Towards Biofunctional Microneedles for Stimulus Responsive Drug Delivery

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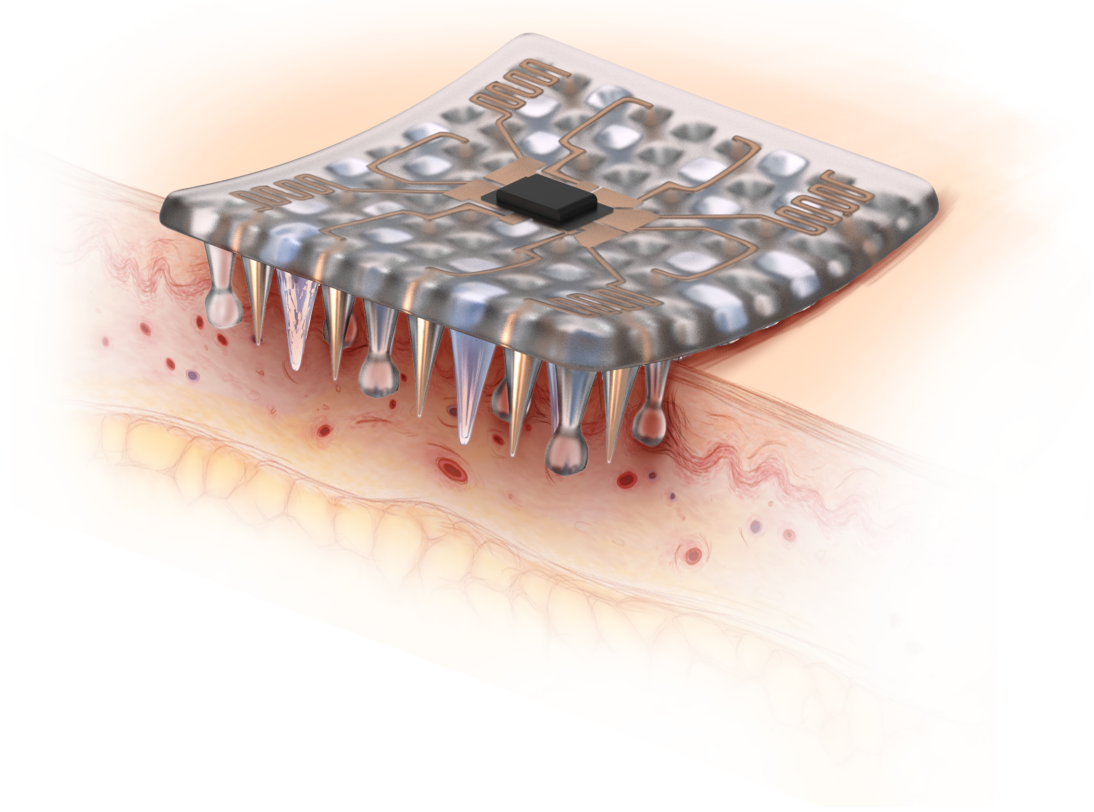
Abstract
Microneedles have recently been adopted for use as a painless and safe method of transdermal therapeutic delivery through physically permeating the stratum corneum. While microneedles create pathways to introduce drugs, they can also act as conduits for biosignal sensing. Here, we explore the development of microneedles as both biosensing and drug delivery platforms. Microneedle sensors are being developed for continuous monitoring of biopotentials and bioanalytes through the use of conductive and electrochemically reactive biomaterials. The range of therapeutics being delivered through microneedle devices has diversified, while novel bioabsorbable microneedles are undergoing first-in-human clinical studies. We foresee that future microneedle platform development will focus on the incorporation of biofunctional materials, designed to deliver therapeutics in a stimulus responsive fashion. Biofunctional microneedle patches will require improved methods of attaching to and conforming to epithelial tissues in dynamic environments for longer periods of time and thus present an assortment of new design challenges. Through the evolution of biomaterial development and microneedle design, biofunctional microneedles are proposed as a next-generation of stimulus responsive drug delivery systems.



1. Introduction

Microneedles are devices with micro-scale protrusions designed to painlessly bypass the body's primary physical barriers in a precise manner to achieve enhanced efficacy of biosignal sensing and/or therapeutic delivery. Typically, microneedles take the form of transdermal patches designed to penetrate the stratum corneum of the skin, however, they are now also being investigated to disrupt the barrier function of other epithelial tissues (eg. gastrointestinal tract[1], sclera[2,3], and endothelium[4,5]). Initially conceived as a more efficient method of painless transdermal drug delivery[6], microneedles have the potential to enhance the resolution of biosignal detection and therapeutic delivery, with minimal risk of infection. Advances in manufacturing processes and cost-effectiveness, disseminating largely from the microelectronics industry, have opened up exciting new possibilities for microneedle technology adoption and adaptation.

The potential for microneedles to act as a drug and vaccine delivery system have been well documented. An extensive review by Kim et al.[7] outline the state-of-the-art in microneedle design, clinical applications and manufacturing methods. Further review papers have focused on microneedle design[8], fabrication methods[9,10], degradable[11] and hydrogel-based[12] microneedle systems, the delivery of vaccines[13,14] and therapeutics[8,15] and the clinical safety of microneedles[10]. In this review, we track the evolution of microneedles from first-generation patches, which act as simple drug conduits, towards new concepts in microneedle design, where the advancement of biofunctional materials is leading to adaptive microneedles designed with integrated sensing and control systems. These next-generation smart-microneedle systems can behave in a stimulus-responsive fashion, facilitating, for example, on demand drug delivery. We track the advancements of microneedles as sensors and therapeutic delivery systems, and their impeding convergence as closed-loop systems. The incorporation of biomaterials that respond to their environment in multifunctional microneedle systems, leads to a host of additional applications and design considerations that are outlined here.

2. Evolution of microneedle biosensors

Historically, biosignal sensing has relied on a combination of blood draws followed by laboratory analysis or on sensors attached to bulky signal processing and monitoring equipment. Biosignal monitoring largely occurred in a clinical setting, until the introduction of point-of-care testing, which can facilitate an immediate electronic record through devices that are more user-centric. For example, glucose monitoring, driven by the rising incidences of diabetes and the necessity for regular measurement, has long been identified as an area that would benefit from less invasive, frequent self-monitoring. The first continuous glucose monitoring (CGM) electrodes were proposed in 1962 for cardiovascular surgery[16] but not until 1999 did the FDA approved the first CGM device for patient use[17]. Today the most common method of monitoring glucose still relies on point-sample drawing of blood, however the invasiveness of this procedure has decreased. A drop of capillary blood is typically sampled by piercing the skin on a finger; the blood is transferred to a disposable test strip and inserted into a digital meter. Huge advances have been made in the development of closed-loop artificial pancreas systems that deliver insulin through algorithmic control in response to measured glucose levels without human intervention. However, challenges still remain in repeatability and relating levels

of glucose in interstitial fluid from subcutaneous sensing to blood glucose levels.[18] Microneedle sensors offer undoubted potential as minimally invasive continuous glucose sensors.[19] The majority of microneedle sensor development to-date has focused on ex-vivo continuous glucose monitoring platforms. Microneedles are used for extraction of interstitial fluid prior to ex-vivo measurement.[20–22] El-Laboudi et al. have outlined the state-of-the-art in the use of microneedles as biosensors for glucose monitoring.[19]

Interest in mHealth (mobile health) apps and devices is soaring, generating a huge social appetite and financial market for wearable sensors. There has been an exponential growth of people monitoring their heart rate, sleep and activity with forecasts of up to 485 million wearable devices to be shipped annually by 2018[23]. This information will not only assist self-tracking but it may provide valuable data for doctors in monitoring rare events and normal activity for diagnosis and remote-monitoring of long-term chronic conditions[24], while also avoiding misdiagnosis due to white coat hypertension[25]. The FDA recently indicated that it does not intend to regulate medical device data systems (MDDS) that store, display, or convert information produced by separate devices. It will not look to regulate low-risk wearable devices designed to promote 'general wellness'. This will undoubtedly aid in the rapid evolution of new hardware and software in mHealth. Whether theses innovations can be applied in an efficient manner to regulated devices for semi-closed and fully closed loop systems, such as in glucose-responsive insulin delivery, remains to be seen. The future regulation of microneedles devices as non-invasive or minimally invasive sensors will be application specific.

Microneedle sensors have been developed for monitoring a variety of different properties including biopotentials and bioanalytes, such as enzymes for example. The primary research focus to-date in transdermal sensing has been to measure physiological electrical activity using electrodes or to measure analytes in-situ via electrochemical activity for instantaneous bioinformation with the aim of achieving long-term continuous monitoring. The microneedle materials are thus electrically conductive or electrochemically reactive.
Electrodes for biopotential monitoring have been produced from PDMS[26,27], silicon[28–31] or glass[32] coated in metal. O'Mahony et al. produced dry electrodes for ECG, EEG and EMG monitoring from silicon coated in silver.[31] Lee et al. produced gold coated borosilicate glass microneedle arrays for in-situ measurement of dissolved oxygen levels and oxidation-reduction potential.[32] Compared to flat wet electrodes, silicon dry electrodes for ECG, EEG and EMG showed better electro-mechanical interface with human skin and showed improved long-term monitoring of ECG[30].
Windmiller et al. produced an acrylate-based microneedle for electropolymeric entrapment of enzymes. Glutamate oxidase and glucose oxidase enzymes were attracted by enzyme-functionalised films and entrapped in cavities in the microneedles, however this system was only suitable for single use.[33] Amperometric sensors for measuring physiological analytes were created by loading reusable hollow acrylate-based microneedles with functionalised metallised carbon paste.[34] The microneedles could be re-used but repacking of the paste was required. Low-potential detection of hydrogen peroxide and sensing of lactate was shown by loading the paste with rhodium and lactate oxidase respectively. The pastes were also altered to enable monitoring of pH levels. Experiments showed that continuous monitoring of lactate, glucose and pH were possible.[35] With further research and influences from biofuel cell technology, the carbon

paste was refined towards sustained continuous glucose monitoring by capturing biochemical energy resulting in a self-powered device outputting a power density proportional to the interstitial fluid glucose concentrations.[36] Monitoring was preformed over a 60-hour period. These experiments show promising progress towards achieving continuous, in-situ sensing. While lab-on-chip devices are leading the way for point-of-care detection of biomarkers, a cost effective device which carries out a microfluidic process from start to finish has yet to be realised.[37] The integration of microneedle sensors into biomicrofluidic devices will form part of the next phase for microfluidic research which, according to Chang et al., will be device integration[37].

3. Evolution to microneedle drug delivery patches

The conventional method of drug delivery, the hypodermic needle and syringe, are a refinement of a device first used by Francis Rynd, an Irish physician, over 150 years ago to treat neuralgia by a subcutaneous injection of morphine acetate.[38] The mechanism of insertion and therapeutic delivery has remained largely unchanged, however through mass production, disposable needles and syringes can today be produced for as little as $0.03-0.04[39]. The major current global challenges related to injections identified by the World Health Organisation (WHO) include (i) reuse of injection equipment, (ii) accidental needle-stick injuries in health-care workers, (iii) overuse of injections and (iv) unsafe sharps waste management. The WHO has targeted the universal adoption of injection devices with sharps injury protection features and reuse prevention mechanisms by 2020.[39] Microneedle-based drug delivery has the potential to overcome device-related and some dose-related aspects of these challenges.

The first microneedle patent was filed in the US in 1976[40], however it was not until the 1990s that appropriate micro-manufacturing processes became widely available to facilitate the commercialisation of microneedle-based products. As safety and cost-effectiveness guide the future development of drug delivery systems, microneedle-based approaches offer a potential paradigm shift in how therapeutics are delivered. Many microneedle systems (e.g. coated[41], dissolvable[42], swellable[43]) incorporate the drug into the device in a solid-state, extending the shelf-life compared to drug solutions in syringes[44]. Post-insertion, these needles are no longer sharp[42,43], thus preventing reuse, needle-stick injury as well as reducing waste management issues. Microneedles typically only penetrate into the outer layer of the epidermis, thereby lowering the risk of blood borne disease transmission[43] and infection, increasing patient compliance[45] , while also allowing for sustained delivery[46] and in some cases requiring a lower dose than traditional hypodermic needle methods[47].

The original cohort of drug delivery microneedle patches were intended for drug delivery applications and were composed of first generation biomaterials, designed to be mechanically robust conduits which induce a minimal toxic response in the host[48]. These microneedles can be categorised by their design: solid microneedles can be used to ‘poke and patch’ (e.g. disruption of the stratum corneum prior to the application of insulin[49]); coated solid microneedles are used to ‘coat and poke’ (e.g. dry-film of ovalbumin protein antigen was coated over the limited surface area of solid microneedles prior to insertion and subsequent delivery to the interstitial fluid to evoke an immune response[45]); or hollow microneedles that can connect to a backing layer reservoir or syringe (e.g.

miniaturized versions of traditional hypodermic needles[1,3]), thus increasing the potential volume for drug delivery.[50]

Although there has been significant pre-clinical evaluation of microneedle technologies, relatively few platforms have been brought through clinical trials. This is due to a combination of technical challenges and dose limitations of most microneedle system designs[13], along with a more complex regulatory pathway for advanced designs. Injector-based devices are recognised by the FDA as Class II devices and thus can be cleared with a 510K submission if they are seen as substantially equivalent to current devices[51]. Many of the devices trialled can be attached to an existing syringe system meaning that primary drug container studies, which normally take 7+ years, are not required. Second generation microneedles with new biomaterials may not be approved with a 510K and so will require more substantial testing and clinical trials for pre-market approval. A total of 34 clinical trials were found using 'microneedle' as a keyword search term on clinicaltrial.gov. Figure 1 provides a snapshot of recent and current microneedle-systems, with stainless steel and silicon being the most commonly selected needle materials.

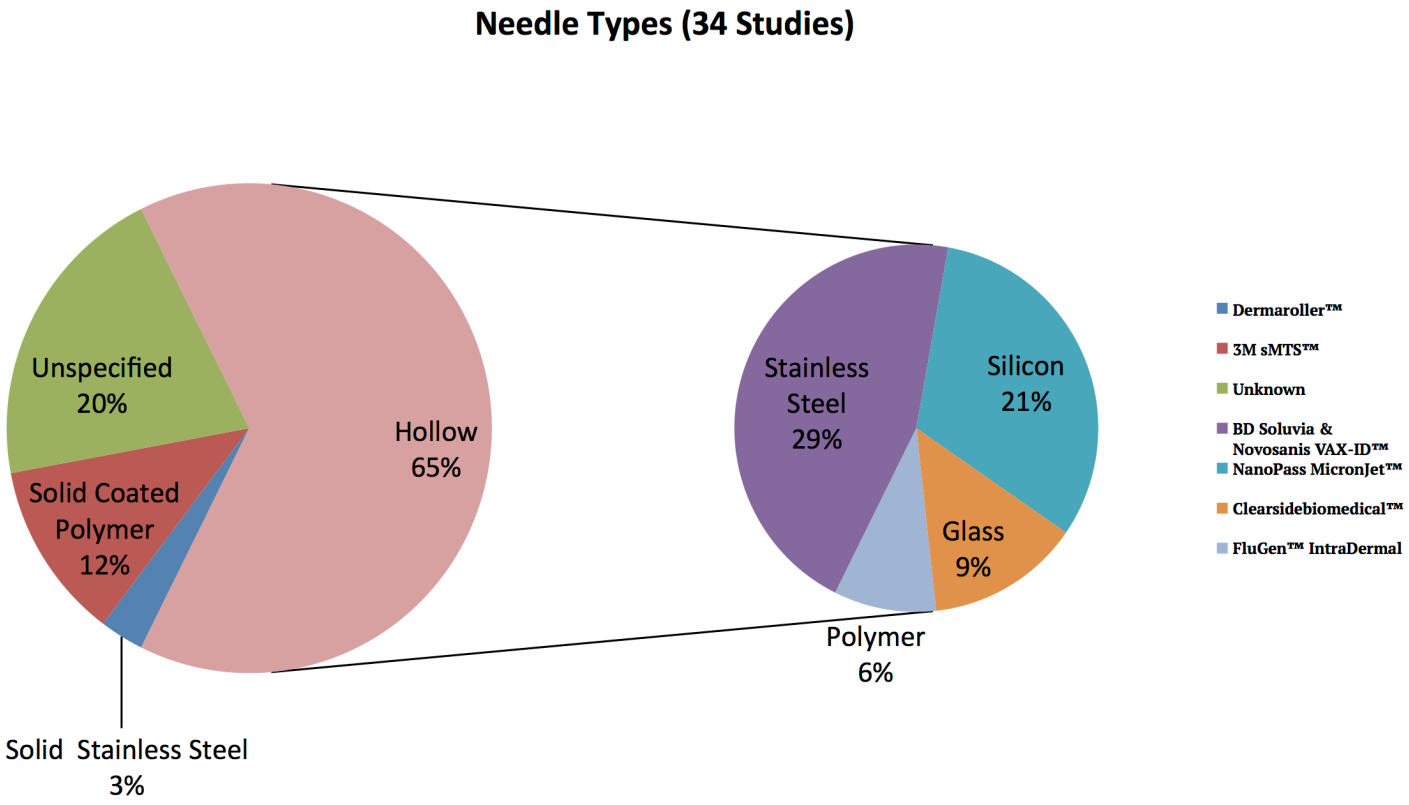


Figure 1 – Current trends in microneedle systems undergoing clinical trials or under review by the US Food and Drug Administration (studies shown found using 'microneedle' as a key word search term on clinicaltrial.gov).

Although microneedles for drug delivery composed of biomaterials have shown promising results in pre-clinical models for several years, it is only now that dissolving microneedles are being advanced to clinical studies. Dissolving microneedles, which are

pre-loaded with drugs, inserted and dissolve *in situ*, mark an evolution in biomaterial selection through the use of bioabsorbable materials for biofunctional microneedles. Biodegradable microneedles incorporate 'second-generation' biomaterials[52] into microneedle design, materials that are bioactive and elicit an action in response to their physiological environment[53]. The majority of dissolvable microneedles rely on simple solubilisation and hydrolysis. Sugar based microneedles dissolve rapidly resulting in a near-instantaneous drug burst release[54,55], while biodegradable polymer-based microneedles can offer a more sustained drug release[56,57]. Through careful selection of material composition or degree of crosslinking, the rate of degradation can be engineered. Biodegradable polymeric microneedles may undergo either surface or bulk erosion or a combination of both, significantly influencing the encapsulated drug release profile.

A number of investigations on the control of drug release profiles for biofunctional microneedles have been carried out. Bediz et al. used corboxy-methyl-cellulose (CMC), poly(vinyl-pyrrolidone) (PVP) and maltodextrin (MD) in a variety of ratios and saw a delayed rate of release of ovalbumin with increased amounts of PVP.[42] Chu et al. produced separable arrowhead microneedles, designed to disengage from the shaft within seconds of insertion. The drug-loaded arrowhead is left embedded in the epidermis and can degrade to a tuneable profile depending on the arrowhead formulation. Polyvinyl alcohol (PVA)/PVP arrowheads and PVA/sucrose arrowheads were produced, inserted and remained in the skin.[58] Lee et al. created dissolving microneedles from CMC and amylopectin. The shafts of the microneedles were loaded with sulforhodamine, which dissolved within 5 minutes, giving a bolus delivery of 0.04ug. The backing layer of these needles was composed of a swellable hydrogel (CMC and amylopectin) loaded with sulforhodamine which allowed for a sustained release of up to 1mg over 72+ hours.[59] Donnelly et al. produced hydrogel microneedles, which upon insertion absorb interstitial fluid in the skin and swell. The microneedles were created from crosslinked poly(methylvinylether/maelic acid) (PMVE/MA)[60] and poly(ethyleneglycol) (PEG)[43] or PMVE/MA crosslinked with glycerol[61]. They provide hydrogel conduits for drugs to flow from a drug reservoir contained in the backing layer. The microneedle crosslinking density controls the delivery rate. Injectable hydrogel studies have shown that sustained release of insulin over 16 days is possible as the hydrogel degrades.[62] While there are remaining challenges to incorporate these specific compositions into microneedle systems, it shows promise for a sustained hydrogel delivery platform.

In parallel with the advancements in degradable and swellable microneedle systems, the capacity of systems to deliver larger molecules and doses have also improved. Clinical trials have been completed with hollow microneedles delivering up to 0.5ml of saline.[63] The delivery of large molecules such as fluorescein-isothiocyanate labelled bovine serum albumin (MW 67,000Da)[43] and human immunoglobulin A protein (MW 150,000Da)[64] using microneedles has been demonstrated. As the size of molecules being delivered grows permeability issues arise. While the microneedle is penetrating the keratinized stratum corneum, the macromolecules still need to permeate through the epithelium to reach the dermis for systemic transportation or delivery to their therapeutic target. Smaller molecules can easily permeate the epithelium but larger molecules are less permeable and can be affected by enzymes in the epithelium. To improve drug

bioavailability, tools used to improve the efficacy of buccal macromolecule delivery could be employed. These methods include chemical permeation enhancers, enzyme inhibitors, lipophilicity modification and adhesion enhancers.[65] As biofunctional microneedle delivery platforms are developed, a key priority will be to ensure drug stability and suitable shelf-life for the specific therapeutic-material combinations.

4. Emergence of smart biofunctional microneedles with combined sensing & drug delivery

As the clinical applications of microneedles move beyond traditional transdermal sensing and drug delivery to applications that require longitudinal sensing and controlled, sustained drug release on dynamic tissue, new design challenges arise. Huang et al. report on a closed-loop system which extracts blood, detects glucose levels and injects insulin.[66] This system shows high sensitivity and the ability to inject precise amounts of insulin. Although Huang et al.'s system relies on blood draws it demonstrates the potential for a closed-loop sensing and delivery system.[66] These types of biofunctional microneedle systems can provide fully closed-loop or semi-closed-loop (with some degree of user intervention) systems for monitoring and response to bioanalyte levels in interstitial fluid, as illustrated in Figure 2. It is envisaged that biofunctional microneedles will be developed in two forms. The first type will be a stimulus-responsive microneedle (SRM) whereby a single microneedle senses a biostimulus triggering the release of a therapeutic from that microneedle. The second form will be a stimulus-responsive microneedle system (SRMS), where one needle or patch senses a biostimulus, which results in a different needle or patch releasing the therapeutic, much like the system developed by Huang et al.. The SRMS will incorporate an embedded or external control system. Both systems will allow for point-of-care continuous monitoring and delivery. Stimulus-responsive polymers are being investigated for disease site drug delivery and have been reviewed extensively[67,68]. A coupling of this knowledge base and that of the advanced fabrication of polymers, and specifically hydrogel microneedles will see the growth of SRM's. To date there is no record of SRM's or SRMS's having gone though clinical trials and to the best knowledge of the authors there is no literature on successful devices.

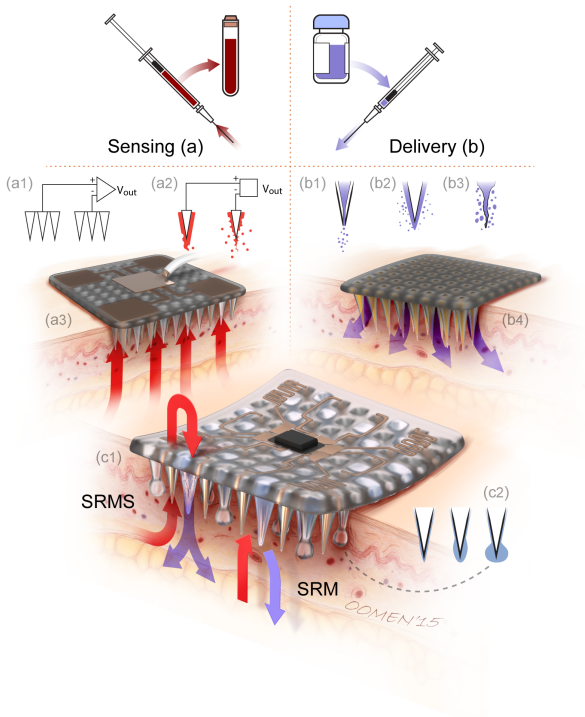


Figure 2 – The evolution of biosensing and therapeutic delivery. From traditional (a) blood draws for laboratory analysis and (b) hypodermic needle and syringe drug delivery. Microneedles are currently used for biosensing with (a1) biopotential and (a2) electrochemical (a3) microneedle patch biosensors, and drug delivery using (b1) hollow, (b2) coated and (b3) dissolvable (b4) microneedle patches. These systems are converging into a (c1) biofunctional microneedle patch for stimulus responsive therapeutic delivery with features such as (c2) swellable microneedles to aid in patch fixation. Stimulus responsive microneedle systems (SRMS) may involve sensing of a biosignal through a sensor needle which can result in therapeutic release from a separate needle or patch in a controlled fashion. Alternatively, individual stimulus responsive microneedles (SRM) may be engineered to deliver encapsulated therapeutics through controlled stimulus responsive degradation.

The design requirements of the first generation of microneedles were simply to pierce the stratum corneum, with minimum pain and ensure needle mechanical integrity was maintained. This was achieved by reducing insertion force, through reducing tip diameter[69,70] thus increasing needle sharpness, balanced with using strong, stiff materials that offer good column strength. Designing microneedles with a high Young's modulus reduces the risk of failure by buckling[70,71], while a high yield strength reduces the risk of failure by fracture or deformation of the tip. The wide variety of materials and their relative stiffnesses (Young's modulus) and yield strengths used for microneedle manufacturing, shown in Figure 3, illustrates that microneedle composition selection has evolved beyond the traditional metals used in penetrative devices. Design for ease of insertion still remains imperative for future biofunctional microneedle systems but the requirement for more longitudinal applications in sensing and delivery, alters the mechanical performance requirements for microneedles.

These systems will be required to exhibit good conformance to the skin during dynamic motion and therefore microneedle compliance, shear strength and fatigue performance will play a more significant role in material selection. Hydrogel-based microneedles that become more compliant on swelling or systems mounted to flexible backing layers, may be advantageous for this purpose[72].

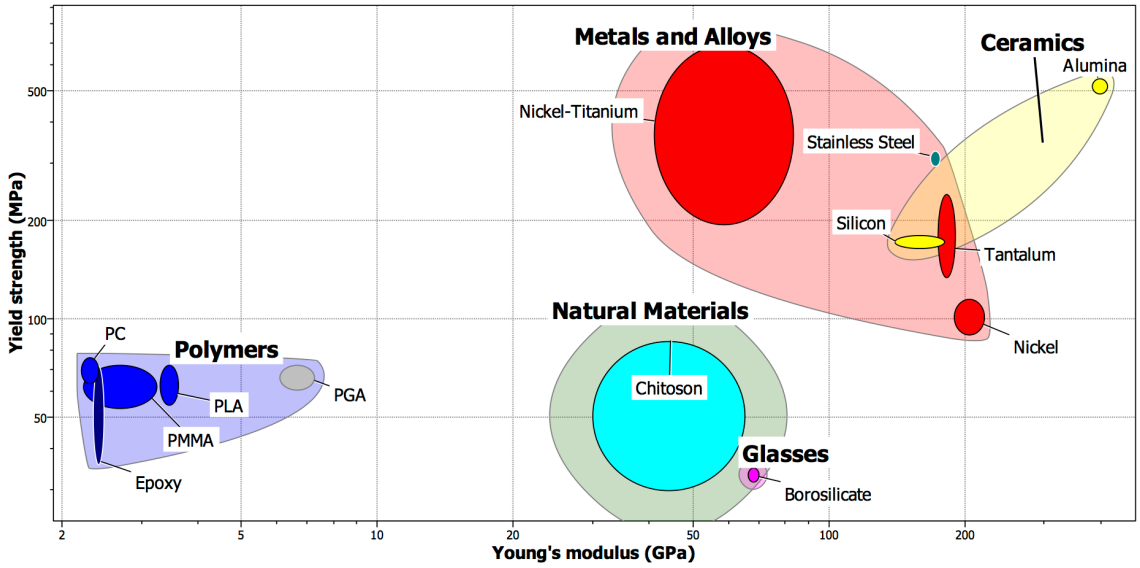


Figure 3 – Yield strength vs Young's modulus of different materials used for the fabrication of microneedles. Plastics – PC[73], Epoxy[74,75], PMMA[76], PGA[56,74], PLA[56,74,77]. Metals and alloys; nickel[78], stainless steel[41,49], tantalum[79] and nickel-titanium[70]. Ceramics; alumina[80] and silicon[81,82]. Chitison[83] and Borosilicate glass[3,45].

Designing and developing biofunctional microneedle patches will require improved methods of sterilisation, precision location and adhesion. Terminal sterilisation techniques can affect the microneedle material properties[84] and the incorporated therapeutic[85,86]. To date existing studies show that aseptic manufacturing can ensure sterility while not altering the device or therapeutic tested. This method is used for drug-device combinations but is not necessarily the preferred method due to high manufacturing costs. The sterilisation method must be carefully considered, particularly the effects on the microneedle and sensor materials as well as the therapeutic when it is incorporated in the device.

Biofunctional microneedles may be applied to a wide variety of transepithelial applications beyond transdermal sensing and delivery, ensuring precision location will become significant. Traverso et al. devised a method of encapsulating microneedles in a tuneable pH-responsive pill that can dissolve in targeted areas of the gastrointestinal tract. Once activated in the GI tract, the microneedles pierce the epithelium and release the therapeutic by peristaltic compression of a drug reservoir.[1] Microneedle patches could also assist in fixing a delivery or sensing device for sustained delivery and continuous monitoring without the need for chemical adhesives. Yang et al. designed a biphasic microneedle system with a solid polystyrene core and swellable amphiphillic copolymer tip made from polystyrene-block-poly(acrylic acid) (PS-*b*-PAA). The swellability can be controlled by altering the molecular weight of the polymer tip. This microneedle patch is suitable not only for transdermal drug delivery but also acts as a mechanical fixation device to dermal and mucosal tissue. The PS-b-PPA microneedles achieved adhesion strength 3.5 times stronger than staples in skin graft fixation as well as a removal force of 4.5N/cm^2.[72]

Microneedle-based sensing can be performed either *ex vivo* or *in vivo*. SRMS devices, which perform *ex vivo* sensing, could extract interstitial fluid and carry out sensing using

a microfluidic biomarker sensor. While implantable sensors have been developed for continuous glucose monitoring, they suffer from limitations in precision and accuracy.[87] Improved sensing capabilities are on the horizon, with influences from lab-on-chip technology, potentially building on miniaturized enzymatic amperometric sensors as described by Senapati et al., where the charge of the captured target molecules is used to block ionic current through an ion-selective membrane[88]. Further advances in decreasing the required sample analysis volume are needed and reducing the size and cost of the sensors. Theranos™ , a Californian based company, perform multiple standard blood tests on a single drop of blood, showing immense potential for small volume biosensing. Fouling of sensors and delivery mechanisms, either by blocking of fluid pathways in SRMS devices or corrosion by untargeted interstitial fluid components of sensors in SRM devices will pose significant challenges. These challenges will grow as target wear-times extend, but sophisticated algorithms, low manufacturing costs and facile application can ensure that microneedle patch replacement provides uninterrupted continuous biosignal monitoring.

5. Conclusion

The evolution of biofunctional materials and manufacturing methods offer new horizons in microneedle patch forms and applications. Materials are becoming more responsive and controllable, therapeutics suitable for transepithelial delivery are diversifying and our increasingly data-driven healthcare systems demand real-time sensors. These key areas are leading to the development of microneedle platforms, which will provide automated or semi-automated closed-loop response systems for user-centric advanced control of monitoring and administration of therapeutics in a stimulus responsive fashion.

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