



# A clinical perspective of chitosan nanoparticles for infectious disease management

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## Abstract

Infectious diseases and their effective management are still a challenge in this modern era of medicine. Diseases, such as the SARS-CoV-2, Ebola virus, and Zika virus, still put human civilization at peril. Existing drug banks, which include antivirals, antibacterial, and small-molecule drugs, are the most advocated method for treatment, although effective but they still flounder in many instances. This calls for finding more effective alternatives for tackling the menace of infectious diseases. Nanoformulations are progressively being implemented for clinical translation and are being considered a new paradigm against infectious diseases. Natural polymers like chitosan are preferred to design nanoparticles owing to their biocompatibility, biodegradation, and long shelf-life. The chitosan nanoparticles (CNPs) being highly adaptive delivers contemporary prevention for infectious diseases. Currently, they are being used as antibacterial, drug, and vaccine delivery vehicles, and wound-dressing materials, for infectious disease treatment. Although the recruitment of CNPs in clinical trials associated with infectious diseases is minimal, this may increase shortly due to the sudden emergence of unknown pathogens like SARS-CoV-2, thus turning them into a panacea for the management of microorganisms. This review particularly focuses on the all-around application of CNPs along with their recent clinical applications in infectious disease management.

**Keywords** Chitosan nanoparticles · Mucoadhesive delivery system · Vaccine vector · Wound dressing

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## Introduction

Infectious diseases can simply be defined as the transmission of pathogens like viruses, bacteria, parasites, and fungi or toxic products from an infected individual to a healthy individual. It has emerged as a disturbing area for medical society by being responsible for around 15 million deaths worldwide. Infectious diseases are life-threatening, so the main objective is to eliminate these disease-causing pathogens [1]. Dealing with these pathogens mostly involves the development of an advanced range of antibacterial and antiviral drugs. However, the accepted antibiotics/vaccines/antivirals implemented as antimicrobials show shortcomings like low bio-availability, untimely degradation, reaching of minimal dosage to the infection site, and the rise of drug-resistant strains [2]. Therefore, to combat these lacunas, the scientific society has been improving the existing therapies by designing and favoring alternative strategies. In this regard, the most recent and upcoming way out is the use of nanotechnology [3].

The relevance and involvement of nanoscience and nanotechnology in providing considerable benefits to society have increased manifolds in the last few decades [4]. The size of the nanomaterials ranges from 0.1 to 100 nm and are embedded with essential properties that arise due to their small sizes like physical strength, magnetism, electrical conductance chemical reactivity, and optical effects. Exploring these properties various types of nanodevices and nanomaterials can be produced. The entire periodic table of elements can be used for the production of nanodevices depending on the target materials [5]. Nanomaterials are strong as well as lightweight making them ideal for the construction and automotive industries. In textile industries, nanomaterials coating on materials for sports equipment and street fashion makes them enduring, water resistant, and stain resistant. Moreover, the antibacterial property of coating nanomaterials on fabrics is being well-studied by many groups. [3, 6, 7]. Quantum dot (QD) technology for LED smartphones and screens relies on nanotechnology to enhance its performance (QDs show precise color production and high resolution). In industrial products, to enhance physicochemical properties like luster, durability, and water resistance, nanomaterials have proved to be advantageous, e.g., in paints to enhance durability silica nanoparticles are added [8]. Titanium oxide and zinc oxide nanoparticles are broadly added to sunblock and creams, to act against UV rays in consumer products [9].

Environmental pollution is a major side effect of industrialization. Different industries release toxic effluents like erythrosine, thymol blue, and methyl orange which contaminate the environment, especially the water bodies [10]. An environment-friendly solution to this problem is to design photocatalytic materials which can degrade these toxic chemicals in presence of visible light [11]. In this context, nanoparticles have been an ideal choice to act as photocatalysts to deal with this menace.  $\text{Nd}_2\text{Sn}_2\text{O}_7$  (Neodymium tin heptaoxepane)-based nanostructure was synthesized by Ajabshir et al. [12] using grape juice as green fuel for the degradation of erythrosine. Similarly, another new photocatalytic nanocomposite of dysprosium oxide–silicon dioxide ( $\text{Dy}_2\text{O}_3\text{--SiO}_2$ ) could display enhanced

photocatalytic activity [10]. In a recent study, Ajabshir and his group were also involved in formulating Zn–Co–O nanostructures that could degrade the pollutant acid brown 14 [10]. Nanostructures like  $\text{Lu}_2\text{Cu}_2\text{O}_5$  and  $\text{MnWO}_4$  both synthesized by green technology emerged as new candidates for removing organic pollutants in water bodies [10, 13].

Nanomaterials serve as solutions to disease treatment, diagnostics, and prophylactics. Nanotechnology helps in monitoring individual cells present in the body [14]. Nanoprobes in association with biomarkers help in early detection and facilitate nanobiosensors in the field of genomics and proteomics which carry the potential for prevention and disease control [15]. Developed countries are now investing in cancer drug delivery via nanoparticles, e.g., US Food and Drug Administration (FDA).

In the context of infectious diseases, nanomedicine offers new tools for their prevention, detection, and treatment, managing to lessen the mortality ratios thereby improving the quality of lifestyle [16]. Nanovehicles are not only efficaciously used as antibacterial or antiviral agents but also are helpful to overcome drug resistance challenges by delivering the agents specifically to the bacterial community efficiently [17]. Due to the emergence of new strains of pathogenic organisms, the problem arises in immunizing the disease. Recently, remarkable progress has been made in the development of nanoparticle-based vaccine candidates to improve the vaccine efficacy of existing vaccines for better immunization strategies and targeted delivery [18]. These vaccine carriers are responsible for eliciting desired immune responses at the cellular level. Owing to their nanostructure, these carriers are easily internalized by antigen-presenting cells [19] and also assist in protecting encapsulated antigens from premature degradation, facilitate better antigen uptake, control release, and also act as adjuvants [20]. Moreover, low toxicity and ease of modification and functionalization add to the dynamic nature of nanovaccines [21].

In the last decades, there has been an advancement in the strategies for the treatment of chronic wounds. Local infection with a prolonged wound-healing tendency may lead to sepsis in severe which can be life-threatening. Nanosystems possess a large area-to-volume ratio that helps in interacting with biological substances and releases the loaded active analytes in an orderly manner [22].

Of all the polymers used to formulate nanovehicles, naturally occurring chitosan is one of the most promising materials in the nanomedicine arena which is used to form chitosan nanoparticles (CNPs). This preference is attributed due to many factors of the polymer-like lack of toxicity, biocompatibility, and cost-effectiveness [23]. One of the significant characteristics of chitosan that lets CNPs be delivered to different transmucosal routes is its mucoadhesive ability [24]. The CNPs antibacterial activity is leaned down by various independent and organized factors, namely bacterial species both gram-positive and gram-negative, pH, cell growth phase, molecular weight, and zeta potential [25]. Exploring these properties, CNPs are being used to develop ideal antibacterial, antiviral, and vaccine delivery vehicles or are being used as wound-dressing materials for infectious disease management. Besides, CNPs are also implemented in the field of agriculture [26], as catalysts for bio-diesel production [27], for scaffolding and bioprinting [28], and as packaging material [29].

Many studies have evaluated all these properties and uses of CNPs independently. However, not many reviews are there which have explored the multifaceted use of CNPs against infectious diseases on one platform. Besides, the role of these magic bullets against new infectious diseases like *coronavirus* has not been explored much. This review gives us a glimpse of attempts made in this direction and their effectiveness and how in the future these CNPs can be modulated to formulate and design a new kind of therapeutic device against infectious disease.

### Factors affecting the antibacterial activity of chitosan

As chitosan is considered quite effective against microorganisms, many factors control the antimicrobial properties of chitosan as mentioned below:

#### Bacterial species

Possessing an extensive range of antimicrobial activity, chitosan demonstrates different effectiveness against different microorganisms. The range of minimum inhibitory concentration (MIC) in the case of fungi, is 10–5000 mg/L but in the case of widely used yeast, i.e., *Candida albicans* the MIC ranged from 1 to 3.5 mg/mL. Chitosan with a molecular weight of 43 kDa and a DA of 94% was noticed to be less resistant in gram-negative bacteria, however, in gram-positive bacteria it differed. A study scrutinized the activity of medium molecular weight (Mw) chitosan against gram-negative microorganisms of warm-water fish and it was found that in the case of *Aeromonas hydrophila* about 0.8% of chitosan subdued growth, whereas about 0.4% of chitosan subdued the growth of *Edwardsiella ictaluri* and *Flavobacterium columnare*. Therefore, it was projected that these discrepancy responses of bacteria were caused due to difference in hydrophilicity observed on the surface of the bacteria and negative charge distribution [30].

#### Cell growth phase

The growth phase of bacteria affects the sensitivity of chitosan. It was observed that the bacteria in the late log phase strike the sensitivity of the bacteria in the sight of inhibitors and the chitosan antimicrobial activity is also affected. Further, the susceptibility of *Escherichia coli* O157:H7 was observed and it was stated that in the mid-exponential phase the susceptibility of *E. coli* O157:H7 was maximumly tailed by the late-exponential phase, whereas the bacteria were found to be more resistant in the stationary phase. Alike results were obtained in the case of *Staphylococcus aureus*, where the bacteria are highest susceptible in the late-exponential phase than in the stationary phase. Variance in the bacterial susceptibility toward chitosan was due to cell surface electro-negativity [30].

## Molecular weight (Mw)

Studies have suggested that chitosan antimicrobial activity is severely affected when there is a variance in Mw. When the antimicrobial activity of chitosan was examined against *E. coli*, it was found that chitosan at lower Mw exhibits better antimicrobial activity. Conversely, in chitosan, bacterial growth can be observed at 90 kDa Mw. The antibacterial activity of chitosan oligomers in the case of gram-negative bacteria was witnessed to be increasing after there was a decrease in Mw but the same was not observed in gram-positive bacteria. According to a study, an enhanced antibacterial effect was observed in the case of *S. aureus* when the Mw was below 300 kDa [30].

## pH

We know that the antibacterial activity of chitosan is affected by the change in environmental pH. Chitosan is soluble in acidic solutions where it becomes polycationic when the pH is less than the pKa of chitosan which is 6.3–6.5. The antimicrobial activity of chitosan was discovered to be decreasing when there is an increase in pH and the antimicrobial action disappears as the pH reaches 7. This condition arises at pH 7, several amino groups become uncharged [30].

## Zeta potential

One of the crucial factors to maintain the balance in aqueous nanosuspension is zeta potential. Considering the reports, it has been proved that in CS-NPs, inhibition in bacterial growth can be observed as the zeta potential increases, as well as the size of CS-NPs is reduced. In contrast, another finding showcases that a rise in the concentration of CS was constructively associated with the size of the NPs [31].

However, an alternative study proved that the zeta potential helps in determining cellular interaction among molecules or charged ions. In the presence of positively charged ions, the zeta potential of the surface increases, however, negatively charged ions decrease the zeta potential. For instance, the zeta potential of the nanoparticles loaded with  $\text{Ag}^+$  was found to be highest because of its positive charged ions and  $\text{Fe}^{2+}$  was found to have the lowest zeta potential because of its negative charged ions and low molecular mass. Hence, it was proved that the zeta potential was directly proportional to the antibacterial activity of chitosan nanoparticles loaded with metal ions. Thus, zeta potential can be effortlessly connected with antibacterial activity [31].

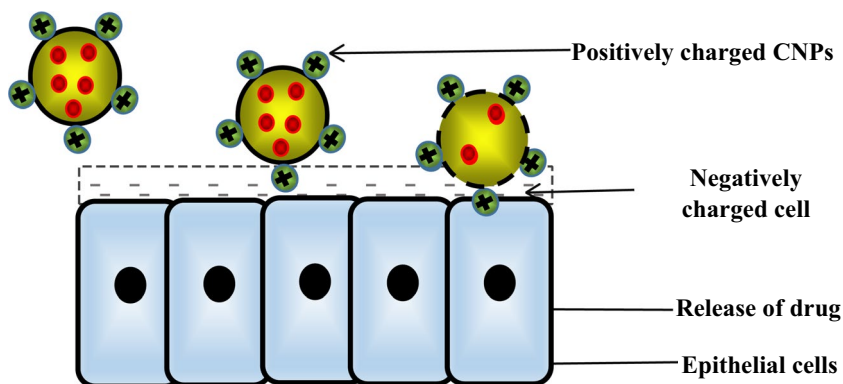
## Advantages of chitosan-based drug delivery systems

Chitosan nanoparticles (CNPs) jointly share the features of both CS and important properties like the smaller size, quantum size effects, and increased surface area of the NPs. Numerous techniques are employed for the production of CS-NPs such as microemulsion [32], spray drying [33], ionic gelation [34], phase inversion

precipitation [35], self-assembly [36], top-down [37], reverse micellar method and emulsion droplet coalescence [38], desolvation and nanoprecipitation [39]. CNPs are biodegradable, pocket-friendly, and biocompatible which make them an ideal choice for various biomedical applications like drug delivery of drugs, adjuvants, vaccines, and bio-imaging markers via oral or intranasal routes [40]. Similarly, CNPs are quite effective as oral drug carriers for proteins, owing to their ability to prevent untimely enzymatic degradation of payload in the gastrointestinal tract. CNPs have unique mucoadhesive properties, which is quite advantageous for their applications in different compartments of therapy. Chitosan can increase the adhesive efficacy of vaccine carriers for achieving long-term retention of the mucosa [41] (Fig. 1). A study has revealed that the adhesive properties of chitosan can be used for treating periodontitis, where it can change the response of the oral cavity so that antibacterial agents can be released and penetrate the bacterial biofilm to achieve the therapeutic effect [42]. Besides, CNPs also proved to be effectual for ocular-targeted drug delivery [43]. Moreover, open tight junctions between cells make CNPs an ideal therapeutic regime for crossing the blood-brain barrier [44].

### Mechanism of action of CNPs against infectious agents

The most widely accepted role of CNPs is as antimicrobial agents. These nanoformulations are quite effective against infectious agents owing to their better ability to interact with bacterial cell membranes or cell walls. The antimicrobial action of CNPs can be observed through the electrostatic interaction between the amino groups of glucosamine (positively charged) of CS with the cell membrane (negatively charged) of the bacteria. This electrostatic interaction introduces various modifications in membrane permeability and discrepancy on the cell surface which successively leads to cell death and osmotic imbalance. This

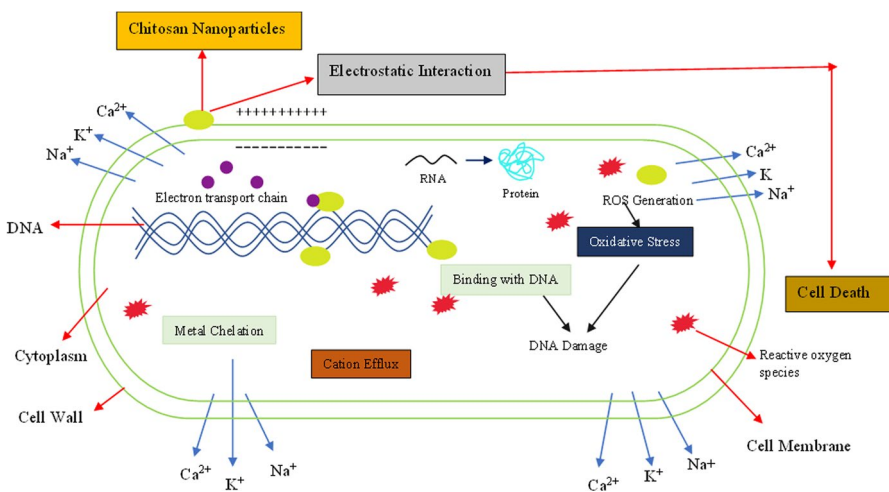


**Fig. 1** Mucoadhesive nature of CNPs. Chitosan has  $-OH$  and  $-NH_2$  groups, which endows them with the ability to form hydrogen and covalent bonds. The cationic nature of chitosan and CNPS provides strong electrostatic interaction with negatively charged components of mucus as well as epithelial surfaces leading to attachment and mucoadhesion

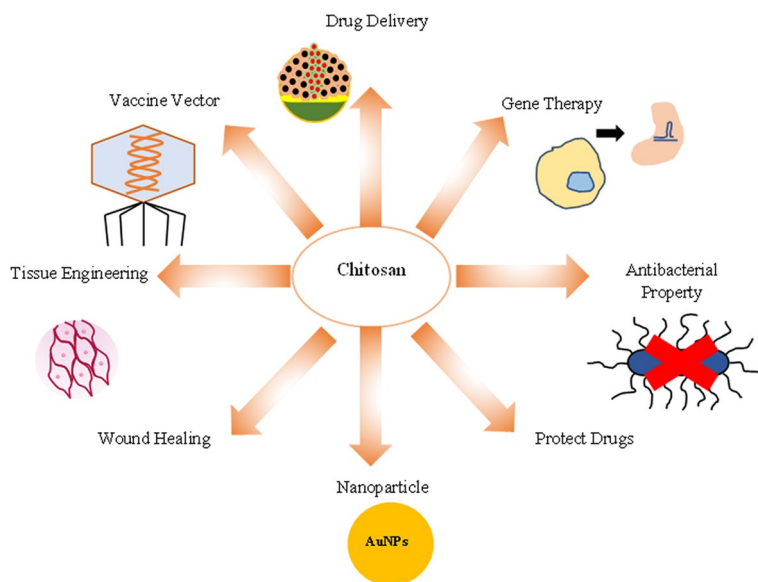
interaction between the bacterial cell wall and chitosan makes way for the penetration of CNPs across the bacterial cell wall initiating a stronger interaction with the charged particles and increasing the accumulation of CNPs at the interacting place. The penetrated CNPs then combine with the DNA and deteriorates DNA replication leading to cell death of the bacteria [31]. According to reports, chitosan binds to teichoic acid in gram-positive bacteria, and lipopolysaccharide in gram-negative bacteria plays an important role in leading to mutation which disrupts cell membrane function resulting in disturbance of cell wall dynamics. Moreover, CNPs have the skill to modify the electron transport chain of the bacteria which can be the reason for the effectiveness of CNPs against microbes [45] (Fig. 2). Although chitosan holds the ability to bind to the DNA, nevertheless, the ability of chitosan in an antimicrobial activity needs to be studied more as chitosan is unable to reach a target in the cytoplasm. A universally acknowledged hypothesis is the direct interaction of polycationic CNPs polycationic to negatively charged surface components present on various microorganisms which leads to modifications to the cell surface, and leakage of intracellular components followed by cell death. This prevents the CNPs from penetrating and reaching any target present in the cytoplasm.

### Wide spectrum application of CNPs

The multifaceted properties of CNPs such as tuneable size, ease of surface modification, nontoxicity, and biodegradability make them an ideal choice for biomedical applications. As a promising candidate for infectious disease management, CNPS finds its usage in various ways. Some of them are enumerated below (Fig. 3).



**Fig. 2** Mechanism of action of CNPs on microorganism



**Fig. 3** Wide spectrum application of CNPs in healthcare

### For antibacterial/antiviral therapy

Developing an alternative remedy to inhibit the occurrence of infectious diseases, CNPs provide a unique opportunity. The CNP's antibacterial properties allow for a versatile approach that is also adaptable. Because of CNP's versatility, it is favored as an alternative or supportive treatment to antibiotics which offers unique advantages such as ensuring a better drug delivery in a controlled manner and offering protection of the drug. Some examples of the use of CNPs for antibacterial therapy are enumerated below. *Brucella spp.* is the contributive factor of brucellosis, one of the infectious diseases of the digestive or respiratory tract in humans and animals. As mucosal immunity is considered the first line of defense against this disease, for induction of the same, three *Brucella abortus* recombinant proteins, namely malate dehydrogenase (rMdh), outer membrane proteins (rOmp) 10 and 19, were encapsulated in mucoadhesive CNPs and induction of immunity was studied in BALB/c (Bagg Albino) mice after a nasal intervention [46]. Similarly, a study by Farhangi et al. [47] demonstrated the superlative antibacterial efficiency of ciprofloxacin-loaded nanomicelles against some important pathogens like *Pseudomonas aeruginosa*. Inflammatory bowel disease (IBD) is an infectious disease that cannot be contained with ease and its recurrence sans proper treatment makes the issues quite difficult for physicians. Rifaximin, a commonly used for IBD therapy, is used to develop a controlled colon-targeted rifaximin-loaded chitosan delivery system to improve drug solubility for overall therapeutic efficacy and can thus be implemented for disease control [48]. Gastrointestinal diseases which are quite rampant in third-world countries need urgent attention and await effective antimicrobial therapies against the causative agents. In this regard, currently, the focus is



now on developing chitosan nanoparticles loaded with phenolic compounds which harness the advantage of both agents for synergistic activity as effective antimicrobial agents. In another independent study, Covarrubias et al. [49] demonstrated the antibacterial efficacy of hybrid copper–chitosan nanoparticles against cariogenic *Streptococcus mutans* that cause tooth decay. CNPs synthesized with chitosan and alginate demonstrated the development of targeted therapy against cutaneous pathogens like *Propionibacterium acnes*, the bacterium responsible for the pathogenesis of acne [50]. Besides, chitosan microparticles (CM) are also known to reduce *E. coli* O157:H7 shedding in a cattle model, with uterine diseases [51]. Similarly, an in vitro time and dose-dependent study using amphotericin-loaded CNPs confirmed the anti-leishmanial activity of these particles. Sohail et al. [52] suggested the use of such amphotericin-loaded CNPs for local therapy against *Leishmania* following in vivo efficacy studies. Vulvovaginal candidiasis is reasoned as a leading health issue among women. Clotrimazole is an antibiotic widely used for the treatment of the disease. For better therapeutic efficacy, the antibiotic was loaded in *O*-palmitoyl chitosan nanoparticles for topical application against the disease [53].

The development of antibacterial resistance against antibiotics is a challenging aspect according to the Infectious Diseases Society of America (IDSA), as it boosts the spread and transmission of infectious diseases. Unable to reach the extent to fight against antibacterial resistance, efficacious approaches are needed to be discovered. CS–Ce6, a photodynamic chitosan nano-assembly, was found to be effective by modifying the morphologies of antibiotic-resistance bacteria such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative *Acinetobacter baumannii* which revealed the improved generation of singlet oxygen, in contrast to vancomycin. To test the antibacterial activity against multidrug-resistant *Escherichia coli* K1 (Malaysian Type Culture Collection 710,859) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Malaysian Type Culture Collection 381,123), Mukheem et al. constructed two-dimensional molybdenum disulfide (2D MoS<sub>2</sub>) occupied nanoparticles using polyhydroxyalkanoate (PHA) and chitosan (Ch). Looking at the multidimensional properties of CNPs, an operative antibacterial drug delivery system can be developed for the management of infectious diseases. Han et al. [54] fabricated a quaternized chitosan (QCS)/silver (Ag)/cobalt phosphide (CoP) nanocomposite against multidrug-resistant *S. aureus* and *E. coli* which proved to be 99.6% efficient within a short span of 10 min. Organisms responsible for severe hospital-acquired infections are *Acinetobacter* and *Klebsiella*, a multidrug-resistant (MDR) gram-negative bacterium (GNB). For the delivery of Colistin, a new diversified chitosan-coated human albumin nanoparticles (Col/haNPs) were formulated which showed a high antibacterial effect along with a remarkable decrease in MIC values, and with increase in time a drastic decline in bacterial growth was observed against Col-resistant strains when compared to free Colistin. Col/haNPs presented a repressive effect on the creation of biofilm, when compared to free Colistin, it was 4–60-fold higher for Colistin susceptible and resistant *A. baumannii* [55]. An endolysin derived from Cp-1 phage was effective against pneumococcal infection models, however, its low bio-availability hinders its use. To overcome this issue, Cpl-1 loaded chitosan nanoparticles were designed and used against antibiotic-resistant *S. pneumoniae* [56].

CNPs have also been explored for the delivery of therapeutics against many viral diseases. In this context, for the expansion of drug access and treatment of HIV-1 in resource-limited countries, poly (lactic-*co*-glycolic acid) (PLGA) chitosan (CS)-coated nanoparticles (NPs) loaded with hydrophilic lamivudine (LMV) or nevirapine (NVP) was developed [57]. Moreover, different doses of Lamivudine-loaded PEGylated Chitosan (LPC) nanoparticles have been more significantly potent in inhibiting HIV replication by limiting the production of HIV virions [58]. Shohani et al. [59] formulated a nanoconjugate using trimethyl chitosan which boosted the anti-HIV effects of Atripla. For targeting HIV-infected brain astrocytes, siRNA needs to be delivered across the blood–brain barrier (BBB) with the help of small interfering RNA (siRNA)/dual antibody-modified chitosan nanoparticles, hence inhibiting HIV replication. It was theorized that bradykinin B2 antibody and transferrin antibody bind to bradykinin B2 receptor (B2R) and transferrin receptor (TfR) were found to be useful in delivering siRNA across the BBB into astrocytes and were proved to be potential targeting ligands [60]. Timur et al. [61] developed tenofovir-loaded chitosan nanoparticle vaginal gels for interfering with HIV transmission in vitro systems.

Against influenza nucleoprotein, siRNA was expressed in chitosan polymer as siRNA/chitosan nanoparticle complex which when delivered through nasal passage displayed antiviral effects and protected BALB/c mice from lethal influenza challenge [62]. A novel diversified nanoparticle system was designed which consisted of chitosan complexed with dual expressing short hairpin RNA (shRNA) recombinant plasmid at its core. For targeting the RSV NS1 and P genes encoded shRNAs, which inhibit the pathogenesis and replication of the virus. RSV replicates inside the infected cells and prevents further viral spread and disease development. The balance and durability of the plasmid DNA are confirmed by the liposomal layer present between the core and the shell [63]. Similarly, curcumin-encapsulated CNPs exhibited to have an antiviral effect against *Hepatitis C* Virus which was confirmed in Human Hepatoma Cell Lines [64].

### As a vaccine carrier

CNPs are employed as vaccine carriers owing to their immune-stimulating activity and bio-adhesive nature that ameliorate better cellular uptake and permeation, as well as guarantee finer antigen protection. These CNPs are being effectively used as vaccine carriers against many infective diseases. Respiratory infectious diseases like influenza A (H1N1) showcase the gravest threat to human health, hence putting more pressure to construct an effective vaccine. In this regard, an influenza A (H1N1) antigen was conjugated to the surface of *N*-trimethyl-aminoethyl methacrylate chitosan (TMC) nanoparticles (H1N1-TMC/NP) to develop a nanovaccine for nasal administration [65]. Similarly, influenza nanoparticle fabricates by utilizing trimethyl chitosan nanoparticles as carriers of recombinant influenza hemagglutinin subunit 2 (HA2) and nucleoprotein (NP) has been developed to tackle the problem of virus antigenic drift and antigenic shift [66]. DNA vaccines structured by combining *Treponema pallidum* glycerophosphodiester phosphodiesterase (Gpd)

to interleukin-2 (IL-2) and using CNPs as vectors were investigated against spirochete infection, and efficaciously reduced the process of formation of syphilitic lesions [67]. Besides, CNPs served as efficient vectors for enhancing the delivery of the Tp92 DNA vaccine in a *Treponema pallidum* rabbit-challenged model which presented great protection against the disease [68]. Enterohemorrhagic *Escherichia coli* (EHEC) O157:H7 is an infectious zoonotic pathogen causing life-threatening complications like hemolytic uremic in human infections resulting in a high number of deaths worldwide. Since the improvement of mucosal vaccines against infectious diseases needs a prompt antigen delivery system, a recombinant protein called EIT was encapsulated in chitosan and its water-soluble derivative, trimethylated chitosan (TMC) using the electrospraying technique for the development of a successful intranasal nanovaccine whose efficacy was tested in the mouse model [69]. *Acinetobacter baumannii* has recently emerged as one of the most important health problems due to its propensity to acquire multidrug, extensive drug, and even pan-drug resistance. A multi-epitope peptide, rOmp22, encapsulated in chitosan-PLGA nanoparticles is being investigated as a vaccine prospect against *Acinetobacter baumannii* infection [70]. Likewise, *Brucella abortus* antigen, malate dehydrogenase (Mdh) when loaded in mucoadhesive chitosan nanoparticles emerged as an effective intranasal nanovaccine candidate in the mouse model [71]. CNPs are not only used as vaccine carriers for human diseases but also against the infectious diseases of animals. Newcastle disease (ND) and infectious bronchitis (IB) are vital diseases, which causes respiratory illness in chickens, following in severe economic losses in the food industry. Similarly, a chitosan nanoparticle-based mucosal vaccine was found to be effective against infectious diseases of poultry and pigs [72], while a chitosan–saponin encapsulated DNA vaccine ensured improved protection of avian bronchitis in poultry [73].

The immunization effect of live attenuated Japanese encephalitis-chimeric virus vaccine (JE-CV)-loaded mucoadhesive NPs was evaluated based on a novel mucoadhesive polymer chitosan maleimide (CM) or chitosan (CS), through IN route enhance mucosal immunization against the Japanese Encephalitis [44] due to the stimulatory effects on both mucosal and systemic immune responses.

Improvement of the self-administered vaccines for Hepatitis B proved to be one of the valuable aspects in developing countries. For this issue, one of the valid approaches is the use of polymeric nanoparticles in nasal vaccination. When studied thoroughly for the delivery system of mucosal vaccine, chitosan NPs/poly- $\epsilon$ -caprolactone (PCL) stated some advantages where PCL indicated higher resistance in case of degradation in biological fluids, mucoadhesive and immunostimulatory properties of chitosan. Also, these NPs were discovered to be capable of entering into the differentiated epithelial cells by retaining mucus-secreting pulmonary epithelial cell lines [74]. To intensify the immunogenicity of influenza A antigen after nasal administration, the (H1N1) antigen was covalently conjugated to the surface of *N*-trimethyl aminoethyl methacrylate chitosan (TMC) nanoparticles (H1N1-TMC/NP) through thioester bonds [65]. For the nasal delivery of r4M2e, *N*-trimethyl chitosan (TMC) nanoparticles were used as a carrier system. As studied on the mice, an M2e-based universal recombinant influenza virus vaccine, i.e., HSP70c, was considered to be an eligible challenger [75].

According to various experiments conducted on polyelectrolyte complexes (PECs), it consisted of chitosan and chondroitin sulfate (ChonS) that was encapsulating the antiretroviral drug tenofovir (TF). When demonstrated for in vitro antiviral activity test, it was observed that the constructed nanoparticles directed toward dose-dependent reduction of HIV-1 infection [76]. Moreover, Wu et al. designed chitosan nanoparticles containing fusion protein (Hsp $\alpha$ -PPE44-Es $\alpha$ V; HPE) and resiquimod adjuvant (HPERC) which elicited robust cytokine secretion in BALB/c mice [77].

## As adjuvants

To fight against the virus, one of the promising and deep-rooted places is achieved by adjuvants. Adjuvants are designated as immunological agents with the ability to not only activate the innate and adaptive immune system but also to enable them to respond rapidly to infections. Nanoparticles hold unique properties in developing adjuvants [78]. The formulated nanoadjuvants are responsible for modulating immune response by regulating the proper release of the vaccine, alleviating the antibody response, and modulating T cell-derived cytokine patterns.

CNPs are considered safe and effective adjuvants against various infectious agents. In this regard, Abkar et al. [79] undertook a comparative study to access the adjuvant and delivery ability of calcium phosphate, aluminum hydroxide, and chitosan nanoparticles, using a model protein of *Brucella melitensis* Omp31. The study highlighted the better adjuvant nature of CNPs.

Dengue virus (DENV) being a mosquito-borne virus causes an unmatched and deadly infection which shows an urgent need for the administration of vaccination in tropical and subtropical locations. In this finding for a non-replicating dengue vaccine, an ultra-irradiation (UV)-inactivated DENV-2 carried by *N,N,N*-trimethyl chitosan nanoparticles (UV-inactivated DENV2 TMC NPs) emerged as a potential candidate. Analyzing TMC in a human ex vivo model, the human monocyte-derived dendritic cells (MoDCs) behaved to be both potential adjuvant and vaccine vehicles [80]. Moreover, dengue vaccines developed from UV-activated DENV-2 (UNI-DENV) and *Mycobacterium bovis* Bacillus Calmette–Guerin cell wall components (BCG-CWCs) were served by CS-NPs as a delivery system and potential adjuvant [41]. In a study conducted by Jearanaiwitayakul et al., a condensed DENV-2 stacked in *N, N, N*, trimethyl chitosan nanoparticles (NS11-279TMC NPs) was arranged through the ionic gelation method in the C-terminal and the immunogenicity of such NPs was examined by the murine model and human ex vivo models. The study proved that the TMC particles not only helped in the easy delivery of NS11-279 protein into monocyte-derived dendritic cells (MoDCs), but effectively instigated those cells resulting in enhanced expression of maturation marker (CD83), co-stimulating molecules (CD80, CD86, and HLA-DR) and helped in the secretion of numerous innate cytokines/chemokines. Hence, TMC when used as a potent adjuvant heightened the delivery and antigenicity of NS1 as a vaccine for dengue [81].

Being the main causative agent of neurological and hand-foot-and-mouth diseases (HFMD), it has become important to develop a secure and effective vaccine for enterovirus 71 (EV71). Here, the efficacy of inactivated EV71 was computed

with  $\gamma$ -PGA/chitosan nanoparticles (PC NPs) which are biodegradable and efficient as an adjuvant. When this inactivated EV71 with PC NPs adjuvants was introduced in the subcutaneous layer, it was detected to be inducing higher levels of virus-specific humoral (IgG, IgG1, and IgG2a) and cell-mediated immune responses (IFN- $\gamma$  and IL-4). PC NPs carrying beneficial qualities as an effective immunogenic adjuvant were found to be a potential candidate for the production of EV71 vaccines [82].

In another survey, poly- $\epsilon$ -caprolactone/chitosan NPs delivered a strong humoral adjuvant effect for HBsAg and induced Th1/Th17-mediated cellular immune responses for the hepatitis B virus vaccine [83]. For an improved influenza immune response, the use of chitosan nanoparticles as delivery antigens and HK-1 as an adjuvant proved to be eligible [84]. For influenza vaccine construction, trimethyl chitosan nanoparticles (TMCNPs) were used as the recombinant influenza hemagglutinin subunit 2 (HA2) adjuvants and which helped in the delivery of HA2 and nucleoprotein (NP) to HNEpCs [66].

The emergence of new vaccine adjuvants is the need of the hour to facilitate new methods for vaccine administration. In this context, tailor-made adjuvants using chitosan:  $\beta$ -glucan particles were formulated for the hepatitis B antigen [85]. A study done by Zhao and his group emphasized the role of *N*-2-hydroxypropyl trimethyl ammonium chloride chitosan (*N*-2-HACC) and *N*, *O*-carboxymethyl chitosan (CMC) as ideal adjuvant and delivery vehicles for vaccine antigens against the disease [86].

## For wound dressing

In surgical wounds, burns, and diseases, local infection is widespread which may lead to prolonged wound healing, dehiscence, abscess formation, and sepsis leading to life-threatening complications [81]. The mucoadhesive property of chitosan has the inherent advantageous role of wound-dressing and antibacterial properties. The infectious environment provides multivalent electronegative molecules or anions where chitosan can form a network through coordination and secondary interactions to form gelling [87]. Natural polymers, like chitosan-based hydrogels, have received special attention due to their biomimetic properties [88], where they can encapsulate active molecules and can form a network through physical interactions or chemical couplings. Carboxymethyl chitosan (CMC)/oxidized dextran hydrogel loaded with ceftriaxone sodium was developed which demonstrated better subcutaneous anti-infective effects [88]. Recent years have targeted the development of advanced wound-dressing materials with rapid healing rates for better wound care. Because a suitable microenvironment is a necessity that will provide a rapid healing rate with the support of cell proliferation, migration to speed up the healing process by preventing inflammation and scarring is very much needed. Epidermal growth factor (EGF)-loaded *N*-carboxymethyl chitosan- and alginate-based hydrogels promote cell proliferation and accelerate wound healing with an antibacterial effect. In another study, Chen et al. [89] fabricated tetracycline-loaded alginate–chitosan hydrogel integrated with gelatin

microsphere for better antibacterial activity and wound healing. Burkatovskaya et al. [90] developed a chitosan acetate bandage for hemostatic and antibacterial effects to reduce the bacterial load in *P. aeruginosa* and *P. mirabilis* in the skin more efficiently. Ye et al. [91] developed a new composite of gelatin–chitosan–silver nanoparticles cross-linked with tannic acid for better wound-healing and antibacterial properties while maintaining low cytotoxicity. Hernandez Martinez et al. formulated a nanocomposite of gold nanoparticles (AuNPs), chitosan, and calreticulin for the therapy of diabetic lesions. The formulated gold nanocomposites without affecting cell viability promote the growth, migration, and differentiation of fibroblast keratinocytes, and endothelial cells in vitro as well as in vivo. Further histological examination described granulation, re-epithelization, and increased collagen synthesis at the wound site [92]. Chitosan nanosheets and honey demonstrated superior wound-healing ability in male BALB/c mice with skin excisional wound injury [93].

## A diagnostic agents

In the age of rising antimicrobial resistance due to bacteria and fungus, the ability to detect infectious microorganisms precisely in clinical specimens is the key to designing a proper therapeutic outcome for the disease. Accurate diagnosis at the right time can alter the outcome of treatments, thus preventing long-term complexity for the infected person. In the last decades, several nanoparticles have been designed and their potential application as diagnostic agents has been assessed for various bacterial and viral diseases like SARS, flu, and dengue. In this context, CNPs as diagnostic agents against infectious agents have also been explored.

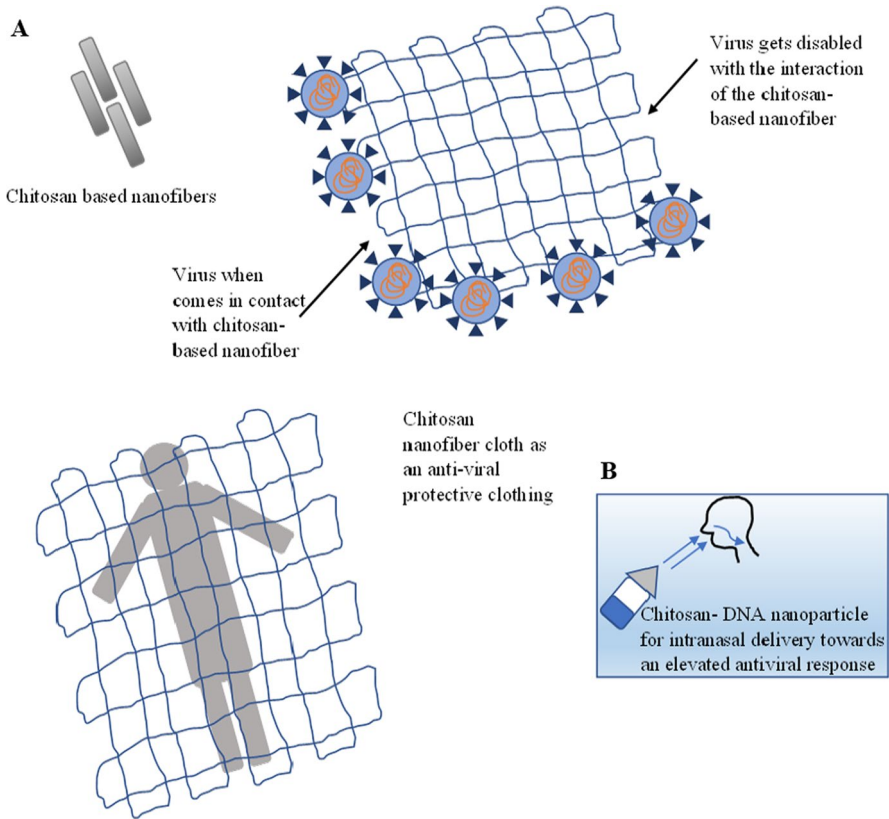
Believed to be an emerging parasitic disease, human echinococcosis so far affects millions of people around the globe. Being a parasite, it severely impacts people; hence, it requires a convenient, economical, and rapid technique for detection. Herein, the recommended diagnosis for cystic echinococcosis (hydatidosis) is an enhanced immune-dot-blot assay. This technique in simple terms can be described as the formation of a sandwich between a gold nanoprobe (chitosan–gold nanoparticle protein A) and cyst antigen (Ag B) holding anti-Ag B antibodies. Protein A was united with chitosan–gold nanoparticles through glutaraldehyde chemistry temporarily. Furthermore, on a nitrocellulose membrane Ag B was immobilized, following the addition of gold nanoprobe and a sera sample. The result can be seen through the naked eye [94]. Similarly, for the detection of broad-spectrum colorimetric bacteria, chitosan-coated magnetic nanoparticles (CS-MNPs) were developed. These CS-MNPs were implemented for the detection of *E. coli* and *S. aureus* in test samples. Gram-negative *E. coli* and gram-positive *S. aureus* were magnificently quantified using ABTS chemistry through the naked eye. Through this observation, we can predict that the CS-MNPs will deliver a brand-new approach to the detection of broad-spectrum bacteria in different samples [95]. Likewise, an ultra-sensitive immunosensor was designed using gold nanoparticles (GNPs) well dispersed in chitosan hydrogels for diagnosis of Salmonella in clinical samples [96].



## Recent use of chitosan nanoparticles: as an antiviral vehicle for SARS-CoV-2

COVID-19 being a contagious disease has a high transmission rate. The dropped aerosol from the infected patients (containing SARS-CoV-2 viruses) poses a threat to the non-infectious persons in the near vicinity while breathing or talking [73]. SARS-CoV-2 itself is regarded as a specific nanoparticle as it shares similar properties to nanoparticles like having positive zeta potential (primarily due to the presence of capsid) [97]. The spike protein of the SARS-CoV-2 contains poly-basic arginine-rich motifs which impart a positive zeta potential at the physiological pH and this unique property distinguished itself from some previous SARS-related sequences [98]. Thus, a particular sequence drives its entry into the host cells along to infer viral replications and infectivity at the host. To confer protection to the healthcare workers against this pandemic, positively charged polymers like chitosan are proposed to be exploited for the preparation of nanofibers that can be incorporated for the exclusive cloth of healthcare providers (Fig. 4). The repulsive electrostatic force between the cloth surface and SARS-CoV-2 would reduce the viral load around the clothed person to reduce the transmissibility of the virus [99].

A study conducted by Milewska et al. reported that chitosan-based anti-coronavirus compounds under *in vitro* and *ex vivo* conditions can inhibit the infection effectively. The interaction analysis study illustrated the constitution of the polymer–protein complex owing to the binding of chitosan derivative to the S protein of the virus. Such an interaction masked the spike protein of the virus forbidding it to interact with the cellular receptor [100]. Further, Milewska et al. used cell culture models that mimic the site of coronavirus replication, i.e., the layer of conductive airways. In the proximity of derivatives of chitosan, the culture model was infected with the virus either SARS-CoV-2 or MERS-CoV [100]. The use of chitosan with DNA to some extent can reduce the inflammation of the lung tissues for getting an elevated antiviral response. In one of the studies, intranasal administration of a DNA vaccine was done using SARS-CoV nucleocapsid in CNPs by Raghuvanshi et al. This nanovaccine increased the efficiency of the immune system by targeting and activating nasal-resident DCs (dendritic cells). This group also confirmed an enhanced repertoire of IgG and nasal IgA following administration of the virus in comparison with the control, for boosting the immune system against SARS-CoV [45]. Besides, SARS-CoV-2 spike glycoprotein encapsulated in *N*, *N*, and *N*-trimethyl chitosan particles was used as a vaccine candidate to study the induction of antibody response following immunization in mice. Upon intraperitoneal administration, the nanovaccine initiated robust production of neutralizing antibodies against SARS-CoV-2 in mice [80]. As a vaccine adjuvant or vehicle, nanochitosan is efficiently explored for the delivery of drugs, siRNA, and peptides via the intranasal route. The ability of chitosan to stimulate the immune system as well as to infiltrate through the tight junction between the mucosal epithelial cells and the possibility of improvement of the antigen molecules' immunogenicity can be considered a choice to



**Fig. 4** Schematic representation of proposed protective-antiviral clothing of nanofibers (chitosan nanoparticles-based) for SARS-CoV-2 B. Delivery of chitosan nanoparticles-based aerosol leading to an efficient therapy against SARS-CoV-2

apply for COVID-19 therapy [101]. For selective targeting of DCs, biotinylated chitosan nanoparticles were operationalized through a fusion protein vector into delivering plasmid DNA encoding SARS-CoV N protein to obtain an elevated mucosal IgA along with a heightened systemic IgG against the N protein after intranasal administration [45]. In 2020, Bioavanta-Bosti (a company) stated the efficacy of CNP technology for the formulation of aerosol anti-COVID-19 drugs. NovoChizol™ nanoparticles based on aerosol formulations can be applied for delivery of any potential anti-COVID-19 drug to the lungs of severely ill patients in ventilators. In fact, through the NovoChizol™ technology, CNPs generated with unique, customizable physicochemical characteristics can be administered to critically ill patients of all diseases. In the respiratory tract, the formulation adheres to the mucosal membrane and the encapsulated drug is gradually released because of slow chitosan degradation. The localized pharmacokinetics in turn ensures a high local concentration of the drug [102].



In an innovative approach, CNPs were used as a detection agent to identify SARS-CoV-2 in a given sample. For the same, a voltammetric genosensor has been designed for prompt diagnosis of COVID-19 using RNA-dependent RNA polymerase (RdRP) sequence as a target for the detection of the virus in sputum samples. RdRP is used by SARS-CoV-2 for the replication of its genome and genes. Hexathia-18-crown-6 (HT18C6)-coated silver ions ( $\text{Ag}^+$ ) were used as a redox probe. For better attachment of the RdRP sequence, the electrode was coated with chitosan and silicon quantum dots modified PAMAM dendrimer. The designed genosensor helped beneficial in quantifying spike concentrations of RdRP sequence in human sputum samples [103].

## Clinical manifestation of CNPs against infectious diseases

The wide spectrum use of CNPs and its advantage look very promising but only in vitro or in vivo studies. Not many of these formulations have found their way into clinics. However, some of them are being investigated at the preclinical level. Chitosan–propolis nanoparticles were estimated against *E. faecalis* procured from patients who suffered from failed root canal treatment [104]. A preclinical analysis of bupivacaine-loaded CNPs revealed the enhanced anesthetic outcome of the payload following infraorbital nerve blockade [102]. Antibiotics-loaded CNPs were studied to combat multidrug resistance due to *A. baumannii* from clinical isolates of AL Kasr Al Aini hospital, Cairo, Egypt [105]. Similarly, ketorolac tromethamine-loaded CNPs were implemented for managing the local inflammatory process in the postoperative stage after the surgical removal of warts [106]. Moreover, there are reports of Rylomine™, a nasal formulation of morphine-loaded chitosan NPS being approved for Phase 2 clinical trials in the UK and EU and in Phase 3 clinical trials in the USA which is an optimistic sign regarding the future of these nanoparticles.

## Drawbacks of CNPs

Even though CNPs have found their way in various applications, there are still some hindrances that prevent them from becoming the gold standard for disease management. One of them is the toxicological profile of CNPs which is still under investigation. So far there are not much clinical data that tell us about the toxicity of CNPs in human volunteers. However, there are some reports which suggest that CNPs might have limited or no toxicity in animal models. In a study done on zebra fish embryo, it was found that CNPs at a size of 200 nm were responsible for inducing malformations and other physiological stress [107]. Likewise, Jesus et al. confirmed that the type of polymer and size of CNPs governed the in vitro immunotoxicity results. Human peripheral blood monocytes (PBMCs) or RAW 264.7 cell lines when treated with different types of CNPs elicited reactive oxygen species (ROS) production, and platelet aggregation and intervened with the inner pathway of coagulation [108]. Similarly, other issues with CNPs are batch-to-batch variation and optimization of techniques to ensure maximum encapsulation of payload. There are many ways of

formulating CNPS; however, one has to find the apt method to do so keeping in mind the properties of the drug which is encapsulated. Moreover, one also must look into the molecular weight and degree of acetylation of chitosan before designing nanoformulations. Similarly, even though some CNPs may have used them as dietary products, yet none of them have been explored as wound-dressing materials in clinics [5]. Moreover, due to the release of a mammoth amount of organic material and alkaline waste, CNPs are also environmentally ill-disposed.

## Conclusion and future perspectives

Infectious diseases since time immemorial have always been a menace to human health which shakes the healthcare sector even today. The efficacy of conventional medicinal agents and strategies has been ever questionable and the lookout has always been on finding easy, cost-effective alternative strategies against these diseases. Nanotechnology offers a wide palette of options for the diagnosis, treatment, and prevention of contagious diseases. Owing to their specificity, targeted delivery, controlled release properties, and low cytotoxicity, these nanodevices have emerged as more expeditious and less invasive therapeutic regimes, contributing to the improvement of personalized treatment for various transmissible diseases.

In comparison with inept and pricey artificial polymers, research and use of natural polymers like chitosan to formulate nanovehicles (CNPs) against infectious disease has gained significant momentum due to its low cost, ease in availability, biocompatibility, and pocket-friendly nature. Chitosan is classified as a bacteriostatic and fungistatic polymer and CNPs as antimicrobial agents have been investigated for an extensive variety of fungi, bacteria, and algae. They have shown great inhibitory effects against numerous gram-positive and gram-negative bacteria, whether it is used in a mixture with other compounds or alone. Besides, in the superbug time, CNPs have established their role as a new approach to fight against resistant bacteria. Engineered CNPs are also being implemented to ferry vaccines against infectious agents and to act as immunostimulatory adjuvants for ensuring augmented uptake by antigen-presenting cells and a consequent elevated immune response. Moreover, the role of CNPs in wound dressing and as antiviral vehicles is also being explored. There are reports of a chitosan-based nasal formulation in clinical trials in the UK, EU, and the USA. It can be conjectured that this formulation may find its way to market soon laying the stepping stone for similar products in the future. Similarly, these CNPs owing to their nontoxicity can emerge as the first choice by researchers as a drug delivery vehicle to combat suddenly emerging new viruses or bacteria.

However, there is growing concern regarding the toxicity of CNPS although the results regarding human toxicity are indecisive to date. Besides, the ability of these CNPs to penetrate vital organs needs to be assessed more critically. Regardless of accomplishing several latest approaches to overcome the shortcomings of chitosan using a wide range of formulated drugs, further research work in chitosan in near future is expected, especially in nasal and pulmonary drug delivery. Importantly, future studies will be needed to explore the potentially deleterious effects of these agents. But it is considered that shortly, numerous chitosan-composite systems

budding to be formulated and implemented for infectious disease treatment will be in clinical practice.

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**Conflict of interest** The authors have no competing interests to declare that are relevant to the content of this article.

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