGH VALUE FORMULATIONS OF PROTEINS"**

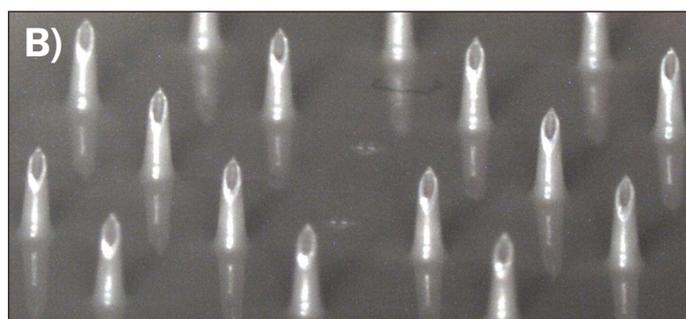
cious therapy and how routinely to deliver drugs accurately and easily into this compartment of the body.<sup>2</sup> Although, historically, development of intradermal delivery methods has focused primarily on vaccines,<sup>3</sup> more recent efforts have considered the broader potential of intradermal delivery to optimise the delivery of drugs targeting local



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**Figure 1: A) Solid, drug-coated microneedles and B) hollow microneedle array. Solid microneedles are 250 $\mu$ m in length; hollow microneedles are 900 $\mu$ m tall. Both solid and hollow microneedles are moulded from medical-grade plastic.**

## AN ALTERNATIVE TO INJECTABLE THERAPIES

In a study published in 2012, researchers discussed results of a series of Phase I studies wherein the safety, tolerability and wear characteristics of a synthetic peptide developed for the treatment of osteoporosis coated on solid microneedles were evaluated. Microneedle-based delivery of the peptide was evaluated *versus* an injectable form of the drug. Data collected in over 300 post-menopausal women aged 50-80 years demonstrated that microneedle-based delivery was fast—nearly complete delivery was achieved in just one minute—and achieved desirable PK characteristics, including rapid absorption of the drug into the systemic circulation.

A subsection of subjects received seven repeat daily doses of the drug coated on microneedles. In this group, a rapid rise in blood levels of a biomarker for bone formation was observed, consistent with data collected previously for this drug when administered by injection.<sup>13</sup> These data were consistent with pre-clinical studies conducted in rats and monkeys<sup>12</sup> and demonstrate the utility of microneedles to provide an alternative delivery option for injectable therapies.

The mechanism credited with the rapid and efficient uptake of biologics delivered to the dermis is the lymphatic system. The dermis is particularly rich with lymphatic capillaries and the rate of fluid exchange in the dermis exceeds any other compartment in the body.<sup>15</sup> Large molecules delivered to subcutaneous or intramuscular tissues may not be absorbed by the lymphatic capillaries as fast as they would be in the dermis; as a result, intradermal delivery is characterised by PK profiles that often show rapid absorption (early  $T_{max}$ ), higher peak blood levels (higher  $C_{max}$ ) and more complete uptake (higher AUC).<sup>4,9</sup> These changes in PK may be ideal for administration of drugs, such as insulin, where rapid absorption is desired or for delivery of high-value drugs where more complete absorption may allow for a reduction in dose.

The skin may be an optimal compartment for vaccine delivery for different reasons. Langerhans and dermal dendritic cells, in the epidermis and dermis respectively, are an important component of the immune system unique to the skin. These cells are sentinels, quickly processing microbial antigens, such that the body can rally defences sooner and more effectively than if the antigen is presented to the intramuscular tissue, as it is with traditional vaccination methods.<sup>16</sup> These unique characteristics of the skin have been leveraged commercially with the introduction of Fluzone®, a vaccine for influenza that is administered into the dermis by a clinician.<sup>17</sup>

An understanding of the unique physiological opportunities the dermis offers provides exciting speculation for utilisation of this delivery route to enhance therapeutic profiles for a variety of existing medicines, including oncology drugs, cancer vaccines, rescue medicines, nanoparticle-based therapies, and delivery of new chemical entities that have volumes or viscosities that make them incompatible with traditional syringe/autoinjector administration.

## BENEFITS FOR INCREASED PATIENT COMPLIANCE

In addition to the potential to improve the efficacy of therapies, microneedles are a compelling delivery route due to their level of overall acceptability by patients and by healthcare providers.<sup>18-21</sup>

Microneedles offer a patient-accepted alternative for the administration of injectable therapies where patient noncompliance, especially in chronic conditions such as rheumatoid arthritis and diabetes, is around 10%;<sup>22-24</sup> needle phobia plays a significant role in this noncompliance. Studies suggest that 10% of all Americans are needle phobic and an even greater percentage cite their dislike of needles as the reason for foregoing medical treatment.<sup>25</sup> Even healthcare professionals avoid routine vaccination because they “dislike shots”.<sup>26</sup> These studies speak to the potential benefit of developing non syringe-based delivery systems for the routine administration of chronic therapies and vaccines.

As our understanding of how to manufacture and where best to apply microneedle-based delivery systems grows, there is the potential for much wider utility of these systems as a means of efficiently delivering drugs and overcoming global compliance challenges.

According to a 2003 WHO report, adherence to long-term therapies is around 50% in developed countries and much lower in countries with emerging economies.<sup>27</sup> A study of compliance in patients diagnosed with osteoporosis found that approximately 75% of women who initiated drug treatment were non-adherent within 12 months and nearly 50% had completely discontinued therapy during this period.<sup>28</sup> This non-adherence has both humanitarian and economic consequences: experts suggest that up to 50% of women and 25% of men older than the age of 50 will break a bone due to osteoporosis.<sup>29</sup> There is a substantial increase in mortality associated with hip and vertebrae fracture in this population.<sup>30</sup> Yearly healthcare costs associated with osteoporosis are expected to top US\$25 billion (£16.5 billion) by 2025.<sup>29</sup>

## CONCLUSION

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. Microneedle delivery may provide enhanced therapeutic profiles for therapeutics and vaccines, allowing for administration of lower levels of drugs to achieve the same therapeutic endpoints. Additionally, microneedles provide an alternative to traditional needles and thus a means of overcoming one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination.

## REFERENCES:

1. Tuft L, Yagle E, Rogers S, “Comparative study of the antibody response after various methods of administration of mixed typhoid vaccine”. *J Infect Diseases*, 1932, Vol 50, p 98.

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2. Prausnitz MR, Langer R, "Transdermal Drug Delivery". *Nature Biotech*, 2008, Vol 26, pp 1261-1268.
3. Lambert PH, Laurent PE, "Intradermal vaccine delivery: will new delivery systems transform vaccine administration?" *Vaccine*, 2008, Vol 26, pp 3197-3208.
4. Hansen K, "Transdermal Delivery of Vaccines and Therapeutic Proteins". *Pharm Tech*, 2010 (November 1st), pp S14-s20.
5. Burton S et al, "Rapid Intradermal Delivery of Liquid Formulations Using a Hollow Microstructured Array". *Pharm Res*, 2011, Vol 28, pp 31-40.
6. Pettis RJ et al, "Intradermal Microneedle Delivery of Insulin Lispro Achieves Faster Insulin Absorption and Insulin Action than Subcutaneous Injection". *Diabetes Technology & Therapeutics*, 2011, Vol 13, pp 435-442.
7. Gupta J, Felner EI, Prausnitz MR, "Rapid Pharmacokinetics of Intradermal Insulin Administered Using Microneedles in Type 1 Diabetes Subjects". *Diabetes Technology & Therapeutics*, 2011, Vol 13, pp 451-456.
8. Zhang Y et al, "Development of Lidocaine-Coated Microneedle Product for Rapid, Safe, and Prolonged Local Analgesic Action". *Pharm Res*, 2012, Vol 29, pp 170-177.
9. Harvey A et al, "Microneedle-Based Intradermal Delivery Enables Rapid Lymphatic Uptake and Distribution of Protein Drugs". *Pharm Res*, 2011, Vol 28, pp 107-116.
10. Prausnitz MR, "Microneedles for transdermal drug delivery". *Advanced Drug Delivery Reviews*, 2004, Vol 56, p 581.
11. Daddona P, Matriano J, Mandema J, Maa Y-F, "Parathyroid Hormone (1-34)-Coated Microneedle Patch System: Clinical Pharmacokinetics & Pharmacodynamics for Treatment of Osteoporosis". *Pharm Res*, 2011, Vol 28, p 159-165.
12. Hattersley G, Determan A, Hansen K, Lyttle CR, paper presented at the American Society for Bone and Mineral Research, Minneapolis, MN, US, October 2012.
13. Hattersley G et al, paper presented at the American Society for Bone and Mineral Research, Minneapolis, MN, US, October 2012.
14. Hansen KJ, in *5th Biologic Therapeutics Research and Development*. (GTC, San Francisco, CA, 2010).
15. Charman WM, Valentino JS, "Lymphatic Transport of Drugs". CRC Press, Boca Raton, FL, US, 1992 (ISBN: 0849363942).
16. Nicolas J, Guy B, "Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice". *Expert Reviews Vaccine*, 2008, Vol 7, pp 1201-1214.
17. Ansaldi F, de Florentiis D, Durando P, Icardi G, "Fluzone® Intradermal vaccine: a promising new chance to increase the acceptability of influenza vaccination in adults". *Expert Review of Vaccines*, Vol 11(1), pp 17-25.
18. Gupta JF, Felner EI, Prausnitz M, "Minimally Invasive Insulin Delivery in Subjects with Type 1 Diabetes Using Hollow Microneedles". *Diabetes Technology & Therapeutics*, 2009, Vol 11, pp 329-337.
19. Laurent PR et al, "Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system". *Vaccine*, 2007, Vol 25, pp 8833-8842.
20. Haq M et al, "Clinical administration of microneedles: skin puncture, pain and sensation". *Biomedical Microdevices*, 2009, Vol 11, pp 35-47.
21. Birchall J, Clemo R, Anstey A, John D, "Microneedles in Clinical Practice—An Exploratory Study Into the Opinions of Healthcare Professionals and the Public". *Pharm Res*, 2011, Vol 28, pp 95-106.
22. Thannhauser JR, Mah JK, Metz LM, "Adherence of Adolescents to Multiple Sclerosis Disease-Modifying Therapy". *Pediatric Neurology* Vol 41, pp 119-123.
23. Chilton F, Collett RA, *Musculoskeletal Care* 6, 1 (2008).
24. Devonshire V et al, *European Journal of Neurology* 18, 69 (2011).
25. Williams JP, Lednar W, *The American Journal of Managed Care* 8, S145 (2002).
26. Heimberger T et al, *Infection Control and Hospital Epidemiology* 16, 412 (1995).
27. WHO, "Adherence to Long-Term Therapies: Evidence for Action". WHO, Geneva, Switzerland, 2003.
28. Weycker D, Macarios D, Edelsberg J, Oster G, "Compliance with drug therapy for postmenopausal osteoporosis". *Osteoporosis Int*, 2006, Vol 17, pp 1645-1652.
29. National Osteoporosis Foundation. ([www.nof.org](http://www.nof.org), 2013), accessed Jan 14, 2013.
30. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D, "Risk of Mortality Following Clinical Fractures". *Osteoporosis Int*, 2000, Vol 11, pp 556-561.

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