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Review article

Microneedles in the clinic

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ABSTRACT

In general, there is a profound influence of reducing physical dimensions of particulates and devices on their physico-chemical and biological properties, and their performance. Reduction in the dimensions of hypodermic needle to micron-scale size has gained tremendous interest among researchers. Research efforts and publications investigating the design, development and applications of microneedles have exponentially increased in the recent years. Especially, microneedles have been widely studied and developed for cosmetic and therapeutic applications. Intense research efforts during the past decade have led to approval and commercialization of several microneedle based/assisted products for clinical use. Furthermore, numerous clinical trials aimed towards investigating the safety and efficacy of microneedle based systems are ongoing. The objective of this review is to provide an overview of completed and ongoing clinical studies performed using microneedle-based technologies for cosmetic, therapeutic and diagnostic applications. The review also provides a detailed overview of designs and applications of microneedle based devices that have been approved or are under clinical investigations. Clinical reports of microneedles for cosmetic applications including acne vulgaris, acne scars, skin rejuvenation and hair growth, and for therapeutic applications including influenza vaccination, polio vaccination, and diabetes are discussed in this review. Overall, this review—for the first time—provides a comprehensive overview of clinical efforts and outcome of microneedle based systems.

1. Introduction

Skin is a formidable natural barrier that has been evolved to protect the human body. It is composed of three layers, epidermis (thickness of 50–150 μm), dermis (thickness of 1–2 mm) and subcutaneous tissue making up a total skin thickness of ~3 mm [1]. The epidermis is the outer-most skin layer and is mainly responsible for the skin's barrier properties. There are five sublayers of epidermis including stratum corneum (SC), stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. SC is the chief barrier of skin composed of 15–20 layers of stratified, lipid depleted and protein enriched corneocytes [1].

Delivery of drug molecules through skin is considered to be an important alternative to oral route of administration. However, the barrier properties of skin limit the transport of molecules. Only molecules with optimal physico-chemical properties can passively diffuse through the skin membrane. Over the years, many different chemical and physical permeation enhancement techniques have been developed. Among the most recent and promising techniques is the application of microneedle (MN) based devices to enhance the skin transport of molecules.

MN could be single or an array of micron-sized needles that can penetrate the epidermis and upper dermal layer of the skin. MN usually has a diameter of a few hundred microns which recedes towards the sharp tip, and has a length of up to 1000 μm [2]. MNs have emerged as a promising technology for cosmetic, therapeutic and diagnostic applications. While cosmetic applications of MNs focus on localized effect in the skin, and diagnostic applications involve extraction of the biological sample from the skin, the therapeutic applications of MNs involve localized or systemic delivery of the drugs or biologics.

MN assisted drug delivery is a hybrid approach which combines the benefits of both non-invasive (topical-transdermal) and invasive (injectable) drug administration approaches, while overcoming the major limitations associated with these delivery methods. Injectable drug delivery systems have several advantages including direct and rapid systemic administration, bypass of first pass metabolism, and avoidance of gastric and intestinal degradation. However, it suffers from the requirement of medical expertise, supervision, and aseptic conditions, and poor patient compliance. Similarly, passive transdermal drug delivery systems provide controlled administration and relatively constant

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plasma profile of the drug, easy application and termination of therapy, and better patient compliance; however, the major shortcoming is the barrier property of the skin not allowing molecules with wide range of physico-chemical properties and in required amount. MNs can offer the advantages of both passive transdermal systems and injectables, while being minimally invasive, with patient compliance and the feasibility of self-administration.

1.1. Development history of microneedles

The term 'microneedle' has been reported in research literature in as early as 1921. Robert Chambers used MN for micro-dissection of echinoderm egg by injecting the needle into the nucleus of the egg [3]. A previous study reported in 1914 by the same author used a similar approach where male germ cells of *Disosteira Carolina*, a grasshopper, and of *Periplaneta Americana*, a cockroach, were dissected using a 'needle' [4].

To the best of authors' knowledge, the concept of MNs for drug delivery was first reported in a United States patent filed on May 17, 1971 (patent granted on June 22, 1976) for an invention by Martin S Gerstel and Virgil A Place [5]. Although the concept of MNs was introduced by Gerstel and Place, the term 'microneedle' was introduced in 1998 by Henry et al. [6]. In the patent by Gerstel and Place, MNs (an array of MN) were described as a drug delivery device comprising a plurality of projections, where the projections extend from the drug reservoir, intended to penetrate into the skin for local or systemic delivery of the drug. The patent described both solid and hollow MNs. The first drug coated MN based device was reported by Pistor Michel Louis Paul [7]. This patent described MNs as a device comprising micropuncturing structure in combination with drug applied on the surface of the MNs or on the skin pretreated with MNs.

The first research report on MNs for skin delivery was published in 1998. Henry et al. prepared MNs using reactive ion etching microfabrication technology and showed enhanced permeation of calcein through excised human skin by up to four orders of magnitude compared with passive topical application [6]. This study was also the first one to report *in vivo* feasibility of the approach and pain perception. In 2001, Alza Corporation reported development of solid metallic MNs for the transdermal delivery of antisense oligonucleotides [8]. The first report on utilization of MN technology for dermal immunization was published in 2002. Mikszta et al. reported the efficacy of silicon microprojections for immunization with naked plasmid DNA in a mouse model [9]. The study also assessed the safety of the microprojections in human subjects based on erythema and edema scores. The first study reporting feasibility of MN assisted transdermal delivery of macromolecules and nanoparticles was published in 2003 by McAllister et al. Solid and hollow MNs were used for delivering insulin, albumin and 100 nm sized latex beads through human cadaver skin [10]. The first dissolvable MNs were reported in 2005 by Miyano et al. [11]. An array of maltose MNs containing ascorbate-2-glycoside as a model drug molecule were prepared and studied in healthy human volunteers. The MNs were well tolerated and they spontaneously dissolved in the skin releasing ascorbate into the epidermis and dermis. In 2005, the first report on use of hollow glass-MNs for extracting dermal interstitial fluid for monitoring of glucose was published [12]. The first report on cosmetic application of MNs (collagen induction therapy) was published in 2005. Fernandes reported skin tightening and wrinkle reduction after application of MN-roller over target skin in the patients [13]. Over the past decade, MNs have not only been developed for cosmetic and drug delivery applications, but also have been explored for biological fluid sampling, allergy testing, vaccination, and photodynamic therapy, among other applications [14–17]. Fig. 1 shows a chronological timeline of the events in MN development.

The online clinical trials registry, www.clinicaltrails.gov, maintained by the United States National Library of Medicine was used to search for the ongoing and completed clinical trials [18]. The search results were further screened to limit the studies with MN for dermal applications. Furthermore, the studies where the device information was not clearly mentioned were excluded from the analysis. Published research literature associated with clinical trials of MNs, as of January 2017, was searched using web search engines PubMed and Google Scholar.

2. Classification of microneedles

MN can be classified based on multiple parameters including composition material, applications, manufacturing technique, and the design. Fig. 2 shows a general classification of MNs. In this review, the designs and applications of MNs in the clinic are discussed.

3. Microneedles for cosmetic applications

3.1. Microneedle designs for cosmetic applications

The concept of microneedling dates back to centuries ago, when the

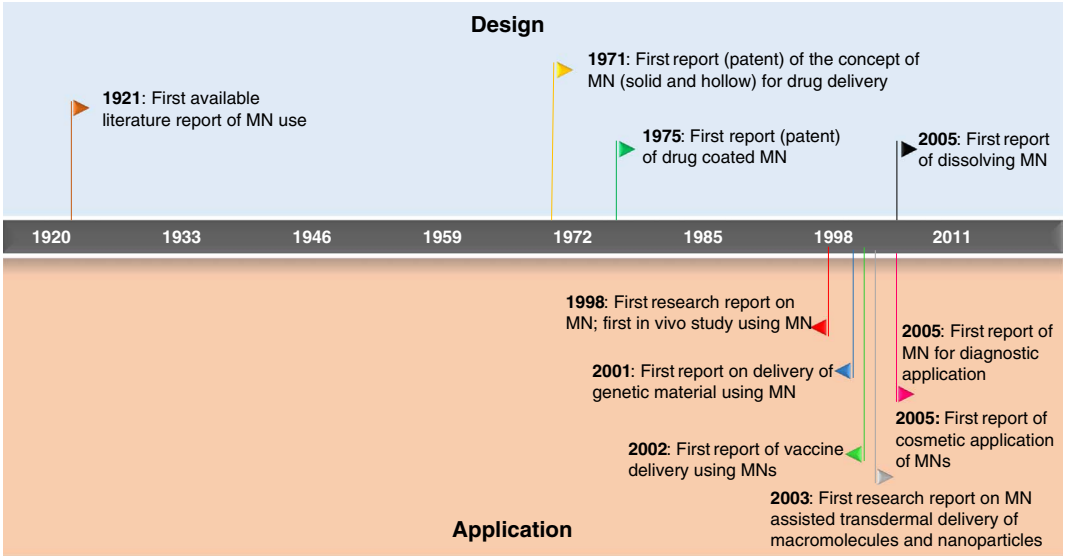

Fig. 1. Chronological timeline of MN development with important design and application milestones.