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Chitosan as an Adjuvant in Viral Vaccine

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ABSTRACT

The current surge in viral diseases has been the matter for concern globally. Despite vast armamentarium to curb the spread of microbes, infectious diseases still pose a threat globally. Henceforth better vaccination need to be developed to improve the efficacy of anti-viral vaccine. Chitosan, a cationic biomaterial acts as an eminent adjuvant and delivery system for antiviral vaccines. It's biocompatible, non-toxic, biodegradable, bioadhesive, cost effective nature makes it an ideal candidate as an adjuvant in vaccine delivery. It has Immunostimulant property which helps to develop better innate as well as the adaptive immunity response. Moreover, future research is anticipated in development of adequate standardization technique and regulatory guidelines for use of chitosan as adjuvant in vaccine development.

Keywords: Vaccine; Chitosan; Efficacy; Adjuvant

Introduction

Infectious disease has been one of the most common causes of morbidity since a very long time leading to an unprecedented burden on the healthcare system. Developing countries like India has experienced outbreak of varied viral diseases leading to great loss of life as well as economy. For countries like India, geo-climatic conditions and overpopulation can be blamed for outbreak of many viral diseases like malaria, influenza, chickenpox etc. Despite of vast armamentarium to curb the spread of microbes, infectious diseases still pose a threat globally. [1] Due to emergence of vaccines and antibiotics, the number of cases has definitely decreased many folds. Vaccination has effectively averted millions of deaths from common viral disease. It has been regarded as one of the most economical and effective means to prevent and control infectious disease. Despite the ever-increasing scope of vaccines, the battle against viral diseases is still to be triumphed. Henceforth, much research has been carried out to strive and improve the immunogenicity and efficiency of the vaccine without compromising the safety parameter of the same. One such way to attain an improved immunogenicity of the vaccine without compromising the safety is by using adjuvants. [2] Adjuvants had been used for more than half a century now to enhance the innate as well as the adaptive immunity response induced using a vaccination allowing for development of effective memory response and thereby better protection against the deadly infections. Despite the magnificent properties and advantages of adjutants, there are only a few adjuvants that have been approved by USFDA. Adjuvants like aluminium salts, saponins, monophosphoryl lipid A and unmethylated CpG oligodeoxynucleotides.[3] Each of the adjuvant is destined to induce a specific immune response thereby resulting in a tailor-made vaccine to target a specific pathogen. However, since only a small number of adjuvants are clinically approved, there is a constant need to find more adjuvants to effectively fine tune the tailor-made vaccines. Continued investigations and research has shown the property of biomaterial like Chitosan to act as a possible adjuvant. Being a biomaterial,

it is non-toxic and bio-compatible in nature and hence can act as an effective adjuvant in vaccine delivery. Moreover, the antiviral property of the chitosan adds as an added advantage in using chitosan as an adjuvant in antiviral vaccines [4].

Chitosan

Chitosan is a cationic polysaccharide biomaterial obtained by partial deacetylation of chitin via alkaline hydrolysis. Chitin is naturally occurring polysaccharide obtained from shells of living organisms like crabs, shrimps, lobster etc. Since this biomaterial is abundantly available in the nature, it is one of the highly researched biomaterials. The unique physicochemical and biological characteristics of chitosan like biocompatibility, non-toxic, biodegradability, cell permeability etc had made it a promising adjuvant. Figure 1 The molecular weight, distribution of acetyl group and degree of deacetylation are some factors which strongly influence the physicochemical as well as the biological properties of chitosan. Commonly commercial chitosan has degree of deacetylation in range between 60 to 100%. However, despite varied advantages chitosan has not been exploited to its full potential owing to its less soluble nature. It has been reported by many researchers that solubility of chitosan can be improved by substantially modification of primary amine group or hydroxyl group [5,6]. Recently due to current surge in viral infections, there has been a drift in interest of many researchers towards the antiviral properties of many biomaterials. It was observed that chitosan had antibacterial activity towards a wide class of fungi, algae and bacteria. Moreover, the minimum inhibitory concentrations reported against different microorganisms were in the range 0.0018%-1%. [7,8] Furthermore, it has been reported that chitosan and chitosan derivative function more rapidly against fungi than bacteria. [9-15]. Following Table 1 depicts different research which depict the antifungal activity of chitosan.

Figure 1: Advantages of chitosan as vaccine adjuvant.

Table 1: Different research depicting antiviral activity of Chitosan.

Virus	Virus Host	Chitosan concentration	Temperature	pH range	Time	Conclusion of the research	Reference
Tobacco mosaic virus	Nicotiana tabacum	1mg/ml	37	7	24 hr	Necrosis could be prevented by 50-90%	[10,11]
Alfalfa mosaic virus (ALMV)	Pisum Sativum	0.1% w/v	23-25	6	24 hr	Reduction in number of infected plants	[12]
Peanut stunt virus (PSV)	Nicotiana paniculata	0.1% w/v	23-25	6	24 hr	Reduction in number of infected plants	[13]
Cucumber mosaic virus (CMV)	Chenopodium quinoa	0.1% w/v	23-25	6	24 hr	Reduction in local lesions	[14,15]

Potato virus X (PVX)	Lycopersicum esculentum	0.1% w/v	23-25	6	24 hr	Reduction in local lesions	[16]
Bombyx mori nucleopolyhedrovirus (BmNPV)	Silkworm larve as host for	0.5 mg/ml	37	7.4	24 hr	The virus titre value declined rapidly	[17]
Autographa californica multiple nucleopolyhedrovirus (AcMNPV)	Sf9 cell	1mg/ml	28	7.4	72 hr	The virus titre value declined rapidly	[17]
Human cytomegalovirus (HCMV) strain AD169	Human embryonic lung fibroblasts	4.5 mg	37	7	72-120 hr	Encapsulation of foscarnet into chitosan nanoparticle reduced toxicity of the drug and extended its therapeutic activity	[18]
Newcastle Disease Virus	10-days-old embryonated Specific Pathogen Free (SPF) chicken eggs	1 mg/ml	37	7	72	Modification of chitosan into 6 amine chitosan increased the antiviral activity. Moreover 6-deoxy-6 bromoN-phthaloyl chitosan depictedbetter anti-viral activity by activating the immune system and by inhibiting the virus transcription	[19]
H1N1 influenza A virus	Madin–Darby Canine Kidney cells	10mg/ml	37	5.2-6.3	1 hr	Chitosan linked with silver nanoparticle depicted significant antiviral activity	[20]
Herpes Simplex Virus-1 and Herpes Simplex Virus -2	African green monkey cells (Vero cells)	0.35%w/v	37	4-5	24-48 hr	Chitosan acts as antiviral agent by being the immune stimulator and as an adjuvant	[21]
Hepatitis C	Human hepatoma cells Huh7	20 µg/ml	37	7	24 hr	High antiviral activity against Hepatitis C virus and 100% reduction in viral titre when curcumin was encapsulated with chitosan.	[22]
Hepatitis B	Spleen cells	0.1%w/v	37	5.4	24 hr	Chitosan depicted antiviral activity by acting as an adjuvant	[23]
Hepatitis A	Vero cells	100 µl/ml	37	3-9	120 hr	When polyquatenary phosphodium oligochitosan was used it depicted reduction in viral percent by 41.4%	[24,25]
Feline Infectious Peritonitis virus	Crandell-Rees feline kidney cell culture	0.1%w/v	37	3	24-48	Curcumin chitosan nanoparticle depicted better antiviral effect and lower toxicity with selectivity index thrice higher than curcumin nanoparticles	[26]

Mechanism of Action of Chitosan as Anti-Viral Agent

The recent surge in viral diseases had drifted the interest of many researchers into developing a novel drug and vaccines for combating the life-threatening viral disease. Chitosan has emerged as an important adjuvant in anti-viral vaccines. its mechanism is attributed to its immune stimulating ability which thereby accumulates and activates macrophages, natural killer cells, poly morphonuclear cells and enhance resistance to infection by activating IL-2, IL-4, IL-10, IL-12, IFN-γ and TNF-α. Chitosan and its derivatives also increase the antibody response and augment the delayed type of hypersensitivity and cytotoxic T-lymphocyte response [16-20]. Therefore, in a nutshell chitosan has the ability to induce both cellular and humoral response and thereby improves the anti-viral activity of the vaccine and hence even the smaller concentration of vaccine can elucidate adequate anti-viral immunization when administered along with adjuvants like chitosan [21-27]. According to Porporatto et al depicted that uptake of

chitosan is facilitated by CD11b/c Antigen Presenting Site. Further, Chitosan up-regulates the MHC class II antigen by increasing the percentage amount of OX62 dendritic cells. Moreover, it elicits the release of TGF-β and activates the CD3+ T-cells in spleen. Another important conclusion drawn from research conducted by McNeela et al showed that mucosal or parenteral immunization with antigen CRM197, chitosan selectively enhanced the induction of Th2 cells [28-29]. Beside immune stimulating property of chitosan, their physicochemical properties like high viscosity, permeation enhancing nature, bioadhesive nature, biocompatible, non-toxic nature etc are added advantage ad it stimulates better absorption of the drug by enhancing paracellular absorption. Hence chitosan act as a promising adjuvant as well as delivery system for anti-viral vaccine which can be administered both parenterally and submucosal route. The mechanism of action of chitosan is depicted in Figure 2.

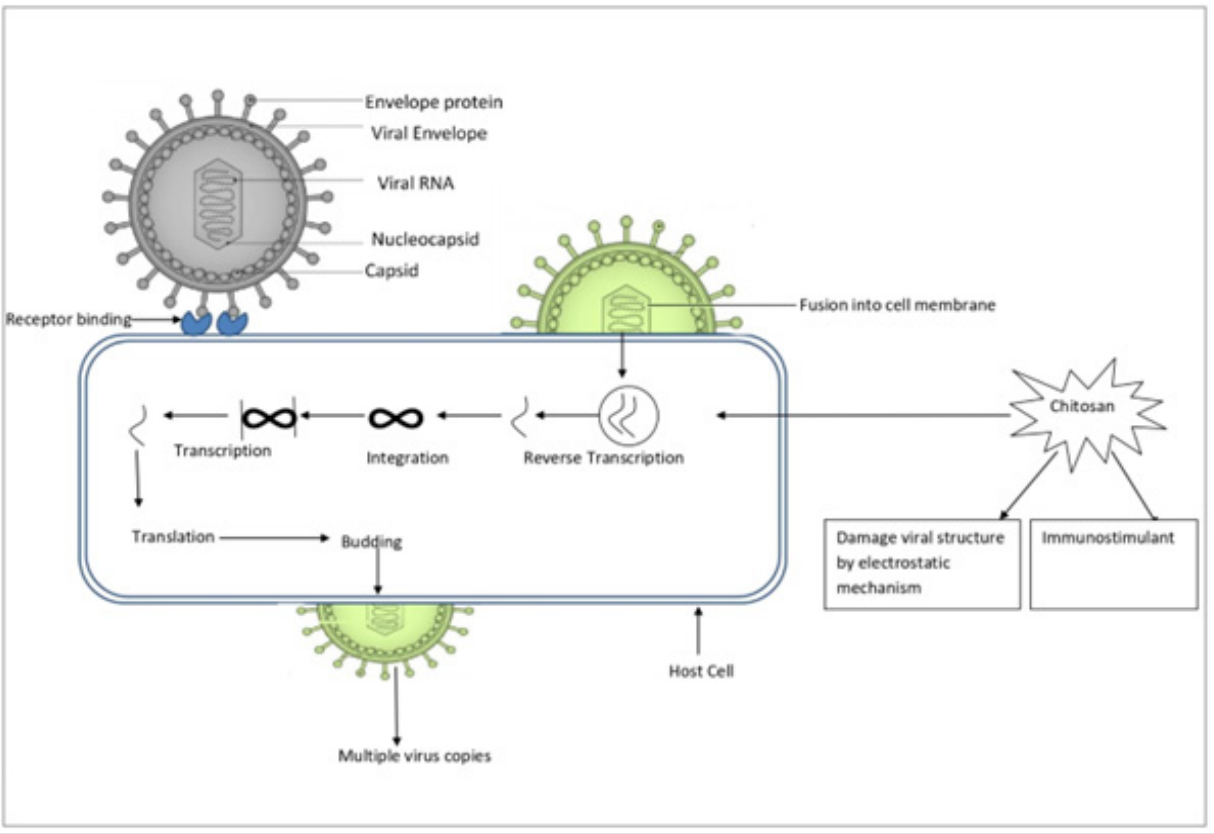

Figure 2: Mechanism of action of Chitosan as antiviral agent.

Chitosan as Adjuvant in Antiviral Formulation

Much research has been carried out to investigate the use of chitosan as an adjuvant in vaccine development. Chitosan has been exploited to a great extent because of its biodegradability, safety, mucosal absorption etc. Intranasal drug can be formulated using chitosan as a mucoadhesive and it also enhance cellular immune response of anti-viral vaccines. Certain spray dried norovirus like particle antigen has been formulated using chitosan and monophosphoryl lipid immunity enhancer. Positive results have been exhibited by these vaccines in phase 1 clinical study and it was observed that the formulation when administered through intranasal route induced the secretion of IgA. Moreover, other research has also depicted the use of chitosan as delivery system where a complex coacervation method was diploid to encapsulate DNA based vaccine in chitosan nanoparticle to treat swine influenza in mice. The research concluded better immune response along with extended release of the plasmid DNA when compared to the plain DNA vaccine. [30-32] Another research concluded that encapsulated siRNA into a chitosan-based nanoparticle and this formulation depicted a better immunogenic response and increased cellular accumulation of siRNA and hence the formulation depicted a better anti-viral activity [33].

Several research have also proved the use of chitosan delivery system in formulation of Hepatitis vaccine. Hepatits B antigen encapsulated into glycol chitosan nanoparticle showed a better mucosal immune response when administered through intranasal route. The plausible reason for above results could be the improved mucoadhesive nature of glycol-chitosan nanoparticle which thereby

increases the resistance time of the vaccine antigen followed by better uptake of vaccine antigen by B cells. [34] Another research by Saraf et al depicted the superiority of hepatits B antigen loaded into alginate coated chitosan nanoparticle anchored with immunity enhancer lipopolysaccharides. This vaccine proved to be a promising oral mucosal vaccine for hepatits B. The alginate coating helped the vaccine sustain the severe acidic condition in the stomach. The results showed an increased quantity of IgA at mucosal secretion and increased quantity of IgG antibodies in systemic circulation. [35] AbdelAllah et al carry forwarded the research and tested the effectivity of alginate coated chitosan nanoparticles in delivering Hepatitis A vaccine. The research concluded an increased level of antibody followed by increased proliferation of splenocyte [25].

Chitosan in Live Vaccines

Chitosan has recently been used to prepare attenuated live vaccines. A famous research where attenuated live vaccine of porcine epidemic diarrhoea virus was encapsulated into chitosan microsphere was conducted by Qigai, et al. [36] The formulation showed a tremendous improvement in immune response and the preparation could be stored for prolonged period with ease of transportation. The virus was inactivated by treating it with chitosan along with varied concentration of acid/alkaline solution, formaldehyde, peroxyacetic acid in a specific temperature range. Chitosan was used by Park et al to inactivate virus for anti-viral vaccines. [37] Live new castle disease virus was encapsulated into chitosan nanoparticle. This resulted in improved antigen loading capacity in the vaccine. Moreover, it also improved the absorption capabilities on mucosal surface [38,39]. In a nutshell, Chitosan adjuvant improves the immunogenicity of the vaccine, and it augments a better and stronger immune response, and it effectively shows desired activity at even small concentration of antigen, reducing the side effects. Moreover, with emerging viral diseases like COVID, influenza etc, chitosan can act as a potential adjuvant in vaccines.

Recent Patents on Chitosan as Vaccine Adjuvant and Vaccine Delivery System

The application of natural based carbohydrate polysaccharide in antigen delivery and its adjuvant properties has gained interest of several researchers. Biomaterial like chitosan especially has garnered a large amount of interest in vaccine development. Following Table 2 depicts the advancement in formulation of vaccines using chitosan as adjuvant and delivery system.

Table 2: Chitosan as adjuvant and delivery system for Vaccines.

Patent Number	Title	Inventors	Publication Year	Summary of invention	Reference
US7323183B2	Vaccine composition including chitosan for intranasal administration and use thereof	Lisbeth Illum, Steven Neville Chatfield	2008	Upon intranasal administration of the vaccine along with chitosan improved the immune response of antigen	[40]
JP4696260B2	Mucosal vaccine using chitosan adjuvant and meningococcal antigen	Giudis Giusepe del et al	2011	Chitosan depicted a tremendous mucoadhesion and thereby improved immunogenic properties	[41]
CN102988978B	Vaccine combination containing porcine circovirus 2 type antigen and haemophilus parasuis antigen and preparation method thereof and application	Xi Xiangfeng et al	2016	Vaccine combination was prepared for prevention and treatment of porcine circovirus 2 type and haemophilus parasuis. chitosan acted as a vaccine adjuvant.	[42]
CN102824635A	Application of chitosan as adjuvant in preparation of influenza virus attenuated live vaccine	Chen Ze	2012	Chitosan when used as an adjuvant enhanced immunogenicity of the vaccine even in lesser amount of antigens.	[43]
KR100919731B1	Chitosan microsheres for vaccine delivery containing polyether as stabilizer	Jojongsu, Kang-ho-rim et al	2009	The vaccine was designed to treat atrophic rhinitis in pig. the vaccine induced systemic and mucosal immune response	[44]
CA2255867A1	Chitosan induced immunopotentiation	Joseph S. Podolski, Miltzi L. Martinez	2008	Chitosan acted as an immunostilmulatory agent	[45]
US9205151B2	Compositions and methods for encapsulating vaccines for the oral vaccination and boostering of fish and other animals	Moti Harel, Brian Carpenter	2015	Chitosan acted as a bioadhesive agent and successfully improved encapsulation of the drug and thereby its immunostimulating property	[46]

Method of Preparation of Anti-Viral Vaccine with Chitosan as an Adjuvant

For preparation of an antiviral vaccine with chitosan as adjuvant, several techniques have been deployed. But the most common method of preparing an inactivated viral vaccine is by first selecting the viral strand and cultivating in an adequate culture media example MDCK cell culture for cultivating Avian Influenza virus. The growth of the virus can be amplified by adding 2 µg/ml of trypsine into the culture media. After an adequate amount of virus is reproduced, the solution is centrifuged at required rpm and treated with formalin solution for 3 days at 36-37 ^{o}C to render the viral strand inactive. The sediment obtained is resuspended into a buffer solution and centrifuged again to uniformly distribute the inactive viral strands. It is then stored at freezing temperature (4 ^{o}C) [40]. Thereafter, chitosan of predetermined molecular weight was dissolved in glutamate buffer solution and added to the inactive virus vaccine and mixed thoroughly [41-46]. The prepared suspension was administered intramuscularly to BALB/c mice for 3 weeks followed by booster dose for 10 days. After 10 days from booster dose, the mice were anesthetized and challenged intranasally with the active virus and survival rate of the animal was recorded [47-49]. Apart from the aforementioned procedure, chitosan can also be used as a delivery system and hence the vaccine could be formulated into nanoparticles, microspheres, liposomes or other novel drug delivery system using chitosan.

Shortcomings of Chitosan as Adjuvant

Though chitosan has shown marvellous results as an adjuvant and as a delivery system of vaccines, there are certain drawbacks associated with it. Chitosan is a biomaterial obtained from chitin. Chitin is obtained from mainly crabs, prawns, shells of crabs, lobster etc. The wide number of source result in chitosan of different chemical and physical properties. the processing of chitin into chitosan also affects the final chemistry of chitosan. therefore, the variability in source and processing techniques yield chitosan of varied physicochemical property like molecular weight, degree of deacetylation, crystalinity, protein content etc. this further affects the biological and anti-viral properties of chitosan. Furthermore, it is often impossible to standardise the formulations with adjuvants since there is no standardised formulation and characterization technique. Moreover, each antigen portrays different intrinsic immunogenicity with different Immunostimulant. Furthermore, standardization of chitosan also poses a challenge. Properties like different molecular weight and percent degree deacetylation affect properties of chitosan. Although extensive research has been carried out in utilizing chitosan and its derivative as delivery system and adjuvant for nasal and parenteral vaccines. But the next step to introduce chitosan as an adjuvant into marketed product would be appropriate standardization and regulatory guidelines for its usage in vaccines. [50-52] Nevertheless, the aforementioned hurdle is surmountable with adjuvants like chitosan which depicted promising results in human studies. Hence it is not long before anti-viral vaccines with chitosan as adjuvant steps in and conquers the market.

Conclusion

Chitosan and its derivatives are well tolerated by human body, biocompatible, and biodegradable and cost effective with promising potential as an adjuvant for viral vaccines. The immune response induced by the chitosan solely depends on the physicochemical properties of chitosan. It is believed that chitosan enhances both humoral and cell mediated immune response. It also is associated with mucoadhesive properties and hence it can be well exploited information of mucosal vaccines. However, due to lack of standardization and regulatory guidelines, chitosan-based vaccines have not entered the market. Hence research should be carried out in standardizing and formulating guidelines for exploiting the full potential of chitosan as adjuvant in viral vaccines.

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