International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 8 Issue 10 ǁ 2020 ǁ PP. 50-57

Review on overview of Chitosan as a Potent Drug Delivery

Geeta Joshi, PayalDudani
D Y Patil School of Biotechnology and Bioinformatics, Navi Mumbai

ABSTRACT:
Chitosan is a positively charged linear polysaccharide, composed of β- linked D- glucosamine and N- acetyl – D – glucosamine which is obtained from the hard outer skeleton of shellfish including shrimp, crab and lobsters. Chitosan, being biocompatible, antimicrobial, biodegradable and nontoxic has a very wide application in the field of medicine and biomedical sectors such as in drug delivery, in wound healing, as a causative agent due to its ability to binds with proteins, metal ions, cholesterol and fats. In drug delivery methods, chitosan have been used in the design of different types of drug carriers for different administration routes. The aim of this review is to summarize an understanding of the origin, properties and potential application of the chitosan as a pharmaceutical drug carrier and drug delivery systems published over the past decade.
KEYWORDS-*Chitosan; polysaccharide; pharmaceutical; drug carrier; drug delivery*

Date of Submission: 20-10-2020 Date of acceptance: 04-11-2020

I. INTRODUCTION:

Drug delivery is the method or process that is used as a medium or carrier for administering a pharmaceutical product to achieve a therapeutic effect in humans or animals. Drug Delivery involves the approach, formulation, technologies and systems thatmonitor the drug released and the location in the body where it is released thus helping in modification of drug released profile, its absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance.Pharmaceutical industry has marked an ever increasing demand for more patient friendly and compliment dosage form. Efforts are focused on the development of new formulations with new excipientsproduced from biomaterial that blend with existing drugs to improve safety, efficiency and cost effectiveness during production (Pethe. *et.al*). As to cope with the environmental and climate challenges faced today, biological macromolecules are gaining attention in various application due to the advantages associated with their natural origin (G.Ren, C.Clancy, T.Tamer*et.al*). Nanotechnology and nano delivery systems offer multiple benefits in treating chronic human diseases by site-specific and target-oriented delivery of precise medicines (Jayanta kumar Patra, Gitishree Das *et.al*). Biodegradable polymeric nanoparticles can act as a structures drug delivery vehicle or carrier for controlled and targeted drug delivery.

Chitosan is one of the most functional natural biopolymer which is being widely used in the pharmaceutical field becauseof its biocompatibility and biodegradability (Naskar*et.al*) into nontoxic and non-allergic products (Brendon Y. Chua. *et. al*). These properties of chitosan hasled to its application in the synthesis of its nanoparticle for drug delivery.Chitosan is made up of β- linked D- glucosamine and N- acetyl – D – glucosamineresidues. It is a non antigenic hydrophilic polymer containing one amino group and 2 hydroxyl group in the restating hexosaminic residue (Agarwal,Strijkers,Nicolay). It is prepared from the exoskeleton of crustaceans, such as crabs & shrimps by alkaline N- deacetylation (Brendon Y. Chua. *et. al*). On commercial scale chitosan is produced by exhaustive deacylation of chitin with concentrated solution of sodium hydroxide (Kafetzopoulos*et.al*).

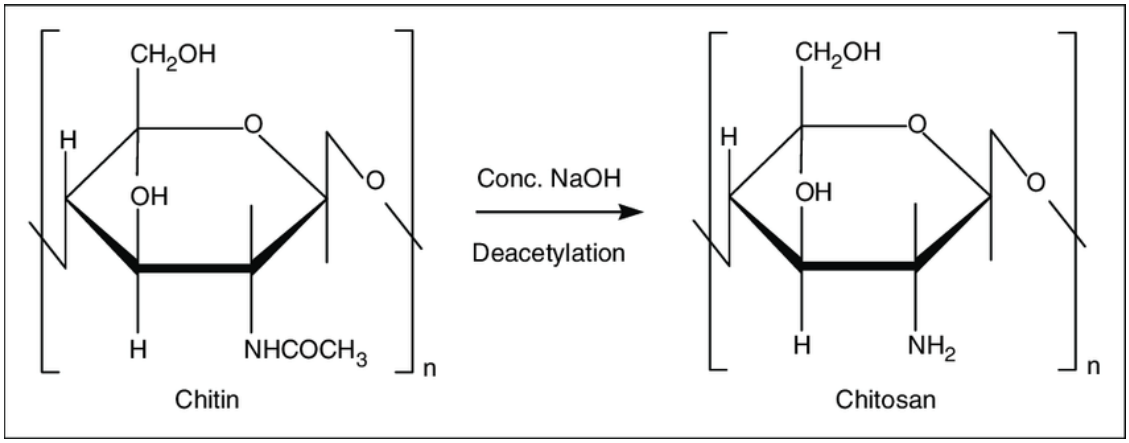

Fig. 1 Structure of chitin and chitosan

II. CHITOSAN NANOPARTICLE:

Chitosan has chemical functional group that can be modified to achieve specific goals, making it a polymer with a tremendous range of potential application. Chitosan nanoparticles have been recorded as a carrier system for various drug delivery systems (Ohya.*et.al*). There are various techniques that have been used to develop chitosan nanoparticles

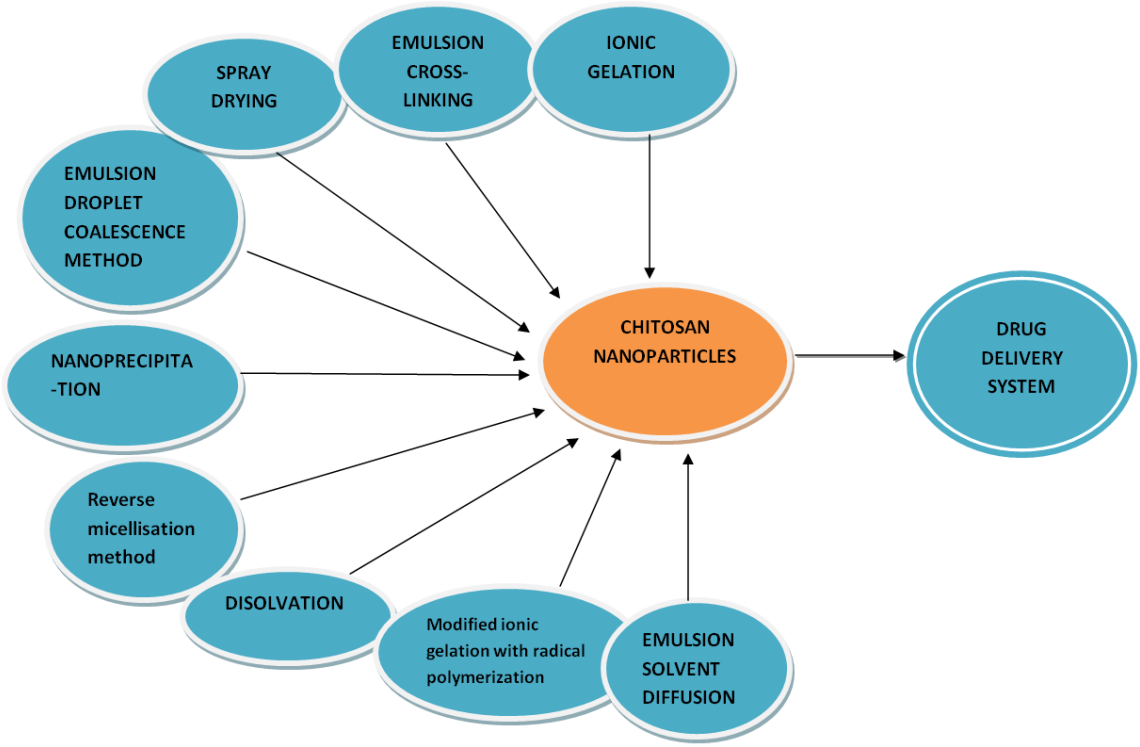

Fig. 2 Schematic representation of diff erent modes of Chitosan synthesis

2.1 Modification of Chitosan:

The backbone of chitosan can be modified to alter its properties such as solubility, adhesion, stability. The techniques carried to modify the chitosan compound can be physical modification or chemical modification.

2.1.1 Physical Modification:

Physical modification of chitosan is being achieved by blending. Blending involves the mixing of two or more polymers. It is the most economical technique by which polymer properites can be altered for specific application (Strobl. G. R.).

2.1.2 Chemical modification:

Chemical modification may be achieved by altering the functional groups in the compound. The chemical modification can be done in several ways including use of chemicals, photochemical, enzymatic grafting, plasma induced, and radiation. Chemical modification alters the physio chemical properties such as electrostatic charging and permeability of polymeric surface (Shukla.*et.al*).

III. PHARMACEUTICAL APPLICATIONS OF CHITOSAN NANOPARTICLES:

PARENTERAL ADMINISTRATION:

The administration of drugs by injection, infusion and implantation or by some other route other than the alimentary canal is defined as parenteral route. The parenteral route of administration termed to be most effective route for the delivery of the active pharmaceutical substance with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients (Neha gulati*et al*., 2011). Nanoparticle size, surface charge, hydrophobicity can vary depending upon their distribution (Tabata and Ikada, 1988, Nazanin hoshyar, 2016). Nanosized particles can be administered intravenously as the diameter of the smallest blood capillary is approximately 4µm. the size of particle which are greater than 100µm are administered by the RES system (reticuloendothelial system) in the spleen, lung, liver and bone marrow. The smaller particles tend to have a prolonged circulation. Frequent coating with polyethylene glycol avoids RES system and increases the blood circulation half life. PEG coating makes the nanoparticle more hydrophilic and neutral allowing them to bypass the immune system more easily; thereby improve the therapeutic efficacy of loaded drug particles (Dreaden EC, Austen LA *et al*., 2012, Wang M *et al*., 2010). Chitosan showed to be RES evading as they are less than 100µm in size and circulate in the blood for considerable amount of time (WareeTiyaboochai, 2010).

3.1 ORAL ROUTE ADMINISTRATION:

Oral drug administration is found to be the most convenient route of delivery for patients due to its convenience, cost-effectiveness and high patient compliance. The oral route becomes problematic because of the unpredictable nature of gastrointestinal absorption and is limited by various physical barriers (Deanna M., Mudie et al., 2010). The designing of the nanoparticle might protect labile drugs from low solubility, low permeability and enzymatic degradation in gastrointestinal tract. Chitosan based nanocarriers have the ability to overcome the physical barriers of the GI tract and enhance drug absorption. After oral administration, the problematic GI conditions could influence stability of delivery system leading to inactivation of drugs and the unsatisfactory therapeutic effect (Cade B.Fox*et al*., 2015).

The variation in the pH of stomach will also results in complications as this could affect drug activity owing to pH-induced oxidation, deamidation or hydrolysis (A.Bernkof-Schnurch et al., 1998). Because of the biodegradability, low immunogenecity and biocompatibility nature of the chitosan and the presence of the reactive functional groups offered great opportunity for enhancing the stability in gastric area and improving drug permeability in intestinal tract. Chitosan grafted hydrophilic or hydrophobic groups could be exploited as temperature sensitive nanocarriers based on the body temperature, which could respond to temperature changes by swelling or shrinking. These nanocarriers were benefit to protect drugs from stomach, controlled release and improve the instability of drugs in GI tract (Lang,X., Wang,T.Sun*et al.*,2020).

3.2 NASAL DRUG DELIVERY:

Nasal drug administration is a non-invasive method of delivering drugs through nasal route to reach the respiratory system, the brain and/or systemic circulation. Recently many drugs have been shown to achieve better systemic bioavailability through the nasal route. Moreover, hydrophilic drugs, proteins, nucleic acids and polysaccharides present complications because of their low permeability across the nasal epithelium. Chitosan has applications in nasal delivery (Casettari,L*et al*.,2014) for overcoming these difficulties as it also exhibits biodegradability, biocompatibility, low toxicity, adheres to mucous and opens the tight junctions of nasal membrane (Lisbeth,I,2013).

3.3 OCULAR DRUG ADMINISTRATION:

Nanoparticles are potential carriers for ocular delivery as they are capable to adhere to the ocular epithelial surface (Wood et al., 1985).Different strategies have been approached to increase thebioavailability of drug substances at the eye level: increased corneal permeability (prodrugs, permeability enhancers and cyclodextrins), increased viscosity of the vehicle (suspensions, ointments and gels in situ), use of dispersion systems (liposomes, emulsions and nanoparticles), increasing contact time with solid matrix (inserts and contact lenses) (Lavik, E., Kuehn, M. H., *et al*.,2011).Researches which are carried out so far proved that chitosan can increase retention time and reduce the frequency of administration. Chitosan not only enhance cornea contact time through its mucoadhesion mediated by electrostatic interaction between its positively charged and mucin negatively charged, its ability to transient opening tight junction is believed to improve drug bioavailability. They are biocompatible, biodegradable and non-toxic, natural abundance, nature-friendly materials, relative ease of isolation and low cost (Felt, O., P. Furrer*et al*., 1999).

Nanoparticle	Charge	Solubility	Properties	Ocular dosage forms	References
Chitosan	Positive	Soluble in solutions of dilute acids such as citric, acidic, tartaric, hydrochloric acid. Insoluble in water. pH<6.5 It is not soluble in phosphoric or sulfuric acid.	Biodegradable, biocompatible, mucoadhesive and non-toxic, pseudoplastic and viscoelastic properties.	In situ gels, nanoparticles, liposomes, micelles microspheres.	Alonso MJ, Sánchez A. et al.,2003, Szymańska E. *et al*.,2015, Başaran E. *et al*.,2012,

3.4 MUCOSAL ADMINISTRATION:

Chitosan can be used effectively as a carrier for mucosal drug delivery because of its mucoadhesive properties. Nanocarriers are used for the protection of drugs at both extracellular and intracellular range due to their small steric obstruction (Liu M. *et al*.,2015, Lavelle Ed. *et al*.,2000).Abeer M. Al-Ghananeem et al. reported in the year 2014 about the potential use of chitosan nanoparticles as a delivery system that enhances the systemic bioavailability of olanzapine following intranasal administration. They prepared nanoparticles by ionotropic gelation method and studied their size, drug loading and in vitro release.

3.5 ANTI-MICROBIAL DRUG ADMINISTRATION:

Cefazolin loaded chitosan was found to have an excellent antimicrobial potential against multi drug resistant *Klebsiella pneumoniae*, *Pseudomonas aeroginosa* and Extended Spectrum Beta Lactamase (ESBL) positive *Escherichia coli* (Bushra Zamil *et al*.,2016). Chitosan was also proved effective against *Mycobacterium* (Tarun Garg, 2015). The chitosan nanospheres adhered tightly to collagen fibrils with a thin coating that facilitates release of VH (Vancomycin hydrochloride), and proved to have clear antibacterial effect (Ziqiang Kong *et al*., 2013).

3.6 COLON DRUG ADMINISTRATION:

Chitosan nanoparticles has widely been used for colonic diseases i.e. Ulcerative colitis, crohn's disease, pseudomembranous colitis and irritable bowel syndrome (Naeem, M. et al.,2020). Chitosan has the ability to dissolve in acidic pH of stomach but get swollen in the intestinal pH (Tozakia H *et al*.,2002). Chitosan microcores entrapped within acrylic microspheres for the colonic delivery of sodium diclofenac by the method of spray-drying and then microencapsulated into Eudragit (Lorenzo-Lamosa ML *et al*., 1998). Chitosan DNA nanoparticles found to be more stable in the upper regions of the small intestine suggested that higher uptake rates may occur in the duodenum compared with the ileum and the colon (Kadiyala I *et al*.,2010). Thesenanoparticles were also developed for improving uptake in HT-29 cell and colorectal cancer (Li P *et al*., 2011).

3.7 PULMONARY DRUG ADMINISTRATION:

Chitosan is apreferredmaterial for pulmonary drug administration (Xiuwen Guan et al., 2019). Chitosan contain many amino groups with a positive charge that can interact strongly with the negatively charged mucosa membranes that facilitates CS adsorption and improves penetration, reducing drug clearance and adhesion rate on the cell membrane. Chitosan can open the tight junctions between the cells, which will promote drug transportation through the epithelial tissues, and increase drug absorption rate and bioavailability (Yamamoto H, Kuno Y, Sugimoto S. *et al*.,2004).

3.8 CANCER:

Cancer is considered to be a serious and a major cause of mortality and morbidity across the world. The process of surgical removal of cancer cells is painful, time consuming and also difficult. To overcome such obstacle nanotechnology proves to be a possible and a promising approach to deliver smaller or larger molecules to the target sites without affecting the healthy cells. (Shanmuganathan.*et al*., 2019). For the delivery of the potent drugs, it can be encapsulated in the chitosan nanoparticle acting as a drug carrier to the specific target cells resulting in the destroying the cancer cells without affecting the normal cells of the patients (Shanmuganathan.*et al.*, 2019). The release of cancer drugs from the chitosan polymer is carried out by both external as well as internal stimuli such as light, ultrasound, mechanical stress, temperature, variation in pH (Karimi.et.al,2016 ; Azhdarzadeh.*et al*.,2016).

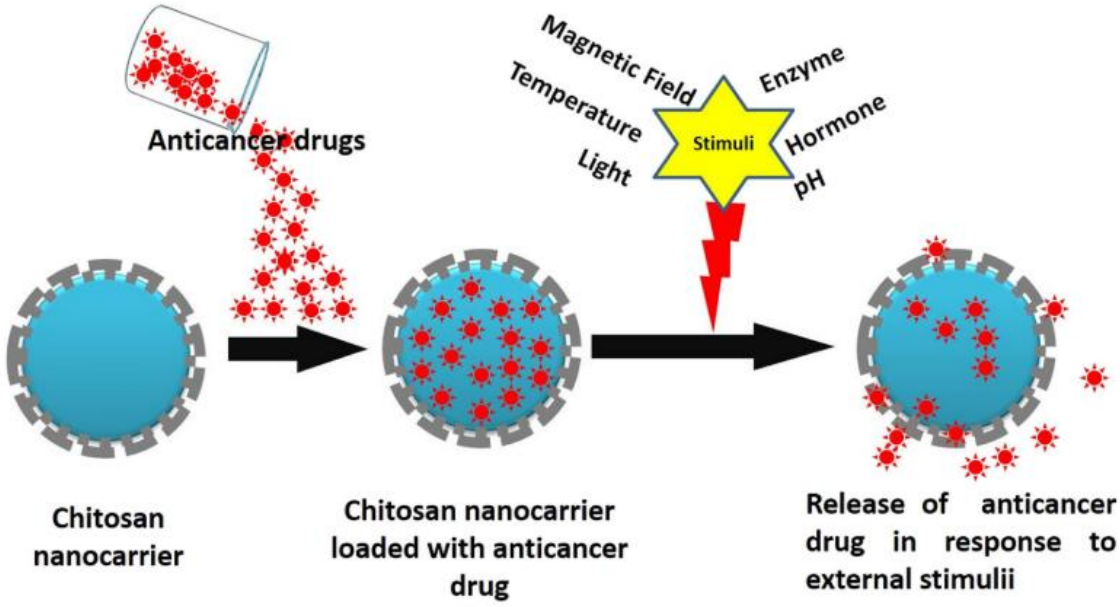

Figure 1Release of anticancer drugs from the chitosan nanoparticle due to external and internal stimuli (source: Shanmuganathan.et.al, 2019)

In the cancer theraphy using the chitosan nanoparticle, chitosan targets the tumor inducing cells by impeding the cell growth and its metabolism leading to the apoptosis of the cell (Duan.*et al*., 2014).

3.9 **ANTI-INFLAMMATORY DRUG DELIVERY:**

For the delivery of anti-inflammatory drugs, chitosan nanoparticles have been greatly used. The drugs delivered using chitosan nanoparticles includes zaltoprofen (Shah.*et al*., 2015), tretinoin (Ridolfi.*et al*., 2012), Ketorolac tromethamine (Fardet, 2007), hydrocortisone (Leon Lopez.*et al*., 2004). The aim of this drug is to increase the anti inflammatory activity, improve efficiency and high physical stability.

3.10 GENE DELIVERY

Gene is the process by which a foreign genetic material whether a DNA or RNA is transferred to host cells for approaches such as genetic research or gene theraphy. Gene theraphy is considerably a challenging task involved in the treatment of the genetic disorder. To achieve a successful gene delivery approach there are many hurdles that need to be overcome such as targeting the cell, movement across the cell membrane, the uptake and degradation in the endolysosome and the intra cellular trafficiking of the DNA to the nucleus (S.A.Agnihotri. *et al*., 2004). As the charge on chitosan tends to be positive, hence it could interact with negatively charged DNA and thus can protect the DNA against nuclease degradation leading to a better result for transfection. Chitosan exhibit a wide array of potentiality for the delivery of the CRISPR / Cas9 system (Chaun.*et al*., 2019).

3.11 VACCINE DELIVERY:

For acting as vaccine carrier, chitosan has been formulated into different therapeutic dosage such as tablets, beads, microspheres and nanoparticle (Liu.*et al*., 2007). It has been specifically investigated that the nanoparticle crossing the intestinal epithelium is more than of microspheres. Hence the preparation of chitosan nanoparticle used as vaccine delivery carrier has drawn attention (Liu.*et al*., 2007) therefore chitosan is one of the extensively studied vaccine delivery and carrier system. Chitosan, has been explored for it's used in vaccine delivery as DNA mucosal vaccines. Illum.et.al has successfully developed a chitosan based DNA flu vaccines (Illum.*et al*., 2001). Chitosan being positively charged can easily form complex with negatively charged polymers. Chitosan is able togelate with specific polyanion such as TPP (Liu.C.,*etal*., 2007). The association of chitosan vaccines to some of the particulate as nanoparticles has shown to upgrade the antigen uptake capacity by mucosal lymphoid tissues, therefore inducing a strong systemic and mucosal immune responses against the antigen (Lubben.*et al*., 2001).

3.12 NON VIRAL MEDIATED:

The nonviral mediated gene delivery method involves the use of synthethic compound, natural compound or physical forces to deliver a piece of DNA in the cell. It was proposed by Mumper.et.al, of chitosan

being used as a promising gene delivering vector. (Mumper.*et al.*). A chitosan polymer possess significantly low toxicity and also lacks mutational potential (Mumper.*et.al*.), marking its suitability for being used as a vector in non viral mediated transfer. Chitosan also tend to increase the transfection efficiency when attached to cell targeting ligand. A liver targeting delivery system was developed by Park.et.al by preparing galactosylated chitosan graft dextran DNA complexes as galactose (Park.*et al.*). Chitosan TPP nanoparticle has shown much potential as viable vector canditates for safer and cost effective siRna delivery (Katas, Alpar, 2006). Due to the high binding capacity and loading efficiency, chitosan TPP nanoparticle with entrapped siRNA have been shown to be a better vector as siRNA delivery vehicles compared to chitosan siRNA complex (Jia *et al.*2005).

3.16 BRAIN TARGETING:

The delivery of drug, targeting the brain is the process of passing the therapeutically active molecules across the blood brain barrier for the treatment. In order to distribute the drugs within the central nervous system, blood brain barrier represents an obstacle. To overcome such obstacle many emerging approaches have been developed. One such approach is the use of appropriate modified nanoparticle as drug carrier system. Chitosan nanoparticle have been utilized for the brain targeting of the drugs after coating them with polysorbate 80 (Soni S., Babbar A., *et al.*, 2005). Chitosan have been utilized to improve the brain targeting efficiency by the direct nose to brain pathway especially for drugs for treatment of central nervous disorders. Further it has been used to combine the active drug for targeting to the olfactory region with controlled release bioadhesive characteristics for maintaining the drug on the absorption site (Charlton S.T., 2007). It has also been reported that both chitosan structural feature and molecular weight plays a key role in promoting the intranasal absorption of 2,3,5,6 – tetramethylpyrazine phosphate (TMPP) (Mei., D., Mav., *et al.*, 2008).

IV. CONCLUSION

Chitosan is an abundant natural based polymer, obtained by the process of N- acetylation ofChitin. Various research on chitosan and its derivatives as a potent drug delivery agents imprintsthe importance of chitosan. Chitosan being a natural, biocompatible, biodegradable,non toxicpossess all the properties for the application in the therapeutic field of science.

Oral drug administration is found to be the most convenient route of delivery for patients due to its convenience, cost-effectiveness and high patient compliance. Chitosan based nanocarriers have the ability to overcome the physical barriers of the GI tract and enhance drug absorption. Chitosan has applications in nasal delivery for overcoming the difficulties faced by the low permeability of polysaccharides, proteins, peptides, hydrophilic drugsas chitosan nanocarriers also exhibits biodegradability, biocompatibility, low toxicity, adheres to mucous and opens the tight junctions of nasal membrane. Nanoparticles are potential carriers for ocular delivery as they are capable to adhere to the ocular epithelial surface. Chitosan can be used effectively as a carrier for mucosal drug delivery because of its mucoadhesive properties. Chitosan have proved to have clear antibacterial effect against *Klebsiella pneumoniae, Pseudomonas aeroginosa, Escherichiacoli, Mycobacterium*. Chitosan nanoparticle provides a wide range of application in the treatment of cancer and also assists in overcoming the obstacle faced in the conventional methodology, helping in bridging thegap between conventional and modern methodology of treatment of cancer. The application ofchitosan nanoparticle in the treatment enhances the effect of drug by specifically targeting thetumor cells. The in vitro as well as in vivo studies have shown chitosan to be a suitable materialfor efficient non viral gene delivery and as an adjuvant in vaccine delivery. As chitosan tends topossess cationic properties it has been widely used in gene delivery. Chitosan nanoparticle isefficiently being used in brain targeting as it can cross the blood brain barrier and thus deliverythe drug marking its efficiency and efficacy. This review summarizes the application of chitosanbeing a potent drug delivery agent. Henceforth we anticipate that more uses of chitosan will beforthcoming as additional derivatives are synthesized and newer formulations are developed in therespective field of drug delivery.

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