



ISSN: 0975-766X

CODEN: IJPTFI

Available Online through

www.ijptonline.com

Review Article

CURRENT ADVANCES IN VACCINE DRUG DELIVERY SYSTEMS

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Received on 20-02-2020

Accepted on: 29-03-2020

Abstract

Vaccines are the preparations of killed micro-organisms, living attenuated organisms, or living totally virulent organisms, that are administered to provide or unnaturally increase immunity to a specific malady. The look for strategies of immunogen delivery, not requiring a needle and syringe has been accelerated by recent issues concerning pandemic malady, biological terrorism, and malady obliteration campaigns. Efforts are being made to deliver vaccines through carriers, as they manage the spatial and temporal presentation of antigens to system so, resulting in their sustained liberation and targeting. Hence, lower doses of weak immunogens will be effectively directed to stimulate immune responses and eliminate the requirement for the administration of prime and booster doses as a vicinity of typical vaccination plan. Needle-free immunogen delivery may aid in these mass vaccinations, by increasing ease and speed of delivery, and by giving improved safety and compliance, decreasing prices, and reducing pain related to vaccinations. The transporter systems such as liposomes, dendrimers, micellar systems, microspheres, nanoparticles, Immuno Stimulatory Complexes (ISCOMs), plant-derived viruses, that are currently being investigated and developed as immunogen delivery systems are reviewed. This review summarizes the principle behind the advances of vaccination techniques.

Key words: Vaccines, immunogen, carriers, vaccination techniques.

Introduction

Vaccine could be a material that induces an immunologically mediate resistance to a sickness, however not essentially an infection. Vaccines are typically composed of killed or attenuated organisms or subunits of organisms or deoxyribonucleic acid programming substance proteins of pathogens. Subunit vaccines, although exceptionally selective and specific in reacting with antibodies, typically fail to point out such

reactions in circumstances like shifts in epitopic identification centre of antibody and are poorly immunogenic. However, the selectivity and specificity of subunits of the causative organism like proteins; carbohydrates can be exploited for producing strong and prolonged immune responses by catering them to the immune system in such the way that, a selected and powerful immune reaction is elicited. These epitopes may permit the generation of vaccines not solely against infectious diseases, however conjointly against chronic diseases like viral hepatitis or cancer. In order to produce a good protecting immunity, these vaccines require boosting with agents called “adjuvants”. Adjuvants are believed to act by forming complexes with the agent to be delivered from whom, immunogens are slowly released.

- Vaccine delivery systems (e.g. emulsions, micro particles, Immune-stimulating complexes ISCOMs, liposomes).
- Immunostimulatory adjuvants: Conserved molecular patterns of pathogen stimulate immunity, as they are identified by pattern recognition receptors such as “Toll” receptors located mainly on B-cells, dendritic cells of mammals (e.g. unmethylated CpG containing DNA).

Adjuvants potentiate the immuno-stimulatory property of the antigen while being non-immunogenic, non-toxic, and biodegradable by themselves. Aluminium salts such as aluminium hydroxide, aluminium phosphate; oil emulsions such as Freund's incomplete adjuvant: particulate matter such as ISCOMS; synthetic poly nucleotides are other types of adjuvants. [1]

❖ **An ideal vaccine**

- ✓ It should not be toxic and pathogenic, i.e. it should be safe.
- ✓ It should have very low levels of side effects in normal individuals.
- ✓ It should not cause problems in individuals with impaired immune system.
- ✓ It should not spread either within the vaccinated individual or to other individuals (live vaccines).
- ✓ It should produce long lasting humoral and cellular immunities.
- ✓ The technique of vaccination should be simple.
- ✓ The vaccine should be cheap so that, it can be easily available.
- ✓ It should not contaminate the environment.

- ✓ It should be effective and affordable.

So far, such a perfect vaccine has not been developed.

❖ **Need for new vaccines**

There are certain infectious diseases for which, no vaccines are available yet e.g. HIV, tuberculosis, malaria, *Neisseriameningitides* Type B, etc. Using traditional approaches to vaccine development, these kinds of diseases are found to be extremely difficult to control. Thus, there is a clear need for the development of new vaccines against these kinds of diseases. New vaccines are required to protect against the influenza virus and antimicrobial resistant organisms. Threat of bioterrorism is also an important reason for the development of new vaccines. There are various emerging infectious diseases, including West Nile, SARS, and Ebola & Hanta, which, if not controlled, would lead to a mass destruction of human kind. New vaccines have to be developed for the prevention of these diseases. There are various micro-organisms which cause chronic diseases e.g. Hepatitis B & C viruses cause Hepato cellular carcinoma, Human papilloma virus causes cervical, anal & vulvar cancer & Epstein-Barr virus causes Burkitt lymphoma. These chronic diseases can be prevented only by novel vaccines. Vaccines are the potential therapeutic agents, which can be used to treat established infections. Thus, novel vaccine delivery technologies will be required to enable the development of these new vaccines. Traditional vaccines, although highly effective and relatively easy to produce at low cost, suffer from the following limitations:

- ✓ In many cases, live vaccines have to be used since killed pathogen vaccines are ineffective.
- ✓ Live vaccines are generally based on cultured animal cells; hence expensive tissue culture set up is essential.
- ✓ Live vaccines are heat labile.

Traditional vaccines carry a variable risk of disease development due to the occasional presence of active virus particles or reversion to virulence after replication in the vaccinated individuals.

- ✓ In many cases, they are difficult to produce, e.g., hepatitis B virus does not grow in high titre in cultured cells.

These limitations have prompted the development of new vaccines, which are rather costly, at least for the present. [2]

❖ Mechanism of uptake and transport of antigens or how do vaccines work?

It has been postulated that, the need for non-specific immune-stimulators for eliciting strong responses to weak antigens is related to the poor antigen processing efficacy or their poor recognition by receptors of T-cells and/or B-cells. It may be possible to achieve much higher immune responses to antigens without the use of potent adjuvants, if antigens are directed to Antigen Presenting Cells (APC) and lymphocytes by coupling them with a ligand of strong binding affinity for molecules of the Major Histocompatibility Complex (MHC).

This approach is particularly attractive for the delivery of synthetic peptides or small recombinant antigens, where the attraction of large number of mononuclear cells to the site of injection is normally needed, in order to affect adequate processing and presentation of small molecules.

Studies in mice have demonstrated that, the coupling of viral antigens to monoclonal antibodies against a mouse Class II MHC molecule has elicited antibody response with much less antigen than needed without the use of the targeting molecule. These responses were obtained without any adjuvant and suggested a promising approach to safer vaccines. This study indicated that, the targeted antigen may be needed only in the first injection to prime the response and that; unconjugated antigen could be used to stimulate secondary responses.

It is noteworthy that, in vitro studies of antigen presentation to T-cells have indicated that, the efficiency of presentation can be enhanced as much as 1,000 fold by coupling antigen with antibodies specific for determinants on the antigen presenting cells. [3]

▪ Vaccine Delivery Systems

Delivery of antigens from oil-based adjuvants like Freund's adjuvant result in doses of immunogen to be administered within the range however, thanks to toxicity considerations like inductions of granulomas at the site of injection, such adjuvants aren't widely used. FDA approved adjuvants for human uses are aluminium hydroxide and aluminium phosphate in the form of alum.

Hence, explore for safer and potent adjuvants resulted within the preparation of substance into delivery systems that administer substance in particulate form, rather than solution form.

Other reasons driving the progress of vaccines as controlled drug delivery systems are as follows:

- Immunization failure with conventional immunization regimen involving prime doses and booster doses, as patients neglect the later.

Vaccine delivery systems on the other hand:

- Provide the incorporation of doses of antigens so; booster doses are no longer necessary, as antigens are released slowly in a controlled manner.
- Manage the spatial and temporal presentation of antigens to the system, there by promoting their targeting, straight to the immune cells.

Vaccine delivery systems can be classified as follows:

- ✓ Solid particulates: Solid particulate systems such as, microspheres and lipospheres are being exploited for vaccine delivery based on the fact that, intestine is an imperfect barrier to small particulates. Antigens entrapped in such particulates, once concerned by M-cells, will generate immunity.
 - ✓ Methods such as light microscopy, confocal microscopy, electron microscopy, extraction of polymer from tissue followed by quantification by gel permeation chromatography, flow cytometry indicated that, micro particulates of $<10\mu\text{m}$ in diameter can enter Gut Associated Lymphoid Tissue (GALT) within 1 hour of oral administration and can be used as antigen carriers for controlled release vaccine applications.
 - ✓ Particle size is an important consideration, while formulating micro particulate systems, as it influences their uptake and release and hence immune responses. Small ($<10\ \mu\text{m}$) microspheres, due to their large surface to mass ratio, are capable of facilitating extracellular delivery of antigen to the phagocytic accessor cells leading to faster release and increased antigen processing. Larger particles could not be phagocytosed by macrophages, until they have disintegrated into smaller debris. A combination of larger and smaller particles might produce a pulsatile pattern for antigen release thus, mimicking an immunization process involving prime and booster shots.
 - Delivery of vaccines by polymeric micro particles through different routes are mentioned in Table No. 1
- Biodegradable polymers, such as PLGA, previously used as surgical implant and suture material, are now being exploited for matrix antigen delivery. PLGA microspheres are rapidly taken up by M-cells

and trans located towards the underlying lymphatic tissue within 1 hour. However, the use of PLGA can be limited by acid hydrolytic degradation products detrimental to the entrapped protein and loss of immunogenicity on storage. Also, organic solvents used to load the antigen onto the polymer can be detrimental to the antigen. [2]

Table No. 1: Delivery of vaccines by polymeric micro particles through different routes.

Antigen	Polymer	Particle size (μm)	Route of delivery
<i>B. pertussis fimbriae</i>	PLGA	0.8-5.3	IP, PO
<i>B. pertussishaemagglutinin</i>	PLGA	1	IN
Diphtheria toxoid	PLGA	30-100	IM
Influenza virus, formalinized	PLGA	2.2-10.8	SC and PO
Tetanus toxoid	PLA and PLGA	10-60	SC
Vibrio cholera cell-free lysate	PLGA	1-10	PO and IT

a) **PLGA**- Poly (Lactic-co-Glycolic Acid) b)**PLA**- Poly Lactic Acid.

▪ Liposomal Delivery Systems

Liposomes and their derivatives “lipoplexes” (liposome/DNA complexes) are hollow spherical constructs of lipoidal bilayers, capable of entrapping deliquescent moieties within the aqueous compartment and hydrophobic moieties within the macromolecule bilayers with cholesterol, imparting rigidity to the bilayer.

However, lipoplexes tend to aggregate during storage, due to neutralization of positive charge on liposomes by negative charge on DNA. This drawback is overcome by formulating Liposomes/Protamine/DNA (LPD). Protamine is an arginine rich peptide. It condenses with DNA, before DNA can complex with positive lipids there by, conferring stability to the preparation.

Viruses, proteins, glycoproteins, nucleic acids, carbohydrates, and lipids can be entrapped and targeted at cellular and sub-cellular level for evoking immune responses.

As vaccine adjuvants, these systems exert immunomodulatory effects by virtue of their particulate nature and their ability to bind with cell surface lipid receptors, such as CD1a after complement activation. The phospholipid bilayer fuses with cell wall hence, tend to get incorporated into elements

Shaikh Firdous Hamid*et al. /International Journal of Pharmacy & Technology of Reticulo Endothelial System (RES) rapidly. The development of polymerized liposomes, which have shown enhanced stability in the gastrointestinal tract, also offers potential for use in mucosal vaccination.

Polymerized liposomes coated with targeting molecules like antibodies, protein fragments, antigens and molecules are capable of binding to specific cell surface receptors found in the mucosal tissue.

Stealth liposomes or sterically stable liposomes contain deliquescent surfaces, due to coating of liposomes with PEG and this covalently binds with the polyethylene found in the lipid bilayer there by, reducing the opsonisation by serum proteins and increasing circulation half-lives.

Liposomal vaccines based on viral membrane proteins (viroosomes) have been approved as products in Europe for Hepatitis A and influenza. [4]

▪ **Dendrimer-based Delivery Systems**

Dendrimers are branched, synthetic polymers with layered architectures. By combining the multifunctional polymeric material with a biologically active substance in an aqueous loading environment, the carrier system can be administered as a drug delivery vehicle to a human subject.

A transfection chemical agent particularly, Super Fect TM, consisting of activated dendrimers is in the market for industrial functions.

A novel approach for the treatment of excretory organ cell carcinomas uses a chimeric molecule, comprising a leucocyte scavenger cell Colony Stimulating issue (GM-CSF), attached to a G250 kidney cancer specific antigen, which is transfected in to the cancerous cell by the use of dendrimer, thereby providing a highly effective “vaccine” that raises an immune response directed against renal cell cancers. [5]

▪ **Micellar Delivery Systems**

Micelles have been well investigated as potential antigen carriers. Micelles are self-aggregated clusters of amphiphilic surfactant molecules. Surfactants higher than Critical Micellar Concentration orient themselves into micellar structures; in order to avoid contact with incompatible external phase and can enclose lipophilic cavity or hydrophilic cavity (reverse micelle) thus, promoting demurrer of antigens for their delivery into the body. Formulations and methods for trans-mucosal delivery of a beneficial agent use a combination of a pH-responsive component and a temperature-responsive component. The

temperature-responsive part in binary compound solutions is capable of undergoing a temperature-dependent sol to gel activity. The temperature-responsive compound is an alkylene oxide copolymer, capable of forming micelles in aqueous solutions. These formulations were found to have bio-adhesive properties and hence, are suitable for delivering wide variety of beneficial agents. [6]

▪ **Virosomal Delivery Systems**

Virosomes are little, spherical, unilamellar macromolecule membranes vesicles (150 nm), embedded with microorganism membrane proteins like, haemagglutinin and neuraminidase of contagious disease virus, however barren of nucleocapsid, together with the genetic material of the source virus.

These proteins alter the virosome membranes to fuse with cells of the system and therefore, deliver their contents—the specific antigens—directly to their target cells, eliciting a specific immune response, even with weak-immunogenic antigens. Once they have delivered the antigens, the virosomes are utterly degraded at intervals of the cells. A microorganism super molecule intercalated into the lipoidal bilayer not solely confers structural stability and homogeneity to virosomal formulations, but it significantly contributes to the immunological properties of virosomes, which are clearly distinct from different liposomal and proteo-liposomal carrier systems. It has been shown that, a physical association between the virosome and the antigen of interest is a prerequisite for the full adjuvant effect of virosomes. Hence, virosomes represent sac systems into that, antigens can be loaded into virosomes or adsorbed onto the virosomal surface through hydrophobic interactions. [7]

▪ **Emulsion Delivery Systems**

Emulsions are heterogeneous liquid systems, may be water-in-oil emulsions, oil-in-water emulsions, or more complex systems such as water-in-oil-in-water multiple emulsions, micro emulsions, or nano emulsions. Antigens are dissolved in a water section and blended within the oil in the presence of an acceptable wetting agent. The controlled unleashed characteristics of an emulsion are determined by factors like viscosity of oil section, oil-to water section relation and emulsion droplet size. For example, high oil content can cause unnecessary injection site irritation and too large a droplet size can result in a physically unstable product there by, reducing its shelf life

Squalene o/w emulsion containing contagious disease vaccine was approved in European country in 1997 and in many extra countries in 2000. [8]

▪ **Polymeric Nanoparticle Delivery Systems**

Polymeric nanoparticles, due to their size are preferentially taken up by the membrane associated lymphatic tissue. They are extensively reviewed for nasal and oral delivery of vaccines. Limited doses of antigen are sufficient to induce effective immunization. Hence, the utilization of nanoparticles for oral delivery of antigens is appropriate, due to their ability to unleash proteins and to shield them from protein degradation within the Gastro intestinal tract.

Biodegradable Poly (alkylcyanoacrylate) (PACA) nanoparticles have been shown to enhance the secretory immune response after their oral administration in association with ovalbumin in rats. Poly (methylmethacrylate) PMMA nanoparticles being very slowly degradable (30%-40% per year) appear to be particularly suitable for vaccine purposes, because prolonged contact between antigen and immune-competent cells favours persistent immunity. Nanoparticles labelled with MAb specific to M-cells, increase the level of absorption of nanoparticulate vaccines and hence, immune response. [9]

▪ **ISCOMs- Immuno Stimulatory Complexes**

ISCOMs are instinctively fashioned spherical, open cage-like complexes when saponin, cholesterol, phospholipid, and immunogen, usually protein are mixed together and have typically a diameter of 30-80nm. ISCOMs combine certain aspects of virus particles such as, their size and orientation of surface proteins, with the powerful immune stimulatory activity of saponins. Unlike other vaccine adjuvants, ISCOMs have shown to promote a broad immune response by simultaneously promoting high levels of antibody and strong T-cell responses, including enhanced cytokine secretion and activation of Cytotoxic T Lymphocyte (CTL) responses in a variety of experimental animal models and has now progressed to Phase I and II human trials.

ISCOM-based veterinary vaccine against equine influenza is commercially available. [10]

▪ **Edible Vaccines**

Subunit vaccines contain specific macromolecules, i.e., one specific epitope from several epitopes present on the antigen. Subunit vaccines are so, safer over typical vaccines, as they eliminate the use of live viruses or microbes to stimulate immunity. But, subunit vaccines involve expensive manufacturing procedures and are thermo labile, necessitating cold chain storage from point of manufacture until,

vaccination which aggravates the expenses in providing costlier facilities like refrigeration to render stability to the preparation.

Production of vaccines in “plants” supply enticing advantages and overcome several of the above-named limitations.

- Plant vaccines function an affordable means of processing and expressing proteins, that can be quite complex to handle, as plants require only sunlight, water and minerals to carry out the process.
- Shunning of contamination with animal pathogens, improved stability of heat labile vaccine components and oral delivery of resulting vaccines are few of many advantages obtained, when plants are used for the expression of vaccines.
- Both, tissue layer and general immune responses are often made by the tissue layer administration of a plant derived vaccine.

❖ **Production of edible vaccines**

Edible vaccines are produced by integrating gene cloning, tissue culture and plant transformation techniques. The first step in the process of creating an edible vaccine is the selection of a suitable immunogen. The gene encoding the antigen is cloned into associate degree expression vector that contains plant restrictive sequences capable of driving organic phenomenon and indicating the gene’s terminus. This vector is then, used in plant transformation.

For example, Agro bacterium is a plant pathogen which, during the process of infecting plants, transfers a portion of its DNA (t-DNA) into plant’s genome by a process, similar to conjugation. Scientists have exploited this property of Agro bacteria to transfer desired sequences through it into plant ordering. Plant tissues are cultured and transformed cells are positively selected and regenerated into transgenic plants. It takes about six weeks to eighteen months to supply a transgenic plant and depends on the kind of species. [11]

▪ **DNA Vaccines**

DNA vaccination could be a technique for shielding associate degree organism against malady, by injecting it with genetically engineered DNA to produce an immunological response. A DNA vaccine accommodates microorganism plasmids into that, specific sequences are incorporated.

Gene expression is promoted by the cytomegalovirus promoter and its adjacent DNA A sequence (ensures high transcription efficiency) and parts sort of a transcription termination signal and a prokaryotic antibiotic resistance gene.

DNA inserted within the inclusion body stimulates immunity, by acting as a Pathogen-Associated Molecular Pattern (PAMP) which, has high affinity for Toll-like receptors (TLRs).TLRs are “pattern recognition receptors” with a capability to spot the preserved molecular patterns of the deoxyribonucleic acid related to pathogens. One such sequence that's common in microorganism deoxyribonucleic acid however, rare in mammalian DNA is the hypomethylated CpG dinucleotide that, mainly binds to TLR-9. Stimulation of a range of TLR9-expressing cells, including B cells and dendritic cells (DC), leads to a cascade of activation, proliferation and differentiation of natural killer cells, T cells and monocytes/macrophages. Attempts are currently being created by the industry to use artificial CpG phosphorothioate oligonucleotides as adjuvants for a spread of various vaccines.

However, one reason that deoxyribonucleic acid vaccines might not be effective for human application is that, TLR9 isn't expressed by myeloid nerve fiber cells however, solely on plasmacytoid nerve fiber cells of the mammals. Interestingly, it was found that, DNA vaccines perform well in TLR9^{-/-} mice, which indicates that, there are alternate pathways apart from TLR-9 stimulation for inducing immune responses.

❖ DNA Vaccine Delivery strategies-

A) Physical methods:

Techniques like tattooing, gene gun, electroporation, ultrasound, and optical laser give energy (electrical, ultrasonic, optical laser beam) that brings a few transient modifications in porosity of cell wall thereby, promoting the entry of immunogenic DNA into the cells. The cell porosity is rehabilitated on the removal of applied energy once a brief period.

1. Tattooing-

It is a physical technique for injecting deoxyribonucleic acid into skin cells. The result of 2 adjuvants, cardiotoxin and plasmid DNA carrying the mouse Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), when given by tattooing and as intramuscular injections has been determined.

Model antigen used in this study was gene encoding the capsid protein of the Human Papilloma Virus type 16 (HPV 16). From the results, it was concluded that, the delivery of the HPV 16 L1 DNA alone, using a tattoo device elicited a stronger and more rapid humoral and cellular immune responses, than contractile organ needle delivery in conjunction with molecular adjuvants.

2. Gene gun-

Gene gun is a biolistic device that enables the DNA to directly enter into the cell, following bombardment of target DNA in the gene gun chamber, kept against the target site.

3. Electroporation-

This technique involves application of electrical pulses to the skin thereby, creating transient pores in the skin, promoting the entry of DNA into the cell. On removal of voltage, skin regains its structure, holding the entrapped immunogenic agent, due to closure of pores.

A therapeutic DNA vaccine given to patients, already infected with the virus in order to clear the infection by boosting immune response, showed acceptable safety, when delivered by electroporation in Phase I/II clinical study.

This was among the primary communicable disease deoxyribonucleic acid vaccines to be delivered in humans, employing electroporation-based deoxyribonucleic acid delivery.

In addition, DNA vaccine delivery by electroporation is being investigated in many cancers such as prostate cancer, metastatic melanoma and is under clinical trials.

4. Ultrasound-

In this, ultrasonic energy is used to disrupt the cell membrane temporarily. In a phase II study, repeated intra-nodal injections of Adenovirus-CD 154 (Ad-ISF35) are being given by ultrasound, in subjects with chronic lymphocytic leukaemia/small lymphocytic lymphoma. Ultrasound and optical laser are raising techniques for the delivery of deoxyribonucleic acid vaccines.

B) Viral and non-viral methods:

Viral vectors like animal virus, Adeno virus, Herpes simplex virus, Vaccinia virus are efficient in DNA transfer, due to their nano scale dimensions, well characterized surface properties,

allowing the incorporation of immunogenic components (e.g. virosomes). But, drawbacks like, the restricted deoxyribonucleic acid carrying capability, toxicity, immunogenicity, the chance of insertional mutations in host deoxyribonucleic acid and high value warrants their use.

Non-viral carriers include microspheres, nanospheres; liposomes find potential application as carriers for DNA vaccines. [12]

▪ **Mucosal Delivery of Vaccines**

Mucosal vaccination offers protection against microorganisms that gain access to body via tissue layer membranes.

Patient compliance, easy administration, reduction in chance of needle-borne injections, stimulation of each, general and tissue layer immunity are a number of the benefits.

Co-administration of antigens with adjuvants like aluminium hydroxide, complete Freund's adjuvant, incomplete Freund's adjuvant, cholera toxin, heat labile enterotoxin of *E. coli*, etc., potentiated immune response of antigen.

Delivery systems like PLG microspheres, PLGA small particles carrying immunogenic agents etc. are taken up by Peyer's patches. Particles of <5 µm further move into lymph nodes and spleen-stimulating-specific IgG, IgM responses. Chitosan, a bio-adhesive polysaccharide is suitable for mucosal vaccination, due to its ability to open up tight junctions and promote paracellular transport of antigen across mucosa.

❖ **Nasal mucosa delivery**

Since 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 nasal epithelium in the form of IgG and secretory IgA. Hence, nasal delivery of vaccines can be used to treat upper respiratory tract infections and also to produce systemic immunity.

Intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and para-influenza 3 virus. [13]

▪ **Needle-free Delivery**

Needle-free vaccine delivery is gaining popularity these days, due to the following reasons:

- ✓ Patient's concern about pain associated with the injections; disposal issues and potential for cross contamination of blood borne diseases is eliminated.
- ✓ Differentiate their products from the existing products, as the pharmaceutical industry faces massive losses in revenues from the expired patents and to withstand pressure from generic companies.
- ✓ Search for alternative ways to deliver growing list of new biopharmaceutical and molecular entities like vaccines, DNA, peptides and proteins, which cannot be delivered orally.
- ✓ Urge to evolve into specialty pharmaceutical companies, developing their own branded pharmaceutical products, based on off-patented drugs.

Following are some needle-free delivery strategies-

A) Jet injectors:

1. Liquid jet injectors
2. Solid dose jet injectors

B) Micro needles

C) Melt in mouth strips

A) Jet Injectors-

Jet injectors uses either, a spring mechanism or pressurized gases-generally carbon dioxide, nitrogen, helium contained in small cartridge or large canister form to force the aerosolized drug solution or suspension through the skin, either directly into the muscles or into the subcutaneous or intra-dermal layers.

1. Liquid jet injectors:

Liquid jet injectors are being developed as single use and multiuse systems. Reusable systems are for chronic conditions like diabetes, where dose can be given once daily for prolonged release. Disposable units are prefilled with drug, once used can be discarded. These are used in emergency situations like treating allergies, intermittent conditions like pain and migraine attacks, for office-based vaccinations and mass vaccination (spread of diseases, due to reuse of needles can be prevented). These systems use a power source, which can be compressed gas or a spring forcing the liquid under high pressures, resulting in the formation of pores in the skin without the use of a

needle. This is followed by reduced pressure profile, which forces the rest of liquid into the skin.

Since, the drug is in liquid form, there is no need of reformulation.

❖ **Limitations-**

- ✓ Careful control over power source is necessary for accurate and reliable delivery of vaccine to different skin types or different skin areas of same person.

Bleeding and pain caused, when the high speed jet bombards with blood vessel and nerves is the other major limitation, which can compromise patient compliance.

2. Solid dose injectors:

Delivering vaccines in solid form ensures that, the therapeutic or immunogenic agent is more stable and avoids any need of cold chain storage. Both, the prime dose and booster shots can be combined in a single administration thereby, increasing patient compliance. Powderject technology used for the delivery of solid formulations fires the drug at supersonic velocities into outer layers of skin, using helium-powered devices. In practice, the device is held against the skin and when the helium micro cylinder is actuated, the pressurized gas entrains the drug particles and accelerates them to velocities, which enable them to penetrate the skin.

B) Micro needles-

Micro needle consists of an array of micro-structured projections, coated with a drug or vaccine, that is applied to the skin to provide intra-dermal delivery of active agents, which otherwise would not cross the stratum corneum.

The delivery of vaccines or drugs is not by diffusion, as in transdermal delivery systems, but by a temporary mechanical disruption of the skin, leading to the placement of the drug or immunogen among the cuticle, where it can more readily reach its site of action.

Micro needles are fabricated on the micro scale (1 mm in diameter and range from 1 to 100 mm in length) and this differentiates them from conventional needles. They are made up of various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. They can be designed to be long enough to penetrate the horny layer, but short enough not to puncture nerve endings. This reduces the possibilities of pain, infection, or injury.

❖ **Types of micro needles-**

Solid (straight, bent, filtered)

Hollow needles: Hollow needle designs include arrays of hollow needles with tapered and bevelled tips, that can contain and deliver micro litre quantities of drugs/vaccines, using simple diffusion or a pump system to very specific locations thus, enabling their targeting.

❖ **Applications of micro needles-**

- ✓ Solid micro needles could be used with drug patches to increase diffusion rates; increase permeability by poking holes in skin, rub drug over area, or coat needles with agent to be delivered.
- ✓ Hollow needles can be used with drug patches and regular pumps to deliver medication at specific times.
- ✓ Also, these micro needles could be used to remove fluid from the body for analysis – such as blood-glucose measurements – and to then, supply micro litre volumes of insulin or other drug as required.
- ✓ These are capable of terribly correct dosing, complex release patterns, promote local delivery and biological drug stability enhancement by storing in a micro volume that, can be precisely controlled.

C) Melt In Mouth Strips:

As the name indicates, these strips containing immunogens are meant to dissolve in child's mouth.

These strips were developed for protection against rotavirus infection.

Rotavirus is a common cause of severe diarrhoea and vomiting in children, leading to about 600 000 deaths, annually. Rotavirus vaccine, at present is available in a liquid or freeze-dried form, which must be chilled for transport and storage, making it very expensive for use in impoverished areas. In addition, newborns sometimes spit out the liquid, a problem that is less likely to occur with a strip, which sticks to and dissolves on the tongue in less than a minute. [14]

Conclusion

Vaccine drug delivery systems are gaining quality recently; thanks to the advantages, they offer.

They avoid the requirement to administer the booster doses and supply a protracted term medical care in little dose. Needle-free technologies, edible vaccines, on the opposite hand, open a lovely avenue for the oral delivery of vaccines.



Fig. No. 1: Gene gun delivery



Fig. No. 2: Pneumatic jet injection.

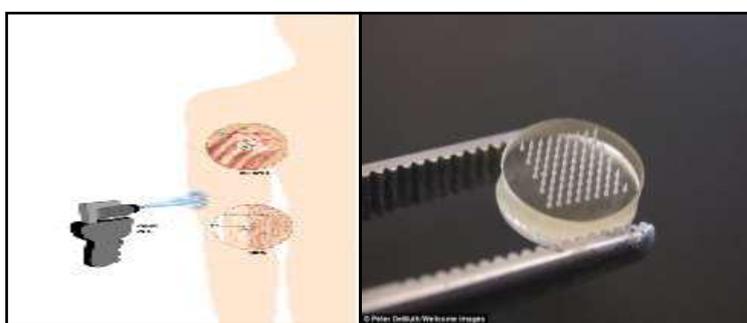


Fig. No. 3: Hypodermic needle injection.

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