Editorial　　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Microneedles: An Emerging Approach for Active Transdermal Delivery of Insulin

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Editorial

Since the discovery of insulin, ninety years ago, long term exogenous insulin replacement therapy has been the most effective treatment of type 1 and advanced type 2 diabetes. Because of its poor absorption, instability in the gastrointestinal tract and short half-life, insulin is conventionally administered by multiple injections, most commonly subcutaneously, to control the blood glucose level in diabetic patients. To date, a variety of injectable insulin products with varying onset and duration of action are used to meet the temporal requirements of an insulin therapy that mimics as close as possible natural production of insulin. However, pain, needle phobia and stress provoked by invasiveness and chronic parenteral therapy in addition to tissue trauma, allergic reactions and less than optimum pharmacodynamic response, have been the main limitations of subcutaneous insulin [1]. Other concerns include disposal and re-use of needles in certain communities, as a source of blood-borne pathogens. Despite improvement in needles and injection devices and infusion pumps [2], invasiveness and discomfort led in many instances to poor patient compliance and delayed insulin therapy in type 2 diabetes. Such inconveniences, on the other hand, directed developments in insulin therapy to alternative non-parenteral delivery strategies that are less invasive [3], a trend greatly enhanced by the availability of recombinant insulin on a commercial scale and a plethora of drug delivery strategies. Insulin delivery systems for oral, inhalation, intranasal, rectal or transdermal administration have been investigated with limited clinical applicability. Direct injection of insulin using a needle remains more effective and provides an avenue for effective development.

In the last decade, microneedle (MN) arrays emerged as a new transdermal drug delivery enhancement technology combining the advantages of a hypodermic needle and the convenience of a patch while reducing their limitations [4]. MN technology is based on miniaturization of multiple needles within a patch to the micron dimensions. When the patch is applied to the skin either manually or using an applicator, MNs with a length ranging from 100 to 1500 μm, transiently and painlessly perforate the stratum corneum (SC) having a thickness of 10-20 μm and penetrate through the epidermis to a depth of 70 to 200 μm. Microchannels thus created, act as temporary in-skin hydrophilic pathways that facilitate delivery of small drugs such as alendronate [5], macromolecules [4,6] and nanoparticles [7] to the skin. The rich capillary bed in the dermis allows for rapid uptake of the delivered drug. Microchannels reclose within hours with recovery of skin integrity as assessed by transepidermal water loss [8,9].

The design of individual MN arrays varies with the application. Common variables include MN geometric features (shape, length, diameter, aspect ratio, tip diameter and sharpness etc.), choice of fabrication material (metal, polymer, glass, ceramic, silicon, polysaccharides, etc.) and physical architecture (solid or ceramics). MN arrays may vary in shape, size, MNs density and interspacing, etc.

Simultaneous modulation of MNs and array variables considerably affects the device characteristics, the application force needed and the ease and cost of fabrication.

As active drug delivery devices, MNs offer great advantages such as painless and fearless drug administration, skin delivery of macromolecules and vaccines, avoidance of first-pass metabolism, possible in-skin targeting, enhanced drug efficacy with reduction in dose and side effects. Finally, modulation of drug delivery rate is possible by coupling MN arrays with a micropump or other physical enhancement techniques such as iontophoresis and sonophoresis [10]. On the other hand, MNs show limitations including dosage accuracy as affected by the device design, fabrication method and application to the skin, possible buckling or fracture of MNs in addition to variability of skin thickness and conditions among individuals. Such limitations have been addressed efficiently during a decade of research.

MNs can be broadly divided into two categories, solid and hollow. Solid MNs include nondissolving and dissolving/degradable MNs. Drugs can be delivered across MN-treated skin using several approaches [11]: a) "poke and patch", an approach involving skin pretreatment with solid MNs followed by topical application of drug formulation or patch on microporated skin; b) "coat and poke" where solid MNs are coated with the drug and inserted into the skin, an approach allowing precise dosing and skin administration of unstable drugs; c) "Poke and release" using drug-loaded solid MNs made of dissolving/ biodegradable polymers or polysaccharides allowing simultaneous skin microporation and drug release in one step. No patch or micropump is needed and no hazardous sharp waste left; d) "poke and flow" where hollow microneedles are used to infuse a liquid drug formulation into the skin. Hollow MNs can also be used to withdraw dermal interstitial fluid for glucose monitoring [4].

MN fabrication is based on microfabrication methods utilizing photolithography, silicon etching, laser micromachining, micromolding and microelectromechanical (MEMS) techniques [4,11]. Selection of MN category, fabrication material and method as well as the drug delivery approach is application-specific. It depends on the drug molecular characteristics, the dose and whether local intradermal or transdermal delivery is required.

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As macromolecules are target candidates of MN-driven transdermal delivery, a great deal of MN-based research has been focused on macromolecular therapeutics with insulin receiving most attention. Proof of concept was followed by progressive improvement using different types of MNs and combined approaches. Preclinical studies using solid MNs for skin pretreatment demonstrated significant increase in delivery of insulin solution and reduction in blood-glucose level [12]. The technique was improved by using MN rollers [13], lyophilized hydrogel insulin patch to replace the insulin solution [14] and by combining MN pretreatment with iontophoresis and insulin-loaded nanovesicles [15]. Simultaneous basal-bolus delivery of fast-acting insulin could also be achieved by pretreating the skin of diabetic rats with short solid MNs (150 µm) and applying an iontophoresis transdermal patch with insulin reservoir for on-demand iontophoresis-triggered dose for postprandial insulin administration [16]. Solid MNs coated with insulin proved to be an alternative single step means for effective insulin delivery [17].

Further, solid MNs of the dissolving/biodegradable type encapsulating insulin, fabricated under mild temperature conditions and circumventing the use of organic solvents were shown to preserve insulin stability and bioactivity and to enable effective delivery upon insertion into the skin [18]. Attempts were made to prolong pharmacodynamic effects in rats by using intermediate-acting insulin [19].

Hollow microneedles present an alternative MN type for insulin delivery via the "poke and flow" approach. They offer advantages over solid MNs by allowing faster active delivery of the drug solution by combining a microneedle injection applicator with a syringe, a hand-pressed flexible drug reservoir, an iontophoresis unit, a micropump or a microfluidic chip [11]. In clinical studies, hollow MNs were more convenient compared to conventional subcutaneous catheters. In addition, hollow MN-driven intradermal insulin delivery induced faster insulin absorption and enabled more rapid onset and offset of metabolic effect on blood glucose levels which was attributed in larger cohorts of type I diabetic patients to rapid lymphatic uptake and distribution of insulin from the skin [20]. Hollow MNs allow the delivery of a larger amount of drug compared to other MN types and hence have been the subject of a large proportion of patents filed based on MN type and clinical studies of insulin delivery to type 1diabetes subjects [21].

Extensive research over the last decade provided ample proof of the potentials of MN arrays with optimized characteristics for the active dermal delivery of insulin and reduction of blood sugar level in a non-invasive painless manner. Clinical findings coupled with patient acceptability and possibility of self-administration put forward MN technology as a platform for an alternative insulin therapy for millions of diabetic patients worldwide, including pediatric and geriatric patients, assuming cost effectiveness.

For effective exploitation of MN technology in the management of insulin therapy, complex interdependencies of technological, pharmaceutical and biological variables involved in the MN-insulin formulation-patient interaction warrant multidisciplinary research and development initiatives. Quality attributes of an ideal MN system for diabetes management will be governed by advances in biomedical engineering, microelectronics and microfluidics. At the broadest level, a prototype MN-based device for diabetes management is an autonomous MN-based automated device whereby a glucose sensor as a diagnostic component is connected with a therapeutic component consisting of a hollow MNs array/micropump for the intermittent active dermal delivery of insulin. Both components are bridged by a feedback microchip which regulates the blood glucose level by adjusting insulin delivery. Such a system allows for accurate patient-specific tailoring of the glucose level versus quantitatively and temporally controlled insulin delivery [22]. However, for years to come, stand-alone glucose sensors and insulin delivery systems will be used by diabetic patients with MN technology providing a future patient friendly therapeutic modality.

Finally, in order to move MNs to the market, specific regulatory guidelines for the development of different microneedle systems should be set by regulatory authorities. Conformation to such guidelines and to quality standards of drugs and bioactive agents will safeguard efficacy and safety of insulin/MN devices. Acceptability of these devices by diabetic patients, long-cherishing a painless insulin therapy, will be maximized by price affordability and evidence for cost effectiveness.

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