

Nanotechnology Provides Advances to Superior Drug Delivery Methods: Transdermal Drug Delivery with MicroArrayPatches (NanoMAPs)

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Bob Irving is Director, Delivery and Sensing at Nanotechnology Victoria Ltd (NanoVic). He has more than 20 years' experience in the development of diagnostics and therapeutics in both human and animal health, and has been involved in three successful start-up companies. Since joining NanoVic in 2004, Dr Irving has been responsible for the project portfolio and engagement with industry to deliver research, and also for commercialisation outcomes based on new nanotechnologies specifically in the bionanotechnology field. He received his PhD for his research into prostate cancer undertaken at the Imperial Cancer Research Fund in London, UK.



Michelle Critchley is Manager, Delivery and Sensing Development at Nanotechnology Victoria Ltd (NanoVic). She has three years' experience in managing the transdermal delivery product development and proof of concept study with the company's research and industry partners, and five years' experience with Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO), working in a variety of client industries including microbiology, aerospace, food safety, polymers and biosensor development. She was appointed to NanoVic in 2004 and is responsible for managing the transdermal delivery projects and intellectual property portfolio. She has a PhD in Biotechnology from Flinders University; she is currently completing a Masters Degree in Intellectual Property Law and is a member of the Law Institute of Victoria.

Introduction

For mass market drugs and therapies such as insulin for diabetes, it is widely recognised that multiple delivery platforms will be required to service the entire market. There are a number of technologies in varying stages of development for delivery of insulin; each is unique in its own way, and each has its own strengths and weaknesses that will ultimately dictate acceptance into the market.

Furthermore, the route by which a drug is administered to a site in a patient's body may profoundly affect the efficiency with which it acts. The two most commonly considered routes of drug entry into the body are (i) by ingestion, with the need to cross the lining of the gastrointestinal tract and survive the stomach and colon environments, and (ii) across the barrier layer, the skin, usually by injection.

Interstitial NanoSystems, a division of **Nanotechnology Victoria Ltd (NanoVic)**, is combining the improved efficacy of nano-drug formulations with delivery methods that are specifically designed to be both consistent with and supportive of the technology for the needs of the end users. Interstitial NanoSystems is the specialist vehicle launched in 2007 from the bionano activities of Nanotechnology Victoria Ltd and established

for the commercialisation of non-injectable delivery platforms for therapeutic nanoparticle delivery. Interstitial NanoSystems is currently optimising transdermal delivery of nanoparticulate drugs through a MicroArrayPatch (MAP) delivery system for large and small molecules crossing the outer impermeable layer of the skin (the 'stratum corneum'). Trials have demonstrated improved efficacy of a range of pharmaceuticals when formulated into nanoparticle structures. This NanoMAP delivery technology has been developed through a NanoVic co-development with the **Victorian College of Pharmacy (VCP)** at **Monash University**, using the fabrication facilities of **MiniFAB** for the production of patches, and **Eiffel Technologies**, which nanostructured the drugs.

Several well-known challenges must be considered when developing methods of delivering therapeutic reagents and drugs by transdermal routes. These include bypassing/crossing the stratum corneum, limitations to the number and molecular size of drugs that can be delivered, maintaining the integrity of the skin to prevent damage and contamination, and increasing the speed of delivery. The skin is structured to provide a protective barrier to the body for the prevention of injury and infection. The stratum corneum consists of a layer of dead epithelial cells that constantly turns over and is renewed after

approximately three weeks. A limited number of drugs on the market readily pass through this outermost layer of skin, and these generally include those with mainly small molecules of less than 400 Da, such as nicotine and fentanyl. Transdermal technologies, including sonication, piezoelectrics and iontophoresis, have been investigated to overcome this hurdle, although their success has not yet been proven and it is not clear whether the positive effects noted to date could be reproduced with sufficient reliability for drug delivery. Methods that erode the stratum corneum, including abrasion, tape stripping and ablation techniques, can also increase skin permeability initially. The degree of drug absorption that is achievable is unpredictable, however, while there is also potential for scarring and the prospects for future efficient delivery at that site are also questionable.

NanoMAP Technology

The Nanotechnology Victoria NanoMAP product, which is currently under development, enables the painless delivery of large molecules (including vaccines, proteins, peptide hormones and other drugs in a nanoparticulate form) through the stratum corneum, and it is poised to revolutionise the delivery of therapeutic agents (including hormones, insulin and erythropoietin) and vaccines.

NanoMAPs are polymer patches that are surface structured, with solid microneedles that are specifically designed to penetrate the stratum corneum. These provide a controlled, direct mechanism of delivery to the underlying tissue. The density of microneedles of each NanoMAP lies in the range of 100–1,000 per square centimetre, depending on the loading of the nanoparticles required. The length of the microneedles is between 100 and 250 μm , depending on the site of application, and their thickness and shape are optimised for penetration and loading. NanoMAPs can be designed for either short-term bolus delivery or sustained release. Drugs are incorporated into the NanoMAP polymer matrix, so that application to the skin results in a slow release of drugs from both diffusion and polymer dissolution.

The drugs are nanostructured by an Australian company, Eiffel Technologies, which uses its supercritical fluid technology to make nanoparticulate drugs; these are then anchored to the patches, either by being coated onto the external surface of the microneedles or through direct inclusion into the polymer matrix. Loadings of drugs are typically in the order of milligrams. The NanoMAPs are engineered to penetrate the stratum corneum and into the epidermis to avoid the dermis, and they thereby also avoid the nerve fibres and capillaries. The drug then diffuses from the polymer patch where it is taken up by the body. This provides a localised, non-invasive drug delivery mechanism that is both pain and blood free.

NanoMAPs have advantages over the traditional methods of drug delivery (which are unsuitable for many emerging DNA and protein therapeutics), since they avoid the hepatic, first-pass route. NanoMAPs enable localised

delivery to specific areas of the body, lower the systemic delivery required, and preserve the effects of medications that rapidly degrade in the body, particularly through gastrointestinal delivery. Localised delivery will also allow more efficient treatment of various skin conditions, such as psoriasis or melanomas, through direct application to affected areas. In addition, as NanoMAP delivery is pain and blood free, patient compliance is increased for many medications. NanoMAPs are easily self-administered, particularly when compared to hypodermic injections, whose use is mainly limited to medical clinics and hospitals. NanoMAPs also reduce the risk of needle-stick injuries to healthcare workers. Disposal issues are easier to manage than with syringes, as the polymers used are naturally degradable. NanoMAPs may not displace injection or ingestion entirely, but they will significantly reduce their use in certain treatments.

Vaccines and Delivery

A major advantage of NanoMAPs is their ability to deliver directly to the antigen-presenting cells in the skin. The skin contains antigen-presenting Langerhans cells in the epidermis, and dendritic cells in the dermis, which are both immunologically sensitive. These cells take up foreign antigens and migrate to the draining lymph nodes that present to the T lymphocytes, thus initiating an immune response. The delivery of antigens to these cells enables NanoMAPs to be used as an alternative form of vaccine delivery, and the nanostructuring, or formation of nanoparticles from the drugs, provides significant benefit in eliciting an effective immune response.

Patch Production

NanoMAPs have been manufactured using novel microfabrication technologies developed by MiniFAB, in Melbourne, Australia. Microfabrication methods used to produce NanoMAPs generally involve lithography, etching processes, laser ablation, moulding and other techniques. The intent is to mass produce a product with high reproducibility between the microneedle structures at a minimum cost. NanoMAPs need to be produced as a sterile product, which requires sterile manufacturing facilities or subsequent irradiation treatment. NanoMAPs will also require sterile packaging as single- or multi-use products, depending on the application.

A critical factor in manufacturing is the choice of polymers. NanoMAPs are made with biocompatible and biodegradable polymers that meet the strict regulatory requirements of Australia's **Therapeutic Goods Administration (TGA)** or the US **Food and Drug Administration (FDA)** for use in humans. The melt temperature for the polymer is highly important, particularly where temperature-sensitive drugs need to be incorporated. The high temperatures that are often used to fabricate these structures can have adverse effects on the structure of many therapeutic proteins, causing aggregation and loss of activity. There is also a requirement

for biodegradable polymers with a tailored degradation time. This is important for applications with implantable NanoMAPs or long-wear patches for release over time.

The nanostructuring of the large molecule drugs for delivery also provides advantages by facilitating solubility, uptake and bioavailability in the body. The various methods that have been investigated for nanostructuring drugs include surface acoustic wave technologies, precipitation and self-assembly. The supercritical fluid process used by Eiffel Technologies for the NanoMAP development work resulted in a high-purity product with no residual solvents. The particles produced also have a narrow and reproducible range of particle sizes and can easily be loaded or incorporated into patches.

The novelty of the NanoMAP technology is in the combination of the nanoparticulate or nanostructured reagents with microarray delivery. MAPs have an enormous range of applications in both animal and human healthcare. For many applications, MAPs may largely replace traditional methods of drug and vaccine delivery, thus enabling the self-administration of agents such as insulin, erythropoietin, parathyroid hormone and antibiotics. Inevitably, MAPs may also allow localised delivery with potential applications for psoriasis, skin cancer treatment and the healing of wounds.



Figure 1 – NanoMAP patch applicator and cartridges.

Patch Applicator

Interstitial NanoSystems has developed a proprietary applicator for applying the NanoMAPs to the skin (Figure 1). The applicator can aseptically load a NanoMAP using a custom cartridge, and it applies the patch with a predetermined force that enables reproducibility in application.

Summary

The NanoMAP technology provides an alternative drug delivery mechanism with a wide variety of applications in both human and animal healthcare. The technology provides a non-invasive, pain- and blood-free method of drug delivery that exploits the significant advantages of nanoparticle drugs and has the potential to change the way medications are administered. NanoVic expects that further development of the technology will result in new commercial products for insulin and vaccine delivery within the next five years. The further specific optimisation of this technology for particular drug delivery by Interstitial NanoSystems will be through co-development with partners and clients, involving nano-drug formulation and delivery platform design and testing to preclinical studies or licensing of this proprietary technology.