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TV Meenambigai
Professor, Vaccine Research Centre – Viral Vaccines, Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai, Tamil Nadu, India

C Sworna Kumari
Vaccine Research Centre – Viral Vaccines, Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai, Tamil Nadu, India

G Sarathchandra
Vaccine Research Centre – Viral Vaccines, Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai, Tamil Nadu, India

YKM Reddy
Vaccine Research Centre – Viral Vaccines, Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai, Tamil Nadu, India

Corresponding Author:
TV Meenambigai
Professor, Vaccine Research Centre – Viral Vaccines, Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Madhavaram Milk Colony, Chennai, Tamil Nadu, India

Dissolving microneedles in drug delivery: An outlook

TV Meenambigai, C Sworna Kumari, G Sarathchandra and YKM Reddy

Abstract
Dissolving microneedle (DMN) are micron sized needle that delivers the drug with painless penetration, excellent therapeutic efficacy, and with relative safety. It has an innovative transdermal delivery system with attractive scientific and industrial interests as oligonucleotide delivery, vaccine delivery and insulin delivery. Dissolving microneedles have a variety of representative biomedical applications such as disease diagnosis and treatment, immunobiological administration, and cosmetology. It holds a great promise for biomedical applications. The wearable device based dissolving microneedle patches will be desirable to integrate disease diagnosis and treatment in future.

Keywords: Dissolving microneedles, drug

Introduction
Dissolving microneedles are ultra small needles with less painful way of delivering active ingredients compared with the hypodermic needle syringe. DMN can potentially improve the quality of life for those who would otherwise need frequent injections. DMN are environmental friendly material, leaving no dangerous or wasteful products behind as these microneedles dissolve into the skin after insertion. DMN has reduced cold-chain supply costs because the solid state of the dissolvable microneedle enables greater stability. Generally it is made up of Solid materials coated with a drug typically using a water-soluble formulation. After insertion of microneedles into the skin, the drug coating is dissolved off the microneedles and into the skin due to the body temperature. Alternatively, microneedles can be made completely out of biodegradable polymer that encapsulates the drug within the microneedle matrix. In this way, the microneedles completely dissolve or degrade in the skin, thereby releasing the encapsulated drug payload and leaving behind no sharps waste, (i.e., because the microneedles have dissolved away).Finally, hollow microneedles can be used for infusion of liquid formulations into the skin or, alternatively, for diffusion into the skin through the needle bore. (Yeu *et al.* 2012) [1].
The fabrication of dissolving microneedles has focused on mechanical strength through choice of materials, geometry and reducing the force which are needed to insert the dissolving microneedles into tissue by increasing tip sharpness. Solid dissolving microneedles have been fabricated out of various materials, including silicon, non-degradable polymers such as photolithographic epoxy, copolymer of methylvinylether and maleic anhydride, polycarbonate, polymethylmethacrylate, biodegradable polymers such as poly-lactic-coglycolic acid (PLGA), polyglycolic acid (PGA) and polylactic acid (PLA), water-soluble compounds including maltose, metals including stainless steel, titanium, tantalum, nickel, and ceramics (Shayan *et al.*, 2019) [13, 27]. As an additional approach, dissolving silicone microneedles have been fabricated to create a grid pattern of deep grooves to serve as neural probes by dicing a silicon substrate and then acid etching the resulting pillars to create sharpened probe tips. (Tejashree *et al.* 2019, yan *et al.* 2010) [12]
In this review we highlight techniques in fabrication of dissolving microneedles, characterization methods and the challenges faced.

Preparation of Dissolving microneedles
Dissolving microneedles are made up of water-soluble materials mainly of polymers (Poly vinyl alcohol, Carboxymethyl cellulose, Dextran), biodegradable polymers (polylactic acid, chitosan, polyglycolic acid, or polylactide-co-glycolide) (PLGA) (Hong *et al.*, 2013) [21]. In contrast to coated microneedles and polymer microneedles, dissolving microneedles have been developed to completely dissolve in the skin and thereby leave behind no biohazardous sharps waste after use.

Most Dissolving microneedles have been prepared on flat, cylindrical and planar substrates, such that all dissolving microneedles are simultaneously pressed into the skin. They not only serve as
piercing structures, but also as vehicles to carry and deposit drug within the skin. In this way, the desired doses of the drugs are delivered into the tissue .The amount of drug that are uploaded or encapsulated is upto 1mg in single array.(Sixing *et al*., 2012) [18]

Fabrication Process
Dissolving microneedle materials are fabricated mainly by using a photolithographic and micromolding process. The photolithographic process depends on thick photoresist polymer SU- 8 by controlling light path and poly-methyl-methacrylate (PMMA) (Xiaoxiang *et al*. 2019) [10]

Lithography
Drawing Lithography
This technique is based on stretching deformation of polymericnor biodegradable polymeric material from a 2-dimensional to a 3-dimensional structure. Melted polymer or any dissolving material is dispensed on a fixed plate and elongated by drawing pillars in the upper-moving plate. The polymer or dissolving materials viscosity is progressively increased by cooling until it reaches the glass transition temperature of the polymer. Further cooling induces a solid polymeric material providing the suitable dMN strength for the skin piercing. The advantage of this fast fabrication method is the minimal dissolving polymeric material wastage due to the dispensed drops on the plate. More importantly, this technique is not appropriate for thermolabile antigens because of high transition and melting temperatures. (e.g. for maltose >95°C). (Jeong *et al*. 2013) [8]

Soft Lithography
In soft lithography dissolving microneedles are fabricated initially by pairing a polymer film with the mold with microcavities and passing them through a heated nip or photo curing. Next, the filled mold is placed on a water soluble substrate with flexiblity, and passed through the heated nip. After separation of the mold, a dissolving microneedle patch remains. Soft lithography similar to drawing lithography, only the manufacturing methods varies with excellent scalability, low cost and short preparation time. While fabricating the matrix thermolabile antigen temperatures should be taken care. (Leo *et al*. 2017) [5]

UV lithography
One of the most common methods used in fabricating dissolving microneedles is UV lithography, which creates fine microsized needles. UV lithography is limited to fabricate 2.5D designs because of the fixed light source, yielding a 3D product. Dissolving microneedles have been fabricated with inclined or rotated UV lithography; UV irradiates the negative photo resist with circular patterns at an angle which results in producing cone-shaped microneedles. Due to the fixed UV light, the substrate resist itself and could be inclined and rotated to fabricate the needles. By adjusting the angle of either the resist or the UV light and tuning the UV energy the shape and density of the needle can be customized as desired. (Chong *et al*. 2017) [9]

Deep X-ray lithography
Deep X-ray lithography results in the production of dissolving microneedles with sharp tips due to the short wavelength of the x-rays and high photon energy. Deep x-ray lithography is a commonly used method for fabricating dissolving microneedles using x-rays. This technique also suffers from the same disadvantage of UV lithography in which the substrate and the X-rays are fixed. The dissolution rate of the polymethylmethacrylate (PMMA) resist was controlled by regulating the absorbed dose with double exposure in the deep x-ray lithography method which facilitates the construction of dissolving microneedles without any type of special apparatus. (Seunghee *et al*. 2019) [27]

Droplet Air Blowing Method
In droplet-born air blowing (DAB), a droplet of plain polymer or any dissolving material solution and another droplet of drug solution are dispensed together on two plates (upper and lower). The upper plate is moved downwards to the lower plate so that the droplets are touching and thereafter plates are withdrawn to a distance corresponding to produce dissolving microneedle with required lengths. The polymer or biodegradable solutions are dried with air flow which results in producing a dissolving microneedle patch or array on each plate. (Kim *et al*. 2013) [7]

Molding & casting
This is the best common approach for fabricating dissolving microneedles of desired shapes, structures and physical or chemical properties by changing the mold structures and/or casting materials. Silicon, metal and polymers are used as base materials for producing the dissolving microneedles. By deep-reactive ion etching of silicon, Silicon base micromolds are fabricated. Metal base micromolds are produced by electroplating the metal on the surface of silicon microneedle masters after the deposition of metal onto the surface of the master. To make polymeric base, micromolds are produced by a mechanical micromilling process using polydimethylsiloxane (PDMS). (kuo and chou, 2004).

Casting in the dissolving polymeric material is an important factor which determines the microneedle characteristic. Some examples of casting materials are polymethylmethacrylate, poly(lactic-co-glycolic acid) (PLGA), carboxymethyl cellulose, hyaluronic acid, polyvinylpyrrolidone, polyvinylalcohol, dextran and sugar, which can be used to make solid and dissolving microneedles.

Coating methods
Coating has been carried out by dipping the casting solution once or repeatedly into a large bath. Layer-by-layer coating techniques have also been applied for casting by coating the negatively charged DNA or protein molecules on metal or polymer base mould and the positively charged polymer or biodegradable solution were alternately dipped to form a poly electrolyte multilayer. Another alternative method of coating is done by spraying the solution using the angled jet or spray coating atomizer onto silicon microneedles. (Sullivan *et al*., 2010) [19].

Drug coating formulation in dissolving microneedle
Dissolving microneedle coating formulations is typically done by dip coating or spreading of drug solution on a microneedle surface with an increased viscosity and reduced contact angle of the coating solution to the substrate e.g., by addition of surfactant which improves the wetting and coating thickness

of the drug. The coating process should not damage the drug and must be compatible with industrial pharmaceutical manufacturing processes. The coating formulation should be water-soluble, not only for effective coating but also for rapid and complete dissolution into the skin in an aqueous environment. Coating should be high enough to keep the drug adherent to the dissolving microneedle during insertion into skin. Coating solution excipients and solvent should not damage coated drugs and should be safe for human use.

Hollow dissolving microneedles

Similar to hypodermic needle, dissolving microneedles are fabricated and named as hollow dissolving microneedle which provides a optimum drug delivery into the skin or other tissues. Pressure, flow rate can be modulated with a slow infusion or a time-varying delivery rate. Hollow dissolving microneedles have also been used as a channel for drug diffusion into the skin from a non-pressurized drug reservoir. (Wang *et al*., 2006) [20]

Evaluation of Microneedles

Characterization methods

The drug can be loaded into the dissolving microneedles either in the form of suspension or dispersion or encapsulated forms such as liposomes, nanoparticles, nanoliposomes. Various physicochemical characterizations methods has been used including polydispersity index, viscosity, and zeta potential standards that has to be evaluated for loading drug depending on the type of formulation used in the microneedles. Drug release, adhesion, permeation tests are performed before and after treatment. The size, internal structure, and crystallinity of the liposomes or nanocarriers can be performed using dynamic light scattering, X-ray scattering, and transmission electron microscopy technique, Optical coherence tomography (OCT) (Lee *et al.* 2014).

Dimensional evaluation

Various methods are used to evaluate the needle geometry and to measure the tip radius, length and height of the microneedle. Most common methods are optical or electrical microscopy. Analysis of a 3D image gives a better picture of needle geometry and helps in quality control. Scanning Electron Microscope (SEM), multiphoton microscopy and confocal laser microscope have been used for this purpose. SEM produces an image of a sample by making use of a focused beam of electrons which interact with the atoms in the sample while scanning and
produces various signals which give information about sample surface topography and composition. Confocal laser microscope produces high-resolution images.

***In-vitro* skin permeation studies**

Techniques for testing the skin permeation are Transepidermal water loss (TEWL) (Gittard *et al.* 2013) [23], electrical resistance (Sivamani *et al*. 2009) [22]. Delfin Vapometer is used to measure the skin penetration studies. (Uppuluri *et al*., 2017) [26] Apart from that diffusion cell apparatus is used to find the permeation of the drug through the skin. The cumulative permeation profiles of microneedle treated and untreated skin were compared. (Ying *et al*. 2017) Numerous dyes have been used to examine microneedle delivery properties, including trypan blue, methylene blue, and gentian violet (Choi *et al.* 2010) [24]

Applications of Dissolving Microneedles

Transdermal Drug Delivery

Amodwala *et al.* 2017 [25]., used Meloxicam drug loaded in the polymeric microneedles using polydimethylsiloxane molds which results in 100% drug release in 60 min using *in-vitro* permeation studies and the amount of drug deposition was found to be 63.37% and 1.60 µg/cm2/hr. was observed with improved transdermal flux.

Tissue Interlocking

Tissue Interlocking-DMN delivered transdermally penetrates the skin and interlocks within the tissues which effectively delivers the encapsulated compounds. TI-DMNs are composed of viscous hyaluronic acid (HA) polymer of a narrow neck, wide body, and sharp tip that improve their skin insertion capability and reduce the chances of detachment from the skin prior to dissolution when comparing DMN.

Vaccine delivery

Microneedles have shown enhanced immune responses (Shin *et al*., 2017) [28]. numerous studies related to various types of virus and bacterial vaccines delivered via microneedles have been reported. .Beals *et al.*, in 2016 showed the effect of a live-attenuated measles vaccine using dissolving microneedles on *rhesus macaques* (Macaca mulatta) and proved that the microneedles
and subcutaneous vaccination produced the same levels of antibodies when administered with the same dose of the vaccine. By using the Hydroxyethyl starch 70000 material, Hepatitis B vaccine with the antigenicity of Hepatitis B adjuvant was maintained for 6 months. (Poirier *et al.* 2017) [31]. By using Hyaluronic acid, Live attenuated BCG vaccine type did not produce any inflammation (Chen *et al*., 2017).
Dissolving microneedle made up of sucrose material was used for Rabies vaccination. A rabies DNA vaccine integrated with dissolving microneedle and rhodamine dye showed ten-fold lower vaccine dose than full-dose intramuscular vaccination using hypodermic needles. Dissolving Microneedle patches resulted in minimal wheal formation, mild erythema and complete resolution of skin reactions within 7 days without generating any systemic adverse events**. (**Jaya *et al.* 2017) [15]

Immunobologicals

Due to complete penetration and dissolving, DMN is taken into consideration for delivering monoclonal antibody using maltose microneedles in 1 min as compared to solid microneedle (Li *et al*. 2009). Sullivan *et al*., in 2010 [19] introduced the biocompatible polymer dissolving microneedles which are integrated with inactivated influenza virus vaccine to improve the vaccine immunogenicity, rather than intramuscular hypodermic injection under the same condition. Raphael *et al*., in 2016 optimized the proportion of different material formulation of dissolving microneedle which were made up of mannitol, sucrose, trehalose, and sorbitol to achieve their required vaccine stability.

Skin pretreatment

Skin pretreatment with dissolving microneedles has been employed to vaccinate diphtheria toxoid adjuvanted with cholera toxin, which generated similar immune responses compared to subcutaneous hypodermic injection. A model antigen, ovalbumin, and CpG adjuvant was coated to the dissolving microneedle which when incorporated with cationic liposome resulted in increased antibody response. (Shubmita *et al*. 2019)

Approved Microneedle Products

There are a numerous count of approved medical and cosmetic products using dissolving microneedles that are sold around the world with low cost and good quality. The first product around the world was the Dermaroller® for cosmetic treatment. Dissolving microneedles patch containing hyaluronic acid named as MicroHyala® is used for the skin to treat wrinkles. Soluvia® is a single hollow microneedle that is 1.5 mm long and is attached to a syringe. It is marketed worldwide prefilled with influenza vaccine for intradermal vaccination as IDflu®, Intanza® and Fluzone Intradermal®. MicronJet® which recently received FDA clearance

Conclusion

As an emerging device, dissolving microneedles possess characteristic advantages like painless and rapid delivery as compared to other systemic administration methods. Dissolving microneedles have made significant progress in immunobiologicals, disease diagnosis, disease long-term treatment, and cosmetic applications. But still there are lots of urgent and unmet requirements for the development of wearable and smart device to realize long-term disease treatment. At last, economic cosmetic products based on dissolving microneedles may achieve their rapid growth and broader prospects over the next decades. In summary, dissolving microneedle holds great promise for biomedical applications. The wearable device based dissolving microneedle patches will be desirable to integrate disease diagnosis and treatment in the near future.

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