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Review Article

# Applications of Nanoparticles to Deliver Vaccines and Associated Obstacles

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**Abstract**

The use of traditional methods in vaccinology is becoming insucient, like introduction of live or killed pathogens produce weak immune response and not eradicated the viral load completely so, nanoparticles gain the attention of many researchers with the numerous striking properties for vaccine development. The aim of this review is to reveal and discuss the significance of virus like particles, liposomes and biodegradable nanoparticles for vaccine delivery. Viruses like particles are nanoscale confirmation without genetic material safe for use to treat the viral infections. Liposomes are amphipathic phospholipids used for vaccine development because, of their high biocompatibility. Now days, biodegradable polymeric carriers are more focused in biomedical field because of their reduced toxicity, minimum side effects, enhanced biocompatibility and sustained release of therapeutic agents. Scientists are hoping that nanoparticle based vaccines can be approached as efficient way of vaccine preparation and delivery system.

**Keywords:** Vaccines; Nanoparticles; Virus like particles; Liposomes; Biodegradable nanoparticles

## Introduction

These days nobody is safe from illnesses, infections, and other medical issues. But with the development of new technologies it is conceivable to keep away from significant health dangers [1]. Vaccination is one of the best accomplishments in medication that has given an extremely accessible way to deal with and fight against irresistible infection by the development of effective adoptive immune response [2].

Traditional immunization techniques include inactivated, lessened or even subunits of pathogens i.e. toxoids and sugars (carbohydrates) as antigens [3]. Unfortunately, downsides have been related with these traditional immunization techniques. Reactivation of the virulent state and extreme side effects in subjects with weakened immune systems are most common adverse effects that have been associated with lessened vaccines. Synthetically inactivated vaccines can't recapture their virulence. But these vaccines induce a weaker immune response. Subunit vaccines are even provided with classical adjuvants (alum), still these vaccines suffer from some extra problems, for example inadequate storage stability and the need of booster shoots to attain active protection [4]. For the invulnerable treatment, the precise and targeted delivery of vaccine is a noteworthy challenge [3].

Nanotechnology in immunization gives the chance of upgrading the safety and steadiness of vaccines by means of improving both cellular as well as humoral immune response. Interestingly, vaccination-using nanotechnology is noninvasive, needle free, cost-effective. In addition improved antigens bioavailability and targeted delivery can also be achieved by nanotechnology [5]. Nanoparticles got the interest of numerous scientists because of some special features they have, for example, "shape, charge, dormancy, biocompatibility, biodegradability" and many others. Due to their small size, they can pass through cell segments by cell endocytosis and in this way they can transport the biological active compounds [1]. The fundamental basis of utilizing nanoparticles to deliver vaccines is their capacity to shield the antigens from proteolytic breakdown thereby enhancing vaccines uptake by the cells [6]. Broad surface area to volume proportion of Nano-carriers as well as their capacity to deliver multiple Nano-preparations like "Nano-crystals, Nano-powders, and Nano-clusters" empowers these to be utilized in treatment and prevention of different ailment like, cancer, influenza, irresistible infections and malaria [1].

First nanotechnology-based vaccine licensed for human use was Virus Like Particle (VLP) based vaccine against hepatitis B virus (HBV) [7]. Based on the composition of nanomaterial, different types of vaccine-associated nanoparticles are present like liposomes, virus like particles, biodegradable nanoparticles and polymeric nanoparticles.

## Virus Like Particles

The discovery of Virus-like particles has led the researchers to appreciate the development of vaccines as bio nanotechnology platforms against many viral infections that are very much complicated to treat after their diagnosis while significantly reducing production time and cost [8].

VLPs are Nano size protein based structures of 30-90 nm being produced from the self-assembly of viral capsid proteins without a nucleic acid genome or a lipid envelope spikes made them non-infectious and safe for use and curative purpose [9].

Researchers have determined the biocompatibility, multiple functionalization response on directed modification of VLPs that were exhibiting high stability and safety, ease of obtaining with scale-up production and purification. They have also focused on immunostimulatory, self adjuvanting and highly vascularized




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properties of VLPs and low proteolytic activity over subunit vaccines based on recombinant proteins.

Researchers have emphasized on better delivery system for VLPs specifically to the nasal site as an ideal carriers of drugs, peptides and whole proteins (antigens, receptors, enzymes, etc.). Researchers also made efforts for edible vaccines that would be transgene in variety of plants so this is the developmental way that could be in use for the human purposes [9].

They have given out the superiority to VLPs over traditional vaccines as polydispersed system, which would show better uptake by dendritic cells, lymph nodes and enterocytes inducing stronger immune responses. Their applications have been found for making commercialized VLP-based vaccines as some of them are licensed against certain viruses that have reached to the market level i.e. Rotavirus, HPV [8].

Others are involved in protection against hepatitis B virus and human papillomavirus infections which have been approved and currently show the potential for cancer and human immunodeficiency [10].

## Rotavirus

Human group A rotavirus, is the most dominant reason of acute infantile and paediatric gastroenteritis as early vaccination strategies did better in treatment but with side effects so there was being considered a need of other vaccine preparation with improved delivery system [11].

It has enlighten the VLP based vaccine and delivery carrier with VP2, VP6 and VP7 (Rotavirus capsid proteins) that were co-expressed in tobacco plants made it transgenic and then expressed, rotavirus-like particles formation and then had checked their immunogenicity. RV- VLPs were purified and analyzed by electron microscopy and Western blot as plant-derived proteins have shown self-assembly then orally delivered to mice with cholera toxin adjuvant, resulting in total soluble proteins which had induced rotavirus-specific higher serum IgG and fecal IgA antibody titers comparable with VP 2/6 and attenuated rotavirus vaccines. These results have shown to be proven a better treatment for rotavirus related diarrhea in human trials.

## HBV

Antigens expression of viral component in plants to make them transgenic and their delivery in many pre-clinical animals has been studied and few clinical trials against liver inflammation caused by Hep-B virus and acute nonbacterial gastroenteritis caused by Norwalk virus have shown wide potential with the use of VLP based vaccine system.

So, [12] have briefly considered the plant expression, VLPs self-assembly, hepatitis B surface antigen and Norwalk Virus Capsid Protein (NVCP) immunogenicity. HBsAg Small (S) protein was present in cultured cell suspensions of tobacco, potato leaf and tuber tissues when made them transgenic and observed under TEM. The potato was found immunogenic as plant-derived recombinant protein in it based on VLP immunization had provoked stronger serum IgG and IgA responses in mice against HBsAg. This HBV-VLP based vaccine has been approved commercially because ingestion of transgenic fresh potato tuber or systemic injection in humans had given the same immune response.

**Recombinant HBV-Based VLPs Containing HCV Epitopes:** Hepatitis C Virus (HCV) demands liver transplantation when condition is becomes severe with liver carcinoma develops cirrhosis that majorly infects 2% of globe. So this viral infection is now partially being addressed with new antiviral therapies because the introduction of Direct Acting Antivirals (DAA) initially are aimed to constrain the function and produce Non-Structural (NS) proteins by limiting the replication of specific viral proteins that brought about high and effective cure rates in most patients but hindered by several factors generally the high viral genome varieties.

Moreover, currently there are no animal models available that can mimic for human's HCV infection so to be treated [13] but described the possibility with insertion of E1 and E2 envelope proteins of HCV that modified the HBsAg-VLPs which would be shown in chimeric HBV-HCV particles as to the wild-type. High titre of cross NAbs was observed in rabbits when they were immunized then showing the ability to neutralize various HCV genotypes or strains.

## HIV

Human immunodeficiency virus, a lenti virus was discovered in 1983 that causes over time Acquired Immunodeficiency Syndrome (AIDS) with HIV infection led toward the stringent conditions that left the patient with failed immune system. Developing an effective, safe and affordable vaccine is like HIV-1 virus-like particles still the first primacy for attaining ultimate control.

Experiments have confirmed that HIV-1 Gag based VLPs were elicited Broadly Neutralizing Antibodies (bNAbs) and had induced strong CD4+ and Gag-specific CD8+ response priming long-lasting CTL action against multiple epitopes in rhesus macaques and chronically HIV-infected patients as efficiently captured by APCs (DCs) for activation and maturation then produced the pro-inflammatory cytokines mediating NK cells without leading to infection or replication and contribute to virus dissemination.

Practically [14] made Chimeric HIV-1 based VLP vaccine was given via intramuscularly priming-intranasal boosting route in guinea pigs with Flagellin as adjuvant enhanced the HIV-1 VLP's immunogenicity has led to improve potency and balanced immune responses in contrast to intranasal administration of traditional vaccines alone with bio-safety issues and alternatively, life-long Antiretroviral Therapy (ART) drugs neither kill nor cure the virus just stopped the growth along with other medications in low CD4 count.

## HPV

HPV (warts or Papilloma) can lead to cancer of mouth/ throat /cervics and anus/rectum. There is no cure for virus itself as HPV infections are necessary originator for cervical intraepithelial neoplasia CIN 2–3, a precursor lesions of cervical cancer if remain persistent but it is now being treated by VLPs based vaccination [15]. Have analyzed the controlled trials of the highly purified and prophylactic vaccine having HPV16 L1 VLPs as peptide antigen carrier that was administered orally or nasally best in animal models, found to be strongly immunogenic had induced high level of antibodies and reduced the cervical cancer during 1.5 or 3.5 years of follow-up, also worked for bivalent strains HPV 16 and 18. It also

helpful when modified VLPs were given to women intramuscularly in 3 shots at day 1, month 2 and 6, aged 16-23 years then observed the high antibody titers in the serum.

Researchers [15,16] had mainly focused on recombinant vaccine was protecting against 4 strains of HPV related symptoms but not eradicating the infection of virus and differing antibodies affectivity that generating the need to develop multivalent vaccine. Gardasil and Gardasil 9 vaccine are VLP based approved vaccine against 9 strains of virus, profitable than Pap testing which has reduced cervical cancer rates but it is considered costly so treatment for Sexually Transmitted Disease (STD) targeting HPV types has also decreased the excisional or ablative treatment needs.

### Influenza virus

H5N1 influenza virus has established the need for improved immunization methods as orthodox vaccinations had shown a principal delay to pandemic spread control. VLPs based approach has been proven useful to improve the coverage for seasonal pandemic viruses may enable self-administration that warrants further studies [17].

Researchers have determined the microneedle administration of a VLP based modified antigen containing the hemagglutinin (HA) of H5N1virus that was delivered into mice skin for protective efficacy that had shown the stimulus for more balanced T-cell immune response followed by increase in both IgG1 and IgG2a antibodies level in spleen and bone marrow both than traditional intramuscular immunization which gave complete response up to 8 months after vaccination. A same aspect has also been studied using microneedles patch format to human skin which had induced CD207+Langerhans cells movement in epidermis toward membrane base that was giving long-lived antibody-producing B cells and also activate dendritic cells effectively.

They had done practical for need of any adjuvant or stabilizer so it was observed that significant level of IgG antibodies specificforH5N1virus after prime-boost vaccination than without trehalose (MN+) [18,19].

### FMDV

Vaccination has been considered the best option to control this disease as inactivated vaccine had made significant aid as preventive measure since 1990s but still there are potential risks accompanied as virus can escape from the production process that may cause the spread of the disease which is acute with low mortality but contributed great loss in livestock worldwide.

VLP based vaccine has gained attention that overcome the side effects as injection of modified vaccine combined with Golden nanoparticles, an adjuvant was given to mice, rats, and rabbits which have activated the signaling pathway and induced cytokines by specific cytotoxic T-cell response because immune effects were mainly observed less effective without AuNs. Killed vaccines, FMDV epitope-based fusion proteins have suggested the use of cost effective adjuvant linked VLP based FMDV vaccine for animal protection [20].

### Anthrax

They had described a potential anthrax vaccine by using a T4 capsid to display and deliver the protective antigen, a component of the anthrax toxin against virulent strains of Bacillus anthracis. This T4 modified vaccine has worked as a universal antigen delivery system that was adapted because no anthrax vaccine is still available for mass protection, approved by FDA [21].

T4 nanoparticle rPA conjugate as vaccine was administered by aerosol, scarification, or subcutaneous injection and intramuscularly to the macaques against Bacillus anthraces had elicited robust immune response with no adjuvant. It has produced the significant results that can be served as next generation anthrax vaccine over conventional methods like Vaccine Adsorbed (AVA) and Anthrax Vaccine Precipitated (AVP).

### NNV

Nervous Necrosis Virus (NNV) infection has imposed serious economic losses in marine fish due to Red-Spotted Grouper Nervous Necrosis Virus (RGNNV) genotype, a causative agent [22].

Fishes were fed with modified OSGNNV-VLPs like virion 4 times via injections, immersion or orally immunized at 7-day intervals and commercial diet supplemented with purified VLPs. The viral challenge tests were done at 30 days of post immunization and its findings had demonstrated that self-assemble modified VLPs have potential as oral vaccine a preferred route, in grouper but it requires 100–1000 time more antigens because it gave insufficient efficacy partly due to harsh gastric environment that breaks the antigen in comparison to intramuscular or subcutaneous routes which produce high titers of neutralizing antibody and provide protective immunity against NNV [23].

### Cancer vaccination

VLNPs have been made functionalized with ligands diversity to tumor-associated targets such as peptides, antibodies, proteins like EGF also glycans, aptamers and small molecules, folic acid have shown remarkably efficient and specific *in vitro* targeting. VLNPs have been used to encapsulate high payloads of small molecule therapeutics like doxorubicin and photodynamic agents for light-triggered reactive oxygen generation [24].

Cancer therapies require targeting specific diagnostic element and a drug to tumor cells without killing healthy cells and tissues. Specialization of the VLPs can be used as a vaccine with no need of adjuvant because their naturally optimized particle size and repetitive structural order. Site-specific drug delivery systems in cancer therapy while dropping the systemic toxicity and the overall damage to healthy cells require the use of nano biotechnology recently [25].

## Liposomes in Vaccine Delivery

Liposomes are spherical, amphipathic vesicles of phospholipid molecules. Liposomes can be utilized for the delivery of both hydrophobic and hydrophilic types of drugs [26]. Upon comparison with other Nano- particles it was revealed that liposomes are advantageous for vaccine delivery in terms of safety and biodegradability. They are being classified on the bases of number of lipid bilayers. Following are the classifications of liposomes:

Small Unilamilar Vesicles (SUV), Large Unilamilar Vesicles (LUV) and Multilamilar Vesicles (MLV).

Size of liposomes ranges from 0.02-1.0μm in diameter. Liposomes

are versatile in in nature, due to their versatility liposomes are being used for the delivery of a large number of antigens [27]. They also have unique tendency to interact with Antigen Presenting Cells (APCs) and induce T-cells and antibody response.

### Principle of liposomal induction

Liposomal vaccines are efficient enough to induce both innate and adaptive immune responses [26]. They can serve as delivery vehicles for vaccine antigens as well as immunomodulatory agents.

First liposomal vaccines induce innate immune response. Innate immune response leads to the production of pro-inflammatory molecules and activation of Antigen Presenting Cells (APCs) and immune modulatory molecules such as chemokines and cytokines [27]. Innate activators are categorized as Toll Like Receptors (TLRs), Non-Toll Like Receptors (NLRs) and C-type Lectin Receptors (C-LRs). All these receptors have the ability to recognize various type of microbial nucleic acids and bacterial cell wall components. After innate immune response adaptive immune response activates [28].

### Factors affecting delivery of liposomal vaccines

Liposomes are efficiently used for vaccine delivery. But there are also some factors that are important to consider for the delivery of liposomal vaccines [29]. These factors are as follows: Nature of antigen, route of administration, immunization schedule, type of immune response, phospholipid composition, particle size, lamillarity, antigen attachment, surface charge, bilayer fluidity and Tm. While preparing liposomal vaccines Tm i.e. main phase transition temperature should be higher. Normally Tm is 37°C [30,31].

### DNA loaded cationic liposomes

DNA loaded cationic liposomes were used in 2017 by Wesley as a vaccine against malarial proteins. DNA loaded vaccines are efficient than recombinant vaccines, because recombinant vaccines show slow immune response [32,33]. Wesley used a combination of naked and liposomes entrapped DNA vaccines. Liposomes based approach provided effective humoral immune response against Plasmodium falciparum rhoptry antigen from Plasmodium vivax and P. falciparum titers. It was concluded that DNA loaded liposomal vaccines are useful than recombinant vaccine [33]. Because, recombinant vaccines cannot be produced when highly specific antibodies are mandatory.

### Cationic liposomes to eradicate tumor in mice

Liposomes based synthetic vaccines were used by Eleni in 2017, for eradication of tumor in mice. Synthetic Long Peptides (SLPs) can be used for therapeutic vaccination against HPV induced tumors [30]. Therapeutic potency of liposomes can be enhanced when equipped with tumor specific Toll like receptors TLRs and synthetic long peptides SLPs. Particle size for cationic liposomes is 160nm. Intranasal administration of vaccine effectively activated T-cells and antigen specific CD8þ and CD4þ T cells. Even low dose of vaccine was enough and cured 75-100% mice having malignant tumors [32]. Vaccinated mice were cured and protected from lethal tumors. This signifies effectivity of liposomal SLPs for the formulation of potent vaccines in cancer immunotherapy.

### Intranasal administration of liposomal vaccine

Administration of cationic liposomes intranasly to enhance granulocyte macrophage colony stimulating factor (GM-CSF) expression that was dispensable for mucosal adjuvant activity. Infectious diseases are causing major threats to humans. The primary method for prevention and treatment of pathogenic strains is vaccination. Mucosal vaccines are particularly promising approach to combat infectious diseases since; mucosal surfaces serve as major entry points for most of the pathogens [32]. Recently, an effective mucosal adjuvant of cationic liposomes that is composed of 1,2-Dioleoyl-3-Trimethylammonium-Propane (DOTAP) and 3β-[N-(N′,N′-dimethyl amino ethane)-carbamoyl] (DC-chol) (DOTAP/DC-chol liposomes) is developed.

This study involved investigation of the role of Granulocyte–Macrophage Colony-Stimulating Factor (GM-CSF), which was reported to act as a mucosal adjuvant, on the mucosal adjuvant activities of DOTAP/DCchol liposomes when intranasal administered to mice [32]. It was concluded that intranasal administration of vaccine along with cationic liposomes enmixed with GM-CSF showed great therapeutic effect.

## Biodegradable Polymeric Nanoparticles and their Types

In the present era, biodegradable nanoparticles got the attention of many researchers for their applications in biomedical field. The reason behind their superiority is their biocompatibility, ease of excretion and safety .Surprisingly, these particles don't accumulate in the body even after the repeated administrations and maintain the sustain release of the therapeutic agent encapsulated in them. Furthermore, their degradation capability could be implied as a tool for drug and plasmid DNA release into cytosol. Biodegradable nanoparticles have the tremendous ability to transport both hydrophilic and hydrophobic molecule, genes and vaccines.

They show great promise in vaccination protecting the vaccines until it is released and produce an optimal immune response in the body. Their flexible nature is also a potential advantage that allows the co-encapsulation of multiple epitopes, antigens and adjuvants within a single carrier. Upon administration, they are degraded into nontoxic, low molecular weight products that can easily eliminate from the body.

### Synthetic Biodegradable polymeric NPs

**PLGA Nanoparticles:** LGA, a synthetic copolymer, is extensively used as a delivery system in biomedical research as it is permitted through European Medicine Agency as well as by US-Drug and Food Authority because it has unique features [34]. PLGA particles are of prime importance showing intrinsic ability of sustaining the release period of encapsulated molecule from days to many weeks and are biocompatible as well as biodegradable in nature [35]. Different types of nano carriers possessing good biocompatibility and degradability (i.e. micro/nanospheres, pellets, film, nanoparticles and capsules etc) can be synthesized using PLGA polymer. Recently, PLGAs were used to deliver prodigiosin (bacterial product) and control release of 30 days was examined [36].

After administration, PLGA polymers undergo hydrolysios in body tissues and results in the release of biocompatible and biodegradable metabolites(lactic and glycolic acid) that are finally secreted from body through TCA cycle ,so there is no or minimum chances of cytotoxicity while using PLGA particles as a delivery

system [35]. For in-vivo applications Nano medicines, nano-vaccines and nanoparticles having genes can be successfully developed using PLGA nanoparticles due to their clinically verified biocompatibility, uniform particle size and better encapsulation power [37].

Material of PLGA has proven safe that is being used as a sew up and an ingredient in drug delivery formulations. They have also increased effectiveness of delivery systems (ability to adjust PLGA particle size) by protecting the encapsulated agent from extracellular degradation. Polyoxyethylene (POE) is usually used for modification of the PLGA NPs and spheres making them efficient for delivery of vaccines and therapeutic agents [36].

**Polylactic-acid (PLA):** These are also synthetic polymers made from lactic acid units. Like PLGA, as it is biocompatible thus upon administration in the body, it degrade into lactic acid. During anerobic respiration, lactide is also produced naturally which in converted into glucose(an energy source) by cori cycle in the liver, so use of PLA as a delivery system is safe and reliable [37]. PLA (and its copolymers) can be obtain from many sources and are acknowledged via FDA.PLA particles possess exclusive characteristics such as safety, biodegradability, elastic modulus and renewability and have applications in regeneration(cartilage, bones etc), repair and regeneration and also in delivery systems and formulation of drugs and vaccines. During in-vivo evaluation, they are used as carriers that maintain the sustained release of the therapeutic agents by slowly degradation and thus lowering the dosing frequency. PLA particles have short half-life and low stability, ease of degradation and minimum toxicity [36]. For vaccine delivery, it has limited applications as compare to PLGAs because of its low degrability. A recent study has revealed their efficiency while comparing both PLGA and PLA, PLA nanoparticles induced an ehnaced immune response during vaccination [34].

**Poly-ε-caprolactone (PCL):** Like PLGA and PLA, PCL is also aliphatic nature polyesters. These are going to be used in biomedical field because of their interesting features (safety, low cost and compatibility). PCL is recently used in delivery systems and as a long-term implantable device and it has more retention time or slow degradation rate in body as compared to PLA making it better for induction of optimal immune response. It is also biodegradable converted into its ester forms on hydrolysis having negligible side effects. In a recent study, PCL nanoparticles were used as a carrier to load tetanus toxoid and they produced a very powerful and long-term immune response (both cellular and humoral) in mice even after the two months of injection without the aid of any booster shot [37].

**Poly-Alkyl-Cyano-Acrylates (PAC):** These are also biodegradable and biocompatible in nature. Upon administration, PAC are degraded by the estrases enzymes found in the body but there is a threat associated to them that their degradation products are may be toxic in nature that can damage the CNS. This is the main hurdle that makes their applications limited for drug and vaccines delivery mainly in humans.

**Poly Urethane (PU):** PU is also a polymer having excellent biocompatibility and many other distinguishing features that are generally not possessed by other synthetic polymers. This makes them a suitable volunteer in biomedical fields for many applications. They also have some special properties including tremendous clotting, non ocogenecity and low side effects. Despite of their admireable characteristics they have a drawback that make their use limited in medical field. PU materials are not biodegradable and aids to environmental pollution. So there was the intense need to prepare biodegradable PU materials to cope with this difficulty. Biodegradable polymeric NPs are used in medical research due to their biocompatibility, biodegradability and many other potential characteristics [36].

## Natural biodegradable polymeric NPs

**Chitosan:** Chitosan polymers are natural made up of carbohydrates and are prepared from natural biopolymer called chitin through the process of partial N-deacetylation. Because of their nontoxic and flexible nature, biocompatibility and biodegradability, chitosan based NPs are widely studied. During development of several vaccines including HBV vaccines these nanoparticles have been used. From several chitinous materials mostly from the exoskeleton of crustaceans chitosan has been extracted and therefore it can be assigned as a green nanoparticle [34]. By electrostatic interaction chistosan bind with negatively charged protein or plasmid DNA and form mixture of polymers that shelter the therapeutic proteins and DNA from degradation, hence appropriate as delivery carrier or an adjuvant. Chitosan also have good absorbability, moisture withholding capacity and permeability [36]. These polymers are preferred over others because they have immune elicting effects. Alginates have also been used as adjuvant, proficient carriers of gene delivery, carriers for gene delivery, carriers for protein and many other drug molecules. These NPs powerfully persuades immunity specifically by up taking via lymphoid tissues of mucosal lining [37].

**Alginates:** Alginates are extracted from the cell wall of algae (brown algae). It is a straight chain copolymer (anionic polysaccharide) made of multiplepolyanionic polysaccharides a-L-guluronic acid and b-D-mannuronic acid units. They have following properties "biodegradable, biocompatible, non-toxic,ease of removal ,enhanced oxygen permeability etc, making these polymers suitable for use in biomedical field and in vaccine delivery systems [36]. Alginates involved in the development of "diphtheria toxoid loaded NPs" and immunization parameters were matched with the classical vaccine. As compare to classical vaccines, these polymeric alginates loaded in alginates show the enhanced and maximum immunity. For vaccination, alginate created NPs provides best nanocarries and adjuvant binding systems. For the protection against breast cancer DNA based chitosan nanoparticles (provided orally) coated with alginic acid are used as carrier for oral delivery, because these are safe as well as proficient implement for oral delivery of legumain-DNA vaccine. Sodium, ammonium and calcium alginates are being now a days common as commercial products of alginate [37].

**Gelatin:** Gelatin is used in biomedical field because of its proficient abilities like controlled release of drug, biodegradability, having both cationic and anionic groups and non toxic nature. Using gelatin, researchers have customized all these characteristics of gelatin to gain the desired shape and type of nanoparticle. Scientists have used the modified versions of gelatin nanoparticles in murine model and have observed the enhanced efficiency after modification [37]. Because of its crosslinking property it plays great role in mechanical

and thermal properties. Since, it is nontoxic, bioactive properties and its reasonable price; gelatin is a useful polymer to be utilized in controlled release of vaccines and drugs.

**Dextran:** Dextrans are polysaccharides with lipophilic nature consisting of straight chain α-linked D- glucopyranosyl units. These polymers are also biocompatible, environment friendly with extensive biodegradability used for the delivery of vaccines. It also has the ability to preserve and stabilize the vaccines in cold conditions. Dextrin can be synthesized chemically and widely used in biomedical field [37].

## Obstacles

Nano-vaccine innovation has been considered a complex procedure for creation novel Nano vaccines that demand a new machines methods and instrument which make the technique expensive. It's extremely hard to modify or alter the size of Nano-materials that may certain toxicity. The creation of Nano-vaccine idea is highly dependent upon the utilization of tiny size material at Nano scale. The associated threat with this preparation is that they may early and quickly clear from the body.

The reason behind the limited use of biodegradable polymer in the strong vaccine system is that they may entangle with the proteins. On storage they may lose their immunogenicity; likewise the liposomal vaccine delivery also demonstrates strange downside in the development that forecast the problem of aggregation on storage. Virus like particles is also being used as new Nano vaccine preparation and for vaccine delivery bitterly but there is associated drawback of cost.

On the other hand, the *in vivo* behavior of the nanoparticle for vaccination offers a major hurdle for the researcher. The reason is absence of key to compare different nanomaterial that is being used in Nano vaccination for example "gold, calcium, phosphate and silica" must be servient before their utilization because each required a tremendous efforts a lot of time and material [1].

## Conclusion

In the last few years there has been an incredible developments in field of nanotechnology and its application in biomedicine specially in vaccine delivery system. Immunogenicity of frail antigens also improved by Nanoparticles and this technique also provide numerous benefits over conventional adjuvant methodologies for example targeted delivery of vaccines, sustained release and many more. In this review we summarize most recent improvements, existing applications and issues related to the toxicity of nanoparticles in vaccine delivery system. The ongoing improvements and additional studies on biocompatibility of nanoparticles may change the perceptions about classical vaccines and this technique may open novel techniques to neutralize the lethal pathogens. For the wide usage of nanoparticles still scientists have to do a lot of work for the improvement of nanoparticles in vaccine delivery system. In near future we are hopeful that more nanoparticle based "drug delivery systems" will become available in the market.

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