



INNOVATIVE DRUG DELIVERY TECHNOLOGY TO MEET EVOLVING NEED OF BIOLOGICS & SMALL MOLECULES

In this article, Lisa A Dick, PhD, MTS Lab Manager, 3M Drug Delivery Systems Division, provides a run-down of the concept, design and development of the company's microneedle drug delivery platform, both hollow and solid needle arrays, including recent clinical trials of the hollow-needle device.

As population demographics shift and new medicines become available, patient preference and new technologies remain top of

This microneedle drug delivery technology provides solid and hollow microneedle options for enabling administration of

both small and large molecules, including difficult-to-deliver biologics. These devices are well suited for dermal skin targets or systemic distribution for drugs that enter the lymphatic system.

Solid microneedles, are coated with drug and focused on relatively potent molecules and peptides that are amenable to being deposited (up to 300 µg)

and dried on the tips of a microneedle array as shown in Figure 1.

For liquid formulations, **hollow microneedles** allow delivery of drug solution into the highly vascularised dermal layer of

"With 3M Hollow Microstructured Transdermal System, it is possible to deliver more viscous solutions, up to 25 centipoise (cp), with options for delivery of up to 80 cp"

mind for 3M. In recent years, 3M has been working on a patient-friendly and easy to use microneedle delivery platform that expands the range of drug molecules and formulations open to dermal delivery.

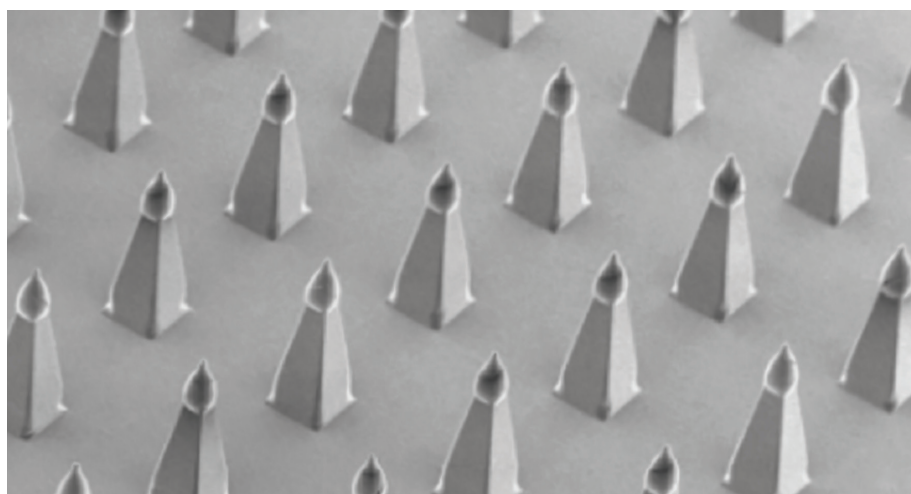


Figure 1: 3M Solid Microstructured Transdermal Array at 25x magnification (sMTS).

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Figure 2: Left – pen injector with single needle, Right – 3M™ Hollow Microstructured Transdermal System with hollow microneedles.

the skin. 3M™ Hollow Microstructured Transdermal System accommodates a wide range of drug amounts (up to 2 mL) and molecule types, as long as stability in liquid form is maintained. This system combines patient-friendly, passive transdermal delivery with the versatility of parenteral syringe injections. For comparison, Figure 2 shows both a pen injector and 3M Hollow Microstructured Transdermal System.

3M Hollow Microstructured Transdermal System is designed for intradermal delivery of liquid formulations, including biologics, such as proteins and peptides, in addition to small molecules. Hollow microneedles have the flexibility to deliver up to 2 mL of high value biologic formulations.^{1,2,3} This system also provides relatively fast delivery of a high volume of a liquid drug formulation. 3M Hollow Microstructured Transdermal System array is a 1 cm² polymeric disk composed of hollow microneedles with a sterile flow path connected to a conventional glass cartridge. During application, the microneedles are inserted into the skin penetrating the *stratum corneum* and epidermis, and creating direct access to the dermis. This hollow microneedle array, as demonstrated in Figure 3, is made from medical grade polymer with 12 microneedles 1500 µm tall. Delivery of the formulation through hollow



Figure 3: 3M Hollow Microstructured Transdermal System, pPolymer microneedle array with 12 hollow microneedles, each approximately 1500 µm.

Drug/Type	Viscosity	Volume (mL)	Injection Time
Cimzia®*	~80 cp	0.5-0.9 mL	1-2 minutes
Monoclonal AB	~20 cp	1 mL	3-5 minutes
Protein	~20 cp	2 mL	2-4 minutes

Figure 4: Injection times in preclinical models for various viscosities tested with 3M Hollow Microstructure Transdermal System. (* Cimzia is a trademark of UCB Pharma.)

microneedles is powered by a mechanical spring. A combination of drug and 3M Hollow Microstructured Transdermal System provides a fully integrated delivery device designed for reproducible intradermal delivery of liquid formulations.

DRUG PRODUCT & FORMULATION CONSIDERATIONS

The target delivery volume of 3M Hollow Microstructured Transdermal System is 0.5-2 mL, making it a viable delivery option for many biopharmaceutical therapeutics. In a recently conducted human tolerability study (3M, 2015), 3M Hollow Microstructured Transdermal System performed well, delivering 2 mL of 5% dextrose in 98% of 56 self-administered injections.

Non-viscous formulations flow readily through narrow flow paths in microneedle-based devices. Viscous formulations

neighbour to act independently. This distance, however, is balanced by the need to have a small array, such that each needle is uniformly inserted on flat skin. Ultimately, the arrangement of microneedles must be in a geometry that is favorable to the desirable drug delivery target.

MANUFACTURABILITY OF INDIVIDUAL MICRONEEDLES

Following successful preclinical and clinical studies, a need for high-volume reproducible manufacturing of microneedle arrays will become critical. This is especially challenging for small companies and universities conducting research on a limited budget and small scale. Based on extensive expertise in drug delivery systems manufacturing and access to broader corporate resources, 3M has chosen to use its proprietary microreplication technology as

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are more prone to plugging in the narrow channels of traditional single-channel devices or require a long delivery time. With 3M Hollow Microstructured Transdermal System, it is possible to deliver more viscous solutions, up to 25 centipoise (cp), with options for delivery of up to 80 cp.

The drug product formulation must also be chemically compatible with the device. This is essential, especially upon stability storage. In addition, drug molecules must be physically able to withstand shear forces when flowing through the device. Such physical compatibility considerations are especially important for biological drugs, which denature or become inactive.

To achieve successful formulation distribution in the intradermal layer, the number and arrangement of microneedles is key. It is desirable to have flow distributed across an array of microneedles. In order to achieve unrestricted flow, microneedles must be far enough removed from a nearest

a method of reproducibly manufacturing microneedle arrays in large volumes.

DESIGN INPUT AND HUMAN FACTORS

To summarise, both hollow and solid microneedle systems offer an alternative delivery method to meet the evolving needs of pharmaceutical companies, providers, and patients. With chronic conditions, non-compliance remains at around 10 percent.^{4,5,6} In some cases, patients may prefer a system designed for self-administration if they can avoid traveling to their physician's office for an injection or avoid outpatient IV administration. Microneedle systems developed in conjunction with a drug may provide convenience to the patients along with overall pharmaco-economic benefits.

While considering patients' comfort and pharmaco-economic benefits associated with self-administration, it's critical to fol-



Figure 5: The 3M Hollow Microstructure Transdermal System device.

low regulatory requirements for patient-centric design and self-administration considerations.

For instance, development of the 3M Hollow Microstructured Transdermal System has been focused on human factors inputs that were gathered during usability trials. Patient acceptance and product concept research resulted in the identification of additional features that were designed to increase convenience during self-administration, especially in dexterity-challenged patient populations.

Human factors research demonstrates that it is desirable for a device to be sized for easy handling and include a textured grip for convenience of patients or their caregivers. Mechanical actuation with an audible click or visual indication, which provides sensory feedback for the patient, is also important. A device with a status indicator, such as a window with a progress bar, provides information about dosing so the patient can see when medication delivery is completed. The combination of these features in 3M Hollow Microstructure Transdermal System, as shown in Figure 5, may allow patients to feel confident in self-administering their medications.

HUMAN CLINICAL TRIAL WITH 3M HOLLOW MICROSTRUCTURED TRANSDERMAL SYSTEM

With the design features identified in human factors testing and built into the device, 3M Hollow Microstructured Transdermal System underwent a number of studies and design verification tests. Then, to reach a stage of clinical readiness, 3M followed a rigorous process, including finalizing the device design, manufac-

turing critical components from medical grade materials, establishing GMP for array manufacturing and device assembly, as well as filing documentation with the US FDA.

In an internal 3M clinical study designed to measure delivery time, device performance with respect to leakage, safety and skin tolerability, thirty healthy volunteer subjects were asked to self-administer four 2 mL 5% dextrose injections to the anterior thigh. As a result, the final device configuration of 3M Hollow Microstructured Transdermal System has been selected for further assessment in potential partners' clinical trials.

For the selected final clinical device design, the following results were obtained:

- 2 mL 5% dextrose self-administered by 29 people (56 deliveries, 98% success rate)
- Average delivery time <2 minutes
- Average pain score of 2.9 on a scale of zero to ten
- Average tolerability scores for erythema and oedema were <2 on a scale of zero to four.

"Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of a range of biologics and small molecules"

These results provided foundational data for assessing the reliability and safety of 3M Hollow Microstructured Transdermal System.

SUMMARY

In conclusion, microneedle-based drug delivery has the potential to be a transformative technology for the delivery of a

range of biologics and small molecules. 3M has taken a platform approach and developed both solid and hollow microneedle systems for use in preclinical and clinical studies. 3M Hollow Microstructured Transdermal System was also studied in a recent human clinical trial for sensation and performance. For companies interested in intradermal delivery, 3M Hollow Microstructured Transdermal System can provide reproducible intradermal delivery of difficult-to-deliver viscous biologic solutions of up to 2 mL. This evidence illustrates the device's readiness for further use with pharmaceutical partners in their preclinical and clinical studies, thus providing new options for delivering biologics and small molecules

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We put no limits on curiosity

Imagination and curiosity are the starting points for 3M innovation – the kind of curiosity that leads to innovative solutions for real world problems – such as creating the first metered dose inhaler, enabling patient-centric transdermal technology and converting microreplication technology to microneedle delivery systems. From development, to scale up and commercialization, let the curious minds at 3M Drug Delivery Systems provide innovative solutions to your drug delivery challenges.

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