Review on overview of Chitosan as a Potent Drug Delivery

Geeta Joshi, Payal Dudani
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

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 that monitor 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 excipients produced 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 because of its biocompatibility and biodegradability (Naskar et al) into nontoxic and non-allergic products (Brendon Y. Chua et al). These properties of chitosan has led 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-glucosaminieresidues. It is a non antigenic hydrophilic polymer containing one amino group and 2 hydroxyl group in the resting 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 (Kafetzopoulou et al).

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

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 properties 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 I.A 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
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.Foxet 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.Sunet 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,Let 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).
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 aeruginosa* 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). These nanoparticles 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 a preferred material 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 technology 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).
In the cancer therapy 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 therapy. Gene therapy 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 intracellular trafficking 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 to gelate with specific polyanion such as TPP (Liu C et al., 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 candidates 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 of Chitin. Various research on chitosan and its derivatives as a potent drug delivery agents imprints the importance of chitosan. Chitosan being a natural, biocompatible, biodegradable, non toxic possess 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 drugs 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 the gap between conventional and modern methodology of treatment of cancer. The application of chitosan nanoparticle in the treatment enhances the effect of drug by specifically targeting the tumor cells. The in vitro as well as in vivo studies have shown chitosan to be a suitable material for efficient non viral gene delivery and as an adjuvant in vaccine delivery. As chitosan tends to possess cationic properties it has been widely used in gene delivery. Chitosan nanoparticle inefficiently being used in brain targeting as it can cross the blood brain barrier and thus deliver the drug marking its efficiency and efficacy. This review summarizes the application of chitosan being a potent drug delivery agent. Henceforth we anticipate that more uses of chitosan will forthcoming as additional derivatives are synthesized and newer formulations are developed in therepective field of drug delivery.

REFERENCES:

Chitosan nanoparticles to cure multidrug resistant gram-negative and Y. lejun.; Preparations, characterizations and applications in Drug Delivery Reviews 51 (2001) 81–90.


Review an Overview of Chitosan as a Potent Drug Delivery


[70] Ziad Al Chami, DeaAlwanneyn, Sandra Angelica De Pascali, Ivana Cavoski and Francesco Paolo Fanizzi ; Extraction and characterization of bio effectors from agro-food processing by-products as plant growth promoters; Chemical and Biological Technologies in Agriculture 2014, 1:17.

[71] Ziad Al Chami, DeaAlwanneyn, Sandra Angelica De Pascali, Ivana Cavoski and Francesco Paolo Fanizzi; Extraction and characterization of bioeffectors from agro food processing by products as plant growth promoters; Chemical ans Biological Technologies in Agriculture 2014, 1:17.