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Microneedle Mediated Vaccine Delivery: A Comprehensive Review

ANUREET ARORA[1], MANJU NAGPAL[1]* AND GEETA AGGARWAL[2]

[1]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

[2]Delhi Pharmaceutical Sciences and Research University, Sector 3, Pushpvihar, New Delhi, India

***Email: ajmergrewal2007@gmail.com**

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Abstract Microneedles can be representative for paradigm shift of drug delivery from patient non-compliant parenteral injections to patient compliant drug delivery system, which can be utilized for administration of vaccines particularly along with macromolecular/micromolecular drugs. The concept of microneedles came into existence many decades ago but the use of microneedles to achieve efficient delivery of drugs into the skin became subject of research from mid of 1990's. Various types of microneedles were utilized to enhance delivery of drugs and vaccines including solid microneedles for pre-treatment of skin to enhance drug permeability, dissolvable polymeric microneedles encapsulating drugs, microneedles coated with drugs and hollow microneedles for infusion of drugs through the skin. Microneedles have shown promising delivery of vaccines through skin in literature. But the successful utilization of this system for vaccine drug delivery mainly depends on design of device to facilitate microneedle infusion, vaccine stability and storage in system, recovery of skin on removal of microneedle and improved patient compliance. This article reviews the conventional and advanced methods of vaccine drug deliver, microneedles for drug delivery, types of microneedles, advantages of microneedles and potential of microneedles for vaccine drug delivery.

Keywords: vaccine, immune, epitope, antigen, transcutaneous, pathogenic

1. INTRODUCTION

Vaccines are the class of matter which unveil the immunologically arbitrated resistance for the disease but is not mandatory in case of an infection. They usually comprise of denatured or killed organisms and subunits of organisms

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or encoding DNA for different antigenic proteins of pathogens. The vaccines subunit type is specially choosey and particular while having interaction with antibodies which generally fail to present these interactions in cases like alterations for epitopic recognition core of poorly immunogenic and also of antibody. Yet, selectiveness and specifies of infectious organisms sub units like carbohydrates, proteins could be altered in case of manufacturing tough and protracted immunological response thru providing them to immune system in a manner that a exact, robust immune response is developed. Epitopes could as well trigger the production of vaccines merely not in contradiction of diseases causing infection, however as well in the case of prolonged diseases like cancer or hepatitis C. In a manner for inculcating a dominant protecting resistance, these vaccines necessitate enhancing by mediators acknowledged as ADJUVANTS. Adjuvant is supposed to present their action via creating complex through a media tor that need to be transported from immune gens which are slowly released(Song, 2012).

The idea of providing vaccines through skin is a very primitive technique. Initially, the Chinese used the technique which was then called as variolation in which the small pox virus i.e. variola virus was dragged out of disease-ridden patients and then abraded between the skin of a healthy individuals. The idea was to purposely incite smallpox infection which may be mild, would offer a protective mechanism contrary to potentially extra powerful natural infection. Being effective in number of cases, its use was associated with substantial death. Finally the word vaccination was termed as the outcome of Edward Jenner's affirmation which states scraping of allied however not much virulent vaccinia virus (cowpox virus), inside the skin can perhaps efficaciously hinder small pox virus contagion. Now a days, vaccination of small pox is carried out via injecting vaccine virus in the skin by method of branched Needles. The things about which the early Chinese or Edward Jenner and his supporters were not aware was that the human skin is highly rigid immune prompting tissue because of the vast accumulation of dominant antigen-presenting cells present inside the human skin, specifically epidermal Langerhans Cells, dermal dendritic cells. During accumulation for smallpox, numerous other vaccines were used on the skin by means of traditional syringes and needles, as stated in the mantoux technique. The above mentioned technique was executed by introducing the regular 26 or 27 Gauze needle inside the skin at a very small angle having a bevel up. Very careful insertion of needle is done adequately inside the skin for complete safeguard of bevel and 0.1 millilitre fluid is inserted inside the skin which results in the creation of the elevated itchy (pruritic) area. This practise demand side-range training and is demanding to be completed consistently (Blank schtein, 2014).

Vaccine transport systems include liposomes, microparticles, emulsions, immune-stimulating complexes ISCOMs. The Immunostimulatory adjuvants in case of pathogens are the preserved molecular designs which enhance immunity being recognized through the receptors such as "Toll" receptors sited primarily on dendritic cells and B cells present in mammals (CpG in unmethylated form which coats DNA) (Schwendener, 2014). Adjuvants vitalize immunostimulatory effect produced by antigen even though they are non-immunogenic, risk-free, and perishable by its own. Salts of Aluminium like $Al(OH)_3$, $AlPO_4$; oily emulsions like Freunds partial adjuvant; particulate material including ISCOMs; artificial polynucleotides are extraneous forms of adjuvants (Schwendener, 2014, Apostolopoulos, 2013).

2. CHARACTERISTICS FOR AN IDEAL VACCINE (SUH, 2014):

- The vaccine should be non-toxic or non-pathogenic which means vaccine is safe.
- The level of side effects in case of normal individuals should be very low.
- Individuals having impaired immune system should not suffer any problem due to this.
- In case of vaccinated individuals or individuals with live vaccine, there should be no spreading of any infection.
- It should yield an extended long-term humoral as well as cellular immunities.
- The method for vaccination must be easy.
- The vaccine must be inexpensive.
- It must not infect the environment.
- The vaccine must be effective.

3. CONVENTIONAL SYSTEMS FOR DELIVERY OF VACCINES

The various types of vaccine delivery systems are:

3.1 Liposomes (phospholipid based vesicles) in 1970s liposome were widely in use for the delivery of drugs targeting locations inside the body. The supplementary favourable feature of this method is its immunoadjuvant action that is revealed to show cell-mediated immune responses and/or humoral responses in lieu of liposomal trapped antigens without or with cytokines or more specific immunologically vitalmediators. Alternate methodology includes samalgamating antigens in the solid elements called ISCOMs (immunostimulatory aggregates). ISCOMs are prepared

from peptides along with adjuvant Quil A. ISCOM components include lower strengths of adjuvants but thereafter substantially enhancing the immunogenicity of the antigen (Saroja, 2011).

3.2 The multiple antigen peptide approach (MAP) These are a type of dendrimers, which are intended for substituting the carrier proteins into a vaccine linked with peptide, having little fundamental unit which can intensify peptide antigens devoid of the short comings linked along the carriers of protein. The back ground of MAP is the central medium that consists of diverging trifunctional amino acids (lysine) having characteristics given below :(i) Non-immunogenic (ii) flexibility for incorporating numerous epitopes (iii) capability to strengthen the peptide antigens within a macromolecule (IV) available in case of chemical reactions. MAP (dendrimer) technique is being in effective use to inculcate immune reactions to antigens (Saroja, 2011).

3.3 Best vaccine for sever alailments is the live at tenuate derived from pathogen which could boost defensive immunity for antigens present upon a pathogen devoid of producing some kind of adverse effects. Hindrances in the growth of these vaccines, gave increment in the problems of raising the pathogen within the laboratory along with problems associated with killing of pathogen. To overcome these barriers the only approach which could be used is the introduction of pathogenic genes inside the non pathogenic organism. In case of expression for genes coding of the antigens is done/ served by non-virulent organism (recombinant virus). The benefit of this is that the recombinant virus immediately develops foreign antigen that is delivered to individual's immune system. There are various vectors that have been examined in the development of vaccines and include avipox virus, adenovirus, alpha virus, enterovirus vectors, vaccinia virus Ankara and vaccinia virus. (Apostolopoulos, 2013).

3.4 Inoculation with non-replicating plasmid DNA (Naked DNA) coding for the viral proteins might be advantageous for the purpose of vaccines, as there is no infective agent used, so as such there is no need of accumulating the virus particles and the choice for determining factor is allowed. In case of the animal models rigid immune responses was developed however, they were not possible to translate within the human clinical trials. The result of this was the necessity of distribution methods for DNA and likewise in vitro, in vivo electroporation, Biojector 2000 and gene-gun were manufactured. Other methods for ease included the non-viral vectors and the receptor linked uptake for DNA within the cells (Chen, 2015).

3.5 Cell penetrating peptides (CPP) or membrane translocating peptides (MTP) are the cluster of cationic peptides which have the capability to enter

inside the cytoplasm of the cells. CPP are capable for transporting a number of antigens which include DNA, drugs, proteins, peptides, RNA and virus particles within the cells. CPP are in fact - (i) human immunodeficiency virus attained from TAT is a trans activator for the transcriptional protein (ii) penetrating obtained from the *Drosophila Antennapedia* domain has been used for the transport of antigens with robust cellular and antibody response initiation (Apostolopoulos, 2013).

3.6 Along with this a compilation of other techniques for vaccine transfer have shown prodigiouspotential in case of animal models and also in human clinical trials. These techniqueencompass the requirement of nano particles, virus-like particles and utilization of *ex vivo* produced monocyte derived dendritic cells and target antigens for dendritic cell receptors which are CIRE, c-type lectin receptors, Clec2, Clec12A and Clec12B, DC-STAMP, DNGR-1, DEC205, DC-SIGN, dectin-1, dectin-2, DCIR, DC-SIGNR, FIRE, Fc receptor, F4/80 receptor, Langerin, L-SIGN, LOX1, MGL, mannose receptor, scavenger receptor. Now a days the increase in knowledge regarding toll-like receptor (TLR) targeting and stimulation for DCs through TLR has helped in this area. These TLR ligands inside mice initiate DCs and trigger immune responses, though, no significant TLR-targeting vaccine trials have/had been completed in humans and its not sure that TLR targeting methodology would offer considerable advantageous outcome in human beings as seen in the case of mice. Moreover, various targeting antigens of chemokine receptors on DCs (CCR1, CCR2, CCR5, CCR6, CXCR1, CXCR4) have shown to yield robust immune responses both invitro and invivo. However, bacterial toxins along with DC binding peptides targeted antigens to DCs lacking the requirement of DC receptor targeting. In case of distinctive apprehension for vaccine delivery, the current techniques for live- killed/weakened bacterial vectors, nano particle dependent vaccines, artificial transporters, cholera toxin subunit B as an adjuvant and in case of GAVI vaccination programs were widely studied (Apostolopoulos, 2013).

3.7 Microspheres

The biodegradable and biocompatible copolymer poly (DL-lactide-co-glycolide) [DL-PLG] was used to develop the vaccines containing microspheres. Subcutaneous immunization in mice was done by using 1- to 10-microns of microspheres which consisted of a toxoid vaccine of staphylococcal enterotoxin B (SEB) which fortified to 500-fold increase in strength of nerve impulses for the allocating antitoxin response. A Constructive adjuvantaction was dependent on the microspheres whose size would have not been more than 10 microns in their diameter and

the presence of antigen inside the particles. The rate at which DL-PLG biodegradation takes place is used for determination of the ratio of lactide to glycolide, and in case of co-injection of SEB toxoid microspheres articulated with two dissimilar DL-PLG ratios encouraged for both a primary and an enhanced reaction of secondary antitoxin response. When DL-PLG was imported by the oral or intratracheal (IT) route, the microencapsulated SEB toxoid was observed to be beneficial in the initiation of concomitant circulation and dispersion of mucosal antibody responses. Female rhesus macaques were vaccinate during a microencapsulated simian immunodeficiency virus (SIV) serum was generated for higher concentration of distributing anti-SIV antibodies, and consequent oral or IT boost, particular antibodies were obtained in vaginal wash fluids. Vaginal challenge with feasible homologous SIV gave rise to infection of three out of four non immunized however only one out of seven microsphere-immunized macaques. Therefore, DL-PLG microspheres are capable technique for the transport of vaccines, assimilation of adjuvant motion with metered release and effective demonstration to mucosally associated lymphoid tissues (MALT) (Stanley, 2013). Table 1 depicts data on marketed vaccines based on conventional delivery systems as per FDA.

Table 1: Some commercial vaccine formulations (http://www.who.int/)

S. No	Vaccine Used	Company name	Description
1	Zostavax	Merck & Co	Shingles, herpes
2	Prevnar 7	Pfizer	Pneumococcal infection, otitis media
3	Fluzone	Sanofi	Influenza
4	Menactra	Sanofi	Meningitis
5	Adacel	Sanofi	Diphtheria, pertussis / whooping cough, tetanus
6	MMR- II	Merck & co	Measles, mumps, rubella
7	Boostix	GlaxoSmithKline	Diphtheria, pertussis / whooping cough, tetanus
8	Biothax	Emergent biosolutions	Anthrax
9	Prevnar 13	Pfizer	Pneumococcal infection
10	PENTAct-HIB	Sanofi	Haemophillus influenza type b, polio, tetanus, whooping cough/ pertussis, Diphtheria.
11	Gardasil	Merck & co	Human papillomavirus
12	Pediarix	GlaxoSmithKline	Hepatitis B, Polio, tetanus,Diphtheria, whooping cough/ pertussis.

S. No	Vaccine Used	Company name	Description
13	Hepatitis vaccine	GlaxoSmithKline	hepatitis A, hepatitis B
14	Celtura	Novartis	Swine flu
15	Varivax	Merck & co	Varicella virus
16	Cervarix	GlaxoSmithKline	HPV
17	Rota teq	Merck & co	Rotavirus gastroenteritis
18	Synflorix	GlaxoSmithKline	Pneumococcal infection, otitis media
19	Rotarix	GlaxoSmithKline	Rotaviral gastroenteritis
20	Pneumovax	Merck & co	Pneumococcal infection

4. ADVANCED CARRIERS FOR VACCINE DELIVERY: MICRONEEDLES

4.1 Introduction

The notion of the bunch of small sized needles for the purpose of drug delivery dates back to 1976 and a patent was filed for this (filed 1971) by Gerstel and Place at Alza Corp. 22. This patent was claimed for a device used for drug delivery and had small projections (i.e. Microneedles) and also had a drug reservoir. Microneedles are generally solid or hollow because of their small size that is capable to penetrate stratum corneum. The Delivery of drug or medicament from such devices can occur through diffusion or by convention by the use of the force for backing of the reservoir (Courtenay, 2016). For the achievement of physiologically related supply rates the micro needle dependent drug transport is normally done with cluster of needles for a specific area. For Insertion of micro needle arrays by a huge amount of needles within the skin by avoiding the use of a distinct insertion tool (e.g. a high-velocity plunger) requires the reduced force for insertion needed to pierce the tissue. Along with this patches are required for delivering drug, so for this it requires penetration regardless of the skin type/age of the subject and the humidity present. The penetration forces can be affected or changed by these above factors. Hence, it's sensible to consider that defence criteria's of 3–5 intervals might be mandatory. When shown practically, the insertion of Microneedles inside the skin is strongly connected with the interfacial area amongst the skin and Microneedles. If the interfacial area is small then the insertion force will be low. It can also be said that the use of sharp needle can be negligible in case of interfacial area so it will pierce the tissue in comparison to blunt needle. (Woolfson, 2012). The evolution of Microneedles in case of delivering the vaccines besides pandemic influenza could include other notable advantages. Firstly, using Microneedles in

case of solid state vaccine transfer preparations might result in a provocatively improved shelf-life of delivery systems like these because of their inherently enhanced durability in case of solid state protein preparations in comparison to their traditional corresponding solutions. This results in more adequate supplies and capabilities for piling the stock which is highly required in case of vaccines in contrast to pandemic influenza are foreseen. Secondly, arrays of Micro needle can probably be self-administered and carefully thrown of, which might be Vital in the occasion of insufficiency of medical persons (Carey, 2014).

4.2 Fabrication of Microneedles

Microneedles are developed on the criteria of micro scale (having 1 μm of diameter and extending from 1 to 100 μm in case of length) and this differentiates them from traditional needles. These are made up of various constituents like: glass, metals, polymers, silicon, silicon dioxide and other ingredients. Microneedles could be designed to be long enough so that they can penetrate the layer of skin (stratum corneum), avoiding the perforation of nerve endings which reduces the chances of any kind of infection, injury or pain (Apostolopoulos,2013). Intradermal delivery of vaccines can be facilitated by the prepared Microneedles which is generally not easy to achieve in case of large populations in a highly reproducible manner. Many micro needle production procedures are dependent on the traditional micro fabrication methods for adding, eliminating and replicating microstructures using photolithographic procedures, silicon etching, laser wounding, metal electroplating, metal electro polishing and micro molding (Jiskoot, 2012).

4.3 Drug delivery through Microneedles

Microneedles consist of the array of micro sized structured projections which are covered by a drug or vaccine which is applicable on the skin to distribute intradermal transport of active agents which else may not be able to cross stratum corneum. The transport of vaccines or drugs is not done by the process of diffusion as in case of transdermal delivery systems however the momentary mechanical interruption of the skin can lead to the placing of the drug or vaccine inside the epidermis layer, where it could reach easily to the specific site for its action.

4.4 Types of Microneedles

Microneedles can be categorised as :

Solid Microneedles which can be used for tissue pre-treatment, Microneedles coated by drug or drug coated, dissolvable/dissolving Microneedles, and

hollow Microneedles. Another categorisation of Microneedles normally used in literature is on the basis of their production methods which could be in-plane or out-of plane microneedles (Jiskoot, 2012).

In-plane microneedles made to have the shaft which is parallel to the substrate layer. The benefit of this technique is the extent of the needle that can be very accuratelymetered. The drawback of this technique is that it hasproblem in developing a two dimensional arrays(Jiskoot, 2012).

Out of-plane microneedles on the contrary, is a substrate projection and they are straight advancing to develop in arrays. Irrespective of the length and height ratios it becomes an essential task for developing these kind of needles. Other than these, beneficial criteria/level is to differentiate that the microneedles could be solid or hollow. Hollow microneedles having needle bore or lumen allow an active liquid transportation above the microneedle (Duan, 2013). Table 2 includes different type of microneedles and its advantage and disadvantages.

Table 2: Various types of microneedles with their advantages and disadvantages

Microneedle type (Material) /Reference	Advantages	Disadvantages

Solid Microneedles (metal, titanium or glass, silicon)/ (Kolli, 2008,Yuzhakov, 2007)	• Enhanced mechanical strength, efficacious insert, designed for various geometrical sizes as well as shapes
	Dual kinds:
	  • Out of plane: permits greater density(per array) of microneedle as the shaft is perpendicular to base.
	  • In plane: the density of microneedle is restricted as the base plus shaft both lie in a similar plane.
	• Drug distribution is diffusion mediated (lateral or vertical)
	• Dissemination via microchannels (withdrawal of microneedle)
		• Requirement of an expensive cleaning room facility for the complex manufacturing of silicon microneedles.
		• Rupturing may occur inside the skin.

Coated Microneedles / (Prausnitz, 2007, Gill, 2007)	• Drug deposition into the depth of the skin • Drug delivery is usually not diffusion dependent. • Single phase performances in case of drug distribution and microporation. • does not dependent on additional microfluidics component or drug reservoir	• Successfulness is dependent on the procedure and formulation of coating. • Coating of inequitable quantity which is appropriate solely in case of potent drugs • Necessary to make sure that coated drug was distributed.

Microneedle type (Material) /Reference	Advantages	Disadvantages
	• effortless and simple usage for drug distribution mechanism in case of finale user which is similar to that of passive patch • comparatively little insensitive environment is required for coating rather than producing dissolvable micro moulding • Appropriate in the distribution of vaccines or peptides, proteins • Dose sparing is allowed.	• Amplified coat might negotiate for sharpness of needle, therefore inclusion.
Dissolving Microneedles (Made from sugars, polymer (PVP), maltose; crystalline GRAS material)/ (Kolli, 2008,Prausnitz, 2004,Raphael, 2010, Park, 2006)	• Micro channels are formed within a minute after dissolution • Dual kind: first is thru enclosed drug besides second is deprived of drug • Control drug discharge via slowly dissolvable polymers • It is Biocompatible and biodegradable leading to reduction of irritability. • No requirement for strident disposal of waste. • Payload distribution is achieved on a larger scale as compared to coated microneedles. • Drug is previously included in microneedles therefore no requirement for reconstituting drug. • No reservoir leakage related issues • Simple and reasonable micromoulding fabrication technique	• In case of drug stability the techniques for fabrication are non conducive because of callous producing environment • Insufficient drug filling capability 1mg for 1000 microneedle • Appropriate in case of entrapment for delicate macromolecules • Need for ensuring that microneedles are left in skin or dissolved completely former to the extracting of the base or requirement of the applicator. • Require cautious selectivity for ingredients for ensuring rapid dissolution.
Hollow Microneedles / (Coulman, 2006,Prausnitz, 2004)	• Distributing fluid preparations • Placement of Drug at accurate depth inside the layers of skin. • Quick start for action of drug is probable.	• High-priced fabrication method • Condensed mechanical vigour in comparison to solid microneedles particularly prepared by silica. • Clogging while inclusion through the tissues of skin. • Outsized diameter of tip might link to poor inclusion • Infusion rates restricted due to Back pressure (10 to 100 ml/minute)

Microneedle type (Material) /Reference	Advantages	Disadvantages
		• Need renunciation followed by insert for helping the amplification of infusion rates • Adjustment of required flow rate.

4.5 Advantages of micro-needle based vaccines

- **Pain-free administration:** Microneedles which have a length in a range of a few hundred micrometres could specifically permeate the superficial layers of the skin whose nerve receptors density is low. The outcome of this is that the insertion of microneedles within the skin is expected to be trouble-free (Gill, 2007)
- **Easy to use:** in case of a normal transdermal patch the patient himself could virtually apply an intended system without any required training. Moreover for attaining this distinct insertion any kind of tool and process parameters are not necessarily required. Therefore, a low insertion strength is required for microneedles and a consistent and vigorous technique is required for insertion. If it is attained then it is logical to consider that the process for numerous medication, can be sold over the counter (OTC) (Gill, 2007)
- **Discreetness:** Incorporating a microneedle-array along with a planar and compact medicating method yields a patch-like discreet device which could be slightly worn beneath the clothing (Gill, 2007).
- **Continuous release:** A non-obstructing device might be worn for larger time duration, hence allowing uninterrupted and constant delivery at therapeutic levels (Gill, 2007).
- **Controlled release:** Controlled release of drug can be achieved by the incorporation of passive components, e.g. flow restrictors or flow membranes and some active devices such as closed loop systems. The delivery on the basis of time and amplitude can be modulated by the possibility of active dosing systems (Gill, 2007).
- **Safer handling:** Microneedles expanded for a few hundred micrometres from the surface show a very less risk of inadvertent needle sticking as compared to that of hypodermic needles. The danger of communication of blood-borne pathogens is very less as the microneedles are not able to reach the blood (Gill, 2007).

4.6 Rationale behind microneedles (Ita, 2015)

- Solid microneedles based patches of drug can be used for intensifying the diffusion rates and can also be used for increasing the penetrability

by punching holes in the skin, rubbing the drug over an area or coating needles by the mediator to be circulated.

- Hollow needles can be used with drug patches and metered pumps for the delivery of drugs at specific time interval. This type of microneedles could be used for removing fluid through the body required in case of analysis – like blood glucose quantitation and then for supplying insulin or other desired drugs in micro liter volumes. They are capable in dosing at a very accurate level, patterns for complex release, for the promotion of local delivery and enhancement in case of biological drug stability by storage in a micro volume which could be controlled precisely. Table 3 shows various transdermal formulations of various drugs (Akhtar, 2014) based on microneedle approach.

Table 3 : Marketed transdermal formulations based on microneedles

S. No	Product	Carrier System	Applications	References
1	Anti-restenosis	Microneedle patches	Target drug delivery in atherosclerosis	(McAllister, 2000)
2	Insulin	Microneedles patches	Reduced glycerol level upto 80% within 4 hours	(Srinivas, 2010)
3	Desmopressin	Microneedles	Enhanced bioavailability	(Cormier, 2004)
4	Immunization (antigen)	Microneedle array patch system	Effective immunization	(Alarcon, 2010)
5	Vaccination (influenza vaccine)	Microneedle patches	Enhanced immune response	(Mortant, 2004)
6	Insulin	Array of solid microneedles	Increases insulin transdermal delivery to lower levels by 80%	(Duan, 2013)
7	Lidocaine hydrochloride	Microneedle array	Repeatable penetration across epidermis	(Ghosh, 2013)
9	Naltrexone and diclofenac	Microneedle array	Effective transdermal delivery	(Donnell, 2009)
10	5- amino levulinic acid	Microneedle array	Enhanced production of photosensitizer	(Back, 2011)
11	Phenylephrine	Microneedle	Enhancement in case of mean resting anal sphincter pressure	(Qiu, 2012)
12	Bovine serum albumin	Polymeric Microneedles	Potential deliver of bovine serum albumin	(Chen, 2012)

S. No	Product	Carrier System	Applications	References
13	Recombinant human insulin	Microneedles hydrogel patches	Sustained release of insulin	(Wermeling, 2008)
14	Naltrexone	Microneedles	Enhanced transdermal delivery	(Ito, 2006)
15	Insulin	Microneedles	Increased percutaneous administration of insulin	(Kocchar,2012)
16	Bovine serum albumin	Chitosan microneedles patches	Sustained delivery of microneedles	(Pawar, 2012)

4.7 Present status of developments on microneedles

Gill *et al.* worked on the consistency of covering the complexes such as bovine serum albumin, calcein, plasmid DNA and vitamin Baltered vaccinia virus and micro particles (ranging from 1 to 20 μm in diameter) on both individual and arrays of microneedles to be used for a unique micron-scale dip-coating method(Gill, 2007).

Matriano *et al.* observed the usage of Microneedles coated by a dry-film of antigen for the delivery of ovalbumin by the model protein antigen by injecting them within the skin of shaved guinea pigs in vivo by means of a high-velocity injector (Matriano, 2002).

Lee *et al.*(Lee, 2010)had worked on microneedles compressed by proteins, DNA etc. which could blend inside the skin in case of bolus or sustained delivery without leaving any kind of bio hazardous sharp medical waste for transdermal drug delivery. These kind of dissolving microneedles could be made-up of polymers such as PVP (commonly used as plasma expander and therefore are harmless) to transport deactivated influenza virus in lyophilized form aimed for influenza vaccination that targets the transfer of vaccine to skin's antigen presenting cells and generates a sturdy immune responses. Polylactic acid, polyglycolic acid along with their copolymers is extensively used in the production of decomposable polymer microneedle (Yuzhakov, 2010).

Therefore, microneedles have been potential carrier for delivery of a number of drugs (enhanced transcutaneous permeation) and simultaneously these have been effectively utilized for more effective vaccine drug delivery systems.

Table 4 includes marketed products based on microneedle approach. Microneedles has been adopted as an approach for efficient delivery of various drugs such as lidocaine in pain management, nicotine for smoking cessation, nitroglycerin for angina etc. A list of products based on microneedle approach with the name of drug and disease has been compiled in table 5. Table 6 depicts data on microneedle based vaccine formulations. A number of vaccines have

been worked out using microneedles e.g. small pox, tuberculosis vaccine and various peptides (bovine serum albumin, growth hormone etc.)

Table 4: Microneedle approach based patent edmarketed products

S. No.	Product	Company Name	Description	References
1	AdminPen®	AdminMed	Microneedle array based pen injector device.	(Desale, 2012)
2	AdminPatch®	AdminMad	Microneedle array	(Desale, 2012)
3	Macroflux®	Macroflux	Microneedle array	(Lax, 2010)
4	Microcore®	Microcore	Dissolved peptide microneedle patch	(Wu, 2012)
5	Microjet®	Microjet	Intradermal microneedle injection system.	(Wu, 2012)

Table 5: Data on FDA approved marketed products of various drugs based on microneedle approach

Drug	Product name	Company Name	Description
Clonidine	Catapres TTS	Boehringer Ingelheim	Hypertension
Estradiol	Alora Estraderm Menostar	Watson Novartis Bayer	Hypoestrogenism
Fentanyl	Duragesic	Janssen	Pain relief
Lidocaine	Lidoderm	Endo	Post shingles pain
Methylphenidate	Daytrona	Shire	ADHD (Attention deficit hyperactivity disorder)
Nicotine	Habitrol Nicoderm Prostep Nicotrol	Novartis GlaxoSmithKline Elan McNeil	Smoking cessation
Nitro glycerine	Minitran Nitro- Dur Transderm - Nitro	3M Schering Plough Novartis	Angina
Oxybutynin	Emsam	Watson	Overactive bladder
Selegine	Oxytrol	Somerset	Depression
Scopolamine	Transderm Scop	Novartis	Motion sickness
Testosterone	Androderm Testroderm	Watson ALZA	Hypogonadism

Table 6: Microneedle based vaccines

Carrier	Vaccine	Discretion
Microneedle (Prausnitz.2009)	Small pox, T.B, yellow fever	Immense clinical study with smallpox, TB and various vaccines showed that vaccine delivery to human skin via conventional intradermal injection had been generally safe and effective and normally the similar immune response at low doses when compared to intramuscular injection. Microneedles being used to deliver whole, inactivated virus, trivalent split antigen vaccines and may provide a safe, effective method to deliver vaccines at lower doses.
Miocroneedles (Donnelly, 2010)	Peptides, DNA, RNA vaccine	Stratum corneum is the main barrier to exogenous substances inclusive of drugs. Drugs having specific physicochemical properties can have successful transdermal administration. There are various problems in transdermal delivery of hydrophilic drugs, molecular agents, peptides, DNA and RNA. Hence microneedles are used to puncture skin which will bypass the stratum corneum to create an aqueous transport pathway having micron dimensions to enhance transdermal permeability.
Microneedle (Milewski, 2010)	Optimization by vesicular, nanoparticles and gel system	The microneedle skin pre-treatment has various effects on drug transport depending on the type of formulation used, formulation characteristics show different effect on transport by untreated skin and microneedle treated skin.
Microneedle array (Woolfson, 2012)	Bovine serum albumin	Microneedles coupled with iontophoresis to have a broad effect for transdermal delivery of peptide (bovine insulin) and protein.
Transcutaneous drug delivery (Wu, 2012)	Sulforhodamine B, methylene blue or model vaccine ovalbumin	To evaluate a safe, ablative fractional laser based technology for enhancing transcutaneous delivery of hydrophilic drugs, vaccine antigens coated on gauze patches.
DNA vaccination (Song, 2012)	DNA vaccine	DNA vaccination in skin by microneedles improved protective immunity as compared to conventional intramuscular injection of plasmid DNA vaccine encoded for influenza hemagglutinin which was evaluated by in vivo fluorescence imaging that showed reporter gene being delivered to skin by solid microneedle patch coated with plasmid DNA. At low dose vaccination via microneedles generated strong humoral response and good protective post challenge response being compared to IM vaccination at low or high dose.

Carrier	Vaccine	Discretion
Microneedle (Jiskoot, 2012)	Protein, peptides DNA, inactivated viruses.	Microneedles are being used for dermal and transdermal delivery of vide range of drugs and delivery of therapeutic proteins and vaccines.
Micro array and microneedle array (Chandrasekhar, 2013)	Vaccines, proteins and peptides	Microneedles, micro array have been used in targeting, delivery of pharmacologically active compounds such as peptides, proteins, and vaccines.
Microneedle patches (Suh, 2014)	DNA vaccines	Microneedles have been developed to target intense network of immunologic antigen presenting cells in dermis and epidermis. Microneedles for wide range of vaccines having comparable or higher immunogenicity to conventional intramuscular route, having dose stability and dose sparing advantages.
Microneedle (Quinn, 2014)	Vaccine delivery	Microneedles have been used to increase transdermal drug delivery by penetration into skins protective barriers by creating pathway for drug permeation to dermal tissue by avoiding first pass metabolism and gastrointestinal degradation
Microneedle mediated vaccine (Carey, 2014)	CD8 T cell	Microneedle-mediated vaccine results in induction of low anti-vector antibody titres by permitting the repeated use of the same adenovirus vaccine vector,that resulted in significant increased antigen-specific antibody responses in mice as compared to ID-treated mice? Microneedle array design don't influence the magnitude of vaccine-induced antibody responses.
Microneedle (Chen, 2015)	Triptolide	Microneedle technology is used for topical formulations to enhance the drug delivery .When triptolide is prepared as TP-LHP, the hepatic first-pass metabolism and digestive toxicity is eliminated.TP-LHP provides stable, long-term release of triptolide, and will have a significant efficacy in the CIA model. The combination of TP-LHP and microneedle technology can provide a safe and efficient method of administration of triptolide for treating RA.
Microneedles (Donnelly,2015)	DNA, Vaccine, Growth Hormone	Microneedles are invasive devices that painlessly and without drawing blood penetrate into the skin's stratum corneum barrier, these systems highly enhance the market size by removing dependence of efficient transdermal transport of drug physicochemical properties by allowing a wide range of drugs which can be delivered transdermally. microneedle arrays already have successfully delivered oligonucleotides, desmopressin, DNA, vaccines, insulin and human Growth hormone in vivo. They have advantages over conventional needle and syringe based on delivery systems for biological agents, particularly reduced pain, infection risk, the ability of controlled administration

Carrier	Vaccine	Discretion
Hydrogels forming microneedles (Ita, 2005)		Microneedles are used to enhance transdermal drug delivery by fabricating in different forms: hollow, solid, and dissolving. There are also hydrogel-forming microneedles, being are innovative microneedles. They do not contain drugs but imbibe interstitial fluid to form continuous conduits Between dermal microcirculation and an attached patch-type reservoir.
Non porous microneedle array (Boks, 2015)	CD8(+) T cells	The use of novel ceramic nanoporous microneedle arrays (npMNA),served as a storage reservoir for vaccines. npMNA enhanced vaccine efficacy by more precisely reaching skin dendritic cells, the T and B cell immunity.
Microneedle vaccine delivery (Raphael, 2016)	Vaccine delivery	A wide range of methods including FT-FIR using synchrotron radiation, nano indentation and skin delivery assays are used systematically to examine the effect of specific bulking agents and excipients, sugars /polyols for material form, structure, strength, failure properties, diffusion and dissolution required for dissolving micro devices.
Microneedles (Courtenay, 2016)	Nanomedicine delivery	This is an emerging and exciting area of pharmaceutical sciences research within the remit of transdermal drug delivery highlighting some of the novel delivery systems which have been described in the literature exploiting these two approaches and directs the reader towards emerging uses for nanomedicines in combination with microneedles

5. CONCLUSION

Microneedles have been exploited as carrier for various drugs due to enhanced permeability thereby improved bioavailability and more patient compliance. This approach has also been adopted for delivery of vaccines but the success of microneedle approach for vaccine delivery is influenced by fabrication of device for infusion in to skin, the stability of the formulation and storage conditions required.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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LIST OF ABBREVIATIONS

ISCOM	Immune stimulating complexes
TOLL	A immune receptor
CpG	Cytosine phosphate guanine
Quil A	A adjuvant
MAP	Multiple antigen peptide approach
CPP	Cell penetrating peptide
MTP	Membrane translocating peptides
TAT	Trans activator of transcription
CLR	C- type lectin

DC-SIGN	Dendritic cell specific ICAM-3 grabbing nonintegrin
DEC 205	Dendritic cell receptor for endocytosis
L-SIGN	Liver specific capture receptor for hepatitis C virus
MGL	Macrophage galactose lectin
DNGR-1	Dendritic cell NK lectin group receptor 1
Clec 12A	C type lectin like receptor
Clec 12B	C- type lectin like receptor
Clec 2	C- type lectin like receptor
DCIR	Dendritic cell immunoactivating receptor
DC	Dendritic cell
DC- STAMP	Dendritic cell specific transmembrane protein
Fc receptor	Fragment crystallisable
TLR	TOLL like receptor
CCR1	Chemokine gene receptor 1
CCR2	Chemokine gene receptor 2
CCR5	Chemokine gene receptor 5
CCR6	Chemokine gene receptor 6
CXCR1	Chemokine gene receptor 1
CXCR4	Chemokine gene receptor 4
MALT	Mucosally associated lymphoid tissues
SIV	Simian immunodeficiency virus
DL-PLG	Poly(DL-lactide –co –glycoside) Bone marrow or bursa derived cells
SEB toxoid	Staphylococcal enterotoxin B
IT route	Intratracheal route
OTC	Over the counter
PVP	Poly vinyl propyledine
SRB	Sulforhodamine B
ADHD	Attention deficit hyperactivity disorder
AFL	Ablative fractional laser
CIA	Collagen induced arthritis
TP- LHP	Triptolifde loaded liposome hydrogel patch
RA	Rheumatoid arthritis
npMNA	Nonporous microneedle array
GAVI	Global Alliance for Vaccines and Immunization