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MICRONEEDLE ARRAYS FOR TRANSDERMAL DELIVERY OF INSULIN: FABRICATION AND SKIN INSERTION STUDIES

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1. INTRODUCTION

People with diabetes who depend on insulin face injections several times a day, and the burden of this routine contributes to missed doses and delayed treatment intensification [1, 2]. Insulin is a peptide hormone of about 5.8 kilodaltons (kDa) that is destroyed in the gut, so oral dosing is not simple, and the skin presents a barrier that excludes almost all molecules of this size [3, 4]. Microneedle arrays offer a middle way. They consist of rows of tiny projections, typically a few hundred micrometres long, which pierce the

Abstract

Microneedle arrays create microscopic channels through the stratum corneum and have been proposed as a needle-free way to give insulin. This review summarises published work on how insulin microneedles are made and how their skin insertion is tested, and it reports no new data. It covers the barrier properties of skin, metal, silicon and polymer fabrication routes, mechanical and insertion testing, drug loading and delivery in animal models, and safety. Reports show that insertion depends on needle geometry, array density and application method, and that insulin delivery in diabetic rodents is feasible. Dose accuracy, long-term skin effects and human glycaemic data are still thinly documented.

outermost layer of skin without reaching the nerve endings and blood vessels that lie deeper, and thus open a route for macromolecules [5, 6]. The concept has moved from laboratory curiosity to a substantial research field.

This article reviews the published work on microneedle arrays for insulin, with attention to two practical questions. How are the arrays fabricated, and from what materials? And how is skin insertion tested, since a needle that fails to penetrate delivers nothing? It is a narrative review and reports no new experimental data. Much of the evidence is from rodent and porcine models and from excised skin, with limited human work, and the review makes clear which type of evidence supports each statement. Because the field was established by a small number of groups, particularly those at Georgia Tech, Queen's University Belfast, and the Taiwanese and Japanese academic centres, findings from these groups appear repeatedly [7, 8].

The sections that follow describe the skin barrier and the insulin problem, then fabrication, insertion testing, and the delivery evidence in diabetic animals, which is summarised in table 1 and fig. 1. A final section considers safety, skin recovery and the gaps that stand between laboratory prototypes and a licensed product. Terminology is kept simple. A solid microneedle is used to pierce the skin and is then removed, coated needles carry drug on their surface, dissolving needles are made from a drug-loaded matrix that dissolves in the skin, and hollow needles contain a bore through which solution is infused [7, 9]. These four categories organise most of the literature.

Table 1: Published microneedle approaches for insulin and their reported features

Approach/Material	Reported finding	Ref.
Solid metal needles pretreatment	Lowered blood glucose in diabetic hairless rats after skin puncture and insulin application.	[10]
Hollow metal needles infusion	Controlled insulin infusion produced adjustable glucose decrease in diabetic rats.	[11]
Silicon needles etched	Increased skin permeability to model compounds by orders of magnitude.	[5]
Dissolving needles insulin-loaded	Self-dissolving arrays reduced glucose in mice.	[12]

Approach/Material	Reported finding	Ref.
Polymer patches dissolving	Rapid delivery to diabetic rats with a glucose profile similar to injection.	[13]
Hyaluronic acid needles insulin	Dose-dependent glucose lowering with retained insulin activity after fabrication.	[14]
Hydrogel-forming needles swelling	Removable arrays release drug from a separate reservoir without leaving polymer.	[15]
Coated needles dip-coating	Coating uniformity depends on viscosity; capacity limited to small doses.	[16, 17]
Glucose-responsive patch vesicles	Hypoxia-sensitive vesicles released insulin in response to glucose in small animals.	[18]
Insertion models Parafilm and skin	Layered film proposed as a standard model for insertion depth.	[19]

2. THE SKIN BARRIER AND INSULIN

The stratum corneum, only about 10 to 20 micrometres thick, is the rate-limiting barrier of skin. It consists of flattened, keratin-filled corneocytes held in a lipid matrix, and it allows passive passage only of small, moderately lipophilic molecules, with a rule of thumb that the molecular mass should not exceed about 500 daltons (Da) [3, 4]. Insulin, at roughly ten times this size and hydrophilic, does not cross intact skin in measurable amounts. Chemical enhancers, iontophoresis and ultrasound have been tried, but they either deliver little insulin or carry other drawbacks [3, 6]. Physical disruption, by microneedles, is a more direct way of avoiding the barrier rather than loosening it.

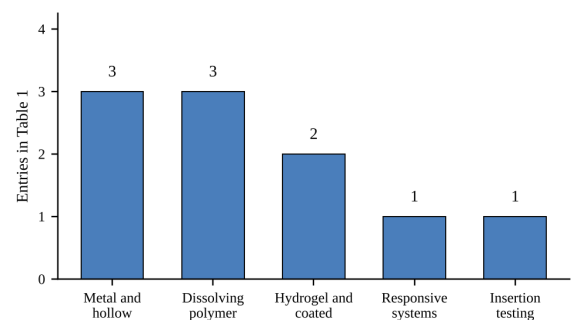


Fig. 1: Number of entries in table 1 by microneedle approach

Below the stratum corneum lie the viable epidermis, which has no blood supply, and the dermis, which is rich in capillaries and lymphatics. A microneedle intended for systemic delivery must therefore deposit insulin at or beyond the epidermal-dermal junction, so that the drug can diffuse to the dermal vasculature, while remaining short enough to avoid stimulating the deeper pain receptors [6, 20]. Needle lengths of 150 to 1000 micrometres have been studied. Skin is also elastic and deforms under pressure, so a needle that is nominally 500 micrometres long may penetrate far less. This difference between nominal length and actual depth is the reason insertion studies form a large part of the literature [21, 22].

Insulin brings its own demands. Dosing is measured in units, and a typical mealtime dose is a few to a dozen units, equivalent to a fraction of a milligram, so a patch must deliver reliably in quantities that a small array can hold [1, 2]. The pharmacokinetic profile is also important. Rapid-acting insulin by subcutaneous injection peaks in an hour or two, and any competing method needs a similar onset to be useful at mealtimes, while basal replacement needs a stable delivery over many hours [1]. Insulin is also sensitive to heat, shear and organic solvents, which limits the manufacturing processes that can be used with drug-loaded needles.

3. FABRICATION OF MICRONEEDLE ARRAYS

The first microneedles were made from silicon using the etching methods of the semiconductor industry. Henry and colleagues produced arrays of solid silicon needles, about 150 micrometres long, by reactive ion etching, and showed that they increased skin permeability to a model compound by orders of magnitude [5]. Silicon is brittle, however, and breakage in skin is an obvious concern. Metal needles made from stainless steel or titanium by laser cutting, electropolishing or wet etching offer more strength [10, 23]. Glass and ceramic needles have also been described. Cleanroom fabrication of these materials is costly and slow, which fits poorly with a product intended for a mass diabetic market.

Polymer microneedles followed. Biodegradable and biocompatible polymers such as poly(lactic acid), poly(lactic-co-glycolic acid) (PLGA), polyvinylpyrrolidone (PVP), carboxymethylcellulose (CMC), hyaluronic acid (HA) and maltose have been moulded into needles that can hold drug within the matrix [14, 24, 25]. Moulding is the central technique: a master structure is made by etching, laser ablation or photolithography, a negative mould of silicone is cast from it, and a polymer solution or melt is filled into the cavities, usually under vacuum or centrifugation, and dried. Donnelly's group described laser-based micromoulding of polymeric arrays with defined geometry and showed that the process was reproducible [26]. Others have pushed the approach towards continuous printing.

Dissolving needles are particularly suited to insulin because they allow loading within the needle tip at low temperature and in water. Lee and colleagues demonstrated that needles made from CMC and sugars dissolved in skin within minutes and released encapsulated molecules, leaving no sharp waste [25]. Water-soluble sugars such as maltose and trehalose also stabilise the protein, as they do in freeze-drying. HA needles loaded with insulin have shown good mechanical strength and a pharmacologic response in rats [14]. Hydrogel-forming needles, which swell after insertion without dissolving, can be removed intact and allow drug to diffuse out from a separate reservoir, a design that avoids polymer residues in the skin [15].

Moulding has practical limits that fabrication papers describe only briefly. Polymer solutions must flow into cavities only a few hundred micrometres deep, and air trapped at the tip leaves blunt or hollow needles unless vacuum or centrifugation is applied [25, 26]. Drying shrinks the needles, and the rate of drying affects both their shape and the distribution of drug within them. For insulin, a common aim is to concentrate drug in the tip, so that the base layer, which never enters the skin, contains no peptide. Two-step casting, with a drug-rich layer first and a drug-free backing second, achieves this, and the approach reduces waste of an expensive

protein [13, 25].

Coated microneedles are made by dipping or spraying metal needles with a formulation of drug, viscosity enhancer and surfactant. Gill and Prausnitz showed that coating thickness and uniformity depend on the viscosity and surface tension of the coating solution, and that dip-coating could place defined doses on the needle shafts [16, 17]. The limitation is capacity. A coating of a few micrometres on arrays of a few hundred needles can carry only microgram quantities, which is less than a typical insulin dose, so coated systems have been explored mostly for potent drugs and vaccines [9, 16]. Hollow needles overcome the capacity problem by infusing liquid through a bore, but they require a pump or pressure source and are prone to blockage by tissue [11, 23].

Sterility and storage are rarely discussed in fabrication papers, yet they are essential for a product. Microneedle patches are not injections, though they breach the skin, and the regulatory expectation is for low bioburden or terminal sterilisation. Gamma radiation and heat can degrade both polymer and peptide, so aseptic processing or ethylene oxide treatment may be needed. Storage in sealed foil with desiccant helps because dissolving needles are hygroscopic and soften in humid air, which weakens them before use [8, 9]. Each of these questions is straightforward to answer, but few papers do so, and a stability study under defined humidity and temperature would be a useful addition.

4. SKIN INSERTION STUDIES

Insertion depends first on mechanics. A needle penetrates when the stress at its tip exceeds the strength of the skin, and it survives only if the force needed to fracture it is larger than the force needed to insert it. Davis and colleagues measured both for metal needles and showed that the margin of safety, the ratio of fracture force to insertion force, is higher for needles with a small tip radius and a thick wall [21]. Insertion force rises with tip area. Needles with sharper tips thus insert more easily and are stronger relative to the load. Polymers have a much lower fracture strength than metal, so compression tests on

polymer arrays against a hard plate are routine in fabrication papers [24, 25].

Mechanical testing of arrays usually precedes any skin work. An array is pressed against a flat metal plate in a texture analyser or similar apparatus while force and displacement are logged, and needle height before and after compression gives the fraction of height lost [24, 25]. Axial failure loads of polymer needles are usually compared with the force needed to enter skin, which for a single needle is of the order of tens of millinewtons in published measurements [21]. Transverse loading is also relevant, since needles can bend during application. Mechanical strength is a necessary condition for insertion, not a sufficient one, because skin deformation and array density change what the individual tip experiences.

Several models serve to test insertion. Excised human or porcine skin is closest to clinical reality, but supplies are limited and mechanical properties alter with storage, hydration and tension. Layered Parafilm M, a wax film, has been proposed as a cheap and standardised model membrane, with the number of perforated layers used as a proxy for depth, and the approach was formally evaluated for microneedle work [19]. Staining with gentian violet or trypan blue after removal reveals which needles pierced the skin, and the pore count gives a percentage insertion. Optical coherence tomography (OCT), confocal microscopy and histology provide cross-sections of the channels and their depth [27, 28].

Array design strongly affects insertion. Many needles on a flat patch spread the applied force across the array, so each tip receives less, and dense arrays can fail to penetrate in the way a single needle would, an effect sometimes called the bed-of-nails effect. Olatunji and colleagues examined array interspacing and found that wider spacing lowered the force needed per needle for successful penetration [29]. Kochhar and co-workers reported that geometry and the supporting substrate both affected penetration, with sharper and longer needles and rigid backing giving better results [22]. Skin extensibility means that penetration is often partial, with measured depths less than

the needle length by a considerable fraction [21, 22].

Application method is equally important. Thumb pressure is variable, and studies using spring-loaded applicators found that impact insertion at a controlled velocity gave more consistent and deeper penetration in dermatomed human skin than slow manual pressing [28]. Skin site, tension and hydration also matter. In human volunteers, Haq and colleagues examined skin puncture, pain and sensation with a range of needle lengths, and reported that insertion was practical with the arrays used [30]. Wear time and adhesion are further considerations for dissolving systems, since the polymer must have enough time in wet tissue to dissolve before the patch is lifted, which may take minutes to hours depending on the matrix.

Recovery of the skin after insertion is a significant part of the insertion literature. In human subjects, the pores created by microneedles close over time, with kinetics depending on whether the site is covered; under occlusion the pores remained open for much longer than when left uncovered [31]. Barrier recovery measured by trans-epidermal water loss (TEWL) and electrical impedance is therefore used to show that the channels are transient. This is reassuring for safety, since closure limits the risk of microbial entry, but it also bears on delivery: with dissolving or coated systems the drug is delivered rapidly, whereas systems that rely on open channels depend on how long they remain patent [27, 31].

5. INSULIN DELIVERY EVIDENCE

Studies in diabetic animals provide the main evidence that microneedle insulin delivery works, and they are summarised in table 1 and fig. 1. Martanto and colleagues used metal microneedles in diabetic hairless rats and showed that blood glucose could be lowered substantially, with the degree of reduction depending on the delivery protocol [10]. Hollow metal needles used to infuse insulin gave a controlled response in diabetic rats, and the rate of fall in glucose could be adjusted by the infusion rate [11]. Ito and colleagues reported that insulin-containing self-dissolving microneedles reduced glucose

in mice [12]. In each case the approach delivered pharmacologically active insulin through skin.

Dissolving and polymer arrays have given the most encouraging data. Ling and Chen reported that dissolving polymer microneedle patches delivered insulin to diabetic rats rapidly and efficiently, with a glucose-lowering profile of the same general type as that after subcutaneous injection [13]. HA microneedles loaded with insulin lowered glucose in a dose-dependent way, and the insulin was reported to remain active after fabrication [14]. Hypoxia-sensitive vesicles loaded into a patch were used to design glucose-responsive release, a design that senses glucose and releases insulin accordingly, although the evidence remains in small animals [18]. Together, these studies suggest that stability during fabrication is manageable when needles are made from water-soluble materials.

Laboratory assessment of release and stability uses several routine methods. Franz diffusion cells with excised skin or a membrane can follow insulin passage over time, and insulin in the receptor fluid is then measured by HPLC or by enzyme immunoassay [12, 13]. Whether the peptide survives fabrication is checked with chromatography to detect degradation and aggregates and with spectroscopic methods that follow secondary structure, and activity is confirmed by the glucose response in animals [13, 14]. Reports differ in how fully they do this. Some show only that glucose fell, which is a relevant but indirect indication of preserved activity, and a complete picture needs both physical and biological evidence.

Interpreting these results requires care. Rodent skin is thinner and more elastic than human skin, and the hairless rat in particular has been a convenient model but not a close predictor of human insertion or absorption [7, 9]. Dose delivered is often estimated rather than measured, because part of the drug remains in the baseline, or on the skin surface, or in the residue of the patch. Relative bioavailability calculated against subcutaneous injection varies greatly across reports, as do dose, species and sampling times [12, 13, 14]. A glucose-lowering effect

proves that insulin has been delivered but does not show how much, and measurement of plasma insulin by immunoassay is the more informative end point.

6. SAFETY, LIMITATIONS AND OUTLOOK

Pain and skin response are the most convincing advantages of microneedles over hypodermic injection. Kaushik and colleagues first reported that insertion of microfabricated needles was essentially painless in volunteers [32], and Gill and colleagues later showed that perceived pain increased with needle length and with the number of needles, though all designs were rated much less painful than a hypodermic needle [20]. Mild erythema at the application site, usually resolving within a day or two, is the most commonly reported local effect, and studies in human skin found no lasting damage in the arrays tested [27, 30]. Infection risk appears low in the short term, but long-term repeated use at the same site has not been studied properly.

Several technical limits persist. Dose accuracy is the first, since incomplete insertion, partial dissolution and drug left in the patch all reduce delivered insulin in a way that is difficult to control [28, 29]. The second is variation between individuals and skin sites. The third is capacity, since the matrix of a patch can carry only a limited mass of drug in its needle tips, so polymer arrays often require a high insulin loading in a small volume [9, 26]. Patient handling is a fourth issue: the patch must be applied with enough force, held for the correct time and not be confused by skin moisture. None of these is insurmountable, but all must be addressed in design.

Evidence on human glucose control is the main missing piece. Almost all insulin data are from rodents, with few clinical studies and, to the knowledge of this review, no adequately powered trial showing tight glycaemic control with a microneedle insulin patch [7, 8, 9]. Future research would benefit from several advances: standardised insertion models and reporting, precise measurement of delivered dose, plasma insulin pharmacokinetics in larger animals with skin

closer to that of humans, and long-term safety in repeated use. Manufacturing at scale, sterility, shelf-life data for the peptide in dissolving matrices and disposal of used patches are also required for a marketable product. With such data in place, microneedle insulin could become a realistic alternative or supplement to injections [3, 8].

Regulatory classification will influence how quickly any insulin patch can be developed. A drug-loaded microneedle patch is likely to be treated as a combination product, in which the drug, the polymer and the device are all assessed, and manufacturers would need to define performance tests for insertion and dose delivery as release specifications [8, 9]. Insulin is already approved in many forms, which helps, but a new route changes the pharmacokinetic profile and so requires fresh clinical data. Training and instructions for patients will also be part of the assessment, because use errors with an applicator or a patch can reduce the dose.

Closed-loop delivery is a longer-term prospect. Patches that sense glucose and release insulin in response, for example through hypoxia-sensitive or enzyme-linked materials, would simplify therapy greatly [18]. At present they are proofs of concept in rodents, and issues such as response time, sensor drift, enzyme stability and repeated cycling have not been resolved. Even so, the idea shows how microneedles can function as part of a system and not only as a replacement for a needle. Combining sensing and release in one disposable patch would also address the dosing accuracy problem more directly than a passive system does.

7. CONCLUSION

Microneedle arrays can open a route through the skin for insulin, and the evidence reviewed here supports their potential, because the evidence reviewed here supports their potential, because the published work shows that several fabrication routes, from etched metal to moulded dissolving polymers, can produce arrays that penetrate skin and lower blood glucose in diabetic animals [10, 11, 13, 14]. Insertion depends on tip geometry, array spacing, backing and the way the patch is applied, and these factors must be

controlled and reported for results to be comparable, which is not yet the norm [21, 22, 28, 29].

The path to clinical use remains long. Dose accuracy, skin variability, long-term safety and manufacturing are not yet addressed in a way that would satisfy regulators, and human glycaemic data are very limited [7, 8, 9]. Standardised insertion testing, plasma insulin measurement and trials in people with diabetes are the next steps, and each should be reported in enough detail for other groups to repeat it. Until they are completed, microneedle insulin delivery should be viewed as a promising technology that is still at an early stage of development, and its success will depend on rigorous and comparable testing.

8. ABBREVIATIONS

Da-Dalton, kDa-Kilodalton, OCT-Optical coherence tomography, PLGA-Poly(lactic-co-glycolic acid), PVP-Polyvinylpyrrolidone, TEWL-Trans-epidermal water loss, CMC-Carboxymethylcellulose, HA-Hyaluronic acid

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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