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Microneedles for drug and vaccine delivery ☆

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ABSTRACT

Microneedles were first conceptualized for drug delivery many decades ago, but only became the subject of significant research starting in the mid-1990's when microfabrication technology enabled their manufacture as (i) solid microneedles for skin pretreatment to increase skin permeability, (ii) microneedles coated with drug that dissolves off in the skin, (iii) polymer microneedles that encapsulate drug and fully dissolve in the skin and (iv) hollow microneedles for drug infusion into the skin. As shown in more than 350 papers now published in the field, microneedles have been used to deliver a broad range of different low molecular weight drugs, biotherapeutics and vaccines, including published human studies with a number of small-molecule and protein drugs and vaccines. Influenza vaccination using a hollow microneedle is in widespread clinical use and a number of solid microneedle products are sold for cosmetic purposes. In addition to applications in the skin, microneedles have also been adapted for delivery of bioactives into the eye and into cells. Successful application of microneedles depends on device function that facilitates microneedle insertion and possible infusion into skin, skin recovery after microneedle removal, and drug stability during manufacturing, storage and delivery, and on patient outcomes, including lack of pain, skin irritation and skin infection, in addition to drug efficacy and safety. Building off a strong technology base and multiple demonstrations of successful drug delivery, microneedles are poised to advance further into clinical practice to enable better pharmaceutical therapies, vaccination and other applications.

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1. Introduction

Most biotherapeutics and vaccines are injected using a hypodermic needle. Injection provides a low-cost, rapid and direct way to deliver almost any type of molecule into the body. However, hypodermic needles cannot be easily used by patients themselves and are therefore utilized primarily in the clinic or at home by patients who have received special training on correct injection method, safe needle disposal, and other issues [1]. Patient compliance is further limited by pain and needle-phobia experienced by many patients [2,3]. Spread of bloodborne pathogens by needle re-use is also a major concern, especially in developing countries [4,5]. Oral delivery largely overcomes these problems, but many drugs cannot be given by this route due to poor absorption and drug degradation in the gastrointestinal tract and liver [6]. Other routes of administration have also been investigated [7,8], but none offer the broad effectiveness of direct injection using a needle.

Rather than avoiding needles, we and others have proposed shrinking the needle to micron dimensions in order to make use of its powerful delivery capabilities while improving patient compliance and safety. As a micron-scale device, a microneedle should be large enough to deliver almost any drug or small particulate formulation, but still be small enough to avoid pain, fear and the need for expert training to administer. In addition, a microneedle allows precise tissue localization of delivery, such as within the skin, the suprachoroidal space of the eye, and the cell nucleus.

Most applications of microneedles studied to date have emphasized drug and vaccine delivery to the skin. Conventional transdermal delivery is limited by the barrier properties of the outermost skin layer, the *stratum corneum* [9]. Various chemical, biochemical and physical methods have been studied to increase skin permeability. However, chemical and biochemical methods do not appear to be broadly useful for delivery of biotherapeutics and vaccines across skin. While physical methods have greater promise for delivery of macromolecules, they typically involve the use of sophisticated devices that are relatively large, costly and require training to use. Microneedles, in contrast, can be prepared as a low-cost patch that is simple for patients to apply for delivery of biomacromolecules, as discussed further in this review. Targeting vaccine delivery to antigen-presenting cells in the skin using microneedles is also of particular interest [10].

Other applications of microneedles have also been explored. Drug delivery to the eye, especially via the suprachoroidal space, has received recent attention [11]. As an extension of micropipette techniques, microneedles have been used to deliver molecules into cells and their nuclei, among other laboratory applications [12,13] .

Since the first papers were published on drug delivery using microneedles in the late 1990's, research activity has grown exponentially (Fig. 1), which has led to published clinical trials, approved products and an active community of academic and industry researchers in the field today. This article reviews this body of work, building upon previous review articles in the field [10,14–33].

2. Fabrication of microneedles

Individual small needles have been hand-crafted for research purposes for decades [34] and already in the 1970's low-cost microneedle arrays were envisioned for drug delivery [35]. However, it was not until the 1990's that the microelectronics industry provided the microfabrication tools needed to make microneedles suitable for pharmaceutical applications [36].

Given the field's beginnings using microelectronics industry technology, the first microneedles were fabricated out of silicon. Since then, microneedles have been fabricated out of numerous materials, including metal, polymer, glass and ceramic, and in a variety of shapes and sizes, as needed for different applications. Most microneedle