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REVIEW

# Hydrogel nanoparticles and nanocomposites for nasal drug/vaccine delivery

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**Abstract** Over the past few years, nasal drug delivery has attracted more and more attentions, and been recognized as the most promising alternative route for the systemic medication of drugs limited to intravenous administration. Many experiments in animal models have shown that nanoscale carriers have the ability to enhance the nasal delivery of peptide/protein drugs and vaccines compared to the conventional drug solution formulations. However, the rapid mucociliary clearance of the drug-loaded nanoparticles can cause a reduction in bioavailability percentage after intranasal administration. Thus, research efforts have considerably been directed towards the development of hydrogel nanosystems which have mucoadhesive properties in order to maximize the residence time, and hence increase the period of contact with the nasal mucosa and enhance the drug absorption. It is most certain that the high viscosity of hydrogel-based nanosystems can efficiently offer this mucoadhesive property. This update review discusses the possible benefits of using hydrogel polymer-based nanoparticles and hydrogel nanocomposites for drug/vaccine delivery through the intranasal administration.

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## Introduction

Recent developments in the science of biotechnology have led to the exploration of a large number of novel therapeutic molecules such as peptides, proteins, and plasmid DNA. The parenteral delivery of these agents are commonly limited by the low permeability across biological membranes and an inadequate stability in the biological medium (Teijeiro-Osorio et al. 2008). Besides, the oral administration of large molecules is accompanied by some problems, including low bioavalability, slow absorption, presystemic enzymatic degradation, and side effects through the gastrointestinal tract. Thus, a large proportion of the focus of pharmaceutical researchers has been on the use of the nasal route as a convenient and reliable method for the delivery of therapeutic agents (Ali et al. 2010; Djupesland 2013). To date, nasal route has conventionally been applied for drug medication for the treatment of local diseases such as nasal allergy, nasal congestion, and nasal infection. Moreover, this procedure has been receiving growing interest in the field of systemic delivery of the low molecular weight drugs, particularly when a rapid onset of action is needed. Nasal drug delivery offers several other advantages like high permeability, high absorption surface area, less enzyme of the nasal fluids, and porous endothelial basement membrane of the nasal epithelium (Illum 2007; Ozsoy et al. 2009). Liver first-pass metabolism may also be overcome if the drug could be preserved and absorbed in the nasal cavity (Wong and Zuo 2010).

Recently, attentions has been focused on the nasal route for the bypassing of the blood brain barrier (BBB) and the

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reaching of the cerebral spinal fluid (CSF) due to the direct delivery of therapeutic molecules to the brain (Mainardes et al. 2006).

On the other hand, nasal mucosa as a portion of the mucosal immune system, can induce antigen-specific immune responses against respiratory pathogens and also protect the host from the respiratory infectious diseases (Nochi et al. 2014). Thus, it is an obvious advantage that the intranasal vaccination confers both mucosal and systemic immunity (Birkhoff et al. 2009).

Among the different formulations prepared for the nasal drug delivery, it has been reported that nanoparticles have the ability to improve the drug absorption through the nasal membrane barrier and show great efficiency in enhancing the drug bioavailability (Mainardes et al. 2006; Mistry et al. 2009). However, the clearance of the mucociliary can help reduce the contact time of drug-loaded nanoparticles with the mucosal surface of the nose. Hence, the application of hydrogel-specific properties is now considered as a useful platform for the preparation of stabilized and smart nanoscopic vehicles for drug delivery purposes (Vinogradov 2010). In addition, the incorporation of nanoparticles within a hydrogel network can offer remote controlled applications and also improve characteristics like the mechanical strength (Meenach et al. 2009).

The present review presents a broad collection on previous reviews by including scientific studies (past and present) of hydrogel nanoparticles which embodies the high potential in improved nasal drug delivery. Additionally, some properties and applications of the hydrogel matrix containing nanoparticles will be discussed at the end of this paper.

## Nasal mucosa as a passage route for drugs

The human nasal cavity has a total surface area of about 150 $cm^2$, and its total volume is about 15 to 20 mL (Pires et al. 2009, Dhakar 2011). The internal surface of the nose is lined by a mucous layer and hairs which play a significant role in its functions, trapping of inhaled particles and pathogens (Pires et al. 2009). A key protein in the mucus, called mucin, has affinity for foreign solutes thus limiting its diffusion (Dhakar 2011). As a result, the new mucus is continuously secreted and the previous layer is quickly replaced. Hence, the particles trapped in the mucus barrier are transmitted with it, and in this way, they are finally evacuated from the nasal space (Türker et al. 2004). This vital key defense mechanism is referred to as the mucociliary clearance. In order to circumvent the nasal mucosal barrier, drugs with low absorption either be co-administered with different types of absorption enhancers or encapsulated into the suitable delivery systems, such as liposomes, microspheres, and nanoparticles (Debache et al. 2011). A perfect nasal carrier system should be more efficient in bypassing the mucociliary clearance barrier and also in resolving the bioavailability problems by prolonging the intranasal residence time, hence making an acceptable therapeutic effect.

## Brain delivery via nose

The efficient delivery of therapeutic agents to the central nervous system (CNS) is a vital challenge in the treatment of neurological diseases. The main problem in the uptake of drugs into the brain following the systemic administration is the presence of a membranous barrier called the blood brain barrier (BBB). The BBB is formed by a system of endothelial cell layers lining the brain capillaries that are connected via tight junctions and alongside separate the brain and CSF from the blood (Talegaonkar and Mishra 2004).

Recent developments in studying the cell biology of BBB have opened new perspectives in directing drugs to the CNS (Al-Ghananeem et al. 2010). Nose-to-brain drug delivery offers a possibility for the direct transport of therapeutic agents from the nose to brain through the olfactory and trigeminal nerve pathways. These nerve pathways begin in the roof of nasal cavity and end in the brain (Pardeshi and Belgamwar 2013). The direct contact of the olfactory receptor cells with both the environment and the CNS provides a potential means of circumventing the BBB to transport neuroprotective compounds to the brain tissue (De Wolf 2007).

However, a relatively wide volume of literature reports that the CSF is drained into the lymphatic vessels and also the nasal mucosa by the olfactory pathways. In fact, a lymphatic network is normally observed near the olfactory nerves at the nasal mucosa which plays the major role in CSF transport (Liu et al. 2012). Paracellularly transported pharmaceutical agents across the olfactory epithelium which enters into the perineural space can penetrate into the brain or can be cleared through the CSF flow into the lymphatic vessels and consequently into the systemic circulation (De Wolf 2007).

## Vaccine delivery via nose

Vaccination is a method of inducing protective immunity against specific diseases by using non disease causing microorganisms, live-attenuated vaccine microorganisms, or subunits of microorganisms. Owing to the low stability of oral vaccines in the gastrointestinal tract and the low absorption through the mucosal surfaces, most of the conventional vaccines are administrated by parenteral injections. However, parenteral administration also has some disadvantages, including the high cost of production,

low patient satisfaction, and need for trained personnel to inject the vaccine. Hence, other alternative routes have largely been considered for injection (Amidi et al. 2006). In the last few decades, because of the possibility of receiving both the local and systemic immune responses, the application of nasal route for the delivery of vaccines has attracted the attention of many pharmaceutical companies (Illum 2007). The nasal mucosa is often the first contact point for inhaled antigens; therefore intranasal vaccination has emerged as the most effective route to induce the mucosal immune responses in the respiratory tract where there are frequent occurrences of primary bacterial and viral infections (Fukuyama et al. 2015).

The main nasal immune responses are believed to be elicited in the nasal associated lymphoid tissue (NALT) which can capture foreign materials from the epithelial surfaces. Thus, the nose contains a large proportion of dendritic cells capable of managing and spreading immune responses (Lee et al. 2015). In addition, mucosal vaccination has many advantages compared to parenteral pathway. Easy administration, low side effects, possibility of self-administration, and improved patient satisfaction are some of these advantages (Gonçalves et al. 2010).

## Nanoparticles

### Polymeric nanoparticles

Polymeric nanoparticles are a group of colloidal particles with a size range of 10 to 1000 nm and various shapes, including spherical or elongated. Therapeutic agents can be encapsulated within nanoparticles or incorporated via surface adsorption or surface conjugation (Adibkia et al. 2009; Salatin et al. 2015b). The integration of therapeutic agents into the nanoparticles with desirable shape, size, and surface physicochemical characteristics imposes a significant effect on improving their solubility, circulation half-life, bio-distribution and reducing the immunogenicity (Sun et al. 2014, Salatin et al. 2015a). Moreover, the uptake of nano-carriers which have optimized physicochemical properties can efficiently be achieved by cells in comparison with macromolecules (Barzegar et al. 2009; Mudshinge et al. 2011).

Recently, there have been many that rather than the soluble form, the nanoparticulate-based systems may be more efficient in transporting the drugs and vaccines through the nasal mucosal barrier (Nagamoto et al. 2004; Corace 2012). The average size of pores in the nasal mucus is approximately 150 $\pm$ 50 nm. Thus, a formulation comprising of nanoparticulate carriers can be used for the efficient delivery of drugs to the pre-intended target sites (Anand et al. 2012). Nanoparticles are applied by either carrying an encapsulated drug through the mucosal barrier or by increasing the residence time inside the nose (Ali et al. 2010). Hence, the success in controlling the progression of the disease depends on the study of the interactions between the nanoscopic materials and the nasal milieu, targeting specific receptors on the cell surfaces, mechanism of drug release, and the stability of biopharmaceuticals in the nasal cavity (Kumar et al. 2014).

In addition to the local and systemic effects produced by nanoparticles, many experiments performed *in vivo* have shown which nanoparticulate carriers can enhance the direct nose-to-brain delivery of drugs in comparison with the equivalent drug solutions (Mistry et al. 2009). In fact, the size of nanoparticles can mediate the passage of the drugs through the biological barriers, including BBB. It is yet unknown whether the drugs incorporated into the nanoparticles are being released in the nose space, or the nanoparticles containing drug are transported by the olfactory or the trigeminal nerves into the CNS, wherein the drug is later released (Wen 2011).

On the other hand, nanoparticulate carriers possess several particular properties that make them ideal vaccine adjuvants for inducing good immune responses (Peek et al. 2008). This is because the nanoparticles can preferably be transferred via the lymphoid tissue found in the nose (NALT) (Illum 2007). In addition, nanoparticulate carriers can efficiently amplify the amount of antigen transferred to the immune system, and also improve the controlled release of encapsulated antigen for a longer period of time (Panyam and Labhasetwar 2003). It has been shown that delivery systems with the average diameters in the size range of hundreds of nanometer have a larger potential to pass through the epithelia than the particles in the micrometer size range (Zhang et al. 2004) so that, the uptake of microparticles with sizes smaller than 10 μm is thought to result from M-cells covering the NALT and transmitted to sub-mucosal layer. However, in the case of the nanoparticles, besides the M-cell-associated phagocytosis, the epithelial cells participate in the transport of nanoparticles by internalization (Donovan and Huang 1998; Chaturvedi et al. 2011).

Despite all the aforementioned advantages, the mucociliary clearance has always been a serious limitation for the delivery of nasal drug by the nanoparticles. There exist several strategies for the reduction of the clearance of nanoparticle formulations from the nasal cavity, resulting in the high absorption of drugs. For example, the application of muco-adhesive polymers in designing the nanoparticulate systems plays a key role in improving the residence time and the action of these formulations on the nasal mucosa (Ozsoy et al. 2009).

## Mucoadhesive dosage forms

Mucoadhesive dosage forms may be designed to provide a controlled rate of drug release through the mucosal surface for improved therapeutic outcome via increased retention at the site of application or absorption. The mucoadhesive ability of a drug delivery system depends on many factors, including the nature of the mucosal tissue and the physicochemical characteristics of the used polymeric material (Nep and Conway 2011). It has been suggested that mucoadhesive polymers might be useful in the development of the appropriate mucoadhesive dosage form. Mucoadhesive polymers are a group of natural or synthetic macromolecules, capable of attaching with the mucus layer covering the mucosal epithelial surface through attractive and repulsive molecular interactions (Amidi et al. 2006; Vashist and Ahmad 2013). Some of the dosage forms, including tablets, gels, and films have been widely developed as mucoadhesive formulations (Fini et al. 2011). Due to the limitations of the size and thickness of the tablets, and the fact that they must be sufficiently soft to be acceptable to patients and not cause any side effects, mucoadhesive injectable gels have been presented as good alternatives to solid forms (Salamat-Miller et al. 2005). Gels are a group of promising semi solid forms that have the advantage of easy dispersion throughout the mucosa surfaces (Boddupalli et al. 2010). Besides, the viscosity of these forms provides a higher and softer surface area for drug release and a prolonged residence time of the formulation at the site of absorption (Khairnar and Sayyad 2010).

## Gel versus hydrogel

A usual misunderstanding in the field of polymer science is the simultaneous employment of the terms 'gel' and 'hydrogel'. Although gels and hydrogels are chemically similar, they are physically different. Commonly, the term gel is used for all types of semisolid systems which form a gelatinous appearance, while hydrogel is a subdivision of the gel which swells in water, and is made up of three dimensional cross-linked configuration of hydrophilic polymers (Gupta et al. 2002). Generally, hydrogels may show high volume transition in response to the various physical and chemical stimuli, including temperature, electric or magnetic field, sound, light, pressure, pH, molecular species, and ionic strength. Thus, hydrogel systems can be designed with controllable responses (like shrinking or expansion) to specific changes in the external environmental conditions. The ever-growing hydrogel technology is based on the simple reaction of one or more monomers to produce cross-linked polymeric network with three-dimensional network, capable of absorbing high amounts of water or biological fluids (Ahmed 2015).

In comparison with the other synthetic materials, hydrogels resemble a native tissue microenvironment because of their porous and hydrated molecular network (Jagtap et al. 2015). Their affinity for water arises from the hydrophilic agents attached to the polymeric backbone, such as –OH, –CONH–, $–CONH_2–$, and $–SO_3H$ used in the preparation of hydrogel networks. These polymers are of two main categories of materials, including synthetic polymers or natural polymers, especially those intended for drug delivery applications and biomedical areas. Although hydrogels made from natural polymers may display immunogenicity or induce inflammatory responses because of the presence of immunogen moieties, they also do represent many beneficial properties, such as being commonly non-toxic and biocompatible. Passive diffusion is the most well-known mechanism of drug release from hydrogel matrix. As a result, molecules with different size and properties are able to easily diffuse into/out of the hydrogel systems, resulting in the exchange of solutes with external phase (Hamidi et al. 2008).

Gelation time and viscosity of hydrogel systems are two significant factors which must be considered for the nasal delivery, as these factors are correlated to the mucosal clearance time and dosing convenience. The formulation of liquid nasal hydrogel with lower viscosity and short gelating time can be well-distributed on the mucosal layer, and swiftly form a thin hydrogel membrane exposed to nasal temperature, resulting in the tight adhesion of bioactive molecules to the mucosal surface (Wu et al. 2012). Hydrogels are widely studied as matrix systems for the controlled release of macromolecules, and can be molded as matrix, film, or micro/nanoscale constructs; on this basis, they have been extensively classified in the literature (Ahmed 2015). The various forms of hydrogel-based systems depend on the specific route of administration (Gupta et al. 2002).

Among the hydrogel polymers frequently utilized for the preparation of the nasal particulate drug delivery systems, the positively charged polymers are more considered, since the hydrogel nature of these polymers can result in the opening of the tight junctions and their close touch with the negatively charged mucosal layer (Chaturvedi et al. 2011). It seems that the use of the benefits derived from hydrogel, in combination with nanoparticles, to design novel systems, plays an important role in improving the absorption of drugs. Two distinct nanoparticle-hydrogel designs can be recommended. They are classified as: hydrogel nanoparticles and nanoparticles entrapped in a bulk hydrogel framework.

## Hydrogel nanoparticles

In most hydrogel dosage forms used for therapeutic objects, response to stimuli from the environment is very slow. One efficient approach to overcome this limitation is to design hydrogel structures at the micro- and nano-sizes (Bamrungsap et al. 2012). Hydrogel nanoparticles have gained noticeable interest as one of the most potential nanoparticulate drug delivery systems that combines both the properties of a hydrogel system (e.g. hydrophilicity and large affinity for water absorption) and a nanoparticle (e.g. ultra small size). These nanoscopic constructs are also referred to as polymeric nanogels or macromolecular micelles due to the cross-linked and mesh-like network which they create. The superior features of nanogels include:

(1) Tendency to form aqueous solutions, high colloidal stability *in vivo,* and possibility of obtaining an excellent chance to internalize and carry the macromolecules, such as proteins and peptides.
(2) High drug loading without chemical reactions and release of incorporated agents in a controlled behavior at the target site.
(3) Ease of surface modifications by a wide range of site specific ligands in order to improve targeted delivery in the body.
(4) Perfect candidates for internalization by the cells like dendritic cells, via phagocytosis.
(5) Potential for administration through different pathways, such as oral, parenteral, nasal, pulmonary, and ocular (Kabanov and Vinogradov 2009; GonÇalves et al. 2010; Debache et al. 2011; Rigogliuso et al. 2012).

A wide range of natural or synthetic polymers may be used for the preparation of nanogels. Among these polymers, polysaccharides are the most often utilized ones (Gonçalves et al. 2010). Polysaccharide materials can be divided into two groups, including polyelectrolytes and non-polyelectrolytes. Polyelectrolytes can be additionally classified based on their intrinsic charge, including cationic (chitosan), anionic (alginate, heparin, pectin, hyaluronic acid), and neutral (pullulan, dextran) (Liu et al. 2008). Among the most frequently used synthetic polymers, block copolymers, comprising two or more parts of simple polymers that unite together to form various arrangements, attract the most attention. Block copolymers can be categorized based on the number of subunits linked along the chain (Gonçalves et al. 2010). Debatable findings regarding the application of nanogels for the delivery of therapeutics through the nasal route have been published (Kumar et al. 2014). The following section describes the main polysaccharides used in the development of nasal nanogels and the various applications of nanogels in the field of nasal delivery applications are summarized in Table 1.

## Cholesteryl group-bearing pullulan-based hydrogel nanoparticles

Cholesteryl group-bearing pullulan (CHP) is a universal protein-based antigen delivery system used as an adjuvant-free nasal vaccination. CHP can self-assemble in water into the nanoparticles and encapsulate pharmaceutical payloads in the interior space through hydrophobic interactions. Therefore, it protects the loaded cargo against mechanical/chemical or enzymatic degradation, and acts as an ideal vehicle for the delivery and release of encapsulated materials in a controlled release profile (Shimizu et al. 2008).

The most important property of CHP nanogels is its chaperon-like activity, since CHPs are able to entrap various proteins, such as cytokines, enzymes, and vaccine antigens via the hydrophobic interactions within a hydrated polymer network without aggregating and releasing them in the native form (Ikuta et al. 2002). Based on these properties, CHP nanogels can be used as promising nanovehicles for the delivery of proteins, particularly in the field of cancer vaccine development (Nochi et al. 2010).

It has been discovered that CHP nanoparticles are effectively transferred to antigen-presenting cells, such as dendritic cells and/or macrophages, and this allows for a stronger immune response (Kobiyama et al. 2014).

Besides, the cationic type of CHP nanogels (cCHP) can be obtained by the addition of amine groups to the CHP nanogels. The cCHP nanogels capable of effectively carrying vaccine antigen to the negatively charged nasal epithelium after intranasal administration (Nochi et al. 2014). A schematic representation of CHP and cCHP nanogels is shown in Figure 1.

Although the use of cationic nanogels does not increase the activation status of the intranasal dendritic cells, however they can importantly enhance the immunogenicity of nasal vaccine owing to the improved antigen residence time in the nasal cavity, which leads to better antigen transport into the nasal dendritic cells (Giese 2013).

Daiki Nagatomo et al. reported the immune-enhancing ability of tumor necrosis factor-α–encapsulated CHP nanoparticles to act as a vaccine adjuvant for inducing systemic IgG1, as well as mucosal IgA via the nasal route of administration in mice. As a result, these nanoparticles promoted antigen uptake by dendritic cells and moderately increased the expression of inflammation-related genes in the NALT (Nagamoto et al. 2004). Besides, promising results were intranasally obtained with cCHP nanogel as an antigen-delivery vehicle carrying the subunit fragment of *Clostridium botulinum* type-A neurotoxin BoHc/A

**Table 1** Selected studies on utilization of hydrgel nanoparticles for nasal drug delivery

| Types of nanogels | Payload | Significant outcome | Reference |
|---|---|---|---|
| CHP | Tumor necrosis factor-α | Superior storage stability, high immune-increasing capacity for stimulation $IgG_1$ and mucosal IgA responses | (Nagatomo et al. 2015) |
| cCHP | Non-toxic subunit fragment of clostridium botulinum type-A neurotoxin BoHc/A | Antigen adhesion to the nasal epithelium and its efficient uptake via mucosal dendritic cells after release from nanogel, induction of the specific IgG and secretory IgA antibody responses with no co-administration of mucosal adjuvant | (Nochi et al. 2010) |
| cCHP | Pneumococcal surface protein A (PSpA) | Prolonged retention of PSpA in the nasal cavity compared to PSpA alone, efficient induction of PspA-specific serum IgG associated with mucosal secretory IgA antibody | (Fukuyama et al. 2015) |
| Alginate coated chitosan nanogel | Recombinant NcPDI | Protection of all mice against infection with Neospora caninum tachyzoites | (Debache et al. 2011) |
| Chitosan | Didanosine | Higher brain/plasma, olfactory/plasma, and CSF/plasma concentration post nasal administration | (Al-Ghananeem et al. 2010) |
| Thiolated chitosan | Leuprolide | Increasing leuprolide transport across nasal mucosa and its plasma concentration compared to nasal solution alone | (Shahnaz et al. 2012) |
| Chitosan | Olanzapine | Enhanced systemic absorption of drug | (Baltzley et al. 2014) |
| Chitosan | Cholinesterase inhibitor | Effective delivery of cholinesterase inhibitor across nasal mucosa to reach the brain | (Sharma et al. 2007) |
| Chitosan | Memantine hydrochloride | Potential to treat alzheimr disease by transport through olfactory nasal route to the brain | (Ruby and Pandey 2014) |
| Chitosan | Plasmid DNA | Evoking humoral and cellular immune responses, efficient DNA vaccine vehicle, and adjuvant for nasal immunization | (Khatri et al. 2008) |
| Chitosan | Piperine | Efficient, safe, and non-invasive piperine delivery with 20-times decrease in oral dose | (Elnaggar et al. 2015) |
| Mannosylated chitosan | Anti-GRP DNA | Significant titers of anti-GRP IgG, ability to suppress the growth of tumor cells | (Yao et al. 2013) |
| Thiolated chitosan | Selegiline hydrochloride | Reducing the oxidative stress and restoring the activity of mitochondrial complex, a severe reduction in the period of immobility time upon treatment, as a promising treatment for emerging diseases such as depression | (Singh et al. 2015) |
| Chitosan | A/H5N1 infulenza vaccine | Stimulating and increasing the rate of specific immune responses and HI titer in mice models | (Dzung et al. 2011) |
| Chitosan | Tetanus toxoid antigen | A prolonged humoral immune response (IgG levels) and the mucosal responses (IgA levels) compared to the fluid vaccine | (Vila et al. 2004) |
| Alginate | Venlafaxine | Higher brain/blood ratio for intranasal venlafaxine nanoparticles compared to intranasal venlafaxine solution | (Haque et al. 2014) |

(CHP_BoHc/A). It is important to note that, the cCHP nanogels with positive zeta-potential were very effective in interacting with the membranes of HeLa cells. BoHc/A released from the cCHP nanogels was continuously attached to the nasal epithelium and was allowed to be efficiently internalized by the mucosal dendritic cells without co-administration of mucosal adjuvant.

Most importantly, this study revealed that CHP_BoHc/A constitute a powerful tool to induce a robust botulinum-neurotoxin-Aneutralizing serum IgG and secretory IgA antibody responses (Nochi et al. 2010). Figure 2 shows the effective uptake of cCHP nanogel-vaccine antigen complex by nasal dendritic cells for the induction of antigen specific immune responses.

*Streptococcus pneumonia* is recognized as a problematic pathogen because of lots of capsular polysaccharides which may be matched with virulent diseases in men. Clinical trials to overcome such problems have led to the preclinical development of the global serotype-independent pneumococcal vaccines which consist of a surface protein common

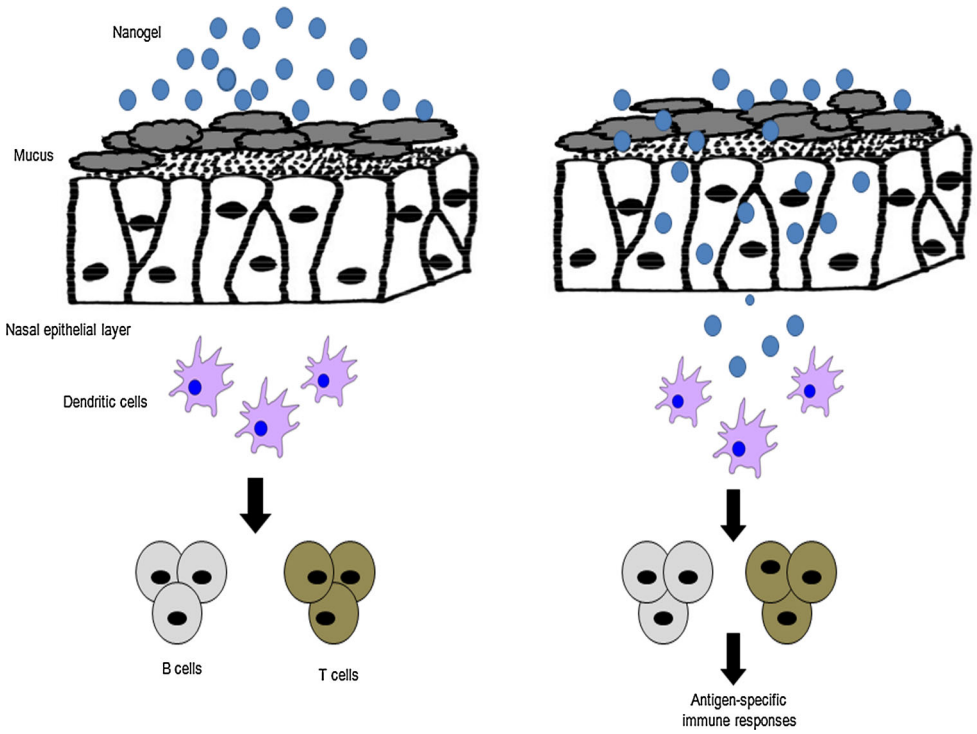


**Fig. 1** Schematic representation of CHP and cCHP created from a non-ionic and cationic type self-assembled nanogel of cholesteryl-group and amino group added chloesterol pullulan (CHPNH2), respectively

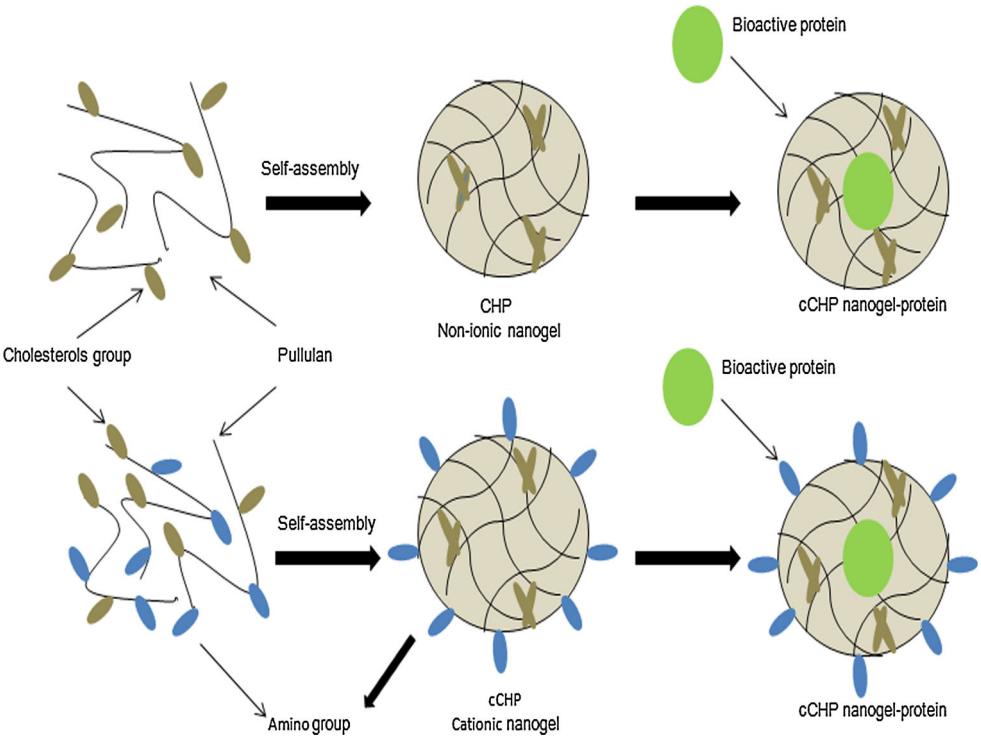


**Fig. 2** Schematic representation of the immunological response of nasal nanogel vaccine delivery system at the mucosal surface by intranasal administration

among all strains. Pneumococcal surface protein A (PspA) expressed on the surfaces of all capsular serotypes of *S. pneumonia* has been found as a potential candidate protein that can induce protective immune responses. Results from a comprehensive re-evaluation study provided evidence that a cCHP nanogel is a promising candidate carrier of PspA to induce systemic and nasal mucosal Th17 responses, and also to prevent both nasal colonization and invasive diseases, unlike mice vaccinated with PspA plus a potent adjuvant (cholera toxin), PspA alone, or phosphate buffered saline only. It has been demonstrated that the survival rates of the mice immunized with cCHP-PspA or

PspA- cholera toxin were statistically improved when the values were compared with the group immunized with PspA alone (Kong et al. 2013). Another alternative example is the work of Fukuyama et al. which showed that the delivery of PspA to the nasal mucosa was potentiated in the presence of cCHP nanogel, which resulted to an increase in efficacy of nasal vaccination against pneumococcal infection in nonhuman primates. These PSpA-nanogels showed a long-term retention in the nasal cavity without any deposition in the olfactory bulbs or brain. Besides, the nanogels were able to induce PSpA specific mucosal and systemic antibody responses (Fukuyama et al. 2015).

## Chitosan-based hydrogel nanoparticles

Chitosan is an effective biopolymer with various structural possibilities for modifications that can be used to create new materials with different features, functions, and applications in many science fields, particularly in medicine. It is mainly composed of D-glucosamine repeating units and is also known as a linear, non-toxic, biodegradable, biocompatible polysaccharide. Chitosan is formed by the partial deacetylation of chitin, and the presence of amine groups offers it a net positive charge (Sajeesh and Sharma 2006). This feature makes chitosan an ideal polymer to interact with the negatively charged therapeutic molecules and macromolecules (Vashist and Ahmad 2013). It has been shown that chitosan can be simply processed into various dosage forms, including gels, sponges, membranes, beads, and scaffolds. On the other side, the viscosity of chitosan and its interaction between the positively charged amino groups and the negatively charged residues on the mucosal surface, renders it its mucoadhesive features (Khom et al. 2014). These functional groups can be chemically modified for creating carrier systems with particular properties which are suitable for the nasal, oral, ocular, and transdermal administrations (Hamidi et al. 2008; Amidi et al. 2010). It has been discovered that chitosan nanoparticles can pass through the nasal epithelia, and hence, deliver the incorporated cargo, especially proteins and peptides (Vila et al. 2004). One interesting characteristic of chitosan is its ability to hydrate and to form gels, which is mainly due to its viscouse nature. When it is used as a semisolid or in solution form, it can form a gel-like structure at the site of administration (Deepak et al. 2012).

The use of peptide (TAT) tagged PEGylated chitosan nanoparticles with size ranges from 5 to 10 nm was demonstrated to improve the delivery of siRNA into the cerebral cortex and cerebellum after 4 h of intranasal adminstration. In fact, the mucoadhesive characteristics of chitosan show an advantage for intranasal delivery. Moreover, TAT peptide incorporated into nanoparticles provide a simple and versatile moiety for cell penetration, resulting in the improved permeation of nanoparticles across the BBB *in vitro* and *in vivo* (Malhotra et al. 2013).

However, the strategy of thiolation of chitosan has been shown to improve the *in situ* gelling features due to the ability of thiol groups to undergo redox reactions at physiological pH-values, which leads to the formation of intermolecular and intramolecular disulfide bridges (Deepak et al. 2012).

The authors reported the efficiency of thiolated chitosan nanoparticles prepared by the method of ionic gelation for increasing the transportation of leuprolide across porcine nasal mucosa by 2.0 and 5.2 folds, in comparison with leuprolide solution and unmodified nanoparticles, respectively. The differences in the results obtained can in part be explained by the unique mucoadhesive properties of thiolated chitosan nanoparticles, since they can interact with cysteine rich subdomains of mucus glycoproteins, hence leading to the formation of disulfide bridges (Gul et al. 2012).

In addition, it was investigated that thiolated chitosan nanoparticles significantly improved the nose-to-brain delivery and antidepressant activity of selegiline hydrochloride because of their excellent mucoadhesion and *in situ* gelling properties (Singh et al. 2015).

Similarly, chitosan-N-acetyl-L-cysteine nanoparticles (140–210 nm in diameter) have been developed as a new insulin-delivery vehicle. *In vitro* release studies displayed an initial burst followed by a slow release of insulin, and the absorption of insulin through the nasal mucosa was in a greater amount compared with the unmodified chitosan nanoparticles and control insulin solution. Wang et al. also described that thiolated nanoparticles with a high thiol-group content exhibited relatively high levels of mucoadhesion when compared with the unmodified chitosan nanoparticles and nanoparticles with a low thiol-group content (Wang et al. 2009).

In another study, chitosan nanoparticles have been investigated to be promising carriers for improving the systemic absorption and concentration of didanosine in brain tissue, olfactory bulb, and CSF when compared with the intravenous (IV) administration of didanosine solution after intranasal administration (Al-Ghananeem et al. 2010).

Chitosan nanoparticles adsorbed with ovalbumin and cholera toxin have been reported to be efficient vehicles in targeting the NALT, and the induction of the immune responses (IgG and IgA antiodies) was comparable with the intranasal administration of intraperitoneal injection (Nagamoto et al. 2004). Similar results were obtained when chitosan nanoparticles were used to provide an improved access of the incorporated antigen to the nasal immune system. This study has shown which mechanism of action of chittosan nanoparticls is not significantly affected by the differences in the molecular weights of chitosan. However,

the levels of immune responces at early time points were generally higher in mice immunized intranasally with low molecular weight chitosan particles due to the inherent immunostimulatory characteristics of chitosan or due to a different release rate of antigen from low vs. high molecular weights chitosan nanoparticles. Here, nanoparticles were more efficient to pass across the nasal epithelia, yielding a high and long-term humoral immune response than the response obtained for the fluid vaccine. Besides, there is a possibility that chitosan nanoparticles could be internalized by NALT cells (Vila et al. 2004). Also, the vaccination of mice by alginate or alginate mannose-coated chitosan nanogels containing recombinant NcPDI antigen that protected 100% of the challenged animals against infection with Neospora caninum tachyzoites was investigated. Such nanosized carriers are ideal options for the uptake via cells incorporating extracellular substances (that is, dendritic cells) through phagocytosis (Debache et al. 2011). Another report demonstrated the adjuvant effect of alginate coated-chitosan nanoparticles associated with the recombinant hepatitis B surface antigen (HBsAg) by measuring the amount of humural mucosal immune responses. This delivery system was able to encapsulate HBs antigen with a high efficiency, and was shown to be internalized by the NALT cells. The results suggest that coating of alginate can be used to modify the profile of antigen release from the chitosan nanoparticles, and also to achieve the protection of antigen against the enzymatic degradation during their passage throughout the mucosal surface of the nasal (Borges et al. 2008).

### Alginate-based hydrogel nanoparticles

Alginate is an anionic unbranched biopolymer, composed of guluronic and mannuronic acid residues (Sangeetha et al. 2010). Owing to its biocompatibility, biodegradability, non-antigenicity, gelation ability and mucoadhesive properties, alginate has been extensively proposed to be applied in designing the novel drug delivery systems. Besides, the anionic nature of alginate renders it a high ability to interact with cationic components. Thus, it can be used in preparing delivery systems for the incorporation of cationic therapeutic molecules (Sun and Tan 2013). Alginate nanoparticles can prolong the antigen release and increase the immune responses when compared with the conventional vaccines, owing to their adjuvant characteristics (Sarei et al. 2013). More recently, alginate nanoparticles have been developed for the nose-to-brain delivery of venlafaxine drug (VLF). The prepared nanoparticles had a mean particles size 173.7 nm and demonstrated a high potential to deliver venlafaxine to the brain by rapid extracellular or intracellular delivery along the olfactory nerves bypassing the systemic circulation in comparison with the VLF solution i.n. and VLF solution i.v. However, the reported data confirmed that during nasal breathing, a fraction of the small particles can pass across the nasal cavity and deposit in the lungs, and drug absorption in the olfactory region of nasal cavity is lost (Haque et al. 2014).

## Composites

### Hydrogel-nanoparticle composi

Modern technologies rely on the preparation of new materials, and these can easily be the ingenious combination of known components. Over the last decades, various applications of hydrogels have emerged, particularly in nasal drug delivery researches. Most of the fast-responding hydrogels release a large percent of drug in a short period of time. Hence, a novel strategy for the reinforcement of polymeric hydrogels, and the inclusion of several multiple capabilities would be to concentrate on integrating nanoparticles within the hydrogel structure (Gaharwar et al. 2014). In fact, the development of injectable hydrogel-based nanocomposites, also referred to as hybrid hydrogels, exhibits an attractive scenario for the design of a new class of minimal invasive drug delivery carriers for *in situ* drug release (Giordano et al. 2011). Besides, the structural combination of hydrogel and nanoparticle may allow for the improvement of mechanical properties of hydrogel, and simultaneously the reduction of aggregation of nanoparticles. As shown in Figure 3, a diverse range of nanoparticles may be immobilized in a hydrogel matrix covalently or non-covalently (Thoniyot et al. 2015). Since drug delivery by the nanoparticulate systems through the nasal mucosa is limited by the mucociliary clearance, integration of nanoparticles into a mucoadhesive hydrogel would be an alternative effective solution. In a recent study, polycarbophil®AA1 having superior mucoadhesive property was proved to be more effective in improving the residence time and avoiding the mucocilliary clearance of risperidone-loaded solid lipid nanoparticles. The *in vitro* diffusion and *ex vivo* release behavior of prepared nanoparticle-hydrogel composite through the nasal mucosa showed a controlled release of risperidone, following a long contact time (Jagtap et al. 2015).

## Conclusion

Intranasal medication delivery is simply an alternative option for the local, systemic, and brain delivery of bioactive molecules in order to achieve a desired clinical effect. Drug dosage forms are cleared rapidly from the nasal cavity after the intranasal administration, resulting in

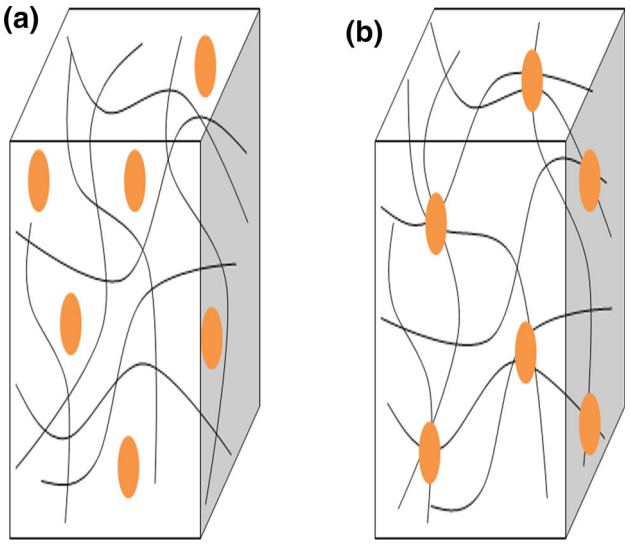


**Fig. 3** Schematic representation of nanoparticle-hydrogel conjugates. **a** Nanoparticles non-covalently embedded in a hydrogel network, **b** Nanoparticles covalently embedded in a hydrogel network

the reduced drug absorption. Various mucoadhesive nanosystems are suited to increase the residence time of drug formulation at the nasal mucus site over many hours and days. Among the available nanosystems, hydrogel nanoparticles and nanocomposites exhibit stimuli responsive and multi-functional properties including ease of design, affordability, possibility to incorporate a variety of drugs and suitability to achieve the ideal of a controlled release of biopharmaceuticals, making them ideal for drug/vaccine delivery by the nasal route. However, the toxicity, transport as well as uptake by the NALT cells of nanogels and nanoparticles entrapped in the hydrogel network in the nasal cavity or CNS have not been widely evaluated, and this demands more detailed considerations; thereby being a significant issue for future researches. Moreover, the hydrogel nanosystems-related drug market is emerged by improving the delivery to CNS and finding ways to cross the BBB, especially for the treatment of tumors CNS.

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