3D-Printed Microarray Patches for Transdermal Applications

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ABSTRACT: The intradermal (ID) space has been actively explored as a means for drug delivery and diagnostics that is minimally invasive. Microneedles or microneedle patches or microarray patches (MAPs) are comprised of a series of micrometer-sized projections that can painlessly puncture the skin and access the epidermal/dermal layer. MAPs have failed to reach their full potential because many of these platforms rely on dated lithographic manufacturing processes or molding processes that are not easily scalable and hinder innovative designs of MAP geometries that can be achieved. The DeSimone Laboratory has recently developed a high-resolution continuous liquid interface production (CLIP) 3D printing technology. This 3D printer uses light and oxygen to enable a continuous, noncontact polymerization dead zone at the build surface, allowing for rapid production of MAPs with precise and tunable geometries. Using this tool, we are now able to produce new classes of lattice MAPs (L-MAPs) and dynamic MAPs (D-MAPs) that can deliver both solid state and liquid cargos and are also capable of sampling interstitial fluid. Herein, we will explore how additive manufacturing can revolutionize MAP development and open new doors for minimally invasive drug delivery and diagnostic platforms.

KEYWORDS: microarray patches, microneedles, transdermal delivery, ISF sampling, 3D printing, additive manufacturing

1. INTRODUCTION

Intradermal (ID) drug delivery is the process of delivering formulations, in a minimally invasive manner, into layers of skin. Often, these treatments target either the epidermal or dermal layers of skin, which are situated above blood vessels and nerve fibers of the skin. It offers an attractive alternative to intravenous injection, which often elicits systemic effects and can be particularly advantageous for targeted, local drug delivery. Key advantages of ID drug delivery include the ability to deliver compounds with a significant first-pass effect, or metabolism by the liver. This can prematurely degrade the therapeutic compound, upon systemic administration. Further, ID access also reduces pain associated with hypodermic injections and can help eliminate the risk of transmitting blood-borne diseases through the generation of dangerous medical waste. Perhaps the most appealing advantage of ID access is that it can be self-administered and can eliminate reliance on trained medical professionals. This could be particularly advantageous in lower resource settings where access to cold-chain facilities is limited and in pandemic settings where risk of disease transmission could be higher.1

1.1. Targeting the Intradermal Space

ID access necessitates puncturing the outermost layer of skin called the stratum corneum, a tough barrier that provides mechanical integrity for the skin. Human skin is a complex, multilayer organ, consisting of the stratum corneum, epidermis, dermis, and hypodermis. The epidermis is considered a tougher layer of skin composed mainly of keratinocytes—cells that produce keratin. The epidermis also consists of dendritic cells (DCs) — a type of antigen presenting cell (APC) whose role is to survey the environment for any foreign pathogens or invaders. The skin-resident subset of DCs is called Langerhans cells (LCs), and they are critical in pathogen recognition and subsequent adaptive immune system activation. The dermis is comprised of a more heterogeneous population including fibrous/filamentous connective tissue such as collagen and elastin, as well as immune cells including...
macrophages, mast cells, and LCs. The hypodermis is predominantly composed of fatty adipose tissue. This subcutaneous layer is meant to serve as insulation and separates nerves and blood vessels in the basal dermal layer from underlying muscular and connective tissue. The stratum corneum is approximately 10 μm thick, while the epidermis and dermis are 2.5−3.1 mm in thickness, collectively. Several therapeutic compounds, including small molecule drugs, hormones, and inactivated viral vaccines, have been approved by the FDA for transdermal administration (Table 1). Conventionally, vaccines, such as the SARS-CoV-2 and flu vaccines, are administered to the muscular layer via an intramuscular (IM) injection. Other vaccines, such as the measles, mumps, and rubella (MMR) combination vaccine, are

Table 1. List of Key FDA-Approved Transdermal Products

| Drug Name/Active Ingredient | Disease Indication                                                                 | Therapy Administration Strategy | Mechanism of Action                        |
|-----------------------------|------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------|
| Butrans/buprenorphine       | moderate to severe chronic pain                                                     | transdermal patch system         | mu opioid partial agonist                   |
| Androderm/testosterone      | primary hypogonadism (congenital or acquired), hypogonadotrophic hypogonadism       | transdermal patch system         | androgen/hormone replacement                |
| Nicoderm CQ/nicotine        | withdrawal symptoms and nicotine cravings associated with quitting smoking          | transdermal film                 | nicotine administration                     |
| Transderm Scop/scopolamine  | nausea and vomiting associated with motion sickness, postoperative nausea and vomiting (PONV) | transdermal patch system         | anticholinergic                             |
| Aldarly/donepezil hydrochloride | mild, moderate, and severe dementia of the Alzheimer’s type                        | transdermal patch system         | acetylcholinesterase inhibitor              |
| Secuado/ascapine             | schizophrenia                                                                      | transdermal patch system         | atypical antipsychotic                      |
| Fluzone Intradermal Quadrivalent | vaccination against influenza virus subtypes A and B                             | intradermal injection            | inactivated influenza virus                 |
| Fentanyl-100/fentanyl        | chronic pain management                                                             | extended-release transdermal film | opioid/analgesic                            |
| Nitro-Dur/nitroglycerin      | prevention of angina pectoris due to coronary artery disease                       | extended-release transdermal film | vasodilator                                |
| Emsam/selegiline             | major depressive disorder                                                           | extended-release transdermal film | antidepressant                              |
| Daytrana/methylphenidate     | attention deficit hyperactivity disorder (ADHD)                                    | extended-release transdermal film | central nervous system stimulant            |
| Estrogel/estradiol           | moderate to severe vasomotor symptoms and vaginal/vulvar atrophy associated with menopause | extended-release transdermal gel | estrogen replacement                         |
| Oxsura/Xulane/ethinyl estradiol and norelgestromin | prevention of pregnancy                                                         | extended-release transdermal film | estrogen/progestin combination contraceptive |
| Catapres-TTS/clonidine       | hypertension                                                                       | transdermal patch system         | α-adrenoceptor stimulant in brain stem       |
| Exelon/rivastigmine          | mild to moderate dementia of the Alzheimer’s type or associated with Parkinson’s disease | extended-release transdermal film | acetylcholinesterase inhibitor              |

Figure 1. Routes of delivery. Layers of the skin and drug delivery strategies to access each layer. The epidermal/dermal layers of skin have 1−2 orders of magnitude more immune cells per unit volume of tissue compared to the subcutaneous/muscle layer. IM = intramuscular; SC = subcutaneous; ID = intradermal; MAP = microarray patch. ID access also enables collection of interstitial fluid (ISF). The scale on the right indicates depths of each skin layer. Created using BioRender.
administered via a subcutaneous (SC) injection. Interestingly, the epidermal/dermal layers of skin contain 1–2 orders of magnitude more migratory immune cells per unit volume of tissue compared to the SC/muscular layers (Figure 1). This observation points to another distinct advantage of ID delivery: the ability to tap into a larger population of migratory APCs. Further, cells and connective tissue in the dermal layer are bathed by a fluid comprised of water, amino acids, and other metabolites. This solution is called interstitial fluid (ISF), and it is a major component of the skin extracellular environment. ISF is fluid from the vascular space and lymphatic drainage that fills the skin interstitium, without being resorbed. As a result, it is critical in regulating osmotic balance and is also composed of relevant metabolites and electrolytes that are necessary for maintaining homeostasis. Due to the frequent filtration of ISF from surrounding lymphatic and blood vasculature, the composition of ISF is representative of metabolites that are in circulation.

These properties of the ID space are advantageous in two key use cases of transdermal access: drug delivery into the ID space for therapeutic applications and ISF sampling from the ID space for diagnostic or health monitoring applications.

1.2. Microarray Patches

As shown in Figure 1, the ID space can be accessed via a hypodermic needle or through a microarray patch/micro-needle array patch (MAP). MAPs are comprised of a series of micrometer-sized projections that can painlessly puncture the skin and access the epidermal/dermal layer. MAPs have been actively explored in the past decade, as a simple, self-administrable ID access method that could eliminate the need for trained medical personnel and hypodermic needles. Several classes of MAPs have been explored, ranging from dissolving MAPs that release cargo into the skin to hollow MAPs that can deliver liquid compounds via diffusion. These constructs are made from a range of diverse materials including polymers and metals.

MAPs have been employed extensively in cosmetic settings as a tool to easily deliver therapeutics into the skin. One of the most popular MAP applications in cosmetics is the Dermaroller, a device that consists of several 0.5–1.5 mm length needles arranged on a roller device. Dermarollers have been used to treat acne scars and stretch marks by penetrating the stratum corneum to create microconduits that stimulate growth factor secretion and collagen production. Conventionally, these microneedles are made of metals, with the use of reactive ion etching techniques. Aside from cosmetics, MAPs have also been employed in transdermal drug delivery. Recently, Rouphael et al. performed a randomized phase I clinical trial wherein dissolvable MAPs were used to administer an inactivated influenza virus vaccine. The study found that MAP-based vaccines generated a humoral and cellular immune response similar to or greater than that generated through IM vaccination, the conventional method of influenza vaccination. Aside from therapeutic delivery, MAPs have also been used in continuous health monitoring applications. Tehrani et al. designed an integrated wearable MAP for continuous monitoring of multiple biomarkers in ISF. The MAP projections were micromachined out of poly(methyl methacrylate) (PMMA), and the device was used to quantify levels of relevant biomarkers such as lactate, glucose, and alcohol. Interest in MAPs continues to grow as the field begins to consider how this technology can be applied in a clinical context. Several papers have evaluated methods to produce and commercially develop MAPs for clinical translation.
a manufacturing perspective, polymeric MAPs and novel cargo loading strategies open up a new design space in terms of material properties and therapeutic applications. This includes the use of MAPs to deliver poorly soluble compounds, such as macromolecules, as well as the use of rapid fabrication strategies to scale up MAP production. Of particular interest is employing these strategies to develop MAP-based vaccines that can be employed in low-resource settings. There is also interest in employing MAPs beyond the dermal context and into other tissues, such as the buccal tissue.

### 1.3. Key Design Criteria

To generate MAP systems that are reliable, it is critical that these devices can produce consistently reproducible access points in the skin. Therapy dosing and MAP administration should also be consistent between applications. This criterion is essential given the heterogeneity in skin properties between individuals as well as between different sites of administration on a given individual. Figure 2 outlines key design criteria that should be considered when designing MAPs. These systems should provide a cost-effective platform that is easy to apply and self-administrable, while having sufficient mechanical integrity to penetrate the skin and remain in the skin for the duration of administration. Penetrating the stratum corneum of human skin requires a force of at least 0.08 N per needle. Thus, to exhibit sufficient mechanical strength, MAPs must be able to withstand at least 0.08 N of force per needle. Further, to make MAPs accessible in diverse settings, it is desirable for the platform to have a longer shelf life. Although shelf life is largely dependent on the therapeutic compound to be delivered, it would be ideal for MAP-based systems to retain compound stability for an extended duration of time (several days) at higher temperatures (4 °C or higher). Simultaneously, MAP administration should be pain-free, with consistent cargo delivery and/or liquid sampling. To achieve this goal, it is critical that MAPs have sufficient skin retention. MAPs must be capable of overcoming viscoelastic forces in the skin to remain embedded for the entire duration of administration. Cargo dissolution profiles and liquid sampling kinetics are largely dependent on MAP geometry and material properties, both of which impact the duration of administration. This can range anywhere from several minutes to several hours. MAPs, therefore, should be retained in the skin, maintaining sufficient contact, during this time. Skin retention can be further enhanced through the use of adhesives in conjunction with improved MAP design.

These design criteria can be achieved by codesigning for optimal MAP geometries and formulation chemistries. Key materials considerations for MAP fabrication include choosing materials with higher yield strengths. Thus, far, MAPs have predominantly been composed of metals, silicon, and polymers. Metal and silicon-based MAPs have increased mechanical strength owing to the high Young’s moduli and yield strengths of these materials. Polymeric MAPs, often used for dissolvable chemistries, are weaker as they have lower yield strengths and are more prone to brittle failure. Another key material consideration is the mode of failure. Since MAPs need to be in contact with human skin, it would be desirable for the projections to undergo ductile failure as opposed to brittle failure. The latter would lead to significant risk as shards of the patch could be left behind in a patient, while the former would improve the patch’s safety. Thus, materials with flexible
chemical bonds, leading to ductile behavior, would be more desirable than materials prone to brittle fracture with needle delamination. 45 Finally, perhaps the most important material consideration when designing MAPs is ensuring that the material is biocompatible as it will be in contact with the skin for extended periods of time. If MAPs are intended to be dissolvable, it is critical that the byproducts of the material’s hydrolytic degradation are not toxic to cells. If the MAP material is meant to serve as a scaffold, the material should not leach any hazardous byproducts and may need to be hydrophilic to promote cargo dissolution or fluid sampling. 46

2. MAP DEVELOPMENT

2.1. History of MAP Development

Despite the promise MAP platforms offer, needle geometries and delivery profiles that can be achieved are limited as fabrication relies on dated methods. Methods for making MAPs have their foundation in manufacturing techniques associated with the microelectronics industry (Figure 3). Generation 1.0 MAPs were made with the use of silicon etching and microfabrication strategies that were tedious and rendered projections with uniform, simple geometries on a single patch. 47 This pioneering work with MAPs demonstrated the opportunities for intradermal delivery; however, the MAPs were expensive, competed with precious manufacturing needs in the microelectronics industry, were limited in materials, and were limited in geometries. This latter point is profound: many desirable MAP geometries of different sizes and shapes on the same patch (to avoid the bed-of-nails effect) or needles with undercuts or lattice structures (for liquid delivery) cannot be fabricated with tools of the microelectronics industry.

Generation 2.0 MAPs were made directly or indirectly by first fabricating master templates using the same techniques used to make generation 1.0 MAPs, followed by the use of soft lithographic techniques to make molds. This process has advantages over generation 1.0 MAPs as it opened the materials space and did not require access to a microelectronics industry factory for scale-up. However, this technique has significant drawbacks. 48 First, the design limitations from generation 1.0 are still a problem. Second, needle sharpness is often diminished after repeated molding, leading to loss of replication fidelity. Third, and most importantly, for molded MAPs, formulation chemistries must be tailored to the mechanical properties required for skin insertion. This restriction will dramatically limit the range of product formulations that can be used, which precludes molded MAPs from being considered a “platform approach”.

2.2. MAP Manufacturing Strategies

Generation 1.0 MAPs predominantly relied on manufacturing strategies that were derived from the microelectronics industry. One of the first patents for MAP devices was filed by Gerstel et al., 49 and it describes a MAP device consisting of several hollow, metallic projections with uniform geometries. 49 In this device, the drug reservoir is expected to be fabricated with the use of a polymeric material. The needles could be micro-machined and were likely intended to be produced in a manner like conventional hypodermic needles. Henry et al. 50 utilized deep reactive ion etching to microfabricate silicon-based MAPs. This process entailed depositing a chromium masking material onto silicon wafers and patterning dots onto the wafer. The wafers were then subjected to a fluorine/oxygen plasma to chemically etch valleys into the silicon mask. Regions protected by the metal mask formed needle projections with a diameter of 80 μm and a height of approximately 150 μm. 47 These examples of Gen 1.0 MAPs highlight how intensive and time-consuming the microfabrication process is. They also bring to light limitations, in terms of material chemistries, that significantly curtailed the diversity of material and mechanical properties of these MAPs. Gen 1.0 MAPs, as outlined above, were predominantly composed of silicon-based materials. To be compatible with microfabrication strategies, one had to use semiconductor materials that could easily be etched and deposited. Despite the manufacturing flexibility they offered, silicon MAPs are more prone to inducing skin fracture upon administration and may also be prone to fracture. 44 Further, due to the constraint of uniform deposition and coating on silicon wafers, one can only produce MAPs with simple geometries on a single patch. Generating needles with higher aspect ratios also becomes difficult as it necessitates multiple coating steps to layer the wafer and subsequently etch surrounding regions. Thus, many of the designs in this space had needle heights below 600 μm.

McAllister et al. 52 bridged Gen 1.0 and Gen 2.0 MAPs by using silicon etching on wafers to create masters which were then coated with additional materials to create a negative mold. Microneedles were patterned onto silicon wafers and then coated with aluminum or copper via electron beam deposition. These positive silicon masters were then coated with polydimethylsiloxane (PDMS) to create a negative mold of the needle. The negative mold could then be filled with polymeric materials or metals to generate multiple MAPs. Metal MAPs were made by electrodeposition onto the PDMS molds. Polymeric MAPs were generated by melting polyglycolic acid and polylactic acid, pouring them into PDMS molds, and curing the needles. This process generated a series of uniform, pyramidal, and beveled needle geometries with a diameter of 80 μm and a needle height of 150 μm. 50 The integration of soft lithography and molding facilitated the replication of MAPs; however, the production of needle masters was still a multistep, intensive process. Further, the reliance on molding limited materials that could be used to produce MAPs as they had to be compatible with the PDMS platform and needed to cure in place. The molding process also introduced defects and nonuniformities across the mold, especially with high aspect ratio designs that had a beveled tip, thus impacting the sharpness and efficacy of skin insertion.

Generation 2.0 MAPs began to harness soft lithography to facilitate scale-up. With the creation of an additional mold, MAPs could be produced without sacrificing the original silicon master—the component of MAP fabrication that is arguably most involved and time-consuming. As such, there was an endeavor to explore other strategies to fabricate needle masters. Pérennès et al. 51 utilized deep X-ray lithography (DXRL) to create poly(methyl methacrylate) (PMMA) masters with a sawtooth, beveled design. To generate a hollow channel in the needle, an X-ray mask with holes had to be precisely aligned on the sawtooth pattern. DXRL was used again to generate holes, and the PMMA master was electroplated with copper. Following this process, the hollow needle channels were etched to completely open the channel and the master was coated with a film of poly(vinyl alcohol) (PVA) to generate an intermediate mold. MAPs were replicated by curing PMMA in the PVA molds. 51 This process generated uniform needles with a hollow channel, with base widths ranging from 360 to 500 μm and heights ranging from...
700 to 800 μm. Although the needles were consistent and sharp, manufacturing needles required several steps, hindering scale-up of production. Lin et al.\(^5\) attempted to address this drawback by replacing microfabrication with a liquid-drawn, UV-cured resin. A UV-curable resin was placed between two parallel plates, and the plate was lifted to stretch the resin and generate a microneedle shape, which was then cured in situ by using UV light. These needle masters were then coated with PDMS to create negative molds that would facilitate MAP replication. This process yielded needles with heights ranging from 400 to 1600 μm and widths ranging from 600 to 1200 μm. Needle width and height were controlled by changing the resin viscosity and the volume of resin initially deposited on the parallel plates.\(^5\) Although this process is not as complex as microfabrication and can speed up master generation, precise control of needle height and width is difficult. Further, needle tips were not uniformly sharp. Moga et al.\(^5\) used a new technique called particle replication in nonwetting templates (PRINT) to design dissolvable, solid MAPs made using polyvinylpyrrolidone (PVP).\(^5\) PRINT combines a “top-down” method of soft lithography with traditional polymerization to create reproducible features on the nanoscale and microscale with precise control of size, shape, and chemical composition. With the use of this technique, needle projections of ~360 μm can be produced. This technology also allowed for rapid array production in less than 5 min for batch processes. Generation of the mold, however, still required silicon wafer processing and multiple coats, which can become a lengthy process.

### 2.3. Current Landscape of MAP Geometries

Generation 1.0 and 2.0 MAPs provided foundational manufacturing techniques that continue to be employed in present-day MAPs. These MAPs largely had uniform, simple needle geometries on a single patch. Recent developments in the MAP space build on these techniques to generate slightly more complex MAPs for both drug delivery and ISF sampling.

On the transdermal delivery front, Yang et al.\(^5\) developed an iontophoresis MAP which integrates a solid MAP with iontophoresis to deliver insulin transdermally and increase penetration into the skin. This system can be controlled by a smartphone and utilizes electroresponsive nanovesicles to deliver cargo. The needle projections used on this device are made with the use of conventional molding techniques wherein PMMA is cured in a PDMS mold. The projections are square pyramidal in shape with a height of approximately 600 μm and a diameter of 200 μm (Figure 4A). This system was able to produce robust hypoglycemic effects in type 1 diabetic rats. However, this manufacturing method only enables the generation of patches with a single geometry and needles of a single height. Given the dependence on lithographic methods, it is evident that the geometries that can be achieved for this design are limited as well.\(^5\)

Li et al.\(^5\) developed a more complex MAP design that incorporates a poly(lactic acid) (PLLA) shell, encapsulating a poly(lactic-co-glycolic acid) (PLGA) core containing the contraceptive hormone levonorgestrel. The shell is meant to be a mechanism for controlling dissolution rate to achieve zero-order, or linear, drug release kinetics. These needles are fabricated with the use of molding strategies wherein PLLA is centrifuged in a PDMS mold and dried to create a shell. Subsequently, the PLGA + levonorgestrel core is added and capped with PLLA and placed on a PVA/sucrose backing (Figure 4B). The needles were conical in shape with a base radius of 150 μm and a height of 600 μm.\(^5\) This design was able to achieve sustained release of levonorgestrel for 180 days, in a linear fashion. Despite the promise for sustained delivery at large time scales, the process to generate these MAPs is still multistep, leading to simple, uniform geometries across the patch. Further, patch design is largely limited to polymeric materials and excipients, due to the reliance on molding to develop these MAPs. Further, these patches were not tested in vivo; thus pharmacokinetic data remains to be understood.

Recently, MAPs have also been employed in transdermal vaccination. Moon et al.\(^5\) developed a dissolving MAP that combines the inactivated poliovirus vaccine (IPV) and inactivated rotavirus vaccine (IRV) for transdermal delivery. Dissolvable MAPs were fabricated with the use of conventional
molding techniques where an antigen solution was first cast in a PDMS mold, followed by a polymer matrix containing the inactivated viruses. After deposition in the mold, MAPs were dried at 35 °C overnight. This process generated conical needles with a height of 700 μm (Figure 4C). The patches demonstrated high stability at 5 and 25 °C, producing a robust neutralizing antibody response in rats. As seen in previous molded MAPs, the dependence on lithography limits materials that can be used, particularly for dissolvable MAPs. This in turn can impact the mechanical integrity of the needles and restrict the MAP design space.

Considering ISF sampling, Samant et al. developed a two-step system to sample ISF by first puncturing the skin using MAPs and then using suction to draw out the fluid. This system was used to study the pharmacodynamics of glucose in children and young adults with diabetes, as well as to study the pharmacokinetics of caffeine in healthy adults. The solid MAPs used had a base diameter of 200 μm and a height of 250 μm and were likely produced with the use of conventional molding strategies (Figure 4D). The need to use vacuum suction to generate blisters that draw up ISF can increase complexity and risks bleeding if MAP projections are too long. Further, the needle geometries of different heights to sample across skin layers are nearly impossible by using molding strategies, thus limiting the diagnostic information that can be accessed with the use of this method of ISF sampling. Sharpness of the needles is also limited with the use of lithography.

Wang et al. generated a bilayer MAP fabrication strategy wherein polystyrene MAPs were produced, coated with a magnetic nanoparticle backing (for downstream processing), and coated with antibodies that could bind protein biomarkers in ISF. Each microneedle is conical in shape with a base diameter of 300 μm and a height of 600 μm. The bilayer MAP design facilitates integration with standard ELISAs and improves the limits of detection of protein biomarkers through the use of plasmonic fluorescence. This system was used to quantify levels of cytokines in mice ISF. Although this bilayer MAP system facilitates downstream processing of extracted ISF, it is difficult to evaluate the tool’s efficacy as biomarker concentrations are not very well characterized in ISF. Further, the simple, uniform needle geometries limit the surface area accessible for antibody functionalization and restrict ISF sampling to a specific layer of skin.

As seen in current MAP designs, the reliance on molding significantly limits the geometries that can be achieved in MAP design. Further, the multistep process required to produce these MAPs severely inhibits scale-up and mass production of the technology. Gen 2.0 MAPs opened material chemistries to include polymeric, biocompatible materials. Although biocompatible polymers offered favorable surface chemistries that were hydrophilic, a significant material limitation that arose was lack of mechanical integrity and uniformity of properties across a patch. The curing process of these patches was not readily controllable and was largely passive. Materials for Gen 2.0 MAPs had to be cured in place and subsequently demolded. During the demolding process, the material had to remain intact, without sloughing off or adhering to the mold. These issues, coupled with the manufacturing challenges outlined, have arguably held back the field of MAPs.

### 3. GENERATION 3.0 MAPS

Generation 3.0 MAPs are a novel class of MAP devices that are fabricated with the use of additive manufacturing to generate more complex projection geometries. Additive manufacturing
enables direct fabrication of needles, in a layer-by-layer or continuous manner. These methods can facilitate the scale-up of MAPs and can open doors for MAP functionalities that were previously inaccessible. The DeSimone Laboratory at Stanford has pioneered new 3D printing techniques that leverage high-resolution printing to develop novel classes of MAPs.

### 3.1. 3D Printing Strategies for MAP Production

Three-dimensional printing is an additive manufacturing technique to produce three-dimensional structures using layer-by-layer fabrication. A 3D file, made using conventional computer aided design (CAD) software, is usually sliced into layer-by-layer fabrication. A 3D file, made using conventional technique to produce three-dimensional structures using resolution printing to develop novel classes of MAPs.

#### 3.1.1. Fused Deposition Modeling (FDM)

FDM, filament extrusion and deposition or through direct fabrication in a resin vat. Considering the former, fusion deposition modeling (FDM), is one of the most common extrusion-based 3D printing techniques. In FDM, filaments, usually polymeric in nature, are melted, extruded to form the desired layer shape, and subsequently cured on a platform. FDM bioprinters have been used to produce MAPs. Wu et al. developed a biocompatible resin comprised of sodium alginate (SA) and hydroxyapatite (HAP) which was then extruded through an Allevi 2 bioprinter to produce MAPs. One nozzle contained the biocompatible resin and was used to print the base plate of the MAP. In the second nozzle, the biocompatible resin was mixed with engineered, glucose-responsive insulin, to print drug-loaded projections which could deliver insulin transdermally. The Allevi 2 is an FDM printer with a precision of approximately 10 μm on each axis. However, the projections that were 3D printed were not sharp and the SA hydrogel was very pliable. To generate sharp tips, a glass coverslip was attached to the drug-loaded projections and drawn up to generate conical needles which were then cross-linked by use of a Ca²⁺ solution. This multistep process resulted in the generation of nonuniform needles with varying degrees of sharpness, as evidenced by nonuniform penetration into the skin of mice (Figure 5A). Reproducible and consistent delivery may be a challenge given the nonuniform nature of the needles. Further, the layer-by-layer deposition process could result in delamination. Nonetheless, this system demonstrated a potential method of delivering insulin into the skin.

Vat polymerization, on the other hand, takes place by shining light of specific wavelengths into a reservoir containing photopolymerizable resin. As the light shines, the resin cures selectively at that point and solidifies, generating a solid part that can be drawn out of the liquid resin. Stereolithography (SLA) is one of the most common types of vat photo-polymerization wherein a single laser traces the outline of a part, fills in the two-dimensional cross section, and cures it, layer by layer. The laser is usually positioned above the resin vat, and this technique is often used with resins that are UV-curable. Although SLA is a common strategy for prototyping, owing to the high resolution and print accuracy, its potential is curtailed by print speed limitations that are dependent on the motion of the laser. Masked SLA (mSLA) attempts to target this limitation by simultaneously curing a single layer, rather than having a laser trace the cross-sectional boundaries. This is achieved by using a set of UV LEDs controlled by an LCD screen above. Effectively, the black pixels on the LCD screen serve as a mask and dictate where UV light will pass through, thus curing those points in the entire part layer. Conven-}

tionally, mSLA printers can achieve pixel resolutions as low as 35 μm/pixel and build rates on the order of 0.1 cm³/min. mSLA has been used to 3D print hollow MAPs for transdermal insulin delivery. Xenakis et al. used the Phrozen Shuffle 2018 mSLA printer to produce MAPs with curved pyramid or syringe needle-like projections. The MAPs were printed with the use of NextDent Ortho Rigid resin, a biocompatible resin that has been used in dental applications. Using this system, the team was able to fabricate hollow MAPs that were 1 mm in height and had fairly reproducible hollow channel dimensions. The luminal volume varied 8–17% between prints (Figure 3B). Although complex needle geometries could be printed with the use of mSLA, the volume of insulin that could be delivered, transdermally, was still quite limited. Further, the mechanical integrity of the MAPs was significantly affected by the hollow channels’ luminal diameter. The lumen appeared to serve as a point of stress on the projection and was a common site for failure.

In addition to mSLA, digital light processing (DLP) is another vat photopolymerization technique which also cures the entire layer of a solid part. This technology uses a UV light projector to spatially control resin curing in a vat. Liu et al. used DLP 3D printing to produce MAPs for continuous glucose monitoring in ISF. A DLP machine called MoonRay was used to produce conical MAPs that were 400 μm in diameter and 1.5 mm in height (Figure 5C). The MoonRay device had a pixel resolution of 100 μm in the x,y plane and a print speed of 0.15 in./h at a z resolution of 20 μm. A clear, biocompatible resin was used to print the solid microneedles. This device was then electroplated for compatibility with glucose sensing electrodes. Glucose oxidase was immobilized on one of the electrodes to continuously monitor glucose levels in ISF. Although this device was able to correlate glucose levels with readings from a commercial blood monitor, the multistep device fabrication process (excluding any post-processing steps) limits scale-up of the technology. Further, the printer’s low resolution also restricts the complexity of geometries that can be achieved.

### 3.2. High-Resolution Continuous Liquid Interface Production (CLIP)

From the additive manufacturing techniques that have been applied in MAP fabrication thus far, it is evident that a faster, high-resolution 3D printing strategy could ameliorate scale-up of MAPs. Continuous liquid interface production (CLIP) is a 3D printing technology that uses light and oxygen to create a continuous noncontact polymerization dead zone at the build surface. The key design feature in this technology is the incorporation of an oxygen-permeable, Teflon window. The presence of oxygen, an inhibitor of free radical polymerization, generates a dead zone at the window. This means that resin can freely flow in this region as the printed part is being pulled up, thus allowing for continuous printing. This allows for rapid production of parts with minimal forces on the growing part, enabling geometries that heretofore have been inaccessible by other 3D printing approaches. Johnson et al. pioneered the use of CLIP to produce MAPs by designing a variety of solid needle projections that could be rapidly manufactured in under 10 min. By optimizing key design parameters, including projection height, aspect ratio, resin cure time, and UV dosage, several solid MAPs with sharp projections and tunable geometries were generated. MAPs were produced using a range of biocompatible polymers
including trimethylolpropane triacrylate (TMPTA), poly(acrylic acid) (PAA), and photopolymerizable derivatives of polycaprolactone (PCL) and polyethylene glycol (PEG).

Needles were 1000 μm tall and 333 μm wide with a radius of curvature under 3 μm. Along with square pyramidal needles, Johnson et al. also showed that CLIP technology could be used to print various solid needle geometries including arrowhead, tiered, and turret MAPs (Figure 6A).

Caudill et al. extended this idea and used CLIP to produce solid MAPs and a custom-designed drug loading reservoir, or a coating mask. The coating mask contained individual wells that needles on a MAP would fit into. The mask was also sectioned such that different cargo formulations could be loaded onto a single MAP. This method enabled spatial control of cargo loading and allowed loading of both bovine serum albumin (BSA) and OVA protein onto a single patch (Figure 6B).

Caudill et al. also demonstrated that 3D-printed CLIP MAPs can deliver model protein-based antigens (OVA) and adjuvants (CpG) and induce 50 times higher OVA-specific antibodies after boost immunization while also eliciting a more balanced T helper cell response. CLIP technology was used to fabricate solid and faceted MAPs that were 700 μm tall and subsequently coated with an OVA protein formulation (Figure 6C). A biocompatible, hydrogel-like resin called polyethylene glycol dimethacrylate (PEGDMA) was used to produce the solid MAPs. These MAPs were printed on the Carbon S1 CLIP prototype printer, which has a 20 μm pixel resolution. The use of CLIP technology enabled rapid, reproducible production of projections with fairly complex geometries.

The DeSimone Laboratory has extended CLIP technology to pioneer a high-resolution CLIP (hi-res CLIP) printer that can rapidly generate MAPs with tunable, precise geometries—a new era for generation 3.0 MAPs. With hi-res CLIP, we are now able to print MAPs with fine details, allowing thin struts (<100 μm) and cells (<500 μm) of a lattice structure to be resolved. Hi-res CLIP is very similar to conventional CLIP in that the cornerstone of its design is the inclusion of an oxygen-permeable window. This creates a dead zone that allows continuous resin flow as the part is being cured, layer by layer, and being pulled out of the resin vat. The novelty in this system lies in coupling high-resolution objective lenses with the rapid printing capabilities of CLIP. The digital light engine used in the hi-res CLIP printer enables printing of smaller, refined features with increased precision and accuracy. Lee et al. integrated high-resolution projections from microstereolithography/MSLA with the rapid production of CLIP to create a new printer that can produce complex parts in a fraction of the time. This printer has a 30 μm pixel resolution and has been used to print complex parts, such as small, kirigami-based stents. Several of these parts were manufactured using TMPTA resin. This printer is approximately 1000 times faster than other high-resolution 3D printing techniques. The lab has since developed an even higher resolution CLIP printer with a 1.5 μm pixel resolution and has used this device to open new, hitherto unseen avenues in MAP design.

3.3. Materials Used in Hi-res CLIP

CLIP is compatible with several photopolymerizable resins that have a wide array of chemical and mechanical properties.
| MAP generation | manufacturing strategy                      | needle geometry                        | materials                          | pros and cons                                                                 |
|----------------|---------------------------------------------|----------------------------------------|------------------------------------|-------------------------------------------------------------------------------|
| 1.0            | deep reactive ion etching microfabrication  | conical, $h = 150 \mu m$, base diameter = 80 $\mu m$ | silicon                            | pros: high aspect ratio needles with sharp tips                                |
|                | silicon etching coupled with electron beam deposition | conical, beveled and square pyramidal, $h = 150 \mu m$, base diameter = 80 $\mu m$ | silicon, metal, glass              | cons: multistep fabrication process for the needles, some needles failed during skin piercing, needle height < 600 $\mu m$ |
|                | conical, beveled and square pyramidal, $h = 150 \mu m$, base diameter = 80 $\mu m$ | conical, beveled and square pyramidal, $h = 150 \mu m$, base diameter = 80 $\mu m$ | silicon, metal, glass              | pros: could make needles with holes, slightly more complex geometries          |
|                | soft lithography/molding                   | conical, beveled, hollow $h = 700-800 \mu m$, base diameter = 300–500 $\mu m$ | PMMA                              | cons: limited materials that are compatible with curing in PDMS, molding process introduced defects, nonuniform sharpness affecting skin penetration |
|                | UV-curable resin drawing                   | conical, $h = 400-1600 \mu m$, base diameter = 600–1200 $\mu m$ | PVP                               | pros: uniform, sharp needles with precisely resolved holes                     |
|                | particle replication in nonwetting templates (PRINT) | square pyramidal, $h = 361 \mu m$, base diameter = 195 $\mu m$ | PVP                               | cons: multistep manufacturing precludes rapid scale-up                          |
|                | fusion deposition modeling (FDM)           | conical, $h = 643 \mu m$, base diameter = 600 $\mu m$ | sodium alginate hydroxyapatite     | pros: rapid production of MAPs                                                 |
|                | masked stereolithography (mSLA)            | hollow square pyramid/syringe needle, $h = 800-1000 \mu m$, base diameter = 1000 $\mu m$ | NextDent Orthorigid Resin (elastomer) | cons: lack of precise control over needle dimensions led to tip rounding and poor resolution/sharpness |
|                | digital light processing (DLP)             | conical, $h = 1500 \mu m$, base diameter = 400 $\mu m$ | biocompatible, light-sensitive resin | pros: fairly rapid, high stability, robust geometries                           |
|                | high-resolution continuous liquid interface production (hi-res CLIP) | conical, square pyramidal, faceted, arrowhead, tiered, turret, $h = 500-1500 \mu m$, base diameter = 100–600 $\mu m$ | TMPTA, PAA, PEGDMA, PEGDA, Keysplint Hard, PCL, PEG | cons: weaker needles, simple needle geometries, limited material selection (all polymers) |

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Materials can be rigid or elastomeric with varying degrees of hydrophobicity. Resins that are compatible with CLIP must be modified to be compatible with hi-res CLIP printing. The main modification is the addition of a UV absorber, which helps redirect scattered rays to improve print resolution and decrease overcuring of small features.

Resins for MAP production must be biocompatible as they will be in contact with the skin and ISF. Thus far, we have explored hydrogel-like resins, including PEGDMA, to print different MAP geometries. PEGDMA is an interesting candidate as it has swelling properties which could alter pharmacokinetics and potentially improve capacity for ISF sampling from MAPs.

Further, completely biodegradable MAPs could also be promising candidates for transdermal drug delivery. To this extent, water-soluble resins, such as poly(acrylic acid)-based systems, could be used to 3D print MAPs that completely dissolve in the skin and release cargo.

We have also taken inspiration from the dental industry and employed resins such as Keystone Industries’ Keysplint Hard resin for MAP fabrication. An advantage of using dental resins is that they have excellent mechanical strength and have been used in FDA-approved products, potentially facilitating clinical translation and commercialization. Keysplint Hard, however, is a slightly hydrophobic resin. Both Keysplint Hard and PEGDMA produced MAPs with failure forces higher than the force required to penetrate porcine skin, suggesting good mechanical integrity. To alter surface properties of the MAPs, we are investigating postprint treatments as well.

A promising candidate for surface treatment is oxygen plasma etching, which can render the surface of the MAP more hydrophilic by depositing a layer of oxygen. This technique could also facilitate adsorption of cargo when surface coating MAPs and may even increase drug loading capacity. Another surface treatment that could substantially improve the mechanical integrity of MAPs is metal sputter coating. MAPs can be sputter coated by the use of inert metals such as gold, thus improving their mechanical integrity as well as biocompatibility.

3.4. Novel MAP Geometries Enabled by Hi-res CLIP

Several manufacturing strategies have been explored, thus far, to produce Gen 1.0, 2.0, and 3.0 MAPs (Table 2). With the integration of diverse materials and higher resolution, enabled by hi-res CLIP, the accessible design space for 3D-printed MAPs has significantly expanded. Particularly, it is now possible to print MAPs with much smaller features, facilitating deviation from standard square pyramidal MAP designs. One of the biggest challenges with molded MAPs is the difficulty in molding hollow structures, particularly at the micrometer scale. Although some of the MAP designs described earlier were able to mold hollow channels, often these designs would take a tedious, multistep process to fabricate. At times, these designs would also negatively impact the MAP’s mechanical integrity, since the hollow channels would serve as sites for fracture. Fabricating hollow structures, without compromising mechanical integrity, is now achievable with hi-res CLIP. Additionally, hi-res CLIP also facilitates the integration of multiple MAP designs on a single patch. With molding, it is extremely difficult to generate needle projections with different heights on a single patch. However, with hi-res CLIP, these needles can be directly fabricated on a single patch in parallel, facilitating scale-up as well. Lastly, molded MAPs have largely been static, meaning they do not interact with the skin to alter its properties. Rather, these MAPs are simply inserted into the skin and removed. This is because the resolution needed to generate dynamic elements in a MAP is very high. Considering these drawbacks, hi-res CLIP opens two new classes of MAPs that cannot be fabricated using existing techniques. These are lattice MAPs (L-MAPs) and dynamic MAPs (D-MAPs). Sections 4 and 5
detail these new classes of MAPs and outline how they can ameliorate both transdermal drug delivery and ISF sampling.

4. LATTICE MAPS (L-MAPS)

Lattices have very interesting mechanical properties, while they reduce the amount of material needed to manufacture a part. We are exploring integrating lattices with MAPs to produce a new class of transdermal drug delivery and ISF sampling devices. L-MAPs are 3D-printed patches where each needle projection is comprised of a series of struts and repeating lattice cell units (Figure 7A). L-MAPs bridge the gap between solid and hollow MAPs as the surface area of the lattice struts can be coated with cargo, while the lattice cells are voids that can trap liquids. This design is impossible to generate through molding as the struts would likely fracture upon removal from a mold. Thus, L-MAPs can only be made with the use of additive manufacturing techniques, with sufficient resolution.

4.1. Design of L-MAPs

Like all 3D printing designs, fabrication of L-MAPs begins with an STL file designed with the use of standard CAD software. To generate the CAD file, a solid part in the shape of the needle projection is first generated. Projection shapes are often square pyramidal or conical; however, they could also be other shapes such as obelisks and pillars (Figure 7B). Next, the solid part is meshed according to the lattice shape selected and the cell size. The lattice structure is then generated by growing the mesh to the desired strut thickness. We have used both nTopology and Carbon’s design engine tool to generate a library of over 100 L-MAP CAD designs (Figure 7C). Lattice shapes range from triangular lattices to more obscure repeating units such as the hexagonal cells in a Voronoi lattice (Figure 8). Each lattice design has different deformation and mechanical properties, thus altering mechanical integrity as well as the amount of cargo that can be loaded in either solid...
or liquid state. Thus, far, we have printed L-MAPs using the biocompatible hydrogel-like resin PEGDMA as well as the dental resin Keysplint Hard. Using the hi-res CLIP printer, we have shown that we are able to resolve these microscale features to reliably produce L-MAPs.

4.2. Drug Delivery Use Cases

L-MAPs can be used for both solid state and liquid drug delivery. In the case of the former, excipients can be added to the formulation, enabling coating and subsequent drying on the L-MAPs. In this case, the surface area of the struts is a critical parameter as drying will likely lead to the formulation predominantly coating lattice struts, owing to the low surface energy (Figure 9A). In the case of liquid cargo loading, L-MAPs can trap liquid droplets in the hollow lattice spaces (Figure 9B). Thus, the critical parameter here will be the void volume, or the hollow volume in a microneedle that can trap liquid. To this extent, the key variables when designing L-MAPs for drug delivery are the strut thickness and lattice cell size. Both parameters will affect the strut surface area and the void volume, which in turn will determine the amount of solid or liquid cargo that can be loaded into the L-MAP.

Currently, cargo is loaded into L-MAPs via dip coating, wherein the drug formulation is loaded into a coating well and the L-MAPs are inserted into the well. To achieve reliable cargo loading and dosing, it is critical that the base of the patch not be coated. This is because the base of the patch will not be inserted into the dermal layer; thus cargo loading will always be higher than the dose delivered to the skin. The coating well can be designed to have raised edges that create a physical barrier which prevents the coating solution from coming into contact with the base, thus preventing base coating. Characterization of cargo loading is done by dip coating the L-MAPs and subsequently dissolving off all captured formulation to quantify the amount of active, therapeutic agent loaded onto the patch. Other cargo loading techniques that will be explored include spray coating and microfluidic injection filling. L-MAPs can load more cargo than conventional solid MAPs because the hollow lattice cells can also capture cargo. L-MAPs can also undergo surface modifications, as outlined earlier, to improve liquid retention by increasing hydrophobicity of the struts.

Another advantage of using the L-MAP system for drug delivery is that needle heights can easily be tuned to deliver cargo into different layers of skin. We have explored generating MAPs with multiple needle heights on a single patch (Figure 3, Gen 3.0 MAPs) ranging from 500 μm to >1 mm in height. This flexibility offers the added benefit of altering needle dimensions for simultaneous delivery into different skin layers and could also reduce patch insertion forces by combating the bed-of-nails effect. Further, L-MAPs are a modular platform that can be used to deliver a variety of cargo including nucleic acids, proteins, small molecules, and perhaps even live viruses/cells. L-MAPs can also be used as a conduit for controlled, liquid drug delivery upon insertion into the skin through the addition of an external reservoir with regulated compound delivery. In this case, the L-MAP would serve to access the ID space with external controls to regulate drug delivery. The DeSimone Laboratory is currently exploring use of L-MAP systems in transdermal vaccination, pain medication delivery, and protein delivery to the skin.

4.3. ISF Sampling Use Cases

A unique advantage of L-MAPs lies in the ability to alter lattice structure and surface properties to promote capillary flow and wicking up of fluids. This property renders L-MAPs amenable to ISF sampling and could lead to applications in transdermal diagnostics. L-MAPs can be inserted into the skin to collect ISF at specified time points, or the system could be integrated with microelectronics for continuous monitoring of relevant biomolecules.

Key considerations in the space of ISF sampling include the L-MAP’s ability to wick up fluid as well as the volume of fluid that can be captured in a single patch. Both properties are driven by the void volume of the L-MAP as well as surface charge interactions. Additionally, L-MAPs can undergo surface modifications to improve liquid retention and prevent fluid evaporation.
properties. Thus, elements that must be optimized when generating L-MAPs for ISF sampling include resin selection, surface modification, and lattice design to maximize void volume. It is critical that the L-MAP be hydrophilic to promote capillary action and fluid uptake. However, excessive hydrophilicity could also lead to protein/small molecular adsorption on the needles, which may alter sensing capacity in continuous monitoring applications. In optimizing the lattice design, one can generate several L-MAP designs and model the void volume as a theoretical indicator of ISF loading capacity. It is likely that an L-MAP design with larger cell size and thinner struts will be conducive to increasing ISF sampling. Yet, it is important to ensure that the L-MAPs have sufficient mechanical strength to penetrate the stratum corneum and enter the dermal layer. A larger cell size with thinner struts will generate L-MAPs that are weak. To balance mechanical strength with volumetric loading, we will employ in silico modeling and machine learning based optimization of needle design. Currently, L-MAPs can hold upward of 0.1 μL per needle, a 3-fold increase compared to solid MAPs.

In summary, 3D-printed L-MAPs, with their versatile materials, design flexibilities, and surface properties, have great potential for drug delivery and diagnostic applications.

5. DYNAMIC MAPS (D-MAPS)

Dynamic MAPs (D-MAPs) are a novel class of 3D-printed MAPs that can alter their geometry in some form, upon or prior to interacting with the skin. With hi-res CLIP and the small features that can now be resolved, it is possible to generate MAPs with moving features. Many of these designs are inspired by mechanical systems such living hinges and compliant mechanisms that can generate motion.

5.1. Dynamic Functions That Facilitate MAP Administration

The advantage of D-MAPs is that MAP needle geometries can change upon deployment to achieve additional functionality. This feature can be used to alter forces at play during MAP administration. Of particular interest is reducing the insertion force, improving the retention of MAPs for reliable administration, and facilitating patch removal (Figure 2).

To improve the retention of the MAPs in skin, we have designed a barbed MAP design which deploys barbs upon insertion into the skin to increase resistance (Figure 10A). These barbs can then be retracted prior to MAP removal to ensure that damage to the skin is minimized. This D-MAP design builds on a commonly employed mechanism in the polymer industry: living hinges. Living hinges are used in many consumer products, particularly in bottle caps that are often flipped open. By decreasing material thickness at the hinge point, the material becomes pliable upon exerting force. A similar concept is applied in the barbed D-MAP where living hinges generate motion upon pushing of the backing to deploy the barbs. Another strategy to reduce insertion force is to alter the skin’s elastic properties. It has been shown that stretching the skin’s elastic properties can help reduce insertion forces. Another strategy is to deploy barbs upon insertion (Figure 10B). Considering skin stretching at the needle level, the projections of the MAP have compliant prongs that will push outward as the needle is inserted into the skin (Figure 10B, right). This will generate local points of stretching; however, this may occur at the cost of increasing MAP insertion forces. At the patch level, the prongs are located on the lateral edges of the patch, stretching the entire area of skin that needles would be in contact with (Figure 10B, left). This would generate a larger area of stretching.

From the perspective of ISF sampling, it has been shown that slight pinching and suction of the skin can increase the volume of ISF sampled from skin. To this effect, we are exploring the creation of D-MAPs that generate pinching and slight suction upon patch insertion (Figure 10C). In this D-MAP design, suction is generated locally, at the site each needle would penetrate the skin. This design is not reliant on compliant mechanisms; rather, it relies on a sliding motion between the pinching ring and the needle that is being inserted.

5.2. Generating Compliant Mechanisms in MAPs

Compliant mechanisms, enabled by hi-res CLIP, are critical in the generation of dynamic elements. The differentiating characteristic of compliant mechanisms is that motion is achieved through elastic deformation of the material. Each flexible section connecting adjacent rigid sections may be manufactured in one step, reducing or eliminating the need for the assembly of a dynamic mechanism. Mechanical properties of the integrated living hinges and compliant mechanisms are varied by altering material composition, material thickness, and part geometries (through the inclusion of cutouts and lattices) and through other methods of achieving mechanical flexibility.

Considering living hinges, such as those employed in the barbed D-MAP design (Figure 10A), a critical element in their design is the generation of a pliable joint that can deform under mechanical stress, without fracturing. To do so, one can employ thinner struts at the hinge site or generate cut-out structures that will add flexibility to the part. Compliant mechanisms are often generated through latticing, which generates regions of reduced density and increased pliability. In the case of the stretch D-MAP design, latticing can be added onto the prongs to facilitate bending and stretching of the skin, as the needle is inserted. The use of elastomeric polymer resin can also facilitate generation of compliant mechanisms as the material itself will have inherent deformation. The key design consideration, however, is ensuring that the MAPs are strong enough to penetrate the skin while being pliable enough to generate motion.

6. FUTURE DIRECTIONS FOR MAPS

6.1. MAP Design Spaces Made Accessible by Additive Manufacturing

Here, we have shown how high-resolution additive manufacturing techniques can revolutionize MAP production and design. Considering the hi-res CLIP tool developed in the DeSimone Laboratory, a key advantage is the ability to resolve features that are tens of micrometers in size. This ability unlocks several MAP geometries and functionalities that were previously inaccessible, for example, the ability to make L-MAPs with thin struts and large cell sizes, as well as D-MAPs with dynamic elements. Direct fabrication enables a bottom-up manufacturing method where layer-by-layer building enables the production of complex geometries that would fail had they been molded. These designs also enable precise tuning of mechanical and drug loading/ISF sampling properties. Further, it has been observed that direct fabrication facilitates
generation of hollow structures in MAP projections while retaining mechanical integrity.\textsuperscript{26}

With the manufacturing methods used to make Gen 1.0/2.0 MAPs, it was difficult to produce hollow structures in needle projections as this would often compromise mechanical integrity and lead to needle failure upon removal from a mold. However, with additive manufacturing, the part can be postcured in its green state to preserve mechanical strength, thus enabling the creation of hollow channels and cells in the projections. In the case of L-MAPs, one can also imagine generating a gradient where the hollow volume fraction changes throughout the projection of the needle, or the lattice shape changes. These gradient structures could generate interesting mechanical properties and ISF wicking properties as well. The current limitation in terms of MAP designs is that the smallest feature should be greater than 40 \( \mu \text{m} \) to ensure MAPs are strong enough and to ensure that features resolve well.

Another aspect of MAP design made possible by additive manufacturing is the ability to integrate several different MAP designs on a single patch. This is particularly beneficial in targeting multiple layers of skin simultaneously. With molding and microfabrication, generating needles with different heights on a single patch would require several hours and multiple levels of photoresist layering and masking. With the use of additive manufacturing, needles of different heights and geometries can easily be printed on the same patch, in a parallel fashion.

The final and perhaps most important advantage of using additive manufacturing to fabricate MAPS is the uniformity and reproducibility of designs. With some of the drawing and curing techniques to generate MAPs (Lin et al. and Wu et al.), reproducibility was a critical issue as needles on a single patch would often have differing angles of sharpness.\textsuperscript{52,50} With additive manufacturing, and hi-res CLIP particularly, needle geometries are consistent and uniform throughout the patch. This feature is critical as it will help ensure that MAPs produce consistent and reliable dosage or ISF sampling. If needle geometries differ, this will also impact utility and dosing reproducibility with the MAP devices.

6.2. Scaling Up MAP Production for Industrial Applications

Additive manufacturing is also touted as an appealing fabrication strategy owing to its ability to be scaled up easily. With conventional techniques such as SLA and DLP, high resolution often occurs at the cost of a slow printing speed. With hi-res CLIP, we can achieve higher resolution and faster print speeds. An L-MAP with six lattice needle projections can be printed in under 10 min. Further, these patches can be tiled together to generate larger patches. We are also exploring multiplexing prints to fabricate patches in parallel, further expanding production.

Another factor to consider for industrial scale-up is part cleaning and sterilization. For medical devices especially, it is critical that the device is thoroughly sterilized and biocompatible. Traditionally, hi-res CLIP printed parts are cleaned with alcohols such as isopropanol (IPA). These parts are then thoroughly washed, dried, and postcured in a UV oven to ensure that the part is fully cured. With the 3D-printed MAPs, centrifugal cleaning has been shown to be effective in removing uncured resin, thus improving feature resolution and cleaning of the part. Pressurized air can also be used to clean. Postcuring, the MAPs would need to be sterilized. Promising sterilization techniques for the polymeric MAPs include lower doses of \( \gamma \) irradiation and potentially some form of chemical sterilization that will not compromise the integrity or material properties of the MAP.\textsuperscript{89} To some extent, scale-up of MAP production will depend largely on the number of printers available and the ability to multiplex patch printing.

6.3. Material Chemistries Needed for Additive Manufacturing of MAPs

With the integration of additive manufacturing in MAP production, it has also become evident that there is a need for novel material chemistries and unique design considerations that were not present when MAPs were molded. In generation 1.0 and 2.0 MAPs, material considerations were largely driven by biocompatibility and mechanical strength. Since these fabrication techniques mostly relied on air drying to “cure” the MAPs, material chemistries were designed for optimal dissolution profiles and sufficient mechanical strength. However, with the integration of additive manufacturing, particularly through photopolymerization techniques such as mSLA and hi-res CLIP, material considerations from the additive manufacturing space are now combined with desirable chemistries from the biocompatible MAP molding design space. Herein, we propose material chemistry considerations for vat photopolymerization techniques, such as hi-res CLIP; however, additional design criteria may be imposed if alternative additive manufacturing strategies are employed.

In the context of vat polymerization, one of the key differences is that the part curing step is driven by the presence of photoinitiators, which generate free radicals and drive the polymerization of monomers in a resin. This results in the formation of a solid part, entirely from a liquid. Many of the polymeric resins used in additive manufacturing result in the development of thermoset polymers. Thermoset polymers become irreversibly solid after the curing process due to polymer cross-linking, leading to the development of non-degradable prints. Further, thermoset polymers also tend to be hard and brittle.\textsuperscript{88} It is desirable for MAPs to undergo ductile failure, rather than brittle failure which could significantly impact device safety. This space provides a promising avenue for further material development wherein resin chemistries can be modified to generate solid parts with more thermoplastic-like properties. One strategy that could be employed is the use of step-growth polymerization to make thermoset polymers that have processabilities similar to those of thermoplastics, while retaining strength and mechanical integrity. This strategy could also open possibilities for additively manufactured MAPs that are biodegradable.\textsuperscript{89}

To generate solid part formulations that are conducive to ductile deformation and are potentially biodegradable, it is necessary to alter polymer formulations. Most resin formulations for vat photopolymerization are predominantly acrylate-based. Acrylates are photoreactive groups that can readily undergo free radical polymerization.\textsuperscript{88} However, acrylates are very toxic to cells, thus making it crucial that printed parts are thoroughly sterilized and all uncured resin is removed.\textsuperscript{90} These considerations raise the need for alternative resin chemistries that are more biocompatible and make thermoplastic-like properties more accessible. Thiol—ene resin chemistries have been touted as a promising alternative to acrylate chemistries for vat photopolymerization based additive manufacturing. These systems integrate step-growth polymerization and have shown tunable mechanical properties with an
added functionality of being degradable. In addition to engineering base polymer/monomer chemistries, it is also critical to ensure that other resin components, such as the photoinitiator and UV absorber, are biocompatible. Conventionally, the photoinitiator has been one of the most cytotoxic elements in resin formulations. With the integration of additive manufacturing and bioapplications such as MAPs, it is critical that further investigation into biocompatible photoinitiators is pursued. Ethyl (2,4,6-trimethylbenzoyl) phenylphosphinate is being explored as a potential biocompatible photoinitiator candidate for use in dental resins. UV absorbers are also a critical component of resin formulation, particularly for higher resolution printing applications. UV absorber dyes commonly employed in consumer settings, such as 2,5-thiophenediyldis-(5-tert-butyl-1,3-benzoxazole), which is used in tissue products, could be promising candidates for biocompatible UV absorbers in resin development.

Thus, far, material chemistries in the context of mechanical properties and biocompatibility have been discussed. However, printability of said material is a very important consideration, particularly for high-resolution MAP printing. A key parameter that affects the printability of a resin is its viscosity. If the resin has a high viscosity, adhesion forces of the part will be too strong, leading to print failure and potential delamination of the print. This process is especially prevalent in hi-res CLIP as continuous printing is dependent on constant resin reflow. Although lower viscosity resins are desirable from a printing standpoint, the cured part from such resins tends to have poor mechanical properties. A key direction for future resin development will be determining the optimal balance between monomer molecular weight, viscosity, and postcuring mechanical properties. Some groups are exploring oligomeric resins with stereochemistry-controlled mechanical properties to achieve lower viscosity resins with improved, elastomeric properties in the cured part.

6.4. MAP Deployment Pipeline

One of the appealing aspects of using MAPs for drug delivery or diagnostics is that they can be self-administered. If designed optimally, a user can simply apply the MAP like a Band-Aid adhesive bandage, from the comfort of their own home. To ensure widespread access of this technology, it is critical that formulation and cargo stability be at the forefront of MAP design. If the cargo can be kept stable on MAPs for extended periods of time, one can imagine developing an off-the-shelf or prescription-based model where MAPs can be shipped and stored for purchase. With the potential for scale-up, it is possible to see a system where MAPs can be rapidly 3D printed, formulation coated, and then deployed for sale. A colorimetric indicator can also be integrated with the MAPs to ensure that the cargo was fully delivered and that the patch was properly administered. With the heterogeneity in skin properties between users and even between different sites of administration, such an indicator would be a prudent feature which could help ensure consistent delivery.

In the case of ISF sampling, the deployment pipeline largely depends on which biomolecules are being screened as well as whether end point or continuous measurements are needed. In the case of biomolecules that require more robust characterization via mass spectrometry or other in-lab techniques, an end point measurement would be desirable. In this case, the MAP would be self-administered, the sample would be collected, and the MAP with ISF sample would be shipped or dropped off to be processed at a laboratory. For continuous biomarker measurements, electronic sensors could be coupled with MAPs to obtain real-time measurements as discussed in some of the current glucose monitoring applications.

A critical aspect of the MAP deployment pipeline will be regulatory considerations associated with commercializing these designs. Currently, additively manufactured medical devices are regulated by using the same regulatory pathways as their nonadditively manufactured counterparts. Several devices have been approved using premarket notification (510(k)) and new drug application pathways. The extent of regulation will likely depend on the invasiveness and complexity of the produced MAP designs. A simple L-MAP design for ISF sampling is likely to face minimal regulatory hurdles. However, an L-MAP used to deliver therapeutic compounds will have more complex regulatory considerations as the integration of biologics will necessitate use of a premarket approval or biologics license application pathway. With these additional considerations come the challenges of adequately designing phase I, II, and III clinical trials and appropriate animal model controls to evaluate the safety and efficacy of the MAP platform. Additional considerations pertaining to 3D-printed MAPs include sterilization of the devices prior to administration, appropriate cleaning of the part to remove any residual, uncured resin, and determining the effects of print parameter and build orientation on MAP properties. In addition to safety data from a biological perspective, thorough mechanical characterization should be performed to ensure reliability of MAP devices. This includes the validation of mechanical integrity under different environmental conditions as well as a function of sterilization and manufacturing parameters.

Regardless of the system and application, hi-res CLIP printed MAPs have immense potential to revolutionize drug delivery and diagnostics. These systems can provide a platform approach with versatile materials, design flexibilities, and surface properties. Namely, they offer the prospect of self-administration which can help reduce reliance on cold-chain processes and can also decrease hesitancy for those suffering from needle phobia. MAPs can seamlessly integrate with existing clinical pipelines to enable widespread access to health care and diagnostics, with rapid production and scale-up.
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Notes

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