Therapeutic Delivery

Micro and nanoneedles for drug delivery and biosensing

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Delivering therapeutics in a painless manner is one of the many objectives for the treatment of clinical conditions. Micro and nanoneedles are small-scale devices that can help overcome the resistance encountered during drug diffusion by creating conduits of small dimensions through biomembranes. Microneedles for drug delivery applications were manually produced until the 1990s and after this the high precision technology from the semiconductor industry was adopted for their production [1]. Over the last decade or so, microneedles for transdermal applications have been widely studied. Currently, microneedle patches, mainly based on hyaluronates, are available over the counter for cosmetic applications. On the other hand, nanoneedles are used in atomic force microscopy, which has been explored for drug delivery and biosensing over the last two decades [2,3]. Micro and nanoneedle-based biosensing also poses potential for environment-responsive drug delivery. In this article, the current research, clinical studies and future perspectives of micro and nanoneedle-based systems are discussed for drug delivery and biosensing applications.

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Micro & nanoneedles for drug delivery

Microneedles for drug delivery

Various types of microneedle devices, either alone or in combination with other therapies, such as radiofrequency [4], iontophoresis [5], photodynamic therapy [6] and laser, have been used for the treatment of skin conditions, such as wrinkles, melasma, photo damaging, hirsutism [7] and scars [8]. The most common forms of the microneedle devices are dermal rollers, microinjections, solid microneedles and drug-laden microneedles. There are several delivery approaches to apply microneedles on the skin, including: poke, poke and patch, poke and flow, coat and poke, poke and release [9].

Zahn *et al.* demonstrated the use of an on-chip micropumping system with microneedles for continuous drug delivery [10]; whereas, Chen MC *et al.* developed the light responsive microneedle patch for tunable drug delivery. The nanostructures were incorporated in the microneedle matrix to serve as a light absorber [11]. 3D printed microneedle devices for personalized drug delivery are also emerging. Lim *et al.* recently developed a personalized device comprising microneedles on curved surfaces for trigger finger treatment [12].

Multiple clinical studies on microneedle-based drug delivery and biosensing are also ongoing; however, none of the nanoneedles have been reported [13]. In these clinical studies, the microneedles include single microneedles, microinjections, microneedle patches, dermarollers, fractional microneedling radiofrequency devices, dissolving microneedles and coated microneedle patches. The microinjections are most widely studied, followed by mi-

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croneedling using either dermaroller or solid microneedles. The majority of these studies (>50%) are clinical trials from Phase 0 to IV, while the others are exploratory clinical studies. Most of the trials are industry-funded, while universities, hospitals, etc., fund other clinical studies. Two trials have reached Phase IV, namely, utilizing microinjections for the treatment of influenza (vaccine) and crow's feet wrinkles. The treatment for migraine, diabetes, uveitis, panuveitis, polio (vaccine) and macular edema are also in advanced clinical phases.

Several clinical studies for fractional radiofrequency microneedling devices have also been reported. These devices combine the microneedling technology with heat generated by radiofrequency, to provide the thermal treatment in deeper skin layers for neocollagenesis. This treatment helps to resolve several skin issues, such as aging, pigmentation, acne and scarring. In addition, this has also been used to treat overactive bladder syndrome. Other than skin treatment, microneedle studies for dental pain, artificial fertilization and eye conditions (uveitis, panuveitis) are in the pipeline.

Nanoneedles for drug delivery

Although microneedles have several advantages, repeated applications may lead to skin irritation. Therefore, as nanoneedles are extremely small, they can often be better in this regard. In contrast to microneedles, much fewer studies have been reported using nanoneedles for drug delivery. Nonetheless, nanoneedles have been extensively studied for biosensing, which may be useful for drug delivery at the cellular level.

Zhu X *et al.* developed the diamond nanoneedle array, which has been demonstrated for intracellular delivery of anticancer drugs [14]. Additionally, Chiappini C *et al.* developed a biodegradable nanoneedle array based on mesoporous silicon, which has been utilized for localized intracellular delivery of nanoparticles in mice [15]. Kohalar P *et al.* also developed nanoneedle-like particles for intracellular drug delivery, which over time lost their functionalities [16].

Micro & nano needles for biosensing

Various studies have been reported for biosensing using either micro or nanoneedles. The high precision of these systems makes it possible to optimize the penetration depth to target specific skin layers. Overall, there are two clinical studies reported that utilize microneedles for biosensing (glucose sensing and diagnostics for tuberculosis), but none for nanoneedles.

Microneedles for biosensing

Various types of microneedles have been used in conjunction with various analytical techniques, (e.g., voltammetry, chronoamperometry, intravital microscopy, cyclic voltammetry, amperometry). In general, microneedles can be used to extract samples in the following ways: collection of the interstitial fluids via capillary action or using micropumps and the adsorption of analytes onto microneedles [17,18].

Electrochemical sensors in combination with microneedles have played a dominant role in biosensing, driven primarily by the challenge of continuous glucose monitoring [17]. Miller *et al.* developed an analytical approach for the *in situ* simultaneous detection of multiple analytes, including glucose, glutamate, lactate, hydrogen peroxide and ascorbic acid using integrated microneedle-electrode devices [19]. Cheng *et al.* has demonstrated the *in vivo* extraction of blood using a microneedle. The hollow microneedles were integrated with a simple elastic self-actuator, which converts finger force to provide power for blood extraction [18]. Schierenbeck *et al.* used microdialysis integrated with a catheter for continuous blood glucose monitoring for up to 48 h in patients undergoing cardiac surgery [17].

In addition to the applications related to monitoring glucose level, several other types of microneedle sensors have also been reported. Tang *et al.* developed functionalized microneedles to monitor nitric oxide release in rats using amperometry [20]. Ciui *et al.* developed a wearable wireless bandage constituting of microneedle sensors for melanoma detection [21]. A chemical (catechol) was immobilized on the transducer surface, which can be converted to benzoquinone with the presence of the tyrosinase, for melanoma detection.

Nanoneedles for biosensing

In contrast to microneedles, nanoneedles have been explored for membrane-penetration to sense the biological processes inside a cell. This causes minimal damage to the cell membrane and/or disruption to the interior environment of a cell. Most of the reported biosensors are based on functionalized nanoneedles, which are surface-coated with proteins, dye and redox metal compounds. The sensors can be classified as force sensors, enzyme

sensors, biomimetic sensors, surface-enhanced Raman scattering sensors, field effect transistor-type sensors and label-free sensors.

The force-based biosensors measure the mechanical force experienced by the AFM cantilevers during cell membrane penetration. The magnitude of force can be used as an indicator to identify normal and abnormal cells [3]. The enzyme-based sensors catalyze the biochemical reactions, leading to an increase or decrease of analytes such as H_2O_2, O^{2-}, glutamate, dopamine in the cell [22,23]. Compared with the enzyme-immobilized biosensors, the biomimetic sensors are advantageous, circumventing problems such as denaturation or metabolism.

The surface-enhanced Raman scattering sensor is based on vibrational spectroscopy. This can be used for the fast detection of analytes at very low concentrations in live cells [22]. The field effect transistor-biosensors measure the electrical changes induced due to interaction with cellular environment such as signals in response to calcium ion concentrations [24]. The label free biosensors are based on the direct electrical detection, measurement of change in ionic strength and modulation of impedance [25].

Future perspective

The market for skin products and treatments, which includes cosmetics, drugs, vaccines and medical devices, is increasing every year. Currently, several microneedle-based cosmetic products, such as derma-rollers, are commercially available while very few can be found for medical products. However, the several studies in advanced clinical trial phases can assure that in the near future, new drug products, vaccines and microneedle-based medical devices are likely to reach the market. Most of the expected microneedle products for launch are based on microinjections, while some can be drug-laden microneedle patches. In addition, various fractional radiofrequency microneedling products will be available for skin treatment.

In addition, many drug delivery and biosensing applications using micro and nanoneedles are still ongoing research topics. Smart microneedle systems may be developed to provide controlled drug delivery based on physiological responses for certain diseases conditions, such as diabetes, epilepsy and pain. Besides, the integration of delivery devices with mobile devices for continuous monitoring of drug dose and physiological response will also be beneficial. Few studies have been reported on such new generations of microneedle delivery systems.

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