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Recent advances in vaccine delivery

Soni Khyati J., Patel Rakesh P., Asari Vaishnavi M. and Prajapati Bhupendra G

Soni Khyati J., Patel Rakesh P., Asari Vaishnavi M., Prajapati Bhupendra G
Department of Pharmaceutics, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat vidyanagar, Kherva, Mehsana-Gozaria Highway, PIN-390 001, Gujarat, India.

***For Correspondence*:**
Dr. Rakesh P. Patel
Associate Professor, S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, Mehsana, India.
Email: raka_77us@yahoo.com

ABSTRACT

Although currently available vaccines represent an outstanding success story in past few years and it is clear that improvements in vaccine delivery and introduction of new vaccines are required. Vaccine delivery improvements may include the use of novel routes of delivery including intradermal, intranasal, tanscutaneous, and needle free delivery. Intradermal delivery includes delivery of vaccine to the dermis or epidermis for enhancement of immunogenicity. Needle free delivery present lowest risk of needle stick injury and transmission of blood borne pathogen through needle and increase compliance. This review represents the different delivery system, characteristics and advancement in the field of vaccine drug delivery.

***Key words*:** vaccine, drug delivery, needle free delivery, intradermal, intranasal, transcutaneous

INTRODUCTION

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe or its toxins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "recognize" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. Some of the most important types and its examples of vaccines are described in Table 1 (Wolfe et al 2002, Stern et al, 2005).

2. Technology for vaccines delivery

a) Auto-disable (AD) syringes and safety boxes

The rationale of AD syringe is lowest risk of person-to-person transmission of blood borne pathogen because it is designed to prevent reuse. It is the disposable equipment of choice for administering vaccines for mass immunization campaigns.

The risk posed to health staff and the general public by contaminated needles and syringes is reduced by the use of puncture-proof containers, known as safety boxes, for the collection and disposal of used disposable and AD syringes, needles and other injection materials. The AD syringes, which is now widely available at low price.

b) Point-of-use sharps processing technologies

Rationale of Point-of-use sharps processing technology is that the hazards of storing and transporting infected syringes and needles to the point of final disposal can be reduced by de-fanging (i.e. separating, encapsulating or destroying the needles), disinfection and compaction. After they have been disinfected the probability of cross-infection is reduced, and after compaction the processes of storage and transportation become more feasible.

A number of technologies exist or are in the process of development which is mentioned below:

- Disinfectants

- Thermoprocessing technology or melting
- Needle destroyer
- Plasma-melting and small-scale incineration Nature of Gating

Table 1: Types of vaccines and its examples

Types of vaccines	Description	Examples
Killed	Contain killed, but previously virulent, micro- organisms that have been destroyed with chemicals or heat.	Influenza vaccine, Cholera vaccine, Bubonic plague vaccine, Polio vaccine, and Rabies vaccine.
Attenuated	Contain live, attenuated microorganisms. Many of these are live viruses that have been cultivated under conditions that disable their virulent properties, or which use closely-related but less dangerous organisms to produce a broad immune response; however, some are bacterial in nature.	Yellow fever vaccine, Measles vaccine, Rubella vaccine, Mumps vaccine and Typhoid vaccine.
Toxoid	Made from inactivated toxic compounds that cause illness rather than the micro-organism.	Tetanus vaccine and Diphtheria vaccine.
Subunit	Contain fragment of an inactivated or attenuated micro-organism.	Subunit vaccine against Hepatitis B virus , Virus-like particle (VLP) vaccine against human papillomavirus (HPV).
Conjugate	Certain bacteria have polysaccharide outer coats that are poorly immunogenic. By linking these outer coats to proteins (e.g. toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen.	Haemophilus influenzae type B vaccine.
Valence	A monovalent vaccine is designed to immunize against a single antigen. A multivalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms.	Pneumococcal vaccine

c) Monodose prefilled injection devices

Rationale of monodose prefilled injection devices is that it eliminates risks of cross- contamination and wastage of vaccine. In addition, the vaccine dose is prefilled into an injection device, the integrity of the dose is guaranteed up to the moment of use. Prefilled monodose injection devices incorporate glass containers and are often more costly than the vaccine itself. A new plastic pouch-and-needle device, developed by the Program for Appropriate Technology in Health (PATH), USA, with support from the United States Agency for International Development (USAID), is being marketed by under the trade name UniJectTM.

d) Thermostable vaccines and vaccine vial monitors

Rationale of this technology is that vaccine distribution without a cold chain would considerably simplify the delivery system and make it easier to integrate with drug distribution in developing countries. Sugar-glass drying technology allows vaccines to be made which can be stored and transported routinely at tropical room temperatures or in freezing climates. Extremes can be monitored by VVMs (Simonsen 1999, Kane 2000, Steinglass 2005).

3. Intra dermal delivery of vaccines

Intra dermal delivery (IDD) is being used as the route of choice for Bacille Calmette Guerin (BCG), Tuberculosis (TB) and Post-exposure rabies vaccination. It has also been investigated in recent decades as an alternative delivery route for hepatitis B (HBV), measles, and influenza (Bernard et al 2005)

Potential benefits of IDD implementation (Belshe 2007)

a) If IDD enhances immunogenicity its potential benefits are

- Reduced dose size and therefore cost
- Increased coverage of the population for antigens with limited manufacturing capacity
- Improved immunogenicity in difficult subgroups
- Avoidance of the need for adjuvants

b) If improved IDD devices are developed its potential benefits are

- Easier and safer administration
- Reduction in risk of needle-stick injuries
- Improved disposal

c) Other benefits are

- Reduction in storage volumes in the cold chain

Some important examples of intradermal delivery devices are described in Table 2 (Stanfield et al ,1972; Weniger et al , 2008; Williams et al , 2000; Chabri et al ,2004; Chen et al ,2009; Cui et al ,2003; Gill et al ,2007; Gutierrez et al ,2007;Laurent et al ,2007; Lee et al, 2008; McAllister et al,2003; Park et al,2005; Pearton et al, 2008; Booy et al, 2007)

4. Needle free delivery of vaccine (Levine et al , 2004; Suman et al , 2003]

Needle-free vaccination includes all methods for delivering vaccines that do not require a needle and syringe for administration. There are a number of delivery options for needle-free vaccinations, ranging from nasal sprays to patches worn on the skin. The advantages of needle free vaccination are summarized below:

- Improvement of safety for administrator, patients and community.

Table 2: Intradermal delivery devices

Devices	Description	Advantages	Disadvantages	Commercial device
Jet injectors	Disposable syringe jet injectors (DSJIs) consisting of a reusable hand-piece containing a propulsion system and a disposable, vaccine-containing needle-free syringe or cartridge (prefilled or end-user filled) that is replaced before each administration.	1.Prevent needle-stick injuries. 2.Reformulation is not needed. 3.Potential for dose sparing.	1.Expensive 2.Reengineering of vaccine filling lines. 3.Damage might due to shearing force.	Zetajet® (Bioject) E-Jet500® (Euroject) PharmaJe® Lectrajet®
Micro needles	The microneedles are sub-millimeter structures that are designed to pierce the skin and deliver vaccines or drugs in the epidermis or dermis compartments. Different type of microneedles are available like hollow microneedle, solid coated microneedles, solid biodegradable microneedles, solid uncoated microneedles	1. Less pain, injury and infection. 2.High accuracy, good reproducibility, and a moderate fabrication cost. 3.Minimal medical training. 4.Highly targeted drug administration to individual cells.	1.Transmit blood-borne pathogens, so need to be treated as "sharps". 2. Delivery of the full dose might be difficult. 3. Hollow microneedles can be prone to clogging and backpressure.	Micro-Trans™ Nanoject® Micronjet Macroflu® system MTS® device VaxMAT® technology Onvax® system
Intradermal (ID) needles	The ID needle category includes devices that use a single needle designed to deliver to the dermis.	1. Simple to use. 2. Compatible with existing formulations of vaccines.	1.Transmit blood-borne pathogens. 2. Prefilled type of ID requires more cold chain storage space than multi-dose vials.	Soluvia® device

- Responsible for increasing compliance with recommended vaccination schedules.
- Reduction of pain and suffering
- Easier and speedier vaccine delivery**.**
- Reduced cost.

Methods of administrating needle-free vaccines

a) Intranasal delivery of vaccine (Suman et al, 2003; Huang et al, 2007; Shaw et al, 2008; Mutsch et al, 2004)

Advantages

- The nasal mucosa is the first site of contacts with inhaled pathogens.
- The nasal mucosa provides a convenient surface for vaccine deposition and for induction of systemic and local mucosal immunity.
- Low cost, patient friendly, non-injectable and safe.
- It has potential to induce both mucosal and humoral immunity.

b) Innovation in Intranasal vaccine delivery

i. Dry Powder Intranasal Vaccine Delivery

- **The GelVac technology** developed by DelSite Biotechnologies (Irving, TX) which consists of dry powder formulations of a vaccine with a natural plant-derived acidic polysaccharide material which is administered into the nasal cavity.

- **The Becton Dickinson** (BD, Franklin Lakes, NJ) T107 Dry Powder Inhaler. In this technology, air from a syringe barrel ruptures the membrane of a capsule containing the vaccine, which can be propelled into the nasal passages.
- **Optinose, Ltd.** (Wiltshire, UK), developed an exhalation-actuated device that delivers intranasal drugs to the nasal cavity without lung deposition of the aerosol known as the Optimist for bidirectional intranasal drug and vaccine delivery.

ii. VersiDoser Intranasal Delivery

An intranasal delivery system has been developed by Mystic Pharmaceuticals for human applications that are novel, simple, disposable, and capable of precise aseptic delivery of formulations in the form of an optimized plume for maximum deposition to, and rapid systemic uptake by the nasal mucosa.

iii. VRx2 Delivery

VRx2 blister contains the sterile freeze-dried vaccine and the sterile diluent solution in separate reservoirs. On activation at the point of use, the vaccine powder is mixed with the diluent to accomplish in situ reconstitution in the delivery system, followed by intranasal delivery.

Transcutaneous immunization

Transcutaneous immunization involves the application of vaccine antigen and often adjuvant to the skin with subsequent penetration to immune cells that reside in the skin. It has a number of attractive features including its ability to induce both systemic and mucosal immune responses and its safety profile. It is well tolerated and not at all painful, but it does commonly lead to a mild rash at the site of immunization. Skin patch delivery has the potential to increase ease and speed of vaccine administration and to decrease costs when compared to vaccination with needle and syringe (Glenn et al, 2004; Jain et al, 2003; Gupta et al, 2005; Mishra et al, 2008).

5. Nanocarriers for Systemic and Mucosal Vaccine Delivery

The primary reason for using a mucosal route of vaccination is that most infections affect or start from mucosal surfaces. Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions, liposomes, polymeric nanoparticles, dendrimers, ISCOMs etc. Some examples of literature-cited nanocarrierbased vaccines are presented in Table 3 (Shahiwala et al, 2007; Tafaghodi et al, 2006; Zho et al, 2002; Tomasi et al, 1997).

6. Latest advancement in vaccines delivery

a) Cancer vaccines

Cancer vaccines are medicines that belong to a class of substances known as biological response modifiers. There are two broad types of cancer vaccines. Preventive (or prophylactic) vaccines and Treatment (or therapeutic) vaccines. Preventive vaccines are intended to prevent cancer from developing in healthy people. FDA Approved preventive cancer vaccines in united state are Gardasil® and Cervarix®, that protect against infection by the two types of HPV - types 16 and 18 - that cause approximately 70 percent of all cases of cervical cancer worldwide.Treatment vaccines are intended to treat an existing cancer by strengthening the body's natural defenses against the cancer. In April 2010, the FDA approves the first cancer treatment vaccine. This vaccine, sipuleucel-T (Provenge®, manufactured by Dendreon), is approved for use in some men with metastatic prostate cancer (Kommareddy et al, 2005; Tindle et al, 1996; Hines et al, 1998; Lowy et al, 1998).

b) Swine flu vaccine

Nasovac, a vaccine for swine flu has been launched by a Pune-based firm Serum Institute of India Ltd. NASOVAC (Influenza Vaccine (Human, Live Attenuated)) Pandemic (H1N1), freeze dried is a live monovalent vaccine for administration by intranasal spray. The influenza vaccine contains Influenza virus cultivated on embryonated eggs. A dose of 0.5 ml is administered as 0.25 ml per nostril using a 0.5/1.0 ml syringe and a spray device. The sprayer device creates a fine spray that primarily deposits the vaccine in the nose and nasopharynx. A single intranasal dose is recommended for people above 3 years of age (Serum Institute of India).

d) AIDS VACCINE (Watkins et al, 2008; Vrisekoop et al, 2009; Marques et al, 2009; Kim et al, 2007; Watkins et al, 2008)

- **AIDSVAX**

AIDSVAX is an experimental HIV vaccine that was developed originally at Genentech in San Francisco, California, and later tested by the VaxGen company, a Genentech offshoot. It contains a synthetic version of a protein called gp120, found on the outer covering of the HIV virus. The AIDSVAX is given to stimulate the production of neutralizing antibodies, proteins that block HIV from infecting cells.

Table 3: Selective Examples of Vaccines Formulated in Nanocarrier Systems

Nanocarrier	Formulation Antigen	Route of Delivery	Outcome
Liposomes	Ricin toxoid vaccine	Intratracheal instillation	Higher titers and better protection against ricin toxoid
Liposomes	Tetanus toxoid	Intranasal administration	Intranasal administration was found more effective for inducing mucosal immunity

Water-in-oil-in-water emulsion	HIV-1 envelope protein	Subcutaneous	Higher antibody titers whereas low mucosal immunization
Multiple emulsion	Cholera toxin	Intranasal	Higher titers both qualitatively and quantitatively in mucosal membranes and systemic circulation
Polymeric nanoparticles	Salmonella enterica serovar Abortusovis	Subcutaneous	Formulation provided protection in single shot and polymeric nanoparticles may be better alternative
Alginate coated chitosan nanoparticles	Ovoalbumin	Oral delivery to Peyer's patches	Better uptake of nanoparticles which provides higher degree of protection
Nanoparticulate vesicular formulation	Bovine Serum Albumin	Oral delivery of liposomes and niosomes	High sIgA levels was noticed with carrier-adjuvant system
Micro- and nanoparticles	Toxoplasma gondii tachyzoites	Intranasal	Increased levels and higher mucosal and systemic immunity
Cationic nanoparticles	Plasmid DNA	Intranasal	25-30 fold higher beta galactosidase response
Dendrimers	Cytotoxic Tlymphocytes	Oral	can elicit systemic and mucosal immunoglobulin response

- **ALVAC**

The ALVAC-HIV vaccine is made of an attenuated (weakened) canarypox virus that has been genetically altered to contain man-made copies of selected HIV genes. The vaccine is manufactured by Aventis Pasteur of Lyon, France. ALVAC-HIV (vCP1452) is given to stimulate the body's production of CTLs against HIV.

Both vaccines are under clinical trial.

c) Meningococcal vaccine

Meningococcal vaccine is a vaccine used against Meningococcus, a bacterium that causes meningitis, septicemia, and rarely carditis, septic arthritis, or pneumonia. Three important types of meningococcal vaccines are described in figure 1 (Mascioni et al, 2008; Vu et al, 2006).

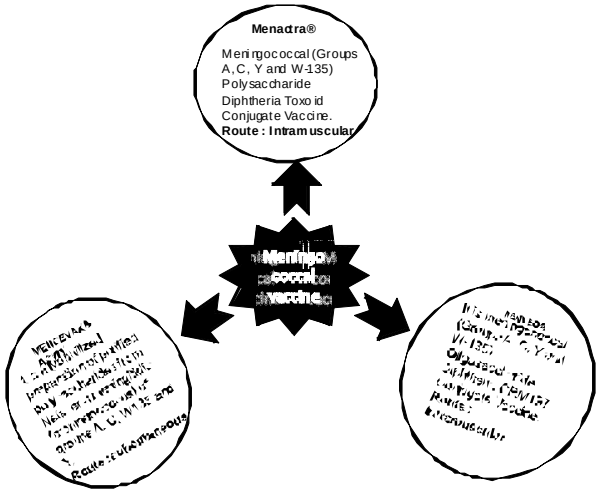

Figure 1: Three types of meningococcal vaccines

e) Nicotine vaccine

NicVAX® (Nicotine Conjugate Vaccine) is a vaccine against nicotine. Nicotine is very small and therefore the human body is not able to make antibodies on its own against it. NicVAX is made of many small nicotine molecules attached to a large protein. When nicotine is attached to a large protein, body is now able to see nicotine and make antibodies against it (Hatsukami et al, 2005; Maurer et al, 2005).

f) Diabetes vaccine

Diamyd, a vaccine to prevent diabetes, may be in the markets soon. It is intended for the treatment of children and adolescents with recent-onset type 1 diabetes. It is currently undergoing Phase III clinical trials in Europe (9 countries) and the US.

7. Conclusion

In the last decade vaccine is delivered by syringes and needles but in these ways major problem is achievement of safety. Vaccine is designed for treatment of infectious diseases so it requires greater safety. From the some point of view safety is bring about by delivery technology so, improvement of technology designed for vaccines delivery is required. Now a day number of significant advances in technologies designed for delivery of vaccine also newer vaccines is identified for infectious diseases. Intradermal delivery designed for delivery into the dermis is both easy and consistent, remove the need for highly trained medical staff and should improve dosing consistency and overall vaccine efficacy. The potential for this technology to reduce the required dose compared with intramuscular delivery could result in health economic benefits and increase the possibility of mass intradermal vaccination campaigns. Needle-free vaccine delivery is desirable for many reasons including improved safety, better compliance,

decreased pain (which is especially important in children), easier and faster vaccine delivery, and likely reduced costs compared to vaccines delivered by needle and syringe. These advantages are helpful in many circumstances and perhaps are most notable in the setting of mass immunizations necessary due to natural pandemics, immunization campaigns in the developing world, and bioterrorism events.

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