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RECENT ADVANCES IN VACCINE DELIVERY SYSTEM : REVIEW

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A vaccine is a biological preparation that improves immunity to a particular disease also the vaccines are the preparations given to patients to evoke immune responses which leads in the production of antibodies in human body. Vaccines have an ability to induce via different routes that can provide prophylactic & therapeutic responses against the various diseases. Number of licensed vaccines are administered through the parenteral route and are not able to bring out protective mucosal immunity. The safety profile of the live vaccines, weak immunogenicity of sub-unit vaccines and immunization failure due to the less patient compliance to enhance the doses which are potentiate the prime doses are the reason for the development of new generation of prophylactic & therapeutic vaccines to promote effective & beneficial immunization. This article explain the various aspects of "Needle-free technologies".

Keywords : Vaccination, immunization, DNA vaccine, virosome, edible vaccine, microneedle, needle free vaccine.

Vaccination is the term which act as an efficient and the cost-effective form used to provide acquired immunity to the particular infectious diseases or preventive method to control the infectious diseases so that can lead to global eradication, as seen for smallpox (1980) and rinderpest (2011). However, there is an immediate and growing need to develop the new , improved and desirable vaccines to control or to prevent the further infectious diseases in future particularly against those which are directly attack or target on respiratory and gastrointestinal tract (GIT). The inadequacy of the effective vaccines is exquisite in the veterinary medicines and is made by extending the multi-drug and antibiotic resistance[1].

As more than 65% of the pathogens has the power to damage or harm the humans originate in animals and hence the vaccines to fight with the zoonoses is essential priority[2].

TYPES OF VACCINE DELIVERY SYSTEM :

DNA VACCINE :

Introduction :

The DNA vaccines are bacterial plasmids that contains the DNA sequence encoding antigen against an immune response is sought, so cells directly produces the antigen, causing protective immunological response[3]. Or the DNA vaccines are those formulations which has formulated by using the DNA plasmid vectors which express the specific type of the antigenic proteins of interest for which an immune response has been modulated. According to the immunogenic use, the DNA was first reported by the Tang and his colleagues which demonstrates that the production of a human growth hormone (HGH) and human α-1antitrypsin (HAAT) specific types of anti- bodies following the injection of HGH DNA into the skin of mouse[4]. Since then, DNA vaccines has been shown the promising results in the number of trials which are carried out to prevent the bacterial, viral, parasitic, autoimmune and neoplastic diseases[3]. Basically, the concept of DNA vaccines is to deliver plasmid DNA encoding for protective proteins into the host cell of an animal where they can directly transcript and translate , effectively transform the vaccinate into a mammalian bioreactor to produces or to make own vaccine[5]. DNA vaccination is also refer as genetic immunization which is a immediate or rapid developing technology which has been described as a third generation of vaccines and seems to offers the newer approaches to prevent & the therapy of several diseases like bacterial and viral origin[6].

Advantages of DNA vaccines :

The capability of plasmid DNA to induce into the cellular and humoral immune responses after the vaccination has been signify in some models of the animals and the ambition increases that its applications will gives some newer or developed therapies for number of diseases [6].

It is cheaper than recombinant protein vaccines, ease and low cost of production[7], easy transportation and Use[6,8].

DNA vaccines are easy to store as DNA is stable molecule and hence it does not required to stored at low temperature.

Disadvantages of DNA vaccines :

The drawback of DNA vaccines are mainly on health, safety and ethical issues. Most of the safety issues regarding to the system are based on the activation of oncogenes as a result of genomic incorporation of immunising DNA, as well as eliciting anti DNA antibodies[4,6]. Taken together, though the possibility of oncogenic integration of the DNA vaccine sequence into host cell of the DNA seems rather theoretical, specific studies should required to determine which kind of plasmid would fulfil the upmost strict criteria for the safety[9]. The insertion has defined for plasmids & recommended as DNA vaccine vectors. Limitations

assessing the maximal acceptable integration rates which are make as standards to prepare the authorisation criteria's[9].

Mode, Site and Routes of Administration of DNA Vaccines :

DNA immunization is the novel technique or method which is used to stimulate the humoral as well as the cellular immune responses to the protein antigens. The direct injection of genetic material into a living host causes small amount of cells to produce the gene products, this inappropriate gene expression within the host has more valuable immunological results in the specific immune activation of host against the gene delivered antigen[10]. Several type studies has shown that the type of immune responses induced by plasmid immunisation is directly affected by a) The mode and site of the gene delivery, b) The dose of plasmid c) The administration of booster or growing injections and the interval or the time between immunisation[6]. DNA vaccines can be delivered through various or different routes, which includes the intramuscular, intradermal, subcutaneous, oral, intranasal, intraperitoneal, intravenous and vaginal route[4,7,11,12,10,13]. The most effective delivery ways for DNA vaccine using the needle injection are Intramuscular and intradermal[14]. An alternative and very efficient method for intradermal delivery is carried out by particles bombardment with the Gene gun, which consists on covering gold micro particles with recombinant DNA and shooting them by using the pressure of gas (normally helium gas is used) on to the skin[10].

How DNA vaccine administered?

Many of the DNA vaccines are injected directly into the muscles, however, a method using a 'gene gun' is being developed that uses the gas (helium) to propel DNA into the cells of the skin.

DNA vaccine delivery strategies:

i. Physical methods
ii. Tattooing
iii. Electroporation
iv. Gene Gun
v. Ultrasound

EDIBLE VACCINE :

Concept of Edible Vaccine Development :

The edible vaccines are the food products that contains antigenic fragments of specific pathogens that evokes the immunity into the consumers. The edible vaccine construction requires a transformation and regeneration protocols for specific plants, the selected gene is transformed into plant cells. The edible vaccines should be designed very carefully and eliminate all the possibility of any pathogenic characters. The productions of conventional vaccines are very expensive and require proper purification and refrigeration for their storage. The edible vaccine has useful for children as it can be taken orally without trained medical persons. The edible vaccine can be easily produced at a higher scale with low cost[15]. Probability to carryout challenges in

experiments on specific animal species has encouraged and resulted in the enthusiastic development of plant based edible vaccines[16].

Advantages of edible vaccine :

An edible vaccine has many advantages like delivery of the vaccine, particularly by the oral route[17].

The production cost of edible vaccine has less as compare to traditional vaccine.

Ease of storage and transportation[18].

The edible vaccines can be created or developed into seeds and oils.

The seeds can be dried and the aqueous extracts of oils can be stored without any cooling condition(refrigeration)[19].

Less risk of contamination.

Does not require sterile conditions[20,21].

Disadvantages of edible vaccine:

Edible vaccines are not currently as much effective as the normal vaccines as they are not injected into the blood.

The edible vaccines can be produces into the beans, potatoes, rice and spinach which cannot be used as a raw; during cooking the antigenic property has lost.

The edible vaccine which is based on the fruit banana requires 2 or 3 years to get mature fruit and is rapidly spoils after the ripening. There will be a variability of dosage and this is not suitable for infants.

Mode of action of edible vaccine :

The edible vaccine induces into mucosal and systemic immune response. The desired proteins released from plant tissue and absorbed in the intestinal wall after delivery. The cellular and gastric enzymatic degradation of vaccine can be protected by bio-encapsulation. The vaccine is absorbed in the form of antigen on the intestinal cell wall and taken by M cells and pass to macrophage and B cells and moves towards the antigen presenting cells and after that they will be moved and present to T and B cells in the payer's patches and gut-associated Lymphoid tissues passed on to macrophages and local lymphocyte population generates serum IgG and IgE responses. The plasma cells generated by the activation of immune cells and they move towards lymph nodes for clonal amplification followed by distribution to other mucosal surfaces. When any pathogenic infection takes place then the memory helper T cells swiftly induces antibody production and secretion and the released antibody immediately neutralizes the invading antigen [22,23].

Strategy for development of edible vaccine :

1. Selection of Plant Candidates for an Edible Vaccines Production.

2. Plastid Transformation.

MUCOSAL DELIVERY OF VACCINE :

Introduction :

Mucosal surfaces are large surface areas that are a common site of entry for pathogenic microorganisms[24]. The presence of antigens, pathogens and vaccines within the body that enters directly via the mucosal surfaces are easily detected by the adaptive immune system from those that are introduced directly into tissues or the bloodstream by either injection or injury. This is clearly indicates that effective mucosal vaccines (oral, nasal, sublingual and genital tract vaccines) can significantly contribute to the improvement of global heath as they have the capability to stimulate protective immune responses not only against mucosal infections but also against HIV and also by producing mucosal antibodies against Vibrio cholerae bacteria and cholera toxin that is associated with resistance to cholera and many other infections[25,26].

Mucosal immunity and vaccine responses :

Most of the mucosal vaccines has been maximumly administered by the oral and nasal route and less frequently or minimum administered by vaginal, rectal, ocular routes . All routes of administration doesn't induces an equivalent immune response in the terms of potency and the longevity which reflecting the differences in the organization and cellular make-up of the lymphoid structures in the various mucosal tissues[27].

Advantages of mucosal delivery of vaccine :

Mucosal vaccination protects from the microorganisms which gain access to body via mucosal membranes. Patient compliance, ease of administration, stimulation of both systemic and mucosal immunity are some of the advantages. Mucosal vaccination is a needle and medical waste free vaccine strategy that provides protective immunity against pathogenic bacteria and viruses in both mucosal and systemic compartments.

Uses of mucosal delivery of vaccine :

Mucosal vaccines have been more successful in the veterinary field with the spray and drinking water vaccines have been used for mass vaccination in poultry farm. Recent introduction of edible gel-bead-based vaccine systems gives more stable mucosal delivery which protects the live vaccines against the inactivation of environment to improve the bioavailability. The use of gel-beads for the delivery of Eimeria spp. oocysts to day-old chicks offers greater uptake of oocysts than that of the water spray containing Eimeria spp. oocysts and significantly higher weight gain post-challenge infection[28]. Since the nasal mucosa is the first contact site for antigens being inhaled, systemic and local immunity can be stimulated by activation of T-cells, B-cells, and dendritic cells present in nasal associated lymphoid tissue located beneath the nasal epithelium in

the form of IgG and secretory IgA. Hence, nasal delivery of vaccines can be used to treat upper respiratory tract infections (RTI) and also to produce systemic immunity. Intranasal vaccines includes those are against the influenza A and B virus, proteasome-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3virus[29].

Strategies for mucosal delivery :

i. Live vectors
ii. Particulate delivery systems
iii. Other strategies to enhance vaccine uptake

- Lectin-mediated targeting
- Antibody-mediated targeting

VIROSOMES :

Introduction :

Virosomes are the Semi-synthetic complexes which are derived from nucleic-acid free viral particles. These are mainly reconstituted viral coats, where the infectious nucleocapsid is alter by the compound of choice. Virosomes retain their activity and delivers the incorporated compound (antigens, drugs, genes) into the target cell and is used for vaccines (VACCINES, VIROSOME) drug delivery or gene transfer.

Mechanism action of virosome :

Virosomes act as a carrier as well as an adjuvant with number of functions during the induction of an immune response. The carrier function comprises the positive effects of embedding the antigen into a higher structure of the virosome particle. The function of adjuvant is directly associated with the immune stimulating properties of virosome and their components on immune system most importantly virosome succeed in the stimulation of specific immunity without causing any non- specific inflammation.

Preparation of virosomes :

Select the virosome then select the antigen then reconstitute the virosome.

Drug delivery approaches of Virosomes :

Bioactive drug compounds are entrapped into aqueous interior of the virosome or in the lipid membrane of the virosome which facilitates the entry of the compounds into the cells[30]. Nucleic acids or genes are delivered by virosome. With the help of endosome or plasma membrane, these compounds have been delivered into the host cell cytoplasm on fusion of the virosome[31]. Nucleic acids or genes encoding a naturally occurring protein can introduced into the host cells which can be expressed and provided that the expression cassette which contains the proper cis-acting regulatory elements[32]. During the time of preparation of virosome the nucleic acids or the drug can be incorporated directly into the virosome. The bioactive compound

which has been adding to the lipid– HA-containing solution follows the removal of the nucleocapsid. The bioactive compound is incorporated into liposome then fused with a virosome which contains two hemagglutinins with different pH thresholds to form a virosome–liposome hybrid[33]. Via the virosome the proteins can be delivered into cells. For example, the gelonin subunit A of diphtheria toxin and ovalbumin have also been successfully delivered to the target cells by the virosome[34] .Virosomes carrying peptides which were derived from the influenza nucleoprotein or intact ovalbumin induced strong cytotoxic T lymphocyte responses and is refers that the encapsulated peptides and proteins gained access to the cytoplasm[35].

NEEDLE FREE DELIVERY OF VACCINE :

Introduction :

The most commonly used immunization techniques are nothing but the use of needles and syringes which are associated with avoidance and phobic behaviours in number of people. Due to the fear of needle the immunization process becomes more stressful, moreover needle-stick injury, the improper use of needle such as re-use of needles or syringes may cause the transmission of blood-borne pathogens which leads to large number of HBV, HCV and HIV cases and are serious problems in world[36,37,38]. Needle-free injection delivery system is advanced method which is used to deliver the vaccine into the proper tissue depth using the driving force for injection[39]. Needle-free vaccine delivery becomes more preferable now a days due to the following reasons[40] :

i. As we know the needle free injection means delivery of vaccine into patients body without using of needle or syringe so it reduces the stressful immunization which may be happened by phobia of needle to patient.
ii. Differentiate their products from the existing products as the pharmaceutical industry faces massive losses in revenues from the patents which have expired and to withstand pressure from generic companies.
iii. Search for alternative ways to delivers the increasing list of new biopharmaceutical and the molecular entities like vaccines, DNA, peptides and proteins that cannot be delivered by oral route.
iv. Need to develop into the pharmaceutical companies which develops their own branded pharmaceutical products which are based on off-patented drugs.

Advantages of needle free delivery of vaccine :

i. Needle free vaccines are less painful
ii. Ease of administration
iii. Ease of transportation

Disadvantages of needle free delivery of vaccine :

i. Improper administration may causes the immediate pain.

Strategies of needle free delivery of vaccine :

i. Needle free jet injection
   a) Liquid jet injectors
   b) Solid dose jet injectors
ii. Microneedles
iii. Melt in mouth strips

Needle free jet injection :

Due to the kinetic energy of a high velocity vaccine jet, the liquid vaccine (live or non living) can be delivered into the skin by using the needle-free injection system. Needle Free Jet Injection can be defined as a needle-free drug delivery method in which the drug is delivered into the skin by using the high-speed stream of fluid which directly impacts the skin[41]. The fluid contains a corticosteroid, an anaesthetic agent[42] , on botulinum toxin A (BoNT-ONA)[43,44], bleomycin[45], 5-aminolevulinic acid (ALA)[46] or any injectable substance.

There are Two types of Needle Free Jet Injectors :

Spring-loaded jet injector Gas-powered jet injector

Spring-loaded jet injector works on a spring mechanism. The spring has gone or release by striking the trigger leads to generate the jet stream of drug for the drug delivery. For further or next administration, the activated spring load must be redrawn manually. Gas-powered jet injector consists of an air or gas cartridge which is directly attached to the gun by the tubing system that delivers pressure to the piston after the actuation of trigger; it releases the piston and creates drug jet stream[47].

The above both methods are suitable for subcutaneous, intramuscular and intradermal use.

Microneedle vaccines :

Microneedles are the micron-sized needles which are constituted with the appropriate formulations of the drug and are directly penetrated into the stratum corneum in a direction which is perpendicular to the plane of skin. The microneedles in vaccine delivery has number of application that provides many logistic and clinical benefits. Micron-scale dimensions of the microneedle shaft allows the simple and direct application into skin. Penetration of microneedle is pain-free because of the small size of the needles. The production of self-administrable microneedle patches comprised of arrays of vaccine coated microneedles that will facilitate the widespread dissemination of vaccines at the time of rapid and uncontrolled onset of disease. The emergence of dry-coated microneedle vaccine formulations in the pharmaceutical industry will decrease the requirement of costly cold chain processes and promote the dissemination of vaccines into rural regions of developing countries. The another important benefit of the microneedles is its dose-sparing quality, in which the direct targeting of the rich network of immunogenic APCs produces the higher immune responses by the microneedles than the conventional intramuscular route. Many research efforts have been conducted globally to qualitatively compare the effective immune responses induced by microneedle vaccination as reversed to

the conventional delivery routes. Recently, there are four important types of microneedles has developed and are given as - solid, coated, dissolving, and hollow microneedles[48].

Melt in mouth strips :

Melt in mouth strips also known as vaccine mouth strips are those strips that contains the immunogens which are dissolve in the mouth of child. These are quick dissolving fil that melts into a liquid that children and infants swallow easily. These strips were first designed by the undergraduate students at John Hopkins in collaboration with Aridis Pharmaceuticals to protect rotavirus infection. Rotavirus is a common cause of severe diarrhoea and vomiting in children which leads 6,00,000 or more deaths per year. Rotavirus vaccine has available in a liquid or freeze-dried form that must be chilled for transport and storage. making of this vaccine is very expensive for use in impoverished areas. In addition the infants or new born babies sometimes may spit out the liquid ,the problem is rarely occurs with the strip that sticks to and dissolves on the tongue immediately or very short time[49].

CONCLUSION :

Because of the benefits and number of effects of vaccination, the vaccines become more popular now a days. Vaccines proves that it is much comfortable for patients as we are taken it via different delivery routes such as needle free vaccine delivery system. The needle free vaccine plays the role of painful immunization, the vaccination also proves that it is patient friendly as we avoid the booster shots of doses. By administering the smaller doses of vaccine produces long term therapy.

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