THE RAPID EVOLUTION OF THE TRANSDERMAL DRUG DELIVERY INDUSTRY SPAWNS INNOVATION

Microneedle-based technology is a significant advance in the delivery of vaccines due to its strong stability and greater effectiveness. In this article, Luis Tissone, Director of Life Sciences, Trelleborg, outlines technological developments behind microneedle design including the use of advanced liquid silicone rubber (LSR) and two-component injection technology, and explores the advantages this offers over traditional intramuscular routes.

The transdermal drug delivery market is growing dramatically as a result of the multitude of benefits it provides for administering certain drugs over conventional systems. The rapid evolution of transdermal delivery is especially apparent with microneedle products due to its ability to provide exciting potential improvements for vaccine delivery (Figure 1).

Amongst all the companies involved in developing microneedle products, almost 50% are start-ups receiving support from financial investors. These start-ups, as well as the more established companies such as Pfizer, Roche, Johnson & Johnson, Novartis and Bayer, are looking at all the ways they can gain a competitive advantage. To ensure optimal performance, such companies are taking into consideration all the components used in their microneedle delivery system design. Knowledge of advanced technologies is crucial (Figure 2).

MICRONEEDLE PATCH TYPES & MARKET GROWTH

Advanced liquid silicone rubber (LSR) and two-component injection technology can accelerate the development of transdermal drug delivery devices such as microneedle patches. There are four types of microneedles currently on the market. First is the hollow microneedle, which only requires a liquid drug formulation to be infused through the bores. The solid microneedle punctures holes in the skin where a patch can then be applied. Then there is the dissolving microneedle that is coated with the drug. Lastly, there are polymer microneedles that are made from special polymers offering dissolving, non-dissolving or hydrogel-forming options.

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All of these microneedle patch types offer an excellent delivery route to enhance

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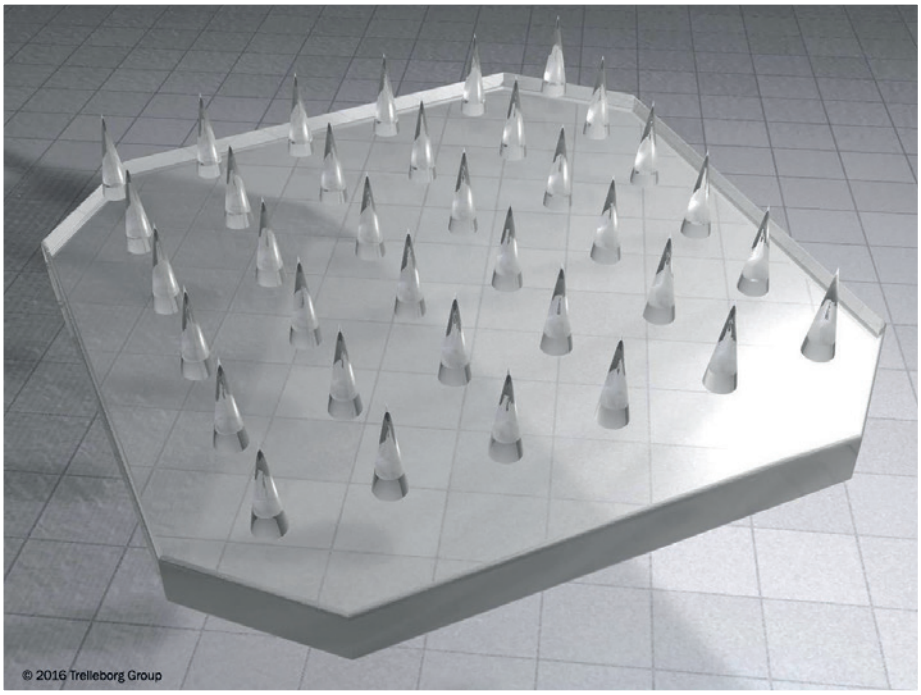

Figure 1: A detail of a transdermal patch using microneedles.

> "Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines."

the vaccination's effectiveness. This is primarily because microneedles possess the ability to target the rich network of immunologic antigen-presenting cells in the dermis and epidermis layers under the skin. Many new studies show that microneedle use for vaccination delivery reveals either comparable or greater immunogenicity, a stronger level of stability and more advantageous dose sparing as compared with the traditional intramuscular routes.

VERSATILE LSR TECHNOLOGY FOR MICRONEEDLE COMPONENTS

Advanced technologies are coming into play in enhancing microneedle components during the design process. For example, product developers and research institutes are looking at the use of LSR technology to enhance the performance of their transdermal delivery systems.

Silicone – and LSR in particular – is becoming an increasingly attractive choice of polymer due to a number of advantages. Silicone is well regarded for its favourable haptic properties and proven generally not to cause skin irritation. In addition, silicone provides biocompatibility and compliance with relevant industry regulations. Most importantly, LSR offers fast, essentially unlimited, processing possibilities for the most complex high-precision technical components in large volumes (Figure 3).

LSR technology is very effective where:

Figure 2: One of Trelleborg's Class 8 cleanrooms where safety-critical medical LSR components are produced fully automatically to a zero-defect policy.

- Customised solutions are needed
- Components with extremely complex, thin, or tiny features are needed, such as a carrier or protective element as part of a microneedle patch
- Multiple materials or layers of materials need to be combined into a composite structure
- The surface texturing and surface enhancements of devices are critical to provide the intended absorption of medicine through the skin
- The highest component precision and consistency of quality are key to provide best possible support to human health.

Examples of micro LSR and two-component parts produced by Trelleborg (ladybird shown for scale).

Advancements in drug delivery systems will be the result of access to newly developed materials, emerging methods of technological delivery and advances in manufacturing capabilities. This is precisely what LSR injection technology is offering. LSR technology can deliver smaller, more robust and stronger polymers to provide more stability, wear and usage. The more demanding requirements of pharmaceutical companies and device manufacturers have led to a more concentrated effort to deliver breakthroughs in LSR technology and microfabrication. This necessitates incorporating the smallest of parts, down to micro- and already nano-gram weights (Figure 4).

MULTIPLE FABRICATION METHODS & USES

Microfabrication manufacturing technology can be of help in delivering innovative microneedle designs. To fully understand microfabrication, it is important first to note that microneedles consist of a plurality of micro-projections, generally ranging from 25–2000 µm in height, of different shapes, which are attached to a base support. There are numerous configurations that can compose a microneedle patch. The flexibility of LSR can assist in achieving those configurations regardless of complexity.

The first microneedle devices were fabricated from silicone but many other materials have also been used in its fabrication; stainless steel, dextrin, glass, ceramic, maltose, galactose and various polymers, for example.

In recent years, manufacturing of microneedles has encompassed conventional microelectronic fabrication technologies,

Figure 4: AQL inspection of micro parts in a Class 7 cleanroom environment.

including chemical isotropic etching, injection moulding, reactive-ion etching, surface/bulk micromachining, polysilicon micro-moulding, lithography-electroforming-replication, and laser drilling. Microneedles have been fabricated with a wide range of designs (different sizes and shapes) and different types (solid, hollow, sharp or flat).

MARKET PROJECTIONS

With silicone and polymer compounds falling within our core area of expertise, the opportunities to enhance transdermal delivery system design is indeed an exciting one. Device manufacturers are investing in R&D and design strategies to support the transdermal drug delivery industry, valued at US$13.5 billion (£9.5 billion) in 2013 and expected to reach $21.7 billion by 2018, according to MicroMarketMonitor (Pune, India).

Microneedles are not limited to any specific class of drugs. According to a 2014 Roots Analysis report, "Microneedles for Transdermal and Intradermal Drug Delivery, 2014-2030", more than 70% of the products in development are patches incorporating solid or dissolvable needles, while the rest are hollow microneedle arrays that employ the use of a syringe. With several new microneedle-based therapeutic product launches expected by the end of this decade, the report concludes that the overall market for microneedle-based delivery devices will reach annual sales of 485 million units by 2030.

LEVERAGING A COMPETITIVE ADVANTAGE

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. It may provide enhanced therapeutic profiles for therapeutics and vaccines. It allows for the administration of lower levels of drug to achieve the same therapeutic endpoints.

Additionally, microneedles provide an alternative to traditional needles. This industry provides a means to overcome one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination. The variation in the microneedle types could also prove useful in controlling the kinetics of vaccine release. Such complex variations will further support the use of LSR technology and will be instrumental in the further evolution in the effectiveness and use of transdermal delivery systems.