Available online on 15.05.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Oral Mucosal Immunization Recent Advancement and Exploit Dendritic Cell Targeting

Daisy Arora[1], Sushmita Rana[2*], GD. Gupta[1] Amit Chaudhary[2], Bhupendra Singh[3]

[1]Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India.

[2] Department of Pharmaceutics, Abhilashi University Mandi, Chail Chowk (H.P), India

[3] Department of Quality Assurance, Abhilashi College of Pharmacy, Mandi (H.P), India

ABSTRACT

Oral mucosal vaccine thrive significant interest in developing vaccines that evoke mucosal moreover systemic immune response i.e. induction of IgA. Oral immunization consistently preferred over conventional immunization because it provides strengthens inpatient acquiescence, needle-free delivery, cost-effective. Thereby strong antibody production at the mucosal site is not refreshing by parenteral administration of the vaccines. Antibodies produced on the mucosal surface instead of it also start common mucosal immune system (CMIS). Vaccines allow particulate delivery protection of antigen. Polylactic-co-glycolic acid, poly lactic acid loaded nanoparticles, liposomes, niosomes, dendrimers; proteosomes are some of the nanocarriers which protect the antigen from their degradation. Authentication concepts of various studies on the mucosal vaccine by using nanotechnology for targeting to dendritic cell presenting on Peyer's patch elicit antibody production. This review sums up current studies on mucosal vaccination by using nanocarrier. More of the studies have been done on mucosal for improvement in methodology.

Keywords: Antigen, Nanotechnology, Dendritic cells, Peyer's patch, Vaccine

Article Info: Received 22 March 2019; Review Completed 09 May 2019; Accepted 12 May 2019; Available online 15 May 2019

Cite this article as:

Arora D, Sushmita R, Gupta GD, Chaudhary A, Singh B, Oral Mucosal Immunization Recent Advancement and Exploit Dendritic Cell Targeting, Journal of Drug Delivery and Therapeutics. 2019; 9(3):704-711

http://dx.doi.org/10.22270/jddt.v9i3.2861

***Address for Correspondence:**

Ms. Sushmita Rana, Assistant Professor, Department of Pharmaceutics, Abhilashi University Mandi, Chail Chowk (H.P)

Introduction:

Immunization mainly produces a resistant to extend contagious disease (transmissible disease) to the population in our surroundings by vaccinations. For the low paid workers immunization is a worthwhile process [1] when pathogen interplays with a mucosal membrane that overseas for the initiation of infection. Some microorganism initiates disease by liberating toxic factors. Moreover, a part of them penetrates into a host of body tissues which gives systemic or organ-specific diseases. So it is necessary for the activation of mucosal defense mechanism for controlling infection and averts diseases [2]. According to WHO the majority of people are died because of transferable diseases. The mucosal system mainly involves interlining of the gastrointestinal, urogenital and respiratory tract. These surfaces have an immediate connection with the outward source so there are sufficient chances for the entry of the pathogens.[3] Traditionally most of the vaccines are administered parenterally. However, this route is not effective for the generation of mucosal moreover systemic immunity [4]. Oral mucosal play a wide role in immunization. Oral immunization produces systemic moreover mucosal immunity. Thereby strong antibody production at the mucosal site is not refreshing by parenteral administration of the vaccines. Antibodies production is done on the mucosal surface alternatively it also stimulates the common mucosal immune system (CMIS). That is why the oral route has many benefits like safety, easy to administer, Avoidance of syringes or needles, Prevention of the relay of contagious diseases that produce due to infected needles [2]. A vaccine delivered by mucosal route undergoes physical, chemical and microbiological limitation; elevate the probability of degradation of antigen. Moreover delivery of antigen through mucosal route is a provocation; It faces various problems such as lack of immunogenicity, ineffectual uptake, and target to M cell, enzymatic disruption [5]. Vaccines allow a particulate delivery for protection of antigen. Some of the nanocarriers are PLA (polylactic acid), PLGA (polylactic-co-glycolic acid) loaded nanoparticles, liposomes, niosomes, dendrimers, proteosomes protect the antigen from their degradation [6]. The Oral route also involves the first pass metabolism in which drug passes through the liver by the

portal vein. More will be the first pass effect fewer drugs reaches to the systemic circulation. Sometimes some section of the drug doesn't absorb when administered orally. Degradation of drugs through gastric juice in the stomach. It shows less effect in case of an emergency. In this article, we discuss to conquer the drawbacks of the mucosal route by improving their effectiveness in the GIT, We recapitulate T&B cell-mediated immunity, mechanism of generation of mucosal system, cells involved in mechanism, traditional route vs. mucosal route (oral, nasal, aerosol, sublingual, Transcutaneous), barriers in mucosal route, nanocarrier based delivery for mucosal immunization. Although the developments of oral mucosal vaccine for usefulness to human and give safe and effective. Nanotechnology improves targeting of particular antigen to the Microfold cell (M cell) including dendritic cell targeting [7].

Cellular Immunity (T Cell-mediated immunity):

Cellular immunity moreover called T cell-mediated immunity. The thymus is the source of origin of T lymphocytes. T cells accomplish to discriminate a relation between the self and non-self antigens. In cellular immunity, T cells involve the defense mechanism against infectious microorganism [8]. They can't recognize antigen in their original form only when they are present on the surface of antigen-presenting cells. When the immune triggers and their arrival into the body that is identified by the immune system. These are called as antigens which actuate the immune system and involve the activation of the antibodies. Cellular immunity involves the stimulation of T lymphocytes and various cytokines. The antigen is identified by macrophage (antigen presenting cells). Macrophage engulfs antigen and displays section of the antigen on the surface of histocompatibility (MHC complex). Due to these Helper T cells are stimulated that further stimulate the emission of cytokines. It activates NK cells (natural killer cells), cytotoxic T cell. There are two types of T cells i.e. Helper T cells and cytotoxic T cells. These cytotoxic T cells kill infected cells [9]. CTL (cytotoxic T cell) represent predominant immune response for the demolition of most of the pathogens. CTL demolition of the infected cells [10]. Distinguish between cellular immunity and humoral immunity are as shown in figure 1.

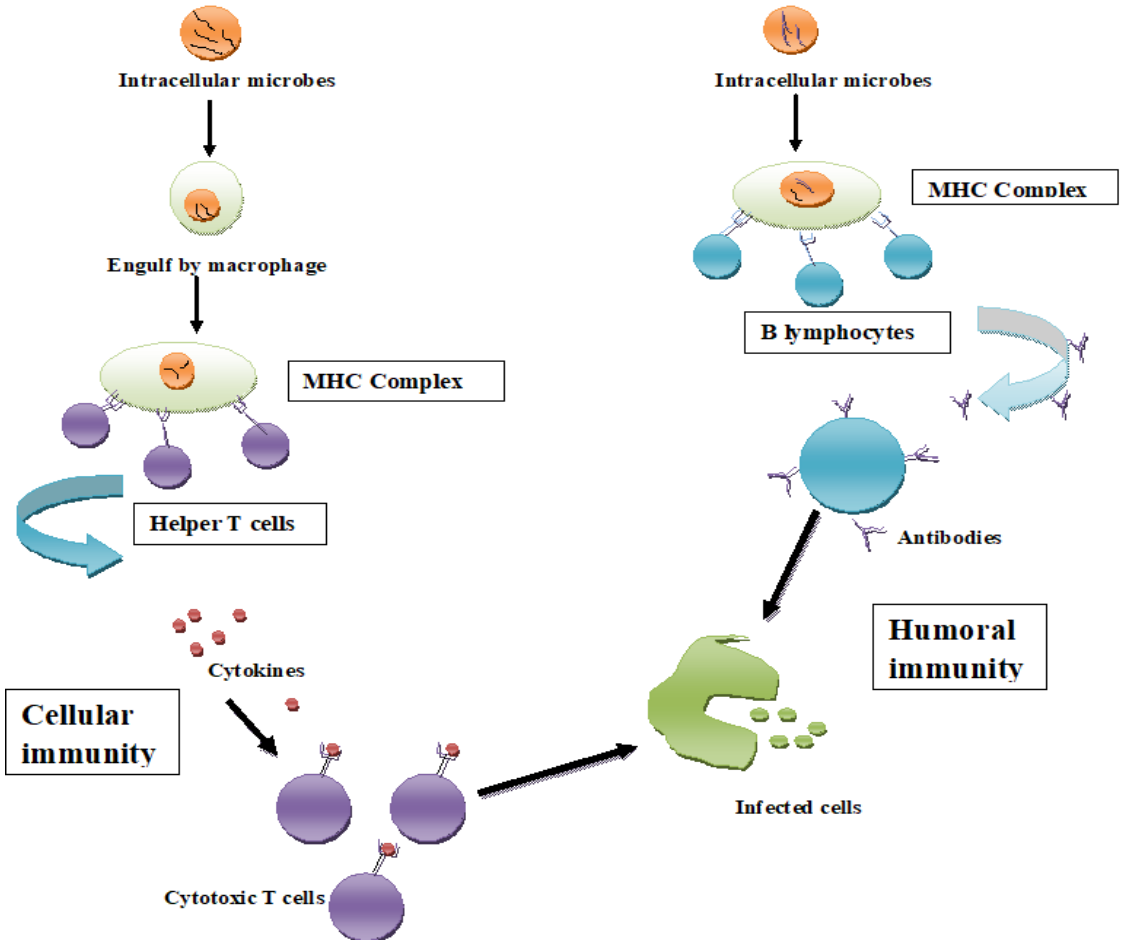

Figure 1: Distinguish between cellular immunity and humoral immunity

Humoral immunity (B cell-mediated immunity):

Humoral immunity found in the extracellular fluid which is mediated by macromolecules. Humoral immunity is also called as B cell-mediated immunity. B cells are derived from liver, spleen and bone marrow. Beyond IgG, IgA and IgE produce humoral immunity that depends on the microbial nature and infection route. The property of memory B cell developed when the B cell antigen receptors (BCRs) that redirect membrane-bound immunoglobulin (MIG) isotypes [11]. B cells produce a response only when it is activated by binding with an antigen. This activation process also essential involving the help from Helper T cells or other stimuli. It requires the activation of B lymphocyte. B cells are inactive firstly when antigen binds to antigen presenting cells then B cells activated. B lymphocyte stimulates

antibodies i.e. effectors cells Ab-secreting plasma cells, IgM and IgG demonstrate B cell IgG, High-affinity IgA demonstrates B cell that stimulates high-affinity IgG and memory B cells. Antibodies help in the demolition of microbes or infected cells. The cell-mediated or humoral response is mainly shown by the mucosal immunization but the traditional route is only parenteral that show only systemic immunity. Moreover, very few mucosal vaccines are available [9].

The mucosal immune system:

Cells involved in the immune system:

Bone marrow is the origin of the cells of the immune system. If the bone is splinter into parts of lengthwise then RBCs and WBCs cells notified. The alternative section of the bone is yellow adipose tissues that are inactivated in nature but when infection occurs the yellow marrow is compassionate to become red marrow to help in the refreshing of the cells of the immune system. The cells driven from the hematopoietic stem cells in the bone marrow which bring on to two pedigrees one is myeloid cells and other is lymphoid cells [12]. The myeloid cells include granulocytes, macrophages, monocytes, dendritic cells, megakaryocytic. Macrophages are the mature form of monocytes circulate in the blood and play a dominant role in innate immunity. Dendritic cells are the antigen presenting cells which recognized antigen on the cell surface. And displace it to the lymphocyte for further recognition. Other cells are lymphoid cells includes T cells (T helper cells, cytotoxic T cells), B cells and natural killer cells (NK cells). Lymphocytes are able to fabricate a specific immune response against the foreign antigen [13].

Mechanism of generation of the immune response:

There are two sites presents in the mucosal immune system Inductive site and effective site. Nasopharyngeal associated lymphoid tissue (NALT) and gut-associated lymphoid tissue (GALT) are the part of inductive sites which are present in the mucosal immune system. Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles are the part of GALT. Whereas NALT contains tonsils, adenoids, inducible bronchus-associated lymphoid tissues, cervical lymph nodes [14]. The antigen is agnized by the epithelial cells and they act as a sensor to detect antigen. It further took up by specialized epithelial cells (M cells) in the mucosal surface. M cell contains various endosomal tubules, vesicles. Foreign material transport to the M cell cytoplasm where the amalgamation of the vesicle occur and releasing of the content by exocytosis. From where antigen migrates to the Antigen presenting cells (APCs) includes Dendritic cells, B lymphocyte and macrophages captured antigen in Peyer's patch via endocytosis or phagocytosis and produce antigen fragments by digestion in the phagolysosome due to proteolytic lysosomal like environment. These peptide fragments are loaded on MHC Class 2 [15]. The peptide is further recognized by CD4+ T-helper cells. CD4+ cells secrete Cytokines and Interleukins (IL-2, IL-4, IL-5, and IL-6) and further stimulate the B lymphocyte to join immune response which enables to activate IgA antibody and help in the demolition of the infected agents [7].

The substantial antibody response is produced by administration orally of the vaccine in the small intestine, ascending colon [16]. A female genital tract of humans or macaques contains large numbers of IgG-secreting plasma cells. It was found that IgA and IgG antibodies are present in high concentration in human cervical and vaginal secretions. IgA and IgG antibodies help in blocking of infection to the body [16]. In intestinal mucosa, antigen enters through M cell and activate dendritic cell which helps in generation of the antibody are as shown in figure 2.

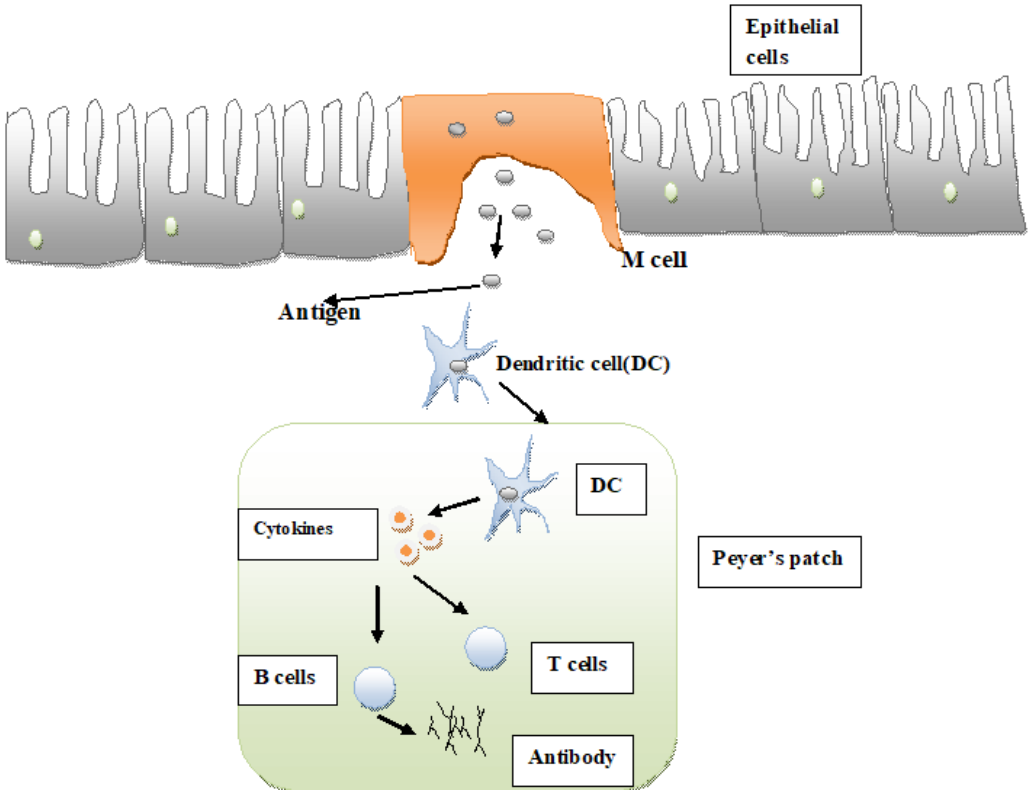

Figure 2: M cell targeting of antigen and generation of an immune response

Traditional Route (parenteral) and drawbacks:

Vaccination is beneficial for contagious diseases. This greatly reduced the effects of infectious diseases. For the administration of vaccines into the body parenteral route taken as a traditional route [17]. Various factors that affect the route of administration i.e. age, sex, adjuvants, vaccine formulation, types of antigen, depth of injection, injection techniques, needle length, body site and pre-existing immunity [18]. The rationale of administration of vaccine by this route i.e. vaccine directly enter into the systemic circulation and produce maximum bioavailability as compared to other routes. It produces rapid onset of action. But this route has wide drawbacks like the need of the trained personnel for the delivering of the vaccine, patient inconvenience, and the probability of the generation of infection due to infected needles like AIDS, Hepatitis, etc. Needle-based delivery causes pain on the site of injection. It produces only systemic immunity that bypasses the body's natural defenses against infection and the product which contained vaccines need proper sterilization and should be pyrogen-free. Due to this the cost of the particular vaccine increases that is not affordable for the poor peoples [19]. whether needle-free route i.e. mucosal route suitable for producing systemic moreover mucosal immunity. It is well accepted by patients and the easy route of administration.

Mucosal routes of administration :

The mucosal surface has the passage of the infectious agents to enter into the body and spread diseases. Infectious agents mainly contain pathogens, bacteria, and other microorganisms. It is necessary to increase immune responses as a defense against diseases and that only happen by the administration of the vaccines through oral, nasal, rectal or vaginal routes. But most of the vaccines are administered by injection nowadays [20].

Oral vaccination:

Oral is one of the cheapest, painless and easy routes for administration. This route faces various challenges like first pass effect (Transported to the liver via a portal vein) greater the first pass effect fewer agents will reach to the systemic circulation, degradation by gastric acid [21]. To vanquish some this effect we make nanocarrier as a defensive agent for the transportation of the agents to the particular receptor or site and they act as carriers. Some of the examples of oral vaccines are as shown in table 6.1.

Table 1: Some of examples of oral vaccines

Oral vaccines	Examples
Polio vaccine	Inactivated poliovirus vaccine
Rota vaccine	Rotarix, Rotateq
Typhoid vaccine	Ty21a
Adenovirus vaccine	the Adenovirus type 4 and 7
Cholera vaccine	Vaxchora, Dukoral, Shanchol

Moreover, there are some special astonish factors in case of young infants i.e. evolution of some level of immunity due to maternal serum IgG antibodies transferred in the uterus and breast milk which have sIgA act as a protective barrier against pathogens [22]. Recent various studies ongoing to oral immunization i.e. development of novel biodegradable polymer carrier (Eudragit L100) coated mannosylated chitosan loaded nanoparticles for oral protein vaccine delivery. It was found that immense growth in the IgG antibody and mucosal IgA response [23]. Other studies suggest that M cell targeting of Co1 peptide-mediated C5aR can be used for the generation of T cell immune response in the oral mucosal administration against dengue virus [24]. Zhang R et al demonstrated that by delivering of Helicobacter pylori HPaA to gastrointestinal mucosal immune site producing mucosal immunity in mice using Lactococcus lactis [25]. All of the studies indicate that oral vaccine produces mucosal moreover systemic immunity.

Nasal vaccination:

Nasal vaccination is also the most effective immunization methods. Most effective antigen immune response is produced by this method. Nasal vaccine is beneficial for respiratory diseases and sexually transmitted diseases. NALT (nasopharynx-associated lymphoid tissues) are present on both basal sides of the nasal cavity. It contains unpaired nasopharyngeal tonsils and the paired palatine tonsils which is overseeing for the development, not of the immune response. The nasal route also has undesirable effects such as significant wheezing and weak immune response to the live vaccine and risk of transport through olfactory nerve to the brain. Some examples are FluMist a live attenuated ted influenza nasal vaccine [26]. Various studies still in progress on nasal immunization i.e. Vemireddy et.al. Reported that chitosan-based nasal emulsion delivery system against recombinant tetravalent dengue antigen which enhances the antigen-specific humoral and cellular response. The emulsion-based delivery system initializes the innate (TLR4) and adaptive immune system [27]. According to other research on chitosan loaded nanoparticles against bronchitis virus vaccine. It was found that IBV-CS well built mucosal immune response compared with marketed induction of IFN$^{\gamma}$ gene expressing and production of IgA and IgG anti-IBV antibodies [28].

Aerosol vaccine:

It is also an alternate method for the effective safe needle-free vaccine which is widely used for the pediatric population. It also produces systemic as well as mucosal immunity. A very fine particle delivered by nebulizer that reaches to the lungs. This route is beneficial for respiratory diseases like infection caused by contaminated air. In case of this delivery system the vaccine is delivered through nebulizer then possible chances of contamination of the vaccine is more. One of the examples of the aerosol vaccine is the measles vaccine. The pulmonary route of vaccine boosting the immunity which is effective and more acceptable. This show stronger and more antibody response than injected measles vaccine. It is given by nebulizer having a particle size less than 5μg in diameter [29]. contemporary study on combined aerosolized Toll-like receptor ligand is effective against influenza pneumonia. This study reveals that when mice treated with combination PUL042 aerosol and oseltamivir give more therapeutic effect as compared to alone [30]. Ortega reported in his study that by evaluating antibody persistence in children at the age of 6 to 7 years following booster immunization with two MMR vaccines administered by aerosols [31].

Transcutaneous immunization:

Transcutaneous immunization (TCI) is an advanced form of vaccination in which vaccine administered through the skin to induce an immune response. According to research on animals, it was found that when we Transcutaneous administered vaccine then vigorously immune response showed via skin [32]. A highly lipophilic vaccine with low molecular weight shows the greatest flow rate through stratum corneum. Wakabayashi reported that by developing a new s/o formulation loaded with melanoma antigen peptide K-TRP-2, as a Transcutaneous cancer vaccine. This study demonstrated that s/o loaded K-TRP-2 peptide elicit the efficiency and skin permeability of the peptide [33]. TCI

with a novel imiquimod Nanoemulsion loaded delivery to generate T cell response and virus protection [34].

Sublingual vaccination:

It is an alternate route of vaccine delivery. Due to recent studies indicating that this route is necessary for the induction of a robust immune response that produces mucosal as well as systemic immune responses. Live attenuated influenza vaccine produce antiviral responses in the lung of mice when administered sublingually. These studies are difficult in case of doing on mice [35]. Preclinical development of sublingual vaccines is influenza WIV (Formalin-inactivated), influenza HA subunit, influenza 3M2eC, etc [36]. Nagai Y et al demonstrated that sublingual antigen can be transported across sublingual ductal epithelial cells to the ductal antigen presenting cells [37].

Barriers in the oral route of administration:

The oral route is the more preferred route for drug delivery. it is the simple, easy and most acceptable route which generally improve patient compliance. Drugs that have nonextreme to the extreme level of bioavailability and have varying Pka value because along with the varying length of GI tract the pH of the gut also varying [38].

Enzymatic barrier:

It is a more valuable and assertive barrier which starts from the site of administration through transport pathway including organs and cells of the body. Pepsin and other proteolytic enzymes like trypsin, chymotrypsin, etc. These proteolytic enzymes are responsible for the degradation of vaccine/drugs [39]. Some Luminal enzymes like (peptidases), peptidyl drugs are degraded by proteolytic enzymes in GIT. Then some ester types of drugs or vaccines are hydrolyzed by esterase present in the intestinal tract. In the gut/wall mucosal enzymes like CYP450 involve in drug metabolism process. CYP3A4 is the part of CYP450 which involve in catalysis the biotransformation of many drugs extrahepatically. The vast majority of metabolism by CYP3A4 is responsible for the poor oral bioavailability of many drugs [40].

Vaccine stability in GIT:

To protect the drugs in gastric acid is also a challenging task. In the case of vaccine or mucosal immunization purpose chances of degradation is more. To avoid it is necessary to protect the drugs or vaccines by some of the ligand or carriers systems. That improves the acid stability of the drugs in GIT [41].

Gastric emptying time and intestinal motility:

Small intestine having large surface area most of the drugs show the greatest absorption in this region. Quick gastric emptying increases their absorption because of the drug enters to small intestine very quickly and vice versa [41].

pH and surface area of GIT:

In entire GIT, every mucosal site is having disparate pH. the pH of the solution is one of the critical parameters to conduct the stability of the proteins or vaccines. Different site disparate different pH which is necessary for the vaccine absorption and their stability [42].

Nanocarriers based delivery for oral mucosal immunization:

Nanocarriers are the advanced form of drug targeting at a particular site. Nanotechnology is an initiative for controlling of the toxicity, immunogenicity, efficacy and pharmacokinetic or Pharmacodynamics of drugs. They are beneficial to overcome vaccine degradation and their loss, prevent undesirable adverse effects and to improve the bioavailability of the vaccines. This nanocarrier mainly contains biodegradable natural or synthetic polymers. These are a wide range of lipid-based nanocarrier developed for the mucosal route of administration like niosomes, liposomes, ethosomes, pharmacosomes, multiple emulsion, nanoparticles, microparticles, and dendrimers [43].

Liposomes:

Lipid-based vesicle delivery is an alternative to drug targeting. Liposome carrier system is entrenched as a vigorous system for the generation of humoral and cell-mediated immunity against contagious disease. Innumerable researchers have done to elicit oral mucosal immunization via encapsulated antigen to liposomes [44]. Liposomes contain cholesterol and nontoxic phospholipids like egg or soybean phosphatidylcholine. Laborde and its co-workers reported that pore-forming protein encapsulated into liposomes to elicit the CTL mediated immune response. Improving results had shown in vivo when administered to mice. In this study, they use PFPs for the improvement of the CTL response. It remains arduous for the delivery of Ag to the antigen presenting cells. When the Ag encapsulating to the PFPs they are able for the generation of CTL response. This study indicates that not only adjuvant is responsible for the generation of CTL response but it comes with PFPs encapsulating liposomes [45]. Talesh et al have developed Nanoliposomes carrier system elicit antitumor immunity in vivo, it becomes an arduous task to deliver the peptide and adjuvant into their target site. This study has been reported that by using cationic nanoliposomes carrier system with adjuvant like DOTAP-CHOL-P5-Poly (I:C) effective for generation of antitumor immunity. It is reported by taking a combination of adjuvant like poly(I:C) and DOTAP with Ag produce robust antitumor responses as compared to individual one [46]. Kawai et al using octa arginine modified liposomes [47]. A recent study has been done by Moignic A.L et.al. They reported that decline in tumor growth observed vaccination with trim-LPR [48]. Some of the marketed formulations of liposomes are as shown in figure 3 [49].

Figure 3: Some of the marketed formulation of liposomes

Niosomes:

Nonionic surfactant vesicles having unilamellar or multilamellar vesicles. It contains cholesterol, Surfactant. Cholesterol provides rigidity to the bilayer vesicles which results in a decrease in the leakiness of niosomes. Niosomes have more advantageous as compared to liposomes; they are more stable than liposomes [50]. In a recent study done by

Mohamed BH et.al. Using niosomes for preventing drug incompatibilities or DI is a significant issue in rigorous care strategy. It was shown by the result that niosomes have the ability for reduction of adverse reactions and improve patient compliance and efficacy of drugs [51]. On the other hand proniosomal gel which contains nonionic surfactant give better results in case of topical delivery of tazarotene used for the treatment of psoriasis. PNG formulation has the potential to elicit drug accumulation in the dermis and epidermis region of skin [52]. Provesicles (containing a nonionic surfactant, cholesterol, and the span 60) as a carrier for drug delivery. Marketed formulation of NTG with Provesicles formulation of NTG and the result show a robust decrease in the blood glucose level in comparison to marketed NTG formulation (Glinate60). Overall this study is beneficial for the treatment of type2 diabetes [53]. Abidin L et.al developed a delivery niotransgel formulation of LUT (luteolin) which have the potency to elicit the anti-arthritic activity [54]. Maheshwari c et.al. Reported that nonionic surfactant vesicles loaded with hepatitis B can be successful for the topical delivery of vaccines [55].

Bilosomes:

A conventional vesicular system like liposomes, niosomes have their own drawbacks because of their stability in the GIT and bile salt degradation of the antigen into the intestine. To overcome this advanced form of the carrier system i.e. Bilosomes containing bile salts which give both mucosal as well as systemic immunity. It is stable in GIT and intestine. According to a research study by [56]. Making tetanus toxoid loaded bilosomes able for the generation of T helper type 2 (Th2) and IgG antibody in Balb/c mice. Recent studies on bilosomes (Bile salts based vesicles) are as shown in table 2

Table 2: Recent studies on bilosomes (Bile salts based vesicles)

Disease	Carriers	Outcomes	Ref
Influenza	Bilosomes	High antibody titers and cell-mediated response.	[57]
Hepatitis B	Mannosylated bilosomes	Elicit immune response with enhanced SIgA level at all local and mucosal sites	[58]
Tetanus	Bilosomes	Induction of Th2 response and significantly increase in systemic and mucosal immunity	[56]
Diphtheria	nanobilosomes	Ag loaded nanobilosomes produce comparable serum Ab titers to IM administered alum-adsorbed Diphtheria toxoid	[59]
Cholera Toxin	Bilosomes	IgA titers obtained enhanced affinity towards M cells of Peyer's Patches	[60]

Similarly mannosylated bilosomes as a carrier system used for the oral mucosal immunization against Hepatitis B virus. It was found that stability and dendritic cell targeting to the particular site more as compared to liposomes or niosomes. The study shows that mannan-coated bilosomes indicate more IgA level in the mucosal system [58]. M cell targeting of the mannosylated liposomes loaded with Leishmania Donovan Ag. In this study, it is reported that Ag loaded mannosylated bilosomes gives positive results of oral mucosal immunization and overcome the side effects of conventional drugs [61].

Nanoparticles:

Nano-size particles are produced at the range of 1nm to 100nm (Khan IB et.al). There are various types of nanoparticles are carbon nanotubes, Metal-based nanoparticles, Dendrimers, and polymeric nanoparticles. Sahu KK et.al. Reported that Eudragit nanoparticles have the potential of targeting to the colonic immunization for the development of humoral and mucosal immune response [62]. Cao Xi et al. Design and develop GLU-FTH based nanoparticles for an anticaries mucosal vaccine that elicit the antibody production and inhibit S mutants infection in rodents [63]. Kaur M et al. Develop a safe and effective carrier system of guar gum nanoparticles loaded with Ag85A which used for oral vaccination against tuberculosis [64]. Harde H et al. Reported that by designing of glucomannosylated chitosan-based nanoparticles tetanus toxoid vaccine for oral mucosal immunization that elicits oral stability as well as enhances immunostimulatory response [65].

Nanoemulsion:

Nanoemulsion is emulsion having a nanoscopic size of the droplets (10 to 1000nm). Nanoemulsion elicits bioavailability, the solubility of poorly soluble drugs. They elicit the effectiveness of the drug and reduced the side effects as well as toxicological reactions [66]. Koneke et.al. Reported that Nanoemulsion adjuvant modifies allergic reactions in food allergy by changing antecedent allergy immunity and elicit mucosal immunity [67]. Bielinska UA et.al. Develop novel mucosal anthrax protective Ag loaded Nanoemulsion against B anthracis spore challenge [68]. Makidon KP et.al. give positive results when developing novel Hepatitis B loaded Nanoemulsion that elicits the mucosal immunization. Some of the marketed products of Nanoemulsion like Estrasorb and Flexogen that is based on Nanoemulsion delivery system. Estrasorb mainly used after menopause to reduce vasomotor symptoms in women [69]. Another one is Flexogen that also a type of Nanoemulsion which is a pain relief cream [70].

Conclusion and future destination:

Authentication concepts of various studies are requisite to provide well being understanding that by using adjuvants like nanocarrier, dendrimers, niosomes, liposomes, nanoparticles, elicit the antibody generation by targeting to dendritic cell presenting on Peyer's patch, production of sIgA and develop a mucosal moreover systemic immune response. Nanotechnology plays a vital role in mucosal immunization by protecting antigen. They act as protective carriers which is responsible for the generation of an immune response. Various researches on a mucosal vaccine using nanocarrier, the immense antibody production in animals are shown. This indicates that they are obliging for the development of a new generation of oral vaccines. There are no. Of oral vaccines developed that has been approved by FDA i.e. live attenuated rotavirus vaccine, cholera vaccine. Nowadays more studies have been done on mucosal for improvement in methodology, growing interest in mucosal immunization gives a better understanding of the mucosal and systemic immunity and several other researchers are in progress.

References:

1. Julia E, Ramirez V. Current state and challenges in developing oral vaccines. Advanced drug delivery Rev 2017; 114:116-131.

2. Magistris MTD. Mucosal delivery of vaccine antigens and its advantages in pediatrics. Adv Drug Deliv Rev 2006; 58: 52-67.

3. Sahu KK, Pandey RS. Development, and characterization of HBsAg loaded Eudragit nanoparticles for effective colonic immunization. Pharmaceutical development and technology Rev 2018, 1-27.

4. Azegami T, Yuki Y. Challenges in mucosal vaccines for the control of infectious diseases, International immunology Rev2014; 517-28.

5. Srivastava A, Gowda VD, Mucosal vaccines: a paradigm shift in the development of mucosal adjuvants and delivery vehicles. APMIS Rev 2015: 123(4):275-88.

6. Nizard M, Diniz OM. Mucosal vaccines. Human vaccines and immunotherapeutic Rev 2014; 10(8):2175-2187.

7. Arora D, Goyal AK, Oral mucosal immunization: Recent advancement and future prospects. Current immunology Rev.2010: 6(3):234-259.

8. K.H.G. Mills, Recognition of foreign antigen by T cells and their role in immune protection, Curr. Opin. Infect. Dis. 1989; 2:804–814.

9. MC Neela, Mills GH. Manipulating the immune system: humoral vs. cell-mediated immunity, advanced drug delivery Rev2001: 43-54.

10. F.W. van Ginkel, H.H. Nguyen. Vaccines for mucosal immunity to combat emerging infectious diseases, Emerge. Infect. Dis. 2000; 6:123–132.

11. Engels Niklas, Wienands Jurgen. Memory control by the B cell antigen receptor, Wiley immunological rev 2018: 283(1):150-160.

12. Cruvinel MW, Junior MD. Fundamentals of innate immunity with emphasis on the molecular & cellular mech. Of inflammatory response, bras J Rheumatol 2010: 434-61.

13. Delves PJ, Roitt D. The Immune System – First of two parts. N Engl J Med 2000; 343:37-50.

14. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008; 8:958-69.

15. Banchereau J, Briere F. Immunobiology of dendritic cells. Annu Rev Immunol 2000; 18:767-811.

16. Neutra RM and Kozlowski AP. Mucosal vaccines: the promise and the challenge Nat Rev.immunol6, Rev2006; 6(2): 148-58.

17. Cook IF. Evidence-based route of administration of vaccines, Human vaccines Riv.2008, 4:1, 67-73.

18. Herzog Christian. The influence of parenteral administration route and additional factors on vaccine safety and immunogenicity: a review of recent literature, expert review vaccines 2014; 13(3):399-415.

19. Irvine RK. Chamberlain RS. Route of immunization and the therapeutic impact of recombinant anticancer vaccines, a journal of the national cancer institute vol. 89.Rev.1995.

20. Kozlowski AP, Uvin CS. Comparison of the oral, rectal and vaginal immunization routes for induction of antibodies in rectal and genital tract secretion for women, Infection and immunity Rev.1997; 1387-1394.

21. Zhu Qing, Berzofsky AJ. Directed safe passage to the front line of defense, gut microbes Rev2013, 4(3):246-252.

22. Levine MM. Immunogenicity and efficacy of oral vaccines in developing countries: lessons from a live cholera vaccine, BMC biology Rev. 2010; 8:129.

23. XuB, Zhang W, Chen Y. EudragitL100- coated mannosylated chitosan nanoparticles for oral protein vaccine delivery, Biological macromolecules rev 2018; 113:534-542.

24. Kim HS, Kim NH. C5a receptor targeting of partial nonstructural protein 3 of dengue virus promotes antigen-specific IFN$^{\gamma}$ producing T cell responses in mucosal dengue vaccine model, cellular immunology Rev 2018: 325:41-47

25. Zhang R, Wang C. Delivery of Helicobacter pylori HPaA to gastrointestinal mucosal immune sites using Lactococcus lactis and its immune efficacy in mice, Biotechnol Lett Rev.2018 40(3): 585-590.

26. Ouchida NR, Yuki Y. Development of nanogel based nasal vaccine as a novel antigen delivery system, Expert review of vaccines Rev.2017 16(12): 1231-1240.

27. Vemireddy S, MC, Kumar SMH. Chitosan stabilized nasal emulsion delivery system for an effective humoral and cellular response against recombinant tetravalent dengue antigen, carbohydrate polymers Rev.2018, 190:129-138.

28. Lopes DP, OkinoHC. Inactivated infectious bronchitis virus vaccine encapsulated in chitosan nanoparticles induces mucosal immune responses and effective protection against challenge, Vaccine, Rev 2018: 2630-2636.

29. Thomas Manjaly RZ, Mcshane H. Aerosol immunization for TB: matching route of vaccination to route of infection, TransR SocRev2015, 109:175-181.

30. Juarez LM, Kirkpatrick TC. Combined aerosolized toll-like receptor ligand are an effective therapeutic agent against influenza pneumonia when co-administered with oseltamivir, European journal of pharmacology Rev.2018: 191-197.

31. Ortega DL, Castaneda D. Antibody persistence in children aged 6-7 years one year following booster immunization with two MMR vaccines applied by aerosol or by injection, Vaccine Rev2017, 35(23): 3116-3122.

32. Premjeet S, Sahil K. Transcutaneous drug delivery system: A comprehensive review, IRJP Rev.2011: 2(12):49-55.

33. Wakabayashi R, Sakuragi M. Solid-in oil peptide nanocarrier for Transcutaneous cancer vaccine delivery against melanoma, molecular pharmaceutics Rev.2018, 15(3):955-981.

34. Lopez AP, Denny M. Transcutaneous immunization with a novel imiquimod Nanoemulsion induces superior T cell responses and virus protection.

35. Czerkinsky C, Holmgren J, Mucosal delivery routes for optimal immunization: targeting immunity to the right tissue, Microbiology and immunology Rev.2010: 1-18.

36. Kraan H, Vrieling H. Buccal and sublingual vaccine delivery, Journal of controlled release Rev2014:580-592

37. Nagai Y, Shiraishi D. Transportation of sublingual antigens across sublingual ductal epithelial cells to the ductal antigen presenting cells in mice, a Basic mechanism in allergic disease Rev.2013: 1-25.

38. Hamman JH, Enslin GM. Oral delivery of peptide drugs barriers and developments, Bio drugs Rev.2005: 19(3):165-77.

39. Engman H. Intestinal barriers to oral drug absorption: cytochrome P4503A and ABC- transport proteins, Rev.2003, 296.61.

40. Song NN, Zhang YS. an overview of factors affecting oral drug absorption, Asian journal of drug metabolism and pharmacokinetics Rev. 2004; 4(3): 167-176.

41. Renukuntla J, Vadlapudi DA. Approaches for enhancing oral bioavailability of peptides and proteins, International journal of pharmaceutics Rev.2013: 75-93.

42. Zhou HX. Overcoming enzymatic and absorption barriers to non parenterally administered protein and peptide drugs, controlled release Rev.1994: 239-252.

43. Khodabandehloo H. Nanocarriers usage for drug delivery in cancer therapy, Cancer prevention Rev.2016, 9(2): 3966.

44. Mody N, Sharma R. Capsaicin-loaded vesicular systems designed for enhancing localized delivery for psoriasis therapy, Therapeutics delivery Rev.2015 6(2), 231-245.

45. Laborde RJ, Ferras SO. Novel adjuvant based on the pore-forming protein sticholysin encapsulated into liposomes effectively enhances the antigen-specific CTL- mediated immune response, immunology Rev.2018 198(7): 2772-2784.

46. Talesh GA, Ebrahimi Z. Poly (I:C)- DOTAP cationic nanoliposomes containing multi epitope HER2-derived peptide promoters vaccine elicited anti tumour immunity in a murine model, Immunology letters Rev.2016: 176, 57-64.

47. Kawai K, Miyazaki J. Bacillus Calmette-Guerin (BCG) immunotherapy for bladder cancer: current understanding and perspectives on engineered BCG vaccine, cancer science Rev.2013: 104, 22-27.

48. Moignic AL, Mallard V. Preclinical evaluation of mRNA Trimannosylated lipopolyplexes as therapeutic cancer vaccines targeting dendritic cells, controlled release Rev.2018, 6; 278: 110-121

49. Nekkanti V, Kale S. Recent advances in liposomal drug delivery: A review, Pharmaceutical nanotechnology Rev.2015, 35-55(21).

50. Jadhav MS, Morey P, Novel vesicular system: an overview, JAPS Rev.2012: 193-202.

51. Mohamed BH, Shanawany SE. Niosomes: A strategy towards prevention of clinically significant drug incompatibilities, Scientific reports Rev2017, 6340.

52. Prasad V, Chaurasia S. Performance evaluation of non-ionic surfactant based tazarotene encapsulated proniosomal gel for the treatment of psoriasis, materials science and engineering C Rev 2017 168-176.

53. Sahoo KR, Biswas N. Development and in vitro/ in vivo evaluation of controlled release Provesicles of a nateglinide-maltodextrin complex, APSB Rev.2014: 408-416.

54. Abidin L, Mujeeb M, Imam SS. Enhanced transdermal delivery of luteolin via non-ionic surfactant based vesicle: quality evaluation and anti-arthritic assessment, drug delivery Rev2014; 23(3): 1079-84.

55. Maheshwari C, Pandey RS.Non-ionic surfactant vesicles mediated Transcutaneous immunization against Hepatitis B, International immunopharmacology Rev.2011: 1516-1522.

56. Mann FS, Scales EH. Oral delivery of tetanus toxoid using vesicles containing bile salts (bilosomes) induces significant systemic and mucosal immunity, Science direct rev.2006: 90-95.

57. Conacher M, Alexander J. Oral immunization with peptide and protein antigens by formulation in lipid vesicles incorporating bile salts (bilosomes), Vaccines Rev2001: 2965-2974.

58. Arora daisy, Khurana Bharat. Oral immunization against Hepatitis B virus using mannosylated bilosomes, J. Of recent advance in pharmaceutical research Rev2011, 1:45-51.

59. Shukla A, Katare OP. Significant systemic and mucosal immune response induced on oral delivery of diphtheria toxoid using Nano-bilosomes, BJP rev.2011: 164, 820-827.

60. Singh P, Vyas SP. Cholera toxin B subunit conjugated bile salts stabilized vesicles (bilosomes) for oral immunization, International journal of pharmaceutics Rev.2004: 379-390.

61. Deepika B, Kumar MS. Development of Leishmania donovani antigen-loaded mannosylated bilosomes to target M cell: In vitro characterization, World journal of pharmacy and pharmaceutical research Rev.2014: Vol (3): 1983-1999.

62. Sahu KK, Pandey RS, Development and characterization of HBsAg loaded Eudragit nanoparticles for effective colonic immunization, Pharmaceutical development, and technology Rev.2018: 1-10.

63. Cao Xi, Ye Ql. A self-assembling anticaries mucosal vaccine containing ferritin cage nanostructure and glucan binding region of S.mutans glucosyl transferase effectively prevents caries formation in rodents, Human vaccines, and immunotherapeutic Rev.2017: 1-29.

64. Kaur M, Malik B. Development and characterization of guar gum nanoparticles for oral immunization against tuberculosis, Drug delivery Rev2014: 1-7.

65. Harde H, Agrawal AK. Tetanus toxoid loaded glucomannosylated chitosan-based nano homing vaccine adjuvants with improved oral stability and immunostimulatory response, pharmacies, Rev.2015: 32(1): 122-34.

66. Jaiswal M, Dudhe R. Nanoemulsion: An advanced mode of drug delivery system, Biotech Rev.2015 5(2): 123-127.

67. Konek J, Landers JJ. Nanoemulsion adjuvant driven redirection of TH2 immunity inhibits allergic reactions in murine models of peanut allergy, J Allergy Clin Immunol Rev.2018. 1-11.

68. Bielinska AU, Janczak WK. Mucosal immunization with a novel Nanoemulsion based recombinant anthrax protective antigen vaccine protects against B. Anthrax spore challenge, Infectious immunology Rev.2007: 1-45.

69. Makidon PE, Bielinska AU. Preclinical evaluation of novel Nanoemulsion based Hepatitis B mucosal vaccine, PLOS ONE3 (8) Rev.2008: 1-16.

70. Patravale V, jain R. Nanoemulsion: an overview, Science direct Rev.2016: 1-13.