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DNA Vaccine Administration Through Transdermal Delivery Systems

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ABSTRACT

Infectious disease is a global problem and it effects almost all sections of peoples. A number of microorganisms are available to cause a variety of diseases. The infectious disease has tremendous impact on human health which has made the life miserable. The basic treatment for the infectious disease is the use of antimicrobials and the use of vaccination. Both of the above methods have the sideeffects. This has lead to the innovation of DNA vaccine which is comparatively more effective and valuable. DNA vaccination is a technology which utilizes genetically engineered DNA to produce an immunologic response which provides immunity. This article is totally based on literature survey. This review will put major emphasis on the on the administration of DNA vaccine through transdermal delivery system. The authors explored the types of transdermal delivery systems like Iontophoresis, Devices based on velocity, Microneedles, Radiofrequency-induced microporation, Laser microporation and Sonophoresis. Much focused were made on merits and demerits the transdelivery systems. The future prospects of this delivery systems were also highlighted. The aim of compiling this article is to help those researchers who are doing research with DNA vaccine. They will come to know about the delivery of DNA vaccine through transdermal delivery systems. This will help them to reach to their target in concerned with this Vaccine.

Keywords: DNA vaccine, transdermal delivery system , iontophoresis, microneedles, sonophoresis, microporation.

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INTRODUCTION

A variety of infectious diseases are caused due to the presence of different kinds of microorganism such as bacteria, virus fungi, arthropods and protozoa as described by this corresponding author [1]. A number of infectious diseases like typhoid [2, 3, 4, 5, 6, 7] cholera, malaria, dengue etc severely affect human health. The number of infections caused by new, reemerging or drug-resistant pathogens is growing day by day. Because of the current global travel and trade, there is no border for infectious diseases. The primary treatment for the infectious disease is the use of antibiotics, vaccination and plant products [8, 9, 10]. Vaccination is the most successful application of immunological principles to human health and its efficacy needs to be reviewed from time to time and its safety is an overriding consideration as reported by the corresponding author[11]. DNA vaccination is a new technology in which genetically engineered DNA is used to produce an immunologic response as described by the corresponding author [11]. The corresponding author also reported a number of gene transfer technologies [12, 13, 14].

DNA vaccines are third generation vaccines which are capable of inducing both humoral and cell mediated immune response [11]. DNA vaccination holds enormous promise as a strategy for activating immune responses against several fatal diseases such as HIV, HBV, Dengue etc. However, the data available so far about the DNA vaccine delivery systems suggests that the intensity of the immune response generated by DNA vaccines is weak. Several strategies have been proposed in order to enhance the efficiency of these vaccines. Some of these approaches include formulation of novel adjuvants, transdermal drug delivery by the use of microneedles, particle mediated delivery, colloidal drug delivery systems, use of chitosan nanoparticles, use of immunomodulators etc.

In the previous communication regarding the DNA vaccine the corresponding author in his review article communicated about the construction, designing, merits as well as demerits of DNA vaccine. Later on the corresponding author with the help of other authors of this article communicated about the delivery methods, mechanism of action of DNA vaccine and also its medical prospective in concerned with infectious diseases [15].

The authors compiled this review article through literature survey by using a number of search engine like PubMed, Google and Science direct. The current references were considered along with few old references. The books and journals were also considered for compiling this article. In this review article the authors mainly focussed on the administration of DNA vaccine through transdermal delivery system. The authors explored the types of transdermal delivery systems like iontophoresis, devices based on velocity, microneedles, radiofrequency-induced microporation, laser microporation and sonophoresis. The authors also tried to explore the merits and demerits of the transdermal delivery system. The main aim of writing this review article is to help those researchers who are devoting their valuable time in doing research in concerned with DNA vaccine. They will come to know about the delivery of DNA vaccine through transdermal delivery systems . This will help them to reach their final goal.

Transdermal Drug Delivery Systems

Transdermal drug delivery has been extensively researched in the field of medical sciences but it is yet to reach its full potential as an alternative choice to hypodermic injections and oral delivery. It has been subdivided into three generations. The first generation systems are used for delivery of small, lipophilic and low dose drugs. The second generation uses chemical enhancers and utilizes iontophoresis to regulate the rate of delivery. The most recent third generation delivery systems aims at the barrier layer of stratum corneum in the skin and it uses microneedles, thermal ablation, electroporation and microdermabrasion [16]. The skin is easily accessible which makes it as a good option for drug delivery. However, majority of the drugs are unable to enter skin at therapeutically useful rates [17]. The skin is an efficient target for vaccine delivery because the epidermis has Langerhans cells and it is populated with two subsets of dermal dendritic cells. The antigen fragments injected via vaccination are processed and presented to naive T cells in this way and it initiates specific immune response.

The stratum corneum layer of the skin acts as a diffusional barrier and it has a remarkable ability to restrict the process of molecular transport. The recent advances in the development of this mode of drug delivery have led to formulation of microneedles fabricated with various sizes, shapes and materials which have shown enhanced skin permeability. Majority of the studies done in this regard have focussed on solid microneedles which enhances skin permeability to a large range of molecules and even nanoparticles *in vitro*. Studies have been performed by using needle arrays which are used to pierce holes in the skin in order to enhance transport. Hollow microneedles have been used to inject insulin into diabetic rats. For estimating the efficiency of this mode of delivery, the ratio of microneedle fracture force to skin insertion force is taken into account. This ratio was found to be optimal for needles whose tip had small radius and large thickness of the walls. The main advantage is that this method has been proven to be painless and it can be used to deliver therapeutic compounds into the skin [18]. By exploiting the second and third generations, transdermal delivery systems will surely fulfil the promises shown earlier.

The delivery of naked plasmid DNA can be done by using arrays which are dipped in the solution of DNA and scraped repeatedly across the skin to create microabrasions. This has shown to increase the expression of luciferase gene upto 2800 fold. These arrays are called microenhancer arrays and they are etched from silicon wafers by using lithography and potassium hydroxide etching [19].

Types of Transdermal Drug Delivery Systems

A drug delivery system can be defined as an interface between the drug and the patient. It may be a device used for administering the drug or a formulation of the drug which enables the application of a therapeutic substance in the body in order to boost its efficacy and safety by regulating the time, rate and site of the release of the drug in the body. Drugs can be administered via various routes in the body. The specific choice for the mode of administration is guided by the diseases, physiological condition of the patient and the properties of the therapeutic compound. Transdermal route of drug delivery is an

approach which is used to deliver drugs through the stratum corneum layer of skin for therapeutic uses. A drug must have suitable lipophilicity and a molecular weight of < 500 Da in order to get delivered through skin. The delivery of the drugs with varying lipophilicity have been reported to improve by active iontophoresis, mechanical perturbation and energy dependent techniques such as ultrasound and needle-less injection.

Iontophoresis

Iontophoresis or electromotive drug administration (EMDA) is a needle-free injection technique which uses electric charge to deliver drugs or chemicals through the skin. An iontophoretic system consists of a positive electrode (anode), a negative electrode (cathode), a microprocessor, a battery and a drug reservoir. A basic iontophoretic system has been depicted in fig 1.

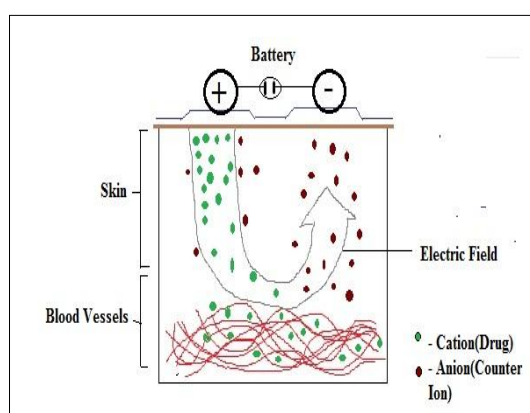


Fig1. An iontophoretic system

Drug formulation is kept in the active electrode compartment and the circuit is completed by the return electrode kept near the skin. On application of electric field, ordered movement of ions present in the formulation and in the skin takes place and it generates an electric current. This phenomenon is termed as electromigration and it is the dominant electrotransport mechanism. The skin acts as a cation selective membrane under physiological conditions and it leads to the generation of a convective solvent flow in the anode to cathode direction, this is known as electroosmosis and it is the minor mechanism for the electrically assisted delivery of cations. It also helps in electrotransport of neutral molecules from the anode [20, 21]. The main advantage of iontophoresis is that it is capable of controlling the delivery kinetics. The rate and extent of the drug delivery is dependent on the duration, intensity and profile of the current being applied.

The challenge in this field is to develop a pre-filled iontophoretic patch system similar to the conventional transdermal patches being used nowadays. Such systems have got the nod of United States Food and Drug Administration and this classifies iontophoresis as one of the most efficient physical enhancement technique for the improvement of drug permeation across the skin [22].

Devices based on velocity

The device known as gene gun is another type of drug delivery system. They propel vaccines from a reservoir into the stratum corneum layer of the skin. Such devices have been redesigned recently and they can now be used to deliver small molecules and proteins from powder and liquid formulations [23]. Liquid jet injectors employ a power source which may be a compressed gas to generate a high velocity jet with velocity 100-200 m/s. This jet is propelled from a nozzle having an orifice of diameter 50-360 μm . The advantages of using needle-free devices include prevention of accidental needle sticks, concerns over disposal, decreased amount of costly and hazardous waste. Still, the risk of cross contamination is not eradicated completely because the interstitial liquid may splash back from the skin and contaminate the nozzle [24]. Thus the multi-use nozzle jet injectors are not used for mass vaccination nowadays and these devices are used for multi dose drug delivery to the same individual. Some examples of partially disposable devices are Sumavel[®] DosePro[®] needle-free delivery system (Zogenix Inc., Emeryville, CA, USA) which was launched in 2010 for delivery of sumatripan [25] and the Biojector[®] 2000 (Bioject Medical Technologies Inc., Tigard, OR, USA) which has been passed by FDA for intramuscular injections. This device is in its clinical trial phase for delivery of DNA vaccines [26].

The functioning of power jet injectors is similar to the liquid jet injectors but power jet injectors promote stronger immune responses because they deliver vaccines to the superficial layers of the skin [27]. The clinical trials of Phase I have proved the efficacy of PowderJect XR-1 in delivering gold particles coated with DNA for hepatitis [28] and influenza [29]. The gold microparticles have got great success in this mode of delivery because they are robust and capable of surviving the highly energetic gas jet within the device and they can sustain the ballistic impact with the tissue. The disadvantages associated with this mode is that it may give pain, bruising, burning sensations, tingling, discoloration, hyperpigmentation, mild erythema at the site of injection.

Microneedles

Microneedles are thin, short, solid or hollow cannulae of micrometer scale size and they can penetrate the stratum corneum and epidermis without getting in touch with the dermis and its pain sensitive nerve endings [30]. Thus, they are minimally invasive, safe and painless mode of delivery [31]. The fabrication of microneedles is an elegant task but the recent advances in the microfabrication technology have led to production of microneedles of varying geometries using a wide range of materials. The techniques which are most commonly used are microfolding which involves filling micromolds with polymer microparticles [32], laser cutting which works by fabricating a mold into which the polymer can be injected repeatedly with a comparatively shorter cycle duration [33], lithography which utilizes a double deep x-ray [34] and wet and dry etching [35]. Microneedles have shown a lot of promise for the transdermal delivery of a broad range of drugs from small compounds to larger proteins and even DNA vaccines. It is a minimally invasive technique but still it disrupts the stratum corneum physically. According to the clinical studies the patients had almost no pain when microneedles were used and the sensation of pressure

associated with the patch application is often reported [36]. The major advantage is that till date no infection has been reported as a side effect in clinical trials of microneedles.

Radiofrequency-induced microporation

Physical energy can be used as an alternative to mechanically induced fissure in the outer layers of epidermis. This approach was developed by Transpharma Medical (Lod, Israel) when they formulated Viador™ technology involving the utilization of radiofrequency to thermally wear away the stratum corneum [20, 21]. The device had an array of microelectrodes which were placed in contact with the skin and when electric current is applied then ions present within the tissue try to re-align in response to the changing electric field which causes frictional heating. The stratum corneum wears away as a result. The local heating causes cell ablation and results in the formation of an array of microchannels in the stratum corneum that function as transport channels. This mode of delivery has shown the ability to deliver recombinant human growth hormone in guinea pigs and in rats also [37]. The device has been represented in fig2.

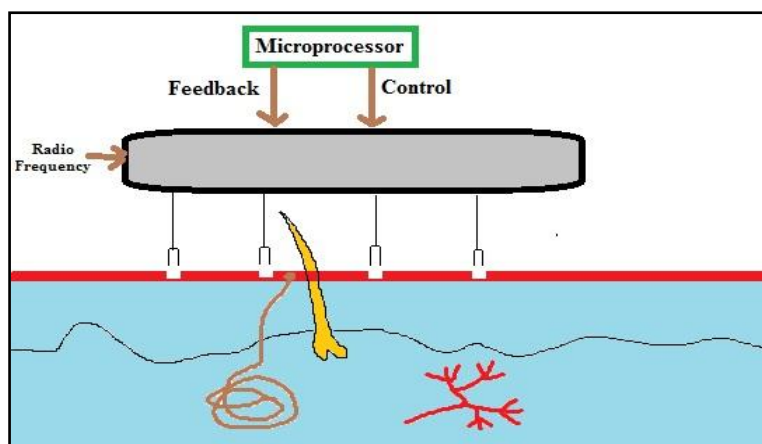


Fig 2. Diagrammatic Representation Of Radiofrequency Induced Microporation Laser Microporation

The creation of micron sized microchannels in the skin which allow the transport of water soluble molecules and macromolecules is termed as microporation. Laser is one of the technologies which can be used to ablate the stratum corneum by microporation [38]. It is an elegant alternative to the microneedle based microporation and it does not involve the use of mechanical force on the skin. The process involves removal of upper skin layers to create aqueous channels that enable diffusion of topically applied biopharmaceuticals such as peptides, proteins, antibodies and nucleotides which are hydrophilic in nature. Laser assisted immunization of DNA vaccines is a feasible approach but there is scope for potential innovation and clinical trials [39]. The depth of the micropores is modulated along with the pore density and this facilitates control of the rate and extent of drug delivery to the skin [40].

Sonophoresis

Sonophoresis is another emerging technology for the delivery of vaccines. It involves the use of low frequency ultrasound (20-100 kHz) or high frequency ultrasound (0.7-0.16

kHz). It has been reported that sonophoresis increases skin permeability to various low and high molecular weight drugs such as insulin and heparin. But the long term safety issues, reduction in cost are some of the issues which need to be addressed in future. The recent research focuses on new formulations for sonophoresis, its synergistic effects with iontophoresis and electroporation, its use in cancer therapy, cardiovascular disorders, hormone replacement therapy and gene therapy. It is done by using SonoPrep® Ultrasonic Skin Permeation Device (Sontra Medical Corporation) which applies a frequency of 55 kHz to the skin for 30 seconds. The device shuts off automatically when the desired level of skin permeability has been achieved. The skin permeability is measured by the current moving through a return electrode. The underlying mechanism is still not clear but it has been proposed that the stratum corneum of the skin layer may get impaired due to collapse of cavitation bubbles formed in the coupling medium [41].

The authors studied the literature available on the drugs for which transdermal drug delivery systems have already been used and it has been summarized in table1. The authors did extensive literature survey to find out the transdermal drug delivery systems which are available commercially along with the drugs for which they are used and some transdermal drugs and their delivery technologies have been represented in table2 .

Table1. List of drugs for which transdermal delivery system has been used

S.No.	Drug Name	Reference
1	Clonidine	[42]
2	Estradiol	[42]
3	Fentanyl	[42]
4	Nicotine	[42]
5	Scopolamine	[42]
6	Testosterone	[42]

Table2. Transdermal Drugs and delivery technologies

S.No.	Drug Name	Delivery System	References
1	AB-1001	Passive	[43]
2	Acyclovir	Iontophoresis	[43]
3	Buprenorphine	Passive	[43]
4	Fertility hormone	Iontophoresis	[43]
5	Granisetron	Passive	[43]
6	Human growth hormone	Thermal ablation	[43]
7	Influenza vaccine	Microneedles	[43]
8	Parathyroid hormone	Microneedles	[43]
9	Testosterone	Passive	[43]

Merits of transdermal drug delivery systems

The transdermal delivery of therapeutic compounds is associated with numerous advantages. The main positive side of this technique is that it is painless, much less intimidating, biodegradable and they pose no major danger in handling. Another merit is that when drugs are administered through transdermal route then they avoid “First Pass Metabolism” and they enter blood stream directly. These delivery systems are highly

efficient as compared to both oral and hypodermic systems. Even the invasive form of transdermal drug delivery system is painless and it heals within few hours. Transdermal drug delivery systems have ethical advantages also, because by using this we are increasing the health and welfare of the public by creating more efficient drug delivery systems which can be much easily disposed as compared to other currently available drug delivery systems [44].

Demerits of transdermal drug delivery systems

Transdermal drug delivery systems have few associated disadvantages and one of them is that therapeutic compounds of larger size can not be administered through this mode of drug delivery. A drug can not permeate through skin if it is non-responsive to transdermal delivery. Some particles, such as a virus particle may take a long time to diffuse through the barrier of skin. This drug delivery system has been reported to cause cutaneous irritation (contact dermatitis) thus it can not be used for a longer duration of time. Poor adhesion of transdermal systems is another issue which must be addressed. Another issue is that few pharmaceutical companies are willing to manufacture transdermal drug delivery systems due to the high cost of production [44, 45, 46, 47].

FUTURE SCOPE

Transdermal drug delivery systems are an extremely promising technology but it is still not understood completely. If proper research takes place on this technology then this type of drug delivery system would revolutionize the field of medicine [46]. The promises shown by the technology includes reduction in contaminated wastes from hypodermics, no diseases by sharing of hypodermics, increased acceptance of medicine into the human body and efficient doses [47, 48]. Current research focuses on utilization of ultrasound to enhance permeability. It would enhance the efficiency of the transdermal drug delivery systems and thus it would be much more helpful in acute conditions [49, 50]. These delivery systems have potential to improve bioavailability of the drugs and thus modify delivery kinetics [51]. Extensive research on formulations and design of the device will lead to a new generation of pharmaceutical products .

CONCLUSION

The authors surveyed the literature and focused on DNA vaccine administration through transdermal delivery system. Moreover much attention have been paid on the types of transdermal delivery systems such as iontophoresis, devices based on velocity, microneedles, radiofrequency-induced microporation, laser microporation and sonophoresis. In addition to this merits and demerits of the transdelivery systems were also discussed. It is the future need to develop the new ways and means to deliver DNA vaccine efficiently so that it will produce good immunity. Moreover the need is to develop more painless and efficient delivery system so to compete with other vaccines in the market.



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