REVIEW ARTICLE

Painless Microneedles for Intradermal delivery of Vaccines

Paromita Bakshi*, Sarbani Roy, Sayantan Sadhukhan, Sabyasachi Maiti

Department of Pharmaceutics, Gupta College of Technological Sciences, Ashram More, G.T. Road, Asansol-713301, West Bengal, India

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ABSTRACT

Commonly, the hypodermic needles are used for the vaccination programs, which is important for improving the quality of life. However, needle phobia retracts the patient from vaccinations. Novel vaccination strategies should be cost effective, employ safer injection practices and should evoke sufficient immune responses in patients. The lack of sensory nerve endings and blood vessels in the epidermal layer of skin opens the door for application of the vaccine in painless way. The dermal lymphatic system causes rapid and efficient uptake of biologics. Furthermore, the dermis is particularly rich with lymphatic capillaries and the rate of fluid exchange in the dermis is found very high than any other compartment in the body. Different types of microneedles have been developed for intradermal delivery of drugs/ vaccines. Out of these, self-dissolving polymeric microneedles has shown a great promise in terms of delivery of the biologics. Moreover, the devices were found equally effective in small doses when delivered *via* intradermal route, compared to others. Needle-free delivery systems could be advantageous in terms of safety and application in mass vaccination programs. This comprehensive review will discuss the recent achievements and scope in the area of polymeric microneedle-based intradermal vaccine delivery systems.

Keywords: Painless vaccination, Intradermal delivery, Polymeric microneedles, Dermal patch

INTRODUCTION

Vaccination helps in the prevention of life-threatening infectious diseases. Despite wider availability of vaccines, infectious diseases still remain a major global concern, especially in developing countries [1]. Most frequently, vaccination requires the needle-syringe assembly for administration, the worst thing being the big, scary hypodermic needle. Needle phobia leads to patient noncompliance and thus questioning the success of vaccination programs worldwide. Further, the application of vaccines *via* needles and syringes carries significant risks. Professional healthcare workers are potentially exposed to needle-stick injuries. The waste management and reuse of needles are also problematic [2]. Some vaccines are too expensive for developing-country immunization programs; while the others are subject to shortages or imperfect distribution systems. These factors are the obstacles for the people in accessing the vaccines that they need. Novel vaccination strategies should be safe, cost-effective and capable of evoking sufficient immune responses in patients [3]. World Health Organization (WHO) (2004) postulated that a safe injection practice is the key towards successful vaccination.

Over the past years, the development of needle-free technologies has experienced a significant upturn [4]. Needle-free injection devices can enhance patient compliance by evoking less pain and stress. Recently, the intradermal layers of the skin are being targeted for vaccination with novel microneedle devices [2]. The purpose of this review is to highlight the role of skin in the delivery of vaccines in painless way, different types of micro-needles, and recent developments in the field of intradermal vaccine delivery.

Address for correspondence

Ms. Paromita Bakshi
Department of Pharmaceutics
Gupta College of Technological Sciences
Asansol-713301,
West Bengal, India
E-mail: bakshi.paromita@gmail.com

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SKIN: AN ATTRACTIVE TARGET FOR VACCINATION

The skin is an attractive target for vaccination as it constitutes the major barrier for the entry of environmental pathogens. However, the shallow, upper tissue layers of skin are easily accessible to vaccine administration [5, 6]. It has been shown that the intradermal delivery of vaccine requires 80% lesser dose than that for intramuscular or

subcutaneous injection to achieve equivalent response. Clinical trials with influenza [7-9] and rabies [10] vaccines verified that intradermal vaccination can elicit equivalent immune responses to the vaccine given intramuscularly or subcutaneously, while utilizing only 10-20% of the antigen dose. The results are quite similar for hepatitis B vaccines [11, 12]. Only limited number of clinical trials has been carried out with other commercially available vaccines such as the polio, measles, tetanus toxoid and hepatitis A [13-15]. Thus, it is apparent that intradermal administration of vaccines could help in lowering the cost of each dose, and enables to stretch vaccine supplies across more patients.

Immunocompetent antigen presenting cells (APCs) such as Langerhans cells (LCs) in epidermis and dendritic cells in underling dermis are able to capture and process foreign antigens [6, 16]. Further, the lack of sensory nerve endings and blood vessels in the epidermal layer of skin provides the opportunity for delivering vaccines without causing any pain or bleeding. In terms of efficiency, the intradermal route induces superior protective immune responses than those induced after intramuscular injection [17].

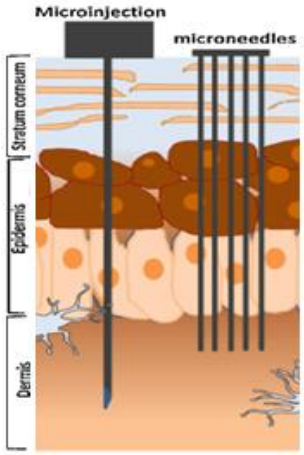

Fig. 1: Intradermal application of vaccines through microinjection and microneedles [4]

The traditional administration of vaccines *via* needle and syringe cannot effectively target the LCs in the epidermis of the skin, as deeper subcutaneous regions or muscle tissue will be reached due to length of the needle and standard application technique [18]. Intradermal injection methods using needles and syringes require considerable expertise and are seldom used for vaccinations. It is mainly used for bacilli calmette guérin (BCG vaccination), tuberculosis and postexposure rabies vaccination. Therefore, there is an urgent need for devices to facilitate correct and accurate intradermal administration [19]. In an effort to leverage the benefits of this route, many different delivery methods have been considered. Perhaps the most active area of development is the use of microneedles to deposit vaccines into the dermis and/or epidermis.

The mechanism credited with rapid and efficient uptake of the biologics delivered to dermis is the lymphatic system. The dermis is particularly rich with lymphatic capillaries and herein, the rate of fluid exchange exceeds any other compartment in the body. Large molecules delivered to subcutaneous or intramuscular tissues may not be absorbed by the lymphatic capillaries as fast as they would be in the dermis. As a result, intradermal delivery is characterized by good pharmacokinetic profiles, indicating rapid absorption, higher peak blood levels and complete uptake [20] of vaccines.

TYPES OF MICRONEEDLES

To increase skin permeability, a number of different approaches have been adopted, ranging from chemical/lipid enhancers [21] to electric fields to pressure waves generated by ultrasounds [22]. Although the mechanisms are different, these methods share the common goal to disrupt the horney skin layer *stratum corneum*, thereby creating large pores for the transport of active molecules [23].

Microneedle arrays add a new dimension in the transport process for the large molecules. Basically, these are small, minimally invasive devices consisting of an arrangement of micron-sized needles. Microneedle arrays are broadly classified as follows: (i) solid microneedles, made from non-degradable, solid material such as titanium[24], silicon [25], stainless steel [26] or glass [24], engraved onto an

adhesive patch; (ii) solid hollow microneedles of similar materials but equipped with a hole in the centre [27] and can be attached to an adhesive patch (iii) polymeric microneedles of either degradable (such as PLG, PLGA, carboxymethyl cellulose) [28] or non-degradable (e.g. polystyrene, polycarbonate) nature [24]; and (iv) self-dissolving microneedles, prepared from sugars [29, 30] or other rapidly dissolving materials [31]. Polymeric microneedles are designed to access the intradermal cells. The dissolvable microneedles use the skin's moisture to dissolve the vaccine into the intradermal layer; whereas hollow microneedles are used for the delivery of liquid drug formulations. It has been advocated that microneedles can deliver even microgram levels of highly potent small/large molecules through skin. Microneedles of different shapes, geometries and lengths [32, 33] can be prepared using chemical etching or laser etching [34] followed by a cleaning with electro-polishing procedure.

To illustrate the concept of polymeric microneedle, one popular method of preparation has been described herein. A vaccine solution of desired concentration is prepared in deionized water and trehalose. Then it is poured into a silicone negative mold (cone shape, 1500 µm height, 670 µm diameter of base) with microneedle-shaped cavities and centrifuged at 3500 rpm for 5 min, and air dried for several hours. Sodium carboxylmethyl cellulose gel (8%, w/v) is cast over the vaccine film and dried overnight. The dried film is cut into one centimeter diameter discs. The microneedle patches thus formed are stored at 5°C prior to administration [35].

Fig.2: A representative microneedle patch where the tip of microneedles was formed from mixture of antigens and sodium carboxymethyl cellulose [35].

MECHANICS OF MICRONEEDLE INSERTION INTO SKIN

The microneedles with the correct geometry and physical properties can penetrate the skin. Some designs require only insertion of needle by hand, whereas others benefit from high-velocity insertion [23]. To determine the effect of microneedle geometry on the force of insertion, individual microneedles were inserted into the skin of human subjects while recording the force and displacement of the needle, as well as monitoring skin resistance (which was used to indicate needle insertion into the skin) [23]. Forces of insertion varied from 1-3N and showed an approximately linear dependence on the area of needle tip. Insertion force was found to be independent of wall thickness; thin-walled hollow needles and solid needles with the same outer tip radii required the same force of insertion.

BD Soluvia™ (Becton Dickinson, Franklin Lakes, NJ, USA) is an intradermal microneedle injection system, consisting of a 30G needle of 1.5 mm in length, and a syringe with capacity of holding 100-200µl of a liquid formulation. This system enables intradermal vaccination [36]. The needle must be inserted perpendicular to the skin surface. A specially designed needle penetration depth limiter ensures an appropriate insertion depth. An additional mechanism integrated into the syringe serves for the prevention of reuse or injury. After vaccine administration, the microneedle is covered with a plastic shield by pressing the plunger further [37]. This system allows untrained staff also for vaccine administration. The microinjection system ensures consistent vaccine dosing and is compatible with conventional liquid vaccine formulations. Due to low penetration depth of the needle, almost no pain sensations are perceived [2].

The hollow Microstructured Transdermal System (hMTS), is a device containing 18 polymeric, hollow microneedles /cm^2 and is connected to a conventional glass cartridge, containing the drug reservoir for intradermal injection. The liquid formulation is forced

through the hollow microneedles by the power of a spring. The patch requires a wear time of 3-40 min, depending on the formulation injected. The pharmacokinetic profiles and relative bioavailability achieved using hMTS were comparable to the profiles obtained after subcutaneous injection. The hMTS has not gained FDA approval yet [2].

The largest and fastest growing group of microneedle arrays investigated over the last few years is the group of self-dissolving needles. These are prepared from sugar or sugar derivatives such as maltose [29, 30], carboxymethylcellulose [38] or amylopectin. These needles have the obvious advantage that they dissolve rapidly within minutes after insertion into the skin, leaving no sharp waste to be disposed of [39]. The material for preparation of self- dissolving needles can be obtained at low cost [40], and many excipients employed in the preparation process are already used in pharmaceutical products without any safety concerns. Additionally, if the self-dissolving needles break upon insertion, no residues will remain in the skin due to fast dissolution of the material. The drug can be incorporated directly into the matrix. Alternately, the microneedles are prepared solely from drug [2].

DELIVERY STRATEGIES VIA MICRONEEDLES

The overarching motivation for microneedles is that they can provide a minimally invasive means to transport molecules into the skin. Guided by this goal, a number of specific strategies have been employed to use microneedles for transdermal delivery. Most of the works focused on making microscopic holes in the skin by inserting solid microneedles. The "*poke with patch*" approach uses microneedles for making holes and then applying a transdermal patch (or some prototype) to the skin surface. Transport can occur *via* diffusion or iontophoresis, if an electric field is applied. Another approach is "*coat and poke*" where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; the entire drug to be delivered is on the needle itself. A variation on this second approach is "*dip and scrape*" where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind drug within microabrasions created by the needles.

In current practice, there is no evidence of microneedles penetrating just 10-20Aº across *stratum corneum* without entering the viable epidermis, where nerves are found. Instead, microneedles are inserted at least into the epidermis and sometimes into the superficial dermis. Nevertheless, microneedles are still reported as painless, probably because their small size reduces the odds of encountering a nerve or of stimulating it to produce a painful sensation [23]. Kaushik *et al.* [25] carried out a trial to determine if microneedles are perceived as painless by human subjects. Microneedle arrays were inserted into the skin of 12 subjects and compared to pressing a flat surface against the skin (negative control) and inserting a 26-gauge hypodermic needle into the skin surface (positive control). Subjects were unable to distinguish between the painless sensation of the flat surface and that caused by microneedles. All subjects found the sensation caused by the hypodermic needle to be much more painful. Other studies have also reported that microneedles can be applied to human subjects in a painless manner [41, 42].

RECENT ADVANCES

In 2009, Program for Appropriate Technology in Health (PATH) formed a collaboration with the Georgia Institute of Technology (Georgia Tech) and Emory University. This project aims to create a microneedle patch that allows people to self-administer influenza vaccine. PATH is trying to evaluate the technology from a variety of angles, including medical, economic, social, and regulatory. PATH will assist Georgia Tech in developing a strategy to address any issues. The team will carry out a cost-effectiveness analysis to quantify the potential cost implications of a self-administered vaccine. They will assess the feasibility of this novel approach for the

introduction of microneedles into clinical practice more effectively. This approach is not yet universal despite clear benefits. This is due, in part, to the difficulty of giving an intradermal injection correctly. Concerns regarding the difficulty and a lack of reliability of conventional intradermal injections limit research in this field and introduction of this technique into immunization programs.

CONCLUSION

Microneedle-based drug delivery has the potential to be a transformative technology for the delivery of biologics and vaccines. Microneedle delivery may provide enhanced therapeutic profiles for therapeutics and vaccines, allowing for administration of lower levels of drugs to achieve the same therapeutic endpoints. Additionally, microneedles provide an alternative to traditional needles and thus a means of overcoming one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination. Delivery systems targeting the skin have attracted growing attention during the last years. Needle-free delivery systems are associated with significant advantages, particularly with regard to safety issues and application in mass vaccination programs. Also, the potential for vaccine dose reduction by targeting the intradermal layers of the skin strengthens the position of intradermal vaccination devices and offers savings in delivery costs and coverage of a broad population with vaccines in limited supply. Even though the potential of needle-free injections and the targeting of the epidermal layer of the skin is the focus of a lot of research groups, only a few delivery devices (PharmaJet®, MicronJet® device) have progressed to clinical trials and are currently approved for commercial use. Microneedle arrays are still in a development process but encouraging data has been reported. Operational challenges like the reproducibility of the coating procedure and of antigen delivery must be overcome in order to gain regulatory approval for such systems. In conclusion, while there has been considerable development of intradermal vaccination devices, there is still a need for further improvement to the design of devices for intradermal administration in order to fulfill their potential to be competitive with conventional needle and syringe forms of administration.

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